Illustrated Textbook of
PEDIATRICS

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SECOND EDITION

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JAYPEE *The Health Sciences Publisher*

New Delhi | London | Philadelphia | Panama

Jaypee Brothers Medical Publishers (P) Ltd

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New Delhi 110 002, India
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Phone +977-9741283608
Email: kathmandu@jaypeebrothers.com

Website: www.jaypeebrothers.com
Website: www.jaypeedigital.com

Illustrated Textbook of Pediatrics

First Edition: 2014

Second Edition: ***2015***

ISBN 978-93-5152-515-8

Printed at

Dedicated to

My Parents
Late Md Abdush Shakur
and
Late Mrs Sayma Khatun
who blessed me with life of peace,
knowledge, dignity, comfort and contentment

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FOREWORD

It is my great pleasure to congratulate the author and the contributors for accomplishing the stupendous job of composing an Illustrated Textbook of Pediatrics.

Textbook remains the mainstay of medical education for centuries. However, due to rapid development of acquiring knowledge effortlessly via the Internet and through handy medical books, gathering knowledge from reading textbooks in conventional way is currently losing its previous attraction. There are many textbooks on pediatrics, but this colorful textbook is unique, containing 1,149 colorful illustrations, which has made the book reading-friendly and will provide a new dimension in the field of textbook of pediatrics. This I believe will also help to bring back the pleasure of reading textbooks in pediatrics to great extent.

This book while providing update informations in pediatrics, emphasized significantly on spectrum of diseases and child health problems of public health importance of Bangladesh. The outstanding effort of the author to cover community pediatric problems of Bangladesh as well as hospital pediatric problems at secondary and tertiary level is praiseworthy. Unlike many textbooks, the author endeavored to incorporate clinical methodology (neurology, cardiovascular and neonatology in particular) with eye-catching illustrations to compliment clinical understanding, which I believe will benefit senior medical undergraduates and postgraduates in pediatrics undertaking clinical examinations. Specialists in pediatrics, postgraduates in pediatrics, pediatric practitioners, general practitioners and senior undergraduate medical students will be enormously benefited from this book. This book will also serve as ready reference to busy pediatricians, trainee doctors and child healthcare providers.

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Professor Md Salim Shakur

ABOUT THE AUTHOR

Professor Md Salim Shakur MBBS (DMC, DU) DCH (Glasgow and Dublin) MRCP (UK) PhD (Nutrition, DU) FRCP (London, Glasgow, Edinburgh) FRCPCH (UK) was born on April 1, 1954 in Dhaka. He passed SSC from Rajshahi Collegiate School in 1970 and HSC from Dhaka College, Dhaka, in 1972. He obtained MBBS from Dhaka Medical College, in 1979. He obtained diploma in child health (DCH) from University College Dublin, Ireland, in 1983 and DCH from Royal College of Physicians and Surgeons of Glasgow, UK, in 1989. He passed MRCP (UK) in Pediatrics from Royal College of Physicians of UK in 1989. Professor Shakur was conferred PhD by University of Dhaka in 2000 as recognition of his work on role of zinc in severely malnourished children suffering from pneumonia.

Professor Shakur obtained higher postgraduate training in Pediatrics and Neonatology in Our Lady's Children's Hospital for Sick Children, Dublin, Ireland, in 1983 and in Royal Hospital for Sick Children, Edinburgh, UK, Western General Hospital, Edinburgh and in Queen Elizabeth Hospital for Sick Children, London, UK, during the years, 1987 to 1989. He was also a postgraduate student at Department of Child Life and Health, University of Edinburgh, UK from April 1987 to September 1989.

He started his academic career as Assistant Professor of Pediatrics (Nutrition and Gastroenterology) at Bangladesh Institute of Child Health (BICH), Dhaka Shishu (Children) Hospital in 1989. He became Associate Professor in 1993 and Professor of Pediatric Nutrition and Gastroenterology in 1999. He held the post of Academic Director of BICH from year 2002 to 2004 and Director of Dhaka Shishu (Children) Hospital during the period of 2004 to 2008. He joined as Consultant and Head, Department of Pediatrics, United Hospital Ltd, Dhaka, in 2009, and currently continuing as Visiting Consultant of Pediatrics in same hospital.

Professor Shakur is involved in activities in many professional bodies. He is founder Chairman of Bangladesh Paediatric Gastroenterology and Nutrition Society (BAPGANS) since 2005. He was member of technical committee of action plan of infant and young child feeding from 2008–2010, Member of Technical Committee for Formulation of National Guidelines for Management of Severely Malnourished Children (2007–2008), Member of Core Committee, Strategy for Neonatal Survival, Ministry of Health in 2007. Professor Shakur was Chairman, Scientific Subcommittee of Bangladesh Paediatric Association (BPA) from 2003 to 2008 and held the post of Vice-President and Executive Member of BPA.

Commencing career as Assistant Professor of BICH in 1990, Professor Shakur engaged himself in research activities in addition to teaching postgraduates and providing clinical service to hospital. He published more than 40 research papers in reputed medical journals of home and abroad. He performed extensive research works on micronutrients, particularly on zinc and notable research papers were published in reputed international medical journals including Indian Journal of Pediatrics (Indian J Pediatr. 2009;76:609-12), American Journal of Clinical Nutrition (Am J Clin Nutr. 1998;68:742-8), Indian Pediatrics (Indian Pediatr. 2004;41:478-81). In addition to articles based on original research works, Professor Shakur published many interesting case reports, including case report of cystic fibrosis, first published case report of cystic fibrosis [Bangladesh J Child Health. 1995;19(1):23-8] from Bangladesh. He was one of the pioneers in bringing use of zinc in clinical pediatric practice, particularly in diarrhea in Bangladesh.

Professor Shakur is honorable Fellow of a number of prestigious learned international medical societies. He was elected Fellow of Royal College of Physicians of Edinburgh (FRCPE) in 1998, Royal College of Physicians and Surgeons of Glasgow (FRCPG) in 2000 and Royal College of Physicians of London (FRCPL) in 2002. He became Fellow of Royal College of Paediatricians and Child Health of UK (FRCPCH) in 2000, the first Pediatrician in Bangladesh to obtain Fellowship of RCPCH (UK) and in the process became prestigious Fellow of all the Royal Colleges of Physicians as well as Royal College of Paediatrics of UK.

PREFACE TO THE SECOND EDITION

It is indeed a matter of great pleasure and pride to present *Illustrated Textbook of Pediatrics* the first ever appearance of Illustrated Textbook of Pediatrics in color, published by well-recognized internationally reputed medical book publisher in India. I am extremely delighted by wide acceptance of the book only within few months of its first publication in February 2014. I am very much thankful to readers particularly to my fellow colleagues who showed keen interest in the book and patronized the book. Not only the book earned admiration in Bangladesh but also it created interest among stakeholders of neighboring countries like India, Pakistan and in overseas countries including UK, Canada and North America. Reputed book publisher based in India "Jaypee Brothers Medical Publishers (P) Ltd." was prompt to show interest to take the responsibility of editing, printing and publishing the second edition of the book only couple of months after the book was first published from Dhaka, which is outstanding. Medical knowledge with learning experience is a global life-saving solution and medical textbooks served as the mainstay of medical education for centuries. However, with rapid development of information technology highway via the Internet, gathering knowledge through reading textbook in conventional way is currently becoming a tedious job and gradually losing its previous glamor. Therefore, efforts were given to revive the pleasure of reading textbook so that it becomes more absorbing and reading-friendly. Accordingly the book has been enriched with more than 1,000 attractive colored illustrations which include clinical photographs, drawings, sketches to complement clinical understanding, believing illustrations which include clinical images worth hundred words.

The book is expected to provide update information of pediatrics with special emphasis attached on pediatric illness of Indian subcontinent particularly child health problems of public health importance of this part of the world. Critical informations were highlighted with bullet points, in boxes and bolding of words and sentences. Colorful flow diagrams and algorithms will guide you through the more complex areas. Where applicable more in depth informations were provided highlighting areas of controversy and stimulating further reading. All are based on best available evidences or on accepted best practices.

A so called traffic light system flow sheet diagram, table or algorithm is used according to severity of clinical condition. In this system, features in green zone indicate low risk or safe zone, amber color indicate intermediate risk and high risk is indicated by red zone which is unique of this textbook. The contents are divided into broad content and more detailed content which will provide readers quick access to reach desired topic. A detailed index is given at the rear to provide easy access to information.

In this second edition, the book has been presented with superior print and in more flawless condition. This edition features more distinct and much higher quality illustrations with better resolution and precision of images.

I would like to acknowledge the contribution of Shri Jitendar P Vij, Group Chairman of internationally reputed medical publication house, based in India M/s Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, India who spent no time to spot the book and kindly accepted to publish this unique book from his famous publishing house. I would like to thank Mrs Ritu Sharma, Head of Undergraduate Textbook Division, Ms Samina Khan (Executive Assistant to Director–Publishing), Mr Sanjoy Chakraborty (Branch Manager, Kolkata) and Mr Sarod Ghosh (Regional Manager, Bangladesh), for their cooperation and coordination in publishing second edition of the book.

We welcome feedback and constructive criticism from all readers and stakeholders which will motivate us to deliver the best in future.

We dedicate this second edition to parents and their pediatric patients whose sufferings provided us with learning experience and helped enormously to publish this wonderful book.

Md Salim Shakur

PREFACE TO THE FIRST EDITION

No book can provide wise head and warm heart that comes only from clinical experience. However, knowledge is generally preferable to ignorance and despite the development of information super highway via the Internet, appropriate knowledge gathering in rational way is still found most easy between the covers of a book. The great physician and teacher Sir William Osler put it more neatly, "He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all."

Textbooks have been the mainstay of medical education for centuries. What does yet another pediatric textbook to current long list of titles? All medical writings are particularly rewriting with addition of recent advances but they are presented in different styles and formats suitable for specific class of readers or users. This book is neither intended to replace the existing textbooks nor it can provide the much details contained in scientific journals. Instead I expects that the book will serve for update review of relevant medical informations and it will be helpful from the start of ones education in pediatrics all the way through higher general and to some extent to subspecialist training in pediatric field. This book is intended to be used in whatever one chooses to practice—hospital, generalist or community and family practice. This book is also expected to be used as a reference book by postgraduate students and pediatricians.

Most of the pediatric textbooks available in Bangladesh are edited by authors of Western countries and definitely of high quality but most of them fall well short of addressing pediatric problems of public health concern of our country. Although this book covering the global pediatric problem considering the fact that a doctor may has to work in different parts of the world, significant effort and emphasis have been attached to clinical and public health problems of developing countries like Bangladesh.

With advances of information technology, textbook reading in conventional way is threatened to lose its appeal. Therefore, efforts have been taken to enrich the book with several colorful illustrations, which include clinical photographs, sketches, drawings, algorithms which have been selected not only to make the book more fascinating to read but also to enhance clinical understanding believing illustration, particularly clinical photographs, worth hundred words.

Each chapter, where appropriate, opens with a brief review of some applied basic science relevant to clinical practice and closes with bibliography. The book also dedicated chapters on basic science required for clinical practice like clinical genetics, fluid and electrolyte balance, blood gas analysis in a simplified way. Clinical methodology particularly clinical examination of central and peripheral nervous system, cardiovascular system and neonatal examination methodology have been elaborately described with illustrations to compliment clinical understanding, which I believe will enormously benefit postgraduates and senior undergraduates undertaking clinical examinations.

I hope the readers through studying the book will increase the knowledge, skill and confidence to manage pediatric clinical problems effectively and safely.

Md Salim Shakur

ACKNOWLEDGMENTS

This book is the fruition of inputs, direct or indirect individuals whose contribution I wish to acknowledge.

I am greatly indebted to Dr Rezwana Rima, Specialist, Department of Pediatric Cardiology, United Hospital Limited (currently working as Assistant Professor, BICH, Dhaka Shishu (Children) Hospital), for significantly contributing in pediatric cardiology, particularly in congenital heart disease chapter.

Thanks to Dr Abdur Rahman, Specialist, Department of Pediatrics and Neonatology, United Hospital Limited, for his substantial contribution in neonatology chapter. Thanks to Dr Nargis Ara Begum, Consultant, Department of Neonatology, United Hospital Limited, for her support and input with update information which helped me in writing neonatology chapter.

I would like to extend my gratitude to Dr Narayan Saha, Associate Professor, Department of Pediatric Neurology, Dhaka Medical College, for contributing in pediatric neurology, particularly epilepsy chapter.

Thanks to Professor Mobin Khan, Chairman, Hepatology Society, Bangladesh; Professor Selimur Rahman, Department of Hepatology, BSMMU, and Dr Bashir, Hepatologist, Bangabandhu Sheikh Mujib Medical University (BSMMU), for their contribution in hepatology chapter.

I am thankful to Dr Fauzia Mohosin, Associate Professor, Department of Pediatrics, Ibrahim Medical College, for enriching pediatric endocrinology chapter of the book by her valuable contribution in childhood diabetes mellitus chapter.

Thanks to Dr Jalal (now in Australia) and Professor Selimuzzaman, Department of Hemato-oncology, Dhaka Shishu (Children) Hospital, and Professor Khairul Amin, currently Professor, Department of Pediatrics, Anwar Khan Modern Medical College, for providing input and update information for writing hemato-oncology chapter.

I acknowledge the contribution of National Professor MR Khan; Professor Mesbahuddin Ahmed, Head, Department of Child Health, Gono Bishwabidyalay, Savar, and Professor Ishtiaque Hossain, Senior Consultant, Apollo Hospital, Dhaka, for their contribution in immunization chapter, particularly in preparing proposed immunization schedule of BPA, which has been included in the book. Dr Suraiya Noor and Dr Moshiur Rahman, Pediatric Consultant, United Hospital Limited also contributed in vaccinology chapter which I acknowledge with gratitude.

I gratefully acknowledge the authors of publications and books from where information have been taken, reference lists have been cited at the end of each chapter and in illustrations wherever applicable, but if some have been left out by mistake, I offer my sincere apology.

I am especially thankful to Dr Shuvro Prokash Paul, currently Senior Registrar, Rajshahi Shishu Hospital, for taking dictation, computing and supplying me with some valuable pediatric update. Thanks to Mr Abu Ayub Ansary, Computer Operator and Graphic Designer, who was also involved in taking dictation and in make-up job of composing the book. Thanks to Mrs Tina Kabir, Artist from Institute of Fine Arts, now in Canada who drew unique clinical figures to compliment clinical understanding. Thanks to Dr Molla Abdul Wahab, Consultant, Department of Nuclear Medicine, United Hospital Limited, for providing few valuable isotopes scans pictures.

I am extremely grateful to my dear patients and their parents, who allowed me to take and use photographs for better illustrations. All the doctors, nurses and auxiliary staffs of United Hospital as well as Dhaka Shishu (Children) Hospital where I worked for 20 years deserve special thanks, for all out contribution and cooperation in helping me to gather materials and inputs for the book.

I am especially thankful to my eldest brother Dr Tasleem Shakur, PhD, working as Senior Lecturer, Human Geography, University of Lanchashire, UK, who constantly encouraged and persuaded me to publish a book on pediatrics. Thanks to my brother-in-law, Professor Rabiul Islam, Professor of Chemistry, Jahangir Nagar University, Savar, for his encouragement to publish the book.

Finally, my sincere thanks to my wife, Dr Parveen Akhter, Consultant Radiologist, Ibn Sina Diagnostic Center, and my daughters Miss Parisa Shakur and Miss Salomee Shakur, Lecturer Department of Economics, North South University and 3rd year medical student, Uttara Adhunik Medical College respectively who have encouraged me all the times to complete the book and in the process have missed out my many sweet memories of family life with them because of my preoccupation with Illustrated Textbook of Pediatrics.

ABOUT THE BOOK

This book is a unique compendium of update and essential information on all range of pediatric topics with emphasis on pediatric problems of developing countries. It is written in a concise, easy-to-read format and is intended for use by pediatric residents, senior medical undergraduates, postgraduates in pediatrics, practicing pediatricians and physicians. While working as a pediatrician for more than 25 years, I was fascinated by the various types of pediatric cases and problems at home and abroad, which I always desired to record. During my service of 20 years in Dhaka Shishu Hospital, in addition to my clinical workload, I was also preoccupied with administrative works even after office hours, particularly with administrative jobs of director of hospital and academic director of Bangladesh Institute of Child Health for significant part of my service in that institute. After joining United Hospital Ltd in 2009, administrative work dropped significantly which provided me with ample opportunity and scope to write the book. Unique combination of my wide pediatric experience in resource-poor developing countries like Bangladesh (Dhaka Shishu Hospital, a government-aided autonomous hospital and United Hospital Ltd, a corporate tertiary care private hospital) in relatively resource-rich Middle East countries and in industrialized countries like UK helped me in writing the book in global perspective.

The book contains almost all the topics of pediatrics with special emphasis on child health and pediatric problems. For instance, significant emphasis has been given on subjects like malnutrition, diarrheal diseases, pneumonia, breastfeeding, infectious diseases like tuberculosis, typhoid, dengue, malaria, neonatal problems like preterm low birthweight baby, neonatal sepsis, birth asphyxia, community pediatrics including integrated management of childhood illness (IMCI). The book has been enriched with colorful attractive illustrations, which include clinical photographs, drawings, sketches to complement clinical understanding. A total of 1,149 such clinical illustrations have been included taken from my personal collection, Internet and other sources which are unique of the book. Clinical methodology particularly clinical examination of nervous system, cardiovascular system and neonatal examination (where postgraduates are frequently puzzled to perform) are discussed with illustrations which I believe will help postgraduates as well as senior undergraduates to perform well at clinical part of professional examinations.

The book contains drug therapy chapter containing names of drugs frequently used in pediatric practice with their generic names, trade names, doses and indications of use in attractive easy-to-find way in order to facilitate drug treatment in hospital setting and writing prescription by practitioners at their private chamber and at community-level practice. It is hoped that the book will serve as useful companion for all the doctors who are involved in pediatric practice and in child healthcare at all levels.

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ABBREVIATIONS

> : Greater than
< : Less than
↑ : Increased
↓ : Decreased
AA : Aplastic anemia
AAD : Antibiotic-associated diarrhea
AAP : American Academy of Pediatrics
ABC : Airway, breathing and circulation
ABG : Arterial blood gas
ABGA : Antibasal ganglia antibodies
ABM : Acute bacterial meningitis
ABR : Auditory brainstem response
ABU : Asymptomatic bacteriuria
ACDWC : Autistic children development and welfare center
ACE : Angiotensin-converting enzyme
AChR : Acetylcholine receptor
ACIP : Advisory Committee on Immunization Practices
ACT : Adenylate cyclase toxin
ACT : Artemisinin-based combination therapy
ACTH : Adrenocorticotropin
AD : Autosomal dominant
ADA : American Diabetes Association
ADE : Antibody-dependent enhancement
ADEM : Acute discriminated encephalomyelitis
ADH : Antidiuretic hormone
ADHD : Attention deficit hyperactivity disorder
ADOS : Autism diagnostic observation schedule
AE : Acrodermatitis enteropathica
AED : Antiepileptic drug
AES : Antiepileptic surgery
AFO : Ankle foot orthoses
AFP : Acute flaccid paralysis
AFP : Alpha feto-protein
AG : Anion gap
Agg-EC : Aggregative adherent *E. coli*
AGN : Acute glomerulonephritis
AHIs : Assistant health inspectors
AHO : Albright's hereditary osteodystrophy
AI : Aortic incompetence
AIDP : Acute inflammatory demyelinating polyneuropathy
AIDS : Acquired immunodeficiency syndrome
AIS : Arterial ischemic stroke
AKI : Acute kidney injury
AL : *Ascaris lumbricoides*
ALF : Acute liver failure
ALK : Anaplastic lymphoma kinase
ALL : Acute lymphoblastic leukemia
ALRI : Acute lower respiratory infection
ALTE : Apparent life-threatening event
AMAP : Acute motor axonal polyneuropathy
AMH : Anti-Müllerian hormone
AML : Acute myeloid leukemia
AMLL : Acute mixed-lineage leukemia
AMSAN : Acute motor and sensory axonal neuropathy
AN : Anorexia nervosa
ANA : Antinuclear antibody
ANC : Absolute neutrophil count
ANLL : Acute nonlymphocytic leukemia
ANP : Atrial natriuretic peptide
anti-dsDNA : Anti-double-stranded DNA
APD : Afferent pupillary defect
APD : Automated peritoneal dialysis
APS : Antiphospholipid syndrome
APSGN : Acute poststreptococcal glomerulonephritis
aPTT : Activated partial thromboplastin time
AR : Aortic regurgitation
ARB : Angiotensin receptor blocker
ARDS : Acute respiratory distress syndrome
ARF : Acute renal failure
ARI : Acute respiratory infections
AS : Aortic stenosis
ASCT : Autologous stem cell transplantation
ASD : Atrial septal defect
ASD : Autism spectrum disorders
ASO : Antistreptolysin O
ATG : Antithymocytic globulin
ATM : Acute transverse myelitis
ATN : Asymmetric tonic neck reflex
ATN : Acute tubular necrosis
AUL : Acute undifferentiated leukemia
AVM : Arteriovenous malformation
AVNRT : Atrioventricular nodal re-entry tachycardia
AVP : Arginine vasopressin
AVRT : Atrioventricular re-entry tachycardia
AXR : Abdominal X-ray
BAL : Bioartificial liver
BAL : Bronchoalveolar lavage
BAV : Bicuspid aortic valve
BB : Borderline-borderline
BBD : Bladder bowel dysfunction
BBS : Bangladesh Bureau of Statistics
BCECT : Benign childhood epilepsy with centro-temporal spikes
BDP : Beclomethasone dipropionate
BDZ : Benzodiazepine
BE : Based excess
BFHI : Baby friendly hospital initiative
BHS : Breath holding spells
BHS : β hemolytic *Streptococcus*
BIA : Bioelectric impedance
BL : Borderline lepromatous
BM : Basement membrane
BMD : Becker muscular dystrophy
BMI : Body mass index
BMR : Basal metabolic rate
BMS : Bone marrow study
BMT : Bone marrow transplantation
BNFC : Benign neonatal familial convulsion
BNP : Brain natriuretic peptide
BP : Blood pressure
BPA : Bangladesh Paediatric Association
BPD : Bronchopulmonary dysplasia
BPV : Balloon pulmonary valvoplasty
BT : Blalock-Taussig
BT : Borderline tuberculoid
Bud : Budesonide
BUN : Blood urea nitrogen
BV : Biological value
BZD : Benzodiazepine

CAE : Childhood absence epilepsy
CAH : Congenital adrenal hyperplasia
cAMP : Cyclic adenosine monophosphate
CAP : Community acquired aspiration pneumonia
CAPD : Continuous ambulatory peritoneal dialysis
CAS : Childhood absence seizure
CaSR : Calcium sensing receptor
CAVH : Continuous arteriovenous hemofiltration
CBC : Complete blood count
CBE : Carbamazepine
CBM : Community-based management
CBT : Cognitive behavior therapy
CBZ : Carbamazepine
CCF : Congestive cardiac failure
CCPD : Continuous cycling peritoneal dialysis
CCS : Comminuted chicken soup
CD : Chronic diarrhea
CDC : Choledochal cyst
CDC : Center for disease control
CDD : Childhood disintegrated disorders
CDGP : Constitutional delay in growth and puberty
CDH : Congenital diaphragmatic hernia
CE : Counter immunoelectrophoresis
CES : Childhood epileptic syndrome
CF : Cystic fibrosis
CFTR : CF transmembrane receptor
CHAQ : Childhood health assessment questionnaire
CHD : Congenital heart disease
CHF : Congestive heart failure
CHI : Creatinine height indices
CHL : Classical Hodgkin lymphoma
CHWs : Community health workers
CKD : Chronic kidney disease
CLB : Clobazam
CLD : Chronic liver disease
CLD : Chronic lung disease
CLF : Chronic liver failure
CLT : Chronic lymphocytic thyroiditis
CMAM : Community-based management of acute malnutrition
CMI : Cell-mediated immunity
CMP : Cow's milk protein
CMPA : Cow's milk protein allergy
CMR : Cardiovascular magnetic resonance
CMV : Cytomegalovirus
CNS : Central nervous system
CoA : Coarctation of aorta
CONS : Coagulase negative *Staphylococcus*
CP : Cerebral palsy
CPAP : Continuous positive airway pressure
CPD : Cephalopelvic disproportion
CPP : Central precocious puberty
CPP : Cerebral perfusion pressure
CPR : Cardiopulmonary resuscitation
CPSE : Complex partial status epilepticus
CRF : Chronic renal failure
CRH : Corticotropin releasing hormone
CRI : Chronic renal insufficiency
CRI : Congenital rubella infection
CRIP : Cysteine-rich intestinal protein
CRP : C-reactive protein
CRRT : Continuous renal replacement therapy
CRS : Congenital rubella syndrome
CRT : Capillary refilling time
CSE : Convulsive status epilepticus
CSF : Cerebrospinal fluid
CSFs : Colony stimulating factors
CSII : Continuous subcutaneous insulin infusion
CSOM : Chronic suppurative otitis media
CSV : Classic simple virilizing
CSW : Classic salt-wasting
CSWS : Continuous spike wave discharges during sleep
CS-WS : Continuous spike-wave in slow sleep
CT : Clotting time
CT : Computerized tomography
CTC : Community-based therapeutic care
cVDPVs : Circulating vaccine-derived polio viruses
CVP : Central venous pressure
CVS : Chorionic villus sampling
CVS : Cyclical vomiting syndrome
CVST : Cerebral venous sinus thrombosis
CVVH : Continuous venovenous hemofiltration
CVVHD : Continuous venovenous hemodiafiltration
CXR : Chest X-ray
CZP : Clonazepam
DA-EC : Diffusely adherent *E. coli*
DALY's : Disability adjusted life years
DAMP : Disorder of attention and motor perception
DAT : Diphtheria antitoxin
DBS : Dried blood sample
DBS : Dried blood spot
DC : Direct current
DCCT : Diabetes control and complication trial
DCD : Developmental coordination disorder
DCL : Diffuse cutaneous leishmaniasis
DEXA : Dual energy X-ray absorptiometry
DF : Dengue fever
DHA : Docosahexanoic acid
DHF : Dengue hemorrhagic fever
DHT : Dihydrotestosterone
DI : Diabetes insipidus
DIC : Disseminated intravascular coagulation
DIT : Diet-induced thermogenesis
DKA : Diabetic ketoacidosis
DM : Diabetes mellitus
DMARD : Disease modifying antirheumatic drugs
DMD : Duchenne muscular dystrophy
DMSA : Dimercaprosuccinic acid
DMST : Dexamethasone suppression test
DNT : Dermonecrotic toxin
DORV : Double outlet right ventricle
DOT : Directly observed treatment
DRCG : Direct radionucleotide cystography
DRV : Dietary reference value
DS : Decreased susceptibility
DSD : Disorders of sex development
dsDNA : Double-stranded DNA
DSS : Dengue shock syndrome
DTPA : Diethylene-triaminepentacetic acid
DV : Dengue virus
DWI : Diffusion weighted imaging
DXA : Dual energy X-ray absorptiometry
EAR : Estimated average requirement
EBC : Expected bladder capacity
EBV : Ebstein-Barr virus
EC : Extracellular
ECF : Extracellular fluid
ECF : Extracellular fraction
ECG : Echocardiogram
ECMO : Extracorporeal membrane oxygenation
EDV : End diastolic volume
EEG : Electroencephalograpgy
EF : Edema factor
EFA : Essential fatty acids
EFS : Event free survival
EFV : Efavirenz
EHEC : Enterohemorrhagic *E. coli*

EHF : Extensively hydrolyzed formula
EHPVO : Extrahepatic portal venous obstruction
EIA : Enzyme immunoassay
EIEC : Enteroinvasive *E. coli*
EIEE : Early infantile epileptic encephalopathy
ELAD : Extracorporeal liver assist device
ELBS : Extremely low birthweight babies
ELISA : Enzyme-linked immunosorbent assay
ENA : Extractable nuclear antigens
ENL : Erythema nodosum leprosum
EO : Eosinophilic oesophagitis
EPA : Eicosapentanoic acid
EPF : Eosinophilic pustular folliculitis
ERCP : Endoscopic retrograde cholangiography
ERG : Electroretinogram
ESM : Ethosuximide
ESR : Erythrocyte sedimentation rate
ESRF : End stage renal failure
ETEC : Enterotoxigenic *E. coli*
ETN : Erythema toxicum neonatorum
ETT : Endotracheal tube
FA : Fanconi anemia
FBC : Full blood count
FBM : Folbamate
FCPD : Fibrocalculous pancreatic diabetes
FDA : Food and Drug Administration
FDC : Fixed-dose combination
FDCs : Fixed drug combinations
FDP : Fibrin degradation product
FEH_2O : Fractional excretion of water and sodium
FFA : Free fatty acids
FFP : Fresh frozen plasma
FGF : Firboblast growth factors
FGFR3 : Fibroblast growth factor receptor 3
FHA : Filamentous hemagglutinin
FHF : Fulminant hepatic failure
FII : Fabricated induced illness
FIM : Fimbriae
FISH : Florescent in situ hybridization
FM : Fat mass
fMRI : Functional MRI
FOSs : Fructo-oligosaccharides
FP : Fluticasone propionate
FP : Foot processes
FPG : Fasting plasma glucose
FPIES : Food protein-induced enterocolitis syndrome
FRNS : Frequent relapse nephrotic syndrome
FS : Febrile seizure
FS : Full resistance
FSGS : Focal segmental glomerulosclerosis
FSH : Follicle stimulating hormone
FTT : Failure to thrive
G6PD : Glucose-6-phosphate dehydrogenase
GA : Gestational age
GABA : Gamma butyric acid
GABA : Gamma-aminobutyric acid
GABHS : Group A β-hemolytic *Streptococcus*
GALT : Galactose-1-phosphate uridyltransferase
GBM : Glomerular basement membrane
GBP : Gabapentin
GBS : Guillain-Barré syndrome
GBWT : Gallbladder wall thickness
GCS : Glasgow coma scale
GD : Graves disease
GE : Gastroenteritis
GEFS+ : Generalized epilepsy with febrile seizure plus
GER : Gastroesophageal reflux
GERD : Gastroesophageal reflux disease
GFB : Glomerular filtration barrier
GFR : Glomerular filtration rate
GH : Growth hormone
GHR : GH receptor
GHRH : Growth hormone releasing hormone
GI : Glycemic index
GIPP : Gonadotropin-independent precocious puberty
GMFCS : Gross motor functional classification system
GMFM : Gross motor function measure
GMH-IVH : General matrix hemorrhage-intraventricular hemorrhage
GnRH : Gonadotropin-releasing hormone
GnRHa : Gradually increase the GnRH analog
GOR : Gastro-oesophageal reflux
GOSs : Galacto-oligosaccharides
GP : General practitioner
GSD : Glycogen storage disease
GTCS : Generalized tonic clonic seizure
H. pylori : *Helicobacter pylori*
HA : Hemagglutinin
HAART : Highly active antiretroviral therapy
HAs : Health assistants
HAV : Hepatitis A virus
Hb : Hemoglobin
HBIG : Hepatitis B immune globulin
HBV : Hepatitis B virus
HC : Head circumference
HCC : Hepatocellular carcinoma
HCCM : High calorie cereal milk
HCG : Human chorionic gonadotropin
HCQ : Hydroxychloroquine
Hct : Hematocrit
HCTC : Heated cow's milk tolerant children
HCV : Hepatitis C virus
HDCV : Human diploid cell vaccine
HDN : Hemolytic disease of newborn
HDV : Hepatitis D virus
HepB : Hepatitis B
HEV : Hepatitis E virus
HF : Heart failure
HFJV : High frequency jet ventilation
HFNC : High flow nasal canula
HFOV : High frequency oscillatory ventilation
HHV1 : Human herpes virus 1
HI : Hyperinsulinemia
Hib : *Haemophilus influenzae type B*
HIDA : Hepatobiliary imidodiacetic acid
HIE : Hypoxic ischemic encephalopathy
HL : Hodgkin lymphoma
HLA : Human leukocyte antigens
HLHS : Hypoplastic left heart syndrome
HOCM : Hypertrophic obstructive cardiomyopathy
HP : Hypothalamopituitary
HPA : Hypothalamic-pituitary-adrenal
HPF : High power field
HPG : Hypothalamo-pituitary-gonadal
HPLC : High performance liquid chromatography
HR : Heart rate
HRAD : Hyperactive airway disease
HRIG : Human rabies immunoglobulin
HRS : Hodgkin Reed-Sternberg
HRV : Human rotavirus
HS : Hereditary spherocytosis
HSCT : Hemopoitic stem cell transplantation
HSDA : Hemodynamically significant ductus arteriosus
HSE : Herpes simplex encephalitis
HSMN : Hereditary sensory motor neuropathy
HSP : Henoch-Schönlein purpura
HSV : Herpes simplex virus

HTN : Hypertension
HUS : Hemolytic uremic syndrome
HVA : Homovanillic acid
HX : Histiocytosis X
IAP : Indian Academy of Paediatrics
IBD : Inflammatory bowel disease
IBS : Irritable bowel syndrome
IC : Intracellular
ICES : International Classification of Epileptic seizures
ICF : International Classification of Functioning
ICF : Intracellular fluid
ICP : Intracranial pressure
ICS : Inhaled corticosteroid
ICU : Intensive care unit
ID : Iron deficiency
IDA : Iron deficiency anemia
IDAS : Infectious Disease Society of America
IDM : Infant of diabetic mother
IDU : Intravenous drug uses
IE : Infective endocarditis
IEDCR : Institute of epidemiology, disease control and research
IEM : Inborn error of metabolism
IFA : Immunofluorescence assay
IFA : Immunofluorescent antibody
IFG : Impaired fasting glycemia
IFI : Invasive fungal infections
IFN-α : Interferon-alpha
IFPRI : International food policy research institute
IFRT : Involved field radiotherapy
IgAN : IgA nephropathy
IGF : Insulin-like growth factors
IGFBP-3 : Insulin growth factor binding protein-3
IGF-I : Insulin-like growth factor-I
IgG : Immunoglobulin G
IgM : Immunoglobulin M
IGRA : Interferon γ release assay
IGT : Impaired glucose tolerance
IHPS : Idiopathic hypertrophic pyloric stenosis
ILAR : International League of Association for Rheumatology
ILI : Influenza-like illness
IM : Intramuscular
IMCI : Integrated management of childhood illness
iNO : Inhaled nitric oxide
INRG : International neuroblastoma risk group
INSS : International neuroblastoma staging system
IPD : Intermittent peritoneal dialysis
IPD : Invasive pneumococcal disease
IPPV : Intermittent positive pressure ventilation
IPSS : Inferior petrosal sinus sampling
IPV : Inactivated poliovaccine
IRT : Immunoreactive trypsin
IS : Infantile spasm
IS : Ischemic stroke
ISPAD : International society of pediatric and adolescent diabetes
ISS : Idiopathic short stature
ITP : Idiopathic thrombocytopenic purpura
ITP : Immune thrombocytopenic purpura
IUD : Intrauterine death
IUGR : Intrauterine growth restriction
IV : Intravenous
IVH : Intraventricular hemorrhage
IVIG : Intravenous immunoglobulin
IVU : Intravenous urography
IYCF : Infant and young child feeding
JCA : Juvenile chronic arthritis
JE : Japanese encephalitis
JIA : Juvenile idiopathic arthritis
JME : Juvenile myoclonic epilepsy
JRA : Juvenile rheumatoid arthritis
KATF : Kala-azar treatment failure
KD : Kawasaki disease
KD : Ketogenic diet
KFT : Kidney function test
KPCs : *Klebsiella pneumoniae* carbapenemase
LA : Left atrium
LABA : Long-acting β_2 agonist
LA-EC : Localized adherent *E. coli*
LAIV : Live attenuated influenza vaccine
LAP : Left atrial pressure
LAV : Live attenuated vaccine
LBW : Low birthweight
LC : Langerhans cell
LCH : Langerhans cell histiocytosis
LCM : Lymphocytic choriomeningitis
LCT : Long chain triglyceride
LD : Learning difficulty
LDH : Lactate dehydrogenase
LEV : Levetiracetam
LF : Lethal factor
LFT : Liver function test
LGG : *Lactobacillus rhamnosus* GG
LGS : Lenox-Gastaut syndrome
LH : Luteinizing hormone
LHA : Lateral hypothalamic area
LHRH : Luteinizing hormone releasing hormone
LIC : Liver iron concentration
LJ : Lowenstein-Jensen
LKS : Landau-Kleffner syndrome
LL : Lepromatous leprosy
LMD : Limb girdle dystrophy
LN : Lupus nephritis
LOA : Lysine, ornithine, arginine
LP : Lumbar puncture
LPS : Lipopolysaccharide
LRNI : Lower reference nutrient intake
LRTI : Lower respiratory tract infection
LS : Lower segment
LTG : Lamotrigine
LTRA : Leukotriene receptor antagonist
LTRA : LT receptor antagonists
LV : Left ventricle
LVEF : Left ventricular ejection fraction
LVF : Left ventricular failure
LVH : Left ventricular hypertrophy
LVOTO : Left ventricular outflow tract obstruction
MAE : Myoclonic astatic epilepsy
MAM : Moderate acute malnutrition
MAPK : Mitogen-activating protein kinase
MARP : Most at risk population
MARS : Molecular adsorbent recycling system
MAS : Meconium aspiration syndrome
MAS : McCune-Albright syndrome
MB : Multibacillary
MBD : Minimal brain disorder
MCDK : Multicystic dysplastic kidney
MCGN : Mesangiocapillary glomerulonephritis
MCH : Mean cell hemoglobin
MCH : Mean corpuscular hemoglobin
MCHC : Mean corpuscular hemoglobin content
MCNS : Minimal change nephrotic syndrome
MCT : Medium chain triglyceride
MCU : Micturating cystourethrogram
MCV : Mean corpuscular volume
MCV : Measles-containing vaccine

MDG : Millennium development goals
MDI : Multiple dose insulin injection
MDI : Metered dose inhaler
MF : Multifocal
MFS : Miller Fisher syndrome
MGD : Mixed gonadal dysgenesis
MHC : Major histocompatibility complex
MIBG : Metaiodobenzylguanidine
MIC : Minimum inhibitory concentration
MIS : Müllerian-inhibiting substance
MMF : Mycophenolate mofetil
MN : Medial nucleus
MODS : Multiorgan dysfunction syndrome
MODY : Maturity-onset diabetes of young
MPGN : Membranoproliferative glomerulonephritis
MPGN : Membranoproliferative GN
MPH : Midparental height
MPS : Mucopolysachharidosis
MRA : Magnetic resonance angiogram
MRC : Medical Research Council
MRCP : Magnetic resonance cholangiopancreatography
MRI : Magnetic resonance imaging
MS : Multisystem
MS : Multiple sclerosis
MS : Multisystem
MSAFP : Maternal serum alpha fetoprotein
MSbP : Munchausen syndrome by proxy
MSRO- : Multisystem risk organ negative
MSRO+ : Multisystem risk organ positive
MSU : Midstream urine
MT : Montaux test
MTCT : Mother-to-child transmission
MTS : Mesial temporal sclerosis
MTX : Methotrexate
MUAC : Mid-upper-arm circumference
MUD : Matched unrelated donor
MusK : Muscle specific kinase
MV : Mitral valve
NA : Neuraminidase
NAC : N-acetylcysteine
NAFLD : Nonalcoholic fatty liver disease
NAI : Nonaccidental injury
NAPC : National autism plan for children
NB : Neuroblastoma
NCS : Nerve conduction study
NCSE : Nonconvulsive status epilepticus
NDM : Neonatal diabetes mellitus
NEAD : Nonepileptic attack disorders
NEC : Necrotizing enterocolitis
NED : Nonepileptic drugs
NEE : Nonepileptic events
NESTROFT : Naked eye single tube osmotic fragility test
NF-1 : Neurofibromatosis type 1
NGAL : Neutrophil gelatinase-associated lipocalin
NHL : Non-Hodgkin's lymphoma
NID : National immunization day
NIPD : Nightly intermittent peritoneal dialysis
NIPPV : Nasal intermittent positive pressure ventilation
NiV : Nipah virus
NLPHL : Nodular lymphocyte predominant Hodgkin lymphoma
NNN : Novy-McNeal-Nicolle
NNRTI : Non-nucleoside reverse transcriptase inhibitors
NPO : Nothing per oral
NPSLE : Neuropsychiatric SLE
NPU : Net protein utilization
NS : Normal saline
NS : Nutritional supplement
NSAID : Nonsteroidal anti-inflammatory drugs
NSP : Nonstarch polysaccharides
NSPR : National strategy for poverty reduction
NsRTI/NRTI : Nucleoside reverse transcriptase inhibitors
NT : Nutritional treatment
NTDs : Neural tube defects
NTP : National TB Control Program
NTS : Nontyphoid *Salmonella*
NVP : Nevirapine
NWTSG : National Wilms Tumor Study Group
NZP : Nitrazepam
OAB : Overactive bladder
OAE : Otoacoustic emission
OC : Optic chiasma
OCD : Obsessive compulsive disorder
ODD : Oppositional defiant disorder
OGTT : Oral glucose tolerance test
OI : Osteogenesis imperfecta
OKN : Optokinetic nystagmus
OMS : Opsoclonus myoclonus
OPC : Organophosphorus compounds
ORS : Oral rehydration salt
ORS : Oral rehydration solution
ORT : Oral rehydration therapy
OS : Overall survival
OSAS : Obstructive sleep apnea syndrome
OXC : Oxcarbazepine
PA : Protective antigen
PA : Pulmonary atresia
PAF : Phospholipid activating factor
PAF : Platelet activating factor
PAH : Pulmonary artery hypertension
PANDAS : Pediatric autoimmune, neuropsychiatric disorders associated with streptococcal infections
PAVSD : Partial atrioventricular septal defect
PB : Paucibacillary
PB : Phenobarbitone
PBF : Peripheral blood film
PBF : Pulmonary blood flow
PC : Pelvicalyceal
PCC : Prothrombin complex concentrate
PCECV : Purified chick embryo cell vaccine
PCOS : Polycystic ovarian syndrome
PCR : Polymerase chain reaction
PCT : Procalcitonin
PCV : Pneumococcal conjugate vaccine
PD : Peritoneal dialysis
PD : Persistent diarrhea
PDA : Patent ductus arteriosus
PDGF : Platelet-derived growth factors
PEF : Peak expiratory flow
PEG : Percutaneous endoscopic gastrostomy
PEG : Polyethylene glycol
PEM : Protein-energy malnutrition
PET : Positron emission tomography
PFT : Pulmonary function test
PGB : Pregabalin
PGL-1 : Phenolic glycolipid-1
PH : Portal hypertension
PH : Pulmonary hypertension
PHA : Phytohemagglutinin
PHIdCV : Pneumococcal, *Hemophilus influenzae* protein conjugate vaccine
PHO : Pediatric hematology and oncology
PHP : Pseudohypoparathyroidism
PHT : Phenytoin

PHT : Pulmonary hypertension
PICL : Percutaneously inserted central lines
PICU : Pediatric intensive care unit
PIE : Pulmonary interstitial emphysema
PIGD : Pre-implantation genetic diagnosis
PIs : Protease inhibitors
PKDL : Post-kala-azar dermal leishmaniasis
PLC : Phospholipase C
PLED : Periodic lateralizing epileptiform discharge
PLW : Pregnant and lactating woman
PM : Primary megaureter
PMN : Polymorphonuclear
PMTCT : Prevention of mother-to-child transmission
PN : Parenteral nutrition
PNDM : Permanent neonatal diabetes mellitus
PNET : Primitive neuroectodermal tumors
PP : Persistent pneumonia
PPD : Purified protein derivative
PPHN : Persistent pulmonary hypertension
PPHP : Pseudo-pseudohypoparathyroidism
PPIs : Proton pump inhibitors
PPTCT : Prevention and parent-to-child transmission
PPV : Pneumococcal polysaccharide vaccine
PRIs : Population reference intakes
PRN : Pertactin
PROM : Premature rupture of membrane
PRP : Penicillin-resistant *Pneumococcus*
PS : Pulmonary stenosis
PSD : Podocyte slit diaphragm
PSGN : Post-streptococcal GN
PSS : Psychosocial short stature
PT : Parathyroid
PT : Pertussis toxin
PT : Prothrombin time
PTH : Parathyroid hormone
PUD : Peptic ulcer disease
PUJ : Pelviureteric junction
PUJO : Pelviureteric junction obstruction
PUO : Pyrexia of unknown origin
PUV : Posterior urethral valve
PV : Pressure volume
PVHD : Posthemorrhagic ventricular dilatation
PVL : Periventricular leukomalacia
PVN : Paraventricular nucleus
PVR : Pulmonary vascular resistance
PVRI : Pulmonary resistance index
PVRV : Purified Vero-rabies vaccine
PWS : Prader-Willi syndrome
QBC : Quantitative buffy coat
QFPCR : Quantitative fluorescence PCR
QPS : Qualified presumption of safety
RA : Rheumatoid arthritis
RA : Right atrium
RAAS : Renin-angiotensin-aldosterone system
RAI : Radioactive iodine
RAIU : Radioactive iodine uptake
RAP : Recurrent abdominal pain
RAS : Rapid antigen screen
RAST : Radioallergosorbent test
RBP : Retinol binding protein
RBUS : Renal and bladder ultrasonography
RD : Respiratory distress
RDA : Recommended daily amount
RDAs : Recommended dietary allowances
RDIs : Recommended dietary intakes
RDS : Respiratory distress syndrome
RDTs : Rapid diagnostic tests
RE : Retinol equivalent
RES : Reticuloendothelial system
ReSoMal : Oral rehydration saline for malnourished children
RF : Rheumatoid factor
rhGH : Recombinant human GH
RICP : Raised intracranial pressure
RIG : Rabies immune globulin
RNI : Reference nutrient intake
RNIs : Recommended nutrient intakes
ROP : Retinopathy of prematurity
RP : Recurrent pneumonia
RPGN : Rapidly progressing glomerulonephritis
RR : Respiratory rate
RT : Reverse transcriptase
RS : Rasmussen's syndrome
RSS : Russel-Silver syndrome
RT- PCR : Real-time polymerase chain reaction
RTA : Renal tubular acidosis
RTD : Renal tubular dysgenesis
RTI : Reverse transcriptase inhibitors
RUTF : Ready-to-use therapeutic food
RV : Right ventricle
RV : Rotavirus
RVH : Right ventricular hypertrophy
RVOT : Right ventricular obstruction tract
RVVO : Right ventricular volume overload
SAA : Severe aplastic anemia
SABA : Short-acting β_2 agonist
SABD : Sleep apnea and sleep associated breathing difficulty
SALF : Subacute liver failure
SALT : Speech and language therapist
SAM : Severe acute malnutrition
SAM : Systolic anterior motion
SARI : Severe acute respiratory illness
SBI : Severe bacterial infection
SC : Sydenham's chorea
SCID : Severe congenital immunodeficiency
SCM : Severe chronic malnutrition
SCUF : Slow continuous ultrafiltration
SD : Standard deviation
SDNS : Steroid-dependent nephrotic syndrome
SDR : Selective dorsal rhizotomy
SDS : SD score
SE : Status epilepticus
SEARO : South East Asia region
SES : Socioeconomic status
SFA : Subclavian flap aortoplasty
SG : Specific gravity
SGA : Small for gestational age
SI : Serum iron
SI : Signal intensity
SIADH : Syndrome of inappropriate ADH secretion
SIE : Subacute infective endocarditis
SLE : Systemic lupus erythromatosis
SMA : Spinal muscular atrophy
SMBG : Self-monitoring of blood glucose
SO : Supraoptic
SP : Sulfadoxine-pyrimethamine
SPA : Suprapubic aspiration
SS : Single system
SSG : Sodium stibogluconate
SSPE : Subacute sclerosing panencephalitis
SSSS : Staphylococcal scalded skin syndrome
SV : Stroke volume
SVP : Sodium valproate
SVR : Systemic vascular resistance
T1DM : Type 1 diabetes mellitus
TA : Triamcinolone acetonide
TAB : Thyroid antibody

TAPVC : Total anomalous pulmonary venous connection
TAPVD : Total anomalous pulmonary venous drainage
TAPVR : Total anomalous pulmonary venous return
TAR : Thrombocytopenic absent radius
TAT : Tetanus antitoxin
TB : Tuberculosis
TBG : Thyroid-binding globulin
TBW : Total body water
TCA : Tricyclic antidepressant
TCR : T-cell receptor
TCRs : Target centile ranges
TDF : Testis-determining factor
TEF : Tracheoesophageal fistula
TEN : Toxic epidermal necrolysis
TFT : Thyroid function test
TG : Thyroglobulin
TG : Triglycerides
TGA : Transposition of great arteries
TGF : Transforming growth factor
TGIs : Thyroid growth-stimulating immunoglobulins
TGTT : Total gut transit time
TH : Target height
TIBC : Total iron-binding capacity
TIF : Thalassemia international foundation
TIG : Tetanus immunoglobulin
TIPS : Transjugular intrahepatic portosystemic shunt
TIPSS : Transjugular intrahepatic portosystemic stent shunt
TIV : Trivalent inactivated vaccine
TL : Tuberculoid leprosy
TLC : Total leukocyte count
TMS : Tandem mass spectroscopy
TNDM : Transient neonatal diabetes mellitus
TNF : Tumor necrosis factor
TNPM : Transient neonatal pustular melanosis
TOF : Tetralogy of Fallot
TPM : Topiramate
TPN : Total parental nutrition
TrAb : Thyroxine receptor antibody
TRH : Thyrotropin-releasing hormone
TS : Turner syndrome
TSH : Thyroid stimulating hormone
TSI : Thyroid stimulating immunoglobulin
TSS : Toxic shock syndrome
TST : Tuberculin skin test
TT : Tetanus toxoid
TTN : Transient tachypnea of newborn
TTP : Thrombotic thrombocytopenic purpura
TUC : Transurethral catheterization
UAC : Umbilical artery catheterization
UC : Ulcerative colitis
UHFWC : Union Health and Family Welfare Center
URA : Unilateral renal agenesis
URTI : Upper respiratory tract infection
US : Upper segment
USG : Ultrasonogram
UTI : Urinary tract infection
UTO : Urinary tract obstruction
UVC : Umbilical venous catheter
VA : Ventriculoatrial
VA : Visual acuity
VA : Vitamin A
VAD : Vitamin A deficiency
VAP : Vaccine-associated paralysis
VAS : Visual analog scale
VATS : Video-assisted thoracoscopic surgery
VCT : Voluntary counseling and testing
VCUG : Voiding cystourethrography
VDDR : Vitamin D-dependant rickets
VEP : Visual-evoked potential
VGB : Vigabatrin
VHR : Very high risk
VKDB : Vitamin K deficiency bleeding
VL : Visceral leishmaniasis
VLCFA : Very long chain of fatty acid
VMA : Vanyllilmandelic acid
VP : Ventriculoperitoneal
VRE : Vancomycin-resistant *Enterococcus*
vSAA : Very severe aplastic anemia
VSD : Ventricular septal defect
VUR : Vesicoureteric reflux
vWD : von Willebrand disease
vWF : von Willebrand factor
VZIG : Varicella zoster immunoglobulin
VZV : Varicella zoster virus
WAO : World Allergy Organization
WD : Wilson's disease
WFP : World Food Program
WFS : Waterhouse-Friederichsen syndrome
WHO : World Health Organization
WMS : Welfare Monitoring Survey
WPWS : Wolff-Parkinson-White syndrome
WS : Warning sign
WT : Wilms' tumor
YOS : Yale observation scale
ZNS : Zonisamide

1 Neonatology

EVOLUTION AND REVOLUTION IN NEONATOLOGY

INTRODUCTION

During the last half century, medical science has developed in all disciplines of medical profession, but perhaps none has progressed beyond perinatal medicine. Neonatal medicine has recently advanced to such a stage, when time has come to consider whether it should be allowed to proceed further. This is because certain genuine ethical issues have been voiced against such advancements, considering later disease burden with possible compromised quality of life among survivors, in spite of high cost involved in their management, which many resource-poor developing countries, in particular, cannot afford.

Infant and neonatal mortality significantly reduced during the last century (20th). During the first half of the 20th century, infant mortality was greatly reduced in industrialized countries compared to the earlier period. The decline was due to general improvement in socioeconomic status of individual countries which provided their communities with better nutrition, control of infectious diseases and improvement of public health measures.

Since the beginning of the later half of the 20th century, more developed countries experienced a slower decline in infant mortality. In the early and mid part of the last century, both mother and baby were under the care of the obstetrician. Pierre Budin introduced certain basic principles in the care of neonate. Among the basic principles, control of environmental temperature and early nutrition to neonate are worth mentioning. This practice was first introduced in USA, but it did not help in improving infant mortality.

From 1940 to 1960 progress in neonatology was arrested and to some extent reversed by some well-intentioned, but unsound damaging therapeutic interventions. Such unsound practices include: (i) overuse of oxygen resulting in retinopathy of prematurity (ROP); (ii) bilirubin encephalopathy (kernicterus) from the use of synthetic vitamin K and sulfonamide; (iii) "gray baby syndrome" from the use of chloramphenicol; and (iv) separating the preterm infant from mother causing negative impact on infant health and development.

REVELATION OF ADVANCED NEONATAL TECHNOLOGIES SINCE 1960

Emergence of Neonatal Intensive Care Unit

In 1960, neonatal intensive care unit (NICU) concept was introduced across USA and other developed countries along with gradual cessation of previous harmful neonatal practices. Understanding of neonatal pathophysiology was better realized since 1960 with application of knowledge in clinical practice of neonatal care. The new developments during that time include: (i) assisted ventilation and continuous positive airway pressure (CPAP); (ii) exchange transfusion and phototherapy for hyperbilirubinemia; (iii) use of xanthines for apnea of prematurity; (iv) early recognition of patent ductus arteriosus (PDA) and the use of indomethacin for pharmacological closure.

Discovery of anti-D and its wide practices in the western countries in 1970s was again a breakthrough in the management of hemolytic disease of the newborn (HDN), helping to prevent neonatal death and infant morbidity significantly.

The most important therapeutic advancement in the 1970s was surfactant replacement therapy for respiratory distress syndrome (RDS). Since then a lot of work has been done for standardization technique of preparation. Currently, new technique of minimally invasive surfactant therapy (MIST) by vascular catheter is being used.

Since the beginning of the later half of the 20th century, most developed countries experienced a slower decline in mortality particularly in the postneonatal period. However, with advancement of improved neonatal care a marked decline of neonatal mortality took place. Since the early 1980s more and more neonates of developed countries started receiving advanced neonatal care and neonatal mortality again started to fall sharply. In UK, the perinatal mortality in the 1960s was approximately 34/1000 live births, which declined sharply to 7/1000 live births in the 1980s with continuing small decline in the 1990s and later (Fig. 1).

Fig. 1: Stillbirth and perinatal mortality rates showing sharp decline of perinatal mortality in England and Wales from about 34/1000 in 1960 to above 8/1000 in 1980 followed by continued slow decline

Source: Reproduced from Balaranjan R, Releigh VS. In: Britton M (Ed). Mortality and geography: A review in the mid 1980s in England and Wales. Series DS 9 no. 9 HMSO, London; 1990

Current Advances in Ventilatory Care

Invention and use of advanced ventilatory care has further improved neonatal outcome. In the 1980s, advanced ventilatory care was available. Various forms of improved CPAP were introduced. Bubble CPAP was introduced recently which improves gas exchange. Among mechanical ventilators, patient triggered ventilation (PTV) and synchronous intermittent mandatory ventilation (SIMV) are worth mentioning, which are associated with few air leaks and shorter duration of ventilation. More modern ventilators introduced are high frequency oscillatory ventilator (HFOV) and volume targeted ventilator which are believed to be associated with less lung injury.

Improved phototherapy: Similarly, improved phototherapy in the recent past has changed the outlook of hyperbilirubinemia, avoiding more invasive exchange transfusion. High-intensity gallium nitride light-emitting diode (LED) is an example of such device, currently well practiced.

Improved Fetal Care by Allied Medical Departments

Improved obstetric care of fetus: As mentioned before, upto early and mid-part of the 20th century both mother and baby were under the care of obstetrician. Obstetric advances providing monitoring fetal growth and well-being, avoidance of reduced gestation period or threatened preterm delivery with appropriate intervention, intensive management of diabetic mother improving fetal outcome, improved lung maturity by antenatal steroids, etc. all helped to improve neonatal outcome after delivery. Liberal indication for cesarean section decreased the incidence of birth asphyxia. Neonatologist and obstetrician working in collaboration in the management of high-risk pregnancies and high-risk infants further improved fetal and neonatal outcome.

Improved Neonatal Transfer by Appropriate Transport

Safe transfer of sick neonates by well-equipped appropriate transport is an essential factor of newborn survival. In the last few decades, it has improved a lot helping to decline neonatal mortality. In UK, mortality of outborn infants was 20.4/1000 in 1979 which dropped to 13.5 in 1982. The drastic fall from 1979 to 1982 was due to wider and better transport of sick infants brought to NICU.

Imaging and Other Diagnostic Advances

Fetal ultrasound: Fetal ultrasound not only detects fetal maturity but also other fetal anomalies like congenital hydrocephalus, spina bifida cystica, hydronephrosis, primary vesicoureteric reflux, etc. which provide opportunity for surgical correction at earliest possible time.

Nuchal thickness ultrasound scanning: Nuchal thickness ultrasound scanning is carried between 11 weeks and 14 weeks gestation for detection of Down's syndrome. May be done at more than 22 weeks gestation in a woman presenting late.

Blood test at 15 to 22 weeks gestation: Maternal alpha-fetoprotein (α-fetoprotein or AFP) in diagnosis of neural tube defects. Triple test [blood test for human chorionic gonadotropin (hCG), α-fetoprotein and estriol] for antenatal diagnosis of Down's syndrome.

Antenatal genetic testing: (i) Fetal blood sampling; (ii) Chorionic villus sampling (CVS); and (iii) Amniocentesis, help antenatal diagnosis of lethal genetic disorders like thalassemia, offering therapeutic abortion and/ or genetic counseling.

Improved Child Survival through Advanced Neonatal Care and Ethical Issue

While great stride in the neonatal management of very sick, low birthweight (LBW), very low birthweight (VLBW) or severely birth asphyxiated infants have led to increased survival rate, there is an understandable concern over subsequent quality of life at the high cost of management of such infants.

Various studies depicted increased adverse neuro-developmental disability among survivors from NICU care with extreme low birthweight (ELBW). Severity of such problem depends on degree of prematurity and LBW. Cerebral palsy, cognitive and learning difficulty, behavior disorders are also common—increasing the burden of neurodevelopmental disorders in the community. In western countries like UK, advanced neonatal care has significantly increased the survival of many ELBW and preterm babies. However, it resulted in increased neurodisability among survivors and one of the most important causes of CP in UK is ex-preterm, LBW babies. Although active resuscitation of a very sick and extreme preterm baby may prevent immediate death, many such infants subsequently succumb during late neonatal or postneonatal period. Therefore, question arises whether active interventions at NICU is preventing immediate death or just prolonging inevitable death at the cost of huge expenditure. Thus, active resuscitation in NICU care has become debatable for such babies due to ethical considerations. Compassionate human care can only be continued when active resuscitation is anticipated not rewarding.

The practice of offering resuscitation and intensive care of extreme low gestation particularly below 25 weeks may vary. Recent guidance from the British Association of Perinatal Medicine suggests the following approach:

- <23+0 weeks—no active resuscitation
- 23+0–23+6 weeks—resuscitate with lung inflation if parents agree, although a decision not to resuscitate is appropriate
- 24+0–24+6 weeks—resuscitate with lung inflation initially, unless there is evidence of significant fetal compromise
- >25+0 weeks—active resuscitation recommended.

If a decision has been made not to start or continue active resuscitation, full humane care must continue until the baby dies. The parents should be kept informed at all times.

TERMINOLOGY, ANTENATAL AND NEWBORN SCREENING, NEWBORN EXAMINATION

TERMINOLOGY INVOLVED IN NEONATOLOGY

- Gestational age (GA)
  - Assessment of gestational age from mother's menstrual history—calculate GA from 1st day of the last menstrual bleed if:
    - Mother's menstrual cycle is regular
    - Mother's memory of the date is certain
    - Mother's last bleed was normal in duration and amount

  - Clinical method:
    - Assess size of uterus
    - Date of onset of fetal movements. Total gestational age is 40 weeks.
- Conceptional age: (gestational age: 2 weeks). The ovum which is fertilized to produce the pregnancy is released 2 weeks after the 1st day of menstrual bleed. So, true gestational period is about 38 weeks (40-2 weeks)
- Term infant or mature neonate: 37–42 weeks of pregnancy or GA
- Preterm or premature: < 37 weeks of gestation
- Post-term or postmature: > 42 weeks of gestation
- Large for date (LGA): Neonate (mature/immature) with birthweight > 90th percentile/(two standard deviations above the mean)
- Macrosomal neonate: Birthweight > 4,500 g
- Underweight or LBW: Birthweight < 2,500 g
- Very low birthweight: Birthweight < 1,500 g
- Extremely low birthweight: Birthweight < 1,000 g
- Incredibly low birthweight: Birthweight < 750 g
- Small for date (SGA): Neonate (mature, immature)—Birthweight below tenth percentile or two standard deviations below the mean for gestational age.

Normal and Abnormal Labor and its Effects on Fetus and Neonate

Labor process consists of three phases:

- First stage of labor: Starts from the onset of true labor pain and ends with full dilatation of cervix. Its average duration is about 23 hours in primigravidae and 6 hours in nuliparae.
- Second stage of labor: Starts from full dilatation of the cervix to delivery of the fetus. Its average duration is 2 hours in primigravidae and 30 minutes in multiparae.
- Third stage of labor: From delivery of fetus to complete expulsion of placenta. Its average duration is 15 minutes.

Prolonged labor results in fetal distress due to hypoxia, hypercapnea which is relieved by free flow oxygen or positive pressure ventilation. If in addition there is diminished perfusion—it leads to hypoxic ischemic encephalopathy (HIE). Fetal abnormalities can be predicted by abnormal amniotic fluid as shown in Tables 1 and 2.

These neonates need positive pressure ventilation, chest compressions, epinephrine, volume expansion and cardiorespiratory support.

ANTENATAL INVESTIGATION

Prenatal Assessment of the Fetus

Purpose of assessment:

- To diagnose abnormalities of the fetus at a stage when pregnancy can be terminated
- To assess fetal well-being, growth in late pregnancy.

Assessment of gestational age, fetal growth and fetal maturity are provided in Tables 3 and 4.

Indication

- Maternal age > 35 years at delivery
- Previous stillbirth, neonatal death, previous child with chromosomal abnormality, malformation or inherited disorder
- Maternal infection with rubella, toxoplasma, cytomegalovirus infection in 1st trimester
- Increased nuchal translucency in first trimester
- Abnormal maternal triple screen marker (AFP, hCG, estriol)
- Maternal diseases: Diabetes mellitus, hypertension.

NEWBORN SCREENING

INITIAL NEONATAL SCREENING

The first screening program developed for phenylketonuria (PKU) in 1962 was the Guthrie test. Of the first 53,000 specimens tested, nine cases of PKU were detected (1/6,000 births, previously believed to be 1/20,000 births). Later screening was developed for congenital hypothyroidism, galactosemia, Maple syrup urine disease (MSUD).

Definition

It is rapid examination or test for the recognition of unidentified disease or disability in an apparently healthy newborn.

Indication of prenatal genetic screening and their procedures are providing Tables 5 and 6 respectively. Flow chart 1 shows the causes of congenital abnormalities.

Aim

- Early diagnosis before presentation
- Early and prompt therapy of treatable cause to reduce morbidity
- Prevention of handicap, reduction of morbidity or mortality
- Genetic counseling
- Support family—prompt referral.

Table 1: Abnormal amniotic fluid and associated conditions

Condition	Definition	Cause
Polyhydramnios	It is an overaccumulation of amniotic fluid (>2,000 mL at term). Sonographically, it is defined when AFI is >25 cm (>95th centile). Polyhydramnios is seen in a condition in which fetal swallowing of urine is impaired	Idiopathic (70%). Other causes are: anencephaly, open spina bifida, esophageal or duodenal atresia—these result in impaired swallowing of fetal urine. Maternal DM leads to hyperglycemia and excessive urination in fetus. Hydrops fetalis, diaphragmatic hernias, skeletal dysplasia often are associated
Oligohydramnios	Reduced amount of amniotic fluid <200 mL at term. Sonographically, AFI is <5 cm (<10th centile). It may cause fetal distortion leading to potter facies, limb anomalies, lung hypoplasia, intrapartum fetal distress	Oligohydramnios is associated with reduced fetal micturation due to renal agenesis, dysplasia, urethral atresia, posturethral valves. Nonrenal factors include IUGR, postmaturity, chromosomal abnormalities, fetal death, intrauterine infection

Abbreviations: AFI, amniotic fluid index; DM, diabetes mellitus; IUGR, intrauterine growth restriction

Table 2: Meconium-stained amniotic fluid

Character of amniotic fluid	Effects on fetus and newborn
• The passage of meconium in utero is not common • Normally, amniotic fluid is colorless to light straw color on centrifugation • Yellow color is seen in hemolytic disease of newborn • Meconium in liquor is a measure of fetal maturity and so it is common in postmaturity • Red color is due to blood in liquor	• Meconium aspiration syndrome (MAS) occurs in term or post-term babies who are usually small for gestational age (IUGR). Chronic placental insufficiency leads to intrauterine hypoxia with passage of meconium. The meconium stained liquor may be aspirated by the fetus in utero or during first breath. The meconium may block the small air passage or produce chemical pneumonitis. Not all infants with meconium aspiration will develop MAS. Features of respiratory distress develop immediately after birth in only 5–10% infants. Meconium in the liquor is usually taken as a sign of fetal distress and birth asphyxia, especially if associated with fetal heart decelerations • Consistency of meconium is an important prognostic factor, if aspiration takes place. Thicker the meconium, poorer the prognosis • The passage of meconium is very rare in asphyxiated preterm • Foul smell is associated with chorioamnionitis

Table 3: Assessment of gestational age and fetal growth

Test	Parameter	Interpretation
Ultrasonographic measurements converted into GA	• 1st trimester: crown-rump length • 2nd and 3rd trimester – Biparietal diameter – Circumference of head and abdomen – Femur length is the best indicator of GA in 3rd trimester	• Fetal size is dependent on GA, so error range is low in 1st trimester • As pregnancy progresses, fetal size correction with GA is altered by genetic or environmental factors and range of error increases
Assessment of fetal growth (both diminished or excessive growth rates are associated with perinatal risks)		
Test	**Parameter**	**Interpretation**
Ultrasonography	Diminished fetal growth	• Early (first trimester): May reflect chromosomal anomaly, intrauterine infection (TORCH) • Late (2nd and 3rd trimester): Growth reflects fetal genetic growth potential and maternal/placental diseases • It results in symmetrical or asymmetrical IUGR

Abbreviations: GA, gestational age; IUGR, intrauterine growth restriction; TORCH, Toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus and herpes infections

Table 4: Assessment of fetal maturity

Test	Parameter	Interpretation
Fetal lung maturity lecithin/ sphingomyelin ratio in amniotic fluid	Lecithin, the active component of surfactant correlates with surfactant production while sphingomyelin is used as internal constant. L/S ratio: 1:1— at 31–32 weeks 2:1— at 35 weeks	L/S ratio >2:1 indicates: • Matured fetal lungs • Gestational age >37 weeks • No chance of RDS L/S ratio of 1.5–1.9 indicates: • Lungs on threshold of maturity (36 weeks) L/S ratio of 1–1.5 indicates: • Immature lung • 34 weeks of gestation • RDS can be possible L/S ratio < 1 indicates: • Very immature lungs • GA <30 weeks • RDS expected
Phosphotidyl glycerol in amniotic fluid	Not detected in blood, meconium, vaginal secretions	Last component of surfactant, hence if present maturity is reassuring

Abbreviations: GA, gestational age; L/S ratio, lecithin/sphingomyelin ratio; RDS, respiratory distress syndrome

Criteria

- It should be simple, quick, easy to interpretate
- Acceptable to the people
- Accurate
- Sensitive, specific.

Types

- Universal
- Selective
- Research purpose.

The relevant history and physical examination for newborn screening are:

Flow chart 1: Important causes of congenital malformations

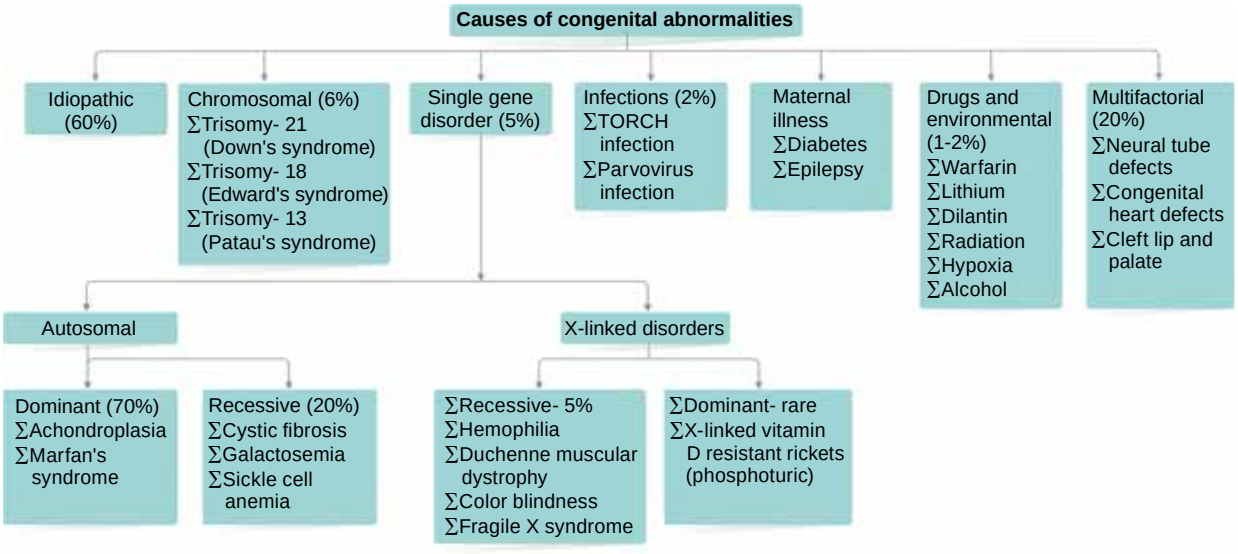


Table 5: Indications for prenatal genetic screening

Maternal risk factors	Prenatal risk factors
• Maternal age ≥35 years: Trisomy- 21, 18, 13 and 47 xxx increase with age	• Oligohydramnios
• Family history of neural tube defects	• Polyhydramnios
• Previous baby born with neural tube defect	• Severe symmetrical fetal growth restriction
• Previous child with chromosomal abnormalities	• Decreased fetal activity
• One or both parents are carriers of sex-linked or autosomal traits	• Uncontrolled, diabetes mellitus in the periconceptional period
• One of the parents is known to carry a balanced translocation	• Contract with infection (teratogenic), e.g. rubella, cytomegalovirus or intake of teratogenic drugs
• A child is born with an unbalanced translocation	• Presence of soft tissue markers of chromosomal anomaly on ultrasonography
• History of recurrent miscarriage	• Abnormal maternal serum screening

Table 6: Procedures for early detection of fetal: (i) Genetic; (ii) Chromosomal; and (iii) Structural abnormalities

MSAFP	Triple test (combined test): MSAFP, unconjugated estriol (E3) and hCG
Chorionic villus biopsy	Cordocentesis
High resolution ultrasonography	Fetoscopy
Amniocentesis	Peri-implantation genetic diagnosis
Fetal cell isolation from maternal blood- genetic analysis from isolated fetal nucleated red blood cells or trophoblast cells	3D or 4D ultrasound with increased resolution

Abbreviations: MSAFP, maternal serum alpha fetoprotein; hCG, human chorionic gonadotropin; 3D, three-dimensional; 4D, four-dimensional

History

- Family history of genetically determined disorder
- Maternal: diabetic mellitus, PKU, alcoholism
- Birth history.

Physical Examination Thoroughly

- Congenital dislocation of hip, cleft lip, palate, etc.

Laboratory Investigation

Prenatal diagnosis by biochemical screening and by more invasive tests (chorionic villus sampling, amniocentesis and cordocentesis) are provided in Tables 7 and 8 respectively.

- Congenital hypothyroidism: Thyroid stimulating hormone (TSH), thyroxine (T4)
- Congenital adrenal hyperplasia (CAH): 17-hydroxyprogesterone (17-OHP)
- PKU: Serum phenylalanine
- Galactosemia: Galactose-1-phosphate uridyltransferase enzyme
- Homocystinuria: Serum methionine
- MSUD: Serum leucine
- Neuroblastoma: Urinary vanillylmandelic acid (VMA).

Specimen

- Noninvasive/bedside:
  - Congenital dislocation of hip (clinical examination and ultrasound scanning)
  - Hearing examinations
  - Autoacoustic emission
- Invasive: Blood, urine, sweat.

Table 7: Prenatal diagnosis: Biochemical and biophysical screening tests

	MSAFP	MSAFP, hCG, unconjugated estriol (UE3)	hCG+ pregnancy associated placental protein-A	Soft tissue marker (nuchal translucency)
Time (weeks)	15–18	15–18	10–14	11–14
Observation	MSAFP (↑)	MSAFP (↓)	β hCG (↑)	Nuchal thickness >3 mm
		UE3 (↓) hCG- (↑)	PAPP- A (↓)	
To detect anomaly	• Open neural tube defects • Gastroschisis • Omphalocele • Congenital nephrotic syndrome	Down's syndrome AFP- also ↓ in Edward's syndrome and fetal death	Down's syndrome	Down's syndrome • Turner's syndrome • Edward's syndrome • Patau's syndrome
Test sensitivity rate	65%	60%	65%	70–80%
False positive rate	3–5%	5%	5%	5–6%
Women who are screen positive, should be offered fetal karyotyping by invasive methods				

Abbreviations: MSAFP, maternal serum alpha fetoprotein; hCG, human chorionic gonadotropin; UE3, unconjugated estriol, PAPP-A, pregnancy associated placental protein-A

Table 8: Prenatal diagnosis: Chorionic villus sampling, amniocentesis and cordocentesis

	Chorionic villus sampling	Amniocentesis	Cordocentesis
Time (weeks)	Transcervical: 10–12 Transabdominal: 10 weeks to term	14–16 weeks (early 12–14 weeks)	18–20 weeks
Materials study	Trophoblast cells	• Fetal fibroblasts • Fluid for biochemical study	Fetal white blood cell
Karyotype result	Direct preparation: 24–48 hours Culture: 10–14 days	Culture: 3–4 weeks	Culture: 24–48 hours
Fetal loss	1–2%	0.5–1%	2–4%
Accuracy	Accurate, may need amniocentesis for confirmation	Highly accurate	Highly accurate
Termination of pregnancy when indicated	1st trimester (safe)	2nd trimester (risky)	2nd trimester (risky)
Maternal effects following termination of pregnancy	Very little	More traumatic, physically and psychologically	Same as amniocentesis
Tests performed	• Direct preparation for chromosomal disorders • DNA extraction and molecular techniques for hemoglobinopathies, hemophilia, DMD, congenital adrenal hyperplasia, fragile X syndrome, cystic fibrosis • Enzyme estimation: lysosomal, paroxysmal disorder	**Culture of cells- fetal fibroblasts used for:** Karyotype analysis Estimation of enzymes (metabolic errors) Radioisotope assay **Biochemical tests:** AFP Bilirubin levels Lecithin/sphingomyelin ratio Abnormal metabolites: Urea cycle disorders, aminoacidopathies, organic acidemias Electrophoresis: Mucopolysaccharidosis	Karyotype—when AFP low, severe persistent IUGR Molecular diagnosis of Fragile X syndrome Hemoglobinopathies Intrauterine infections (specific IgM) for rubella, cytomegalovirus and especially toxoplasmosis which can be treated during pregnancy

Abbreviations: AFP, alpha fetoprotein; IUGR, intrauterine growth restriction; DMD, Duchenne muscular dystrophy; DNA, deoxyribonucleic acid

Diseases which can be Identified

- *Metabolic*: Congenital hypothyroidism, CAH, PKU, MSUD, galactosemia, homocystinuria
- *Hematological*: Sickle cell anemia- Hbs
- *Infection*: Congenital toxoplasmosis (IgM)
- *Genetic*: Cystic fibrosis (CF), Duchenne muscular dystrophy (DMD) (↑ CPK)
- *Malignancy*: Neuroblastoma (genetic marker screening).

Assessment of birth defects and genetic disorders, techniques for prenatal detection of fetal abnormalities in various stages of pregnancies and noninvasive techniques for prenatal detection of fetal abnormalities are provided in Tables 9 to 11 respectively.

Currently, Tandem mass spectrometry (TMS) is used for more than 20 inborn errors of metabolism. A blood spot on a filter paper serves as the specimen. Metabolically important compounds within the blood specimen undergo ionization (e.g. amino acids, conjugates of organic acids and fatty acids intermediates) producing characteristic daughter ions that are subjected to mass spectrometry. These are identified rapidly at low concentration than conventional modes of analysis.

Table 9: Assessment for birth defects and genetic disorders	
Birth defects	**Modality of screening**
Congenital malformations	• High resolution ultrasound • Maternal serum alphafetoprotein • Maternal screening for diabetes and TORCH infections
Chromosomal abnormalities	• Maternal age • Maternal serum factors • USG for IUGR and nuchal translucency or thickness
Hemoglobinopathies	• Family history • Carrier detection for β thalassemia • Sickle cell anemia
Lysosomal storage disorders Tay-Sachs disease	• Carrier detection for hexosaminidase A
Cystic fibrosis	• DNA base blood or buccal test for carrier detection

Abbreviations: IUGR, intrauterine growth restriction; TORCH, Toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus and herpes infections; DNA, deoxyribonucleic acid

Table 10: Techniques available for prenatal detection of fetal abnormalities		
Time	**Invasive**	**Noninvasive**
First trimester	• Transvaginal USG • Early amniocentesis • CVS • Embryoscopy • Embryobiopsy • Maternal serum AFP	• High resolution USG • Maternal serum AFP
Second trimester	• Amniocentesis • Fetal blood sampling • Placental biopsy • Fetoscopy • Fetal biopsy—fetal skin, liver, lung, kidney and muscle biopsy	• Maternal serum AFP • High resolution for anomaly scan • Fetal ECHO for heart malformation • Fetal MRI for brain malformation

Abbreviations: USG, ultrasonography; CVS, chorionic villus sampling; AFP, alpha fetoprotein; MRI, magnetic resonance imaging; ECHO, echocardiography

Table 11: Noninvasive techniques for prenatal detection of fetal abnormalities	
Test	**Result**
High resolution USG with high geometric and gray scale resolution done in 15–18 weeks. A targeted anomaly scan in the 2nd trimester	It detects congenital anomalies Abnormalities of amniotic fluid volume Fetal size—early onset of IUGR—chromosomal abnormalities Skeletal dysplasias, bone defects, limb anomalies
Fetal ECHO at 22 weeks	All forms of congenital heart defects can be detected antenatally
Maternal serum AFP	AFP is a globulin. It is normally produced by fetal liver and secreted in the urine. It is an important constituent of amniotic fluid. The greatest concentration in amniotic fluid is in the 1st trimester and is equilibrated with maternal serum. Serum AFP is a useful screening test for neural tube defect and is obtained between 16 weeks and 18 weeks of gestation

*Abbreviations:*USG, ultrasonography; AFP, alpha fetoprotein; ECHO, echocardiography; IUGR, intrauterine growth restriction

All babies should be screened for disease before leaving hospital. Follow-up is also necessary.

Of the more common treatable/preventable diseases, that are easy to remember, are the target for neonatal screening. For easy remembering, one can use the abbreviation PGCMH which stands for postgraduate combined military hospital.

PGCMH:

- P—Phenylketonuria
- G—Galactosemia
- C—Congenital hypothyroidism
- C—Congenital adrenal hyperplasia
- C—Congenital dislocation of hip
- M—Maple syrup urine disease
- H—Hemoglobinopathies
- H—Homocystinuria.

Investigations that are Commonly Done

- *Congenital hypothyroidism*: TSH
- *Metabolic disease*: TMS
- *Hemoglobinopathies*: Electrophoresis (Hbs): Sickle cell disease, thalassemia.

Importance of Screening

- To save the child from early death as in galactosemia
- To lead a normal life—when adequately and regular interval treatment given—hemoglobinopathies
- Simple feeding management can save life—in PKU, galactosemia
- To save physical and mental status by giving drug—T4 in hypothyroidism.

Although screening is most important for life saving of the newborns, unfortunately most of such diseases are not screened in developing countries.

Neonatal Screening to Reduce Sequelae of Hypothyroidism

- Prevalence of hypothyroidism (congenital) is 25/100,000 live births. Usually perform 5–7 days of life
- Capillary blood is taken by heel pricking (Fig. 2).

Blood is Screened for Hypothyroidism

- TSH only (may miss secondary or tertiary hypothyroidism)
- T4 only (may miss compensated hypothyroidism)
- Both TSH and T4
- Practices of options depend upon center.

Thyroid-stimulating Hormone Measurement

- If TSH > 40 U/L—almost diagnostic. If T4 < 6.5 µg/dL—further screening
- If TSH is 15–40 U/L—suspected.

All screening positive infants are evaluated by free thyroxine (FT4) and other confirmatory tests.

Follow-up

- *Clinical*: Clinical symptoms weight/height/occipitofrontal circumference (OFC)—once every 3 months in the first 2 years and then less frequently
- *Biochemical*: Levels of free T4 and TSH should be monitored monthly in the first 6 months of life and then every—2 to 3 monthly between 6 months to 2–3 years, yearly after 3 years and maintain in the normal age subsequently
- *Dosage*: Levothyroxine—initial dose in case of newborns: 10–15 µg/kg, 4 µg/kg in older children
- *Radiological*: Radiologically, bone age should be checked annually, bone age should not be advanced by > 2 years of chronological age
- Evaluation for transient hypothyroidism should be at 3 years of age after discontinuation of T4.

Prevention

- All newborns should be screened between 5 days and 14 days of age measuring TSH and free T4
- Early diagnosis and adequate treatment in the first weeks of life—decrease mental retardation and help in normal linear growth and intelligence.

Fig. 2: Shaded areas showing suitable sites for heel pricking for capillary blood collection

Prognosis

Early diagnosis, rapid intervention (provision of T4), maximum benefit.

EARLY IDENTIFICATION OF HEARING LOSS

Newborn Hearing Screening Program (Otoacoustic Emission and Auditory Brainstem Response)

Hearing screening involved all newborns with special attention to the high-risk group which include the following:

- Family history of hereditary childhood sensory neural hearing loss
- Intrauterine infection such as cytomegalovirus, rubella, toxoplasmosis, herpes
- Birthweight < 1,500 g
- Ototoxic medications including aminoglycoside
- Bacterial meningitis
- Apgar score 0–4 at 1 minute or 0–6 at 5 minute
- Hyperbilirubinemia at serum level requiring exchange transfusion
- Craniofacial anomalies including those with morphological abnormalities of the pinna and air canal (Treacher-Collins)
- Mechanical ventilation lasting 5 days or more
- Stigmata or other findings associated in the sensory neural and/or conductive hearing loss.

Ideally, two tier screening programs should be done. Infants are first screened with otoacoustic emission (OAE) (Fig. 3). Infants who fail OAE are screened with auditory brainstem response (ABR) which is more expensive. Screening test takes only about 3–4 minutes if the baby is in a neutral sleep. Older babies may require sedation.

Auditory brainstem response assesses the auditory function from the 8th nerve through the auditory brainstem. ABR testing helps in assessing the whole system, from periphery to the auditory nerve and brainstem.

Both OAE and ABR serve as a first objective screening test for normal cochlear function.

ROLE OF NEONATAL SCREENING FOR PREVENTION OF MENTAL RETARDATION

Mental retardation can be defined as a group of disorders that have below average intellectual function with associated deficits in adaptive behaviors present from childhood.

Prevention of Mental Retardation by the Following Measures

- Genetic counseling:
  - Discouraging consanguineous marriage
  - Parents are told that they may get similarly affected baby in subsequent pregnancies in metabolic disorder
  - Older mother (> 35 years) should be informed regarding risk of Down's syndrome baby
- Social awareness:
  - Regarding smoking and alcohol intake injurious to baby
  - Encouraging use of trails and guards to prevent fall and accidents at home
  - Ensuring safe sexual practices to prevent adolescent pregnancies and sexually transmitted diseases (STDs) including human immunodeficiency virus (HIV)

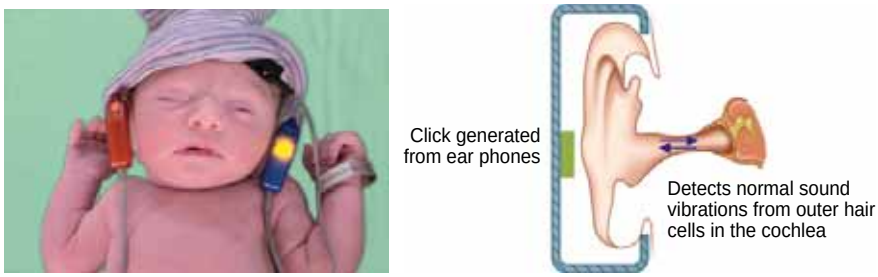


Fig. 3: Newborn hearing screening by otoacoustic emission (OAE)

- Vaccination:
  - Against rubella—preventing teratogenic hazard in the 1st trimester
- During pregnancy:
  - Avoid the use of teratogenic drugs and hormones, promote maternal folic acid and antenatal checkup
  - Protection against exposure to persons suffering from viral illness
- During labor:
  - Good obstetric supervision to prevent birth asphyxia
- Postnatal period:
  - Newborn screening
  - Metabolic disorders, e.g. PKU, galactosemia, homocystinemia
  - Hypothyroidism
  - Hyperbilirubinemia—treated by phototherapy, exchange transfusion
  - Omission of pertussis vaccine in progressive neurological disease
  - Program to avoid lead, mercury exposure
  - To reduce poverty
  - For ensuring proper nutrition.

The common inborn errors of metabolism (IEM) having good prognosis on early detection and management are as follows:

Phenyl Ketonuria: Screening at Birth

- Guthrie test (a bacterial inhibition test)
- TMS
- Ferric chloride ($FeCl_3$) test of urine turns green in PKU
- Urine aminoacid chromatography.

Clinical Features

- Mental retardation
- Microcephaly
- Cerebral palsy
- Eczema, fair hair and skin, blue eyes.

Treatment

- *Dietary*: Diet low in phenylalanine at least until puberty
- Psychosocial
- Genetic counseling.

Galactosemia

Clinical Features

Vomiting, lethargy, poor feeding, diarrhea, jaundice (mostly unconjugated 1st week, thereafter conjugated with elevated liver enzymes) with later cirrhosis. In addition, there is—hypoglycemia, Gram-negative sepsis (*E.coli*), and cataract.

- Red cell galactose-1 phosphate uridyltransferase deficiency (GALPUT)—confirmatory
- Reducing substance in urine Clinitest®—positive and Clinistix®—negative
- TMS.

Treatment

- *Dietary*: Lactose and galactose-free diet throughout childhood. For example, soya-based formula or formula free of lactose (pregestimil, galactomin). Dietary restrictions should be strict during the first 2 years of life but there is lifelong restriction of milk and milk products
- Psychosexual: As infertility and mental retardation may develop.

Management of Pubertal Disorder (Hypergonadotropic Hypogonadism)

- Genetic counseling (autosomal recessive).

Prognosis

Cataract—may become normal by medical treatment only. Mental retardation, learning problem and infertility may remain.

Homocystinuria (Autosomal Recessive)

- Guthrie test: Positive
- Homocystine in urine
- Cyanide nitroprusside test (goes purple): Positive
- Blood level of homocystine and methionine: Diagnostic.

Clinical Features

- Mental retardation, malar flush, fair hair
- Osteoporosis, joint stiffness
- Mental retardation, coronary artery thrombosis
- Myopia, lens dislocation, retinal detachment
- Arachnodactyly, pectus excavatum, high arch palate, kyphoscoliosis.
  A fully developed case resembles Marfan's syndrome.

Treatment

- *Dietary*: Diet with low methionine
- *Drugs*: Oral pyridoxine and folate [which stimulates the cofactor for cystathionine β-synthase (CBS)]
- Early recognition and treatment of complications
- Counseling and psychological support.

Tyrosinemia (Autosomal Recessive)

- Increased AFP
- Increased Urinary succinylacetone

- Decreased Blood sugar
- Positive ferric chloride test.

Clinical Features

Vomiting, diarrhea, failure to thrive (FTT), liver damage, hepatosplenomegaly, ascites, cirrhosis, vitamin D-resistant rickets.

Treatment

Low tyrosine and phenylalanine diet.

AN APPROACH TO INBORN ERRORS OF METABOLIC SYNDROME

PRESENTATION

An inborn error of metabolism should be considered in the differential diagnosis of a severely ill neonatal infant and special studies should be undertaken if the index of suspicion is high. Infants with metabolic disorders are usually normal at birth. The presentation of:

- Lethargy
- Poor feeding
- Poor peripheral perfusion
- Convulsions
- Vomiting and
- Metabolic acidosis—may develop as early as a few hours after birth.

A history of clinical deterioration in a previously normal neonate should suggest an inborn error of metabolism. Lethargy, poor feeding, vomiting, diarrhea, dehydration, hypoglycemia, convulsion, shock and collapse, metabolic acidosis may also be seen in an infant with CAH. The presentation of lethargy, poor peripheral perfusion and a metabolic acidosis in a neonate is also suggestive of neonatal sepsis. The three most likely causes are considered, such as—sepsis, congenital heart disease and a metabolic disorder. Remember that the presence of a metabolic acidosis together with hypoglycemia should strongly suggest metabolic disorder. Sepsis commonly produces a metabolic acidosis but is usually accompanied by hyperglycemia and abnormal temperature (high/low). Most inborn errors of metabolism are autosomal recessive traits. History of consanguinity, death in the neonatal period and/or family history of similar illness also strongly suggest inborn error metabolism.

PHYSICAL EXAMINATION

The physical examination reveals nonspecific findings with most signs related to the central nervous system (acute encephalopathy in the neonate). Hepatomegaly is a common finding in a variety of inborn errors of metabolism. Occasionally, a peculiar odor may help in diagnosis.

Abnormal Odor in Urine (and Sweat)

IEM	*Urine odor*
• MSUD	Maple syrup
• PKU	Mousy or musty
• Tyrosinemia	Boiled cabbage
• Isovaleric acidemia	Sweaty feet.

Ammonia Metabolism Disorders

Ammonia metabolism disorders (Flow chart 2) are found in many inborn errors of metabolism. Laboratory investigations in such cases are:

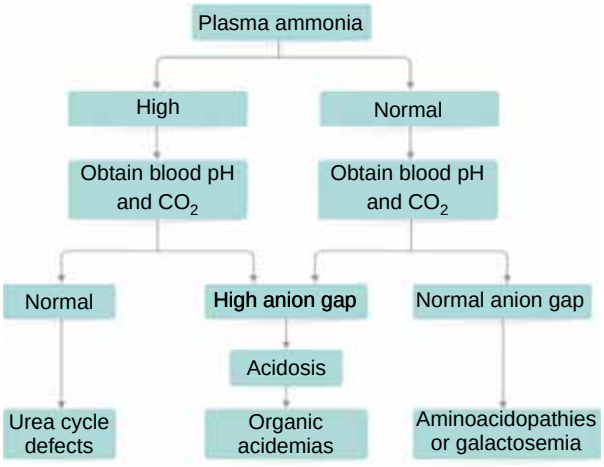
- *Blood gas*: Metabolic acidosis (with increased anion gap)
- Organic acidemias
- Lactic acidemias
- *Plasma lactate*: Elevated in lactic acidosis and organic acidemias
- *Plasma glucose*: Hypoglycemia in fatty acid oxidation defects, galactosemia, glycogen storage disease, MSUD and some organic acidemias
- *Urinary ketones*: Ketoacidosis with ketonuria—organic acidemias
- *Reducing substance in urine*: Galactosemia, fructosuria, Fanconi syndrome
- Ferric chloride reaction is positive in:
  - PKU (green)
  - MSUD (green—fading rapidly)
  - Alkaptonuria (dark brown)
- Specific enzyme assay:
  - Lysosomal enzyme study in leukocyte—lysosomal storage disorder
  - Red blood cell (RBC) enzyme study—Galactose-1 phosphate uridyltransferase deficiency: Galactosemia
  - Liver enzyme study.

Cerebrospinal fluid (CSF study), fundoscopy, ultrasound/CT scan of brain, EEG—for neonatal causes of acute encephalopathy.

MANAGEMENT

- *Hydration*: Hydration with 25–50% of maintenance
- *Reduction of catabolism:*
  - Nothing peroral for 1–2 days
  - High intravenous glucose: 10% dextrose or higher, e.g. 2 mL/kg/bolus followed by an infusion. Initial infusion rate is 6 mg/kg/min (= 3.6 mL/kg/h 10% glucose)
- *Nasogastric tube feeding*: Until patient is stable, followed by oral feeding—when patient is stable.
  - Feeding: changing feeds, giving fruit juice for first time and weaning. Removal of offending diet:
  - Restrict protein if organic acidemia, urea cycle defect or amino acid disorder (PKU) is suspected

Flow chart 2: Ammonia metabolism disturbance in inborn errors of metabolism



- Use lactose- and galactose-free milk—if galactosemia is suspected
- *Correction of acidosis by*: $NaHCO_3$—1 mEq/kg as bolus followed by continuous infusion
- *Elimination of toxic metabolites:*
  - Hyperammonia- Na- benzoate or Na- phenylbutyrate (IV) also may help to reduce blood ammonia level
  - L-carnitine, 100 mg/kg/day (oral/IV)—may be given to help conjugate toxic metabolites
  - Dialysis
    - Peritoneal
    - Hemodialysis (most effective).

To remove the excess accumulated molecules

- Cofactor supplementation with thiamine, pyridoxine, Vitamin B_{12}
- Treatment of precipitating factor when possible, e.g. infection, excess protein ingestion or elimination of gut bacteria with neomycin, gut bacteria is a source of organic acid
- Counseling and psychosocial support.

TWIN PREGNANCY

Simultaneous development of two fetuses in the uterus is the most common variety of multiple pregnancy.

Types

There are two types of twins (Table 12):

1. Monozygous (uniovular): It results from division of a single fertilized egg.
2. Dizygous (Binovular): It results from two separately fertilized ova with separated amnion and chorion.

Morbidity

- Growth retardation
- Twin-to-twin transfusion: [one polycythemic, one anemic—difference in hematocrit (Hct) > 20%]
- Birth asphyxia—due to malpresentation—twins (50–60%). Lowest (8%): in dichorionic twins.

HISTORY TAKING OF NEWBORN INFANTS AND NEWBORN EXAMINATION

History for Prognostic Pointers for Newborn Infants

- Family history of:
  - Congenital malformation
  - Chromosomal anomaly
  - Metabolic disorder
  - Coagulation disorder
- Maternal disease: Maternal chronic medical disease:
  - Renal disease
  - Diabetes mellitus (DM)
  - Heart disease
  - Collagen disease
  - Anemia: Hb% is < 8 g/dL
- History of previous pregnancy:
  - Intrauterine death (IUD)
  - H/O neonatal death
  - Excessive bleeding
  - Intrauterine growth restriction (IUGR), premature onset of labor
  - Cephalopelvic disproportion (CPD)
  - Previous history of cesarean section (CS)
- Present pregnancy: Antenatal checkup. Risk factors include:
  - Maternal age: < 18 or > 35 years
  - Pregnancy:
    - Weight: < 40 kg
    - Height: < 145 cm
- Other relevant history include:
  - Last menstrual period (LMP)
  - Blood group of mother
  - Primigravida or grand multipara
  - USG of pregnancy profile
  - Amount of amniotic fluid
  - Location of placenta
  - Maternal fever, rash
  - Lower abdominal pain
  - Drugs (T4)
  - Eclampsia/PET
  - Systemic lupus erythematosus (SLE) of mother
  - Drug abuse
  - Tocolytic agent to delay delivery
- During labor and delivery:
  - Onset of labor: Spontaneous/induced
  - Oxytocin drip: yes/no
  - Rupture of membranes: Spontaneous/artificial/premature rupture of membranes (PROM)
  - H/O prolonged labor: 1st stage >2 hours
  - H/O obstructed labor
  - Abnormal lie/presentation
  - Mode of delivery: CS or normal vaginal delivery (NVD)
  - Cried immediately after birth
  - Fetal tachycardia >160/min
  - Fetal bradycardia <100/min
  - Meconium stained or meconium aspiration syndrome (MAS).

Examination

At good surface of light and in comfortable environment.

- Assess Apgar score (Tables 13 and 14).

Examination should be started from head to toe- large or small. The whole body must be inspected to look for any of the findings listed in Table 15.

Table 12: Basic differences between monozygous and dizygous twins

Monozygous (identical)	Dizygous (nonidentical)
Same sex and blood groups	Different sex and blood groups
Placenta	Placenta
• Monochorionic; Monoamniotic	• Dichorionic
• Monochorionic; Diamniotic: 60%	• Diamniotic
• Dichorionic; Diamniotic: 30%	

CRITERIA OF A TERM NORMAL NEWBORN

- Gestation: 37–42 completed weeks
- Birthweight: 2,500–4,000 g
- Breathing: Spontaneous, regular and rate between 30–59/minutes

Table 13: Apgar score

Sign	0	1	2
Heart rate	Absent	Below 100/min	100/min or higher
Respiratory effort	Nil	Slow, irregular	Regular, with cry
Muscle tone	Limp	Some tone in limbs	Active movements
Reflex irritability	Nil	Grimace only	Cry
Color	Pallor or generalized cyanosis	Body pink, extremities blue	Pink all over

Table 14: Apgar score interpretation

	A baby has APGAR score	Score 0-3 at 1 minute	Score 4-6 at 1 minute	Score 7-10 at 1 minute
	It means	Severe asphyxia	Moderate depression	Normal infant
A	Appearance	Pale or blue	Dusky	Pink
P	Pulse	< 0	< 100	>100
G	Grimace	No response	Feeble response	Loud cry
A	Activity	Flaccid	↓tone	Flexed extremities normal tone
R	Respiratory effort	Little or none	Shallow irregular	Vigorous breathily effort

- Color: Pink but slight peripheral cyanosis soon after birth is considered normal
- Heart rate: 100–160 beats/min
- Axillary temperature: 97.7°–99.3°F (36.5°C–37.5°C)
- OFC: 33–38 cm
- No obvious congenital malformation
- Most babies pass urine within 24 hours of birth but some may not pass urine for up to 48 hours of birth
- Most of the babies pass meconium within 24 hours of birth but some may not pass meconium for up to 48 hours of birth. A newborn usually sleeps around 18 hours a day.

CHECK THE FOLLOWING POINTS WITHIN FIRST 24 HOURS OF LIFE

- *History*: Ask about breastfeeding and if urine and meconium have been passed
- *Delivery*: Any problem during labor or delivery?
- *Parent's concerns*: If any particular worries that the parents may have
- *Overall impression*: Observe the face, trunk, limbs and activity to gain a general impression
- *Skin color*: Is the baby pink. Assess degree of any jaundice
- *Measurement*: Birthweight, OFC and length if possible
- *Head*: Look and feel the fontanels, sutures and any trauma, e.g. cephalhematoma, superficial injuries, etc.
- *Eyes*: Look for discharge, redness and cataract (absent red reflex)
- *Mouth*: Cleft lip or palate
- *Upper limbs*: Evidence of brachial palsy and extra digits or any other abnormality
- *Chest*: Breathing rate and pattern
- *Heart*: Heart rate and listen for normal/abnormal sounds
- *Umbilicus*: Any signs of infection (redness discharge, bad smell)
- *Abdomen*: Distension, organomegaly and other masses
- *Genitalia*: Any ambiguity, hernia. If female newborn small amount of mucus discharge with few spots of blood may be present, this is normal
- *Anus*: Present, patent or incorrect position of anal verge

Table 15: Features of examination of newborn (for relevant clinical pictures see Figs 4 to 38)

What to examine?	Normal findings to look for	Abnormal findings not to miss
a. Sign of well-being or of illness	Active with flexor tone, normal breathing, pink color, sucking and swallowing normally (Fig. 4)  **Fig. 4:** Normal pink color term baby with flexor tone	Unresponsive, flaccid, cyanotic, pallor, pathological jaundice, hypothermia, respiratory distress
b. Observe posture, color, activity	Active movements of all four limbs, good tone and cry, pink color	Lethargic or dull looking or ill looking, irritable, asymmetric movements of limbs
c. Anthropometry		
• Weight	Weight: 2.5–3 kg	<2.5 kg, >4 kg
• Length	Length 50 cm (46–57cm)	<45 cm, >58 cm
• Upper segment (US) Lower segment (LS)	US:LS: 1.7:1	Abnormal in skeletal dysplasia
• Occipitofrontal circumference (OFC)	Head circumference: 35 cm (32–35 cm)	<32 cm, >36 cm >37 cm—hydrocephalus

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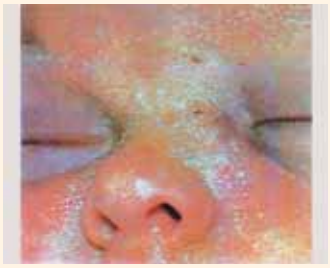
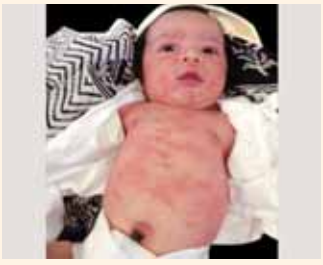
What to examine?	Normal findings to look for	Abnormal findings not to miss
d. Vital parameters	Axillary temperature	
• Temperature	36.4–37.0ºC (97–98.5ºF)	Hypo- or hyperthermia
• Respiratory Rate (RR)	RR: 40–60/min	>60/min: distress, grunting, nasal flaring
• Heart Rate (HR)	HR: 100–160/min	< 100/min, > 160/min
e. Skin	Pink (normal)	Pallor suggests anemia due to postnatal hemorrhage associated with decreased pulses, early shock
• Color	Cyanosis (acrocyanosis—normal immediately after birth)	Central cyanosis—is always abnormal
	Jaundice: normal > 48–72 hours (physical jaundice)	Abnormal in first 24 hours
	Plethora	• Infant of diabetic mother (Fig. 5)  **Fig. 5:** Plump plethoric face of infant of diabetic mother • Late cord clamping • Recipient of twin-to-twin transfusion • Small for gestational age
• Rashes	Milia: Fine yellow sebaceous concretions on nose, cheeks that disappear gradually (Fig. 6).  **Fig. 6:** Milia	Septic spots and paronychia—with surrounding edema
	Erythema toxicum (Fig. 7): It is a very common lesion that occurs in 50% of newborns during the first few days after birth. The lesions are yellow-white papules (1–2 mm) with surrounding erythematosus flare. The condition is benign and usually disappears over few days  **Fig. 7:** Erythema toxicum over chest and trunk	

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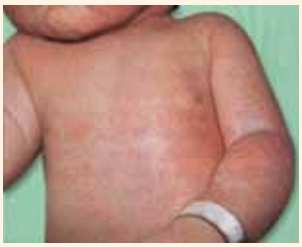
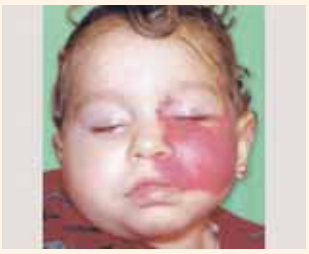
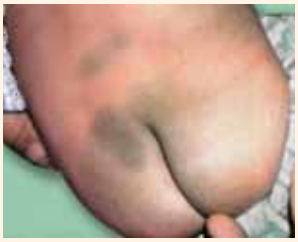
What to examine?	Normal findings to look for	Abnormal findings not to miss
	Miliaria (Fig. 8): Fine vesicular rash on limbs, forehead without surrounding edema  **Fig. 8:** Miliaria rubra	*Candida* mainly on oral mucosa, also in groin, perineum (Fig. 9)  **Fig. 9:** Oral candidiasis with white flaky plaques on buccal mucosa and tongue
	Transient neonatal pustular melanosis— fine vesicles filled with opaque fluid without surrounding edema	Initially vesicular with surrounding edema, later pustular and confluent
• Nevi	Stork bites—macular hemangiomata—30–40% of normal newborns have on eyelids, forehead and back of neck (Salmon patch). Always disappears (Fig. 10)  **Fig. 10:** Salmon patch on the back of the neck benign nevus	• Portwine stain over forehead and upper eyelid Sturge–Weber syndrome (Fig. 11)  **Fig. 11:** Portwine stain on the face • Strawberry nevus (cavernous hemangioma): disappear with age
	Mongolian spots: Blue spots over back and buttocks which are pressure areas during fetal life (Fig. 12)  **Fig. 12:** Mongolian blue spots	• Café-eu-lait spots—if more than five suggests neurofibromatosis
f. Head	Caput—Soft, edematous, nonfluctuant, ill-defined swelling of presenting part. The edema subsides spontaneously within the first few days (Fig. 13)  **Fig. 13:** Caput succedaneum	• Microcephaly, macrocephaly, rounded head in breech delivery. Cephalohematoma— fluctuant, clearly defined, non-crossing sutures, tender, well-defined, subaponeurotic hemorrhage—is common in forceps delivery from frontal to occipital region (Fig.14).  **Fig. 14:** Cephalhematoma (left sided)
		• Increased intracranial pressure—anterior fontanel (AF) bulges, sutures unduly separated
• Shape		
• Size	Normal size- OFC (35 cm), anterior	
• Feel fontanels and sutures	AF is 2.5 × 2.5 cm—diamond shape, post fontanel (0.5–1.5 cm)—tip of finger overlapped sutures are normal	

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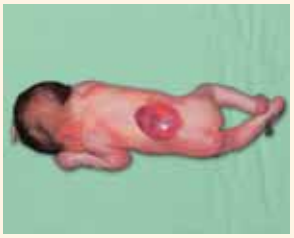
What to examine?	Normal findings to look for	Abnormal findings not to miss
g. Face	Look at face—for any congenital anomaly. Normal distance between the eyes. Ears upper 1/3rd is at the level of eyes	Hypertelorism—widely separated eyes. Low set ear or absent ear. Facial nerve palsy face deviates to opposite site (Fig. 15)  **Fig. 15:** Hypertelorism-Widely separated eyes
h. Ears	Folded pinna is common. Patent external ear opening	Periauricular pits, tags, low set floppy ears are associated with renal anomalies
i. Eyes (most easily seen when infant is feeding in indirect light)	Bilaterally symmetrical. Eyes open on tilting forward and backward, some focusing on light. Normal red reflex, edema of lids, redness of conjunctiva, subconjunctival hemorrhage is normal in absence of bleeding at other sites	Bilaterally asymmetrical. Do not open on movement and may not focus at bright object. Absent red reflex, if cataract (Fig. 16), corneal haziness  **Fig. 16:** Cataract
j. Nose: Listen for audible breathing with the help of stethoscope near nares	Patient nostrils. Neonates are obligatory nose breathing	Obstruction due to choanal atresia. Bloody purulent discharge found in congenital syphilis
k. Mouth	• Intact lips and palate • No teeth • Epstein's pearls—small white swelling on hard palate	• Cleft lip or palate • Short lingual frenulum (tongue tie) • Ranula—a blue domed cystic swelling on the floor of the mouth, thrush—white patches on tongue and buccal mucosa
l. Neck: To examine neck elicit rooting reflex to get easy view of the opposite side of the neck	• No mass on medial or lateral side. Soft sternomastoid muscle of normal length	• Goiter in the midline • Sternomastoid tumor is visible with tilting of head to opposite side. Short neck, low hairline, webbing of neck—Turner syndrome
	• Palpate clavicle	• Fractured clavicle in shoulder dystocia
	• Look for sinuses	• Sinuses of thyroglossal cyst
m. Back: Lay baby prone with head to one side	• Look at spine and confirm that it is straight • Look for abnormal pigmentation on lower spine • Look for sacral pits and dimple and look for blind end	• Look for obvious meningomyelocele on the back (Fig. 17)  **Fig. 17:** Meningomyelocele • Hairy patches indicate underlying vertebral anomaly • Café-au-lait spots. Suspect sinus communicating with underlying spinal cord, if no blind end

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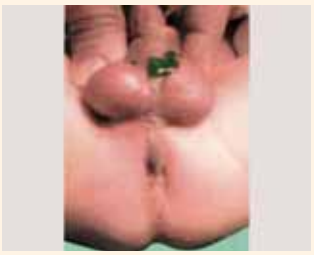
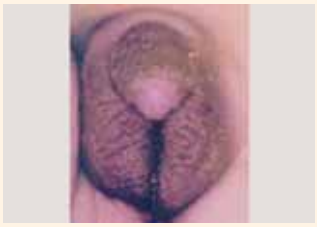
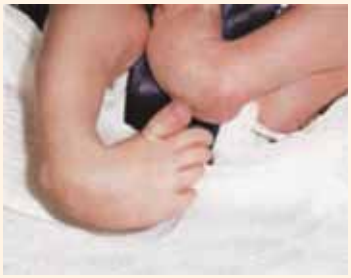
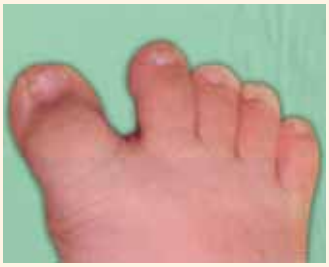
What to examine?	Normal findings to look for	Abnormal findings not to miss
n. Anus	Normally placed, visibly patent anus. Passage of meconium within 48 hours of birth.	Absent anal verge or anteriorly placed anus. Passage of meconium may be seen on scrotal raphe in male (Fig. 18) or through rectovaginal fistula in female  **Fig. 18:** Anorectal malformation (low variety with meconium on scrotal raphe)
	Look for tone of anus and anal sphincter contraction (stroke with blunt end of needle)	Patulous anal sphincter suggest denervation of anus in spina bifida
o. Genitalia	Male: Normal prepuce, central position of urethral meatus	Hooded penis is associated with hypospadias
	Palpate testes from appear end of scrotum to prevent retraction	Cryptorchidism absence of testes in the scrotum
	Female: Examine labia, clitoris, separate labia minora and inspection of introitus and hymen	Mucoid bloody discharge due to estrogen withdrawal is normal. Fused labia, enlarged clitoris in CAH (Fig. 19)  **Fig. 19:** Fused labia with labioscrotal fold in CAH
p. Feel the patella and knee joint	Normally, extension at knee is limited	Genu recurvatum is common after breech delivery
• Look for talipes (position abnormality) in all cases of talipes exclude congenital dislocation of hip (CDH), spinal abnormalities	Talipes (varus—inversion, valgus— eversion, Equines—planter flexion, calcaneus—dorsi flexion)	Talipes equinovarus (Fig. 20), Talipes calcaneovarus, metatarsus varus are common malformations position abnormalities  **Fig. 20:** Talipes equinovarus
• Count the toes	Normal distance between great toe and 1st toe	Increased distance between great toe and 1st toe. Suggestive of Down syndrome (Fig. 21)  **Fig. 21:** Big space between first and second toes characteristics of Down syndrome

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What to examine?	Normal findings to look for	Abnormal findings not to miss
• Count digits	Check for syndactyly and accessory digits	It may be an isolated phenomenon or an autosomal dominant condition
	Elicit Moro's reflex for movements of both upper extremities	Absence of movement suggests fracture, brachial palsy, Erb's palsy
q. Examination of hip to exclude congenital dislocation of hips (CDH): This examination must never be omitted	Normally hips can be adduced and externally rotated with abduction without click. Positive Ortolani and Barlow test. With the infant supine (Figs 22 to 24), the hips are flexed to a right angle and the knees brought together. Pressing gently backwards the hips are slowly abducted and extended. If the hips are unstable, the first part of the maneuver will push the head of the femur out of the acetabulum. As abduction proceeds, the head of the femur will be felt to click back into place  **Fig. 22:** Ortolani test: Abduction and extension of hip by gentle backward placing  **Fig. 23:** Click felt as abduction proceeds as head of the femur comes back into acetabulum  **Fig. 24:** Telescoping head of the femur in acetabulum	Positive family history of CDH, breech delivery should alert for occurrence of CDH. Neonates with meningomyelocele and paralysis of the legs may have completely dislocated hips and it may be impossible to relocate. Greater trochanter may be felt at superior iliac spine
r. Respiratory system	Respiratory pattern	
• Inspection	Abdominothoracic respiration RR- 40−60/min	>60/min, abnormal, indrawing of sternum and intercostals suggests respiratory distress
• Palpation	Feel for trachea	Central or deviated
• Auscultation	Of limited value if neonates is healthy	If in distress look for air entry and added sounds
s. Cardiovascular system		
• Inspection	Heart rate (HR): 100−160/min normally— 140−160/min if neonate is crying or feverish. HR>160/min tachycardia- >220/min	<100/min—bradycardia ≥160/min—tachycardia Tachycardia, sweating, gallop rhythm and hepatomegaly suggest CHF
• Palpation	Look and palpate precordium and pulses	Hyperdynamic precordium and bounding pulses suggests L to R shunt
• Auscultation	Second heart sound splits after 48−72 hours. Pansystolic TR murmur is present at birth, disappears by 48 hours, ductus murmur disappears by 3rd day. Feel femorals and dorsalis pedis	If remains single after 72 hours—suggest PPHN, PS or AS, TOF. If continues beyond suggests PPHN, PS. If ductus murmur persists—it suggests PDA—which is common in preterm babies. Absence of femorals suggests coarctation of aorta.

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What to examine?	Normal findings to look for	Abnormal findings not to miss
t. Abdomen (palpation of abdominal viscera while feeding the neonates)	• Xiphoid process is often prominent in thin infants • Look for visible peristalsis and distension • Palpable liver—1−2 cm below the costal margin is normal • Spleen: Occasionally palpable • Kidney—Right kidney may be normally palpable if neonate is relaxed • Bladder may be palpable if not passed urine • Umbilicus: Inspection for discharge and hernia into cord	Danger signs: • Persistent vomiting • Vomiting with bile • Abdominal distension • Failure to pass urine within 48 hours • Failure to pass meconium within 36−48 hours • Persistently palpable bladder suggests obstructive uropathy • Redness, edema of the skin at base of umbilicus and flare of erythema suggest infection has extended to umbilical vein
u. Neurological [Cranial nerves (CN)] and developmental examination	Blink response to light (Fig. 25)  **Fig. 25:** Blink response to light	No blink response persistent squint and gross nystagmus, failure to follow moving object
• CN (II, III, IV, VI)	Follows bright moving objects	
• CN—V	Normal corneal reflex	Absent corneal reflex
• CN—VII	Normal without deviation of angle of mouth while crying	Deviation of angle of mouth on either side on crying (Fig. 26) due to VII nerve palsy (deviation to healthy side). May be due to absent levator angularis oris  **Fig. 26:** Asymmetric cry with deviation of angle of mouth
• CN—VIII	Startle response to loud noise	No response to loud noise
• CN—X, XII	Ability to suck, swallow and normal rooting reflex (Figs 27 and 28)  **Fig. 27:** Sucking reflex  **Fig. 28:** Rooting reflex	Inability to suck and swallow
v. Motor system: Tone, resistance of muscle to stretch	Resistance to extension and after full extension recoil to a flexed position is normal	Absence of recoil or increased resistance with exaggerated recoil suggest CNS dysfunction
• Phasic tone high amplitude and short duration stretch	Tendon reflexes	Absence of tendon reflexes suggests either dysfunction of motor unit or cerebral disorders as in HIE
	Ankle clonus	Sustained ankle clonus suggests early spasticity

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What to examine?	Normal findings to look for	Abnormal findings not to miss
• Postural tone low amplitude sustained stretch reflex	Some degree of head lag is usually present during newborn (Fig. 29). Normal traction response is to lift the head parallel to axis of the body  **Fig. 29:** Normal head in newborn	Significant head lag during lift suggests hypotonia (Fig. 30)  **Fig. 30:** Significant head in newborn
	Vertical suspension leads to flexion against gravity in lower limbs.	Absence of flexion of lower limbs against gravity is abnormal
	Placing reflex: (Touching the dorsum of feet against edge of table) The normal baby will try to climb on table (Fig. 31)  **Fig. 31:** Placing reflex	Absence of normal placing and stepping reflex in newborn or exaggerated or persistence of placing and stepping reflex beyond 6 months of age is abnormal
	Stepping reflex: Placing child on the table in standing position with gentle push- normal newborn will tend to walk (Fig. 32).  **Fig. 32:** Stepping reflex	
	Normal horizontal suspension leads to intermittent raising of head with flexion of limbs	Inability of intermittent raising of head in horizontal suspension suggests hypotonia
• Galant and Perez reflex: Stroking the back in ventral suspension from down to upward along and beside vertebral column	Normally causes bending of the trunk (Figs 33 and 34)  **Fig. 33:** Galant reflex  **Fig. 34:** Perez reflex	Absence of such reflexes during newborn is abnormal. Over performance or persistence of such reflexes beyond 6 month is abnormal.

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What to examine?	Normal findings to look for	Abnormal findings not to miss
• In prone position	Newborn baby, pelvis high, knees drawn up under abdomen (Fig. 35)  **Fig. 35:** Normal term baby: Pelvis high, knees drawn up under abdomen	In hypotonia and in preterm baby hyperabducted hip (Fig. 36)  **Fig. 36:** In hypotonia and in preterm baby with hyperabducted hip
Integrated reflexes:		
• Moro reflex (Fig. 37)  **Fig. 37:** Moro reflex	Coordinated extension flexion (clutching) movement of extremities to sudden sensation of falling	Absent in cerebral depression Unilateral absence suggests brachial plexus palsy
• Asymmetric tonic neck (ATN) reflex (Fig. 38)  **Fig. 38:** Asymmetric tonic neck reflex	Turn head to one side increased extensor tone on that side and flexor tone on contralateral side	If response is excessive and obligatory suggest neurological abnormality
• Cross extensor reflex: Are helpful in neurological evaluation	Sticking the sole of one foot with a pin causes flexion movement and extension on opposite side- normal	Abnormal response suggest disorders of motor unit
x. Peripheral nerves:	Elicit Moro reflex	Unilateral absence suggests Erb's or Klumpke's palsy or fracture clavicle

Abbreviations: OFC, occipitofrontal circumference; AF, anterior fontanel; CDH, congenital dislocation of hips; CAH, congenital adrenal hyperplasia; HR, heart rate; PPHN, persistent pulmonary hypertension; PDA, patent ductus arteriosus; CN, cranial nerve; CNS, central nervous system; HIE, Hypoxic ischemic encephalopathy; ATN, asymmetric tonic neck.

- *Lower limbs*: Evidence of congenital dislocation of hip (CDH) and extra digits or any other abnormality
- *Femoral pulses*: Present/absent or radiofemoral delay
- *Spine*: Any deformity or abnormality
- *Neurology*: Behavior, primitive reflexes (specially Moro, sucking, rooting).

ROUTINE CARE OF THE NEWBORN AT DELIVERY AND AFTER DELIVERY

Most babies require only simple supportive care at and after delivery

- Clean delivery and clean cord care to prevent infection.
- After a clean and safe delivery—Hold the baby at the same level of the mother.
- The umbilical cord is clamped soon after delivery (Fig. 39) and cut within one minute in the following way: Cord should be tied in three places, two fingers away from the umbilicus (abdominal wall), the second tie should be one finger width away from the first one and the third tie should be four finger widths away from the 2nd one. The cord must be cut with a clean blade in between the last two cord ties and about one finger width away from the 2nd tie. If any bleeding from the cord stump is noted, another cord tie should be applied.

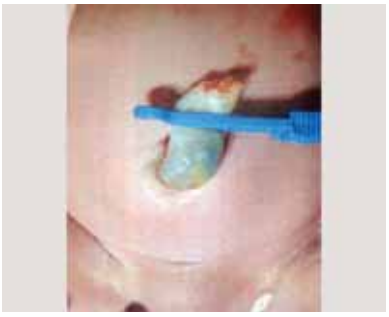
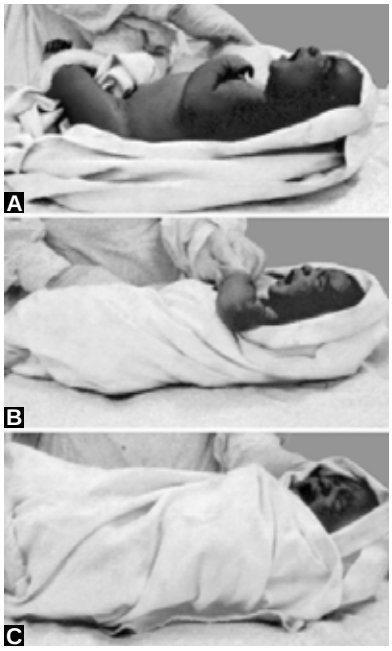


Fig. 39: Correct application of the umbilical cord clamp



Figs 40A to C: Showing drying and wrapping of newborn after birth

- Use two dry and warm clean clothes to dry the baby thoroughly with one and cover with other (Figs 40A to C).
- Check baby's breathing and color (done at the time of drying and wrapping).
- Keep the mother and baby together to establish early breastfeeding, if the baby is well. Reassure mother about baby's condition.
- Encouraging early (within half an hour of birth) and exclusive breastfeeding. Do not offer any other food/medicine.
- Bathing baby immediately after birth or using oil to clean the vernix are not necessary.
- It is not necessary to shave the head.

CARE FOLLOWING BIRTH

- Introduce colostrums with in half hour of birth.
- Exclusive breastfeeding on demand.
- Keep the baby warm, avoid draughts at all times.
- Do not bath the baby until 72 hours of life.
- Keep umbilical cord clean, dry and bare washing with spirit or use of drugs is not required.
- Check for passage of urine (voided at least 6/8 times) in 1st 24 hours and passes of meconium (black stool) in 1st 24 hours.
- Immunization—give BCG, OPV and hepatitis-B vaccine within fourteen days of life.
- Vitamin K (in Konakion MM 2 mg) should be given orally to all newborns at birth.

EVALUATION OF BIRTH INJURY AND SCALP SWELLING

Common birth injuries are mentioned in Table 16.

Other Birth Injuries

- Intracranial hemorrhage
- Subdural hemorrhage
- Periventricular and intraventricular hemorrhage
- Nerve injuries

a. Facial palsy (Fig. 41)
b. Erb's palsy (Fig. 42)
c. Klumpke's palsy (Fig. 43)

Table 16: Common birth injuries

Bruise	Is seen over the presenting part in a baby born after prolonged and difficult labor. It resolves spontaneously.
Abrasion, laceration	Molding of the head and overriding of the parietal bones are frequently associated with caput succedaneum. They disappear in 1st week of life.
Head molding	Common causes of scalp swelling
Caput succedaneum	
Cephalhematoma	
Subaponeurotic hemorrhage	
Chignon/vacuum caput	

(Note: Cranial meningocele/encephalacele also cause scalp swelling)

Fig. 41: Asymmetric cry with deviation of angle of mouth due to VII nerve injury

Fig. 42: Erb's palsy showing pronation of right hand with flexion towards body due to damage of C5, C6, ±C7

Fig. 43: Klumpke's palsy involves C8, T1 with typical claw hand (right). This rare lesion may complicate breech delivery and may be accompanied by Horner's syndrome

- Fracture clavicle and long bones
- Subconjunctival hemorrhage: No treatment is required
- Sternocleidomastoid tumor → Traumatic—may resolve over 4–6 weeks. It may cause torticollis.

CAPUT SUCCEDANEUM

This is the swelling of the soft tissue of scalp over presenting part during NVD (Fig. 44).

Characteristics

- Present/seen at birth
- Diffuse, soft, edematous, pitting, non fluctuant

Fig. 44: Child with caput succedaneum caused by birth trauma

Fig. 45: Cephalhematoma

- Crosses suture line → Not limited with suture lines and disappears spontaneously within 1st few days of life.

Treatment

No treatment is required. If extensive ecchymoses are present, hyperbilirubinemia may develop and need phototherapy.

CEPHALHEMATOMA

- Hemorrhage under the periosteum of the skull bones and collection of blood following trauma during birth due to rupture of subperiosteal blood vessels (Fig. 45).
- Incidence: 1–2% of live births.

Characteristics (Fig. 46)

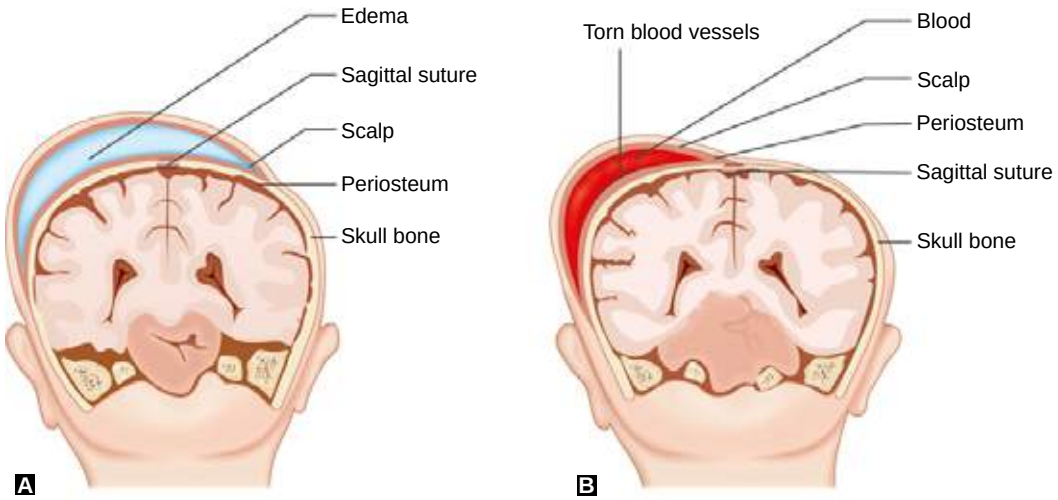
- Swelling appears after 4–8 hours of birth and reaches maximum size by 3rd day.
- Common site: on parietal, also occipital and frontal bones.
- Does not cross the suture line—limited by suture line.
- Usually unilateral—when bilateral, it may be associated with skull fracture.
- Swelling is: Fluctuant, irreducible, nonpulsatile, non-increasing in size during crying, well-defined margin.

Fate

- Swelling disappears between 2nd week and 3rd month—depending on its size.
- The lesion becomes a firm, calcified swelling by the end of 2nd week before getting resorted.
- A few remain for years as bony protuberances and are detectable by X-ray as widening of diploic space (Fig. 47).
- Cyst-like defects may persists for months or years.
- An underlying linear skull fracture may be associated with 10–25% of cases.

Treatment

- No specific treatment is required
- Explanation and reassurance to the parents
- Resolves spontaneously over a variable period of time



Figs 46A and B: (A) Caput succedaneum; (B) Cephalhematoma

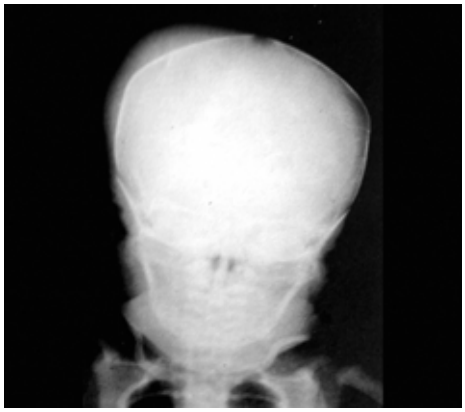


Fig. 47: Skull X-ray of a patient with cephalhematoma showing swelling over right parietal bone. The soft tissue swelling is limited by sagittal suture superiorly and tempero-squamous suture inferiorly

- Avoid aspiration of the swelling
- If hyperbilirubinemia develops, phototherapy may be required.

SUBAPONEUROTIC HEMORRHAGE

- Collection of blood beneath the aponeurosis (in the soft tissue space) that covers the scalp and extends from the orbital ridges to the occiput posteriorly and laterally to the ears.
- They are usual from the vacuum assisted delivery or less commonly following after instrumental delivery or secondary to a linear skull fracture, sutural diastasis or fragmentation of the superior margin of the parietal bone and/or rupture of the emissary vein.
- It may be associated with a hereditary coagulopathy (hemophilia).

Characteristics

- Swelling of the scalp that crosses the midline, suture line—firm fluctuant mass—which increase in site after birth
- Superficial bruise, laceration may present
- Baby may be pale, in shock with tachycardia and low blood pressure, depending on the amount of hemorrhage
- Baby may be hypotonic, seizure may present and later may develop hyperbilirubinemia.

Investigations

- Blood grouping and cross matching
- Bleeding time (BT), clotting time (CT)
- S. bilirubin—later.

Differential Diagnosis

- Caput succedaneum
- Cephalhematoma
- Meningomyelocele.

Treatment

Supportive

- Inj. Konakion: IM route
- If significant pallor develops—blood transfusion may be needed
- If baby develops hypotension and shock—infusion and measures accordingly for reversal of shock
- If clotting factor abnormal: Fresh frozen plasma (10 mL/kg) may be given
- If there is hyperbilirubinemia—phototherapy, exchange transfusion may be needed
- Local antibiotic ointment—in lacerated area of scalp
- Surgery—if bleeding does not subsides.

Complications

- Profound pallor
- Shock
- Jaundice.

Prognosis

Good, if there is good supportive care and no major complications like shock.

INFANT AND YOUNG CHILD FEEDING (IYCF)

BREASTFEEDING AND COMPLEMENTARY FEEDING

Breastfeeding

It is a well recognized fact that early initiation of breastfeeding and exclusive breastfeeding up to 6 months and continued breastfeeding from 6 months to 2 years along with complementary feeding improves both child and maternal health which in turn will help reaching millennium development goals (MDGs) goal 4, 5 and MDG goal 1, which aims to reduce extreme hunger and poverty by half by year 2015.

According to UNICEF, child mortality has reduced from 13 million globally in 1990 to about 8 million in 2009 due to some simple low-tech interventions like early and exclusive breastfeeding up to 6 months. In developing countries, about 50% of under-five-years death and more than 65% of infant mortality are attributable to neonatal or newborn deaths.

There is evidence to suggest that early initiation of breastfeeding (within 1 hour) can decrease neonatal mortality by 22%. There are also compelling evidences to suggest that by implementation of 10 steps of breastfeeding of baby friendly hospital initiative (BFHI) with continued postnatal support, contributes to increased breastfeeding initiation and exclusive breastfeeding up to 6 months at local, national and global levels.

Exclusive Breastfeeding

Exclusive breastfeeding means that

- No drinks or foods other than breast milk are given to a baby
- No pacifier, dummies or artificial teats are given to a baby. Exclusively breastfed babies are at decreased risk of diarrhea (breastfeed baby may pass frequent loose stool, this is normal), pneumonia and ear infection.

Advantages of exclusive breastfeeding:

- Complete food, species specific
- Easily digested and well absorbed
- Protects against infection
- Promotes emotional bonding
- Better brain growth.

Benefits to Mother

- Helps in involution of uterus
- Delays pregnancy
- Lowers risk of breast and ovarian cancer
- Decreases mother's workload.

Benefits to Family and Society

- Saves money
- Promotes family planning
- Decreases need for hospitalization
- Contributes to child survival.

Types of Breast Milk

The composition of breast milk varies at different stages after birth to suit the needs of the baby. Milk of a mother who has delivered a preterm baby is different from milk of a mother who has delivered a full term baby.

- Colostrum is the milk secreted during first week after delivery. It is yellow, thick and contains more antibodies and white blood cells. Though secreted only in small quantities, it has higher protein content and is sufficient for the needs of the baby.
- Transitional milk is the milk secreted two weeks following delivery. Immunoglobulin and protein content decreases while the fat and sugar content increases.
- Mature milk follows transitional milk. It is thinner and watery but contains all the nutrients essential for optimal growth of the baby.
- Preterm milk is the breast milk of a mother who delivers prematurely. It contains higher quantities of proteins, sodium, iron, immunoglobulins that are needed by her preterm baby.
- Fore milk is the milk secreted at the start of a feed. It is watery and is rich in proteins, sugar, vitamins, minerals and water and satisfies the baby's thirst.
- Hind milk comes later towards the end of a feed and is richer in fat content and provides more energy, and satisfies the baby's hunger. For optimum growth, the baby needs both fore and hind milk. The baby should therefore be allowed to empty one breast. The second breast should be offered only after emptying the first.

Key Messages to Promote Exclusive Breastfeeding

- Put baby to breast as soon as possible after birth within 1 hour. This is important for the mother, baby and for milk production.
- Do not give sugar, water, honey, mustard oil, misri (sugar cube), water, distilled water, glucose to baby after birth.
- On the first day, breast milk is thick and yellowish (known as colostrum). Feeding this milk provides nutrition and prevents infections. DO NOT DISCARD COLOSTRUM. This is first oral vaccine to baby.
- Keep baby close to mother. It is safe for baby to sleep with mother.
- Mother may lie down, sit on a bed, chair or floor to breast feed her baby.
- Breast feed during day and at night at least eight times, whenever baby cries with hunger.
- The more the baby sucks at breast the more milk the breast will produce.
- Allow baby to feed at one breast until he/she leaves the nipple on his/her own. Then feed him/her at the other breast if he/she is still hungry.
- Give baby only breast milk for the first 6 months (180 days).
- Never use bottles or pacifiers. They are harmful and are likely to make baby frequently ill.

Breastfeeding should be continued during diarrhea as well as other illnesses. It helps the baby to get optimal nutrition and recover from the illness faster.

Breastfeeding: Initiation in the 1st Hour Can Save More than One Million Newborns

It is estimated that 4 million newborn deaths occur every year globally. Recent research shows that 22% of newborn deaths could have been prevented if newborns were breastfed within 1 hour of birth. If all world newborns are offered breastfeeding within 1 hour of birth, of the estimated 4 million newborn deaths about 1 million lives will be saved.

There is also published evidence to suggest that under five mortality rate can be reduced by 13% by exclusive breastfeeding up to 6 months. Continued breastfeeding with proper complementary feeding up to two years will further reduce 6% of under-five mortality rate. These will contribute to achieve MDG-4.

The Amazing First Hour of Life

When healthy infants are placed skin-to-skin on their mother's tummy and chest immediately after birth, they exhibit remarkable capabilities. They are alert. They can crawl, stimulated by mother's gentle touch, across her tummy, reaching her breast. They begin to touch and massage the breast. This first gentle touch of a baby's hand or head at the breast stimulates the release of maternal oxytocin, thus beginning both the flow of milk and enhancing the feelings of love for the baby. Then the baby smells, mouths and licks the mother's nipple. Finally, he or she attaches to the breast and feeds. This sequence of events is important for the survival, growth and development of young human.

Optimal Breastfeeding

The WHO/UNICEF Global Strategy for Infant and Young Child Feeding recommends that children should breastfeed exclusively for the first 6 months of life, and then continue breastfeeding with proper complementary food up to 2 years and beyond. Initiation of breastfeeding sooner after birth begins with skin-to-skin contact, and helps mothers and infants to achieve optimal breastfeeding. This is required in the BFHI, specifically in Step 4 of the WHO/UNICEF 10 Steps to Successful Breastfeeding.

Skin-to-skin contact after birth and breastfeeding within the first hour of life are important for following reason:

1. The mother's body helps to keep the baby appropriately warm, which is especially important for small and LBW babies.
2. The baby is less stressed, calmer and has steadier breathing and heart rates.
3. The baby is exposed first to the useful bacteria called probiotics (lactobacillus, bifidus bacteria) from the mother which are mostly harmless, or against which the mother's milk contains protective factors. The mother's bacteria colonizes the baby's gut and prevents colonization of harmful bacteria, thereby protecting from neonatal

sepsis. Breastfeeding also helps prevention of necrotizing enterocolitis (NEC)

4. The significance of colostrum as first feeds. Colostrum is considered "**liquid gold**", sometimes called the **gift of life**.
   - Colostrum serves as the baby's first immunization, as it is rich in immunologically active cells, antibodies and other protective proteins.
   - It contains growth factors, which help the infant's intestine to mature and function effectively.
   - It is rich in Vitamin A, which helps to protect the eyes and reduce infection
   - It stimulates the baby to have bowel movements so that meconium gets cleared quickly from the gut. It therefore prevents enterohepatic circulation of bilirubin, which helps to get rid of jaundice quickly.
5. Mother experiences incredible satisfaction with the first meeting of her child, and father often shares this delight. The process of bonding between mother and baby begins.
6. Touching, mouthing and suckling at the breast stimulates oxytocin release—this is important for many reasons:
   - Oxytocin causes the uterus to contract. This may help delivery of the placenta and reduce maternal bleeding after the birth
   - Oxytocin stimulates other hormones which cause a mother to feel calm, relaxed, and some would say "in love" with her baby
   - Oxytocin stimulates the flow of milk from the breast.

How to Initiate Breastfeeding in the First Hour of Life

1. Encourage nonpharmacologic measures to help support women through labor (massage, aromatherapy, water injections, movement)
2. Provide appropriate, culturally sensitive and supportive labor companionship to mothers
3. Allow delivery to occur in the position preferred by the mother
4. Dry the baby quickly, preserving the natural white cream (vernix) that soothes a baby's new skin
5. Place the baby bare skin-to-skin on mother's bare chest, facing her and cover them together
6. Breast crawl method (Fig. 48): The method of breast crawl can be adopted for early initiation. Allow the baby to seek the breast. The baby will crawl and find breast nipple to suck. The mother will stimulate the baby with her touch and may help position the baby closer to the nipple.
7. Baby should be fed on cues (Figs 49A and B): The baby in early feeding with cues include sucking movements and sucking sounds, hand to mouth movements, rapid eye movements, soft tuning or sighing sounds, lip smacking, restlessness. Crying is a late cue and may interfere with successful feeding and therefore feeding should be established with early feeding cues before crying.
8. Keep the baby skin-to-skin with the mother until the first feeding is accomplished and as long as she desires thereafter
9. Women who have surgical births should also have their infants skin-to-skin after delivery
10. Delay invasive or stressful procedures. The baby should be weighed, measured and given preventive medications after the breastfeed
11. No prelacteal liquids or feeds should be given unless there is a clear medical indication.

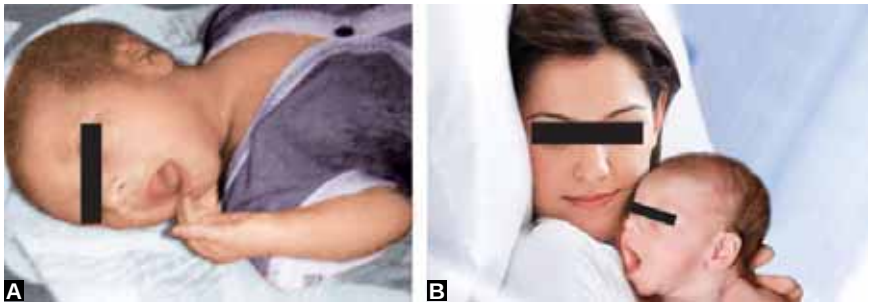
Fig. 48: Breast crawl

Other Technical Guidelines for Successful Breastfeeding

- Pre-birth counseling individually or in groups organized by maternity facility regarding advantages of breastfeeding and dangers of artificial feeding would prepare expectant mother for successful breastfeeding.
- Every mother, specially if the first time mother would receive breastfeeding support from the doctors and the nursing staff, or community health workers with regards to correct positioning, latching and treatment of problems, such as breast engorgement, nipple fissures and delayed "coming-in" of milk.

KANGAROO MOTHER CARE

Kangaroo mother care (KMC) is a care to babies particularly to preterm and LBW infants carry skin to skin with the mother (Fig. 50).



Figs 49A and B: Feeding cues: (A) Hand to mouth movement; (B) Sucking movement

Fig. 50: Diagram showing kangaroo mother care in sleeping position

Clinical Benefits

- KMC significantly increases milk production in the mother
- KMC increases the exclusive breastfeeding rates
- KMC reduces the incidence of respiratory tract and nosocomial infections
- There is improved weight gain
- It improves thermal production in these infants and mother
- KMC reduce the duration of hospital stay.

KMC Procedure

KMC positioning: The baby should be placed between the mother's breasts in an upright position. The head should be turned to one side and in a slightly extended position. This slightly extended head position keeps the airway open and allows eye to eye contacts between the mother and her baby. The hips should be flexed and abducted in a 'frog' position, the arms should also be flexed. Baby's abdomen should be at the level of the mother's epigastrium. Mother's breathing stimulates the baby thus reducing the occurrence of apnea. Support the baby's bottom with a sling/binder. KMC positioning can also be performed in sleeping position (Fig. 50).

Feeding: The mother should be explained how to breastfeed while the baby is in KMC position. Holding the baby near the breast stimulates milk production. She may express milk while the baby is still in KMC position. The baby could be fed with spoon or tube depending on the condition of the baby.

Does Skin-to-Skin Contact Matter for Women Who are HIV Positive?

Even women for whom replacement feeding is acceptable, feasible, affordable, sustainable and safe (AFASS), and who choose not to breastfeed, should have skin-to-skin contact with their babies. These mother-infant couples are particularly vulnerable. Skin-to-skin contact provides a special closeness, beginning the mother-child relationship.

If conditions are not AFASS, it is very important for mothers and infants to have skin-to-skin contact immediately after birth and to start breastfeeding in the first hour. For these babies, exclusive breastfeeding carries a lower risk of mother to child transmission of HIV than mixed feeding.

MISTAKEN BELIEFS: BARRIERS TO NORMAL BREASTFEEDING INITIATION

- **Infants need special teas or other fluids before breastfeeding**
  Wrong concept: Any prelacteal feeds (feed given before breastfeeding has started) increase the infant's risk of infection, reduce the likelihood of exclusive breastfeeding and shorten the duration of breastfeeding. Therefore, no prelacteal feed should be given.
- **Is colostrum harmful?**
  Colostrum is physiological and essential for the newborn:
  - It protects against intestinal and other infections
- **Babies will not get enough food or fluid with only colostrum and breast-milk**
  Wrong concept: Colostrum is sufficient for a baby's first feeds. It is normal for a newborn to lose 3–10% of birthweight. A normal full term baby has enough glycogen stores and can produce ketones as fuel in case of hypoglycemia. Therefore, breast-milk substitute should not be given even there is insufficient breast-milk in first few days of life.
- **Mothers are too exhausted after labor and delivery and, therefore, should not feed their baby immediately**
  The concept is wrong. The surge of oxytocin that comes with skin-to-skin contact and breastfeeding helps to calm a mother after the birth of her baby.
- **Oropharyngeal suction of baby after birth is essential**
  The concept is wrong. Suctioning of the normal healthy newborn does not reduce the occurrence of meconium aspiration, and may injure the tissue of the mouth, throat or vocal cords. It also interferes with breastfeeding.
- **Women require pharmacologic intervention to cope with the pain of labor**
  Generally not required. Use of labor analgesia/anesthesia may sedate the baby, hindering breast-seeking behavior and delaying initiation of breastfeeding for hours or days.

POSITIONING AND ATTACHMENT

Mother should be in a comfortable position. She may sit on a chair, bed, stool or ground with back properly supported. She should slightly recline backward and should not lean on the baby. She can feed the baby in lying or semi-reclining posture.

Proper Positioning of Baby while Breastfeeding (Fig. 51)

Look for:

- Infant's head and body straight
- Facing her breast, with the infant's nose opposite her nipple

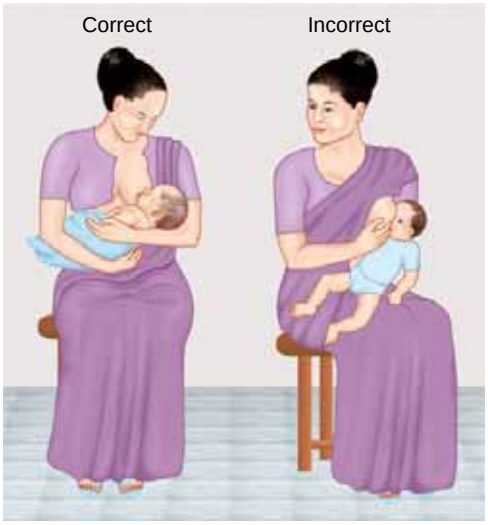


Fig. 51: Positioning during breastfeeding

- Infant's body close to mother's body
- Whole body fully supported.

Proper Attachment (Figs 52 and 53)

Look for:

- Chin touching breast
- Mouth wide open
- Lower lip turned outward
- More areola seen above than below the mouth.

Causes of Poor Attachment

- Use of feeding bottles
- Lack of skilled support
- Inverted nipples.

Poor Attachment Results in:

- Pain or damage to nipple or sore nipple
- Breast milk not removed effectively thus causing breast engorgement
- Breast produces less milk resulting in frustration to baby and refusal to suck. This leads to poor weight gain

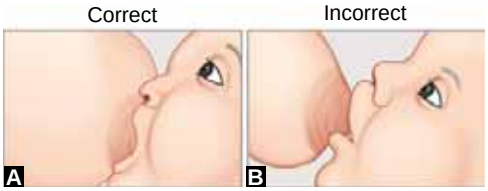
Proper positioning and attachment is very important for successful breastfeeding.

Indicators of Adequate Breastfeeding

- Baby passes urine 6 or more times in 24 hours
- Gains weight 20–40 g/day.

HOW TO SUSTAIN OPTIMUM BREASTFEEDING

- Putting the baby to the breast within first hour of birth
- Giving no prelacteal feeds
- Keeping the mother and the baby in the same bed
- Breastfeeding baby on demand, at least 8 times in 24 hours
- Frequent suckling as well as feeding during night, increases the quantity of milk
- Ensuring proper positioning and attachment
- Giving no feeding bottle or pacifier
- Giving pregnant or lactating mother a little more of the varieties of family foods



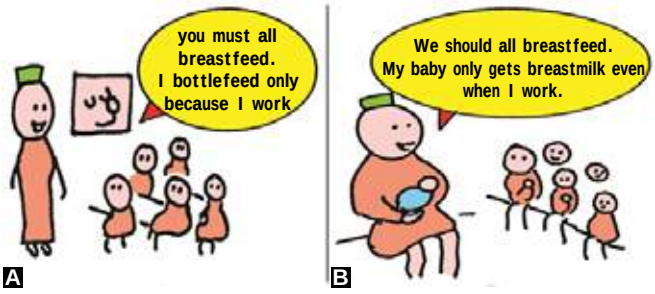
Figs 52A and B: Attachment during breastfeeding

- Starting complementary feeding from 6 months (180 days) of age
- Breastfeeding should be continued after 6 month along with complementary feeding for a minimum period of two years and beyond depending on the choice of mother and the baby. Even during second year of life the frequency of breast eeding should be 4–6 times in 24 hours including night feeds
- Mothers need skilled helps and confidence building during all health contacts and also at home through home visits by trained community worker, especially after the baby is 3 to 4 month old when a mother may begin to doubt her ability to fulfill the growing needs and demands of the baby
- Mother who is unwell or on medication should be encouraged to continue breastfeeding unless it is medically indicated to discontinue breastfeeding. Breastfeeding can be given even if mother has tuberculosis or hepatitis B positivity in developing countries
- At every health visit, the harms of artificial feeding and bottle feeding should be explained to the mother. In advertising of infant milk substitute in health facility should be avoided. Artificial feeding is to be practiced only when medically indicated
- If the breastfeeding is temporarily discontinued due to an inadvertent situation, relactation should be tried as soon as possible. Such cases should be referred to a trained lactation consultant/health worker. The possibility of "induced lactation" shall be explored according to the situation
- Mothers who work outside should be assisted with obtaining adequate maternity/breastfeeding leave from the employers, should be encouraged to continue exclusive breastfeeding for 6 months by expressing milk for feeding the baby while they are out at work and initiating the infant on timely complementary foods. They may be encouraged to carry the baby to a work place wherever such facility exists (Figs 54A and B)
- The concept of allocated rooms at work place where working mothers can express milk and store in a refrigerator during their work schedule may be considered. Every mother during the maternity facility should be taught manual expression of her breast milk
- All efforts should be taken to remove hurdles impeding breastfeeding in public places.

Historical Development in Global Initiative and International Policies to Support and Promote Breastfeeding

In 1989, a joint WHO, UNICEF statement of protecting, promoting, supporting breastfeeding was adopted. The special role of maternity services was published including the ten steps to successful breastfeeding.

Figs 53A to C: Showing proper attachment during breastfeeding: (A) Bring baby to the breast with his head slightly tilted back; (B) Baby's chin will press into the breast first. More of mother's breast will be covered with his lower jaw; (C) When baby is latched well, his chin should be pressed into the breast, and his nose slightly away from it.



Figs 54A and B: Which communicate better? Answer B

In 1990, the innocenti declaration was signed by 10 UN agencies and 32 countries, calling upon all countries to develop national breastfeeding policies and to set appropriate national targets for the nineties.

THE FOLLOWING ARE THE TEN STEPS TO SUCCESSFUL BREASTFEEDING

Every facility providing maternity services and care for newborn infants should:

1. Have a written breastfeeding policy that is routinely communicated to all health care staff.
2. Train all health care staff in skills necessary to implement this policy.
3. Inform all pregnant mothers about the benefits and management of breastfeeding.
4. Help mothers initiate breastfeeding within an half-hour of birth.
5. Show mothers how to breastfeed, and how to maintain lactation even if they get separated from their infants.
6. Give newborn infants no food or drink other than breast-milk unless medically indicated.
7. Practice rooming and allow mothers and infants to remain together—24 hours a day.
8. Encourage breastfeeding on demand.
9. Give no artificial teats or pacifiers (also called dummies or soothers) to breastfeeding infants.
10. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic.

BABY-FRIENDLY HOSPITAL INITIATIVE

UNICEF and WHO launched BFHI in Ankara, Turkey in 1991, to ensure that all maternity services in hospitals and nursing homes are made breastfeeding friendly and support for breastfeeding becomes a central point of their program as a standard for care. To qualify for being designated as "baby friendly", a facility needed to implement all "The Ten Steps to Successful Breastfeeding." This included training of all staff working in the maternity and child care sections to provide skilled support for early initiation and exclusive breastfeeding. In addition, the facility could not accept free or low-cost breastmilk substitutes, feeding bottles or teats. The 10th step of BFHI also included establishment of community outreach support systems for breastfeeding mothers.

One of the operational targets of the Innocenti Declaration of 1990 was that by 1995, all governments would have ensured that every facility providing maternity services fully practiced all 10 steps to successful breastfeeding.

The indicator to assess BFHI addresses the need for implementing breastfeeding-friendly policies both in hospitals and outside hospitals.

Countries that track exclusive breastfeeding (from birth up to 6 months) are shown in Figure 55.

HIV INFECTION AND BREASTFEEDING

- Current WHO recommendations advocate that all mothers known to be HIV-infected should be provided with antiretroviral therapy or antiretroviral prophylaxis to reduce mother-to-child transmission and in particular to reduce postnatal transmission through breastfeeding.
- HIV-infected mothers on antiretroviral therapy (whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for 6 months of life, introducing appropriate complementary foods thereafter and continue breastfeeding for first 12 months of life. Breastfeeding should then only stop once a nutritionally adequate and safe diet without breastmilk can be provided.
- If a HIV positive mother chooses not to breast feed in spite of receiving ARV prophylaxis, Zidovudine or Nevirapine is indicated for 6 weeks for the baby from birth. Replacement feeding as mentioned below is advocated if replacement feeding is AFASS.

CONTRAINDICATION OF BREASTFEEDING

Chronic infections of mother like tuberculosis, hepatitis B infection or medical conditions like hypothyroidism do not warrant discontinuation of breastfeeding. Breastfeeding is contraindicated when the mother is receiving certain drugs like anti-neoplastic agents, immuno-suppressants, antithyroid drugs like thiouracil. Drugs like antibiotic, anesthetic, antiepileptic, prednisolone, propanolol, diuretic, digoxin, antihistamines are considered safe for breastfeeding.

HOW BREASTFEEDING CAN HELP ACHIEVING MDGS?

Facilitate Breastfeeding in the First Hour of Life

At the United Nations Millennium Summit in September 2000, world leaders agreed on critical goals related to child mortality and hunger. Many of the poorest nations are lagging behind in reaching these MDGs. Initiating breastfeeding in the first hour can help achieve MDG #1 and #4. This was reconfirmed at the UN Standing Committee on Nutrition in 2003, where those assembled called for a global initiative for early initiation of breastfeeding.

MDG #1: Eradicate extreme poverty and hunger—reduce by half the proportion of people who suffer from hunger

Starting to breastfeed in the first hour of life is associated with increased rates of exclusive breastfeeding and longer duration of breastfeeding. This contributes significantly to meeting children's nutritional needs during the first two years of life, thus preventing malnutrition and stunting which usually have their origin at this age.

Key:	
No color	Data was not reported
Red	Below 29%
Yellow	30-49%
Blue	50-89%
Green	90% and above

***Note**: It is important to include the timing of first breastfeeding as an indicator of best practices. However, very few countries do so. Of the 60 countries with the highest rates of malnutrition, only 38 reported the frequency of initiating breastfeeding in the first hour of life.*

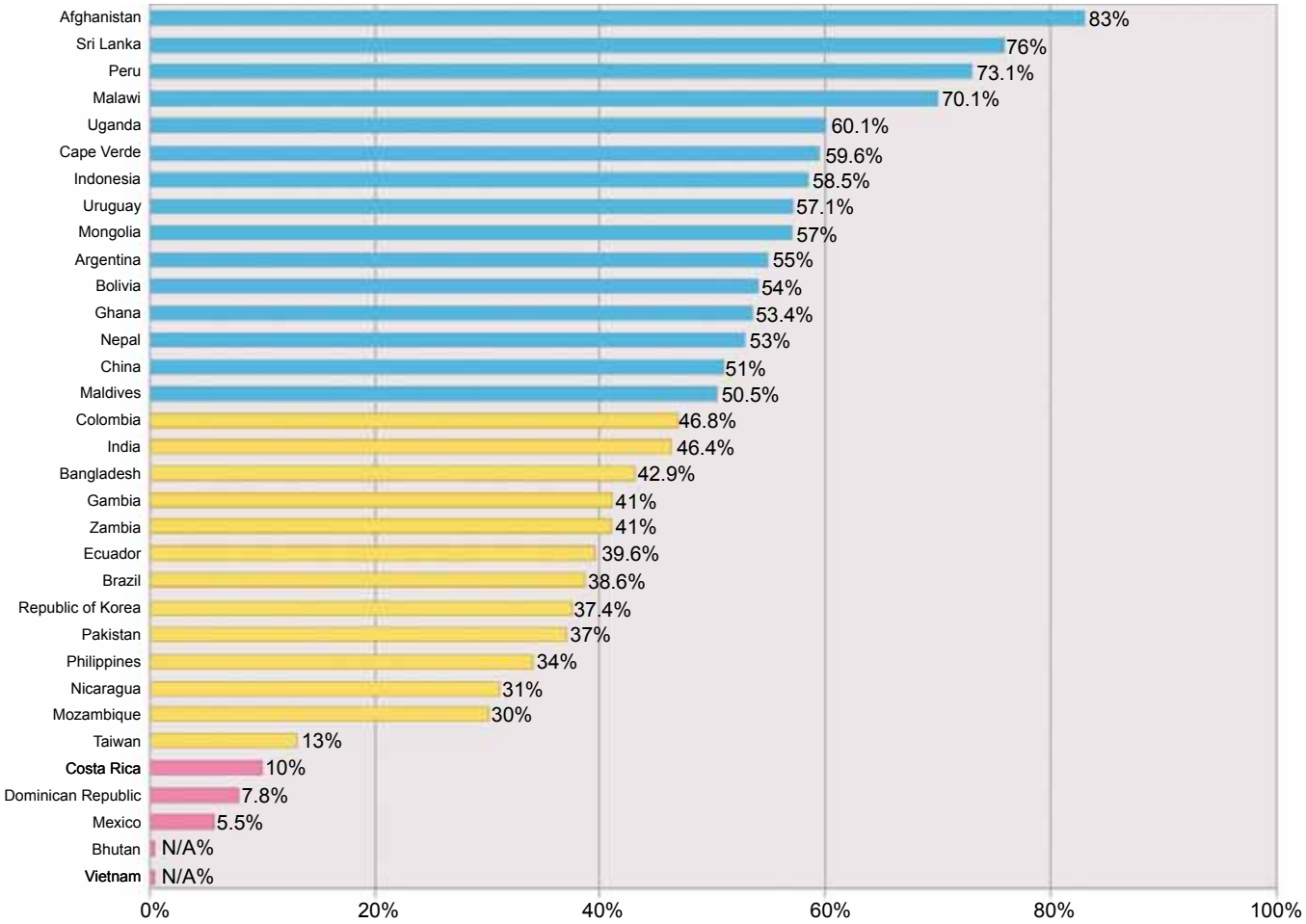


Fig. 55: Percentage of infants 0–6 months of age exclusively breastfed in the last 24 hours in 33 countries
Source: The State of breastfeeding in 33 countries 2010, World Breastfeeding Trends Initiate (WBTi)

MDG #4: Reduce child mortality—reduce by two-thirds the mortality rate among children under five

Most child deaths are caused by diarrhea and respiratory illness, which are more common and more serious with suboptimal breastfeeding. About 45% of the deaths occur in the first month of life, which is a major barrier to attaining this MDG. Breastfeeding in the first hour could reduce newborn deaths and increasing optimal breastfeeding could reduce overall child mortality.

ACTION IDEAS

Initiation of breastfeeding within the first hour of life has the potential to make a major contribution to the health of the world's children. It can significantly contribute to meeting MDG #1 and #4. Policy changes that encourage promotion of timely breastfeeding initiation must improve locally and globally.

For Hospitals and Maternity Facilities

- Assess birthing sites—what are the barriers to normal breastfeeding initiation? Develop action plans to address any barriers that are identified
- Encourage all facilities to keep records on whether or not initiation proceeds in the first hour
- Carry out monthly "rounds" on early breastfeeding initiation to consider what can be done programmatically and practically to improve the rates
- Implement the newly revised BFHI materials
- Review the impact of birthing practices on breastfeeding initiation so that disruptive practices can be modified.

For Health Workers

- Teach birth attendants in health facilities and in the community how to facilitate breastfeeding initiation in the first hour
- Review curricula of health providers and traditional birth attendants related to labor, birth and breastfeeding to assure that information about this important step is included
- Support at least one mother a day.

For Family and Community Members

- Provide education to families regarding the importance of breastfeeding during pregnancy and soon after birth. Include grandmothers and other influential family members in this discussion
- Identify the natural community leaders and communicators as persons who can bring this message to every woman and

man, young and old, to support mothers in breastfeeding initiation and exclusive breastfeeding
- Enlist the popular press in bringing the message to the people. Give one coverage per month for breastfeeding.

For Policy Makers

Encourage maternities, health ministries and other influential bodies such as United Nations agencies and the Joint Commission on Accreditation of Healthcare Organizations to include timing of breastfeeding initiation as an indicator of best practices in maternal child care.

BREASTFEEDING IN SPECIAL SITUATION

Optimizing Breastmilk in Preterm LBW Babies

Mother of preterm baby experiences physiological and emotional challenges that may adversely affect breastfeeding outcome following delivery. Therefore, it is not surprising that this mother starts and sustains breastfeeding at lower rates then mothers of term babies. Preterm delivery adversely affects initiation of lactation for following reasons:
- Mammary growth may be incomplete in a substantially shortened pregnancy and poor placental function with low levels of placental lactogen may exacerbate this problem further.
- The mammary epithelium may not be sufficiently prepared by the hormones of pregnancy to respond with efficient milk synthesis.
- Lactation may be inhibited by stress, fatigue and anxiety.

Optimizing Lactation Success

Mother should be given realistic expectation regarding the initial milk volume because the amount produced can be as little as a few drops of colostrum at each expression for the first 24–48 hours postpartum. Mother should be encouraged to express at least 8 times in 24 hours because any break in the frequency of effective milk removal at this time may seriously compromise with the potential to maximize milk production. The goal is to establish a milk supply of at least 750 mL/day by day 10 because milk production is the most powerful determinant of lactation success, typically plateaus by 2 weeks postpartum. When the milk supply is low at a day 10 (<350 mL/day) despite frequent milk expression, it is important to ensure that the milk expression technique is optimal, which includes:
- A supportive environment for the mother
- Regular breast massage using a good technique
- Simultaneous expression of milk from both breasts.

The most common misconception that undermines successful lactation for mother of preterm infants is that initiation of milk expression can be delayed until an infant is stable. To overcome this problem collaborative effort should be taken in place so that midwives and neonatal nurses can work together to ensure the early establishment of frequent milk expression.

A mother's commitment to supplying her milk will probably have considerable medical benefit for a preterm VLBW baby, both in short and long term.

In most instances, successful expression in the early stages will lead to successful preterm breastfeeding which should be the ultimate goal.

Feeding of LBW babies differs from that of normal birthweight babies. The LBW and preterm babies require higher calories and proteins. Milk of a mother who has delivered prematurely has higher protein content and fulfills the requirements of her preterm baby. The higher level of immunoglobulin does protect the baby from infections. These babies especially those <1.5 kg have difficulty in taking milk directly from breast and may need special support.

Methods of Feeding

For the first few days, a baby (<1.5 kg) may not be able to take any oral feeds. Oral feeds should begin as soon as the baby is reasonably prepared to take orally. However, as mentioned above, for successful lactation initiation of milk expression of mothers of preterm infants should not be delayed, even if the infant is not stable.

Feeding and Maintenance of Nutrition in LBW Babies

- **<1.2 kg:** Baby needs IV fluids initially. Then initiate NG feeding (expressed breastmilk preferably) gradually.
- **1.2–1.5 kg:** Initiate IV fluid (baby may need IV fluid initially), if stable, start NG feeding (expressed breastmilk preferably) gradually.
- **1.5–1.8 kg:** Start cup/spoon feeding; initiate intake of breastmilk by breastfeeding gradually.
- **>1.8 kg:** Breastfeeding as normal birthweight babies, but monitor the baby closely.

Babies who are less than 1.5 kg usually need nasogastric tube feeding. Give expressed breast milk by tube. Try cup or spoon feed once or twice a day while the baby is having feeds by tube, reduce the number of tube feeding, if the baby accept cup or spoon feed well. It is better if the mother lets her baby suck on her breast for stimulating her lactation before she expresses the milk.

Babies between 1.5–1.8 kg are usually able to take feeds from cup/spoon.

Babies more than 1.8 kg are able to feed on the breast. Let the mother put her baby to breast as soon as she feels well enough. These babies usually take what they need directly from the breast of their mother. Continue to follow up babies, regularly to ensure that they are getting enough breast milk as they need.

Procedure of Nasogastric Tube Feeding

When the baby is stable he/she will require NG tube feeding initially. Start with 1–2 mL/kg, feed 2 hourly. Deduct the total feed volume from total daily fluid requirements. If the feed is well tolerated increase the feed volume gradually and reduce IV fluid volume accordingly to maintain the target daily total volume as per recommendation.

Symptoms and Signs of Feeding Intolerance

- Abdominal distension
- Vomiting
- NG suction return before another feed. Significant means greater than 50% of previous feed. Aspirated gastric content if blood or bile stained
- Respiratory distress.

Fig. 56: Procedure of cup and spoon feeding

CUP/SPOON FEEDING

Procedure of Cup/Spoon Feeding (Fig. 56)

- Place the baby in upright posture with cotton napkin around the neck to mop the spillage. Take the required amount of expressed milk in the cup.
- Fill the cup with milk little short of the brim, place it at the lips of baby in the corner of the mouth and let the milk flow into the baby's mouth without spill. Baby will actually swallow the milk. For spoon feeding small amount of milk should be poured directly into the side of the mouth.
- Repeat the process until the required amount has been fed. If the baby does not actively accept and swallow the feed try to arouse the baby with gentle stimulation.
- While estimating the intake, deduct the amount of milk spilled.
- After feeding, the utensils should be washed thoroughly with soap and water and dried. Boil for ten minutes to sterilize before next feed.
- Try cup or spoon, feed once or twice a day while the baby is still having most of his/her feeds by tube and then reduce the number of tube feeds if the baby accepts well.

Advantages of Cup/Spoon Feeding

Simple and effective method to feed babies who are not able to suck directly at the breast. Reduce risk of infection. This method has replaced bottle feeding in nurseries. The method is easy to follow and socially acceptable.

Advantage of Cup or Spoon Feeding over Bottle Feeding

- Cup or spoon feeding is an active process. The person who feeds the baby involves him/her self and provides contact.
- A cup does not interfere with the suckling on the breast. There is no chance of nipple contusion.
- Cups are easy to clean with soap and water if boiling is not possible.

BREASTFEEDING TWINS AND HIGH MULTIPLES

Mothers of twins consistently release twice the volume of milk as mothers of singletons. Mothers of triplets are capable of producing up to a remarkable volume of more than 3 litres/day when the infants are aged 2.5 months. The concentrations of lactose, protein and mixed fat in the milk are variable but adequate in all groups of mothers. Thus both the volume and the content of breast milk can be adequate to feed multiples and therefore mothers may be advised that the more they nurse the baby more the milk supply will be.

How to Increase Milk Supply

What should be done?

- Resting adequately: although sometimes seemingly impossible, is important
- Drinking at least 1,800 mL fluids
- Eating a nutritious diet, nursing frequently, and choosing a night-time sleeping arrangement that allows the best sleep for all involved are important issues that are often overlooked.

What should not be done?

- Stop smoking: Smoking reduces prolactin
- Wearing a tight bra or a sling pressing on the breasts, taking allergy drugs and sleeping prone are all recognized reasons which can reduce breastmilk.

Nutrition of Mother of Twins and High Multiples

- The total amount of breast milk produced can be up to 1.2 litres a day during the first month after delivery and 2 litres a day in the second month. The average energy content is 275–314 KJ (67–75 kcal) per 100 mL, and the efficiency of production is 80–90%. Thus, at the end of the second month of nursing twins, the mother will require about 5025–6280 kJ (1200–1500 kcal) a day.
- Current recommendations for energy supplementation during breastfeeding are 2100–2500 KJ (500–600 kcal) per baby per day. A mother nursing multiples will thus use a combination of reserves stored during pregnancy and increased intake during nursing. The diet should be well balanced (protein 20% of total calories, carbohydrates 40% and fat 40%) and include vitamin supplements. Many mothers may benefit from the help of an expert, such as a dietician.

Stress Relaxation Therapy

Stress relaxation therapy has been used to improve lactation performance and to prolong "breastfeeding".

Galactagogues

Fenugreek seeds are used as traditional medicine for diabetes, high cholesterol, wound repair, and more. It is a widely used galactagogue and found useful for producing breastmilk in Indonesia. The dose is 500–700 mg/day. Cumin seed (Kalojira) is also popularly used as a galactagogue for increasing lactation in woman of Indian subcontinent. Other herbal galactagogues that are available commercially include fennel, rescue remedy, ignatia-6x, and others.

Domperidone and metoclopramide are peripheral dopamine antagonists that are indicated for upper gastrointestinal motility disorders. They also stimulate milk production, probably by increasing prolactin secretion. The dose is Domperidone 20 mg 3 times daily for 4–6 weeks. These drugs should be saved as the last resort after excluding all the factors that may result in insufficient milk supply (such as correcting the baby's latch and sucking problems and using milk compression after feeds to increase supply). Transient side effects include headache, abdominal cramps, and dry

mouth. Use of Domperidone is preferred because it crosses into the brain and into the breast milk to a lesser extent than metoclopramide, decreasing the risk of toxicity to both mother and infant and possibly making it an attractive alternative.

Methods of Breastfeeding

- Breastfeeding of twins can be done either simultaneously at a time or alternatively
- Positions for simultaneous breastfeeding are shown in the Figures 57 and 58.

PROBLEMS WITH BREASTFEEDING WHICH MAY CAUSE FAILURE OF BREASTFEEDING

Not Enough Milk

Mothers may complain that they do not have enough milk. One has to make sure that her perception about adequacy of milk is true. Reassurance is needed if baby is gaining weight and passing adequate amount of urine. Common causes of not enough milk include infrequent breastfeeding, too short or hurried breastfeeds, incorrect positioning and attachment, breast engorgement or mastitis.

Remediable Reasons for Baby Who May Not Get Enough Breastmilk (Insufficient Breastmilk)

- Delayed starting
- Short feeds
- Poor attachment
- Incorrect positioning
- Feeding at fixed times
- Infrequent feeds
- No night feeds
- Use of bottles, pacifiers

Fig. 57: "Double football" position for simultaneous breastfeeding

Fig. 58: "Double cradle" position for simultaneous breastfeeding

- Offering other fluids (sugar, water, honey, etc).
- Lack of confidence
- Worries, stress
- Unwilling for breastfeeding.
- Tiredness
- Illness
- Pain
- Smoking of mother.

Insufficient Breastmilk in Malnourished Mother

Breastmilk in malnourished mother (BMI <18) not infrequently associated with insufficient breastmilk. It is frequently observed that mothers of severely malnourished children also have insufficient breastmilk. Although quantitatively less, quality of breastmilk of malnourished mother is similar to breastmilk of welnourished mother. Due to insufficient breastmilk frequently found in malnourished mother of severely malnourished children, in the feeding management of severe acute malnutrition (SAM), F75 and F100 formula based milk are offered to malnourished children without giving allowance to breastmilk. However, such mothers are encouraged and supported to improve their nutritional status and lactation during rehabilitation phase.

Management of Not Enough Milk

- Ask mother to feed the baby more frequently especially at night
- Make sure that positioning is correct and attachment is good
- Take care of any painful condition in mother such as sore nipple and mastitis
- Back massages are especially useful for stimulating lactation.
- Some drugs may also help in some cases.

Rubbing Mother's back to Stimulate the Oxytocin Reflex

Back massage (Fig. 59) is helpful in relaxation of mother thus stimulating hormone production. The technique of massage should be demonstrated to the relative who can provide it to the mother. Massage should be provided for 15–30 minutes, three–four times a day.

Fig. 59: Back message for improving insufficient breastmilk

Delayed Establishment of Breastfeeding

Delayed establishment of breastfeeding is associated with following conditions which may cause breastfeeding failure, if not properly counseled and tackled.

- Dehydration
- Delayed passage of meconium
- Early breastmilk jaundice
- Delayed discharge from hospital in comparison to formula fed infant
- Maternal exhaustion with difficulty in expressing breastmilk
- Hypernatremic dehydration associated with convulsion and brain damage (mostly reported from Western countries).

How to Overcome the Problem Associated with Delayed Establishment of Breastfeeding?

- Long discussions on benefit of breastfeeding are not enough
- Antenatal classes should prepare mother to understand the situation and to tackle the problem of the time taken to get feeding established
- Video demonstration may also be helpful
- To remain calm despite babies crying for delayed establishment of breastfeeding.

Other Problems Associated with Breastfeeding

- Breastmilk diarrhea
- Breastmilk jaundice
- Apprehensions of not getting enough breastmilk (pseudo-insufficient breastmilk).

Breastmilk Diarrhea

It is a frequent loose pasty stool associated with breastfeeding. It is a benign condition and does not affect growth and development. However, it may cause significant anxiety to mother.

Management

The mother should be given assurance by counseling that good -ness part of milk is absorbed and the benefit of breastmilk far outweighs the side effects of benign loose motion which may only trouble mother in changing nappies and cleaning perianal areas. Mother should be shown the growth chart at every visit to show that her baby is growing normally, even with the loose motions.

Breastmilk Jaundice

Similarly, breastmilk jaundice is also benign condition and does not cause brain injury (kernicterus). Here also advantage of breastmilk far outweighs the benign jaundice associated with breastmilk. If the breastmilk is stopped temporarily jaundice also disappears and reappears after breastfeeding. Breastfeeding should not be stopped due to breastmilk jaundice.

Apprehensions of Not Getting Enough Breastmilk (Pseudo-insufficient Breastmilk)

Since mothers milk compared to artificial feeding by bottle feeding cannot be measured externally mothers apprehends that her child is not receiving enough breastmilk and may desire to feed artificial milk along with breastmilk (mixed feeding). This condition usually happens during third or fourth months of baby's life. In such circumstances mother should be reassured that her child getting enough breastmilk by showing growth chart that her child is gaining weight normally and as expected. The mother should be asked whether she feels heaviness at breast before feeding and lightness at breast after feeding her child. The breastfeeding technique including attachment and positioning should also be checked.

Cleft Lip and Cleft Palate

Most of the cases mother is able to breast feed in this special situation. In few cases, express milk need to be given by long spoon.

Factors which do not Affect the Production of Breast Milk

- Cesarean section
- Preterm delivery
- Medication, e.g. antibiotics and contraceptive
- Size of the breast.

RELACTATION

Relactation is re-establishing adequate milk production in a mother who has a greatly reduced milk production or has stopped beast feeding.

How to Help a Mother for Relactation?

- Motivate the mother
- Ensure support and encouragement from family and health care team
- Put the baby to the breast frequently for sucking
- Expresses milk between breastfeeds
- Reduce supplementation slowly as the milk production increases
- Feed the baby only at the breast, with a breastfeeding supplementer.

Procedure of Relactation by Using Breast-feeding Supplementer

Breastfeeding supplementer is a fine feeding tube, with one end attached to a 50 cc syringe (Figs 60 and 61) containing expressed breast milk or infant formula and the other end of the tube taped to the breast near the nipple. Syringe is to be placed below the breast. The baby will get milk from the tube and from the breast when he/she sucks. This increases calorie intake and stimulates milk production because the baby stays longer at the breast and facilitates effective suckling.

Fig. 60: Breastfeeding supplementer using feeding tube

Fig. 61: 50 cc syringe

COMMON BREAST PROBLEMS

INVERTED/FLAT NIPPLES

Flat or short nipples that become prominent or pull out easily do not cause difficulty in breastfeeding. Explain to the mother that it is the areola not the nipple, which baby should take inside the mouth for sucking. Inverted or retracted nipples make attachment to the breast difficult. They should be diagnosed in the antenatal period. These mothers need additional support to feed their babies. Help the mother to learn the technique. Treatment should be started before birth of the baby. Nipple is manually stretched and rolled out several times a day. A plastic syringe is used to draw out the nipple and the baby is then put to the breast.

SORE/CRACKED/FISSURED NIPPLE

A Sore/Cracked/Fissured nipple is caused by incorrect attachment of the baby to the breast. A baby who sucks only at the nipple does not get enough milk so he sucks more vigorously resulting in a sore nipple. Frequent washing with soap water and pulling the baby off the breast while he is still sucking may result in a sore nipple.

Causes

- Incorrect attachment: Nipple sucking
- Frequent use of soap and water
- Fungal infection of nipple
- Oral thrush of baby.

Treatment

- Continue breastfeeding in correct positioning and good attachment
- Apply hind milk to the nipple after breast feed
- Avoid frequent washing with soap water
- Give antifungal if required.

BREAST ENGORGEMENT

Milk production increases during the second and third day after delivery. If feeding is delayed or infrequent or the baby is not well attached to the breast, the milk accumulates in the alveoli. As milk production increases, the amount of milk in the breast exceeds the capacity of the alveoli to store it comfortably. Such a breast becomes swollen, hard, warm and painful and is termed as an engorged breast.

Treatment

Breast engorgement can be prevented by early and frequent breastfeeding and correct positioning and attachment of the baby to the breast. Apply warm cloth before feeding and gently express the milk to soften the breast, then help the mother to correctly latch the baby to the breast. Ask mother to express by herself by hand expression or warm bottle method of expression (Fig. 62). Paracetamol can be given to the mother to relieve pain.

BLOCKED DUCT

If milk from one part of the breast does not flow well a lump of secreted milk blocks the ducts around.

Treatment

Check that baby is well attached. Advise mother to breast feed frequently. Offer the affected breast first.

MASTITIS/BREAST ABSCESS

It is an infection in the breast. In this condition, patient is febrile and the infected area is swollen, painful, red and hot. If untreated it may develop into breast abscess.

Treatment

Advise mother not to stop breastfeeding. Try to improve positioning and attachment, advise mother to avoid pressure from clothes or fingers, give frequent feeding, gently massage the breast and apply a warm compression before feeding. If there is no improvement, refer the mother to an appropriate health care provider. Mother must be treated with analgesics and antibiotics. The abscess must be incised and drained. Breastfeeding must be continued from the other breast.

During Counseling Few Points Needs to be Discussed with the Mother. These are:

- Put the baby at breast as soon as possible, within 1 hour of birth
- Do not discard colostrums
- Give baby only breast milk for the first 6 months
- Do not give sugar water, honey, mustard oil, misri (sugar cube) water, glucose water to the baby

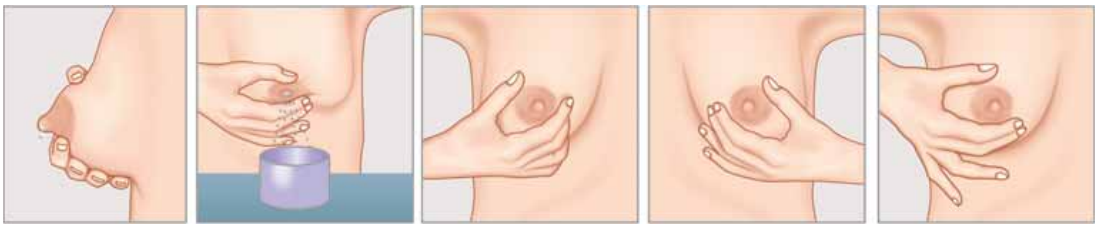


Fig. 62: Process of hand expression of expressing milk

- Never use bottle or pacifier which creates nipple contusion
- Breast feed during day and night at least 8 times within 24 hours
- The more the baby sucks at breast the more milk will be produced
- Keep the baby close to the mother in the same bed and in some room
- Urinemore than 6 times in 24 hours, indicates that the baby is getting enough milk
- Mother should take all the family food plus extra 450 kcal/day, (1 cup rice, 1 cup dal, 1 banana and some amount of vegetable cooked with oil = 450 kcal)
- Complementary food should be started after the ageof 6 months of the baby along with breast milk
- The mother can continue breastfeeding as long as she wishes but at least for 2 years.

COMPLEMENTARY FEEDING

Appropriately thick homogenous complementary foods made from locally available foods should be introduced at 6 completed months to all babies while continuing breastfeeding ad libitum. This should be the standard and universal practiced. The term weaning should be avoided.

IDEAL CHARACTERISTICS OF COMPLEMENTARY FEED

- Each meal must be made energy dense by adding sugar and oil. In place of sugar, jaggery may be used and in place of oil, butter or ghee may be used if affordable. To provide more calories from smaller volumes, food must be thick in consistency- thick enough to stay on the spoon without running off, when the spoon is tilted
- Food can be enriched by adding germinating or sprouting flour or by making a fermented porridge
- Adequate total energy intake can be ensured by an addition of one to two nutritious snacks between the three main meals. Snacks are in addition to the meals and should not replace meals
- Parents should be advised to prepare homemade staple food comprising of cereal-pulse mixture as these are cheap, clean and fresh
- Iron and zinc-fortified foods, iodized salt, vitamin-A enriched food, etc. are to be encouraged. Boiled smashed green banana, mixed leafy vegetables, boiled chicken liver, egg yolk, etc. contain high iron. Boiled smashed meats are also good source of zinc. Fermented or germinated legumes or cereals are also cheap source of zinc
- A list of appropriate acceptable foods can be prepared from population-specific dietary guidelines based on food composition of locally available foods
- A balanced diet is defined as nutritionally adequate and appropriate which provide all the nutrients in required amount and proper proportion. It should be easily available and cost-effective. A combination of carbohydrate rich food (any cereal, fruits and vegetable) a protein source (egg, meat, fish, pulse, milk and milk products) and a fat (oil, butter, ghee) should be used to make nutritionally adequate food to feed. The diet should ideally contain 55–60% calories to carbohydrate, 10–12% proteins and 25–30% fat
- Avoid junk and commercial food. Avoid giving ready-made, processed food from the market, e.g. soft drinks, potato crisps, bakery products, tinned foods/juices, chocolates, energy drinks, etc
- Hygienic practices are essential for food safety during all the involved steps, which includes preparation, storage and feeding. Freshly cooked food should be consumed within one to two hours in hot climate unless refrigerated. Hand washing with soap and water at critical times, including before eating or preparing food and after using the toilet
- **Avoid force feeding and prepare practice responsive feeding**:
  Young children should not be forced to feed, rather should be encouraged to take feed by praising them and their foods. Forced feeding may lead to negative feeding behavior, which is difficult to tackle as the children may consider feed as a torture
- Consistency of foods should be appropriate to the developmental readiness of the child in munching, chewing and swallowing. Avoid foods that can pose choking hazard. Introduce lumpy or granular foods and most tastes by about 9–10 months.

READY-TO-USE THERAPEUTIC FOOD

Ready-to-use therapeutic food (RUTF) is preferably used in therapeutic management of SAM. RUTF is an energy-dense food enriched with minerals and vitamins with similar nutrient profile but greater energy and nutrient density than F-100, the diet recommended by WHO in the recovery phase of treatment of SAM. The original RUTF recipes contains 5 ingredients, peanut-butter, vegetable oil, powdered sugar, dried skimmed milk and a vitamin mineral mix. In contrast to water based F-100, RUTF is an oil-based paste with extremely low water activity. As a result, RUFT food does not grow bacteria, allowing it to be kept unrefrigerated in simple packaging for several months. As the food is eaten uncooked, heat labile vitamins are not destroyed and labor, fuel and water demands on poor household are minimized. The production process is simple and RUTF can be made from local crops with basic technology that is readily available in developing countries.

- RUTF foods are currently have to be imported.
- RUTF needs to be more easily accessible and affordable for the approach to be sustainable. Local production of RUTF needs to be promoted for increase access and availability to RUTF through reducing cost.

Controversy of RUTF and Home-based Nutrient-dense Foods

- There is some merit in arguments on emphasis of wide use of RUTF in impoverished communities of developing countries, considering-
  - The cost of imported RUTF
  - It also presents an opportunity for commercialization of baby foods for malnutrition through multinational companies' product-based nutrition therapy
- Home-based nutrient-dense food has been found to be cost effective and has been recommended during rehabilitation phase of treatment for malnutrition in areas where follow up is possible
- These programs have reported successful rehabilitation of children with SAM, discharged at home after one week of inpatient management with mixtures of local foods combined with provision of multivitamins and

minerals. The cost was found much lower than that of hospital care
- Commercially available nutrient-dense food is expensive. RUTF itself is used in acute phase of rehabilitation and prescribed as therapeutic item not as food. Therefore, locally made RUTF in the community-based treatment of childhood malnutrition is feasible and desirable. The success of home-based treatment of severe malnutrition will require the provision of homemade nutrient-dense food supplement which can be safely stored and administered without much preparation by caregiver.

PRETERM, LOW BIRTHWEIGHT AND INTRAUTERINE GROWTH RESTRICTION

- Birthweight is the most powerful predictor of newborn outcome
- Infant born LBW or preterm are at substantially higher risk of dying in the first year of life, later neurodevelopmental disability and chronic health disorder in adult life than larger and older newborn babies
- In 2012, more than 20 million newborns—an estimated 15% of all babies born globally had low birthweight.

TERM RELATED TO LBW BABY

- Preterm: infant <37 weeks of gestation
- Late preterm (near term): >34/0–<36/6 weeks
- Very-preterm: infant <34 weeks of gestation
- Extremely preterm: <26 weeks of gestation
- Low birthweight (LBW): Birthweight <2500 g (5 1b 8 oz)
- Very low birthweight (VLBW): Birthweight <1500 g (3 1b 5 oz)
- Extremely low birthweight (ELBW): Birthweight <1,000 g (2 1b 3 oz)
- Incredibly low birthweight: Birthweight <750 gm.

Characteristics clinical features of preteam and IUGR babies are mentioned in Table 17.

TWO TYPES OF LBW

1. Constitutionally normal (appropriate for age of gestation)
2. Inappropriately low or small for gestation age (SGA) also called IUGR usually fetal weight is less than 10 centile of birthweight.

THREE TYPES OF IUGR

1. IUGR in preterm with inappropriately LBW for age of gestation
2. IUGR with term/post-term neonate with birthweight inappropriately low for term/post-term neonate
3. Normal birthweight IUGR (with/without prematurity).

Normal Birthweight IUGR

Although LBW is usually associated with IUGR, however IUGR can occur without LBW. Birthweight or fetal weight in such circumstances are within normal range, but low according to genetic growth potential. It carries similar health risk postnatally and in later adult life as LBW IUGR (discussed later).

NORMAL GROWTH AND RETARDED GROWTH OF FETUS DURING PREGNANCY

Basics

Normal growth of fetus in length starts after 3 weeks of implantation, while weight remains minuscule till 12 weeks (see Table 18). For normal fetal growth:

Table 17: Characteristic difference of clinical features between preterm LBW and IUGR (Figs 63 to 66)

Clinical features		
Parameters	**Preterm**	**IUGR**
Skin color	Red/very pink	White or pale pink
Skin texture	Shiny, transparent, thin, edematous	Dry, loose, thick (parchment-like) may be cracked
Lanugo hair	Present	No lanugo, thick, dark hair
Size	Small but plump	Wasted
Weight for age	Corresponds gestational age	Less than gestational age
Head	Is proportionate to body size, dolichocephalic shape	Head disproportionately larger than body size
OFC	<35 cm	>35 cm
Length	<50 cm	>50 cm
Muscle tone	Hypotonic (Apparently Floppy)	Good muscle tone
Ear lobule	Not recoil (32 weeks: slowly recoil; 32-36 weeks: Immediately recoil)- Term baby	Like term baby
Sole creases	<32 weeks- No creases 32–34 weeks → Anterior one third + middle one third of sole >36 weeks → Full creases	Full creases
Breast buds	Less developed	Well developed
Labia majora	Widely separated	Normal
Scrotal rugae	<32 weeks—No rugae >32 weeks—rugae develop gradually	Normal rugae
Abdomen	Distended with visible coils of intestine (gut pattern)	Usually like that of normal term baby

Table 18: Normal growth of fetus

Age of fetus		
In weeks	**Length (cm)**	**Weight (g)**
12	10	
16	19	
20	23	400
24	30	700
28	36	1,100
32	40	1,650
36	43	2,600
40	46	3,000

- Fetus should be intrinsically normal, e.g. normal genetic potential for growth
- Absence of congenital malformations
- Absence of nonbacterial intrauterine infection
- Normal maternal: fetal-placental unit.

Abnormal intrauterine growth starts either early in gestation or later half of gestation.

Early IUGR

First trimester—Common causes are:

- Congenital malformations (chromosomal, e.g. trisomies or non-chromosomal abnormalities, e.g. syndrome complexes, radiations, etc.)
- Chronic non-bacterial intrauterine infections, e.g. rubella, syphilis, cytomegalovirus.

It leads to symmetrical growth retardation (hypoplastic).

Postnatally these infants show:

- Universally diminutive size—head, length, weight reduced proportionally
- Subcutaneous fat is appropriate for age
- Normal hematocrit value
- Congenital malformation or nonbacterial infections are common
- Hypoglycemia, hypoproteinemia (uncommon).

Growth Retardation in Later Half (Late IUGR—3rd Trimester) is due to:

- Maternal diseases:
  - Toxemia of pregnancy
  - Hypertension, renal disease
  - Diabetes
  - Hypoxemia (heart/lungs cause)
  - Malnutrition/chronic illness.
- Placental insufficiency leading to diminished substrate (nutrient) availability.
- Maternal drugs (narcotics, alcohol, antimetabolites) and habits (smoking, cigarettes, alcohol, cocaine).

It leads to asymmetrical growth retardation.

Postnatally these infants show:

- Disproportionately reduce size. Weight is affected more than length and head size (large head)
- Loss of subcutaneous fat
- High hematocrit value
- Congenital malformations and intrauterine infection.

Normal Birthweight IUGR and Its Possible Risk

Although LBW is usually associated with IUGR, a newborn whose birthweight is within normal range may have IUGR. Birthweight is not always an indicator of IUGR and therefore in such circumstances (normal birthweight IUGR) counseling to parents for possible risk of IUGR in later life is difficult. It is difficult to know weight of a baby at birth according to age of gestation. A 3,500 g birthweight baby who should have weighed 4,000 g due to its genetic growth potential with well built parents is just as growth retarded as 2,300 g baby who should have weighed 2,800 g. Both such babies have similar cardiovascular and other health risk at later adult life. These features are difficult to know but can be suspected from growth and birthweight of other siblings and growth pattern of parents.

RISK OF PRETERM LBW BABIES

Various complications occur at various stages of life which consist of immediate, intermediate, late and problem affecting adult health (Table 19).

Immediate Problems

- Feeding problem
- Respiratory distress syndrome (RDS), Apoea, Transient tachypnea of newborn (TTN), pneumothorax, sepsis, Persistent ductus arteriosus (PDA), Necrotizing enterocolitis (NEC), Intraventricular hemorrhage (IVH), Periventricular leukomalacia (PVL)
- Hypoglycemia, hypothermia, jaundice of prematurity
- Vitamin K deficiency bleeding (VKDB)
- Polycythemia with hyperviscosity syndrome
- Meconium aspiration (IUGR and post-term babies).

Intermediate Problems

- Retinopathy of prematurity
- Osteopenia of prematurity
- Anemia of prematurity.

Late Complications

- Growth problem (more associated with IUGR)
- Neurodevelopmental disorder
  - Cerebral palsy (Cerebral diplegia), developmental delay, cognitive and learning difficulty. Behavioral disorder [Attention deficit hyperactivity disorder (ADHD)]
  - Premature adrenarche.

Problem Affecting Adult Health

- Chronic non-communicable/degenerative disorder in adult life
  - Cardiovascular: Coronary heart disease, hypertension, cerebrovascular accident (stroke)
  - Type-II diabetes
  - Dyslipidemia
  - Premature adrenarche.

Table 19: Problems and prognosis of preterm LBW and IUGR

Problems	Preterm	IUGR
1. Intrauterine hypoxia	+	++
2. Respiratory problems		
a. RDS	++	0
b. Apneic spells	++	+
c. Meconium aspiration	0	+
d. Birth asphyxia	+	+
3. Feeding problem		
a. Inability to suck and swallow	++	0
b. Aspiration of feed	++	0
4. Hypoglycemia	+	+
5. Hypothermia	++	+
6. Hyperbilirubinemia	++	+
7. Anemia of prematurity	+	0
8. Liabilities of infection	+	+
9. Necrotizing enterocolitis	+	0
10. Hemorrhage		
a. Intraventricular	++	0
b. Pulmonary	+	++
11. Prognosis		
a. Immediate	High mortality	Better prognosis
b. Intermediate and later childhood (ROP, osteopenia, anemia, cerebral palsy, etc.)	More commonly associated	Not commonly associated
c. Late—future physical growth and adult health	Good—if no perinatal complication develop	Poor in hypoplastic baby, poor postnatal growth with later adult health problem

Abbreviations: LBW: low birth weight, IUGR: intrauterine growth restriction, RDS: Respiratory distress syndrome, ROP: Respiratory of prematurity

Fig. 63: Normal pinkish appearance neonate.

Fig. 65: IUGR with asymmetric growth retardation with relatively large head baby (late trimester IUGR)

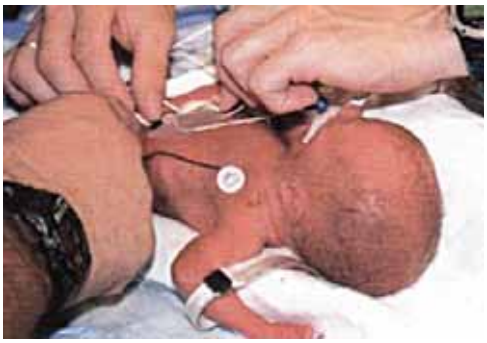


Fig. 64: Preterm baby with reddish color and dolichocephalic head

Fig. 66: IUGR with symmetric growth retardation with microcephaly due to congenital CMV infection (early trimester IUGR)

Fig. 67: IUGR in a smaller of the discordant twin (multiple pregnancy as a cause of LBW)

Factors that affects birthweight

- Genetic
- Maternal and environmental:
  - General maternal environment
  - Immediate maternal environment
  - Maternal age and parity
  - Multiple pregnancy (Fig. 67)
- Social: Social gradient in birthweight.

Genetic

- Parental (polygenic)
- Fetal gene [insulin like growth factor-I (IGF-I, IGF-II)]
- Chromosomal: Down syndrome, Turner syndrome.

There is significant correlation between parenteral birthweight and birthweight of index case. Genetic influence of maternal birthweight is more than paternal birthweight.

Fetal Gene

- Fetal IGF-I, IGF-II, IGF receptor type-I, and insulin and insulin receptor substrate resistance are responsible for fetal growth
- IGF-I gene defect (delation of exon 4 and 5 of IGF-I) associated with IUGR
- Placental gene: Placental genes are genetically identical with fetus. However, up to 20% of idiopathic IUGR term babies show placental mosaicism, which affects fetal growth in yet unexplained way.

Maternal and Environmental Factors

Maternal nutrition: Maternal nutrition encompasses the complete supply line of maternal intake, circulatory concentration of nutrients, uteroplacental blood flow and nutrient transfer across placenta. Therefore, maternal nutrition comprises of maternal nutrients and net fetal substrate supply.

Maternal Nutrient Proper Consist of:

- Maternal nutrition in childhood
- Maternal nutrition during pregnancy.

Fetal Substrate Supply Depends on:

- Uteroplacental blood flow
- Nutrient supply across placenta
- Maternal smoking
- Pre-eclampsia
- Maternal diseases (obstetrical, respiratory, cardiac, renal, collagen, etc.)
- Placental anomalies
- Twin-to-twin transfer syndrome
- Infectious diseases (TORCH, malaria, etc.)
- IGF-I.

Maternal Nutrition in Childhood

The effect of maternal nutrition during pregnancy alone is not sufficient to influence the weight of the fetus. Nutrition will also exert its effect on birthweight over longer period through effect on maternal growth in childhood. Maternal height is an important determinant of birthweight. Girls in rural developing countries are more neglected and nutritionally deprived. It has been found that in developing countries generally a female child receives less protein per day in comparison to the male child.

MATERNAL NUTRITION DURING PREGNANCY

Maternal Nutrition as a Determinant of Birthweight

Maternal nutrition has a dominant influence on IGF-I concentration prenatally and there is a positive correlation between birthweight and IGF-I.

Two different adverse effects on fetus that occur in two different stages of maternal nutrition deficiency are:

a. Late maternal nutrition deficiency
b. Early maternal nutrition deficiency.

Late Maternal Nutrition Deficiency

The effect of severe macronutrient defect depends on stage of gestation. Macronutrient deficiency in later pregnancy is expected to exert the greatest impact on birthweight, the human fetus weighs only 20% of term weight at 24 weeks. Micronutrient supplements with folic acid-iron have been found to be associated with increase in birthweight in Nepal.

EFFECT OF EARLY MATERNAL NUTRITION RESTRICTION: NUTRITION PROGRAMMING AND ITS EFFECT ON LATER ADULT LIFE

LBW, Glucocorticoid Excess and Type-II Diabetes, Hyperlipidemia and Hypertension

Although severe macronutrient deficiency in later pregnancy exerts its greatest effect on birthweight, nutrient deficiency in early pregnancy has the significance that it is associated with adult health disorder, particularly with later development of chronic non-communicable or degenerative diseases. Nutritional deprivation redistributes maternal cardiac output away from uterus. Fetus as a result undergoes chronic stress response. Due to nutrient-deprived stress both maternal and fetal glucocorticoid increase. Effects of fetus on over exposure to excess maternal and fetal glucocorticoid persist in postnatal life, later adolescent and adult life. It appears that earlier maternal nutrient restriction, which is frequently found in developing countries, increases placental size and alters the expression of genes regulating the glucocorticoids and renin-angiotensin system. This effect may be manifested later in adult life as type-II diabetes, hyperlipidemia and hypertension.

LBW, Cardiometabolic Risk and Nonmetabolic (Anatomical) Coronary Heart Disease

Cardiometabolic risk factor in later postnatal life in ex-LBW individual occurs due to increased insulin resistance, increased waist circumference during catch-up growth in the first two years of life. Increased insulin resistance is considered as an independent cardiometabolic risk factor of LBW and later cardiovascular disease in adult life.

Under programming hypothesis fetus also primarily undergoes adaptation. Under programming hypothesis, fetus under adverse condition of undernutrition and hypoxia, adjusts itself by reducing fetal growth. However, such adaptation is associated with pathophysiological changes in various system of fetus that may lead to detrimental effects in postnatal life. Modifications of structures of large conduit arteries take place in order to maintain fetal circulation, which may lead to blood vessels that are less compliant in later adult life. Coronary arteries are also similarly affected with higher death rate from coronary heart diseases.

The increased preponderance of IUGR and LBW babies in developing countries are associated with increase risk of death from ischemic heart diseases. An association of 45% excess of death from cardiovascular diseases observed in Bangladeshis, Pakistanis and Indians living in UK has been found to be attributable to growth retardation during fetal life.

Effect of Risk of IUGR on Individual and Community

Risk of later degenerative diseases may not be significant individually in some circumstances, but it may have significant effect on community leading to public health problem. For example, if birthweight is 500 g less it may be associated with only 1–2 mm Hg increase in individual systemic pressure. However, together with other ex-IUGR it contributes to increase in mean population blood pressure in the community, thereby increasing the incidence of risk of stroke in the population significantly.

Association of Pattern of Postnatal Growth and Cardiovascular Risk in Ex-IUGR

Recent research has focused on the extent to which postnatal growth can modify or add to the risk established in utero. Excessive weight gain during postnatal life was initially thought to be only associated with increased cardiovascular risk. However, currently both excessive weight gain and poor infant growth are thought to be associated with increased risk. Promotion of normal infant growth and avoidance of obesity should be advised to parents for immediate and long term health benefit of their ex-LBW children associated with IUGR in particular.

LBW and Premature Adrenarche

LBW has been found to have increased association with premature adrenarche (appearance of secondary sexual hair in girl and boys below 8 and 9 years, respectively), particularly in girls. It, however, varies in different population. Marked association has been found in ex-LBW girls of Caribbean Hispanic and African American girls in United States. Here also insulin resistance in ex-LBW girls found to primary feature, which links premature adrenarche. Increased insulin associated with increased insulin resistance syndrome exerts as stimulant of zona reticularies of adrenal glands, which secretes adrenal androgens.

ENVIRONMENTAL FACTORS ASSOCIATED WITH LBW

Birthweight varies within genetically similar population suggesting that environmental factor play a significant role. Secular changes in birthweight suggest and environmental influence.

Environmental and Social Factors

- Maternal nutrition current and during childhood (discussed before)
- Maternal ill health
- Maternal smoking
- Low maternal age
- Multiple pregnancies with decreasing spacing.

Social Ingredients and Inequality

32% or greater than 32% of birthweight in a country of less than 2,500 g at birth is a serious social inequality. This inequality negatively affects the birthweight. In a published study, it has been shown that the top inequality pattern is in the sector of anteratal care and skilled delivery. Social inequality not only affects birthweight but also negatively affects neonatal and infant mortality which may hinder to achieve MDG goal-4 by 2015.

The social gradient in birthweight probably arises as a result of accumulation and addition of risk and protective factors overtime and across generation rather than resulting from risk exposures within the index pregnancy. Poor socioeconomic circumstances in early life may lead to biological vulnerability in later life and adult health behaviors seem to have socio-economic roots early in life.

MANAGEMENT OF PRETERM LBW BABIES AND IUGR

- Management consists of broad based strategy to reduce incidence of preterm LBW and IUGR babies in developing countries by intervention targeting social inequality (social ingredient intervention)
- Identification and prevention in woman at risk of delivering LBW, IUGR baby
- Identification and prevention of fetal risk factor of IUGR and LBW.

Social Ingredient Intervention

Interventions to improve birthweight in disadvantages groups have been largely unsuccessful and although mean birthweight of many developing countries has increased, but the rate of change is slow and the gradient remains unchanged. In general, most government and international organizations have shaped health interventions programs based on national or regional averages of health outcomes, programs have not been designed to explicitly influence within community inequities.

Equity among populations especially those consistent with goals of proverty reduction needs to be improved. Targeting appropriate and tailor-made health intervention to poor people

as well as steps to establish universal coverage of health and nutrition is needed, if improvement of neonatal health which include birthweight as well as more child survival are to be seen.

Prevention of Prematurity (Decrease Gestational Period) and Management of Preterm Labor

Preterm delivery is not only associated with LBW babies, but also associated with immediate and long-term complications like cerebral palsy, neurodevelopmental delay and chronic lung diseases.

It is, therefore, important to prevent prematurity and preterm labor by identifying and preventing risk factor in pregnant woman and in fetus.

Identification and Prevention in Women at Risk

- Previous history of preterm delivery
- A positive swab for vaginal fetal fibronectin (second and third trimester)
- Short cervical length
- Screening for bacterial vaginosis
- Maternal progesterone deficiency.

Previous History of Preterm Delivery

It is a single greatest risk factor of preterm labor, but cannot be predicted in first pregnancy.

Positive Swab for Fetal Fibronectin

A positive swab for vaginal fetal fibronectin taken in second or early third trimester increases the likelyhood of delivery before 34 weeks. A positive test is also helpful for subsequent preterm delivery.

Short Cervical Length

Ultrasound screening for short cervical length is determined as risk pregnancy for premature delivery. The rate of preterm delivery in 32 weeks is high (>75%) if cervical length is <5 mm, whereas it is less (1%) if cervical length is 25 mm.

Mean cervical length is shorter in woman with a history of preterm delivery.

Cervical Cerclage

Elective cerclage may be indicated when there is a congenital or acquired weakness in the cervix that increases the risk of miscarriage or preterm delivery. The diagnosis of cervical weakness can be made on clinical symptoms, e.g. usually painless dilation of the cervix or spontaneous rupture of membranes before the onset of labor in late second or early third trimester.

Screening and Treatment of Bacterial Vaginosis

Bacterial vaginosis is a polymicrobial condition associated with preterm delivery. High risk woman (history of or symptoms of bacterial vaginosis) should be screened (culture of vaginal swab) for bacterial vaginosis.

Treatment: All positive diagnosis women should be given systemic metronidazole. Currently topical clindamycin is considered as first drug of choice.

Progesterone Prophylaxis

Progesterone promotes pregnancy and therefore administration of progesterone for prevention of preterm delivery makes a sense. Both 17α-hydroxyprogesterone (17OH) and natural vaginal progesterone reduce the risk of preterm delivery. In high risk women intramuscular 17OH may produce significant decrease of preterm delivery and reduction of birthweight less than 2,500 g. However, routine use of progesterone prophylaxis requires further evidence for routine practice.

Management of Preterm Labor

Delivery can be delayed to increase gestational age to facilitate fetus attain birthweight after considering pros and cons of delaying delivery. Woman admitted in threatened preterm labor should be appropriately assessed to determine the optimal time of delivery. While significant benefit can be obtained by prolonging gestational age in uncomplicated preterm labor with intact membrane, presence of fetal compromise can danger prolonging the pregnancy.

Pharmacological Treatment to Prevent Preterm Labor and Prolonging Gestational Age

Tocolytics, antibiotics and steroids.

Aim of Treatment to Delay Preterm Delivery

- Increase duration of gestational age to improve neonatal or infant outcome
- To get enough time to administer antenatal steroid to reduce incidence of RDS, IVH and perinatal death
- To get enough time to transfer mother to an appropriate referral hospital.

Tocolysis

Tocolysis is likely to be beneficial in uncomplicated preterm labor.

Drugs used: Nifedipine, Indomethacin, Atosiban, Ritordrine.

Nifedipine: Nifedipine prevents the calcium influx critical for myometrial cell contraction. It has been found superior to ritordrine for neonatal outcome. If preterm labor continuous, a second drugs like indomethacin an effective tocolytic may be added as a rescue drugs.

Atosiban: Atosiban is an analogue of oxytocin that inhibits activity at oxytocin and vasopressin receptors. Oxytocin level is increased at onset of labor and it seems logical to use atosiban to prevent uterine contraction during preterm labor.

Ritordrine: Ritordrine was previously used as tocolytic of choice. Recent tocholytics have been found superior to ritordrine.

Antibiotics

Preterm delivery is often associated with chorioamnionitis. However, currently antibiotic cannot be justified for treatment of preterm labor in the absence of premature rupture of membrane. Erythromycin is the first choice antibiotic, which is associated with prolongation of pregnancy and improved neonatal outcome.

Steroids

There is a good evidence suggesting the use of antenatal steroids who have threatened preterm labor, where it is associated

with reduce incidence of RDS, IVH, PVL and perinatal death. Single dose of intramuscular betamethasone should be given to almost all mothers in threatened preterm labor. Instead of betamethasone intramuscular dexamethasone can be used.

ASSESSMENT OF FETAL RISK FACTOR OF IUGR AND LBW

The clinician should identify fetus at risk of IUGR due to adverse uterine environment and intervene properly by correcting remediable causes. Diagnosis of LBW (IUGR) can be made from history, clinical examination and appropriate investigations.

Investigation

- Ultrasound (USD) in early pregnancy for crown-rump length (CRL)
- Serial ultrasound for fetal growth, second and third trimester
- USD for fundal height.

Doppler Velocimetry

- Doppler USD to measure umbilical artery (UA) diastolic flow
- Umbilical artery systolic diastolic flow ratio (UA PI Index).

Assessment of Amniotic Fluid Index

- There is strong association between oligohydramnios and markedly increase risk of growth restricted fetus and increase perinatal mortality
- Amniotic fluid index (AFI) less than 5 cm is alarming, while normal AFI is reassuring
- Once IUGR has been detected, the management should depend on a surveillance plan that maximizes gestational age, while minimizing the risk of neonatal mortality and morbidity. Correction of remediable causes like avoidance of smoking, alcohol consumption, substance use, avoidance of stress, nutritional therapy by dietary intervention and supplementation when indicated should be taken.

SPECIAL CARE FOR PRETERM LBW (VLBW)

PREVENTION OF INFECTION

- Wash hands with soap and water before touching the baby
- Dry the hands with a clean towel before handling each baby
- Minimum handling
- Avoid over crowding
- Aseptic technique for all sorts of procedure
- Skin care to maintain integrity of the skin.

KEEPING THE BABY WARM

- Baby should be wrapped well and the room should be kept warm. A cap on the head and socks for hands and feet should be used to keep the baby warm. Warmers can be used or hot water bottles covered with linens can be kept near the baby (not direct contact) to keep the baby warm
- By keeping the baby in incubator
- By using radiant warmer
- Using of thin transparent plastic barrier may be fixed to supporting walls of radiant warmer (this will increase local humidity and limit air movement and thereby decrease insensible water loss without interfering thermo neutral environment)
- Kangaroo mother care: It is a skin-to-skin care particularly useful for LBW infant below 2,000 g.

Fig. 68: Kangaroo mother care

Procedure of KMC (Fig. 68)

- The baby should be placed between the mother's breast in an upright position
- Baby's head on either side of mother's chin
- Baby's abdomen should be somewhere at the level of the mother's epigastrium.

Advantages of KMC

- Cheap and easily available
- Thermal control and metabolism
- Improve breastfeeding
- Increase mother bond and keeps into increase oxytocin secretion
- Thermal control much more safe and reduces risk of hypothermia.

EARLY IDENTIFICATION AND TREATMENT OF COMPLICATION

Apnea, respiratory distress, jaundice, NEC, hypoglycemia, hypocalcaemia, etc. should be treated accordingly (Discussed later).

FLUID AND ELECTROLYTE MANAGEMENT (TABLE 20)

Insensible loss is higher in preterm infants due to thinness of the skin, respiratory distress, use of radiant warmer, etc. As the skin matures in a preterm baby insensible loss decreases and become similar to a term baby by the end of first week. In extreme LBW babies there is variable insulin response and persistent endogenous hepatic glucose production. So administration of 10% dextrose to these babies will produce an excessive glucose load.

FEEDING MANAGEMENT (TABLE 21)

Coordinated sucking, swallowing, breathing occurs after 34 weeks of gestation. At about 32–34 weeks of gestation the neonates are in a position to swallow the feeds satisfactorily, but may not sucking and swallowing may not be coordinate. Whenever possible enteral route is preferred. Because enteral feeding is generally safer, less expensive and more nutritionally complete. Moreover lack of enteral feeding can lead to intestinal mucosal atrophy. We encourage starting

Table 20: Guidelines for fluid and electrolyte management

Birthweight	Age	Amount (mL/kg/day)	Type of fluid
<1,000 g	<24 hours	80	5% DA
	24–48 hours	100	5% Dextrose in 0.225% normal saline
	48–72 hours	120	10% Dextrose in 0.225% normal saline
1,000−1,500 g	<24 hours	80	10% DA
	24–48 hours	95	10% Dextrose ¼ normal saline
	48–72 hours	110	10% Dextrose ¼ normal saline
>1,500 g	<24 hours	60	10% DA
	24–48 hours	75	10% Dextrose in 1/4th normal saline
	48–72 hours	90	10% Dextrose in 1/4th normal saline

Note:
1. Daily requirement of fluid for normal term newborns starts with 60 mL/kg and for low birthweight it can be started with 80-100 mL/kg/day
2. Normal increment in fluid requirement in normal weight babies is 20 mL/kg/day and in low birthweight babies it is 15 mL/kg/day. In low birthweight babies amount of fluid can be raised upto 200 mL/kg/day by 14 days and 180 mL/kg/day by day 10
3. Babies receiving phototherapy will need 10−15 mL/kg/day extra fluid daily
4. Conditions to decrease fluid- perinatal asphyxia, neonatal sepsis, NEC, cardiac failure, renal failure (fluid restricted to 2/3 of maintenance)
5. These are general guidelines but fluid demand should be individualized according to other associated condition

Table 21: Modes of providing fluid and feeding

Weight Age	<1,200 g <30 weeks	1,200−1,500 g 30−32 weeks	1,501 to 1,800 g 32−34 weeks	>1,800 g >34 weeks
Initial	IV fluid	IV fluid	Cup/spoon feeding	Breastfeeding, if unsatisfactory feeding with small spoon
After 3−4 days	NG tube feeding gradually	NG tube feeding	Breastfeeding gradually- if unsatisfactory feeding with small spoon	Breastfeeding
Later	Breastfeeding, if unsatisfactory feeding with small spoon	Breastfeeding, if unsatisfactory feeding with small spoon	Breastfeeding	Breastfeeding

Note:
- When the baby is on NG tube feeding or feeding on spoon, it is important to put the baby on the breast before feeding. It will enable the baby to learn how to suck and promote lactation.
- Shifting from one mode of feeding to another should be slowly and then build up gradually

low volume "trophic feeding" for a stable neonate and then gradual cautious increment. As Vit-K is synthesized in the gut bacteria and establishment of gut bacteria depends on enteral feeding. So Vit-K should be supplemented weekly before full establishment of enteral feeding.

Feeding Problem in Preterm LBW and Role of Speech and Language Therapy

Feeding difficulties due to poor sucking and aversion are frequently associated with preterm neonates. Expressed breastfeeding may have to be given by nasogastric tube in significant oral feeding problem particularly in extreme preterm baby. Feeding difficulties may cause chocking and milk aspiration pneumonitis.

Role of speech and language therapy in feeding difficulties associated with preterm neonates: Speech and language therapist are not only involved in the management of speech and language disorder in children, but also take part in improving feeding problems in neonate particularly in preterm neonates. The role in neonate is twofolds:

1. To ascertain the safety of the suck-swallow- breathing mechanism, which is essential for safe and productive feeding
2. To promote background of early interaction developing

Speech and language therapy at neonatal period also improve non-nutritive sucking as part of their program which increases intestinal transit time, improve weight, improve oxygen saturation and reduces overall hospital stay. It also reduces negative feeding behavior and improve mother-child bonding.

Total Parental Nutrition (TPN)

Rarely and extreme preterm LBW neonate TPN may be required.

Monitoring Blood Sugar

Done by heel pricking using a glucometer. If it is below 2.5 mmol/liter, it should be corrected by IV 10% dextrose (2–4 mL/kg) bolus, if needed maintenance 4–6 mg/kg/min (Discussed in detail in Hypoglycemia chapter).

PROPHYLAXIS WITH VITAMIN K1

It is given 2 mg orally or 1 mg IM/IV once at birth. If given orally a second and third dose of 2 mg should be given at 1 week and at 4–6 weeks respectively (particularly in breastfeed babies).

VITAMINS AND MICRONUTRIENT SUPPLEMENTATION

Multivitamin and folic acid from second week and iron from the age of 4–6 weeks.

KEEPING DAILY WEIGHT CHART

Up to 10% weight loss is normal in first week of life.

REGULAR AND CAREFUL FOLLOW-UP

Watch for any complications and prompt treatment, if present.

Management of Jaundice (Discussed More in Neonatal Jaundice Chapter)

Up to 60% of term and up to 80% of preterm babies develop jaundice during first week of life. Although most of the neonatal jaundice are physiological but it should be always special attention because of the serious toxic effect of unconjugated bilirubin to the brain (kernicterus). Jaundice appears at first 24 hours of life is always pathological and requires evaluation.

Dermal staining of bilirubin may be used as a clinical guide to the level of jaundice (Table 22).

Treatment Options

- In most physiological jaundice spontaneous recovery is usual within 7–10 days
- Explanation and reassurance of parents

Table 22: Guide to dermal staining with the level of bilirubin

Area of body	Level of bilirubin (mg/dL)
• Face	4–6
• Chest, upper abdomen	8–10
• Lower abdomen, thigh	12–14
• Arms, lower leg	15–18
• Palms, soles	15–20

- Ensure exclusive and frequent breastfeeding (feeding increased gut motility → increased gut flora → Bilirubin excretion). Lack of breastfeeding increased the duration of jaundice cure
- Give phototherapy if:
  - Term baby: Serum bilirubin ≥15 mg/dL
  - Preterm baby: Serum bilirubin ≥12 mg/dL
  - Extra fluid- 10–20 mL/kg- During phototherapy
- Exchange transfusion—When indicated (Table 23).

INITIAL MANAGEMENT OF THE EXTREMELY PRETERM INFANT

- This refers to the babies of less than 26 weeks gestation, i.e. near the limits of viability
- Senior input should always be available for these babies
- A detailed review of clinical circumstances leading to the premature birth should be made, and plans made in the light of this
- An experienced member of the team should speak to the parents before birth wherever possible to explain the possible outcomes and potential problems, and agree a plan of management
- Difficulties may occur when gestation is not accurately known.

Resuscitation at Birth

- Decisions regarding initiation and continuation of resuscitation should be made by experienced staff in consultation with parents
- An extremely preterm baby who is in poor condition at birth with a low heart rate, no respiratory effort ± severe bruising must already have suffered considerable hypoxic-ischemic insult, which is likely to have affected the fragile brain
- If the baby is apneic at birth, it is often reasonable to attempt lung inflation, with further management guided by heart rate response
- If there is no response to attempted lung inflation, cardiac resuscitation (i.e. cardiac massage and/or adrenaline)

Table 23: Indication of phototherapy and exchange transfusion in neonatal jaundice (Figures are serum bilirubin)

Age	Phototherapy				Exchange transfusion			
	Healthy term baby		Preterm or any risk factors		Healthy term baby		Preterm or any risk factors	
	mg/dl	µmol/L	mg/dl	Mmol/L	mg/dl	µmol/L	mg/dl	µmol/L
Day-1	Any visible jaundice				15	260	13	220
Day-2	15	260	13	220	25	425	15	260
Day-3	18	310	16	270	30	510	20	340
Day-4 and thereafter	20	340	17	290	30	510	20	340

(*Source*: Pocket book WHO, 2005)

Note:

a. Risk factor- include small size (less than 2.5 kg at birth or born before 37 weeks' gestation), hemolysis and sepsis.
b. Term babies- who are clinically jaundice before 24 hours are not considered healthy and require evaluation.
c. Exchange transfusion soon after birth is indicated if:
   Cord Hb level is <10 g/dL
   Cord bilirubin level is >5 mg/dL.
d. Subsequent exchange transfusion is indicated if:
   - Bilirubin- >10 mg/dL within 24 hours of age
   - Bilirubin- >15 mg/dL between 25–48 hours of age
   - Bilirubin- >20 mg/dL after 48 hours of age
   - Rate of rise of bilirubin is >5 mg/dL/day.

is unlikely to be helpful at these gestations and is not recommended
- Recent guidance from the British Association of Perinatal Medicine suggests the following approach:
  - <23+0 weeks—no active resuscitation
  - 23+0–23+6 weeks—resuscitate with lung inflation if parents agree, although a decision not to resuscitate is appropriate
  - 24+0–24+6 weeks—resuscitate with lung inflation initially, unless there is evidence of significant fetal compromise
  - ≥ 25+0 weeks—active resuscitation recommended
- If a decision has been made not to start or continue active resuscitation, full human care must continue until the baby dies
- The parents should be kept informed at all times.

Fluid Balance

- The skin of the less than 26 weeks newborn is unkeratinized and extremely thin, leading to massive evaporative water and heat loss
- To reduce loss of water and heat, the baby should be put in a plastic bag (or wrap) from birth without prior drying at least until on NICU
- Nurse babies in high humidity (about 90%) in a closed environment (usually a servo-controlled incubator). Humidity can be reduced after about a week.

Initial Respiratory Support

- Babies may have initial minimal ventilation ("honeymoon period"), but may still progress to severe chronic lung disease
- Oxygen tension should be tightly controlled, avoiding both hyperoxia and hypoxia. Start resuscitation in air
- Attention is increasingly focused on reducing the incidence and severity of chronic lung disease:
  - Early use of CPAP is increasingly used in even these most preterm babies
  - Monitoring and controlling tidal volumes in addition to ventilatory pressures.

Other Aspects of Initial Care on NICU

- Most babies will require insertion of arterial and central venous lines (e.g. umbilical)
- Babies should be handled as little as possible ("minimal handling")
- Initial cranial US should be performed within 4 hours.

Discharge from the Neonatal Unit

All babies being discharged (to home, postnatal ward, or another hospital or ward) will need the following:
- A thorough clinical examination with discharge weight and head circumference (plotted on their centile chart)
- A hand-held Child Health Record ("red book") with relevant sections completed
- Discharge summary completed, with a copy provided to parents.
- A copy should also be sent to GP, health visitor, community midwife, referring obstetricians and/or pediatricians
- Discharge medications prescribed
- Parents informed regarding follow-up arrangements
- General advice given to parents regarding how and when to seek medical advice if there are any concerns.

Additionally, in some babies, the following should be done/arranged as relevant:
- Cranial ultrasound
- Immunizations
- Hearing screening
- Screening for retinopathy of prematurity
- Hip US (e.g. if family history of CDH or breech delivery)
- Referral to appropriate services, such as physio and speech therapy
- Referral to other specialties, such as cardiology, orthopedics, plastics
- Teaching of basic resuscitation to parents.

Special Circumstances

- If the baby is discharged in home oxygen then the relevant equipment and safety measures should be in place with input from outreach or community nurses
- Consider any extra community support that may be required for vulnerable families, including referral to Social Services if required. If there are significant social concerns, a named social worker (if available) should be identified prior to discharge when such facilities are available
- Parents of babies with extra needs will need appropriate support and training prior to and after discharge, e.g.
  - Nasogastric or gastrostomy feeding
  - Tracheostomy (including skills in care and tracheostomy tube replacement)
- If babies are being discharged for palliative care, parents will need appropriate care and counselling prior to discharge, and community nurses and GP informed.

Follow-up

- If the admission is brief, many babies will not require specific neonatal or pediatric follow-up
- Very LBW and babies born significantly preterm should have regular follow-up designed to pick up developing problems:
  - Growth and feeding
  - Neurodevelopment
  - Other medical problems
- Babies less than 1,500 g or less than 32 weeks gestation should be followed up until at least 2 years corrected age with detailed developmental assessment.

Outcome after Preterm Birth (Table 24)

- Preterm birth is associated with increased mortality and morbidity compared with birth at term
- Adverse outcomes increase with increasing prematurity
- Outcome data must be interpreted with caution for many reasons, e.g.
  - Mortality at gestations more than 24 weeks has reduced over the last 10–15 years and there is a lag between this trend and publication of up-to-date data
  - Studies of outcome have shown significant variation even between developed countries

Table 24: Preterm birth survival rates and neurodevelopmental problems. Figures are for live births and are composites from the studies listed in references

Gestation	Survival	Neurodevelopmental problems	
		Cognitive delay	Cerebral palsy
22	<1%		
23	15–25%	75%	25%
24	35–50%	40–50%	15–20%
25	55–70%		
26	70–80%		
27	90%	30–40%	10–15%
28	95%		
29	>95%		
30	>97%	25–35%	5–10%
31	>98%		
32	≥98%		

(*Source*: Oxford handbook of neonatology, 2009)

  - At extremely low gestations, particularly less than 25 weeks, the practice of offering resuscitation and intensive care may vary
- Survival data will also be affected by the population studied, e.g. whether data includes all births including stillbirths, all live born babies or only babies admitted to NICU, and therefore not including babies who die on labor ward.
- Outcomes are better for girls, singletons, babies exposed to antenatal steroids and those of higher birthweight for gestation.

Neurodevelopmental Disability

- It include mild, moderate, and severe disability
- In addition to motor and cognitive deficits, preterm babies have increased incidence of visual and hearing deficits, communication disorders (e.g. autism) and behavioral problems (e.g. ADHD).

Other Long-term Outcomes

- Chronic lung disease:
- 3 out of 4 babies less than 26 weeks are still requiring oxygen at 36 weeks corrected age
  - Many require domiciliary oxygen, but most are out of oxygen by 1 year
  - Higher rates than the general population of re-admission for viral RTI (especially RSV), PICU admission, and mortality
  - Abnormalities on lung function testing persist for years
- Feeding and growth:
  - Feeding difficulties due to aversion may require speech therapy
  - Growth often remains poor following discharge.

LOW BIRTHWEIGHT SCENARIO AND ITS MANAGEMENT

STRATEGY TO IDENTIFY AND MANAGE PRETERM LBW BABY

Prematurity (<37 weeks gestation at birth) and/or IUGR are the two main causes of LBW especially in developing countries. Infants born with LBW (less than 2,500 g) are disadvantaged from the very beginning of their lives and have poor survival rate as most (85%) deliveries occur at home the exact prevalence of LBW is not known.

Major determinants of LBW in developing countries are maternal under nutrition, adolescent pregnancy, acute or chronic infections and malaria during pregnancy in endemic zones.

IUGR and preterm babies have to survive against a spectrum of risk conditions like birth asphyxia/respiratory distress syndrome, hypothermia, hypoglycemia, septicemia, hyperbilirubinemia, etc. As such the LBW neonate deserves special attention to prevent and manage the potential complications.

The strategy provides a series of interventions to improve identification and management of LBW neonates:

- Weighing all neonates at facility and community levels and identifying LBW neonates
- Managing LBW neonates at all levels as per approved guidelines
- Expanding education services for adolescent girls and mothers to reduce risks related to LBW
- Strengthening interventions that directly relate to risk factors for LBW throughout childhood, adolescence and reproductive life of a woman. These include nutrition supplements for high risk mothers, iron and/or folate for adolescent girls and mothers, and screening and management of bacteriuria
- Expanding focused nutritional interventions for vulnerable groups, especially in food insecure areas.

Management for LBW Neonates (Tables 25 to 28 and Flow Chart 3)

The strategic aims and guidelines for management of LBW are designed to improve the outcomes for LBW infants, by providing guidance for limiting risk factors for LBW, increasing attention to these higher risk infants and improving management of conditions that disproportionately affect LBW infants.

Table 25: Broad strategic actions by level of care	
Level	**Strategies**
At all levels	All newborn attendants should be trained on ENC including special care of LBW
Home and community level	• Weighing all neonates within 2−3 days
	• Raise awareness of risks for LBW, by expanding educational efforts for adolescent girls and pregnant women
	• Increase attendance at birth of a trained newborn care giver. Increase home visits by trained provider following delivery
Union and Sub-District	• Expand services provided to mothers that directly reduce risk of having a LBW infant
	• Increase community outreach and facility services designed to provide special care to LBW infants designed to reduce the risk of mortality
District level and above	• Support lower level workers by providing supervision to improve service delivery for LBW infants
	• Strengthen capacity for management of very LBW infants through improved facility care
Abbreviations: ENC: Essential newborn care; LBW, Low birthweight.	

Table 26: Guidelines for low birthweight interventions	
Interventions	**Guidelines and activities**
Weighing all neonates	• Include weighing of neonates for all early (within 72 hours) visits by CHWs and other health workers
	• All CHWs record birthweight, and age at which weight is taken
	• Salter or equivalent standard spring scale can be used
Identification and management of LBW neonates at all levels	• Increase the frequency of visits to identified LBW infants to 3 visits within 1st week of life (Day 1,3,7), followed by visits at approximately 14 and 28 days old
	• Management by level of care and severity of LBW (see below)
Expanding education services for adolescents and mothers to reduce the risks related to LBW	• Pre-pregnancy messages are provided by all levels of health workers
	• Education messages (and health curricula) for adolescent girls include information on the neonatal consequences of early or late pregnancy, high parity, short birth interval and other risk factors for LBW
	• Nutrition services to reduce maternal undernutrition expanded
	• Inclusion of LBW and IUGR in anti-smoking messages
Strengthening interventions for adolescents and mothers that directly relate to risk for LBW	• Focused ANC visits • Iron/folate for adolescent girls and pregnant women, screening of pregnant women for bacteriuria and treatment of positive cases per ANC guidelines
Expanding focused nutritional interventions for vulnerable groups, especially in food insecure areas	• Nutritional supplementation for selected high risk mothers
Note that mothers' assessment may be adequate to identify LBW in the absence of weighing	
Abbreviations: CHW: Community health worker, ANC: Antenatal care	

Table 27: Guidelines by level of care for low birthweight neonates	
Level of care	***Type of care guidelines***
Home and community level	Prevention of hypothermia: • Keep baby clean, dry and warm • Delay bathing • Practice skin-to-skin care, e.g. kangaroo mother care (KMC) and proper wrapping
	Feeding for stable LBW newborn (wt >1,800 g, >34 weeks): • Put baby on mother's breast immediately but not later than 1 hour of birth • Feed on demand (at least 8 times in 24 hours, day and night)
	Feeding for sick or smaller newborn: • Feeding expressed Breast milk by cup and spoon and if not possible refer • Refer to a facility with newborn services
	Prevention of infection: • Hand wash each time before touching the baby • Do not overcrowd baby's room • Minimum handling • Ensure exclusive breastfeeding • Healthy skin, cord and eye care

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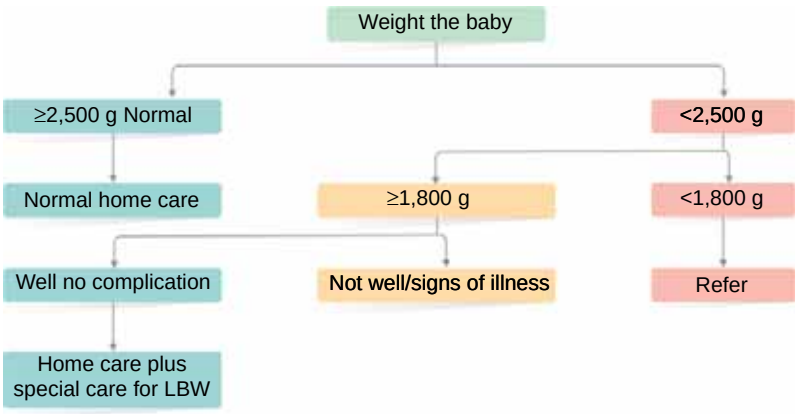
Level of care	***Type of care guidelines***
	Treatment of infection: • Minor infections (eye, skin, umbilicus) can be treated at home by local antiseptics/antibiotics • Appropriate referral for possible severe bacterial infections
Union level	Same as home level
Upazilla (sub-district) level	Prevention of hypothermia: • Baby should be dried and wrapped properly immediately after birth (for inborn babies) • More stable babies can be dressed in clothes and caps and covered with blankets • Keep the room warm with heater • Warm cot can be used • Skin-to-skin care (KMC)
	Feeding for stable LBW newborn (weight >1,800 g, >34 week): • Put to the breast immediately and no later than 1 hour after birth • Feed on demand (at least 8 times in 24 hours, day and night) • Feed breast milk by cup and spoon
	Feeding for sick or smaller newborn: • Nasogastric feeding with expressed breast milk. • NPO with intravenous fluid if abdominal distension exists • If above service is not available, refer to higher health facility
	IV fluid infusion (day 1-2): • Dextrose (5-10%) in aqua
	IV fluid infusion (>day 2): • Dextrose (5-10%) in 0.225% saline Above if service available, otherwise refer to higher health facility
	Prevention of infection: • Minimum handling • Follow strict aseptic techniques, especially hand washing, before handling the baby
	• Barrier nursing • Meticulous skin care • Early identification and treatment with antibiotic or refer to higher center/facility if not improving
	Treatment of infection: • Clinical monitoring and follow-up • Prompt treatment with injectable antibiotic if any one or more signs are detected, • Refer to higher center with first dose of antibiotic, if service is not available
District and tertiary care level	Prevention of hypothermia: • All measures of upazilla level plus • Use incubator when available, kept at an appropriate temperature (Usually 32−35°C with humidity 50%)
	Feeding for stable LBW newborn (weight >1,800 g, >34 week): • Put to the breast immediately and feed on demand • Feed breast milk by cup and spoon
	Feeding for sick or smaller newborn: • Feeding with breast milk (gradually increasing the volume) • Intravenous fluid (if needed keep neonate nothing per oral)
	IV fluid infusion (day 1-2): • Dextrose (5−10%) in aqua
	IV fluid infusion (>day 2): • Dextrose (5−10%) in 0.225% saline
	Prevention of infection: All measures of upazilla level plus • Early identification of infection and treatment of infection with antibiotic
	Treatment of infection: All measures of upazilla level plus • Prompt treatment with injectable antibiotic if any one or more of signs are detected

Table 28: Algorithm for follow up of LBW babies at home
i. A Normal, well and thriving baby is:
• Of good color (pink) • Breathing calmly and quiet (no severe chest in drawing, RR <60/min) • Suckling breast effectively • Empties bladder normally
• Moves bowels normally (0-several times per day, soft, no blood) • Not too hot, not too cold • Active • Looks happy and well
ii. Home care
• Hand washing each time before touching baby / clean mother / clean, warm and dry baby • Initiate breastfeeding immediately after birth and no later than 1 hour, ensure exclusive breastfeeding for 6 months • Skin-to-skin care (KMC) • Minimal handling • Do not overcrowd baby's room • Do not allow any infected/sick person in baby's room • Watch for signs of sickness/illness
iii. Not well/signs of illness/problems
• Color off, bluish, mottled, yellow, pale • Lethargic • Breathing fast or labored (severe chest indrawing and / or RR >60/min) • Reluctant to feed / no attachment at all / not suckling well • Vomiting • Urine not passed • Eyes with pus or discharge • Belly distended • Red skin around umbilical stump / foul smelling discharge • Many skin pustules, any large abscess • Too hot / cold skin (fever or hypothermia) • Obvious congenital anomaly present • Premature rupture of membrane (prom) >18 hours • Bad obstetric history (IUD, previous neonatal death, unexplained infant death) • Rh negative mother • Bleeding manifestation
iv. Special care for LBW:
• Home care, plus • Start following supplements at 2 weeks of age - Multivitamin pediatric drops - Folic acid - Iron pediatric drop • Give mother vitamins and extra nutritious foods (baby gets it through breast milk) • Help mother taking adequate rest, to take care of baby • Weigh baby and plot on chart monthly to follow if gaining weight satisfactorily
v. Refer:
• Give first dose of antibiotic for suspected sepsis • Contact the referral center beforehand if possible • Counsel parents/care giver how to keep baby warm and prevent low blood glucose on the way to referred center

Flow chart 3: Summarizes the algorithm for follow up of LBW babies at home



Evaluation of Preterm and Ex-Preterm

Clinical presentation: A stable premature from neonatal unit, stayed for a short/long period and about to be discharged.

Scientific Background

- Very LBW (<1,500 g) preterm infants survive with sequelae. The clinical examination should target suspect areas specific to such ex-preterm babies (Table 29).
- Suspect areas are:
  - Shape and size of the head which may be dolichocephalic in preterm (Fig. 69)
  - Proportionate short stature for the age
  - Cataract (Fig. 70)
  - Retinopathy of prematurity
  - Skin stigmata of congenital infection such as congenital rubella syndrome associated with low birth weight (Fig. 71)
  - Visual and auditory perception
    i. Chronic lung disease
  - Patent ductus arteriosus
  - Anemia of prematurity
  - Early signs of neurological sequelae
- Orthopedic deformity like talipes equinovarus (Fig. 72)
- Metabolic bone disease of prematurity (Fig. 73).

MORE SERIOUS IMMEDIATE COMPLICATIONS OF PRETERM LOW BIRTHWEIGHT

BRAIN INJURY IN PRETERM INFANTS

Definition

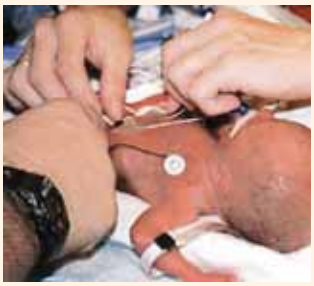
Spectrum of intracranial bleeds in preterm using cranial ultrasound and MRI.

General Matrix Hemorrhage—Intraventricular Hemorrhage (GMH-IVH)

Incidence

Incidence increases with decrease of prematurity and LBW. Affects approximately 10% of babies below 10 weeks gestation and 40% babies with weight <1,500 g may show evidence of IVH. Incidence is decreasing in western countries with increasing use of antenatal steroid, surfactant and regulation of hemodynamics.

Table 29: Key clinical features for presentation

Anthropometric measurement	Length, weight, head and chest circumference if on the lower side for the age suggests proportionate short stature
Vital parameter	Temperature, respiratory rate, heart rate
Skin	• Scarring of skin may be present at IV drip sites, trauma from heel pricks for blood sampling, dark complexion due to phototherapy • Thoracic scar of thoracocentesis for pneumothorax • Capillary hemangiomas occur more commonly in preterm babies
Size and shape of head	 **Fig. 69:** Dolichocephalic head in preterm • Most infants born before 32 weeks have a long, narrow head (scaphocephaly/ dolichocephaly) due to an initial inability to turn the head from side-to-side • Large head- hydrocephalus secondary to intraventricular hemorrhage • Small head- intrauterine non-bacterial infection, periventricular leukomalacia, cerebral atrophy
Oral cavity Visual auditory perception	• Palatal groove: prolonged endotracheal intubation may cause alteration in the shape of soft-palate called palatal groove  **Fig. 70:** Cataract • Retinopathy of some degree is common in very preterm babies • Cataract due intrauterine infections and retinopathy causes absence of red glow when light is directed at pupils • Hearing impairment is common due to prematurity or due to use of aminoglycosides for infection

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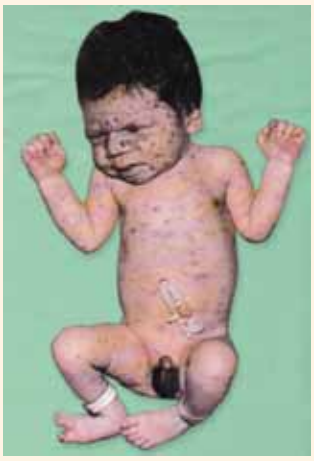
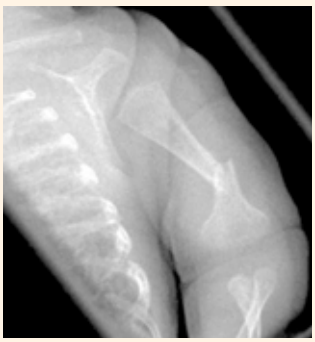
Pallor, purpura, echymosis (anemia of prematurity)	 **Fig. 71:** Purpuric rash in congenital rubella • Pallor is common due to frequent blood samplings, chronic infection during nursery stay, anemia of prematurity, iron deficiency • Thrombocytopenia is common in well or ill preterm babies and may be secondary to intrauterine or extrauterine infections
Look for talipes equinovarus (TEV) club foot	 **Fig. 72:** Talipes equinovarus • TEV is common in preterm male infants. Fixed structural deformity with involvement of forefoot and hind foot with wasting of calf muscles
Respiratory system	• Delayed pulmonary insufficiency of preterm infants—either due to ventilator induced lung injury (VILI), e.g. bronchopulmonary dysplasia or due to pulmonary immaturity, e.g. Wilson-Mikity syndrome is common. Also osteopenia of prematurity contributes to respiratory distress due to bony deformity of thoracic case. Preterm babies develop signs of tachypnea, subcostal recession, abdominal distension and slowness of feeds at times with cyanosis. Feed the child and look for breathlessness. If there is continued dyspnea, without being ill-think of BPD, anemia of prematurity, late metabolic acidosis of prematurity
CVS	• Inability to ductus closure due to increased prostaglandin levels presents with pansystolic murmur or continuous murmur with collapsing pulse and wide pulse pressure
Neurological assessment	• Muscle tone: Both postural and phasic tone should be assessed. Significantly low tone is suggestive of floppy baby
Look for signs of early cerebral palsy	• Gross motor status: – Head control is delayed – Abnormal fisting, if present open the palm and look for accumulation of dirt in palmar creases. Moist and pale skin is suggestive of abnormal clenching of the hands – Persistent ankle clonus and brisk jerks – Obligatory Moro's and asymmetric tonic neck reflex
Metabolic bone disease of prematurity (osteopenia of prematurity)	 **Fig. 73:** Fracture of humerus in osteopenia of prematurity

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	• The calcium and phosphorus accretion in fetal bones occurs in the last trimester. Calcium and phosphorus stores are inadequate in the preterm infants, that lead to metabolic bone disease, called osteopenia of prematurity not due vitamin D or PTH deficiency (discussed in later)
	• Low phosphate intake due to breastfeeding (breast milk contains less phosphorus), prolonged total parenteral nutrition, frequent infections are additional factors of diminished calcium- phosphorus supply
	• Clinically the metabolic bone disease is recognized by presence with bone deformity of thoracic case with beading, epiphyses thickening. Craniotabes may be occasionally present in ex-preterms. On biochemical examination alkaline phosphatase is significantly elevated which is the earliest evidence of osteopenia of prematurity. On X-ray there is osteopenia of the metaphyseal palate, but typical widening and flaring of metaphysis, characteristic of nutritional rickets are usually late sign of advanced case
	• The treatment is supplementation of oral phosphates and if calcium is very low, calcium also need to be supplemented

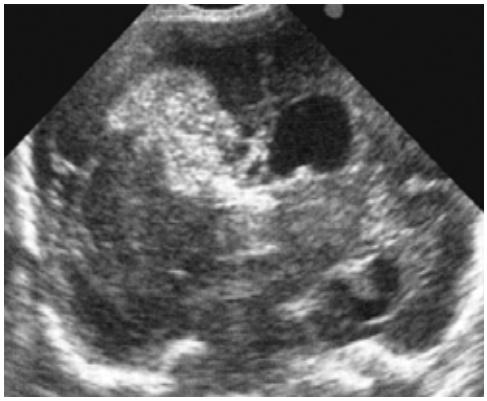


Fig. 74: Coronal ultrasound scan showing large right IVH with hemorrhagic parenchymal infarction

Grading of IVH (depending on extent of hemorrhage)

- Subependymal
- Intraventricular (IVH)
- IVH and ventricular dilatation (VD)
- Periventricular parenchymal extension with infarction

May be associated with cystic lesion, porencephalic cyst.

Anatomical Site Vulnerable for Hemorrhage

Bleeding occurs from fragile highly vascular subependymal germinal matrix that lies between caudate and thalamus. The site and extent of IVH can be seen by ultrasound scan of brain (Fig. 74). This area becomes more resistant to hemorrhage as gestation approaches term.

Critical Factors for IVH

- Loss of vascular autoregulation
- Blood pressure swing.

Clinical Features of IVH

Not present at birth but usually present in first 72 hours of life

- Fifty percent silent
- Apnea
- Pallor
- Shock
- Irritability
- Hypotonia.

Risk Factors of IVH

Maternal:

- Toxemia
- Diabetes
- Infection
- Multiparity
- Prolapsed cord
- Prolonged labor
- Abnormal presentation (breech).

Neonatal Risk (In addition to LBW/Prematurity)

- RDS
- PDA
- Pneumothorax
- Infection
- Convulsion.

Prevention

- Reduce the severity of respiratory distress associated with prematurity by antenatal steroid, early surfactant replacement in risk infant
- Avoid blood pressure swing by stabilizing BP and PCO_2
- Correct coagulopathy (Vit-K, fresh frozen plasma)
- Minimum handling of infant, minimal ETT suction
- Appropriate synchronized ventilation setting to prevent baby struggling with ventilator.

Treatment

Mostly supportive: Short-term treatment include:

- Stable the infant hemodynamically
- Transfuse blood to treat anemia
- If hypotensive start inotropes (dopamine)
- Coagulation screen: Administer FFP, Vit-K if indicated
- Control seizure
- Serial LP, remove 1-1.5 mL of CSF/kg, if little or no CSF is obtained obstructive hydrocephalous is likely, ventricular or reservoir tap and adjunctive treatment with frusemide or acetozolamide.

Serial cranial ultrasound to assess evolution of hemorrhage (weekly).

Complications of IVH

Immediate complication

- Hypovolemic shock
- Apnea

Intermediate complication

- Periventricular leukomalacia (PVL): Wide softening around ventricles (Fig. 75).

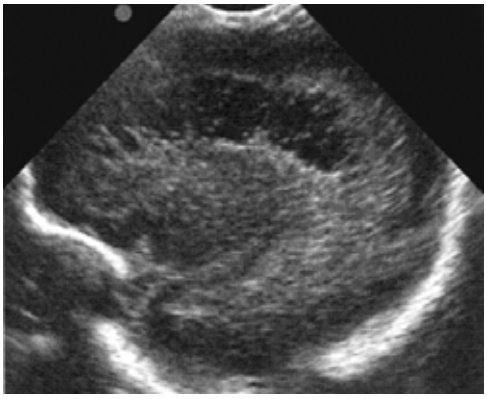


Fig. 75: Parasagittal ultrasonogram showing cystic lesions of PVL
Abbreviation: PVL, periventricular leukomalacia

Risk Factors of PVL

- Prematurity
- Infant with cardiorespiratory disturbance
- Grade-III, IV IVH

PVL is associated with later development of spastic diplegia.

Posthemorrhagic Ventricular Dilatation (PHVD)

Usually develops 2–3 weeks after IVH. Usually lead to hydrocephalus mostly associated with grade-III-IV IVH.

Assess speed of ventricular dilatation by serial weekly ultrasound. Perform LP to remove 1 to 1.5 mL/kg of CSF/day. Serial LP may be required

If dry LP consider obstructive hydrocephalus and liaise with neurosurgery to consider either ventricular tap, or management by reservoir. Ventricular shunt may required later.

Porencephalic Cyst

Associated with larger intraparenchymal hemorrhage with later formation of cyst with ventricular communication.

Indication for Neurosurgical Intervention

- Rapid progression with deterioration in clinical status
- Low progression refractory to temporary measures beyond 4 weeks.

Prognosis

- Good prognosis with small and moderate IVH (Grade-I, II)
- Large IVH (>50% ventricle) are associated with poor outcome with later development of neurodisability
- PHVD: Up to 30% developed significant hydrocephalus requiring shunt

PVL: PVL is associated with later CP (spastic diplegia).

PERSISTENT DUCTUS ARTERIOSUS IN PRETERM WITH OR WITHOUT RDS

Persistent ductus arteriosus is commonly found in a preterm baby due to abnormal metabolism of prostaglandins in preterm. PDA is more common in preterm associated with RDS with delayed closure of PDA. Low oxygen tension on ductal tissue, increase prostaglandins and acidosis contribute to delayed closure of PDA.

EFFECT OF PDA IN PRETERM

- Hypotension with myocardial ischemia (steal effect)
- Heart failure
- Intraventricular hemorrhage
- NEC
- Increase requirement for ventilation.

CLINICAL FEATURES

- RDS failing to improve or deteriorating at 1 week of age
- Evidence of poor perfusion: Tachycardia, dynamic precordium, high volume bounding pulse due to wide pulse pressure.

Heart Sound

- Gallop rhythm
- Murmur: Misleading and difficult to hear due to noisy breathing when associated with respiratory distress, may be initially not murmur heart as there may be delay in fall of pulmonary vascular resistance (PVR). Due to hypoxia associated with RDS with reverse (R → L) shunt
- As PVR falls reverse shunt decline
- As PVR start to fall initially only systolic murmur may be heard later continuous murmur heard at left sternal age.

Investigation

- ECG: LVH, less reliable
- Echocardiogram: >1.5 TDD is diagnostic
- Biochemical markers: β-type natriuretic peptide (BNP), Pro-BNP, serum cardiac troponin T (cTnT).

Significance of Biochemical Markers

- Raised biochemical are suggestive of hemodynamically significant PDA. Normal biochemical markers at 48 hours of life are associated with spontaneous closure of PDA
- There is increase association IVH-III and IV associated with PDA with high biochemical markers
- Echocardiography alone cannot identify the high risk PDA group. However, addition of biochemical markers can delineate infants with PDA and severe IVH/or death.

MANAGEMENT CONSIST OF NO TREATMENT, MEDICAL TREATMENT, SURGICAL TREATMENT

No treatment: Many asymptomatic preterm infant with PDA do not require any intervention during neonatal period.

Number of PDA may undergo spontaneous closure.

Medical treatment: Symptomatic PDA initially treated with fluid restriction, (130 mL/kg beyond 3rd day), correction of anemia and diuretic.

Drug Treatment

Prostaglandins Inhibitors (If Conservative Management Fails)

- Indomethacin IV 3 dosages of 0.2 mg/kg in 8–12 hours
- Ibuprofen IV 6 dosage 0.1 mg/kg 24 hour referred.

If the infant is on ventilation than adjustment of ventilation by reducing inspiratory time and giving more positive end expiratory pressure (PEEP).

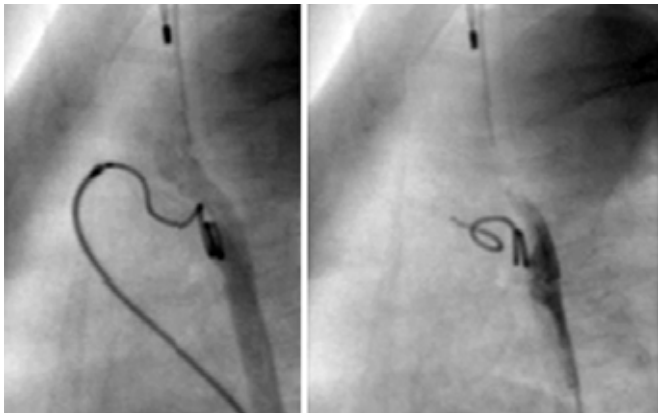


Fig. 76: Device closure of PDA. Aortograms before and after release of a coil in a 1.6 kg infant (*Reproduced from* Roberts P, et al. Arch Dis Child Fetal Neonatal Ed. 2007;92:F248-50.)

Surgical Closure

Surgical ligation of PDA is well tolerated procedure with low morbidity and mortality even in preterm babies.

Indication of Surgery

- Failure or relapse following 2 drug regimen of NSAID
- PDA remains hemodynamically significant.

Catheter Closure of PDA

Catheter closure is usually not practiced in newborn and early infancy. For avoidance of thoracotomy in infant with chronic lung disease, catheter closure of PDA in preterm is worthwhile (short surgical procedure) and considered where appropriate expertise is available (Fig. 76).

Closure in Asymptomatic Case

Catheter device closure in asymptomatic cases usually done at 1 year old when duct is large enough for device closure.

NECROTIZING ENTEROCOLITIS (NEC)

INTRODUCTION

It is the most common intestinal emergency in the NICU

- A disease primarily affecting bowel of mainly preterm of LBW infants with inflammation of bowel leading to necrosis and perforation of gut.

Actual cause is not known

- Characteristics features are abdominal distension lathargy, apnea, bilious, vomiting, gastric, aspirate, pneumatosis intestinalis and blood in stool (hematochezia).

EPIDEMIOLOGY

- Inversely proportional to birthweight and age of gestation. Approximately 10% occurs in extremely LBW infants (<1,000 g)
- Uncommon in term infant
- Despite advances in neonatal care, NEC incidence with its morbidity is not decreasing due to increase survival of LBW babies
- Male LBW babies are more affected
- Up to 50% require surgical intervention
- Mortality is 15–30% and is higher (up to 40%) in stage-III (Bells staging) and with surgical intervention
- Age of onset of NEC is directly related to birthweight and gestation age, preterm present at second and third week of life while term infants present in first few days of life.

ETIOLOGY AND PATHOGENESIS

Actual cause is not known.

The cause is multifactorial but prematurity is the only definite risk factor.

- Bowel ischemia
  - Hypoxia-ischemia—associated with IUGR, perinatal asphyxia
- The diving reflex → Redistribution of blood to vital organs (brain, heart) away from bowel
- Infection
- Formula feed instead of breast feed (immune immunological mechanism)
- Hypertonic feed
- Early enteral feeding (currently not evidence based)
- Rapid enteral feeding (currently contradictory evidence).

Bowel Ischemia

As mentioned above is the most favorite theory. In addition to conditions mentioned above other conditions associated with bowel ischemia are:

- Congenital anomaly of bowel (Hirschsprung disease)
- Anemia
- Hypotension
- Cardiac failure
- PDA
- High PCV (polycythemia)
- Exchange transfusion.

Infection

Triggering factors: *E.coli, klebsiella, enterobacter* and coagulase negative *Enterococcus* bacteria are usually involved. Up to 50% of infants with NEC will have positive blood culture.

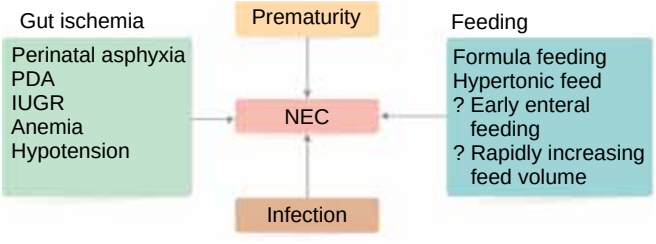
Fungal sepsis (nosocomial): Fungal sepsis is also implicated.

Immunological factors: Formula feed infants is more affected. Macrophage present in breast milk probably helps prevention of NEC.

In summary, for NEC (pathogenesis) to develop need: (Flow chart 4)

- Bowel ischemia (hypoxic ischemic condition)
- Abnormal colonization of gut
- Formula feeding.

Flow chart 4: Risk factors for necrotizing enterocolitis



EARLY FEEDING AND NEC

Early enteral feeding has been implicated in the pathogenesis of NEC and accordingly initiation of enteral feeding is often delayed for several days to weeks. However, recent evidences suggest early enteral feeding (starting on day-1 of life) is not associated with additional risk of NEC compared to late (2–5 days) starting of feed, rather early enteral feeding is associated with a reduced risk of nosocomial sepsis.

Feeding Volume and NEC

Aggressive feeding regimes have been implicated in the pathogenesis of NEC. However, there are conflicting evidences showing no additional risk of NEC with higher (30–35 mL/kg) feeding volume increments against smaller feeding (15 mL/kg) volume increment.

PATHOLOGY

The main histopathological lesion of NEC is coagulation necrosis and inflammation of gut. The usual anatomic site of lesion is ileocecal region. However all parts of intestine may be affected. Necrosis is out of proportion of inflammation.

The hallmark of the disease is pneumatosis intestinalis which occurs due to bacterial fermentation. Pneumatosis is located in the submucosal region and between muscle layers.

Bells Staging (Table 30)

Bells staging can be used to guide management. Stage-I suspected, Stage-II confirmed and Stage-III advanced.

Currently modified Bells staging is used to assess to severity of the disease more precisely.

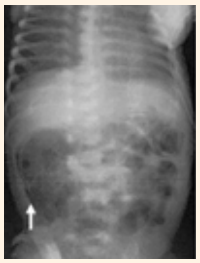
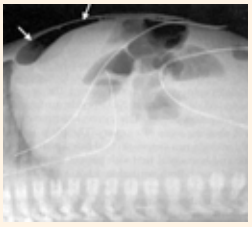
CLINICAL FEATURES OF NEC

- Onset is usually second or third week of life in preterm and first few days of life interms infants (uncommon in term infants)
- Onset may be rapid or insidious

Gastrointestinal Signs

- Abdominal distension
- Visible intestinal loops
- Decreased bowel sound
- Change in stool pattern

Table 30: Bells staging of NEC

Stages	Systemic signs	Intestinal signs	Radiographic signs
IA Suspected NEC	Temperature instability, apnea, bradycardia, lethargy	Gastric retention, abdominal distension, emesis, hemopositive stool	Normal or intestinal dilation, mild ileus
IB Suspected	Same as above	Grossly bloody stool	Same as above
IIA Definite, mildly ill	Same as above	Same as above, plus absent bowel sounds with or without abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis (Fig. 77)  **Fig. 77:** Pneumatosis intestinalis (Bells stage-IIA)
IIB Definite, moderately ill	Same as above, plus mild metabolic acidosis and thrombocytopenia	Same as above, plus absent bowel sounds, definite tenderness, with or without abdominal cellulitis or right lower quadrant mass	Same as IIA, plus ascites
IIIA Advanced, severely ill, intact bowel	Same as IIB, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, DIC, and neutropenia	Same as above, plus signs of peritonitis, marked tenderness, and abdominal distension	Same as IIA, plus ascites
IIIB Advanced, severely ill, perforated bowel	Same as IIIA	Same as IIIA	Same as above, plus pneumoperitoneum (Fig. 78)  **Fig. 78:** Pneumoperitoneum (Bells stage-III)

Hematochezia (Hemopositive Stool)

- Palpable abdominal mass
- Erythema of the abdominal wall.

Systemic Signs (One or More of the following)

- Decreased peripheral perfusion
- Circulatory collapse
- Respiratory failure.

DIFFERENTIAL DIAGNOSIS

- Sepsis with abdominal distension due to septic ileus.
  Point against primary sepsis. No pneumatosis intestinalis in septic ileus
- Inspissated meconium syndrome—may present with abdominal distension
  Points against these babies are presented with obstructed signs without evidence of sepsis.

INVESTIGATION

- FBC increased with shift to left
- Hb decreased
- CRP increased
- Serum electrolytes: Progressively worsens (hyponatremia)
- Blood gas: Metabolic (lactic) acidosis
- Test for occult blood: In stool and in aspirate occult blood test will be positive in NEC
- Blood culture: Up to 50% culture positive.

IMAGING

Plain Radiography

Bowel distension on plain abdominal radiograph. It is the earliest sign of NEC and precedes clinical signs of NEC. Asymmetric and persistent (fixed at one location) dilatation usually correlates with disease severity.

Pneumatosis Intestinalis

- This is the hallmark of diagnosis of NEC. However, unlike bowel distension its presence does not correlate with disease severity. Intramural gas is frequently seen in distal small bowel of abdomen. It is produced by fermentation of bacteria. It may appear as linear, curvilinear or cystic radiolucent area or soap bubble pattern in the intramural or subserosal area
- Gas may be seen in the portal venous system
- Free abdominal gas
- Free gas (pneumoperitoneum) is present if bowel perforation occurs. A lateral decubitus X-ray better delineates free gas if bowel perforation is suspected. On lateral view the free gas appear as a triangular lucency between loops of bowel anteriorly just beneath the abdominal wall.

MANAGEMENT

Medical Management

- Aim of medical management is to stabilized the infant and prevent further deterioration
- Stop feeding and decompressed the gut by nasogastric suction (10-12F tube)
- Monitor serum electrolytes, FBC, blood gas 6 hourly if unwell
- X-ray abdomen 12 hourly for 48 hours (perforation usually occurs within 1st 48 hours) then daily until improving
- Fluid resuscitation if hypovolemic as fluid is lost into the abdomen. Inotropes as needed
- Blood transfusion (red cells if anemic)
- If evidence of coagulopathy, fresh frozen plasma (FFP), platelet, cryoprecipitate may be indicated
- Most require mechanical ventilation (MV). Tracheal intubation and MV is preferred to CPAP to prevent aerophagia and greater bowel distension
- Start antibiotic therapy guided by pattern of resistance in the individual unit. Broad spectrum antibiotic cover. Empirical treatment with third generation cephalosporin antibiotic or Ampicillin/Amoxicillin and Gentamycin. Anaerobic cover with Metronidazole may be necessary. Antifungal like Amphotericin is recommended in vulnerable infants receiving broad spectrum antibiotic and with long lines like percutaneously inserted central lines (PICL)
- Probiotics may be tried to prevent disease progression from stage-I to II or greater
- Remove umbilical artery catheter in confirmed cases
- Restart feeding if the disease stabilizes. Re-feeding is done in most centers after 7/14 days with stage-II/III disease respectively. When feeding is resumed, breast milk is preferably given and advanced slowly. If there is recurrence of features of NEC stop feeding again
- If there is a recurrence intolerance to feed then an oral contrast stud should be done to rule out presence of stricture
- Total parental nutrition is available and is required if feeds are to be stop for long time (>48 hours). Insert central venous line to administer TPN.

Surgical Management

- Surgical management up to 50% of infant with NEC may require surgery.
- Indications of surgery are:
  - Perforation of gut
  - Failure to respond or worsening of condition with medical management
  - Pneumoperitoneum is considered as absolute indication of surgery
  - Fixed mass on palpation which may indicate intraperitoneal abscess or aggregate of coalesced intestine is indication of surgical intervention
  - Gastrointestinal obstruction secondary to stricture formation (late complication) is indication of surgery
- Surgery involves laparotomy with resection of necrotic bowels with primary repair
- If more extensive two stage repair with bowel resection and enterostomy followed later with intestinal reanastomosis.

Prevention

- Prevent prematurity
- Prevent and manage HIE adequately
- Avoid formula feed and offer breastfeeding

- Trophic feeding (minimal volume of enteral feed) can be initiated. Early feed currently found to be not associated with increase risk of NEC
- Avoid hypertonic feed and rapid increased of feed (currently conflicting evidence)
- Maintain blood pressure, hydration.

Role of Probiotics in Prevention of NEC

Probiotics are like bacterial supplement that colonize the gastrointestinal tract and provide benefit to the host. When compared to term infants, preterm VLBW infants have paucity of normal gut flora which facilitates abnormal gut colonization, one of the major risk factors of NEC. Probiotics (bifidus, lactobacillus, saccharomyces etc.) which behaves like normal gut flora, provides increased barrier to migration of abnormal bacteria and their products across the mucosa. Competitive exclusion of pathogenic bacteria and increased IgA mucosal response also contributes to prevention of abnormal gut colonization. The probiotics have been found useful in preventing stage-II or greater NEC in preterm neonates. The probiotics for prevention of NEC have been found to be effective if given in neonates of gestation age of less than 33 weeks and birthweight of less than 1,500 g, started within the first 10 days of life with a duration of at least for 7 days.

Role of Vitamin A in Prevention of NEC

Vitamin-A (VA) plays an important role in regulating cell differentiation and the maintaining epithelial barrier defenses and modulating various components of innate and acquired immunity which helps to maintain disease resistance and improves healing. Vitamin A deficiency (VAD) results in a progressive sequence of histopathological changes in the epithelial lining of GI and respiratory tract. In developing countries both VAD and preterm delivery are quite frequent which makes the newborn vulnerable to NEC and sepsis. In developing countries babies are born with poor VA reserves due to poor maternal VA content in the mother not only during pregnancy, but also before pregnancy for obvious reasons (religious and cultural practice of clothing covering the skin). Therefore, VA supplementation makes very sense for affordable intervention to prevent NEC and sepsis in resource constraint developing countries.

Single dose of VA 50,000 units can be offered selectively to vulnerable newborn to prevent NEC and sepsis. However, VA supplementation for prevention of NEC and sepsis in vulnerable children require further evaluation and multicenter studies to establish itself in neonatal practice.

PROGNOSIS

- Overall mortality 10–20% with higher incidence in more preterm, LBW infants with extensive disease (Bell II-B, III-A, B), multiorgan failure.
- Recurrence of NEC occur in 4–6% cases
- Postsurgical immediate complications include wound infection, stroma stenosis and intra-abdominal abscess.

LONG-TERM COMPLICATIONS

- Stricture, malabsorption and short-gut syndrome
- Neurodevelopmental disability is more frequently associated with NEC then extreme LBW alone without NEC
- Infants who require surgery for NEC have even higher risk of neurodevelopmental disability than those who receive only medical treatment.

EVALUATION OF RESPIRATORY DISTRESS IN PRETERM AND TERM NEWBORN INFANTS

A baby in respiratory distress will present with one or more of the following features:

- Tachypnea (R.R >60/min) indicates either oxygenation or ventilation is inadequate and chemical stimuli of low PaO_2 or high $PaCO_2$, increased respiratory rate
- Subcostal retraction and nasal flaring indicates presence of substantial respiratory inadequacy and neonates use all available respiratory muscles to compensate.
- Severe chest indrawing.
- Grunting: Expiratory grunt suggests infants breathe out against partially closed glottis. It is a physiological response to increased lung volume to prevent alveolar collapse.
- Cyanosis. Reflects an increased desaturated Hb (>3–5 gm/dL) in the neonate.
- Apnea: Respiratory pause with decline in heart rate due to immature respiratory center.

CAUSES OF RESPIRATORY DISTRESS

- Common causes:
  - Transient tachypnea of the newborn (TTNB)
  - Respiratory distress syndrome
  - Congenital pneumonia
  - Meconium aspiration syndrome (MAS)
- Less common causes are:
  - Congenital diaphragmatic hernia- Surgical condition
  - Tracheoesophageal fistula (TEF)- Surgical condition
  - Pneumothorax
  - Milk aspiration
- Nonpulmonary causes of respiratory distress:
  - Congenital heart disease
  - Perinatal asphyxia with HIE
  - Severe anemia
  - Metabolic acidosis.

Features Suggestive of Respiratory Distress due to Respiratory Conditions

- Respiratory distress with cyanosis
- H/O prematurity, meconium stained amniotic fluid, prolonged rupture of membranes
- Normal pulses, no significant murmur, abnormal air-entry, added sounds on auscultation
- Abnormal X-ray chest
- Arterial blood gas (ABG)—respiratory acidosis.
- Hyperoxia test—PaO_2 >150 mm Hg.

Pathophysiology of Frequent Respiratory Diseases in Newborn

- Retained lung fluid—Transient tachypnea of newborn
- Deficient surfactant, alveolar collapse—Hyaline membrane disease (HMD) or RDS

- Alveolar inflammation—Group-B β-hemolytic streptococcal pneumonia
- Inhaled meconium—Meconium aspiration syndrome
- Air in the pleural cavity—Pneumothorax
- Intrathoracic lesion—Diaphragmatic hernia.

TRANSIENT TACHYPNEA OF NEWBORN

Presentation

- Usually full-term, often having history of cesarean section delivery
- Tachypnea from birth—With some recession, grunting, with or without cyanosis

  Chest X-rays showing well-expanded lungs but streaky shadows spreading out from the mediastinum.

Diagnosis: Transient tachypnea of newborn (TTN)

It is a disease of term or near term infants who have respiratory distress shortly after delivery. It is due to delayed resorption of fetal lung fluids which can resolve by 3 days. Increased fetal epinephrine concentration during labor normally reduces lung fluid production and activates sodium channels leading to reabsorption.

Risk factors involved:

- Prelabor delivery
- Delivery by cesarean section
- Delivery prior to 36 weeks
- Male sex.

Transient tachypnea of newborn is essentially a diagnosis of exclusion: RDS, sepsis and heart failure should be ruled out.

Clinically TTN resembles RDS but no grunting and chest X-ray shows streaky lung opacities with fluids in the transverse fissures and often cardiomegaly, but no air bronchogram characteristics of RDS (Fig. 79).

Some babies may require blood gas estimation and carbon dioxide retention rarely occurs. The main difficulty lies in distinguishing it from an early streptococcal infection. If there is doubt, septic screening should be done.

No specific treatment is required, but some may need supportive therapy, e.g. oxygen supply, diuretic and maintenance of nutrition and temperature. Breastfeeding if tachypnea is minimum and no oxygen dependence. Antibiotics in case of severe respiratory distress and until the blood (CBC-CRP, blood C/S) reports are available.

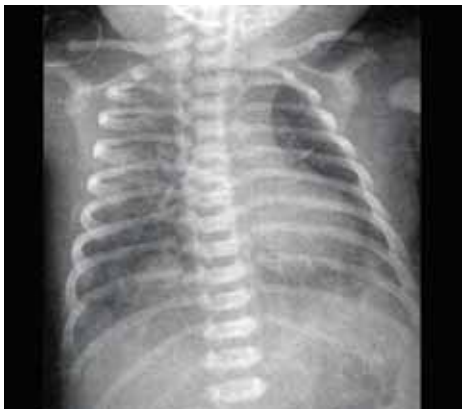


Fig. 79: X-ray chest showing fluid in the transverse fissure and some hyperexpansion in TTN

APNEA OF PREMATURITY

DEFINITION OF APNEA

Pause in breathing more than 20 seconds or less than 20 seconds associated with bradycardia and/or cyanosis. Apnea can occur in term baby but more associated with preterm. Incidence decreases with increasing gestational age, approximately 50% at 30–31 weeks and 7%, 34–35 weeks.

Apnea occurs in two phases:
Initial primary apnea with a rapid gasp followed by slow gasping and finally secondary apnea with last gasp (Fig. 80).

Fig. 80: Showing stages of apnea

Resuscitation should be done during primary apnea after rapid gasp, during secondary apnea more invasive intervention like intermittent positive pressure ventilation should be done to prevent last gasp and death.

Apnea may be:
Central: Absent respiratory effort and nasal air flow. Apnea of prematurity falls under this category.
Obstructive: Only nasal air flow is obstructed. Examples are choanal atresia, macroglossia, micrognathia.

OTHER CAUSES

Perinatal: IVH, birth asphyxia
Postnatal

- Metabolic: Hypoglycemia, hypoclcaemia, hypothermia
- Sepsis
- Gastroesophageal reflux, NEC
- Cardiac: PDA.

MANAGEMENT

Monitoring: It is essential to monitor all babies with risk factors of apnea (preterm <34 weeks), RDS using 1 of the system currently available. Apnea alarm beep can be used which will alert the health care providers to deal with apnea quickly. As these babies tend to have periodic respiration an alarm delay of 10–15 seconds is appropriate. Most of the apneic attacks are brief and self-limiting. Any trigger factors causing symptomatic apnea should be corrected such as anemia or incubator temperature.

Treatment aim at resuscitation followed by correction of underlying cause:

- ABC with continuous cardiac monitoring
- If apneic gentle surface stimulation
- No response: Oxygen by bag and mask
- CPAP may be required if recurrent apnea, rarely intubation and MV may be required.

Drug Treatment of Apnea Prematurity

- Methylxanthines are used for babies less than 34 weeks
- Aminophylline /theophylline 6 mg/kg IV initially, than after 12 hour 1–2 mg/kg 12 hourly. Can be increased to 3 mg/kg in second week and 4 mg/kg in third week. Stop stimulants when apnea disappears

- Caffeine citrate (1 mg of Caffeine citrate = 0.5 mg of Caffeine base)—Caffeine citrate can be given IV or orally. Loading dose is 20 mg/kg once daily. Maintenance dose 5 mg/kg/day. Both the loading and the maintenance dose can be safely doubled
- Admit in NICU for apnea due to treatment of underlying condition (correction of hypoglycemia and dyselectrolytemia and sepsis). If gastroesophageal reflux stop feed and starts IV fluid.

CONGENITAL PNEUMONIA

PRESENTATION

- Respiratory distress may develop in an initially healthy baby or as a complication of RDS or MAS. Some babies show deterioration in responsiveness and develop hypotonia after having previously been alert
- The baby becomes less active reluctant to feed, sometimes developing abdominal distension. Those with orogastric feeding are unable to tolerate the volume of milk that previously was not a problem
- Some develop attacks of apnea
- Maternal history of prolonged rupture of membranes—(>18 hours), offensive liquor, maternal pyrexia, culture—positive vaginal swabs
- On examination the babies appear pale and lack of normal spontaneous activity, shocked, hypotensive, hypotonic, acidotic or apneic and temperature instability
- The white cell count may be elevated or depressed. Thrombocytopenia commonly accompanies sepsis in neonates.

DIAGNOSIS OF CONGENITAL PNEUMONIA/SEPSIS

The frequency of congenital pneumonia and sepsis increases with prematurity, especially if there is prolonged rupture of membrane. Group B streptococcus is the most common pathogen involved in western countries. In developing countries gram negative bacteria (*E.coli*, *Klebsiella pneumoniae*, acinetobacter, etc.) more frequently involved. In respiratory distress of preterm associated with RDS it is impossible to exclude infection (pneumonia). For this reason empirical treatment with antibiotic is mandatory in respiratory distress in moderately preterm infant.

RESPIRATORY DISTRESS SYNDROME (RDS)

PRESENTATION

- Preterm baby
- Tachypnea, recession, with or without grunting and or cyanosis apparent within 4 hours of birth and becoming progressively worse
- Maternal history of taking antenatal steroid (before delivery). But less frequent in developing countries of taking antenatal steroid
- Chest X-ray showing hypoinflated, dense/opaque lung fields with possible atelectasis, ground glass appearance of the lung field with blurring of cardiac border and often presence of air bronchogram (caused by the airfilled airways surrounded by dense lung tissue). Changes are usually symmetrical.

As mentioned in the above case, RDS presents as evidence of respiratory distress of variable severity in preterm babies occurring immediately after birth (usually within 4 hours) with variable complications in untreated cases. Clinical problems like bronchopulmonary dysplasia (BPD), pneumothorax, chronic lung disease (CLD), etc. may also occur as a complication of treatment.

PATHOPHYSIOLOGY OF RDS

Surfactant deficiency is the main cause of RDS leading to various lung pathophysiological abnormalities. Surfactant which is produced by alveolar type-II pneumocyte is produced sufficiently in full term neonate and its production is proportional to age of gestation, the lower the preterm lesser the surfactant (pneumocyte starts producing surfactant by 24–26 weeks of gestation).

Composition of Surfactant (Fig. 81)

- Lipid 92% protein—8%
  - Phosphatidycholine 80%
  - Phosphatid glycerol 4%
  - Phosphoethalonamine 5%
  - Sphingomyelin 2%.

Surfactant deficiency lead to:

- Poor lung compliance, required for chest expansion during inspiration.

Lung Functions in RDS

Lung compliance: It is the change of volume of lung in mL per unit of pressure change in cm of H_2O. Lung compliance is expressed as mL/cm/H_2O.

In adult volume change is 200 mL/cm/H_2O.

In term baby—6 mL/cm/H_2O

In preterm baby—0.5-3 mL/cm/H_2O

Poor lung compliance is associated with atelectasis and alveolar collapse particularly at end expiration due to increase surface tension.

Low lung volume in RDS:

- Functional residual capacity (FRC) is significantly low in RDS
- FRC in normal newborn is 80 mL, in RDS may be as low as 10 mL
- Reduce tidal volume: Leading to hypercarbia (↑PCO_2)
- Term newborn has tidal volume of 16 mL, in preterm with RDS, it may be decreased up to 5 mL.

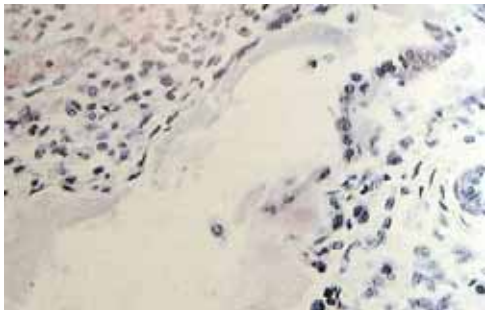


Fig. 81: Histology showing pink color surfactant lining the terminal bronchiole in a preterm newborn baby

Alveolar Ventilation

- Alveolar ventilation is decreased in RDS leading to hypoxia ($\downarrow PCO_2$)
- Alveolar ventilation in term neonate is 100–150/mL/kg/min. In preterm with RDS it may be reduced significantly (<50 mL/kg/min) leading to hypoxia
- Hypoxia may cause metabolic acidosis and decreased cardiac output and decreased blood pressure.
- Hypoxia also delays postnatal fall of pulmonary vascular resistance (PVR) with right to left shunting
- Both hypoxia and hypercarbia (↓ tidal volume) lead to type-II respiratory failure and combined metabolic and respiratory acidosis.

RDS AT AUTOPSY

- Solid lung
- Pink stain hyaline
- Evidence of pulmonary edema
- Lymphatic obstruction.

RISK FACTORS OF RDS

- Prematurity
- Infant of diabetic mother
- Sibling history of RDS
- Male baby
- Asphyxia
- Delivery by cesarean section
- Meconium aspiration syndrome.

OTHER IMPORTANT TRIGGERING FACTORS FOR RDS

- Cold
- Hypoxia
- Acidosis.

All these factors switch off type-II pneumocyte with subsequent decrease in surfactant volume.

POSSIBLE RELIEVING FACTORS

- Maternal steroid
- Toxemia of pregnancy
- Prolonged rupture of membrane
- Female gender
- IUGR in babies born >28 weeks.
- Maternal drugs (opiates, cocaine, alcohol and smoking), however possible benefits of these are heavily outweighed by their overall health risk of mother and fetus/ newborn babies.

DIAGNOSIS

Diagnosis is made by characteristics respiratory distress in preterm neonate and with typical X-ray chest and ruling out other causes of respiratory distress in newborn.

X-ray Chest

Dense opaque lung field with atelectasis. Ground glass appearance of lung field with presence of air bronchogram caused by air filled airways surrounded by dense lung tissue. Although air bronchogram is characteristics of RDS

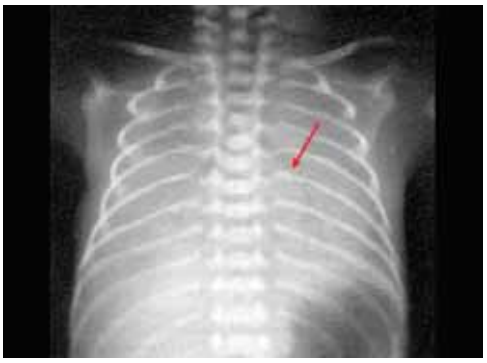


Fig. 82: X-ray chest showing homogenous opaque (ground glass) lung field with obscured heart borders and air bronchogram (arrow) characteristics of RDS

(Fig. 82), but it is not pathognomonic as it occurs in other clinical conditions like pulmonary hemorrhage, group-B streptococcal pneumonia in neonate. Changes are usually symmetrical. May become whitish enough which may become difficult to differentiate from congenital pneumonia (Group B streptococcus in particular) and pulmonary hemorrhage. Evidence of pneumothorax may also be seen.

Blood gas study: Combined metabolic and respiratory acidosis.

MANAGEMENT: PREVENTION AND TREATMENT

Prevention

- Long-term prevention: Prevent prematurity
- Short-term prevention: Antenatal (24–32 weeks) steroids (Betamethasone/Dexamethasone). Avoid cesarean section.

- Prevention and treatment of → Hypoxia, Cold, Acidosis
  - Hypoxia: Treated with humidified oxygen inhalation to keep SPO_2 >94%.
  - Hypovolemia: Corrected with normal saline, 5% albumin.
  - Cold: Keep the baby warm, radiant heater may be used.

Treatment

Many babies with RDS will require little or no intervention, but it is well known that early intervention (surfactant, CPAP) in babies with RDS of even less severe nature in the moderately preterm infant often prevents further complications with better outcome. Treatment includes supportive care including respiratory support and more definitive treatment of exogenous surfactant therapy depending on severity of RDS.

Oxygen therapy in RDS: Still important whether ventilation is used or not.

Very mild cases of respiratory distress may be successfully managed in incubator with nasal cannula oxygen. Supplemented oxygen may be given via head box (Fig. 83), hood or nasal cannula. In premature baby the aim is to keep tissue oxygen sufficient to maintain metabolism viable for life but avoiding oxygen toxicity. The oxygen saturation should be around 88–95% and PaO_2 in the range of 6–10.5 kPa (60–100%).

Fig. 83: Baby receiving oxygen therapy through head box

Any sign of increased work of breathing or increase oxygen requirement suggest the need of early institution of positive pressure support. Babies should not be allowed to become sufficiently acidotic (pH <7.25) without escalating support.

Surfactant Therapy

Exogenous surfactant replacement therapy in RDS and mechanical ventilation is the standard treatment for severe RDS. It improves lung function, decreased mortality and results in better long term neurodevelopmental outcome. In severe cases exogenous surfactant is given via ET tube along with ventilatory support.

Surfactant:

- Survanta/bovine lung extract with added phospholipid: 100 mg/kg or 4 mL/kg via ET (endotrachea tube) 6 hourly 2–4 doses

OR

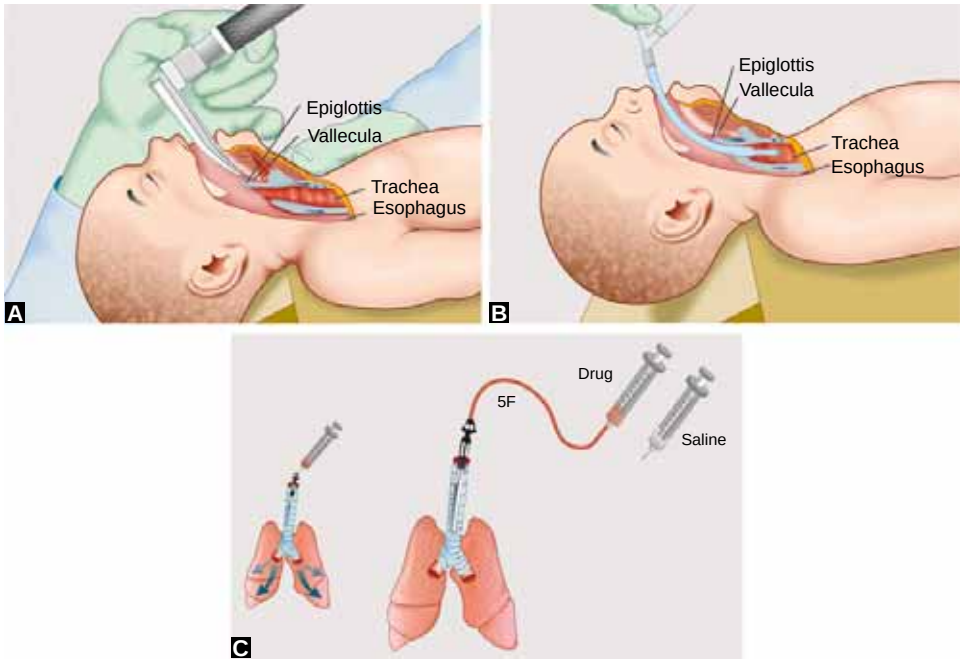
- Exosurf (previously available synthetic preparation): 5 mL/kg via ET 12 hourly or 67.5 mg per kg—12 hourly—2–3 doses.

Role of Surfactant as Prophylactic and Early Rescue Management of RDS

Early prophylactic use of surfactant in preterm below 27 weeks and preterm below 32 weeks who has risk factor for RDS are found to be benefited by surfactant replacement before clinical feature of RDS develop. The requirement of mechanical ventilation is also reduced significantly. Such infants when administered prophylactic surfactant within 15 minutes of age followed by brief mechanical ventilation with planned extubation to nasal CPAP within 1 hour has been found to improve significantly in terms of survival, decrease requirement for oxygen supplementation, low incidence of severe RDS and chronic lung disease including BPD. Moreover incidence of pneumothorax and pulmonary emphysema due to air leak is also minimum as mechanical ventilation use is minimum.

How to Administer Surfactant (Fig. 84)

- Counseling and consent of parents for administration of surfactant (Survanta)
- Two persons should be required to perform the procedure
- Setup—Level-III NICU
- Baby should be intubated (endotracheal) and on mechanical ventilation
- Clear the trachea of mucus
- Pre-oxygenate the lungs to minimize the risk of cyanosis during administration
- Surfactant which should be kept previously at 2–8°C for up to 12 hours in a refrigerator should be defrosted to room temperature without shaking
- Surfactant should be drawn in 10 mL syringe
- An infant feeding tube of 5 Fr size should be cut with its distal end 0.5 cm longer than the length of ET tube. Feeding tube through which surfactant should be delivered is



Figs 84A to C: (A) Intubation of neonate position; (B) Position of endotracheal tube; (C) Surfactant administration in the lungs through endotracheal (ET) by infant feeding tube

measured as FT = Length of ET tube (tip to lip distant) + ET tube adaptor + 0.5 cm
- Surfactant filled syringe attached to feeding tube
- Disconnect the ventilator for short duration from the infant and place the infant in supine position
- Instill the necessary dose of surfactant (Survanta) in the feeding tube down the endotracheal tube. 2–4 boluses may be required
- Remove the catheter and ventilate 0.5–2.0 minutes between doses, so that total doses are usually given for 3–5 minutes. Between boluses reconnect ventilator and wait at least 60 sec till SaO_2 gets stable
- Changing the position of the baby during or after instillation may improve distribution
- The ventilator settings need to be adjusted after giving surfactant. If there is inadequate chest movement or oxygenation, increase PIP by 2 and/or FiO_2 0.05–0.1.

New Techniques of Minimally Invasive Surfactant Therapy (MIST)

Exogenous Surfactant Therapy without Tracheal Intubation

With the evolution and refinement of intensive care for preterm infants, the place of exogenous surfactant therapy is changing. Recognizing the merits of surfactant, especially when given early, some clinicians choose to intubate infants on CPAP solely for the purpose of giving surfactant, followed by immediate extubation and return to CPAP.

However, intubation of the trachea with an endotracheal tube can be hazardous and is usually undertaken with premedication, which may contribute to a delay in extubation once surfactant has been administered.

Therefore, several newer less invasive newer techniques without intubation of trachea called MIST have been discovered.

However all such therapies are not widely practiced and require further evaluation. The following are the examples of mixed therapies:
- Nasopharyngeal instillation
- Aerosolization
- Catheterization of trachea with 5–6 FG feeding tube without intubation
- Surfactant delivery via vascular catheter.

In this MIST procedure, the CPAP face mask or prongs are removed and direct laryngoscopy is performed using a standard laryngoscope and Miller 00 blade. The instillation catheter is inserted through the vocal cords to the desired depth and manually held in position at the lips. After tracheal catheterization, the surfactant syringe is then connected to the catheter hub, and the dose of exogenous surfactant administered in one bolus (25–28 weeks) or two boluses 10s apart (29–34 weeks). The tracheal catheter is immediately withdrawn, and CPAP reinstituted by mask, with positive pressure inflations as necessary if the infant is apneic or bradycardic (Fig. 85).

Non-invasive Assisted Ventilation in RDS

Non-invasive respiratory support
- Continuous positive airway pressure (CPAP)
- Nasal intermittent positive pressure ventilation (NIPPV)
- High flow nasal cannula (HFNC).

Fig. 85: Catheter used for MIST. Top: 16 gauge vascular catheter used for the MIST procedure, with external diameter of 1.7 mm. This catheter is semirigid and can be guided through the vocal cords without a trochar. Bottom: Standard 2.5 mm internal diameter endotracheal tube for comparison. This tube has an external diameter of 3.5 mm

More Invasive Mechanical Ventilation

Frequently required in severe RDS and in neonates with less than 30 weeks of gestation.

Continuous Positive Airway Pressure (CPAP)

- It is indicated in moderate RDS with PO_2 <8 kPa or <60 mm Hg
- Recurrent apnea
- Weaning from mechanical ventilation.

It is given to prevent alveolar collapse during expiration. CPAP is the mainstay of ventilatory care in RDS in moderately preterm infants. The CPAP has mechanical ventilation (MV) sparing effect which is more invasive. Early surfactant therapy with short mechanical ventilation followed by extubation to CPAP has been found to be effective in RDS management of preterm less than 30 weeks and greater than 30 weeks (30–34 weeks preterm) with risk factors.

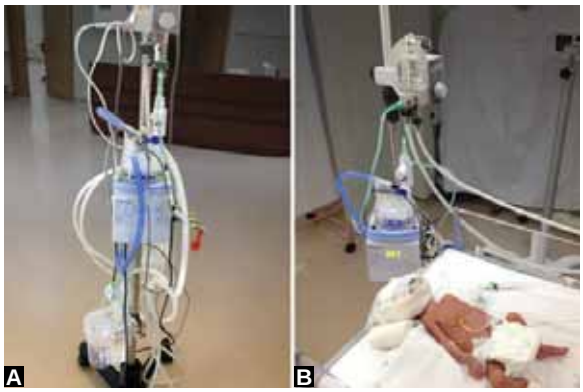
A continuous distending pressure of 4–10 cm water is applied via nasal prong (NCPAP) with initial pressure of 4–5 cm of water and gradually increased to maximum 10 cm water.

There are many ways of delivering CPAP and no clear evidence as to which is the best. Bubble CPAP improve gas exchange (Figs 86A and B).

Various types of CPAP are discussed in the chapter: Newborn Ventilation.

Humidified High Flow Nasal Cannula Therapy

Humidified high flow nasal cannula therapy (HHFNC) system (Humicare, Vapotherm) allows delivery of warmed humidified gases via small caliber nasal cannula at flow rates greater than



Figs 86A and B: (A) Bubble CPAP; (B) A newborn with RDS receiving respiratory support by bubble CPAP

1 L/min without causing the excessive airway drying, mucosal damage, bleeding and increase risk of infection.

HHFNC is increasingly used as an alternative to NCPAP at all gestations. Despite its emerging popularity, the evidence that HHFNC is as effective as CPAP is largely anecdotal or retrospective.

INVASIVE VENTILATION

Mechanical Ventilation (MV)

Mechanical ventilation (MV) should be used for minimum possible time and with lowest possible mean airway pressure to reduce barrow trauma and ventilation induced lung injury (VILI). The minimum possible FiO_2 should be used to maintain normal blood gas.

Intermittent positive pressure ventilation (IPPV): In IPPV, the following devises are present and the values are set according to various conditions of respiratory distress in newborn.

- FiO_2 (Fraction of inspired oxygen concentration): It is usually set between 0.6–1 (60–100%). In RDS, it can be raised but not exceeding 1 (100%)
- PEEP: Usually set between 3–7 cm of H_2O. In RDS, it can be raised to maximum 4 cm of H_2O to overcome significant pulmonary resistance
- Ventilatory rate is usually set at 40/min but in case of severe RDS it can be raised to 50–60/min (range 30–60/min)
- PIP: It is usually set at 18–20 cm of H_2O. During ventilating a case of severe RDS or meconium aspiration syndrome (MAS) where pulmonary resistance are more it can be increased up to 28. In preterm LBW infant with recurrent apnea it should be started at lower pressure of 18 cm of H_2O
- Ti (Inspiratory time): Short inspiratory <0.5 sec should be used in preterm infant with RDS. This reduces the incidence of air leak in babies with less complaint lung. Expiratory time (Te) also important
- Ti/Te: Ratio of Ti/Te is also important. It is usually maintained at 1:2 but in case of significant respiratory distress ratio should be prolonged, i.e. 1:3 or 1:4 to prevent air trapping
- Usual ventilatory setting in different respiratory problem in newborn given in Table 31.

OTHER TYPE OF VENTILATORS

Patient triggered ventilator (PTV) and SIMV (synchronous intermittent mechanical ventilator): These are designed to synchronize patients own ventilatory efforts with that of ventilator. Synchronous ventilator is now standard practice and is associated with fewer air leaks and shorter duration of ventilation (Fig. 87).

Fig. 87: A baby with RDS receiving mechanical ventilation with SIMV

High Frequency Oscillatory Ventilation (HFOV)

- It is primarily used as rescue treatment. A continuous pressure is applied and gas exchange occurs by a vibrator operating at ~10 Hz
- Volume targeted ventilation reduces the frequency of excessive tidal volume associated with lung injury thereby decreasing in advertent hypoventilation
- Ventilation support strategy varies from center to center. However, Table 31 shows the usual range of various parameters of mechanical ventilator.

WEANING PRETERM BABIES OFF CPAP

Most preterm babies less than 30 weeks gestation will require assisted ventilation. Ventilation strategies varies in different settings and with resource available. Mechanical ventilation (MV) although very effective and standard treatment for the RDS and for other respiratory distresses in preterm infants, it is more invasive and more associated with lung injury. The aim of positive pressure ventilation is to minimize use of MV and its duration and switching on to CPAP as early as possible. In fact early use of surfactant followed by brief MV and then switching on to CPAP has been found very effective in many centers.

Table 31: Usual ventilatory settings in different respiratory distress of newborn

Indication	Usual range PIP cm of H_2O	PEEP cm of H_2O	Max FiO_2 (Range)	Max Rate/minute	Mean duration of ventilation (hours)
RDS	23–26	4	1.0 (0.8–0)	50–60	60–80
Birth asphyxia	21–23	3–4	1.0 (0.6–1)	50–60	60–80
MAS	21–23	3–4	1.0 (0.7–1)	50–60	70–90
Apnea	22–24	4	1.0 (0.6–1)	50–60	60–80
Pneumonia	22–24	4	1.0 (0.6–1)	50–60	65–85
Septicemia	23–25	3–4	1.0 (0.6–1)	50–60	55–80

RDS, respiratory distress syndrome; MAS, meconium aspiration syndrome; PIP, peak inspiratory pressure, PEEP, positive end expiratory pressure

However prolonged CPAP is also not without side effects and attempts and steps should be taken to wean preterm infants OFF CPAP as early as possible.

There is little evidence on the best method of weaning infant of CPAP. However the following criteria may be adhered to wean OFF CPAP.

The infant should be stable for ≥12 hours

Stability criteria (must have all 8 stability criterias for more than12 hours)

1. Oxygen requirement <25% and not increasing
2. CPAP 4–6 cm H_2O
3. Average saturation >86% most of the time or PaO_2 >45 mm Hg
4. Respiratory rate <60/min
5. No significant chest recession (sternal-diaphragmatic)
6. Less than 3 episodes of self-reverting apnea (<20 seconds) and, or bradycardia <100/min and or desaturations (≤ 85%) in 1 hour for previous 6 hours
7. Tolerated time OFF CPAP during care (up to 15 minutes)
8. Not currently treated for PDA or sepsis.

Weaning Methods

There are different ways of weaning.
Taken OFF CPAP

- CPAP is taken OFF and the premature infants remain in crib oxygen or air with a view to stay OFF CPAP. They are replaced on CPAP if infant fails without CPAP support
- Cycle on and CPAP with intermittent time OFF.

Here CPAP is weaned gradually by cycling between intervals of period of time OFF followed by a fixed period of 6 hours ON CPAP

Weaning from the initial CPAP pressure are better achieved by gradually decreasing the CPAP pressure rather than slowly cycling the time OFF CPAP at the initial pressure.

Low flow and high flow nasal cannula are now being used more frequently for both weaning and as a replacement for nasal CPAP.

Criteria for Failed Trial "OFF" (at least two of the followings)

- Increased work of breathing (intercostal recession and accessory muscles contributing for respiration) with respiratory rate greater than 75/min
- Increased apnea and/or bradycardia and/or de-saturations >2 in 1 hour for the previous 6 hour period
- Major apnea or bradycardia requiring resuscitation
- Increased oxygen requirement >25% to maintain oxygen saturation >85% and/or PaO_2 >45 mm Hg
- pH <7.2
- $PaCO_2$ >75 mm Hg.

ASPIRATION OF FEEDS

PRESENTATION

Sudden onset of respiratory distress- with tachypnea, expiratory grunting, recession.

- History of regurgitation of feeds and history of coughing and cyanosis during or soon after a feed
- X-ray showing generalized mottling.

DIAGNOSIS

Aspiration of Feeds

Aspiration of feeds is a common occurrence in preterm and full-term babies with neurological or other cardiorespiratory problems. Babies with bronchopulmonary dysplasia often have gastro-esophageal reflux, which predisposes to aspiration. Infants with a cleft palate are prone to aspirate respiratory secretions or milk.

Symptoms are again those of tachypnea, recession and expiratory grunting, often following a history of coughing and cyanosis during or soon after a feed. If the aspiration episode is noted, the damage can be minimized by prompt nasopharyngeal suction and tipping. On examination—coarse crepitations can almost always be heard.

PNEUMOTHORAX

Presentation

- Baby presented with respiratory distress—associated with tachypnea with grunting and often cyanosis
- More frequently associated with preterm then term infant
- There may be a history of a traumatic delivery and evidence of birth trauma
- There may be history of ventilation (perhaps over-vigorous resuscitation, high PEEP, H/O ventilation for RDS)
- Infants oxygen requirement is—increased
- Barrel shaped chest and chest movement reduced on the affected side, air entry and breath sound reduced on the affected side
- Hyperresonant, hyperexpanded asymmetrical chest
- Trachea and apex beat stifled towards opposite side.

Diagnosis

The relative lack of surfactant at 32–34 weeks renders the immature lung less compliance which increase the risk of pneumothorax and air leak causing pneumomediastinum. It is rare at this gestation without RDS. Air leak may occur spontaneously due to positive pressure ventilation. Pneumothorax also occurs spontaneously in about 1% of all deliveries.

In RDS— air from the overdistended alveoli may track into the interstitium, resulting in pulmonary interstitial emphysema (PIE). In up to 20% of infants ventilated for RDS, air leaks into the pleural cavity and causes pneumothorax and pulmonary interstitial emphysema- both cause acute barotrauma. When this occurs, the infants oxygen requirement usually increases, the tidal volume decreases and the breath sounds and chest movement on the effected side are reduced, although this can be difficult to detect clinically. A pneumothorax may be readily demonstrated by transillumination (Fig. 88) with a bright fiberoptic light source applied to the chest wall. Although occurring most commonly as a complication of continuous distending pressure, IPPV or meconium aspiration syndrome, symptomatic pneumothoraces can occur spontaneously. The symptoms are those of respiratory distress with hyperinflation of thorax. Displacement of cardiac apex is often difficult to detect in small babies, but there is usually asymmetry of air entry.

Investigations

Radiological Diagnosis

May show hyperlucent thorax, low flat diaphragm and mediastinal shifting.

Other Investigations

- CBC: For septic screening
- Blood gas: ABG.

Treatment of Pneumothorax

- Small pneumothorax (less symptoms): Air is absorbed spontaneously within few days and needs close observation
- Large pneumothorax or tension pneumothorax: Oxygen inhalation and propped up position. Historically, 100% oxygen has sometimes been used as treatment for smaller pneumothorasis; however evidence for poor efficacy and given the added concern of oxygen toxicity in the preterm infant, 100% oxygen is not recommended by some authors
- Tension pneumothorax, hypoxia and respiratory failure are the indications to insert a chest drain
- Thoracostomy tube is inserted into the pleural cavity in the second intercostal space along the midclavicular line (preferable)
- Pigtail catheters inserted using the Seldinger technique has been found effective, easier, quicker method and less scarring than traditional chest tubes (Figs 89 and 90)

Prevention: Infants are ventilated with the lowest pressures that provide adequate chest movement and satisfactory blood gases and ventilation is adjusted to avoid the infant breathing against the ventilator.

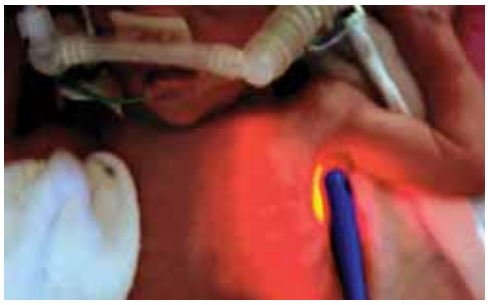


Fig. 88: Positive transillumination test showing large glowing area of redness when a light from transilluminator (otoscope) is focused on chest

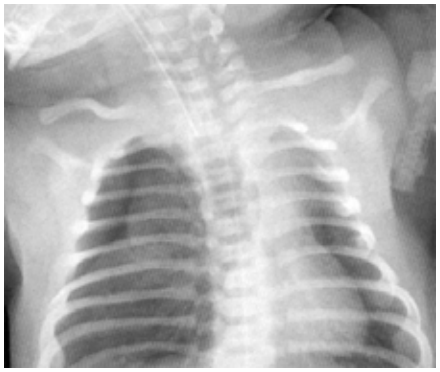


Fig. 89: Right-sided pneumothorax

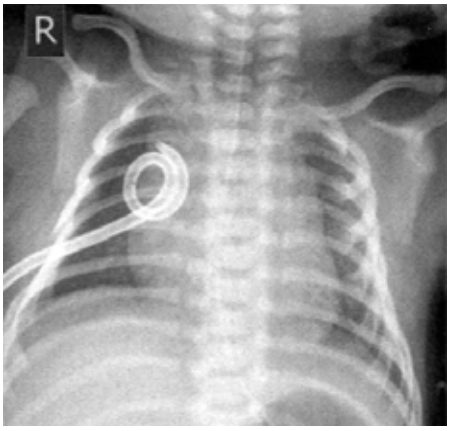


Fig. 90: Resolution of pneumothorax after insertion of Pigtail catheter

PULMONARY INTERSTITIAL EMPHYSEMA (PIE)

Mediastinal and PIE can occur due to surfactant deficiency of preterm lungs which renders the lung less compliant. This it may cause pulmonary interstitial emphysema (Fig. 91) which may lead to pneumomediastinum (Fig. 92) and pneumopericardium (Fig. 93). It may also subsequently result in pneumothorax. This is similar to pathogenesis of pneumothorax in moderately preterm infant with surfactant deficiency. In many cases pneumomediastinum and PIE may lead to frank pneumothorax. PIE occurs most often in ventilated preterm infant with RDS. PIE frequently develops in the first 24 hours of life and associated with hypoxia, hypercarbia, hypotension and bradycardia.

Treatment of PIE

Aims at preventing further barotrauma of lung. Attempt should be taken to decrease MAP by decreasing PEEP, PIP and inspiratory time. High frequency oscillatory ventilation may work as a rescue agent.

Treatment of Pneumomediastinum

- Needle aspiration (like pneumothorax treatment)
- Nitrogen washout (controversial)
- Rarely mediastinal tube inserted is required should be performed by pediatric surgeon.

BRONCHOPULMONARY DYSPLASIA (BPD)

It is also known chronic lung disease (CLD): With improvement in neonatal care there are more survivors receiving conventional positive pressure ventilations who continue to require supplemental oxygen. When this requirement extends beyond 4 weeks or to the point of hospital discharge with typical X-ray chest finding, these infants are regarded as having BPD.

Alternate definition often used in VLBW babies. Requirement for respiratory support with supplementary oxygen +/– mechanical ventilation more than 36 weeks corrected gestational age, with typical chest X-ray changes. Incidence varies according to distribution of gestational age in population as well as difference in levels of oxygenation received in different neonatal units.

Risk factors involved:

- Preterm birth
- Severe RDS

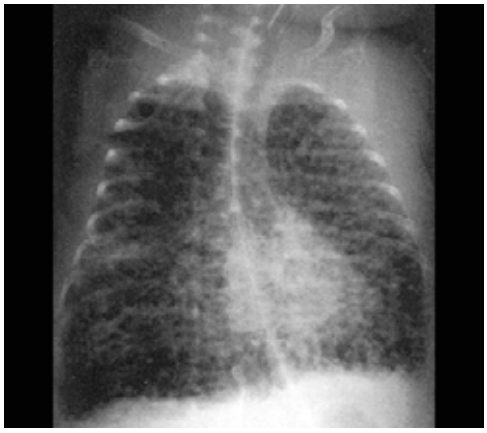


Fig. 91: X-ray chest of PIE showing nodular translucencies emerging from hila and extending to perivascular distribution also shows honeycomb appearance

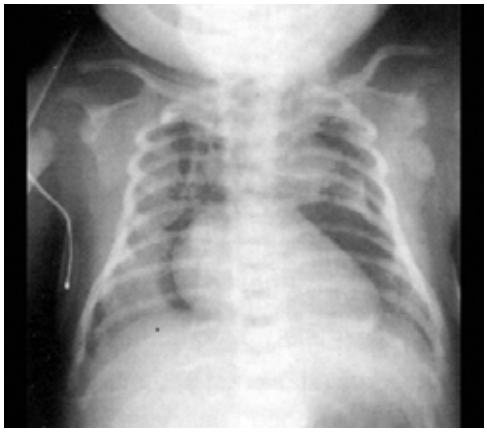


Fig. 92: X-ray chest showing pneumomediastinum with air adjacent to heart borders but not all around the heart borders. Thymus elevated away from heart

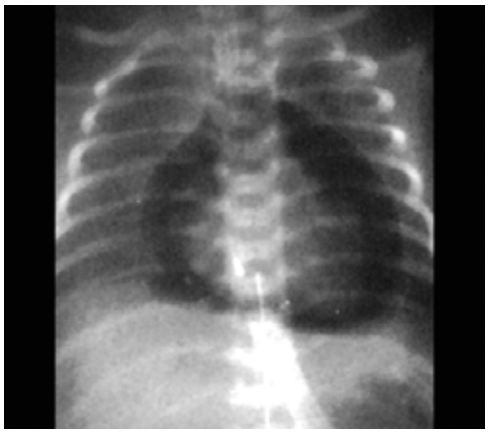


Fig. 93: X-ray chest of pneumopericardium showing air all around the heart borders

- Prolonged positive pressure ventilation
- Lung over inflation
- Hyperoxia
- Pneumothorax and PIE
- Maternal chorioamnionitis
- PDA
- Postnatal sepsis.

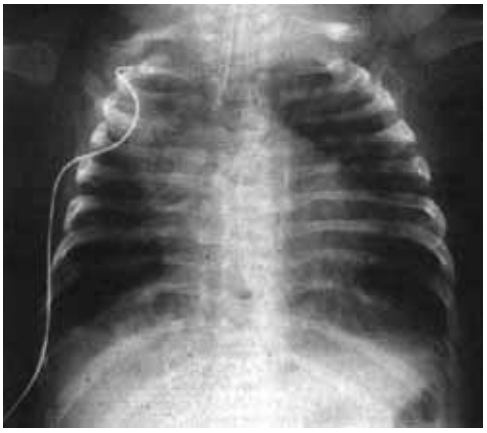


Fig. 94: Chest X-ray of BPD showing bilateral lower lobe hyperinflation with patchy areas of collapse/consolidation

Presentation

- Chronic oxygen/ventilation dependents
- Increased work of breathing
- Frequent apnea, bradycardia and desaturation episodes
- Often have feeding difficulties and growth failure
- Clinical evidence of pulmonary hypertension (loud single second heart sound, right ventricular hypertrophy, murmur of TR)
- Chest X-ray showing generalized opacification of lung filled initially with later changes in severe cases with areas of patchy opacification and over inflation (Fig. 94).

Pathology and Pathophysiology

Pathologically it is a condition characterized by abnormal capillary morphology with variable interstitial cellular and fibroproliferation and appearance of alveolar simplification. A reduction in the number and size of intra-acinar pulmonary areas has been shown in infants with BPD. This contraction of pulmonary vascular bed alone or in combination with abnormal pulmonary arterial muscularization can result in increase pulmonary vascular resistance (PVR) and consequential pulmonary hypertension (PH).

Management

- Best treatment is prevention.
- Avoid hyperoxia in babies at risk of developing BPD. Maintain oxygen saturation at 88–92% and PO_2 6–8 kPa, before pulmonary hypertension develops
- If echocardiography results suggest pulmonary hypertension than oxygen saturation should be maintain at >95%
- Early CPAP may reduce risk of CLD
- Careful attention to nutrition and growth is required. Calorie requirement is likely to be as high as 120–150 kcal/kg/day
- Monitor for and treat metabolic bone disease of prematurity
- Vitamin A supplementation has been shown to reduce the incidence of BPD in preterm neonates
- Treat gastroesophageal reflux disease (GERD)
- Intercurrent infection will increase oxygen requirement and, therefore, should be effectively treated.

Management of pH in BPD

Whereas inhaled nitric oxide (iNO) has the potential to better match lung function to ventilation, oral pulmonary vasodilators (sildenafil) have a less specific effect and do not preferentially vasodilate the better ventilated areas of lungs.

Systemic Steroids

- May facilitate weaning off ventilator and reduce risk of BPD
- Dexamethasone is considered in babies with worsening BPD. However the following conditions should be excluded before dexamethasone administration:
  - Exclusion or treatment of significant PDA
  - Exclusion or treatment infection
  - Exclusion or CMV infection.

Dose of dexamethasone: 0.3 mg/kg/day for 3 days then 0.2 mg/kg/day for 3 days, then 0.1 mg/kg/day for 3 days then stop. It is given as 2–3 divided doses.

Discharge of Infants Requiring Oxygen Supplementation

It is possible to discharge babies of BPD requiring oxygen supplementation if:

- Oxygen requirement is present but stable (not increasing)
- There is no other acute medical condition
- Parents are prepared to take baby home
- Home circumferences are adequate for oxygen supplementation
- Community support is available.

Follow up should be arranged.

Prognosis

- Most babies can be weaned off oxygen few weeks after discharge. However few may require oxygen beyond 1 year of age.
- Readmission may be required more than once within first 2 years
- Recurrent bouts of cough and wheeze may occur in first few years of life
- There is high risk of neurodevelopmental disorder.

OTHER CAUSES OF RESPIRATORY DISTRESS, NOT CHARACTERISTICS OF PRETERM INFANTS

MECONIUM ASPIRATION SYNDROME

Problems

- Usually a history of post-term delivery and a history of fetal distress
- May occur in preterm associated with IUGR
- Meconium- stained liquor with meconium in the mouth and pharynx and also in the skin, nail, umbilicus
- Tachypnea, recession, often grunting with or without cyanosis or apnea from birth
- Barrel-shaped chest (↑anterior and posterior diameter shown in Fig. 95).

Diagnosis

Meconium Aspiration Syndrome (MAS)

The presence of meconium in the amniotic fluid is a warning sign of fetal distress. This may be aspirated by the fetus in the uterus prior to delivery or by the newborn during labor and delivery. Aspiration of thick meconium by the baby can cause airway obstruction.

Fig. 95: Infant with MAS (under mechanical ventilation) showing hyperinflated chest (↑ anterior posterior diameter)

Large airway obstruction causes—hypoxia, small airway obstruction causes atelectasis, ball and valve mechanism causes hyperinflation and pneumothorax. Meconium aspiration causes chemical pneumonitis—leads to surfactant production inhibition and persistent pulmonary hypertension. If the meconium is thick give suction of the mouth immediately after delivery of head but before the shoulder is delivered.

Assessment of the Baby with MAS

Immediate Assessment of Vitals Signs

Respiration, heart rate, temperature, including color, perfusion, oxygen saturation, muscle tone.

General Physical Assessment

The baby may present with dyspnea, tachypnea, subcostal and intercostal recession, nasal flaring, expiratory grunting with or without cyanosis and apnea. Meconium staining present in the skin, nails, umbilicus and even all over the body.

Systemic Assessment

- Respiratory rate:
  - Respiratory system: RR- may be >60/min.
  - Anterior posterior diameter of the chest is increased (Barrel-shaped chest)
  - Poor air entry
  - Bilateral coarse crepitation and rhonchi may be present.
- CNS: Some of these babies will have associated asphyxial encephalopathy- so neurological status should be assessed.
- Musculoskeletal system: Some of these babies may present with poor muscle tone and present as flaccid baby.
- Evaluation of history and overall condition-
  - Commonly seen in post-term baby (30%), term with IUGR.
  - There may be history of fetal distress, perinatal asphyxia, meconium-stained amniotic fluid.

Investigations for Diagnosis and Management of the Patient

- Radiological diagnosis: by chest X-ray (Fig. 96)
  - Hyperinflation of lungs field
  - Low flat diaphragm
  - Patchy opacity
  - Pneumothorax and pneumomediastinum.
- Clinical diagnosis and assessment:
  - Direct laryngoscopy- Shows that meconium is present in the oropharynx.
- Complete blood count (CBC)- for septic screening.
- Other investigations- for management purposes:
  - Blood gas-Respiratory acidosis- Hypoxia, increased PCO_2 decreased pH
  - Echo-Color Doppler- May show:
    - Intra-atrial shunt
    - PDA may be found
  - Cranial USG: To exclude asphyxial encephalopathy
  - Blood sugar and serum calcium- To exclude hypoglycemia, hypocalcemia.

Treatment of MAS

As the baby presented with respiratory distress—resuscitate the baby first at the same time with ABC management. Rapid assessment of the vitals signs—Respiration, heart rate, temperature, color, O_2-saturation, capillary refilling time and blood is sent for blood gas analysis (if facility is available).

- Antenatal management:
  - Identification of high risk pregnancies.
  - Institutional delivery
  - Follow-up—clinical and by USG—for assessment of condition of the baby
  - Biophysical profile and delivery as early as possible.
- Postnatal management:
  - Suction: Proper and adequate suction- First orally and then nasally. If thick meconium and direct laryngoscopy shows that meconium is present in the oropharynx at birth, the baby should be intubated immediately and meconium should be aspirated from the larynx and trachea.
  - Oxygen inhalation
  - Cleaning of the baby
  - Maintenance of temperature
  - Maintenance of nutrition—IV 10%/ dextrose- 2/3rd of the daily requirement

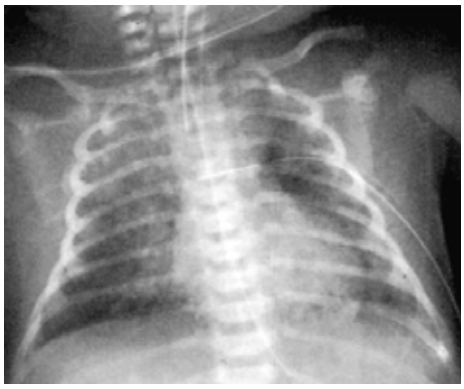


Fig. 96: X-ray chest of MAS showing hyperinflation with low flat diaphragm, nodular opacity and air leaks

  - Antibiotics- Inj. Ampicillin + Inj. Gentamycin (Meconium aspiration increases the risk of secondary bacterial infection)
  - If cyanosis, respiratory distress, gasping and flat baby- shifted to NICU.

In NICU- oxygen inhalation- by Hood box

↓

Arterial blood gas

↓ If ABG shows

Hypoxia, hypercarbia and impending respiratory failure- Then

↓

Arrange for mechanical ventilation- with high PIP pressure and ventilatory rate and shortening of inspiratory time and prolong expiratory time (increased Ti/Te ratio) which relieves cyanosis and remove CO_2.

An ideal ventilatory setting for MAS as follows: PIP 21–26 cm of H_2O, Ventilatory rate- 50–60/min, Ti/Te ratio 1:4 (See Ventilatory setting in RDS chapter).

Treatment of complication- accordingly if any.

Complications of MAS

- Chemical pneumonitis
- Pneumothorax
- Air leak syndrome
- Respiratory failure
- Persistent pulmonary hypertension of the newborn (PPHN)
- Intracardiac shunt
- Chronic lung disease
- Bronchopulmonary dysplasia.

Prognosis

Death rate: 5% with all support available.

CONGENITAL DIAPHRAGMATIC HERNIA

PRESENTATION

- Severe respiratory distress soon after birth. Respiratory distress may be mild, if present beyond the neonatal period
- Cyanosis
- Vomiting
- Increase discomfort- following feeding
- Vomiting, constipation, mild respiratory distress- late presentation
- Scaphoid abdomen, hyperinflated chest (affected side)
- Displacement of cardiac impulse away from the affected side.

DIAGNOSIS: CONGENITAL DIAPHRAGMATIC HERNIA

Differential Diagnosis

- Eventration: Absence or weakness of diaphragmatic musculature without an abnormal opening or paralysis of phrenic nerve leads to eventration of diaphragm. Figure 97 shows characteristic X-ray (chest) of eventration of diaphragm

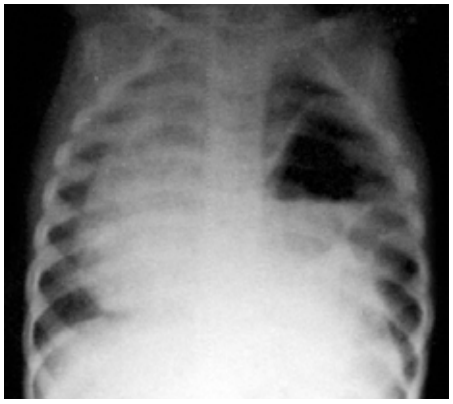


Fig. 97: Eventration of the left-sided diaphragm showing thin left diaphragmatic muscle with funding gas shadow just below left diaphragm. Mediastinum is shifted to the right

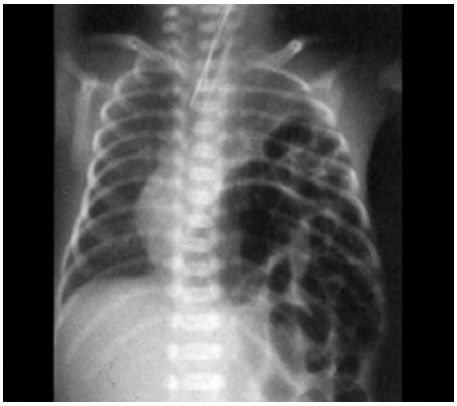


Fig. 98: Chest X-ray showing left-sided diaphragmatic hernia with airfilled loops of bowel in left hemithorax with mediastinal displacement

- Cystic adenomatoid malformation of lung: Are caused by irregular dilatations of the bronchi leading to variable airfilled cystic mass that are usually found in a single lobe. If wide spread, it may present at birth with respiratory distress and may require surgical resection.

Diagnosis: From clinical feature and from radiological finding.

Investigations

- X-ray chest including abdomen: Non-homogenous opacities (gas filled loop) with displacement of the mediastinal structure to the opposite side. Dome of diaphragm not visible, atelectasis of the contralateral lung. Abdomen is gasless (Fig. 98).
- ABG—May show— decreased PO_2, increased PCO_2, decreased pH (hypoxia, hypercarbia, respiratory acidosis)
- USG of chest—for movement of dome of diaphragm. USG during pregnancy: Polyhydramnios, chest mass, mediastinal shift, gastric bubble or a liver in the thoracic cavity.

Differential Diagnosis: Congenital Cystic Adenomatoid Malformation (CCAM)

Treatment

Suppurative

- Nothing per oral
- Maintenance of IV nutrition and temperature
- Oxygen inhalation (mask avoided)- through nasal prong
- Keep the baby 30° head up lateral position.
- Immediate nasogastric suction: To empty the stomach.

Surgery

Surgical repair of the defect and reposition of the herniated viscera.

- Treatment of complication—accordingly:
  - Pulmonary hypertension
  - Pneumothorax
  - Bronchopulmonary dysplasia
  - GERD.

Prognosis

Early presentation bad prognosis and late presentation good prognosis.

TRACHEOESOPHAGEAL FISTULA (TEF)

PRESENTATION

1. Newborn presented with frothy discharge from mouth and nostrils and difficulty in feeding associated with respiratory distress since birth
2. Maternal history of polyhydramnios
3. Failure to pass a tube with a radio-opaque marker into the stomach.

DIAGNOSIS

Trachea and esophagus are formed from the primitive foregut around the fourth weeks of intrauterine life. Any abnormalities in this process causes this anomaly. It is a surgical emergency. Esophageal atresia (EA) is one of the most common congenital anomalies. Affects 1 in 3,000–4500 neonates, of these greater than 90% have an associated TEF. Most common form of EA—the upper esophagus ends in a blind pouch and the TEF is connected to the distal esophagus (Fig. 99).

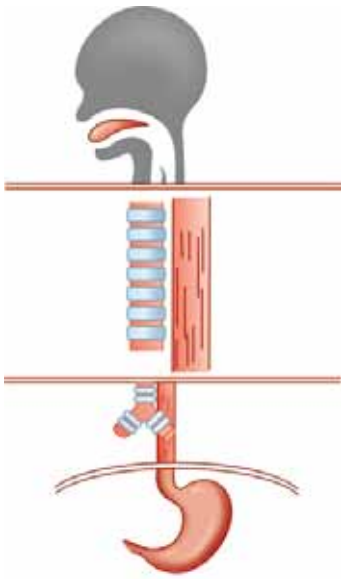


Fig. 99: Figure showing esophageal atresia with tracheoesophageal fistula

ASSOCIATION

50% of infant, have associated anomalies most often associated with VATER/VACTERL (vertebral, anorectal, cardiac, tracheo-esophagus, renal, radial and limb) defect.

TYPES (FIG. 100)

- Esophageal atresia (EA) with distal TEF: Most common—85% (upper blind esophageal pouch and lower pouch communicates with the trachea).
- Isolated EA without TEF (8%)—EA with no tracheal communication.
- Isolated TEF (5%) without atresia (H type): No EA but fistulous communication with the trachea. The "H" type of TEF may remain undetected for long time as this variety does not have acute symptomatic presentation at birth. They usually preset as frequent cough after feed, GERD and recurrent chest infection due to aspiration pneumonitis.
- EA with proximal TEF (1%)—EA with fistula from upper pouch.
- EA with both proximal and distal TEF (1%): Both pouch communicates with the trachea.

INVESTIGATION FOR DIAGNOSIS AND MANAGEMENT OF THE PATIENT

Radiological Diagnosis (Figs 101 and 102)

- X-ray neck including chest and abdomen (with radiopaque marker—size 10 red rubber catheter) failure to pass catheter into stomach because it has become coiled up in the atretic esophageal pouch

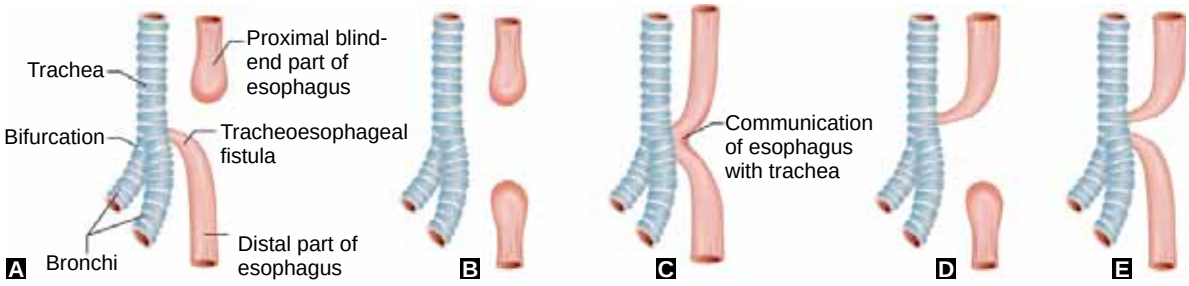
  Note:
  - The absence of abdominal gas and scaphoid abdomen-suggest EA without TEF
  - Presence of abdominal gas (air distended stomach) suggest EA with TEF
- When a plain X-ray is not conclusive—(in isolated TEF)—esophagogram with water soluble dye (contrast medium) may demonstrate the defect.
- Other investigations according to need
  - CBC: for septic screening
  - ABG.

TREATMENT

- EA is a surgical emergency. The goal is to prevent aspiration, provide nutrition and support before definitive surgical procedure
- A gastrotomy is indicated to decompress the abdomen to prevent the aspiration of gastric contents
- Surgery (Fig. 103): Surgical repairs (Transthoracic extrapleural tracheoesophageal disconnection with end anastomosis).

Prognosis

- Early recognition, term baby with normal weight, gap (upper and lower part of esophagus) <2 cm and no pulmonary and cardiac complication- prognosis is relatively good with improved NICU care
- Preterm low birthweight (PTLBW) with pneumonia, sepsis, gape >2 cm with cardiac and pulmonary complication: bad prognosis.



Figs 100A to E: Various types of tracheoesophageal fistula (TEF)

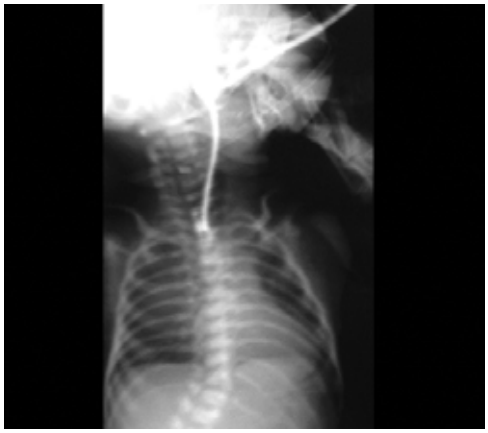


Fig. 101: X-ray showing radiopaque tube in the esophageal pouch absence of air within the stomach suggests there is no fistula

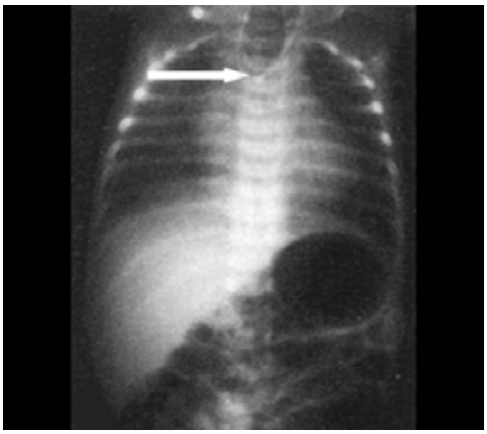


Fig. 102: X-ray chest showing coiling of the feeding in esophagus and gas shadow in the abdomen. Characteristics of esophageal atresia with tracheoesophageal fistula

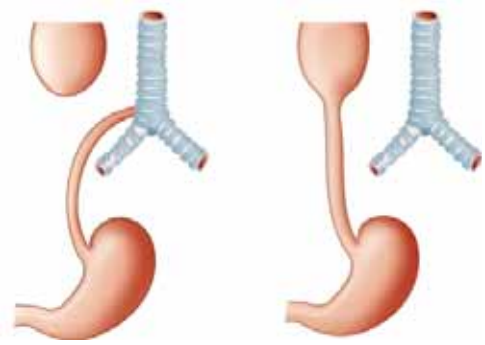


Fig. 103: Tracheoesophageal fistula before and after surgical correction

PULMONARY HYPERTENSION AND PERSISTENT PULMONARY HYPERTENSION

PROBLEMS

- Respiratory distress and cyanosis (central)—occurs soon after birth
- Fetal distress or difficult delivery (usually, but not always)
- Single loud pulmonary second sound
- Tricuspid regurgitation murmur
- Chest X-ray showing—Normal size heart, well expanded oligamic lungs
- Blood gases—show hypoxia with a relatively normal PCO_2
- Often little improvement in saturation—on 100% oxygen inhalation.

DIAGNOSIS

Most neonates with clinically significant pulmonary hypertension (PH) will have either persistent pulmonary hypertension of the newborn (PPHN) or BPD.

Main causes of PH in newborn include:

- PPHN
- Pulmonary vein stenosis
- PH secondary to left heart disease
- PH secondary to lung disease and/or hypoxia.

PATHOGENESIS AND PATHOLOGY

Pulmonary hypertension (PH) in neonate occurs when mean pulmonary artery pressure greater than or equal to 25 mm Hg. PH occurs when raised pulmonary vascular resistance (PVR) in utero fails to drop immediately after birth. PVR in utero is about 10 times high than newborn level. The systemic vascular resistance is low in utero by virtue of placental circulations. The forum and ovale and arterial duct both serve to bypass the high resistance of pulmonary vasculature. The normal fall of PVR at birth occurs: (a) In response to activation of stretch receptors following lung impletion with onset of breathing and (b) by potent effect of oxygen as a pulmonary vasodilator. While there is an abrupt fall of PVR after birth, it may take up to 6 weeks for complete fall of PVR (Fig. 104).

PERSISTENT PULMONARY HYPERTENSION OF NEWBORN (PPHN)

Failure of PVR to fall after birth is the most common mechanism of PPHN. It affects principally in infants at or close to term. The pathophysiology is divided into three varieties:

- Secondary to hypoxia, hypercapnia and acidosis due to coexistent lung pathology causing pulmonary vascular constriction. The most frequent clinical conditions associated are:
  - Meconium aspiration syndrome
  - Surfactant deficiency
  - Pneumonia
  - Perinatal asphyxia
  - Congenital diaphragmatic hernia

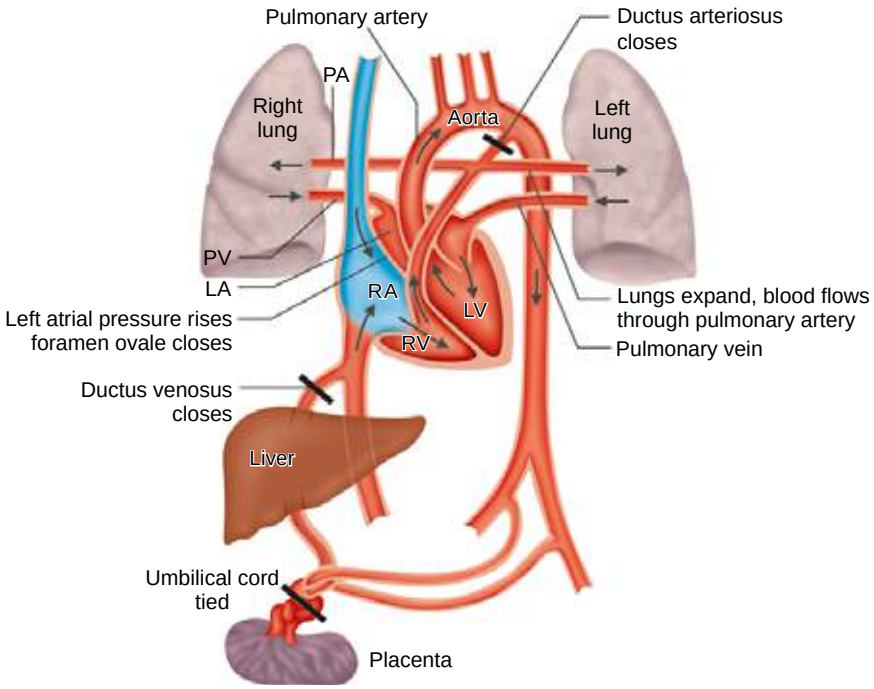


Fig. 104: The figure showing fetal circulation with changes in circulation at birth. Solid lines indicate closure or ductus arteriosus, foramen ovale and ductus venosus. Umbilical cord is tied and cutoff from placenta at birth
Abbreviations: PA: Pulmonary, RV: Right ventiricler artery, LA: Left atrium, PV: Pulmonary vein

- Idiopathic PPHN: Normal lung parenchyma but abnormal remodeling of pulmonary vasculature. X-ray chest will show reduce pulmonary vascular markings. Echocardiogram is useful to rule out congenital cyanotic heart disease.
- Less common but potentially more catastrophic group: Hypoplastic pulmonary vasculature with pulmonary hypoplasia and renal agenesis.

Clinical Presentation

- Cyanosis at birth with little improvement in oxygen saturation with 100% oxygen
- Evidence of underlying parenchymal lung disease (MAS, RDS etc.) but hypoxemia is out of proportion of lung disease
- Single loud second heart sound
- Murmur of tricuspid regurgitation

Investigation

- ECG: Right ventricular hypertrophy
- Echocardiography: The mainstay of PPHN diagnosis. Detection of tricuspid regurgitation (TR) (Fig. 105), measured with continuous wave Doppler
  - Detection of pulmonary artery systolic pressure (↑)
  - Detection of poorly functioning right ventricle (important when pulmonary artery pressure is normal)
  - Serve to exclude congenital heart disease
- X-ray chest: May show oligemic lung filled with normal heart size
- Blood gas analysis: Hypoxia with or without hypercarbia

Treatment

Correction of hypoxia, hypothermia, acidosis and poor perfusion. Other treatment include sedation, commonly paralysis, use of surfactant.
For perfusion improvement: Use of inotropes to decrease right ventricular after load.
Correction of acidosis: Use alkalinization (debatable).

Correction of Hypoxia

- Initially supplemented oxygen but cyanosis is usually refractory leading to escalation of therapy
- Positive pressure ventilation initially but contributes lung injury and chronic lung disease
- High frequency oscillatory ventilation (HFOV): More useful. Maintains oxygenation at low tidal volume thus reduces lung injury by minimizing barotrauma.

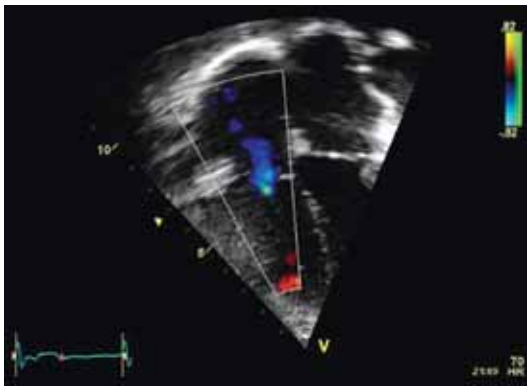


Fig. 105: Color flow map of tricuspid regurgitation (TR) on echocardiography

Inhaled Nitric Oxide (iNO)

- Standard practice of PPHN. It is important pulmonary vasodilator. It acts through stimulation of cyclic GMP (cGMP). By inhalation iNO selectively vasodilates pulmonary vasculature in comparison to oral vasodilators. It is also bronchodilatation property and improve ventilation perfusion mismatch.
- An initial dose of 20 ppm is commonly used. However, the dose can be lower subsequently.

Phosphodiesterase Inhibitors: Sildenafil

Phosphodiesterase (PDE) are potent smooth muscle constrictors. PDE5 is the most potent PDE which is abundantly present in the lung. Sildenafil and related compounds are selective PDE5 inhibitor. Sildenafil acts by increasing intracellular cGMP like iNO. It is orally active.

Although iNO is the drug of choice to treat PPHN, sildenafil perhaps is the first drug of choice in developing countries when iNO is not available.

Dose of oral Sildenafil: Starting dose 0.25–0.5 mg/kg/dose up to 2 mg/kg/dose 4–6 hourly.
Intravenous preparation is also available.

Prostaglandins

Prostacyclin is a potent pulmonary vasodilator whether administered intravenously or by inhalation. Higher doses may be required (20 ng/kg/min) than older infants. Where there is suspicion of ductal dependency (transposition physiology or ductal dependency of systemic and pulmonary circulation) prostaglandins E1 or E2 are routinely infused to maintain ductal patency.

Extracorporeal Membrane Oxygenation

It should be considered in any term neonate with PPHN refractory to above therapies.

CONGENITAL HEART DISEASE PRESENTING AS RESPIRATORY DISTRESS IN NEWBORN

PROBLEMS

- Respiratory distress- which is aggravated with feeding and after crying
- Increasing sweating during feeding since birth
- Feeds take longer time to complete
- Irritability, excessive sweating, poor and difficult feeding
- H/O recurrent respiratory tract infection
- FTT, metabolic acidosis, collapse and shock
- Dyspnea, tachypnea, tachycardia, cyanosis, murmur, weak-pulses, hypotension, cardiomegaly, dysmorphic features (Down syndrome).

DIAGNOSIS: CONGENITAL HEART DISEASE IN NEWBORN (DISCUSSED IN DETAIL IN CARDIOLOGY CHAPTER)

Diagnosis: Based on C/F and related investigations.

INVESTIGATION

- X-ray chest: Cardiomegaly, pulmonary vascular change
- ECG: Not diagnostic but can say the primary heart defects

- Echocardiography: Demonstrate the extent of cardiovascular dysfunction and the cause of heart failure
- Blood: TC and DC of WBC, PBF
- ABG: Metabolic acidosis.

Heart failure in neonate: The most common signs of heart failure on examination are:

- Dyspnea, increased rate and difficulty in breathing is always present even during sleep
- Central cyanosis—relieved by oxygen (in non-cyanotic congenital heart disease) and grunting respiration—occur if there is pulmonary edema
- Tachycardia is usual even at rest (HR- >160/min in a child under-12 months old, >120/min- child 12 months to 5 years)
- Gallop rhythm with basal crepitation- on auscultation
- Enlarged tender liver
- In infants—fast breathing (or sweating), specially when feeding.

TREATMENT

- **Supportive**
  - Bed rest in head up position
  - Oxygen inhalation- Cool, humidified oxygen by hood/box mask or nasal prongs
  - Maintenance of temperature
  - Control of infection- by appropriate antibiotics- if any
  - Maintenance of fluid and nutrition by:
    Feeding: Breastfeeding or nasogastric feeding of foods rich in calorie and low sodium diet.
    Control of fluid overload by:
    - Fluid restriction: by 25–30%
    - Diuretics: Frusemide, thiazide or K+ sparing diuretics.
  - Control of underlying causes and precipitating factors.
- **Drug therapy**
  Inotropic agents: In severe acute heart failure, an IV infusion of dopamine (5 µg/kg/minute) will improve cardiac output. In less severe cases- digoxin can be used. Digoxin particularly effective in infants and children with poor myocardial function (endocardial fibroelastosis, myocarditis, cardiomyopathy or obstructive lesions like coarctation).

  It is much less effective when there is volume overload (VSD, PDA, AV canal defect, truncus arteriosus) and often not used in such lesions. It should not be used in the preterm infant with a PDA.

Digoxin Dosage

Digitalization- 40 µg/kg/day in three divided doses over the first 24 hours, by mouth. If oral route cannot be used, the intravenous dose is 30 µg/kg/day in three divided doses, each given over 15 minutes, over the first 24 hours.

Maintenance: 10 µg/kg/day in two divided doses, by mouth. Therapeutic level: 1–3 µg/mL.

Diuretics

Frusemide (2 mg/kg/day in 2 divided doses) is the most effective. If used in the long-term a potassium supplement (kCl 2 mmol/kg/day in 2 divided doses) or a potassium sparing diuretics, such as spironolactone (2 mg/kg/day in 2 divided doses) is necessary.

Vasodilators

These are used in children with vulvular lesions or myocardial disease to supplement diuretic therapy. They should be used with caution to avoid hypotension and should be started in hospital. Captopril, enalapril (after load reducing agents) and hydralazine are alternatives.

Follow-up

• Respiratory rate • Heart rate • Liver size • Body weight	To assess the response to treatment

Continue treatment until the respiratory rate and heart rate are normal and the liver is no longer enlarged.

Counseling parents about problem and psychological support.

NEONATAL VENTILATION

DEFINITION

Mechanical ventilation in the newborn may be defined as movement of gas into and out of the lungs by an external source (resuscitation bag, CPAP device or ventilator).

AIM

To optimize both gas exchange and clinical status at minimal FiO_2 and ventilator pressure.

TYPES OF VENTILATOR SUPPORT

- Continuous positive airway pressure (CPAP):
  Can be delivered by following devices:
  - Face mask
  - Nasal or nasopharyngeal prongs (nCPAP)
  - Endotracheal tube.
- Mechanical ventilator:
  - Bag and mask or bag to endotracheal tube
  - Pressure control ventilators
  - Synchronized and patient triggered ventilator
  - Volume control ventilator
  - High frequency ventilator
  - ECMO (extra corporeal membrane oxygenation).

COMMON TERMS USED IN MECHANICAL VENTILATION

- PIP (peak inspiratory pressure): To inflate the chest adequately. Normal volume 15–20 cm of H_2O. It ensures tidal volume (4–6 mL/kg)
  - Increased PIP → may cause pneumothorax
  - Decreased PIP → may cause hypoventilation.
    Initial PIP is selected by chest movement and air-entry, later, PIP is adjusted by blood gas to achieve optimum tidal volume.
- PEEP (positive end expiratory pressure): Distending pressure during the expiratory phase, to maintain functional residual volume. It allows alveolar ventilation & varies from 3–7 cm of H_2O.
  - Increased PEEP → air trapping → decreased CO_2 retention
  - Decreased PIP → lung collapse.

- Ventilatory rate: Varies from 20–60/minute. Match with patient own respiratory rate.
- FiO_2 (fraction of inspired O_2). 21–100% O_2. The goal is to maintain adequate tissue oxygenation by PaO_2 of 60–80 mmHg. Simple and most direct means of improving oxygenation. Raising MAP (mean airway pressure) improve oxygenation.
- IT (Inspiratory Time): Most commonly 0.25–0.5 seconds. Must allow for adequate expiratory time.
- Gas flow: 7–12 L/min. Is required to provide square pressure wave form. High flow needed for very high PIP.
- MAP (Mean airway pressure): The average proximal pressure applied to airway throughout the entire respiratory cycle.

FORMULA

$$\frac{R \times IT \times PIP + (60 - R \times IT) \times PIP}{60}$$

Determined by the above ventilatory setting varies from 5–15 cm H_2O. Excessive MAP may interfere with venous return.

Initial Ventilator Strategy

Depends on disease states and pulmonary mechanics.

Diseased Lung

- RDS
- Congenital pneumonia
- MAS
- PPHN
- Diaphragmatic hernia.

Ventilatory Setting in Diseased Lung

- FiO_2—if cyanosis 100% O_2 (range 60–100%)
- PIP—18–25 cm of H_2O
- PEEP—4–6 cm of H_2O
- RR— 60/minute (range 40–60/min)
- IT— 0.4–0.5 second.

Clinical conditions with respiratory problem with primarily normal lung:

- Perinatal asphyxia
- Apnea (recurrent)
- Drugs (maternal GA drugs)
- Neuromuscular disease (congenital myopathy)
- IEM (inborn error of metabolism
- Postoperative.

Ventilatory Settings in Normal Lung

- FiO_2: 10–30% (0.1–0.3)
- PIP: 15 cm of H_2O (range 10–15)
- PEEP: 3 of H_2O (range 3–4)
- RR: 30–40/minute
- IT: 0.3 sec (range 0.3–0.4 second).

Safety Limit of Mechanical Ventilation

- FiO_2: <60%
- PIP: <20 cm H_2O
- PEEP: <4 cm H_2O
- MAP: <15 cm H_2O.

CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP)

Features (Fig. 106)

- Continuous flow of heated, humidified gas at 4–8 cm of H_2O
- Maintains end-expiratory lung volume in spontaneously breathing baby
- It is distinct from IPPV or IMV in which breathing is taken over by the ventilator machine completely and the increase in pulmonary pressure occurs during both inspiratory as well as expiratory phases.

Indication of CPAP

- Early treatment of mild RDS (FiO_2 >0.4)
- Moderately frequent apneic spells
- Meconium aspiration syndrome
- For extubation from IMV (prevent postextubation atelactasis)
- After recent extubation (if retraction)
- Weaning ventilator dependent infants.

Guidelines for Initiation of CPAP

The following guidelines essentially apply to a baby with RDS due to mild to moderate hyaline membrane disease. For practical purpose, it is the nasal CPAP that is most relevant to neonatal care:

- Start with nasal CPAP of 5–6 cm H_2O and FiO_2, <0.6 (60%) if required
- Reach a level of 8–9 cm H_2O
- Now increase FiO_2 in steps of 0.05 (5%) to a maximum of 0.8 (80%).

Figs 106A to D: (A and B): Bubble CPAP; (C and D) and a baby with RDS receiving positive pressure ventilation through nasal CPAP

Aim of CPAP

- To achieve satisfactory clinical and blood gases status.

Weaning from CPAP

- Reduce nasal CPAP to a level of 8 cm H_2O
- Reduce FiO_2 by 0.05 (5%) decrements to reach FiO_2 of 0.04
- Now reduce CPAP by 1 cm H_2O decrements
- Reach a level of CPAP of 4 cm H_2O and FiO_2 of 0.4
- Remove CPAP and place the baby in the oxygen hood.

Adequacy of CPAP

- Absence of cyanosis
- Absence of retractions, grunting
- Comfortable baby
- Capillary refill time <3 seconds
- Oxygen saturation: 90–93%
- Blood gases:
  - pH: 7.35–7.45
  - PaO_2: 60–80 mm Hg
  - $PaCO_2$: 35–45 mm Hg.

Advantages

- Prevents alveolar and airway collapse when used in early RDS
- Less invasive and causes less barotrauma
- Decreases frequency of obstructive and mixed apneic spells.

Disadvantages

- Does not improve ventilation and may worsen it, not suitable for severe parenchymal lung disease or obstructive airway disease
- Swallowed air may elevate diaphragm and compromise respiratory function
- Excessive pressure may lead to CO_2 retention.

MECHANICAL VENTILATION/INTERMITTENT MANDATORY VENTILATION (IMV)

Function: Two Main Functions

- Re-establishes loss of tidal volume and improves oxygenation
- Removes CO_2.

Indications of Mechanical Ventilation

- Prolonged apnea > 20 second
- Apneic spell with bradycardia or cyanosis
- Cyanosis with FiO_2 > 0.4
- Frequent apnea unresponsive to drugs
- pH- <7.25, PaO_2- <50 mm Hg in FiO_2 >1.0, $PaCO_2$- >60 mm Hg
- Impending or existing shock
- Retractions—moderate to severe/relieving "increase work of breathing"
- General anesthesia.

Basic Ventilator Setting on IMV (Fig. 107)

- Intubate baby, fix endotracheal tube, check ventilator. Air/oxygen should be warmed to 37°C and humidified to 70–100%.
- Initial settings

FiO_2	:	0.5
PIP	:	10–14 cm (in normal lungs) 16–20 cm (in diseased lungs)
PEEP	:	4–5 cm H_2O
Rate	:	40–50 per minute
IT	:	1:1–1.5:1.

- Observe infant for cyanosis, absence of retractions, chest wall movement and breath sounds.
- If ventilation is inadequate, increase PIP by 1 cm H_2O every few breaths until air entry appears adequate.
- If oxygenation is inadequate as indicated by cyanosis or poor saturation on pulse oximeter, increase FiO_2 by 0.05 (5%) every minute until cyanosis is abolished or the saturation reaches 90–95%.
- Draw arterial blood gas.

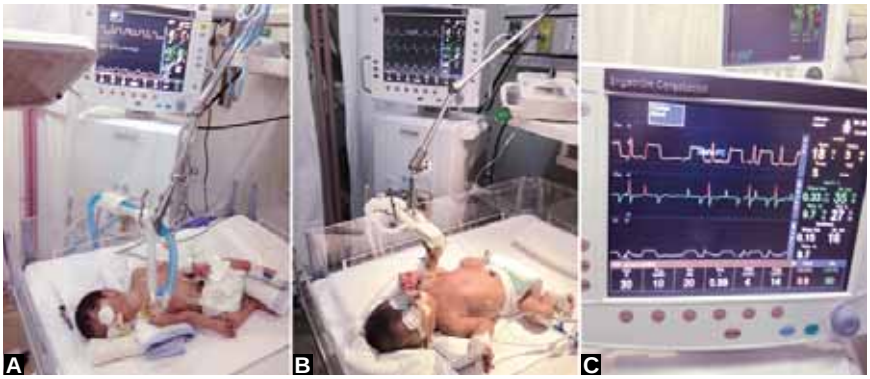
HIGH FREQUENCY VENTILATOR

Features

- Delivers rapid rates (300–1500 bpm, 5–25 Hz) with tidal volume (TV) equal to or less than anatomical dead space.
- Applies continuous distending pressure and small TV superimposed at high rate.

Types

- High frequency oscillatory ventilation (HFOV)
- High frequency jet ventilation (HFJV).



Figs 107A to C: (A) Neonates with RDS; (B) and MAS; receiving mechanical ventilation; (C) showing ventilator setting monitor (SIMV)
Abbreviations: RDS: Respiratory distress syndrome, MAS: Meconium aspiration syndrome

Advantages

- May be useful in pulmonary air leak syndrome
- Allows the use of a high mean airway pressure (MAP) and may be helpful in babies with severe respiratory failure requiring MAP on conventional mechanical ventilation (CMV).

Disadvantages

- No significant clinical benefits have been demonstrated over CMV
- More complex and expensive.

Basic Ventilator Setting on IMV

See Tables 32 to 35.

Monitoring of Adequacy of Mechanical Ventilation and Monitoring of Baby in a Ventilator

The parameters indicating adequacy of ventilation are given below:

- Clinical parameters: Comfortable baby, absence of cyanosis, absence of retractions, prompt capillary filling, normal blood pressure, adequate chest expansion, adequate air entry.
- Pulse oximetry: Saturation—90–93%
- Blood gases
  PaO_2 : 60–80 mm Hg
  $PaCO_2$: 35–45 mm Hg
  pH : 7.35–7.45.
  - ABG- To assess the severity of the condition. It should be done:
    - 30–60 minutes after setting
    - Before and after giving surfactant—usually after 30–60 minutes of surfactant therapy
    - Normally 12–24 hourly
    - After extubation. If PaO_2 not increased and ↑$PaCO_2$ → consider tuber block.
- Radiological assessment
  - At setting
  - After intubation—To see tube position—Tube should be just above the carina (second and third thoracic vertebra)
  - After giving surfactant
  - When clinically pneumothorax is suspected

Table 32: How to change ventilator setting on IMV for different purpose

	FiO_2	PEEP	PIP	Rate	Flow	IT
For decreasing $PaCO_2$	-	↓	↑	↑	↑	-
For increasing $PaCO_2$	-	↑	↓	↓	-	-
For increasing PaO_2	↑	-	↑	↑	-	↑
For decreasing PaO_2	↓	-	↓	↓	-	↓

- ↑ PIP → Associated with pneumothorax
- ↓ PIP → Associated with hypoventilation
- ↑ PEEP → Associated with air trapping → CO_2 retention
- ↓ PEEP → Associated with lung collapse.

Table 33: Requirements of PEEP with FiO_2

FiO_2	PEEP (cm H_2O)
0.3	3
0.4	4
0.5	5
0.6	6
0.7-0.8	7
Above	8

  - After extubation
  - Sudden deterioration of patient: Suspect-
    - Tube block
    - Pneumothorax
    - Severe IVH
    - Pulmonary hemorrhage
  - Gradual deterioration of patients: Suspect
    - Sepsis
    - Electrolyte imbalance
    - Hypoglycemia
    - Hypothermia
    - Hypotension
    - Anemia
    - Partial tube block.

Steps to be take if a patient deteriorates inventilation are provided in Flow chart 5.

- Hematological assessment:
  - Septic screening
  - CBC, CRP → daily
    - Hb%
    - Should be >13 g/dL. If <12 g/dL blood transfusion preferably packed RBC (PRBC) should be given.
- Bacteriological assessment
  - 2–3 times/week blood culture
  - Culture of cutting tube end.
- Biochemical assessment:
  - RBS- 4–8 hourly
  - S. electrolytes—daily
  - S. calcium—daily.

Weaning from the Ventilator

Depends on evidence of improvement- includes clinical and biochemical parameters.

Flow chart 5: Steps to be taken if patient deteriorated in ventilator

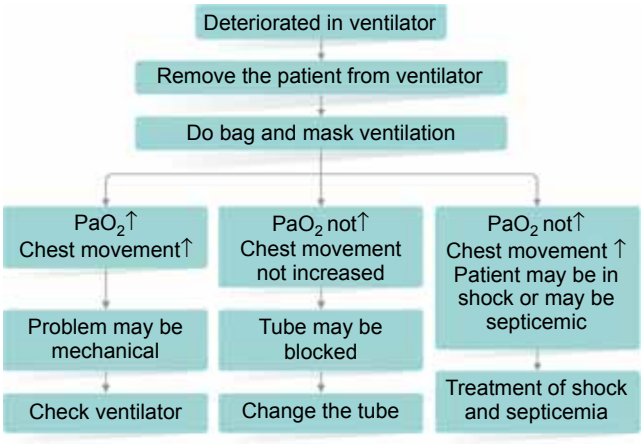


Table 34: Usual effects of changing ventilator settings

Increasing	PaO_2	$PaCO_2$	pH	Complications
FiO_2	↑	-	-	O_2 toxicity (Bronchopulmonary dysplasia), ROP, Absorption atelectasis
CPAP/ PEEP	↑	0/↑	0/↓	Hypoventilation with respiratory acidosis, combined with metabolic acidosis: air leaks
PIP	↑	↓	↑	Barotrauma with air leaks. Bronchopulmonary dysplasia (BPD), respiratory alkalosis
Rate	-	↓	↑	Respiratory alkalosis
I/E ratio (1:1 to 3:1)	↑	0	0	Increased intrapleural pressure, ↓venous return

Table 35: Probable causes of no improvement in mechanical ventilation

Findings	Possible causes
No air entry bilaterally	• Air leak
	• Plugged ET tube
	• Accidental extubation
Diminished air entry	• Air leak
	• ET tube too high
Air entry over stomach	• Accidental extubation
Air entry unequal	• Air leak
	• ET tube too low
Cardiac point of maximal intensity shifted	• Air leak with tension

- Arterial blood gases are stable and in the physiological range
- There are spontaneous respiratory efforts against ventilator
- There is increased activity and muscle tone and progressively decreased FiO_2 requirements.

How to do Weaning?

- One ventilator setting at a time is changed and arterial blood gases, pulse oxymetry values are evaluated to determine the infant response before another adjustment is made.
- FiO_2 is usually lowered first as hyperoxia causes BPD and ROP (reduced 5–10% increments at a time)
- PIP- is lowered in 1–2 cm increments
- Rate- is lowered in 1–5/minute.

When to Extubate?

- FiO_2: 0.3
- PIP <15 cm H_2O
- Rate <30/minute
- Adequate oxygenation and ventilation on CPAP alone has been maintained.

Prerequisite for Extubation

- Sucker machine
- O_2—hood
- >10% O_2 supply should be given
- CPAP for 2–3 days in case of sick baby
- Corticosteroid- if intubation for prolonged time
- Injection aminophylline—should be given 12 hours before extubation- <32 weeks or <1500 grams baby.

RETINOPATHY OF PREMATURITY (ROP)

This is a disorder of retinal vasculature affecting premature babies. The disorder ranges from mild transient retinal disorders to severe vasoproliferative disorder, retinal detachment and blindness. It is a leading cause of blindness in developing countries.

RISK FACTORS

- Prematurity (<32 weeks), LBW (<1,500 g)
- Male sex and supplemented oxygen therapy
- Genetic: Genetic polymorphism controlling retinal vasculature development also contribute.

PATHOGENESIS

In premature infants there is a large area of avascular retina, more near to optic nerve. It is possible that hyperoxia causes retinal vasoconstriction in peripheral vessels with resulting upregulation of angiogenic factors and abnormal neovascularization.

INTERNATIONAL CLASSIFICATION OF ROP (FIG. 108)

- Stage 0: Incomplete vascularization of retina
- Stage 1: A white demarcation line between vascular and avascular zone
- Stage 2: Elevation and thickening of the demarcation line to form a broad thick ridge
- Stage 3: Extraretinal fibrovascular proliferation into the vitreous
- Stage 4: Contraction of the neovascular ridge pulls the retina up with subtotal detachment
  4a- Does not involved fovea
  4b- Involved fovea
- Stage 5: Retinal detachment (retrolental fibroplasia).

"Plus disease" indicates engorged and tortuous vessels around the optic nerves and indicates more advanced and aggressive form of retinopathy.

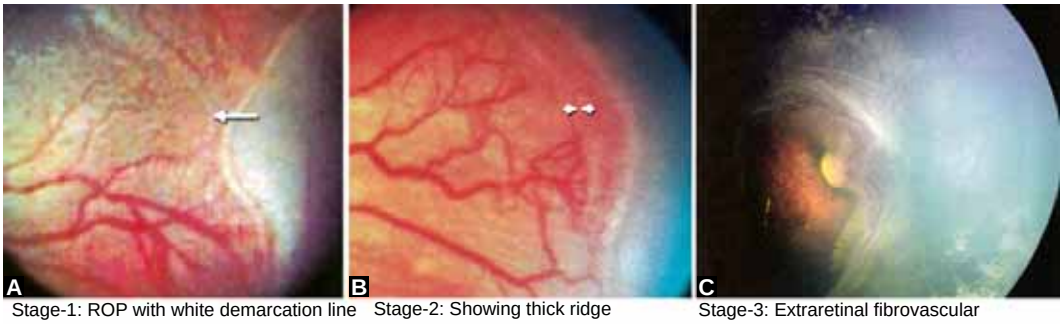
MANAGEMENT

Screening: Screening should be done routinely for all infants below 31 weeks gestation or weighing <1,500 gm at birth.

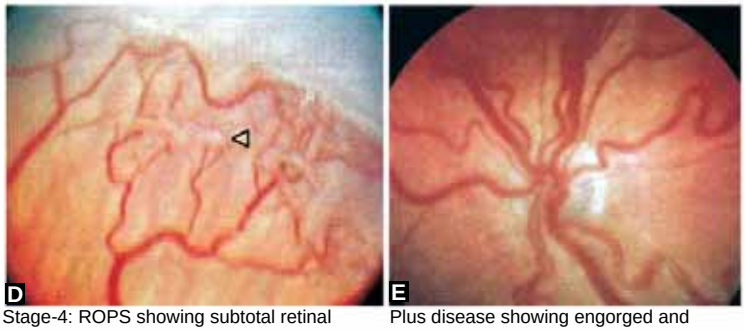
Time of screening: 6–7 weeks of postnatal age.

- Stage 1 and 2 : No treatment is necessary
- Stage 3 : Laser ablation under general anesthesia of avascular retina anterior to the ridge in eyes with sight threatening ROP
- Stage 4 and 5 : Rare but serious. Treatment is complex

Prognosis: >90% of infants with stage 1 to 3 retinopathy do well and have good vision.



Stage-1: ROP with white demarcation line | Stage-2: Showing thick ridge | Stage-3: Extraretinal fibrovascular proliferation



Stage-4: ROPS showing subtotal retinal detachment | Plus disease showing engorged and tortuous vessels of advanced ROP

Figs 108A to E: Showing various stages of ROP

METABOLIC BONE DISEASE OF PRETERM BABY (OSTEOPENIA OF PREMATURITY)

DEFINITION

Metabolic bone disease, also known as osteopenia of prematurity, occurs due to inadequate bone mineralization in preterm babies.

PATHOGENESIS

Maximum (two-thirds) phosphorus and calcium accretion of fetal bones occurs during third trimester of pregnancy from which the fetus is deprived, when infant is born preterm.

- Poor intrauterine phosphate and calcium accretion during intrauterine life is followed by poor postnatal intake coupled with high growth velocity.
- Phosphate is more critical than calcium as it is used for other metabolic process.

RISK FACTORS OTHER THAN PREMATURITY

- Prolonged parental nutrition.
- Breastfeed without phosphate and calcium supplement in preterm.

NORMAL REQUIREMENT POSTNATALLY IN PRETERM BABIES

- Calcium: 2.5–3.0 mmol/kg/day.
- Phosphate: 2.1–2.6 mmol/kg/day.

BREASTMILK CONTENTS OF PHOSPHATE AND CALCIUM

- 180 ml (6 oz) of breast milk provide only:
  - 1.6 mmol of calcium, and
  - 0.9 mmol of phosphate.
- The deficit can be corrected if breastmilk fortifier (BMF), or supplementary phosphate and calcium are provided.

CLINICAL PRESENTATIONS

- Osteopenia occurs in approximately 50% preterm babies less than 1,000 g and 30% preterm babies less than 1,500 g.
- Recurrent chest infection due to poor osteopenic rib cage.
- Slower linear growth occurs.

BIOCHEMICAL

Raised alkaline phosphatase (ALP) (> 1000 IU/L)

- Hypophosphatemia (< 1.8–2.2 mmol/L).
- Calcium normal or raised, but may be low in advanced disease.

RADIOLOGICAL CHANGE

- Initially osteopenia, if untreated for more than 6 weeks, features of rickets and fracture (Fig. 109).
- Urine: Urinary calcium/phosphorous (Ca/P) ratio is greater than 1 due to phosphate depletion and relatively increased calcium.

MANAGEMENT

- Prevention and treatment.
- Oral vitamin D 400 IU/day.

Phosphate Supplement (Julic Solution Containing Sodium Phosphate)

- If birthweight is less than 1,500 g and ALP is greater than 500 IU/L and plasma phosphate less than 1.8 mmol/L:Dose = 1 mmol/kg/day
- Add calcium supplement, if despite phosphate supplement
  - Phosphate (PO_4) less than 1.85 mmol/L

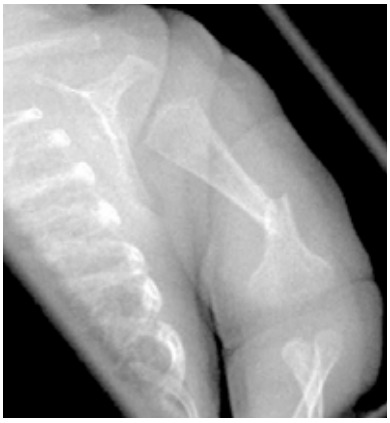


Fig. 109: X-ray showing fracture of shaft of humerus due to osteopenia of prematurity

  - Rising ALP
  - Radiological change
- Add alfa calcidol, if ALP is greater than 1,000 IU/L.

PROGNOSIS

- Bone mineralization and fracture risk decreased by 2 years.
- Short stature can occur at 18 months.

ANEMIA OF PREMATURITY

INTRODUCTION

Anemia of prematurity is a multifactorial condition due to:

- Immature erythropoiesis
- Recurrent phlebotomy
- Reduced erythropoietin production in response to hypoxia.

The hemoglobin (Hb) level in fetus increases as gestational age increases, being 14.5 g/dL at 28 weeks and increases to 16.8 g/dL at term (40 weeks). After birth, Hb level again start to fall until 8–12 weeks. Preterm babies are born with low Hb reserve compared to term and its low Hb continues to decrease further during early postnatal weeks (Table 36).

DIAGNOSIS

In a well term infant, the hemoglobin continues to fall during early postnatal weeks and hemoglobin is as low as 9.4–11 g/dL that occurs at 8–12 weeks of age. For preterm infants, the nadir in hemoglobin occurs in earlier at 4–8 weeks of age and is lower (6.5–9 g/dL) than in term babies. The diagnosis is made in clinically well preterm baby having low hemoglobin levels normocytic normochromic blood film and no nucleated red cell.

PRESENTATION

Anemia may produce multiorgan dysfunction due to inadequate tissue oxygen delivery. Acute anemia is usually symptomatic while chronic anemia is asymptomatic and subtle.

- Cardiovascular: Tachycardia, hypotension, prolonged capillary refill.
- Respiratory: Apnea, respiratory distress, raised oxygen requirement.
- Other: Pallor, lethargy, feed intolerance, poor weight gain.

MANAGEMENT

Four stages:

1. Exclude other causes of anemia.
2. Avoidance of phlebotomy.
3. Reducing the need for blood transfusion.
4. Blood transfusion.

Exclude other causes of anemia by appropriate test where indicated. Also, mother's blood is tested for fetomaternal bleed, if suspected (Fig. 110).

Simple algorithm to exclude neonatal anemia other than anemia of prematurity has been described in Flow chart 6.

If all the above conditions are negative and the reticulocyte is normal with blood film being normocytic normochromic, the most likely diagnosis is anemia of prematurity.

Avoidance of Phlebotomy

Reduce phlebotomy losses by only performing necessary blood test, utilize microsample, use technology, such as transcutaneous monitoring (pulse oxymetry).

Reducing the Need for Blood Transfusion: Hematinic and Erythropoietin

Hematinic

A severity of anemia of prematurity and need for blood transfusion can be reduced by:

- Iron and folate supplement in all preterm infants; iron 3 mg/kg/day from 4–6 weeks of age for 6–12 weeks.
- Folic acid 50 µg daily or 500 µg once daily.

Erythropoietin

- Judicious use of erythropoietin can reduce the requirement of blood transfusion (BT) in otherwise normal preterm babies with anemia.

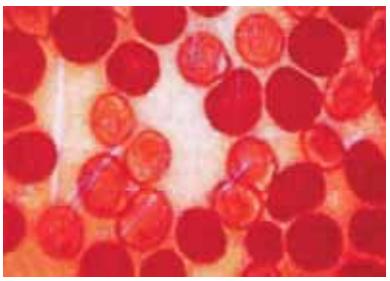


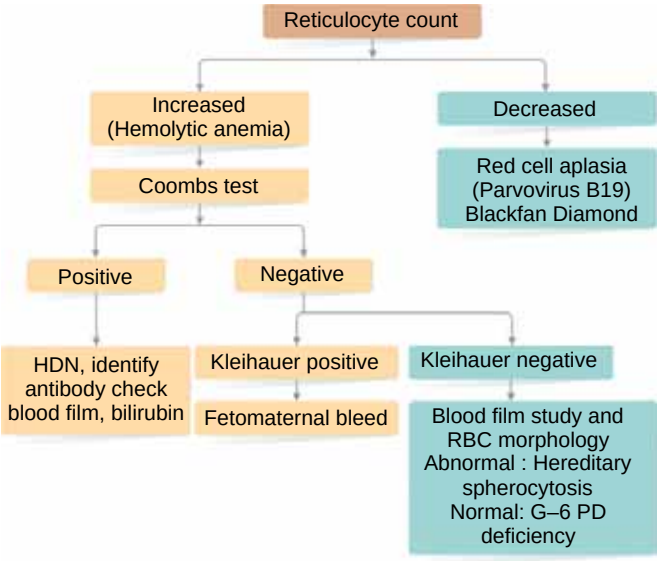
Fig. 110: Blood film of mother with fetomaternal bleed showing dark red color cell containing hemoglobin F resistant to acid elution while maternal cell are pale color due to elution of hemoglobin A appearing as ghost (Kleirhauer positive)

Table 36: Normal hemoglobin values in preterm and term

	Preterm		Term	Postnatal term babies		
	28 weeks	34 weeks	40 weeks	First day	1 week	2 weeks
Hb (gm/dL)	14.5	15	16.8 (14–20)	18.4 (15–23)	17 (13–22)	16.8 (13–20)

Abbreviation: Hb, hemoglobin

Flow chart 6: Algorithm for diagnosis of anemia in newborn



Abbreviations: HDN, hemolytic disorder of the newborn; RBC, red blood cell; G6PD, Glucose-6-phosphate dehydrogenase

- Drug preferably used: Recombinant erythropoietin epoeitin-β preferably used instead of epoeitin-α.
- Dose and route: 300 µg/kg as a single subcutaneous injection, three times a week, starting in the first week of life.
- Hemoglobin start to rise 10–14 days after erythropoietin injection.
- Iron supplement should be started as soon as possible to prevent erythropoietin related iron deficiency.

Blood Transfusion Indication

- Signs of shock (hypotension, tachycardia, poor perfusion, lactic acidosis).
- Hemoglobin less than 7 g/dL in any stable growing preterm infant.
- Hemoglobin less than 8 g/dL in any stable growing preterm, if requiring nasal cannula or tachycardia (heart rate >180/min), tachypnea (>80/min) or increasing apneas.
- Hemoglobin less than 10–11 g/dL in a baby requiring ventilation or nasal continuous positive airway pressure (NCPAP).
- Threshold for BT will be higher, in any unstable preterm baby (sepsis, cardiovascular instability).
- Type of blood to be transfused: In acute symptomatic anemia uncross-matched O RhD negative red cells may be given.
- Quantity of BT: 15–20 ml/kg of packed red blood cells (PRBC) slowly over 4 hours.

BIRTH (INTRAPARTUM AND PERIPARTUM) ASPHYXIA/HYPOXIC ISCHEMIC ENCEPHALOPATHY

INTRODUCTION

Birth asphyxia and hypoxic ischemic encephalopathy (HIE) are synonymously used. The operational definition of birth asphyxia is failure to initiate and sustain breathing at birth. However, more scientifically, the term birth asphyxia is defined as impairment of placental or pulmonary gas exchange during intrapartum or peripartum period, resulting in hypoxemia, hypercapnia, and mixed respiratory and metabolic acidosis. There is simultaneous occurrence of hypoxemia and ischemia, and the term hypoxic ischemia is preferred. Consequently, upon hypoxemia and ischemia, vital organs like brain, kidney, heart and liver may be damaged, which is called hypoxic ischemic injury (HII). When there is brain damage as evidenced by significant encephalopathy, the term HIE is used. This term HIE more accurately describes the pathophysiology and has replaced the term birth asphyxia.

There is considerable debate regarding the contribution of hypoxemia ischemia during perinatal period to the totality of brain damage. According to definition of birth asphyxia, HII should take place during perinatal (intrapartum and peripartum) period, not before or after that period. It has been suggested that not infrequently, the brain may have been significantly injured by hypoxemia or nonhypoxemic events throughout the pregnancy and birth asphyxia is only the final insult with relatively small contribution of perinatal HII on overall brain damage of the fetus.

SIGNIFICANCE OF HYPOXIC ISCHEMIA ENCEPHALOPATHY

It is an important cause of neonatal mortality making it a leading cause of death for newborns. Birth asphyxia is responsible for 900,000 infants death as estimated by WHO. In the US, this is listed as 10th leading cause of neonatal death. It is also important cause of neurodisability in developing countries including Bangladesh and elsewhere.

CAUSES OF FAILURE OF BREATHING AT BIRTH

Failure to establish spontaneous respiration at birth can occur in other conditions, in addition to perinatal asphyxia. They are divided into:

- Failure to breath
- Failure to expand chest.

Failure to Breathe

- Prolonged intrapartum asphyxia
- Recent intrapartum or peripartum asphyxia
- Maternal narcotic ingestion
- Brainstem injury of newborn
- Cerebral dysgenesis.

Failure to Expand Chest

- Extremely preterm
- Congenital anomaly of respiratory tract
- Airway obstruction.

Throughout the world, HII of brain remain an important cause of perinatally acquired brain injury. However, it is more relevant to brain injury in term infants. In preterm, LBW infants, many antenatal insults like infection, chromosomal anomalies, etc., are more associated with preterm LBW babies than previously thought, and those factors could itself be responsible for preterm delivery. These preterm babies with immature subependymal germinal matrix are vulnerable to hypoxia associated with postnatal problems, such as respiratory distress syndrome (RDS), and may lead to intraventricular hemorrhage

(IVH) and periventricular leukomalacia (PVL). Therefore, it is difficult to measure the contribution of intrapartum or peripartum event (hence, the term birth asphyxia) in causing HIE in preterm infants.

As mentioned earlier, there are many conditions other than perinatal asphyxia in which the newborn cannot breathe spontaneously at birth and all of them are not birth asphyxia. They present with lethargy and poor activity. It is better to designate as "depressed neonate" instead of out-rightly term as birth asphyxia until there is/are strong evidences of birth asphyxia. All neonates requiring resuscitative measures at birth are not suffering from birth asphyxia. Ascribing all such depressed neonates as perinatal asphyxia or HIE is not fair as perinatal asphyxia has medicolegal implications. Similarly, all neonatal encephalopathy are not due to birth asphyxia. Features associated with neonatal depression and neonatal encephalopathies are discussed below, as they are relevant to HIE.

NEONATAL DEPRESSION

Neonatal depression can occur other than hypoxic ischemic encephalopathy. Neonatal depression describes infants who have a prolonged transition from intrauterine to extrauterine environment, with poor activity and also low American Pediatric Gross Assessment Record (APGAR) score. It is not a serious condition like neonatal encephalopathy and many conditions other than birth asphyxia may develop transient neonatal depression.

NEONATAL ENCEPHALOPATHY

It is a clinical term used to describe an abnormal neurobehavioral state that consists of decreased level of consciousness. It characteristically begins within the first postnatal day and may be associated with seizure like activity, hypoventilation or apnea, depressed primitive reflex, low APGAR score and the appearance of brainstem reflex. Moderate or severe neonatal encephalopathy is suggestive of birth asphyxia (intrapartum/peripartum).

Causes of Neonatal Encephalopathy

- HII
- Meningitis
- Septicemia
- Cerebral malformation
- Maternal anesthesia and sedation
- Metabolic disease (hypoglycemia, hypocalcemia, hyponatremia)
- Maternal substances abuse/neonatal abstinence syndrome.

The identifying points of perinatal asphyxia in depressed neonates or in neonates with features of encephalopathy include evidences of:

- Moderate or severe encephalopathy (Sarnat grade II and III) in association with near term (> 34 weeks) delivery
- Typical late neuroimaging findings for perinatal timing of injury
- Diffuse cortical atrophy, bilateral cortical lesion in cortical watershed areas [magnetic resonance imaging (MRI) finding], bilateral basal ganglia lesion (MRI finding)
- Umbilical arterial acidosis (pH < 7.0 and base deficit > 12 mmol/L) or fetal scalp/early newborn acidosis of similar degree with any combination of the following
  - Abnormal heart rate on tocograph
  - Difficult delivery or other history suggestive of hypoxic event around the time of labor
  - Need for resuscitative measure at delivery
  - Low APGAR score (<7 at 5 minute)
  - Early multiorgan dysfunction
  - Early injury suggestive of acute cerebral injury, e.g. cerebral edema on cranial ultrasound (USD).

In preterm infants, if IVH and PVL are detected in brain by USD, other etiologies and risk factors contributing to hypoxic ischemic insult must be considered.

EVIDENCES AGAINST INTRAPARTUM HYPOXIA (BIRTH ASPHYXIA)

- Intrauterine growth restriction
- Evidence of congenital infection [toxoplasmosis, others, rubella, cytomegalovirus, herpes simplex (TORCH)]
- Cerebral dysgenesis (Lissencephaly)
- Systemic infection
- Reduce heart rate variability from onset of labor
- Congenital microcephaly
- Prolonged postnatal risk factors, prolonged hypotension or hypoxia
- Early neuroimaging suggests long-standing injury like ventriculomegaly, cystic encephalomalacia.

RISK FACTORS FOR HYPOXIC ISCHEMIC ENCEPHALOPATHY (BIRTH ASPHYXIA)

There is a fundamental impairment of oxygen and perfusion.

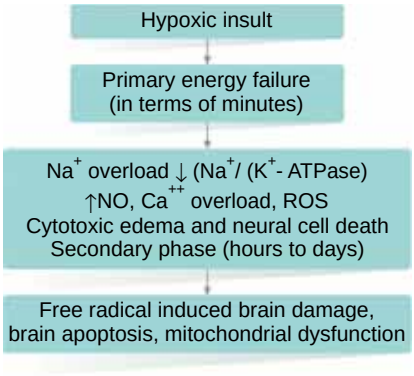
- Impaired placental supply of oxygen due to uterine contraction (including in appropriate use of oxytocin), placental abruption and placental insufficiency.
- Impaired umbilical arterial supply due to cord compression/prolapsed cord.
- Impaired uteroplacental supply due to any cause of maternal hypoxia or hypotension.
- Impaired neonatal oxygen supply due to difficult delivery and inadequate resuscitation. This is more relevant in developing countries, where domiciliary delivery rate is high with inappropriate resuscitation of newborn by untrained birth attendant.

PATHOPHYSIOLOGY (FLOW CHART 7)

Hypoxic ischemic injury may be acute or chronic. Although, brain injury occurs at the time of insult (primary neuronal injury), majority of the damage occurs over the subsequent hours or days (secondary neuronal injury) as a result of cascade of biochemical and cellular process, including free radical production, proinflammatory cytokines, nitric oxide (NO) and damage due to apoptotic triggers.

Brain damage in HIE occurs in two phases. Initially hypoxemia and ischemia cause reduced blood flow and reduced cerebral perfusion. Initial cerebral perfusion cause primary energy failure, associated with cerebral edema and necrotic cell death due to glutamate mediated excitotoxicity and accumulation of Na^+/K^+ ATPase, increased cellular

Flow chart 7: Pathophysiology of hypoxic-ischemic brain injury



Abbreviations: ROS, reactive oxygen species; NO, nitric oxide

permeability to Ca^{++}, increased NO and increased reactive oxygen species (ROS) also responsible for neuronal damage at this phase.

After initial cerebral hypoperfusion, cerebral perfusion is again maintained by cerebral autoregulation mechanism, which reperfuses brain by distribution of blood to essential organs, which include brain, heart and kidney. During this reperfusion phase, further brain damage occurs by ROSNO and production of increased free radical. Free radicals cause brain damage by damaging deoxyribonucleic acid (DNA), mitochondria and tissue damage by lipid peroxidation.

PATHOLOGY

There is no distinct pathological pattern of brain injury of HIE. Pathology depends on severity of HII, timing and duration of insult, regional variation of vulnerability, and developmental maturity of brain.

Cerebral edema: As mentioned in the pathophysiology cerebral edema occurs due to cytotoxicity at neuronal level. Gross swelling of cerebral tissue occurs within 24–48 hours of insult. There will be marked widening and flattening of gyri and obliteration of sulci. It can be seen by MRI or at postmortem.

Involvement of Cerebral Cortex

Gray matter of cerebral cortex, particularly of term infants, is vulnerable to HII. The cerebral cortex layers III and IV, and hippocampus are more vulnerable.

Parasagital areas of cerebral cortex are also vulnerable as there is already reduced blood supply due to vascular watershed zone of anterior, middle and posterior cerebral arteries (Figs 111A and B). Clinically, it is manifested later by spasticity of lower limb, due to upside down position of human body representation in brain. It is manifested clinically by high T1 signal from cerebral cortex by MRI (Fig. 112).

Basal Ganglia Lesion

Basal ganglia are also vulnerable to HIE. It is manifested clinically by high T1 signal from basal ganglia by MRI (Fig. 113). There may be microcalcification initially in basal ganglia followed by abnormal myelination pattern.

It is clinically manifested as dystonic and dyskinetic cerebral palsy.

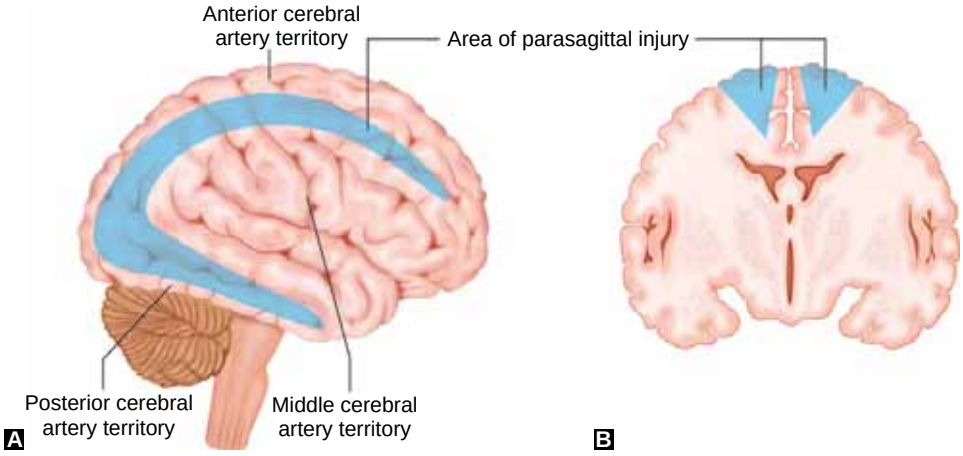
White Matter Injury

Hypoxic ischemic encephalopathy in white matter may cause periventricular leukomalacia in preterm infants. It is clinically manifested later as spastic diplegia in affected children.

Majority of ischemia are due to occlusion and infarction of major cerebral artery like middle cerebral artery. Thrombophilia is also associated with stroke.

CLINICAL FEATURES

- Evidence of a peripartum insult (fetal distress, low APGAR score, depressed condition at birth/need for resuscitation).
- Fetal distress, i.e. poor cardiotocography (CTG), acidotic fetal blood sample, meconium stained liquor, acidotic umbilical blood sample.
- Encephalopathy (discussed in detail in neonatal encephalopathy section).
- Clinical feature evolve over the first 72 hours, milder case may only become symptomatic once in the postnatal ward. Most important early clinical presentation at birth is respiratory system related problems. The clinical features of various systems are mentioned below:
  - Respiratory rate (71–86%): Apneas, pulmonary hemorrhage, persistent pulmonary hypertension (PPHN), acute respiratory distress syndrome (ARDS).
  - Renal (46–70%): Oliguria, hematuria, increased blood urea nitrogen (BUN), high output renal failure.



Figs 111A and B: Parasagittal injury: (A) Lateral view of the cerebral cortex, (B) Coronal section

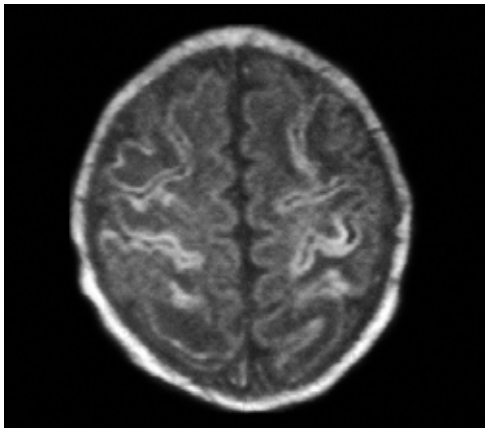


Fig. 112: MRI showing cortical highlighting in high axial T1 section predicting adverse outcome

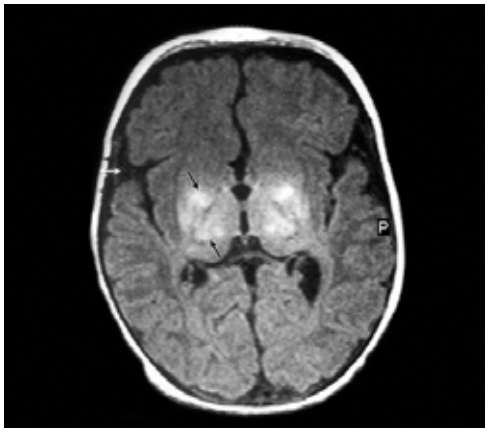


Fig. 113: Early MRI changes predicting adverse outcome. High signal on T1 axial section in the basal ganglia (arrows)

- Gastrointestinal: Poor food tolerance, necrotizing enterocolitis (NEC).
- Cardiac (43–78%): myocardial ischemic hypotension.
- Metabolic: Acidosis, hypoglycemia, increased alanine transaminase (ALT), increased lactate dehydrogenase (LDH), jaundice, hyponatremia. Fluid overload and syndrome of inappropriate antidiuretic hormone (SIADH), hypocalcemia.
- Hematological: Disseminated intravascular coagulopathy (DIC), neutropenia, thrombocytopenia.
- Liver (80–85%): Elevation or liver enzymes hyperammonia and coagulopathy can be seen.

Identification of simple clinical features suggestive of birth asphyxia which can be easily understood by birth attendants at community level of resource poor countries is useful. The following simple clinical features are useful at community level of developing countries for diagnosis of birth asphyxia:

- No respiration, no cry, gasping respiration with long pause in between.
- In facility level of developing countries, the following simple clinical features are useful: No respiration, no cry, gasping respiration with long pause, blue or pale color, heart rate absent or less than 100 bpm, flaccid or reduced muscle tone and low APGAR score.

ROLE OF APGAR SCORE IN HYPOXIC ISCHEMIC ENCEPHALOPATHY (BIRTH ASPHYXIA)

Over the time, APGAR score has been universally used to adopt it as a marker of birth asphyxia, since it was devised by Virginia Apgar, an obstetric anesthesiologist, in 1952. Most commonly, 1 minute less than or equal to 3 or 5 minute APGAR less than or equal to 7 have been taken to indicate HIE. It is still a useful practice at community level to use APGAR score for operational diagnosis of birth asphyxia in resource constraint countries:

- It can be low in conditions other than birth asphyxia, like condition associated with neonatal depression (prematurity, neuromuscular disorder).
- APGAR score has a poor correlation with the long-term outcome.

Many such conditions have initial low APGAR score, which subsequently improves as neonatal depression is overcome. An extended APGAR score, recorded 20 minutes after birth, increases the sensitivity and the specificity of APGAR score for birth asphyxia, and can more accurately predict early death and disability of a newborn, born with HIE.

ENCEPHALOPATHY ASSOCIATED WITH BIRTH ASPHYXIA

Although there is multiorgan involvement of birth asphyxia, the hallmark of birth asphyxia is the neurological involvement. Clinical features starts from intrapartum stage, in case of intrapartum asphyxia.

During intrapartum stage, evidence of:

- Fetal distress, i.e. poor CTG, acidotic fetal blood sample, meconium stained liquor, acidotic umbilical blood sample.

During peripartum stage, evidence of peripartum insult, characterized by:

- Low APGAR score at birth
- Depressed condition at birth
- Need for resuscitation.

Clinical Features of Encephalopathy

Clinical feature evolve over the first 72 hours. Milder case may only become symptomatic over on the postnatal ward. The most likely clinical features over 72 hours after birth are mentioned below.

Birth to Twelve Hours

Usually there are evidences of bilateral cerebral hemisphere disturbances with change in sensorium. The infant in severe case is either comatose or stuporous. There may be apnea or hyperventilation or hypoventilation. Majority are markedly hypotonic. Less severe case may not be hypotonic (particularly if basal ganglia lesion predominate) or breathing problem not marked.

Twelve to Twenty-Four Hours after Insult

The clinical condition is variable. Infants with severe disease remain stuporous, while less severely affected show some degree of improvement in sensorium. Infant with basal ganglia lesion may show hypertonia. Seizure often occurs in this period.

Twenty-Four to Seventy-Two Hours

Severely affected children deteriorate at this time with deepening of coma. Babies who die of HIE, often do so at this time. Preterm babies may have intraventricular hemorrhage at this time.

After Seventy-Two Hours

Infants, who survive, improve over this period. Level of consciousness improves but feeding difficulty is common. Hypotonia is common, except those with basal ganglia lesion, who develops hypertonia.

Grading of Encephalopathy

In 1976, Sarnat and Sarnat published grading of neonatal encephalopathy depending on clinical feature and electroencephalography (EEG) of term infants, who showed evidences of fetal distress. Sarnat's clinical grading of hypoxic ischemic encephalopathy is mentioned in Table 37.

Laboratory Studies

There are nonspecific test to confirm or exclude a diagnosis of HII. As mentioned earlier, diagnosis is made on clinical features of encephalopathy, APGAR score and intrapartum or peripartum metabolic acidosis. Laboratory tests are done to assess severity of HII. The following investigations are helpful:

- Blood gas study: Immediately after birth to assess hypoxia, hyperpnea, metabolic acidosis.
- Serum electrolytes: To monitor serum electrolytes level as a measure of kidney function status and possible SIADH.

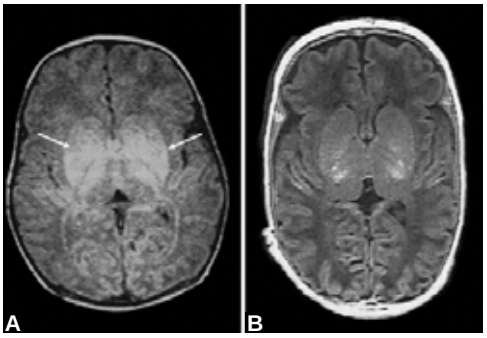
Neuroimaging: MRI

The imaging modality of choice is MRI with diffusion weighted imaging (DWI). It is better to perform on/after third day of life (optimum time 7–10 days) because of pseudonormalization of brain during first few days of life. Common patterns of abnormalities are:

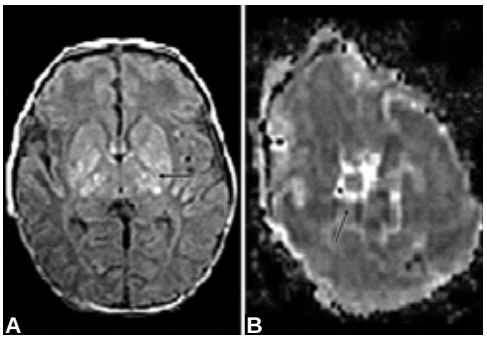
Table 37: Grading of neonatal encephalopathy

Conscious level	Mild (I) Hyper alert	Moderate (II) Lethargic	Severe (III) Comatose
Tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebrate
Reflexes	Increased	Increased	Decreased/ absent
Clonus	Present	Present	Absent
Suck	Weak	Weak/absent	Absent
Moro	Strong	Weak, incomplete	Absent
Pupil	Dilated	Pin point	Unequal, unreactive
Autonomic	Sympathetic	Parasympathetic	Depressed
Heart rate	Tachycardia	Bradycardia	Variable
Gastrointestinal motility	Normal/ decreased	Increased	Variable
Seizure	None	Common, focal	Difficult to control

Note: Sarnat grade II and III are usually associated with HIE



Figs 114A and B: MRI of brain of a neonate suffering from birth asphyxia showing abnormal (white) signal in the basal ganglia and thalami (arrows) and absence of signal in the internal capsule bilaterally, due to myelination of posterior limb of internal capsule (PLIC), characteristics of HIE on the right: normal scan showing gray basal ganglia and a white signal from myelin in the posterior limb of the internal capsule



Figs 115A and B: (A) Axial T1-weighted image showing abnormally increased signal intensity (SI) in the basal ganglia and thalami (arrow). (B) Showing abnormally low signal intensity in the posterior limb of the internal capsule (arrow)

- Selective neuronal necrosis, basal ganglia and thalami abnormality with high signal on T1 axial section (Figs 114 and 115). Myelination of posterior limb of internal capsule (PLIC) may be found and is useful guide to prognosis. There may be cortical and hippocampal lesion. Early changes in basal ganglia are associated with neurodisability.
- Focal or multifocal cortical necrosis due to loss of perfusion in vascular areas results in cystic encephalomalacia and later spastic (pyramidal) cerebral palsy (CP).
- Watershed infarction: Due to hypotension causing loss of perfusion of border zones, results in parasagittal and parietooccipital white matter lesions. Associated with spastic diplegia in preterm infants and visioauditory and language problem later.
- Head USD or CT to rule out hemorrhage, evidence of edema or infarct.

ELECTROENCEPHALOGRAPHY

Electroencephalography is done to look background voltage, seizure and burst suppression. An activated EEG (a-EEG) provides better information to evaluate severity of HIE. Considerable training is required in conducting and interpreting the a-EEG findings.

Traditional multichannel EEG is also useful. It is a valuable tool to assess the severity of the injury and evaluate for subclinical seizure.

MANAGEMENT OF BIRTH ASPHYXIA

Management depends on available resources in developing or developed countries. It also varies in community care or facility based care. Management includes effective resuscitative procedure according to standard guideline. After initial stabilization by resuscitation, the remaining management is largely supportive.

Management of Hypoxic Ischemic Encephalopathy in Facility-based Care

The perinatal asphyxia must be promptly diagnosed and adequately treated for better survival and quality outcome. The obstetrician and pediatrician (Perinatologist) should work as a team.

All deliveries must be attended by a qualified health personnel, who is trained in neonatal resuscitation. All newborn babies need assistance at birth, whether asphyxiated or not. The protocol of management of a neonate depends upon the stage of parturition.

- Before delivery
- During delivery
- After delivery.

Before Delivery

A physician responsible for caring the newborn infant must be available in the labor room at least 30 minutes to 1 hour before delivery. He/she must obtain proper maternal history in order to find out any high-risk factors which may affect the newborn. The maternal age, parity, blood group, Hb, blood pressure (BP), status of antenatal check-up, history of chronic illness, premature rupture of membrane, fever, pain in lower abdomen and drug intake in the mother must be recorded. Any evidence of fetal distress, as manifested by fetal heart rate abnormalities, meconium stained liquor and acidosis in fetal scalp blood, must be recorded. Though the risk of perinatal asphyxia is associated more with young primi, multipara mothers suffering from chronic illness like anemia, diabetes, hypertension and third trimester bleeding per-vagina (PV) are also vulnerable for birth asphyxia of their babies. Therefore, as a policy, perinatal asphyxia must be anticipated in every delivery and all preparations should be made beforehand for neonatal resuscitation.

An area in the labor room should be earmarked for the baby. The "baby area", either should be warmed to 30–31°C, or a servocontrol open care system be used and segregated from the mother's view by a screen, should any need for resuscitation arise. Following preparations are made before second stage of labor:

- All equipments and supplies must be available in the baby area completely sterilized and functional. A list of the items may be kept in the baby area and, before each delivery, the used items may be replaced. The physician must check all equipments under aseptic precautions that these are working properly.
- The actual resuscitation of the newborn may require two well-trained persons, if there is need for chest compression and medication. It is important that the obstetrician and staff nurse assisting the delivery must be conversant with the steps of neonatal resuscitation, who may be called, if required. The responsibility of persons may be fixed like, he will do bag and mask ventilation and she will give chest compression. The person who provides positive pressure ventilation by bag and mask is the team leader, and he/she directs the steps to be taken for resuscitation.

Suction equipment:

- Mechanical suction
- Suction catheters, 10F or 12F
- Delee catheter/mucus trap
- Feeding tube: 6F/8F
- 20 mL syringe.

Bag and mask equipment:

- Neonatal resuscitation bag with oxygen reservoir
- Face masks number 00, 0, 1
- Oxygen cylinder with flow meter, tubing and key.

Intubation equipment:

- Laryngoscope with straight blades, number 0 (preterm) and 1 (term)
- Endotracheal tubes: 2.5, 3.0, 3.5, 4.0 mm
- Stylet
- Scissors.

Medications:

- Epinephrine (adrenaline)
- Naloxone hydrochloride
- Normal saline, ringer lactate, 10% dextrose
- Sodium bicarbonate
- Distilled water
- Dopamine.

Miscellaneous:

- Linen, shoulder role
- Radiant warmer
- Stethoscope
- Adhesive tape
- Syringes 1, 2, 3, 4, 5, 10, 20, 50 mL
- Gauze
- Umbilical artery catheter 2F, 5F
- Three-way stopcocks
- Gloves
- Scalped blade
- Airway
- Cord tie
- Stop watch/watch with second's hand
- Arrange container and vials for collection of samples, if necessary
- Cord blood for blood groups, direct Coombs' test, blood sugar, complete blood count, reticulocyte count, serum bilirubin, umbilical artery blood gas analysis, etc
- Gastric aspirate for polymorphs count
- Meconium stained amniotic fluid for meconium crit
- All health personnel should wash hands, wear gown and mask, and be ready to receive the infant.

During Delivery

- Keep in touch with the obstetrician to know about the fetal distress and progress of labor.
- Remain by the side of the obstetrician to observe cord round the neck, color of the liquor and difficulty in expulsion of the body from the birth canal. This gives important clues of subsequent events to follow after birth.

If second stage of labor is prolonged, cord around the neck is present or shoulder dystocia occurs, baby may suffer from birth asphyxia and birth injuries.

Initial resuscitation: It is important to establish adequate oxygenation and restore circulation by rapid and effective resuscitation. Initial resuscitation of suspected HIE is similar to resuscitation required for neonate, who are not breathing well due to causes other than HIE (neonatal depression). Resuscitation follows ABCD (air, breathing, circulation and drugs) principles of basic life support. However, difference in neonate includes:

- Head position
- Position of hands for chest compression
- Early reassessment after intervention
- Different drug doses for treatment of asystole.

Head position (Fig. 116):

While mopping and drying of the head and trunk is done immediately after holding the baby with the help of the linen in which infant was received, the neonate is quickly moved towards the baby area, placed on a firm surface, preferably on a servocontrolled open care system, in supine posture and Trendelenburg position, with head towards the health personnel, neck slightly extended and face turned to one side. If position of the head cannot be maintained due to caput succedaneum or relatively large head, shoulder role 1–1.5" thick may be placed under the shoulders to maintain position.

Also, it should be remembered to keep the baby warm.

Air versus oxygen in resuscitation of newborn: Traditionally neonates have been resuscitated with 100% oxygen. However, recent meta-analysis indicates mortality is reduced, if resuscitated in air.

Airway and breathing

- To maintain adequate airway; head in the neutral position
- Support breathing, deliver inflation breaths. Bag and mask ventilation will be adequate for almost all asphyxiated newborn. Tracheal intubation can be performed at any stage of resuscitation (in facility based management).

Number of breaths: Five

1. Pressure: 25–30 cm of water for term and 25 cm in preterm
2. Each inflation breath with bag and mask should last at least 2 seconds
3. Watch carefully to see chest movement
4. If no chest movement than it is most likely that the airway is not in open position consider,
5. Reposition of the head between each attempt
6. A jaw thrust maneuver: This is the process of lifting job forward with fingers by pressing gently the jaw bone at each angle (Fig. 117).

A second person to hold mask in position whilst providing jaw thrust may help.

- Airway obstruction, direct inspection of oropharynx and suction with a wide bore catheter under direct vision.
- If chest movement still not present, consider stiff lung, pneumothorax, diaphragmatic hernia (scaphoid abdomen), etc. May need to increase breathing pressure to 40 cm of water.
- Manage according to protocol of facility based care or refer to appropriate facility based center.

The resuscitation mask, which covers upper part of the chin, mouth and nostrils, and spares the eyes, and is round-shaped with cushioned margins. It is ideal as it provides excellent seal and does not harm the eyes (Figs 118 to 120).

Reassess

- If chest is still not moving, repeat above maneuvers and consider intubation in facility based care (or refer to facility based center).
- If chest is moving and heart rate has increased, but baby fails to establish regular breathing, continue bag mask ventilation breathing for a further 30 second and reassess.
- If opioids have been given within an hour of delivery, the baby may require 0.1 mL/kg of naloxone. If heart rate is under 60 bpm and not increasing after 10–20 seconds of adequate lung aeration, commence chest compression.

Circulation: Do not start chest compressions until the chest is moving adequately. Grip chest in both hands (Fig. 121). Place thumbs on sternum just below an imaginary line joining nipples and fingers over the spine. If there is no assistance, then use two fingers and keep other hand holding mask over mouth.

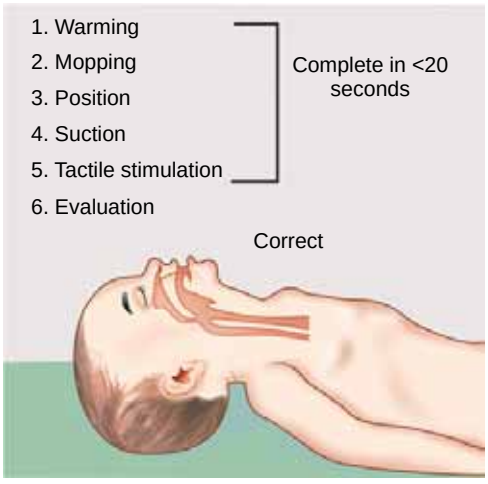


Fig. 116: Neutral position of head

Fig. 117: Showing jaw thrust maneuver

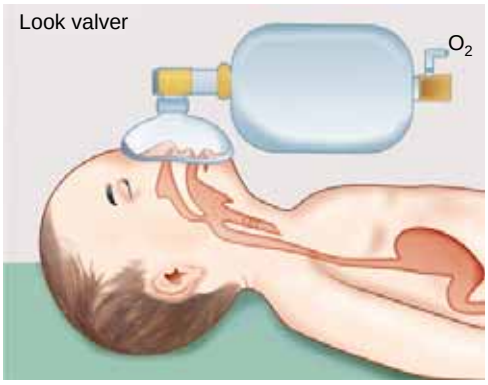


Fig. 118: The right process of bag and mask ventilation of neonate

Fig. 119: Diagram showing right and wrong positions of mask

Fig. 120: Inappropriate position of mask showing leakage of air due to inadequate seal

Fig. 121: Method of chest compression during neonatal resuscitation

- Aim to depress chest half the distance between sternum and spine.
- Three chest compressions to one breath (3:1).
- Continue for 30 seconds.

Reassess: If there is no improvement, repeat chest compression for further 30 seconds, then reassess. If still heart rate is inadequate, proceed to "drugs" (Table 38). Also consider hypoglycemia and septicemia in a neonate, which may simulate shock and treat accordingly.

During and after resuscitation, efforts should be made to maintain optimum temperature in the resuscitation room and during transfer of baby to neonatal unit or referred hospital.

Look for following features while effectively resuscitating hypoxic ischemic encephalopathy:

One should remain professional and should not make negative comments on midwifery or obstetrical care.

- Assess severity of encephalopathy
- Look for risk factors, like sepsis, hypoglycemia and take necessary steps [blood culture, blood sugar, lumbar puncture (LP), commence antibiotic]
- Look for possible birth trauma.

Table 38: Neonatal resuscitation drugs and dose

Drugs and dose	Dose
IV adrenaline	
First dose (1 in 10,000)	0.1 mL/kg
Second dose (1 in 10,000)	0.3 mL/kg
IV glucose (10%)	2.5 mL/kg
Volume expander	
Blood or normal saline	10–20 mL/kg
Sodium bicarbonate (4.2%)	4 mL/kg

Abbreviation: IV, intravenous

Management is supportive other than therapeutic hypothermia and neuroprotective pharmacological treatment like allopurinol.

Following resuscitation, respiratory support may be required, particularly for those with severe encephalopathy:

After Delivery

Assisted ventilation: Consider ventilatory support early. Ventilation may be compromised by encephalopathy, seizure, meconium aspiration. However, elective ventilation should be done in spontaneously breathing infant. If there is $PaCO_2$ rise above 7 kPa (53 mmHg), ensure adequate oxygenation, but hyperoxia should be avoided.

Aiming for $PaCO_2$ 4.5 kPa or 6 kPa has greatest neuro–protective effect. Mean $PaCO_2$, at least above 3.5 kPa, prevent cerebral vasoconstriction and preserve cerebral perfusion.

- If no signs of improvement; intubation and mechanical ventilation is required
  - Insertion of endotracheal tube (ET tube)
  - Starting of chest compressions
  - Keep adrenaline ready.
- Approximate length of endotracheal tube: Weight in kilogram (kg) plus 6 cm. It should be easy to handle and should not be inserted too far to produce resistance to airflow (Table 39).
- The lower end of ET tube should be at the level of clavicles which will give enough length to secure ET tube.
- ET tube connector should be tightly fitting, if loose may cause inadvertent separation.

How to prepare laryngoscope (Fig. 122):

- Select proper size of blade: No. 0 for preterm, no. 1 for term babies.
- Check light source: See batteries and bulb are working, and bulb is tightly screwed to avoid flickering.

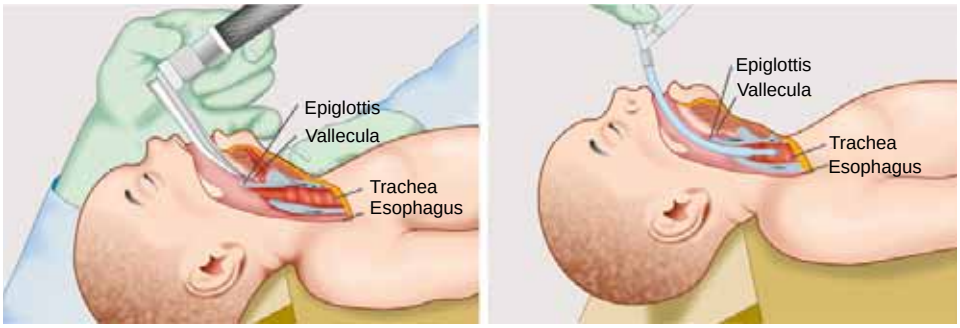


Fig. 122: Intubation of neonate by laryngoscope

Table 39: Selection of proper size of endotracheal tube according to weight of the baby

Tube size (mm) (inside diameter)	Weight (g)	Gestational age (weeks)
2.5	<1,000	<28
3.0	1,000–2,000	28–34
3.5	2,000–3,000	34–38
3.5–4.0	>3,000	>38

Table 40: Selection of suction catheter according to the size of endotracheal tube

ET tube (mm)	Catheter size (F)
2.5	5
3.0	6
3.5	8
4.0	8–10
Abbreviation: ET, endotracheal	

- Select proper suction catheter; selection is done according to ET tube size (Table 40).
- Keep resuscitation bag and mask ready.
- Turn on oxygen.
- ET stabilizer and tape.

Ventilator care of newborn: Detailed ventilator care of newborn described in "ventilator care" section.

Cardiovascular support:

- Continuous BP monitoring and early inotropic support
- Try to maintain mean arterial blood pressure (MABP) greater than 40 mm Hg to ensure adequate cerebral perfusion, in hypotensive or impending hypotension
- In case of hypotension requiring inotrope therapy, it is better to start with dobutamine (5–15 µg/kg/min) due to its lack of alpha effect, thereby decreasing cerebral blood flow. Add dopamine upto 10 µg/kg/min
- Try to avoid fluid resuscitation, only give if there is good evidence of hypovolmia
- If the baby is in shock [cardiac resynchronization therapy (CRT) > 3 second] volume expander: Normal saline/blood or colloid solution, 10–20 mL/kg over 5–10 minutes should be given
- Electrocardiography (ECG) and echo can be done to maintain cardiac function
- Monitor hemoglobin: Sudden fall indicates intracranial bleeding.

Metabolic:

- Aim to maintain normoglycemia (2.6–8.0 mmol/L). Both hypoglycemia and hyperglycemia are harmful. Hypoglycemia (< 2.5 mmol/L), needs to be corrected. Increase glucose concentration in maintenance, rather than increasing fluid volume
- For hypoglycemia: 10% dextrose, 2–4 mL/kg, then 6–8 mL/kg/min
- For hyperglycemia: Injection insulin 0.05–0.1 unit/kg/hour in infusion, followed by 0.05–0.1 unit/kg/h in infusion as needed (check blood glucose hourly) to maintain normoglycemia
- Introduction of enteral feeding, as soon as tolerated, may hasten sugar control by inducing gut hormonal secretion
- Hypocalcemia (serum calcium <1.7 or ionic calcium < 1 mmol/L). Injection 10% calcium gluconate 2 mL/kg intravenous (IV).

Control of seizure: Look for abnormal movements indicative of seizure activity. Seizure may present as oculo-orofacial activities, tonic, clonic and myoclonic movement, and central autonomic activities (like apnea, bradycardia). Seizure is a bad prognostic indicator, particularly burst suppression on EEG and discontinuous recording on EEG predict poor outcome. Therefore, prompt seizure control is necessary.

- First line: phenobarbitone (20–40 mg/kg IV)
- Second line: Phenytoin (20–40 mg/kg IV)
- Third line: Consider 1 week trial of pyridoxine (100 mg orally, once daily)
- Fourth line: Benzodiazepine, midazolam (200 µg/kg), lorazepam (100 µg/kg) or clonazepam (100 µg/kg). Consultation should be sought with pediatric neurologist.

After control of seizure maintenance dose of phenobarbitone (5 mg/kg/day in two divided doses) is continued until EEG is normal or no clinical seizure within 2 months or more.

Fluid management:

- Initially, fluid restriction of 60–80% of requirement while oliguric, followed by liberal fluid when urine output improves
- Fluid restriction in case of SIADH
- Hyponatremia: Fluid restriction with administration of 3% NaCl in symptomatic hyponatremia (serum sodium < 120 mEq/L). IV frusemide may be required
- Cerebral edema: Fluid restriction of 20–25%, IV mannitol (20%), 1–2 gm/kg in 30 minutes.

Infection:

As mentioned earlier, neonatal meningitis may resemble HIE. If in doubt, LP should be done and antibiotic be given

accordingly. Routine use of antibiotics without clinical or laboratory evidence of infection is not recommended.

Avoidance of hyperthermia: Although it is recommended to keep the body warm in neutral thermal environmental condition, hyperthermia may aggravate birth asphyxia and should be avoided.

Treatment of other complication:

Renal insufficiency: Fluid restriction and checking of dosage of nephrotoxic drugs, correction of acidosis (by $NaHCO_3^-$ only after establishment of respiration) and dyselectrolytemia (hyperkalemia by glucose, insulin, salbutamol nebulization, IV calcium gluconate in hypocalcemia and correction of acidosis).

Pulmonary complications (pulmonary hemorrhage, pulmonary edema or increased pulmonary vascular resistance): managed with oxygenation, ventilation, diuretics and blood transfusion.

Liver failure: Injection vitamin K1, albumin and avoid hepatotoxic drugs.

NEC: Nothing per oral (debatable, currently orally allowed) gut decompression by suction, trophic feeding, IV antibiotics and metronidazole plus surgical opinion, fresh frozen plasma (FFP), platelet or blood transfusion.

Disseminated intravascular coagulation (DIC): Managed with injection vitamin K1, FFP, exchange transfusion, antibiotics (if maternal fever, leaking membrane, forceps/vacuum extraction).

Steps of resuscitation in short:

- Warm reception, clearing, drying, wrapping. Tactile stimulation, positioning and suction, if meconium aspiration occurs
- Assist ventilation with mouth to mouth breathing or bag and mask ventilation
- Chest compression
- Intubation
- Administer medications, if all the parameters are adequate and no improvement of heart rate (< 60 bpm), then adrenaline. Naloxone may be given if apnea is due to maternal opiates.

More Specific Treatment of Birth Asphyxia

- Therapeutic hypothermia
- Neuroprotective pharmacological treatment, like allopurinol.

Therapeutic hypothermia: Evidences suggests therapeutic hypothermia decreases brain tissue injury in asphyxiated newborn, as demonstrated by less cortical gray matter lesion, less basal ganglia and thalamic lesion on MRI, especially in infants with initially abnormal aEEG. Although, it is a relatively easy and safe procedure, it should be done in a specialized center under expert supervision. In resource poor country, this method should undergo rigorous safety studies to test their safety and efficacy.

Criteria for therapeutic cooling are:

- Term or near term infants (gestational age > 36 weeks)
- Early cooling—age less than 6-hour-old, weight 1,800–2,000 g or more
- No major congenital abnormalities
- Evidence of moderate to severe encephalopathy
- APGAR score less than or equal to 5 at 10 minutes, with continued resuscitation; pH less than or equal to 7 in first hour, barium enema (BE) less than or equal to 16 in first hour
- Clinical evidence of seizure
- aEEG, lower margin less than 5 μV, upper margin less than 10 μV.

Two methods of cooling are:

1. Selective head cooling.
2. Whole body cooling.

In selective head cooling, a cap (cool cap) with channels for circulating cold water is placed over the infants head and a pumping device facilitate continuous circulation of cold water. Rectal temperature or nasopharyngeal temperature is maintained at 34–35°C for 72 hours.

In whole body hypothermia, a cooling blanket is wrapped around the baby to keep core temperature between 35°C and 36°C for 72 hours.

Pharmacological treatment

Long-term neuroprotective effect of allopurinol after moderate perinatal asphyxia: Reperfusion of previously ischemic brain tissue is now recognized as an important mechanism for substantial additional brain injury due to formation of toxic free radicals. There are recent evidences to suggest that reperfusion injury may be ameliorated by neuroprotective strategies, such as hypothermia, along with early post asphyxial pharmacological intervention, such as allopurinol, a xanthine oxidase inhibitor. Two doses of allopurinol 20 mg/kg IV starting within 4 hours of birth with an interval 12 hours have been found to lower the risk of death or severe disability on the long-term (at 4–8 years) in moderately asphyxiated infants. High dose of allopurinol, so far, did not show any evidence of significant side-effects. The advantage of allopurinol is its cheaper intervention. However, it requires further studies for wider neonatal practice.

Management of Birth Asphyxia (Table 41)

The 4 million global neonatal deaths that occur annually accounts for two-thirds of all infant deaths and two-fifths of all under-five deaths. Most neonatal deaths take place in developing countries at home and in the absence of skill care. The Lancet series on neonatal health reported that distribution of direct causes of death indicate the preterm birth (28%), severe infection (36%) and complications of asphyxia (23%) accounts for most of neonatal death.

The main causes of neonatal death are birth asphyxia, LBW and possible severe infection.

Several important insights have been gained in the last several years about the epidemiology, diagnosis and mechanism of brain injury, but the medical management still remains stereotyped.

The need for clinical guidelines on basic newborn resuscitation, suitable for setting with limited resources, is universally recognized.

The objective of these updated WHO guidelines is to ensure that newborns in resource-limited settings who require resuscitation are effectively resuscitated. These guidelines will inform WHO training and reference materials, such as—pregnancy, childbirth, postpartum and newborn care. A guide

Table 41: Broad strategic actions by level of care

Level	Strategies
At all levels	• Increase availability of trained health personnel at birth, including CSBAs, nurse midwives, midwife cadres, and increase their coverage of home and facility deliveries
	• Strengthen the linkage between communities and facilities to improve referral services
	• Establish GOB-NGO partnership/collaboration to improve community and union level maternal and neonatal services
	• Develop and implement a comprehensive and integrated BCC plan to improve awareness and behaviors related to ENC, including maternal and neonatal danger signs (see below)
Home and community level	• Raise awareness about risk factors and harmful practices those contributing to birth asphyxia
	• Orient family members in early recognition of birth asphyxia
	• Train FWA, Female HA, CSBA and CHWs on recognition, first line management and appropriate referral of neonates following birth asphyxia
	• In case of eclampsia first dose of magnesium sulfate can be given by CSBA at community level and patient referred to EMOC facility
Union and Upazila (subdistrict) levels	• The strategic aims and guidelines for management of birth asphyxia are designed to reduce the impact of birth asphyxia on overall neonatal mortality by reducing risk factors and ensuring adequate initial management of neonates with difficulty initiating breathing
	• Increase capacity for provision of expanded interventions for maternal conditions increasing risk of birth asphyxia (e.g., identification and treatment of bacteriuria, management of preterm deliveries, management of eclampsia, screening and management of risk diseases, presumptive treatment for malaria)
District level and above	• Increase capacity for management of obstetric complications contributing to birth asphyxia
	• Increase capacity for management of neonates with postasphyxia complications

Abbreviations: CSBA, community skilled birth attendant; GOB-NGO, Government of Bangladesh, nongovernment organization; FWA, family welfare assistant; HA, health assistant; CHW, community health worker; EMOC, emergency obstetric care; ENC, essential newborn care; BCC, behavior change communication

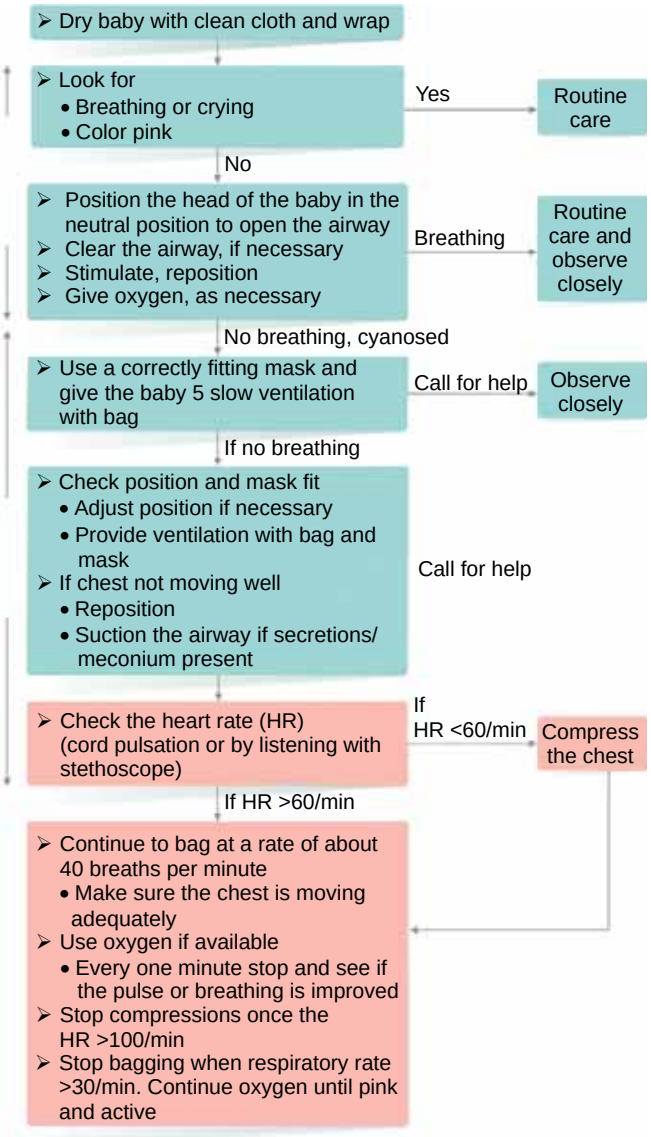
for essential practice, essential newborn care course, managing newborn problems.

These guidelines will assist program managers responsible for implementing maternal and child health programs to develop or adopt national or local guidelines, standards and training materials on newborn care.

The strategy to reduce birth asphyxia related mortality and morbidity include following interventions:

- Increasing capacity for identification of birth asphyxia among mothers and all levels of health workers.
- Strengthening awareness of risk factors and preventive measures to reduce birth asphyxia and its consequences.
- Increased coverage and quality of antenatal care, and identification of high risk cases.

Flow chart 8: Algorithm for birth asphyxia management



Abbreviation: HR, heart rate

- Increasing capacity for early management of birth asphyxia among all levels of health workers present at delivery.
- Improving postresuscitation referral and management.

Seventy percent of neonates with birth asphyxia do not need any resuscitation beyond essential newborn care (ENC).

Establishing appropriate management of asphyxia at all levels of healthcare will require time with measures to be implemented immediately, and at medium and long terms (Flow chart 8).

GUIDELINES FOR BIRTH ASPHYXIA (TABLES 42 AND 43)

Birth asphyxia is defined as a failure to initiate and sustain breathing at birth. It is associated with various conditions, including prolonged labor, inappropriate use of oxytocin, poor placental function of any cause, prematurity, cord prolapse or compression, placental abruption, severe meconium aspiration, congenital cardiac or pulmonary anomalies and

birth trauma. Birth asphyxia can be recognized by following symptoms/signs:

- *Community-level*: No respiration, no cry; gasping respirations with long pauses in between.
- *Facility-level*: No respiration, no cry; gasping respirations with long pauses in between; blue or pale color; heart rate absent or less than 100 bpm; flaccid or reduced muscle tone; low APGAR score.

Invertogram for Neonatal Resuscitation

- Drying, wrapping, tactile stimulation, positioning, suction may or may not be necessary, if meconium
- Mouth-to-mouth breathing
- Bag and mask ventilation
- Chest compression
- Intubation
- Drugs (Table 44).

Some of the harmful resuscitation practices have been stated in Table 45.

Help Baby Breaths Initiative

Help baby birth is an attempt to minimize unacceptably high incidence of birth asphyxia related mortality and morbidity. The goal of HBB initiative is to improve the knowledge and skill of skilled birth attendant (SBA) to identify and manage the newborn having birth asphyxia. To achieve above goal, the following objectives are taken:

- To train the service providers of selected government and nongovernment hospitals (urban) on ENC and newborn resuscitation.
- To train SBA, including family welfare visitor (FWV), family welfare assistant (FWA), and female health assistant working at community level on ENC and newborn resuscitation.
- To increase the capacity of SBA for identification of newborn having birth asphyxia and to increase the capacity for mouth-to-mouth and bag and mask resuscitation measures for workers involved in neonatal care.

Help baby breathe is an initiative of the American Academy of Pediatrics (AAP) in consultation with World Health Organization (WHO). The collaborators signed a global public-private alliance to launch the initiative as part of the annual meeting of the global health council, June 14–16 in Washington, DC. In a day-long training session, 100 internationals were trained. The WHO estimates that 1 million babies die each year from birth asphyxia or the inability to breathe immediately after delivery.

Help baby breathe can be a catalyst to increase the selected attendance at birth, build linkages between communities and health facilities and strengthen health systems.

Table 42: Guidelines for birth asphyxia interventions

Interventions	Guidelines and activities
Increase awareness of risk factors and preventive measures to reduce birth asphyxia and its consequences	• Promote ENC at all levels • Promote delayed age at first pregnancy, increased birth spacing, use of antenatal iron/folate, avoidance of harmful practices, such as inappropriate oxytocin use • Promote complete ANC, birth preparedness and awareness of maternal and neonatal danger signs • Depending on level of care, include the following: – Use partograph during labor at Upazila (subdistrict) and above level – Use of corticosteroid for preterm birth – Magnesium sulfate for management of eclampsia – Appropriate management of breech delivery (external cephalic version after 37 weeks, possible C-section) – Consider labor induction after 41 weeks – Calcium supplementation for prevention of preeclampsia to be explored
Increase capacity for identification of birth asphyxia at all levels	All health workers and birth attendants should be able to recognize signs of birth asphyxia
Increase capacity for immediate management of asphyxia	• The following should be done to help initiate breathing: – Drying and wrapping, tactile stimulation – Ensuring open airway: position baby in neutral position (the neck should be neither flexed nor extended) by placing a rolled piece of cloth about 2 cm (1") thick beneath the shoulder so that the face is in line with the body – If secretions, blood or meconium are present, use gentle suction (routine suction not required) • Resuscitation should be performed as follows: – Community level resuscitation: mouth-to-mouth – Facility level resuscitation (including community clinic): Bag and mask, chest compression, drugs • Parents should receive counseling, if their baby had difficulty with initiating breathing or needs resuscitation.
Improve postresuscitation referral and management	• All community level resuscitated neonates should be referred for facility-based care • Facility care includes close follow-up • All district facilities should have improved maternal and neonatal care with special neonatal care units at district hospitals; with an adequate backup support through neonatal and maternal intensive care units (NICU and MICU) at medical college hospitals and tertiary level institutes

Abbreviations: ANC, antenatal care; NICU, neonatal intensive care unit; MICU, maternal intensive care unit

Table 43: Management of birth asphyxia

Interventions	Guidelines and activities
Preparation for managing birth asphyxia	• Warm, well lighted and draught-free room
	• Clean flat surface to place the baby on
	• Soap, water for hand washing
	• Two clean, warm and dry clothes for cleaning and wrapping the baby; one piece of smaller cloth rolled up to 1" thick, to place under the shoulder (often provided by family)
	• Pieces of clean gauze
	• Sterile blade or scissors, sterile cord ties
	• Clock with second hand
Immediate care: should not take more than 60 seconds	*All these process should not take more than 60 seconds*
	• Drying and wrapping
	• If no response, tactile stimulation is given (tactile stimulation is given by rubbing the back gently)
	• Position baby in neutral position to ensure open airway (the neck should be neither flexed nor extended) (see Fig. 116)
	• Bag and mask/mouth to mouth resuscitation (see Fig. 117)
	• If, by this time the baby has started to breathe normally, no further action needs to be taken
Principles of resuscitation	*Follow ABCD principles*
	A: Patent airway
	B: Initiate breathing
	C: Maintain circulation
	D: Drugs
	Additional components are
	E: Environment (keep baby warm)
	F: Family (counseling)
Mouth-to-mouth resuscitation (community level resuscitation)	• Clean the baby's mouth with gauze piece.
	• Open the mouth
	• Place a dry gauze over mouth
	• Block the nose
	• Blow air into mouth (Nose can also be included in this procedure in which case the nose is not blocked)
	• Assess chest movement:
	– If chest moves: Continue mouth-to-mouth breathing
	– If chest does not move: Reposition and wipe out mouth with gauze, again blow air into mouth
Bag and mask resuscitation (facility-based)	• To be carried out at facility level following the algorithm for birth asphyxia (Flow chart 8)
Chest compression	• Grip the baby's chest with both hands placing the thumbs on the sternum or by index and middle fingers just below an imaginary line between the two nipples (Fig. 121)
	• Compress the chest 50-–75% and rapidly release:
	– Provide 3 compression, 1 breath (1 CPR cycle), provide 3 CPR cycles
	• Assess heart rate:
	– If 100 bpm or more, stop cardiac massage and continue bagging at about 40 bpm until breathing is regular and spontaneous.
	– If heart rate is less than 60 bpm, give another 3 cycles of chest compression and check each step again

Abbreviation: CPR, cardiopulmonary resuscitation

Help bay breathe is "the golden minute" within one minute of birth, a baby should be breathing well. Realistic newborn simulators boilable bag-mask ventilation devices and boilable bulb suction devices are made available at cost of millennium development goal-4 countries.

Help baby breathe is targeted to the 63 countries which participated in millenium development goal-4, which aims for reduction in under 5 child mortality by two-thirds from 1990 levels by the year 2015. Neonatal mortality in the first month of life accounts for more than 40% of child mortality worldwide. The materials have been tested in the five pilot sites in Bangladesh, India, Kenya, Pakistan and Tanzania.

Table 44: Drugs used in neonatal resuscitation

Before Initiating drug treatment, check the following:
- Whether the airway is open?
- Whether the chest inflates with inflation breaths?
- Whether cardiac massage is given properly?

If the newborn does not respond even after the airway is open, the chest moves easily with inflation breaths and effective cardiac massage has been given, then drugs may help.
- Injectable adrenaline 1:1,000: 1 mL mixed with 9 mL of distilled water to make a 1:10,000 dilution. Give 0.1–0.3 mL/kg IV

Additional drugs:
- *Injectable dextrose 10%*: Give 2–4 mL/kg IV.
- *Injectable naloxone 0.4 mg/mL*: Give 0.5 mL/kg, if laboring mother received opiate within 4 hours of delivery.

Table 45: Harmful resuscitation practices

- Avoid following harmful resuscitation practices
  - Slapping the baby on the back
  - Hanging upside down by the feet
  - Milking the cord
  - Routine suction of baby's mouth and nose
  - Throwing cold water on the baby's face and body
  - Giving injections of respiratory stimulus
  - Blowing into the ears and nose
  - Stimulating the anus
  - Squeezing the rib cage
  - Heating the placenta
  - Dipping the baby's cord alternatively in hot and cold water
  - Bending the legs on the abdomen
  - Keeping the placenta and cord attached for long time, till baby cries

NEONATAL SEPSIS

INTRODUCTION

Neonatal sepsis remains a major cause of mortality and morbidity, including neurodevelopmental impairment, despite advances in perinatal and neonatal care. It is also associated with prolonged hospital stay. In neonates, early warning symptoms of septicemia are often minimal, but the clinical course may be fulminant due to immaturity of immune system of neonate. Therefore, antibiotic treatment of neonates with suspected sepsis must start without delay. As microbiological and antimicrobial susceptibility results are not immediately available, initial antimicrobial treatment, usually empirical with an aim of being effective against the most likely pathogens. Pathogens causing neonatal infections and their antibiotic susceptibility patterns change overtime and differ between countries, and even in different places of same country. In order to guide empirical prescribing, it is crucial to monitor changes in the pattern of causative organisms and their antimicrobial susceptibility profiles.

Bacterial infection is the most common cause of neonatal sepsis. Other causes include fungal sepsis and viral etiology [herpes simplex, cytomegalovirus (CMV)].

EPIDEMIOLOGY AND ETIOLOGY OF NEONATAL SEPSIS

Definition of Sepsis

Definition of sepsis varies between networks but all consists of a combination of clinical and laboratory parameters. Neonatal sepsis, therefore, can be defined as clinical syndrome resulting from pathophysiological effect of local and systemic infection supported by relevant laboratory findings in the first 4 weeks of life.

Most septic babies will present within the first week of life, but some perinatally acquired infection can present upto 3 months of age.

Factors Influencing Development of Infection

- *Underdeveloped immune system:*
  - Low total number of neutrophils and neutrophil progenitors, and reduced neutrophil function
  - Low complement level
  - Naïve T and B cell-mediated immunity
  - Protective maternal immunoglobulin crosses placenta to fetus only after 28–32 weeks gestation.
- *Reduced barrier to infection, particularly important with preterm babies:*
  - Fragile immature skin
  - Immature gut, may have over growth of pathogenic bacteria, if delayed feeds or no breast milk
  - Relatively open blood brain barrier predisposes to meningitis
  - Impaired mucous membrane and ciliary function, if needing respiratory support.
- *Environmental factors:*
  - Antenatally acquired infection, blood born from mother via the placenta
  - Perinatally acquired infection from female genital tract, group B streptococcus (GBS), herpes simplex virus (HSV)
  - Rupture of membranes, particularly if prolonged (> 18 hours), exposes baby to microorganisms.
- *Nosocomial infection in newborn intensive care unit (NICU) or special care baby unit (SCABU)*
  - Difficult infection control (crowded, high intensity)
  - Warm humid environment (e.g. incubator, ventilator circuit)
  - Frequent use of prolonged (>5 days) broad spectrum antibiotics.
- *Medical management factor:*
  - Antibiotic therapy: Frequent use of prolonged (>5 days) broad spectrum antibiotics
  - Invasive procedure:
    - Intravascular access allows microorganisms into blood stream
    - ET tube allows access of microorganisms to respiratory tract.
  - Skin easily abraded by routine care.
- *Preterm, LBW newborn are more vulnerable to develop sepsis.*

Bacterial Etiology of Neonatal Sepsis

The profile of organism causing neonatal sepsis is geographically variable. While Gram negative bacteria (GNB) predominate in all stages of neonatal sepsis, particularly in early onset sepsis (EOS) in Southeast Asia, GBS and coagulase negative staphylococcus (CONS) are the major pathogens in EOS and late onset sepsis (LOS) in western countries.

Frequent bacterial causes of neonatal sepsis:

- Gram negative bacteria, which includes:
  - Family of enterobacteriaceae:
    - *Klebsiella pneumonia*
    - *Escherichia coli*
    - Enterobacter
    - Serratia.
  - Other gram negative bacteria:
    - *Pseudomonas aeruginosa*.
    - Acinetobacter.
- Gram positive bacteria:
  - More frequent in western countries:
    - *Staphylococcus aureus*.
    - CONS.
    - GBS, commonly associated with EOS in western countries.

Early Onset Sepsis and Late Onset Sepsis

Early onset sepsis is defined as infection in the first 48–72 hours of life and LOS defined as infection occurring thereafter upto 28 days of life.

Route of Transmission of Organisms

- Vertical transmission.
- Horizontal transmission.

Vertical transmission (perinatal transmission): Vertical transmission of infection takes place from mother to newborn. Best example of infection due to vertical transmission is GBS infection in neonate. Many other bacterial and viral infections [TORCH and human immunodeficiency virus (HIV)] in newborn may occur due to vertical transmission. Majority of EOS are due to vertical transmission.

Horizontal transmission: Majority of horizontally transmitted infection are nosocomial and occur in hospital or medical setting. *Staphylococcus aureus* as well as CONS are involved in horizontal transmission and responsible for late onset sepsis. Most of the risks around antibiotic resistance relate to horizontal transmission in LOS.

Early Onset Sepsis (General Consideration and Background)

Etiology

- Vertical acquisition from mother but can also occur after birth due to horizontal transmission.
- Organisms can invade neonate via placenta and membranes or by aspiration of fetal liquor.
- Important organisms include following:
  - Enterobacteriaceae, which includes acinetobacter, klebsiella, pneumonia and *E. coli*
  - Other organisms are pseudomonas and serratia, etc
  - In western countries GBS and listeria are important pathogens of EOS.

Risk factors of early onset sepsis:

- Prematurity (<37 weeks)
- Premature rupture of membrane (>18–24 hours)
- Maternal pyrexia (temperature >38°C for >1 hour)
- Evidence of maternal sepsis [positive blood culture, raised white blood cell (WBC) or C-reactive protein (CRP)].

In industrialized countries (like UK and USA):

- Maternal GBS colonization
- Urinary tract infection (UTI) in current pregnancy
- Previous baby with GBS disease

Clinical presentations of early onset sepsis:

- History may reveal risk factors
- Temperature change: Temperature less than 36°C or greater than 37°C often present with respiratory distress (congenital pneumonia) after aspiration of infected liquor, apnea
- There may be lethargy, poor feeding
- Irritability, seizure
- Jaundice, hypoglycemia
- Cardiovascular features, like, tachycardia, pallor, mottled skin, capillary refill greater than 3 seconds, shock with rapid deterioration to death
- Gastrointesinal tract (GIT): Poor feeding, vomiting, abdominal distension with ileus, jaundice.

Late Onset Sepsis (General Consideration and Background)

- It is usually horizontally acquired from environment or contact mostly hospital (NICU, nursery unit, maternity unit) and acquired nosocomial infection. Vertically transmitted infections, however, can also occur in late neonatal period or afterwards.
- Also can directly occur from community living in unhealthy environment, coming in contact with healthy persons carrying community associated organisms, like community acquired methicillin resistant *S. aureus* (CA-MRSA), mostly reported from USA. They contain virulent pantone-valentine leukocidin factor causing serious disease to transmitted person.
- Meningitis and other focal infections (umbilical sepsis, abscess, septic arthritis) are more frequently associated with LOS.
- Common organisms are Gram negative organisms (*Pseudomonas, Klebsiella*, Aacinetobacter, *E. coli*), Gram positive organisms, like *Staphylococcus*, GBS (in Western countries).
- Also, fungal sepsis, particularly *Candida albicans* sepsis, are more associated with LOS with prolong use of broad spectrum antibiotics.

Risk factors of late onset sepsis: Although both neonatal and maternal risk factors are involved, neonatal risk factors are more associated with LOS. Maternal risk factors, however, can also predispose to bacterial sepsis, beyond 7 days of life.

Neonatal risk factors: Neonatal risk factors are particularly associated with late onset Gram negative sepsis and meningitis (LOGNS).

- Neonatal risk factors include:
  - Preterm, LBW baby
  - Prolong use of broad spectrum antibiotic
  - Ventilation use, its type and duration
  - Total parenteral nutrition (TPN) use and its duration
  - Presence of NEC.

Premature infants are at particular risk of late onset infections as a result of their immature immune system, further compromised by an ineffective skin barrier and increased need for invasive devices to sustain life supporting care.

Maternal risk factors:

- Chorioamnionitis
- Intrapartum antibiotic prophylaxis (IAP) used particularly for GBS, in USA

- Prolonged rupture of membrane
- Antenatal steroid.

Presentation of late onset sepsis: Similar to early onset sepsis with change in behavior like irritability, lethargy, poor activity, change of appetite with poor feeding or intolerance to food. Sudden pallor, appearance of jaundice or persistence of neonatal jaundice are suggestive of sepsis. Meningitis is more frequent in late onset sepsis. Seizure may present as abnormal oro-oculofacial movement, apnea, generalized tonic or frank convulsion. Evidence of septic focus, like umbilical sepsis, abscess, IV line infection may be present.

Investigations of suspected sepsis (standard septic screen):

- Full blood count (FBC), blood film, differential white cell count
- CRP
- Blood culture:
  - Take adequate volume (at least 0.5 mL), plus
  - When clinically indicated
- X-ray chest, if respiratory signs (common)
- Lumbar puncture (LP), if neurological signs/symptoms or proven sepsis (raised septic markers or blood culture positive for organisms)
- Rapid antigen screen from blood or cerebrospinal fluid (CSF) useful, if antibiotic already started
- Microscopy and culture of broken areas, like pustule, swabs of purulent discharge, if present
- Urine, preferably clean catch or suprapubic aspiration (SPA). Microscopic exam for yeast, if fungal sepsis is suspected
- X-ray abdomen, if abdominal distention. ET tube secretion culture
- Culture of tip of umbilical/central lines and ET tube, when removed.

Additional investigations to consider:

- Blood gases, serum electrolytes, serum calcium, coagulation screen
- Maternal vaginal swab culture
- Placental swab with or without placental pathology (GBS, listeria)
- Viral studies (exclude viral sepsis).

Interpretation of results: Definitive culture results take too long to obtain to influence the initial decision; about whether to treat with antibiotics depend on results of investigations for septic screen, which are available within 1–2 hours. They are relied on to influence a decision which is essentially a clinical one.

Results that mandate early antibiotic treatment include:

- Neutropenia (neutrophil <1,500/mm^3) or neutrophilia (> age specific)
- Band form cell count (I) to total neutrophil count (T) ratio (I:T) greater than or equal to 0.2
- Thrombocytopenia (platelet count <100 × 10^9/L)
- Raised CRP
  - CRP may be normal initially. Raised procalcitonin and IL-6 are early indicators, but not widely available
  - Urine white cells
  - CSF: 21 × 10^9/L white cells, protein greater than 2 g/L in-term infants, glucose less than 40% of blood glucose, organisms are seen.

Treatment: In addition to any supportive care, systemic antibiotic are indicated on suspicion of sepsis after sending sample of body fluids for culture.

GENERAL PRINCIPLES

Empirical Choice of Antibiotic

Empirical choice of antibiotics varies from country to country and even for different hospital set up of same country.

The initial choice depends on local pathogens incidence and their sensitivity pattern, which also change from time to time. Cost and availability of drugs are also considered. Narrower spectrum antibiotics (like ampicillin, gentamycin) are preferred, unless otherwise, indicated by severity of initial clinical condition and local high incidence of multidrug resistance bacteria. Initial narrow spectrum antibiotic can avoid potential promotion of multidrug resistant bacteria and can prevent subsequent nosocomial fungal sepsis. Narrow spectrum antibiotics are also less expensive, which suits for treatment of septic neonates in resources poor developing countries. Narrow spectrum antibiotics are also recommended for empirical treatment of neonatal sepsis in the UK where amoxicillin, gentamycin and, occasionally, cefotaxime have been found adequate.

An aminoglycoside, such as gentamycin, is usually indicated to cover coliform, a second or third antibiotic is given depending on which organism is common and their antibiotic sensitivity.

First-line of Antibiotics

Gentamycin and ampicillin: Injection gentamycin: 5 mg/kg/day IV in single dose for 7 days and injection ampicillin: IV 100 mg/kg/dose, twice daily for 7 days.

Instead of ampicillin, amoxicillin IV can be used. Flucloxacillin IV can be used instead of ampicillin/amoxicillin, if Staphylococcus as nosocomial infection is suspected, particularly in late onset sepsis.

When C/S is not available, clinical judgment will help to continue treatment. If no clinical improvement or deterioration and culture not available or negative (culture not highly sensitive test), but clinical condition do not improve with presence of increase surrogate markers of bacterial infections (CRP, procalcitonin), then second line of antibiotics are given.

Second-line of Antibiotic

Third generation cephalosporin: Injection cefotaxime/ceftazidime (50 mg/kg/dose twice daily IV) for 7 days and injection amikacin IV (7.5 mg/kg/day) twice daily for 7 days.

Ceftriaxone is avoided during neonatal period for possible cholestasis.

Instead of amikacin other aminoglycoside, like gentamycin or netilmicin, can be used along with cephalosporin.

If organisms are isolated and resistant to first line or second line, or culture is negative, but clinical sepsis does not improve in presence of bacterial markers or clinical condition deteriorates further, third line drug is chosen. One

or occasionally more than one of the following drugs is/are chosen.

Carbapenems

- Imipenem/meropenem: 20–35 mg/kg/dose in 2–3 times daily
- Ciprofloxacin: 15–20 mg/kg in two divided doses
- Concern about necrotizing enterocolitis (NEC), add metronidazole IV
- If methicillin resistant *S. aureus* (MRSA), vancomycin, 15 mg/kg/dose, 6–12 hourly
- True coagulase negative staphylococcus (CONS) bacteremia is unlikely, unless there is more than one CONS culture positive
- If there is proven CONS sepsis associated with long line (or other central venous line), consider continuous vancomycin infusion.

If fungal infection is present, oral or injection fluconazole or injection amphotericin B.

In vulnerable babies (preterm taking broad spectrum antibiotic for prolong time), oral nystatin or oral fluconazole can be offered as fungal prophylaxis.

Duration of Antibiotic Therapy

- Stop all antibiotics after 48 hours, if culture and septic markers (CRP, procalcitonin) are negative and clinical condition improve
- Antibiotic course varies depending on type of infection, condition of the baby, change in inflammatory markers, but usually 5–10 days
- In pneumonia: 10 days
- In meningitis: 14–21 days
- In osteomyelitis: 4–6 weeks.

Antibiotic Resistance

Multidrug resistance (MDR) of the organisms causing sepsis is rapidly emerging, causing potentially disastrous consequence. MDR bacteria are becoming increasingly common in the developing countries of South Asia, including Bangladesh and India.

Multidrug resistant neonatal sepsis is usually defined as resistance to all three types of antibiotics: ampicillin, gentamycin and cefotaxime/ceftazidime.

The alarming picture and pattern of recent MDR of the organisms causing neonatal sepsis in developing countries of Asia, including Bangladesh, Pakistan and India, created a growing concern, challenge and threat to neonatal survival. The various data obtained from this part of the world is in sharp contrast to recent recommendation for empirical treatment of neonatal sepsis in the UK, where amoxicillin, gentamycin and cefotaxime, have been found adequate.

Most frequent pathogens involved in MDR severe neonatal sepsis is GNB. In Indian subcontinent, *Klebsiella pneumoniae*, acinetobacter, *E. coli* and *Pseudomonas aeruginosa* are most frequently isolated. Early recognition and early aggressive use of appropriate broad spectrum antibiotics should be started, when they are isolated or when there is clinical suspicion of antibiotic resistant bacteria, in order to prevent catastrophic consequences.

However, the use of broad spectrum antibiotics (cephalosporin, carbapenem) substantially alter the colonization pattern of neonatal intestinal flora, increase the risk of subsequent invasive fungal infection, promote MDR bacteria and increases the risk of subsequent NEC.

The bed side physician should analyze the risk benefit of administering empirical broad spectrum (cephalosporin, carbapenem) antibiotic in suspected sepsis in which the physician must weigh the broad spectrum induced potential consequence of change of neonatal intestinal flora with subsequent development of invasive fungal infection, NEC and promotion of MDR bacteria (NICU public health) against potential short-term (48 hours mortality) benefit of broad spectrum antibiotic in preventing neonatal death, keeping in mind that neonatal sepsis is a leading cause of neonatal death in developing countries.

This is often difficult decision and requires a multidisciplinary approach to the collection and interpretation of data.

Treatment of Antibiotic-resistant Infection

Antibiotic-resistant Gram-negative Bacteria

These are more frequently found in all stages of neonatal sepsis in South Asian countries, compared to western countries. Most dominant organisms are *K. pneumonia, E. coli*, acinetobacter, pseudomonas and, less frequently, serratia. Until recently enterobacteriaceae had predictable antibiotic susceptibility with β-lactam antibiotics. During the past decade, extended spectrum β-lactamase (ESBL) producing enterobacteriaceae has become important cause of community and hospital acquired infection. ESBL often coexist with fluoroquinolone and aminoglycoside resistant, along with penicillin and cephalosporin.

Carbapenem resistant enterobacteriaceae:Carbapenems have become the mainstay of treatment of serious infections with ESBL producing Gram negative bacteria. Carbapenems should normally be used as monotherapy because there is no evidence of any benefit from addition of an aminoglycoside. High dose of (35–40 mg/kg/dose, twice daily) carbapenem may be tried in case of low level of resistant. Fluoroquinolone (ciprofloxacin) may be given a trial, if susceptible.

However, in most circumstances they are not effective, then following drugs should be used:

Colistin: Dose, 40,000–225,000 IU/kg/day by slow IV infusion in three divided doses. Plasma-concentration monitoring is required in renal impairment.

Tigecycline: It is active against many MDR gram positive bacteria and GNB, except *P. aeruginosa*. It is a tetracycline analogue and may cause bone defect and dental staining, and therefore, should be used when there is no alternative. It should be given in IV infusion.

Antibiotic-resistant Nonfermentive Gram-negative Bacteria

P. aeruginosa:

- Resistant with antipseudomonal antibiotic including aminoglycoside, third generation cephalosporin, antipseudomonal penicillin and carbapenem.
- A combination of two antibiotics with different mechanism of action or colistin is usually recommended, in case of MDR.

Colistin is given IV in MDR pseudomonas infection. Aerosolized colistin in pseudomonas pneumonia is used as last resort.

For MDR acinobacter infection, carbapenem is the drug of choice. Some strains show discordant resistance to carbapenems, being susceptible to imipenem but resistance to meropenum. In carbapenem resistant acinobacter, aminoglycoside, especially tobramycin, can be used.

Antibiotic-resistant Gram-positive Bacteria

Gram-positive bacteria is more frequent in western countries. It is also called healthcare associated bacteria. Mostly, MDR staphylococcal infection occurs in NICU. Both *S. aureus* and CONS may show methicillin resistant strain (MRSA), usually healthcare associated pathogens. Community acquired-MRSA (CA-MRSA) is also increasingly found in young healthy persons, particularly in the USA. It is possible that in the future, mother to baby transmission of highly virulent CA-MRSA containing pantone-valentine leukocidin could become a problem.

Vancomycin: Vancomycin, a glycopeptide antibiotic, is the mainstay of treatment of most MDR staphylococcus infection in NICU. Vancomycin is also mainstay of treatment of infection with penicillin resistant pneumococcus (PRP).

If CSF involvement is present, where vancomycin penetration is less, vancomycin is combined with rifampicin or cefotaxime.

Combination therapy with linezolid, clindamycin and/or rifampicin is also very effective. Dose of vancomycin is usually 40 mg/kg into three divided doses. Other resistant antigram positive antibiotics include Linezolid, which has been used with success in neonatology. Linezolid may be useful in refractory staphylococcal infection. It is also orally active.

Other used drugs:

- Daptomycin, useful in persistent staphylococcal infection, 6 mg/kg/dose, 12 hourly
- Other antibiotic in pipeline: Against resistant gram positive bacteria are ceftaroline, ceftrobiprole.

Control Measures for Antibiotic-resistant Bacteria

Infection control measures should be taken to prevent person to person transmission of bacteria, along with treatment of MDR bacteria.

General Measures

Hand washing, hand decontamination and disinfection:

- Hands and forearms should be washed each time the NICU is entered
- No rings or watches to be worn, sleeve above elbow, no ties
- Disposable sterile cotton or synthetic gown, mask, head cap and sterile shoe cover (if shoes are not taken off) should be used before entering neonatal unit
- After hand washing, always apply alcohol gel and allow to drug before handling baby
- Use alcohol gel on entering and leaving all clinical areas, and before and after each patient contact
- Hands become contaminated (body fluids, etc.); wash with soap and water.

More Specific Measures to Prevent Drug-resistant Bacteria

Identification of Patient Infected or Colonized with Bacteria

Patient colonized or infected with antibiotic-resistant bacteria that are not considered to be part of normal flora of NICU or neonatal unit should be isolated. Outbreaks of infection or colonization on NICUs are frequently difficult to control, and for this reason surveillance cultures, especially of the respiratory and gastrointestinal tracts are increasingly being used to identify colonized patients early.

Antibiotic Risk Factor

Antibiotic use is an important risk factor for colonization or infection with antibiotic resistant bacteria. Unnecessary use of antibiotics should not be practiced. Unfortunately upto 95% of neonate admitted in NICU receive empirical antibiotic in the first postnatal days, despite the fact that the fraction of blood culture positive for bacteria in this population is 1–5%.

It is important that antibiotic prescribing policies on NICUs minimize the use of antibiotics that are implicated in spread of MDR bacteria. Relatively narrow spectrum (ampicillin, gentamycin) antibiotic is better for empirical treatment of presumed sepsis. Cephalosporins have been implicated in the emergence and spread of both Gram positive bacteria and GNB. The choice of empirical antibiotics must also take account of local antibiotic susceptibility patterns, which may change according to which pathogens are predominant at any point of time.

SUPPORTIVE TREATMENT OF NEONATAL SEPSIS

- Prevent hypothermia; keep the baby warm: Wrapping, keeping under radiant warmer or in incubator
- Hypoglycemia: By IV 10% glucose
- Feeding: Breastfeeding; if not possible, then nasogastric (NG) feeding of expressed breast milk (EBM). If the baby cannot tolerate oral or NG feeding, then IV nutrition [10% dextrose + 0.225% normal saline (NS), 20–25% less than normal daily allowance) should be given
- Provide oxygen [cyanosis, grunting, severe chest indrawing; respiratory rate (RR) >70/minute, repeated seizure]
- Monitoring and treatment of apnea
- Infusion of normal saline, if perfusion is poor (capillary refilling time is >3 sec), 10–20 mL/kg over 5–10 minutes. Repeat the same dose in the next 30–45 minutes, if perfusion is continued to remain poor.

ADJUNCT THERAPY

- Exchange transfusion, if indicated
- IV immunoglobulin (IVIG): 250 mg/kg/day
- Transfusion fresh frozen plasma and concentrate platelet for bleeding.

FRESH BLOOD TRANSFUSION

Indications

- Hb less than 12 g/dL (in neonatal sepsis)
- Sclerema
- NEC
- Hb less than 10 g/dL in a symptomatic baby (poor weight gain, poor feeding, tachycardia)
- Hb less than 8 g/dL is a asymptomatic baby
- Acute blood loss
- Heart failure due to anemia.

Situations Requiring Intravenous Infusion (Nutrition)

- Birthweight less than 1,200 g
- Gestational age less than 30 weeks
- Severe perinatal asphyxia
- Severe respiratory distress (severe chest indrawing, tachypnea, gasping, grunting, cyanosis)
  - Apnea
  - Recurrent seizure
  - NEC/intestinal obstruction
  - Absent bowel sound
  - Feeding intolerance (poor sucking, choking, vomiting, abdominal distension, gastric stasis, blood in the stool).

Follow-up of Sepsis Cases

Every 4–6 hours to monitor

- Vital signs: Heart rate, respiratory rate and temperature
- Primitive reflexes: sucking, rooting, Moro and others
- Skin condition: Texture, color, tissue perfusion, any mottling, etc.

PREVENTION OF INFECTION (TABLES 46 AND 47)

Prevention of Infection is more Cost-effective than Treating Infection in Neonates

Normally, the newborn is free from harmful organisms for initial few hours after birth. Staff working in hospitals tends to transmit organisms during routine procedures, thus leading to colonization of organisms. Various instruments and utensils use routinely in nursery should be made sterile with disinfectants regularly (Table 46). Disinfectants and germicides frequently used are mentioned in Table 47.

Basic Requirements to Prevent Sepsis in Hospital

- Strict hand washing
- Elbow operated taps
- Running water supply
- Soap
- Hand drier/autoclaved towel/paper towel/autoclaved newspaper
- Promotion of breastfeeding
- Rational antibiotic policy
- Adequate disposables
- Restriction of visitors.

Guidelines for Entry into the Baby Care Area

- Remove shoes, rings, watch, bangles. Fold the full sleeves upto elbow. Do not keep long nails
- Put on nursery slippers, wash hands with soap and water for 2 minutes (follow six steps of hand washing).

Steps of Effective Hand Washing

- Use plain water and soap, wash parts of the hand in the following sequence (Fig.123):
  - Palms and fingers, and web spaces
  - Back of hands
  - Fingers and knuckles
  - Thumbs
  - Fingertips
  - Wrists and forearm upto elbow.

Once hands are washed, one should not touch anything, e.g. hair, pen or any fomite till one carry out the required job.

Policy Regarding Visitors/Caregivers

- Personnel with active infection should not be allowed entry into the baby care area
- Only mother/one female caregiver should be allowed to stay
- Parents/caregivers should be guided and supervised about proper hand washing technique and cleanliness
- Parents of the babies should be allowed into the nursery.

Table 46: Disinfectants of routines

Name	Disinfectant method	Frequency and other considerations
Oxygen hood	Wash with soap and water	Daily in morning shift. Dry with autoclaved linen
Syringe pumps	Clean with wet clean cloth. If blood stained use soap and water	Daily in morning shift, if possible in each shift
Thermometer, BP cuffs, stethoscope measuring tape, probes of radiant warmer incubator	Clean with spirit swab	Daily
Laryngoscope	Clean with spirit swabs thoroughly daily and after each use. Wrap in autoclaved cloth, put date on cover	Never put in cidex. If used for an infected baby, wash with soap and water, blade after removing bulb can be put in 2% cidex, wash thoroughly, dry and wrap in an autoclaved linen, put the date
Face mask	Clean with soap and water, immerse in cidex for 20 minutes, rinse in distilled/running water, dry with autoclaved linen, and wrap in autoclaved linen and put date	Daily and after each use.

Abbreviation: BP, blood pressure

Table 47: Disinfectants and germicides

Name	Indication for use	Direction for use and special considerations
Formalin (40%)	Fumigation of nursery	Routine fumigation: 30 mL formalin with 90 mL water per 1,000 ft^3 area. Nursery is to be sealed properly. Switch off AC and seal AC duct. Switch on the machine for half an hour. Open and clean the nursery after 6 hours
Sodium hypochlorite (bleach)	Sharps/needles and disposables	Keep the solution covered, change it every 24 hours
Bacillocid spray (2%)	Walls of nursery, incubators and warmers (when not in use) surface of weighing machine	Prepare solution as per instruction of manufacturer, put of air conditioners at the time of spray
Cidex (2%) (glutaraldehyde)	Oxygen/suction tubings face mask and ambu bag reservoir	Before immersing into cidex, clean thoroughly with soap and water. Once solution prepared is active for 14 days.
		For sterilization: 4–6 hours
		For disinfection: 15 minutes
Spirit	Skin preparation, cleaning laryngoscopes blades, tape measures stethoscope	Don't use to clean incubators and warmers
Soap and water	Oxygen hood, feeding utensils, tray, face mask, buckets	After washing in soap and water, boil the feeding utensils for 15 minutes
Betadine	Skin preparation	
Phenyl	Cleaning floors	

Fig. 123: Six steps of hand washing

Sterile Gloves

- Always use sterile gloves for invasive procedures, like sampling, starting IV lines, IV injections.

Nursery Environment

- The environment should be calm and clean
- The nursery temperature should be maintained between 28 and 30°C
- Overcrowding should be avoided
- Ensure 24 hours water and electricity supply with adequate lighting and ventilation
- Covered dustbin should be used
- Dustbin must be lined with polythene; should be changed daily or whenever full
- Clean the walls with 2% of bacillocid once in a week
- Floor should be cleaned with diluted phenyl once in a day and when required. No dry mopping, only wet cleaning should be done.

Skin Preparation for Insertion of Intravenous Cannula, Venipuncture and Other Procedures

- Skin preparation should be done meticulously to avoid entry of pathogens during insertion of IV cannula or any invasive procedure. The following procedure should be followed:
  - Wear sterile gloves after proper washing and drying of hands
  - Swab the skin selected with spirit first and allow it to dry
  - Select skin site, confine to smallest possible area of skin.
  - Swab with iodine on site, and allow it to dry and swab again with spirit to wipe off iodine
  - Allow it to dry
  - The procedure is now complete for venipuncture and procedure.

MANAGEMENT OF LOW BIRTHWEIGHT NEONATES (TABLES 48 TO 51)

Among the main causes of neonatal death severe infection is attributable to 34% neonatal death in developing countries. Since infection in neonates progress rapidly, it is a particular concern in situations where facility of delivery is low. It has been found that one-third reduction in neonatal mortality compared to control areas by introducing home-based identification and management of possible severe neonatal infection by trained community health worker (CHW).

With sepsis contributing to one-third of neonatal deaths, the strategy aims to reduce risk factors associated with sepsis, increase early recognition of sepsis and ensure quality care for potentially septic neonates.

Table 48: Broad strategic actions by level of care

Level	Strategies
At all levels	• Develop CHWs' capacity to classify and manage neonatal infections
Home and community level	• Raise awareness of families and communities on risk of infections, and promote practices to reduce risk and promote timely care-seeking for illness
	• Raise mother and community awareness of danger signs for infection, and improve self-referral for early infection management
	• CHWs and lower level (nonphysician) health workers will follow the sepsis algorithm to classify and manage neonatal sepsis
	• Equip and upgrade community clinics for management of neonatal sepsis
Subdistrict levels	• Develop and strengthen facilities for management of newborn infections, including treatment and/or upward referral of sick newborns with danger signs
	• Strengthen staff capacity to recognize sick newborns and treat appropriately according to protocols
District level and above	• Offer comprehensive newborn care services with proper diagnosis and management of sick newborns
	• Physician or skilled health worker judgment in conjunction with more complete examination and available laboratory assessment is needed to make a firm diagnosis of sepsis

Table 49: Guidelines for neonatal sepsis interventions

Interventions	Guidelines and activities
Home visit to increase awareness and promote ENC	• Use standardized messages and interventions included in ENC package • Educate mothers on increased sepsis risk among LBW infants
Establishment of a birth and death registration system	• All CHWs record births in register and include 2 month follow-up visit, recording status of neonate at that time • All deaths < 28 days recorded in CHW register (either through home visit or by family reporting death)
Expansion of community-based IMCI to include the entire neonatal period	• Develop integrated package of services that can be included with the scaling up of C-IMCI
	• Revise IMCI materials to include Neonatal Health Strategy interventions to scale up C-IMNCI program
	• Health workers provide ANC and PNC as per guidelines
Evaluation of the role of all levels of health workers in providing improved maternal and neonatal care, including sepsis management	• Review roles of existing cadres of workers in provision of maternal and neonatal interventions, with a focus on filling the gap in community-based service delivery, particularly for identification and management of sepsis
	• At community level: – Apply results of operations research on community management of sepsis (see below)
	• At facility (union level: UH and FWC and union subcentre): – Link up with Upazilla (subdistrict) and district level facilities for referral of sick babies – Ensure safe and rapid transport with thermal protection, breathing stabilization and continued supportive care on the way to a facility providing an appropriate level of neonatal care – Support CHWs in their home-based management of neonatal infections
	• At Upazilla (subdistrict) level facility (UHC): – Manage newborn infections with appropriate antibiotics – Link up with district and above level facilities of care for referral of appropriate cases of sick newborns
Strengthening the link between maternal health and neonatal health programs	• Evaluate models for linkage of postnatal newborn care, including sepsis management, with maternal health programs • Develop a standard package of care for sepsis that can be provided through an integration of services delivered by different ministry sectors
Initiation of community-based operations research to improve the management of neonatal infections	• Initiate operations research on CHW classification of neonates as having possible severe bacterial infection (likely sepsis) based on an algorithm, and provide guidelines for initial treatment and referral: – CHW (HA and/or FWA and possibly NGO-CHWs) management of sepsis, including use of oral drugs, home-based IM injections (penicillin or gentamycin), consistent with IMCI guidelines
	• Assess optimal treatment regimens and antibiotic delivery mechanisms for different levels of care
Strengthening community mobilization for management of sepsis	• Evaluate approaches to community mobilization for promotion of effective linkages between community and facilities to improve management of neonatal infections

Table 50: Algorithm for management of neonatal sepsis at home, community and union level facilities (Community clinic/UH and FWC/union subcentre)

Assess the baby for possible sepsis	Signs	Classify	Treatment
Ask: • Is the baby able to feed? • History of convulsion *Look, listen, feel (Note: Newborn baby must be calm to assess breathing)* • Look for convulsion • Count the breaths in 1 minute • Repeat the count, if increased (i.e. 60/minute or more) • Look for severe chest indrawing • Measure axillary temperature (for 3 minutes) • Look at the newborn baby's movements If infant is sleeping, ask the mother to wake him/her • Does the infant move on his/her own? If the infant is not moving, gently stimulate him/her • Does the infant move only when stimulated, but then stops? • Does the infant not move at all?	If there is one or more signs: • Not feeding well* • Convulsions* • Fast breathing (>60 bpm on second count) • Severe chest indrawing • Low body temperature (<35.5°C or 95.9°F) • Fever (>37.5°C or 99.5°F) • Movement only when stimulated or no movement at all	Possible sepsis	• Give first dose of IM antibiotics: injectable gentamycin (5 mg/kg) and – oral amoxicillin (50 mg/kg), or – oral cotrimoxazole (5 mg/kg) • Treat to prevent low blood sugar: Ensure proper feeding • Refer urgently to a hospital – If able to take feed continue feeding. – Advise to keep the baby warm by skin to skin contact on the way to the hospital If referral fails • Follow-up the baby and continue treatment at home: – Injection gentamycin (5 mg/kg/day in single dose for total 7 days) and oral Amoxicillin (50 mg/kg/dose, twice daily for total 7 days) or oral cotrimoxazole (5 mg/kg/dose, twice daily for total 7 days) • Counsel the mother for referral, if sign persists • Inform the supervisor for the failed referral

*Based on history and assessment

Abbreviation: IM, intramuscular

Table 51: Algorithm for management of neonatal sepsis at facilities [Upazilla (subdistrict) health complex/district hospital/maternal and child welfare center/medical college hospital]

Assess the baby for possible sepsis	Signs	Classify	Treatment
Ask: • Is the baby able to feed? • History of convulsion *Look, listen, feel (Note: Newborn baby must be calm to assess breathing)* • Look for convulsion • Count the breaths in 1 minute Repeat the count, if increased (i.e. 60/minute or more) • Look for severe chest indrawing • Measure axillary temperature (for 3 minutes) • Look at the newborn baby's movements If infant is sleeping, ask the mother to wake him/her • Does the infant move on his/her own? If the infant is not moving, gently stimulate him/her • Does the infant move only when stimulated, but then stops? • Does the infant not move at all?	If there is one or more signs: • Not feeding well* • Convulsions* • Fast breathing (>60 bpm on second count) • Severe chest indrawing • Low body temperature (<35.5°C or 95.9°F) • Fever (>37.5°C or 99.5°F) • Movement only when stimulated or no movement at all	Possible sepsis	First-line treatment: • Injection gentamycin IV or IM (5 mg/kg/day in single dose for 7 days) plus: – Injection ampicillin IV or IM (50 mg/kg/dose, twice daily) for 7 days, or – Injection procaine penicillin IM (50,000 IU/kg as single, daily for 7 days), or – Injection benzylpenicillin IM (50,000 IU/kg/dose 6 hourly, for 7 days) Second-line treatment: Injection ceftazidime/cefotaxime IV or IM (50 mg/kg/dose, twice daily for 7 days) plus Injection amikacin IV or IM (7.5 mg/kg/dose twice daily for 7 days).

*Based on history and assessment.

IDENTIFICATION OF NEONATAL SEPSIS: DANGER SIGNS

Potentially sick neonates should be identified by mothers or family members based on the neonatal danger signs for sepsis (see below). These danger signs require no equipment and are designed to increase the likelihood that mothers seek early care for sick neonates.

- Not feeding well
- Convulsions
- Fast breathing (> 60 bpm on second count)
- Severe chest indrawing
- Low body temperature (< 35.5°C or 95.9°F)
- Fever (more than 37.5°C or 99.5°F)
- Movement only when stimulated or no movement at all.

CONGENITAL INFECTION: GENERAL PRINCIPLES

INTRODUCTION

- Conventionally described as the TORCH infections: toxoplasmosis, rubella, CMV, HSV. Strictly speaking, TORCH infections are not all genuinely congenital or intrauterine, but usually perinatal
- Other infections which are perinatal acquired: hepatitis B virus (HBV) and hepatitis C virus (HCV), parvovirus B19, human immunodeficiency virus (HIV) infection
- Some important aspect should be seen before ordering congenital infection screening investigations on babies. These are as follows:
  - Serological diagnosis may be made on mother's blood and some viral infections excluded by testing mother's blood [e.g. HBV and HCV, HIV, human T lymphotropic virus (HTLV)]
  - Some infections cannot be ruled out on clinical evidence alone, e.g. perinatal hepatitis B (HB) and hepatitis C (HC) are almost always asymptomatic and do not cause neonatal jaundice
  - Baby's serology may reflect mother's long-term past infections
  - Baby's IgM although indicates present infection but not always reliable as a marker of congenital infections
- Diagnosis may be best done by direct detection:
  - Molecular techniques, such as polymerase chain reaction (PCR), to detect viral genomes
  - Rapid culture
  - Immunofluorescence for viral proteins (e.g. CMV in urine).
- Some infections need follow-up for up to 18 months before maternal antibody has decayed to exclude congenital infection, e.g. toxoplasmosis, syphilis, HCV, HIV.
- Virology department should be involved for the diagnosis of congenital viral infection.

SOME IMPORTANT CLINICAL FEATURES TO BE SEEN (TABLE 52)

- IUGR is an important feature suggestive of congenital infection
- Symmetrical IUGR with microcephaly is more indicative of congenital infection
- Hepatosplenomegaly usually indicates extramedullary hemopoiesis

Table 52: Some important clinical features of congenital infections

	Toxo	Rubella	CMV	HSV
IUGR	✓	✓	✓	
Cardiac				
• Structural	✓	✓	✓	
• Inflammation			✓	
Ocular				
• Cataract		✓		
• Conjunctivitis	✓	✓	✓	✓
Hepatic (jaundice, hepatitis)	✓	✓	✓	✓
Hematological	✓	✓	✓	✓
Purpura/petechiae	✓	✓	✓	✓
Hepatosplenomegaly		✓	✓	
Respiratory (pneumonitis)			✓	
Neurological				
• Microcephaly	✓	✓	✓	
• Calcification	✓		✓	
• Hydrocephalus	✓		✓	
• Encephalitis		✓		
• Deafness		✓	✓	

Abbreviations: IUGR, intrauterine growth restriction; CMV, cytomegalovirus; Toxo, toxoplasmosis; HSV, herpes simplex virus

Fig. 124: A baby with congenital rubella with purpuric skin rash

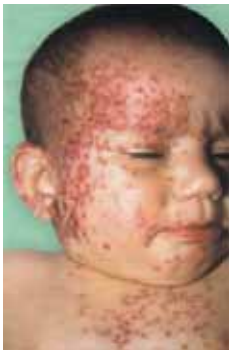


Fig. 125: A baby with skin rash with generalized herpes

Fig. 126: An infant with chorio-retinitis microphthalmia and strabismus

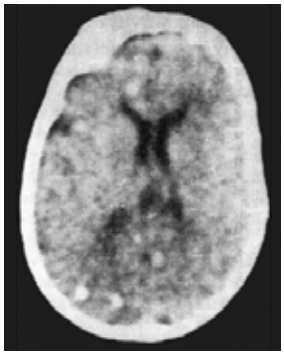


Fig. 127: CT scan of brain showing diffuse calcification

- Cerebral calcification is diffuse in toxoplasmosis (Fig. 126); whereas in CMV (Fig. 127C) it is periventricular
- Pneumonitis may present in preterm infants with unexpectedly severe chronic illness
- Purpura or petechiae usually due to thrombocytopenia.

Figures 124 to 128 show clinical features of TORCH infection.

Figs 128A to C: Congenital toxoplasmosis. (A) A child with CMV with microcephaly during newborn period; (B) The same child at 6 months showing microcephaly with spastic quadriplegia; (C) CT scan of the child showing ventriculomegaly with periventricular calcification

INVESTIGATIONS

- Try to make a presumptive diagnosis and send appropriate laboratory investigation requests
- Discuss tests in advance with virology
- Request a TORCH screen, if indicated.

PERINATALLY ACQUIRED HEPATITIS B INFECTION

- Babies can acquire HBV perinatally or postnatally
- Neonatal HBV is usually asymptomatic and has a high incidence of chronic infection (90%)
- Antenatal screening of mothers for HB should be done routinely
- Maternal serology is used to interpret the risk of perinatal transmission (Table 53):
  - HB surface antigen (HBsAg) indicates maternal carrier status
  - HB e antigen (HBeAg) correlates with viral replication and high levels of virus (i.e. high infectivity)
  - HB e antibody (anti-HBe) correlates with the loss of replicating virus and with lower levels of virus (i.e. low infectivity)
  - Viral load may be useful where there is unknown "e" status or baby is negative for HBeAg and anti-HBe. Viral load greater than 106 IU/mL indicates high infectivity.
- Transmission risk from HBeAg positive mother is 70–90% without immunization and less than 10% after immunization. If a mother is HBsAg positive and anti-HBe positive, the transmission without immunization is about 10%.

Table 53: Hepatitis B status of mother and treatment of baby

HB status of mother	Baby should receive	
	HBV vaccine	HBIG
Mother HBsAg positive and HBeAg positive	Yes	Yes
Mother HBsAg positive, e-markers not present or not determined	Yes	Yes
Mother has acute HBV during pregnancy (HBc IgM positive)	Yes	Yes
Very low birthweight baby <1,500 g and mother HBsAg positive (regardless of e-antigen status)	Yes	Yes
Mother HBsAg positive, HBeAg negative, anti-HBe positive	Yes	No

Abbreviations: HB, hepatitis B; HBV, hepatitis B virus, HBIG, hepatitis B immunoglobulin; HBsAg, HB surface antigen; HBeAg, HB e antigen; HBc IgM, hepatitis B core antigen immunoglobulin M

HEPATITIS B IMMUNIZATION

Preventing First Episode of Disease

- All infants born to HBV infected women, including HIV coinfected women, should receive HB vaccine and hepatitis B immune globulin (HBIG) within 12 hours after birth, a second dose of HB vaccine at the age of 6 weeks, and a third dose at the age of 14 weeks
- Currently, two well-recognized strategies are taken for primary HB vaccination. One preferable strategy is to give primary series vaccine at birth, followed by 6 weeks and third dose is given between 6 months and 18 months. Another strategy, if not given at birth, is to vaccinate at 6 weeks, 10 weeks and third dose is given between 6 months and 18 months. However, third dose can be given as early as 14 weeks which facilitates HB vaccine to be given together with HB containing combination vaccines like penta or hexa in same visit with one prick. The efficacy is found similar when third dose is given at more than 16 weeks after first dose. Similarly, at 6 weeks and 10 weeks first and second dose can be given as combination vaccine with penta and hexa with third dose vaccine given at 14 weeks with penta and hexa. In the same fashion, if first dose is given at birth, the subsequent vaccines can be given with primary penta or hexa series. In that case, one additional vaccine (1+3 primary vaccine) given will not be a problem
- For preterm infants weighing less than 2,000 g, the initial vaccine dose given at birth should not be counted as part of the vaccine series because of the potentially reduced immunogenicity of HB vaccine in these infants; three further doses of vaccine (for a total of four doses) should be administered at the beginning, when the infant reaches age of 6 weeks followed by at 10 weeks and 14 weeks, if HB containing combination vaccine is given or at 10 weeks and between 6 months and 18 months (final vaccine), if monovalent HB vaccine is used
- A three-dose HB vaccine regimen is 95% effective in preventing HBV infection in HBV-exposed infants. Postvaccination testing for antiHBs and HBsAg should be performed at age 9–18 months in infants born to HBsAg positive women. The level of anti-HBs that is considered protective is greater than 10 mIU/mL. Infants who are HBsAg negative and have antiHBs levels less than 10 mIU/mL should be revaccinated with a second three-dose series of HB vaccine and retested 1–2 months after the final vaccine dose.

- The three-dose series of HB vaccine also is recommended for all children and adolescents aged less than 19 years who were not previously vaccinated. However, antibody responses to HB vaccination may be diminished in HIV-infected children, especially in older children or children with CD4 counts less than 200 cells/mm^3.

Breastfeeding in Hepatitis B Positive Mother

Although HB virus is secreted in breast milk, the possibility of acquiring infection from mother to child through breast milk is remote possibility. The advantage of breast milk far outweighs the remote possibility of acquiring infection through breast milk. The anti-infective property present in breast milk has the potentiality to defuse infectivity of HBV.

Therefore, there is no contraindication to breastfeeding with HB positive mother.

DELAYED PASSAGE OF MECONIUM

INTRODUCTION

Most of the babies pass meconium within 24 hours of birth. 99% of term neonates and 95% of preterm neonates will pass meconium within 48 hours of birth.

CAUSES OF DELAYED PASSAGE OF MECONIUM

It is delayed in ill preterm babies and infants of mothers who are on antihypertensive drugs.

Other Causes

- Ileal atresia
- Meconium plug syndrome
- Cystic fibrosis (meconium ileus)
- Hirschsprung's disease.

In all these conditions abnormal meconium is seen in appearance, consistency and amount. Prolonged delay is associated with vomiting and abdominal distention.

WHAT IS MECONIUM ILEUS?

- It is obstruction of distal ileum secondary to accumulation of tenacious meconium
- Cystic fibrosis results in failure of cell membrane chloride pump leading to tenacious meconium. It occludes distal ileum and obstructs bowel. It can result in perforation with meconium peritonitis
- Presents with failure to pass meconium.

HOW WILL YOU INVESTIGATE?

- X-ray abdomen: Multiple dilated loops of small bowel
- Enema with water soluble contrast: It differentiates between Hirschprung's disease distal small intestinal or colonic atresia, meconium ileus. Affected ileum looks dilated with multiple filling defects
- Protein contents of meconium
- Serum immunoreactive trypsin (IRT) for screening for cystic fibrosis
- Sweat test (not usually done in newborn) to rule out cystic fibrosis
- T3, T4, thyroid stimulating hormone (TSH) to rule out hypothyroidism.

EVALUATION OF NEONATAL JAUNDICE (HYPERBILIRUBINEMIA)

INTRODUCTION

About 60% of term and 80% of preterm infants develop jaundice during first week of life. Most of the jaundice of the newborns is physiological.

WHY JAUNDICE IS MORE IN NEWBORN?

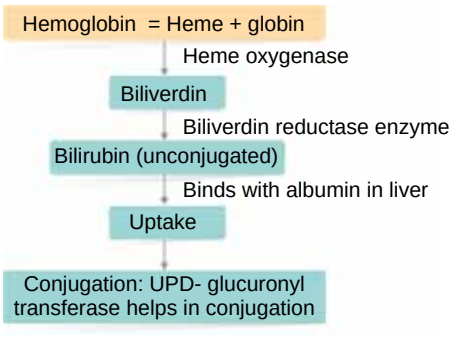
- More fetal blood volume in newborn (100–120 mL/kg) and more break down of RBC, so increase bilirubin load
- Short RBC life span (60–90 days)
- Cytochrome is more in newborn (heme containing compound)
- Uridine diphosphate glucuronyltransferase (UDPGT) decrease in newborn leads to decreased conjugation
- Increased enterohepatic circulation and increased uptake of bilirubin
- Immaturity of excretory function of liver in relation to more production of bilirubin
- Decreased bacterial flora.

Synthesis of hemoglobin has been described in Flow chart 9.
Neonatal jaundice is called physiological jaundice if following criteria are present:

CRITERIA OF PHYSIOLOGICAL JAUNDICE

- Baby is otherwise healthy
- Indirect hyperbilirubinemia
- Jaundice appear on second or third day of life, peaks on third or fourth day in case of term, fifth or sixth day in case of preterm baby
- Time of disappearance: Within 1–2 weeks (mostly 7–10 days) in-term baby and within 14 days in preterm baby
- Resolves spontaneously
- Exclusion of the cause of pathological jaundice which include:
  - Any clinical jaundice appearing on day 1 (within 24 hours)
  - Total serum bilirubin greater than or equal to 250 µmmol/L by 48 hours
  - Total serum bilirubin greater than or equal to 275 µmmol/L by 72 hours

Flow chart 9: Synthesis of hemoglobin



- Total serum bilirubin greater than or equal to 300 µmmol/L by 96 hours.

Note: Cord serum bilirubin: 20–35 µmol/L, normal.

DIAGNOSIS OF SEVERE JAUNDICE

The term neonatal jaundice does not signify or provides information about the severity of neonatal jaundice. If unconjugated bilirubin is very high, it may affect the brain of newborn baby causing bilirubin encephalopathy and kernicterus, resulting in cerebral palsy and other neurodevelopmental disorder. Therefore, severe neonatal hyperbilirubinemia should be differentiated from nonsevere hyperbilirubinemia.

Severe neonatal hyperbilirubinemia includes one or all of the followings:

- It is defined as unconjugated serum bilirubin of greater than or equal to 510 µmol/L in the first month of life. It is also defined as malignant or extreme hyperbilirubinemia of newborn
- Total serum bilirubin greater than 350 µmol/L in the first 48 hours of life
- Rapidly increasing bilirubin (>10 µmol/L/hour).

TOTAL OR UNCONJUGATED BILIRUBIN

Total bilirubin levels are used for treatment threshold with no substitution of conjugated elements.

Significance of Preventing Severe Neonatal Hyperbilirubinemia

Despite the advances in neonatal care, there has been recent resurgence of bilirubin encephalopathy and clinical kernicterus in several parts of the world including North America and Europe. Severe hyperbilirubinemia can cause encephalopathy with important sequelae among surviving infants, including athetotic cerebral palsy, sensory neural hearing loss, paralysis of upward gaze and dental enamel dysplasia.

Kernicterus is a preventable condition and failure of clinical observation and awareness to identify severe jaundice in a timely intervention to prevent brain injury may be disastrous. Babies with severe jaundice merit multiple phototherapy delivery and with the most excellent equipment.

Symptoms Consistent with Encephalopathy

- Impaired consciousness
- Hypotonia
- Opisthotonus
- Seizure.

Causes of Exaggerated Physiological Jaundice

- Prematurity
- Maternal-fetal transfusion
- Extravasated blood: Intraventricular hemorrhage (IVH), concealed hemorrhage, cephalhematoma, birth injury
- Polycythemia
- Late cord clamping
- Recipient of twin-twin transfusion
- Dehydration
- Delayed passage of meconium
- Less intake of breast milk
- Swallowed maternal blood.

CONJUGATED OR DIRECT HYPERBILIRUBINEMIA (CHOLESTATIC JAUNDICE)

Cholestasis is defined as the condition where absolute direct bilirubin value is greater than 2 mg/dL with total bilirubin greater than 10 mg/dL or value of direct bilirubin that represents more than 20% of total bilirubin, if the total bilirubin is less than 10 mg/dL. It is often associated with dark urine and pale stool. Cholestatic jaundice is always pathological.

Criteria of Pathological Jaundice

- Jaundice in first 24 hours
- Bilirubin rising more than 100 µmol/L in 24 hours (> 5mg/dL/day).
- Serum bilirubin more than 300 µmol/L at any time
- Persists more than 2 weeks in-term babies
- Persists more than 3 weeks in preterm babies
- More than 20% direct hyperbilirubinemia.

Prolonged Jaundice

If jaundice persists more than 2 weeks in terms and more than 3 weeks in preterm babies, it is called prolonged jaundice.

CAUSES

Prolonged Unconjugated Hyperbilirubinemia

- Breastmilk jaundice
- Hypothyroidism
- Idiopathic hypertrophic pyloric stenosis (IHPS)
- Infection (sepsis)
- Hemolytic anemia: Glucose-6-phosphate dehydrogenase (G6PD).

Common Causes of Unconjugated Hyperbilirubinemia

- Physiological jaundice
- Jaundice of prematurity
- Breastmilk jaundice
- Hemolytic disease of newborn (HDN):
  - ABO hemolytic
  - Rh hemolytic.
- Sepsis: congenital or acquired
- Cephalhematoma
- Bruising
- Hypothyroidism
- Hypertrophic pyloric stenosis
- Infant of diabetic mother
- Crigler-Najjar syndrome.

Prolonged Conjugated Hyperbilirubinemia

- Biliary atresia
- Neonatal hepatitis
- Inborn error of metabolism: Galactosemia
- Cystic fibrosis
- Congenital infection, e.g. rubella, CMV, toxoplasmosis
- Wilson's disease
- Choledochal cyst (typically a variable jaundice).

BREAST MILK JAUNDICE—CLINICAL INDICATORS

Healthy and exclusively breastfed baby with jaundice peak starts in later part of first week or beginning of the second week and lasts for 2–3 months. Sometimes it may be continuation of physiological jaundice. The following are the types of jaundice associated with breastfeeding:

Jaundice Associated with Breastfeeding Beginning in the First Few Days of Life

This occurs in the first few days of life when breastfeeding is not well established. This is associated with delayed passage of meconium due to decrease gut motality, associated with decreased or insufficient breastfeeding, causing increased enterohepatic circulation. This prevents bilirubin excretion through feces (Flow chart 10).

Breast milk Jaundice Beginning in the Second Week of Life

Jaundice appearing in the second week of life in breastfed babies is called breast milk jaundice, which may continue for several weeks. Although the two types jaundice associated with breastfeeding are separate entity but they may overlap.

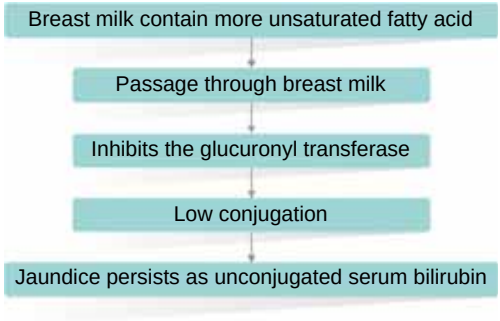
Characteristics of Breast Milk Jaundice

- In term and preterm healthy baby, jaundice persists for more than 14 days, and serum bilirubin is usually not more than 18 mg/dL. When breastfeeding is stopped, serum bilirubin decreases 6–8 mg/dL within 72 hours. When breastfeeding is again offered, serum bilirubin rises again
- Urine and stool color normal
- No Hepatosplenomegaly
- Serum bilirubin may need up to 2 months to become normal
- Exclusion of other causes of pathological jaundice that occurs after 2 weeks, e.g., congenital hypothyroidism, galactosemia, hemolytic anemia, biliary atresia, infection (suddenly, jaundice increased in 4–5 days) is essential.

Significance and Advantage of Breast Milk Jaundice

Although breast milk increases unconjugated bilirubin and helps to continue neonatal jaundice (persistent unconjugated hyperbilirubinemia), nevertheless breastmilk jaundice has cerebroprotective function and prevents kernicterus. In neonatal jaundice with unconjugated hyperbilirubinemia, where there is no contribution of breast milk, the probability of kernicterus is higher than where breast milk contributes to neonatal jaundice. The probability of bilirubin encephalopathy is higher in dehydration following failure to establish breastfeeding.

Flow chart 10: Breast milk jaundice persisting as unconjugated serum bilirubin



Clinical Evaluation of Nonphysiological Jaundice

- Age of appearance of jaundice: Within first 24 hours, blood group incompatibility (ABO and Rh) and rarely G6PD deficiency, congenital infection
- Sex: Male suffer, female carrier—G6PD (X-linked). More in first born male baby called idiopathic hypertrophic pyloric stenosis (IHPS)
- Order of pregnancy: Rh incompatibility—increase tendency to second and subsequent pregnancies
- Blood group and Rh typing of baby and mother: If mother is "O^+" and baby is "A" or "B", chance of ABO; if mother is Rh- and baby is Rh+ chance of Rh incompatibility
- History of (H/O) jaundice of previous child, H/O abortion, intrauterine deaths in any mother with Rh- blood group.
- A family H/O jaundice, splenectomy, early gall bladder disease suggests hereditary hemolytic anemia, like congenital spherocytosis (autosomal dominant)
- A family history of liver disease, particularly with H/O consanguity, may suggest galactosemia, α-1 antitrypsin deficiency, Crigler-Najjar syndrome, cystic fibrosis—mostly autosomal recessive disorders
- Maternal illness during pregnancy with fever and rash may suggest congenital infection (TORCH particularly rubella, cylomegalovinus)
- Exclusively breastfeeding, healthy baby—peak jaundice at the end of first week or early part of second week: breast milk jaundice
- H/O delayed passage of meconium, constipation, hoarse cry, less activity and excessive sleepy with prolonged jaundice: suggestive of congenital hypothyroidism
- Usually first born male baby with prolonged nonbilious vomiting, dehydration, olive like mass in the abdomen: jaundice due to IHPS.

Physical Examinations

- Extent and severity of jaundice (visual assessment) .
- Intermediate jaundice: Congenital spherocystosis:
  - The baby looks more yellow than biochemical jaundice
  - Jaundice with features of prematurity; jaundice of prematurity.

The visual assessment of extent of jaundice as determined by Kramer scale (Table 54, Fig. 129), moderately correlates with bilirubin level, but cannot be used accurately to predict the infant absolute bilirubin level or risk of developing significant hyperbilirubinemia. Darkly pigmented infants are more difficult to assess clinically for jaundice. Although the correlation of visual assessment with bilirubin level is not very strong, but negative predictive value of complete absence of jaundice (Kramer grade 0/1) is high and informative. The predischarge bilirubin value of infant with no jaundice is almost always in the low risk zone.

- Early jaundice and pallor (anemia): Within first 24 hours:
  - Blood group incompatibility (Rh incompatibility)
  - G6PD
  - Congenital spherocytosis
  - Congenital infection.

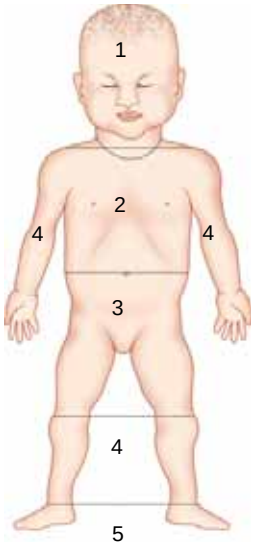


Fig. 129: Kramer grading of extent of jaundice

Table 54: Kramer grading of extent of jaundice

Grade	Affected body part	Content
0	None	
1	Face and neck only	4–6 mg/dL
2	Chest and back	8–10 mg/dL
3	Abdomen below umbilicus to knee	12–14 mg/dL
4	Arms and legs below knee	15–18 mg/dL
5	Hands and feet	> 18 mg/dL

- Hepatosplenomegaly: Septicemia, congenital infection, galactosemia; Hepatomegaly: Biliary atresia; With only splenomegaly: Hereditary spherocytosis
- Cataract: TORCH infection, galactosemia
- Any evidence of sepsis: Septicemia
- Micro/macrocephaly: TORCH infection
- Visible olive like mass: IHPS
- Coarse facies, cool and rough skin, large tongue, umbilical hernia and pot belly, hypotonia: congenital hypothyroidism.

Identify Severe Jaundice

Severe jaundice should be identified earlier so that timely intervention (phototherapy ± exchange transfusion) can be taken to prevent brain injury. Identify risk factors for kernicterus. Risk factors include:

- Shortened gestation
- Failure to establish adequate breastfeeding
- Dehydration
- Male baby
- G6PD deficiency
- Racial pigmentation masking jaundice.

INVESTIGATIONS

- Serum bilirubin (total, direct, indirect): If it is increased and if indirect bilirubin level is high, then likely clinical condition are physiological jaundice, jaundice with prematurity, jaundice with infection, HDN (ABO, Rh) and in breast milk jaundice. Direct bilirubin, 20% or more of the total conjugated hyperbilirubinemia, leads to biliary atresia, neonatal hepatitis syndrome, TORCH infection
- Blood grouping and Rh typing of both mother and baby: ABO and Rh incompatibility
- Peripheral blood film:
  - Features of hemolysis: Hemolytic (Heinz body, nucleated RBC, fragmented RBC) anemia
  - Spherocyte: Spherocytosis
  - Toxic granules: Sepsis
  - Bite cells: G6PD.
- Reticulocyte count: Increase in hemolytic anemia (> 6%)
- Coomb's test (direct/indirect), if previous child is Rh incompatible
- TORCH screening (if conjugated hyperbilirubinemia)
- Septic screening [complete blood count (CBC), CRP, blood culture and sensitivity (C/S), urine C/S]
- Thyroid screening (T3, T4, TSH), if suspicion of hypothyroidism. Currently, routinely done for neonatal screening in developed as well as in developing countries, where facilities are available:
  - Low T3, T4; high TSH: primary hypothyroidism
  - Low T3, T4; low TSH: secondary hypothyroidism.
- G6PD enzyme assay: G6PD deficiency
- Clinitest of urine (urine for reducing substance): Galactosemia
- Ultrasonography (USG) of hepatobiliary scintigraphy (HBS) and hepatoiminodiacetic acid (HIDA) scan: For biliary atresia.

CLINICAL APPROACH AND INVESTIGATION TO DIAGNOSE NEONATAL JAUNDICE (FLOW CHART 11)

It will be unwise and not cost-effective to perform a series of investigations blindly in order to diagnose cause of neonatal jaundice. Investigation should be tailored and targeted depending on type of hyperbilirubinemia and in correlation with clinical condition. Therefore, standard clinical practice guideline and algorithm should be followed. However, clinical practice guidelines cannot replace clinical judgment rather it can help taking clinical decision.

If there is clinical jaundice then estimate total serum bilirubin (TSB) and direct bilirubin. If jaundice is found to be pathological, then further investigation depends on the type of hyperbilirubinemia. Unconjugated jaundice indicate number of distinct clinical conditions and relevant investigations are required to diagnose such conditions, while conjugated hyperbilirubinemia indicates another set of clinical conditions and require different type of investigations.

Initially, simpler, cheaper, noninvasive and treatable causes of jaundice should be thought of, and investigations should be done accordingly unless otherwise indicated.

Initially, FBC, peripheral blood film, blood group of mother and baby, and reticulocyte count should be done. Thyroid function test (T4, TSH) is routinely done irrespective of jaundice as neonatal screening in western countries and in some centers of developing countries. If not routinely done, it should be done in second or third week of life, if jaundice is persistent.

If above investigations suggest significant hemolysis, as evidenced by very high bilirubin, increase reticulocyte count, blood film study (spherocytosis, nucleated RBC or incomputable blood group of mother and baby), then direct agglutination test (DAT) should be done. DAT should also be

done at initial investigation, if jaundice appears in first 24 hour of life suggestive of HDN.

If DAT (Coomb's) is positive, it is suggestive of HDN, either RhD HDN or ABO HDN. Investigations showing strong positive Coomb's test, significant anemia (low Hb) and blood film showing nucleated RBC is suggestive of RhD HDN. Bilirubin should be high in ABO HDN, but there will be high unexplained bilirubin with normal Hb in ABO HDN, blood film will show spherocytosis but no nucleated RBC. Coomb's test may be weakly positive or negative.

If evidence of hemolysis is present but DAT result is negative, then consider nonimmune hemolysis and do relevant studies:

- RBC membrane study: Congenital spherocytosis
- RBC enzyme study: G6PD deficiency
- Hemoglobinopathy: α-thalassemia major (hydrops fetalis).

If initial investigations are not suggestive of hemolysis but suggestive of sepsis [decreased or increased WBC, decrease platelet, peripheral blood film (PBF) showing increase immature granulocyte or toxic granules] then complete septic workup should be done (CRP, blood, urine, CSF and umbilical discharge culture). There may be other evidences of clinical sepsis (abnormal temperature, poor activity, poor feeding).

If there is no evidence of sepsis or hemolysis with prolonged jaundice (second/third week), then hypothyroidism (T4, TSH) must be ruled out, if not done at birth by routine screening. Other investigation like pituitary function test may be done, if indicated (persistent jaundice, hypoglycemia and micropenis).

If unconjugated hyperbilirubinemia is prolonged and deepening, with no clinical condition detected by above investigations, then consider for rare conditions like disorder of bilirubin metabolism, e.g. Crigler-Najjar syndrome type I and type II, Gilberts disease, etc.

An outline of approach to investigate for diagnosis of neonatal jaundice is given in the Flow chart 11.

TREATMENT OF UNCONJUGATED HYPERBILIRUBINEMIA (TABLE 55)

- Phototherapy and exchange transfusion, if indicated. Depends on gestational age, postnatal age, associated risk factors and serum bilirubin level. Babies with severity of jaundice merit multiple phototherapy delivered by most efficient equipment. If intensive phototherapy has failed to reduce serum bilirubin and chance of kernicterus, exchange transfusion is required
- There is no fixed threshold for treatment of neonatal jaundice. It varies from center to center
- For preterm and for sick babies the treatment threshold is lower than well term-infant
- Infection: antibiotics
- TORCH: Symptomatic and supportive treatment, e.g.
  Herpes: Acyclovir
  CMV: Gancyclovir
  Toxoplasmosis: Spiramycin.
- Hypothyroidism: Thyroxin lifelong should be started, as early as possible
- Breast milk jaundice: Counseling of the parents:
  - They are thriving well
  - Never kernicterus
  - Continuing breast milk.
- Preventable jaundice must be excluded: Congenital hypothyroidism, galactosemia, hemolytic anemia, biliary atresia, infection (septicemia).
- Surgery:
  - For biliary atresia: Kasai procedure (hepatic porto-enterostomy)
  - Choledochal cyst: Removal of cyst
  - Infantile hypertrophic pyloric stenosis: Ramsted procedure
  - Splenectomy: If indicated for congenital spherocytosis (usually after 5 years)
  - Counseling and psychological support.

CLINICAL PROBLEM AND DIAGNOSIS

- A newborn baby developed jaundice within first 24 hour of life
- H/O jaundice of previous child
- H/O death of baby due to jaundice
- H/O intrauterine deaths, abortion in mother with Rh- blood group
- On examination:
  - Pallor (develops within 4–5 hours)
  - Jaundice (develops within 24 hours)
  - Hepatosplenomegaly
  - Ascites
  - Heart failure and growth failure.

Diagnosis

RhD Hemolytic Disease of Newborn

The global burden of Rh disease:

Rh negative woman, who delivers a Rh+ baby, is at risk of developing anti Rh antibodies. Rh+ babies born to this mother will develop Rh HDN. This is a serious condition responsible for:

- Death in utero or in neonatal period
- Severe jaundice with brain damage
- Untreated surviving infants may develop:
  - Dyskinetic (athetoid) CP
  - Sensory neural hearing loss
  - Dental enamel hypoplasia.

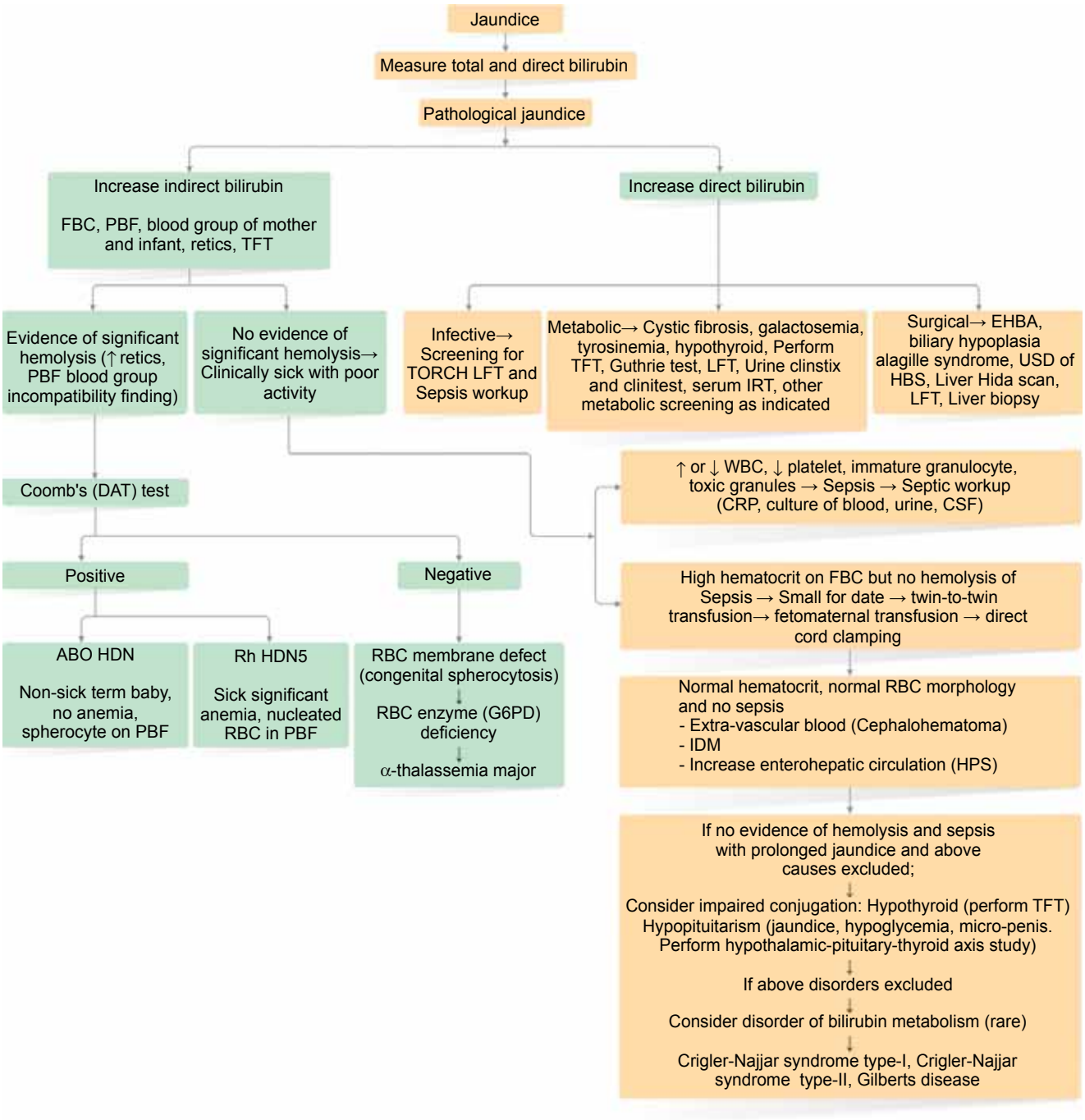
Rh Negative Mother is Much Higher in Developed Countries but Burden of Rhesus Hemolytic Disorder of Newborn is Higher in Developing Countries

- In developed countries like North America or Europe, the prevalence of Rh negative mother is 15%
- In low income developing countries, it is substantially low (5% in India, 0.3% in Thailand)
- Rh HDN in western countries are less due toAll Rh- postpartum women, whose babies are Rh+, are given 100–300 μg of anti-D γ globulin within 72 hours of delivery, which has dramatically reduced this form of HDN.

Burden of Rhesus Hemolytic Disorder of Newborn in Developing Countries

Although the incidence of Rh– mother is low (5% in developing countries), the absolute number of Rh- mothers in some developing countries is very high. In India, it is estimated as 1,345,650; in Pakistan 400,225 and in Nigeria 301,400. It is estimated that, annually, in these three low income countries,

Flow chart 11: Diagnosis of jaundice through clinical approach and investigation



Abbreviations: FBC, full blood count; PBF, peripheral blood film; retics, reticulocyte count; TFT, thyroid function test; TORCH, toxoplasmosis, others, rubella, cytomegalovirus, herpes simplex; LFT, liver function test; IRT, immunoreactive trypsin; EHBA, extrahepatic biliary atresia; USD, ultrasound; HBS, hepatobiliary scintigraphy; HIDA, hepatoiminodiacetic acid; DAT, direct agglutination test; WBC, white blood cell; CRP, c-reactive protein; CSF, cerebrospinal fluid; HDN, hemolytic disease of newborn; G6PD, glucose-6-phosphate dehydrogenase; RBC, red blood cell; IDM, infant of diabetic mother; HPS, hemophagocytic syndrome

Table 55: Suggested threshold for treatment of jaundice

	Consider phototherapy (µmol/L)	Phototherapy (µmol/L)	Exchange transfusion if intensive phototherapy fails (µmol/L)	Exchange transfusion + intensive phototherapy (µmol/L)
Term + well Term + sick or	>290	>340	>430	>510
30–36 weeks	>225	>250	>310	>340
< 30 weeks + well or 30–36 weeks + sick	>100	>150	>200	>250
< 30 weeks + sick	>85	>130	>180	>205

more than1,000,000 Rh– women do not receive anti-D prophylaxis and more than 100,000 children are born with Rh disease annually.

The following are the characteristics and essentials of Rh HDN:

- Rh+: DD homozygous, DD heterozygous
- Rh–: DD homozygous
- Anti-D was discovered in the year 1960
- Rh locus is present on chromosome 1
- If it is a Rh– mother and Rh+ fetus or newborn, 10–15% chances of Rh incompatibility are present
- If incompatibility is present, it leads to features of hemolysis, i.e. scalp edema (earliest sign), hepatosplenomegaly, ascites, hydrops
- If no features are present, there is no incompatibility
- Incidence according to severity:
  - 45–50%: No or mild anemia, and no measure is taken
  - 25–30%: Moderate (measure is taken)
  - 20%: Severe anemia (hydrops fetalis)
- Pathophysiology: Fetomaternal transfusion
- Risk factors:
  - Fetomaternal age: Abortion, previous Rh+ blood transfusion amniocentesis, Chronic Villous Sampling (CVS).
  - Birth order: More in the second and subsequent pregnancies
  - ABO incompatibility: Less chance
  - Male: Increase chance of incompatibility
  - Maternal antibody response: 10–50% no antigenic response
  - H/O cesarean section: Increase chance of fetomaternal hemorrhage.

Note: Minimum 0.1 mL blood is needed for sensitization.

CLINICAL FEATURES

History

- A sibling with history of jaundice and/or anemia, mother Rh– and baby Rh+, may give history of Rh+ blood transfusion or spontaneous abortion or history of any procedure—amniocentesis or CVS
- History of any jaundice within first 24 hours of life and early pallor (within 4–5 hours)
- H/O jaundice in previous child
- H/O death of any baby due to jaundice
- H/O intrauterine death
- Order of pregnancy: More in second and subsequent pregnancy.

Examination

- Pallor (may develops within 4–5 hours)
- Jaundice: Develops within 24 hours
- Hepatosplenomegaly and ascites
- Hydrops fetalis
- If features of hemolysis:
  - Scalp edema (earliest sign)
  - Hepatosplenomegaly
  - Ascites.
- Fetal heart failure and growth failure
- Inspissated bile syndrome (rapid destruction of RBC, obstruction of bile cannaliculi)
- Kernicterus (severe cases): Abnormal neurological behavior.

INVESTIGATION

- Cord blood: Hb% less than 10g/dL. Carboxy Hb more than 1.4%, significant
- Serum bilirubin may increase to as high as more than 0.5mg/dL/hour
- PBF: Nucleated RBC, no spherocytes
- Blood grouping and Rh typing of baby. Mother and father blood group (before delivery) is informative. If mother is Rh–, anti-D transfusion is required.
- Direct Agglutination Test (DAT)/Coomb's test (direct): Positive, indirect if previous child was Rh incompatible.

Significance and Fallacy of Positive Direct Aggluttination Test (Coomb's test)

The DAT is one of the cornerstones of diagnosis of HDN. It is a screening test for nonagglutinating antibodies present on an individual's RBC. In modern neonatal practice, ABO incompatability is most frequently associated with DAT positivity.

Poor Positive Predictive Value of Hemolytic Disease of Newborn Requiring Intervention

- Majority of infant with positive DAT test will not require intervention (phototherapy ± exchange transfusion)
- Upto 15% of infants will have DAT (Coomb's positivity), whose Rh-D negative mothers receive routine anti-D immunoglobulin in the third trimester. This is due to achieved transfer of anti-D administered to the mother during pregnancy.

MANAGEMENT

Antenatal Management (Antibody Titer of Mother)

Antibody titer estimation should be done:

- 10–16 weeks
- 24–28 weeks
- 34–36 weeks
- 26 weeks in measurable amount is significant.
- 28–32 weeks: 1–4 weekly, if significant.
- 34–36 weeks: 1:64 significance.
  - If titer is significant, amniocentesis is done to measure bilirubin by optic density, i.e. spectrophotometric examination of amniotic fluid obtained by amniocentesis.
  - Assessment of the fetus:
    - Clinical: Fetal heart sound, fetal growth
    - Sonographic assessment: Every week
    - Blood examination of mother: By serial Coomb's test (by titer).
  - Reduction of maternal antibody:
    - IVIG: Block FC receptors
    - Plasmapheresis
    - Anti-D: 28–32 weeks, 300 µg deep IM.
  - Injection glucocorticoid to mother for preterm pregnancy to prevent respiratory distress Syndrome (RDS).
  - If any H/O abortion, Rh+ blood transfusion or any procedure is present, administer anti-D 100 µm IM.

- Intrauterine transfusion (intrauterine transfusion of blood in the peritoneal cavity of fetus).

  Intrauterine RBC transfusion: Impact on neonate
  - In newborns that have been treated with successful intrauterine transfusion program until near term, neither neonatal jaundice nor immediate anemia occur after birth
  - Exchange transfusion is less frequently required
  - However, late anemia can occur in such case
  - RBC transfusion is only required in symptomatic cases.

Postnatal Management

- *Observation*: All babies should be observed for minimum 48 hours.
- *Hospitalization*: When incompatibility is suspected, e.g. serial serum bilirubin estimation usually increases to more than 0.5 mg/dL. Estimate reticulocyte count: Resuscitation, if needed; care about asphyxia:
  - Hb% less than 10 g/dL
  - Reticulocyte: More than 15%
- Resuscitation, if needed, care about asphyxia.
- Cord blood for:
  - Hb%, reticulocyte count
  - Serum bilirubin
  - Blood grouping
  - Coomb's test (direct).
- *Anti-D*: 250–300 µg to mother should be given within 72 hours of child birth.
- Phototherapy (may need double or intensive photo-therapy).
- Exchange transfusion: Mostly needed:
  - Exchange transfusion soon after birth is indicated, if:
    - Cord Hb level is less than 10 g/dL
    - Cord bilirubin level is more than 5 mg/dL
  - Subsequent exchange transfusion is indicated, if
    - Bilirubin is more than 10 mg/dL, within 24 hours of birth
    - Bilirubin is more than 15 mg/dL, within 24–48 hours of birth
    - Bilirubin is more than 20 mg/dL, within 48 hours of birth.

Rate of rise of bilirubin is more than 5mg/dL/day.

CHOICE OF BLOOD (SEE ALSO PROCEDURES CHAPTER)

- *Rh iso-immunization:* Always Rh– blood group. The best choice is O- or ABO compatible with baby, e.g., If mother is Rh, baby should be provided ABO.
- *ABO iso-immunization:* Only O– blood group should be used for exchange and Rh should be compatible with baby. Other situation: Crossed match with baby's blood group (for illustrated procedure, see Procedure chapter).
- *Blood volume used*:
  - Double volume exchange: (28×5×body weight in kg/mL):
    - Push for 3–5 minutes
    - Pull for 2 minutes.
  - Principle of exchange:
    - Correction of anemia
    - Removal of antibody coated RBC
    - Removal of bilirubin.
- *Pre-exchange investigation:*
  - Blood group and Rh typing of mother and baby
  - Hb% (<10 g/dL)
  - Blood film (enucleated RBC.
  - Reticulocyte count (>15%, may be up to 40%.
  - Cord bilirubin (>5mg/dL).
- *Postexchange follow-up:*
  - Just after exchange
  - After 6 hours
  - 12 hourly
  - Daily.

INVESTIGATIONS

- Serum bilirubin (direct, indirect)
- Hb%
- Random blood Sugar (RBS)
- Serum electrolytes
- Serum calcium.

IMPROVED PHOTOTHERAPY

As the efficacy of phototherapy increases, the role of exchange transfusion in the acute management of HDN, particularly ABO HDN, is rapidly decreasing. Considerable advancement has been made in phototherapy and it is now appreciated that the efficacy of phototherapy in reducing neonatal hyperbilirubinemia has changed the outcome of HDN.

Factors Affecting Efficacy of Phototherapy

- Spectral quality of the delivered light (optimal wave–length range 400–520 nm with peak imitation of 460 nm)
- Irradiance (intensity of light)
- Surface area receiving phototherapy
- Duration of exposure
- The device needs to used effectively
- The distance between device and patient, and ensuring proper maintenance and servicing of phototherapy unit is essential
- In short, phototherapy is now available alternative to the planned use of exchange transfusion in the treatment of even moderate to severe HDN of Rh or ABO incompatibility.

Types of Light

- Special blue lamps with a peak output at 425–475 nm are most efficient (Fig. 130)
- Double surface phototherapy is more effective than single surface (Fig. 131)
- More efficient high intensity gallium nitrite light emitting diode (LED) is useful.

Procedure of Providing Phototherapy

The baby should be undressed and eyes and male genitalia should be closed to prevent danger of bright light. Keep the baby at a distance of 30–45 cm from the light source. The body should be turned after each feed to get maximum exposure of body surface area to phototherapy. Phototherapy should be provided continuously except during breastfeeding. Serum bilirubin should be monitored every day. Phototherapy should be discontinued when serum bilirubin falls below age specific phototherapy cutoff point.

Fig. 130: Baby receiving phototherapy by high density blue light emitting diode therapy

Fig. 131: Double surface special blue light for phototherapy

HIGH-DOSE OF INTRAVENOUS IMMUNOGLOBULIN (IVIG)

High-dose of IVIG therapy is now effective in reducing the need for exchange transfusion in hemolytic disease due to Rh or ABO incompatibility. It also reduces the total length of phototherapy and length of health stay. IVIG is given in dose of 500–1,000 mg/kg as slow infusion over 2 hours. IVIG is not useful in nonimmune hemolytic anemia.

COMPLICATIONS OF UNTREATED RH INCOMPATIBILITY

- *Immediate Problem:* Anemic heart failure.
- *Bilirubin encephalopathy:* Neonatal death.
- *Late complications:* Survivors develop CP (mostly dyskinetic type) and other neurodevelopmental disorders.
- *Prevention:* By anti-D transfusion.
- *Prognosis:* Depends on:
  - Titer of mother
  - Gestational age of baby
  - Early diagnosis
  - Early treatment.

Hemolytic Disease of Newborn Due to Non-Rh Incompatibility, Mostly ABO Incompatibility

Forty years ago, HDN was almost synonymous with Rh-D alloimmunization and was a common neonatal problem. It was usually unmodified by antenatal therapy and caused overt fetal and neonatal hemolysis.

Since 1970, routine postnatal prophylactic anti-D IG for Rh-D negative woman has dramatically reduced this form of HDN in developed countries and is one of the great successes of modern perinatal care.

Although neonatal burden of severe HDN has decreased, particularly in developed world, it has not disappeared. More subtle and less serious form of HDN, particularly ABO incompatible HDN, has become more frequent than Rh-HDN, in general, all over the world.

Non-Rh HDN should be considered in the neonate in contemporary neonatal practice when there is one or more of the followings:

- Rapidly developing or severe hyperbilirubinemia not predicted by maternal antibodies screening in a term nonsick infant
- Prolonged hyperbilirubinemia
- Absence of significant anemia (except for α-thalassemia major)
- A positive direct antiglobulin test (DAT/Coomb's test)
- Hemolysis on blood film examination.

Characteristics of ABO Incompatibility (Table 56)

- Early onset (first 48 hours) jaundice
- No significant anemia and normal healthy looking baby
- Unexpected rapidly developing jaundice (serum bilirubin may exceed 300 μmol/L)

Table 56: Characteristic differences between RhD and ABO HDN

	RhD HDN	ABO HDN
Incidence	More frequent in low income developing countries than developed countries	More frequent in developed world as anti-D has significantly reduced RhD HDN in western world
Presentation	Sick, pale, anemic heart failure, hydrops fetalis	Though severely jaundiced but not sick or significantly anemic. No hydrops fetalis
Appearance of jaundice	Appears within first 24 hours of life	Appears within first 48 hours of life
Predictability of jaundice	Can be predicted by antenatal antibody screening of mother	Unexpectedly high bilirubin, unpredictable by antenatal maternal antibody test
DAT test	Strongly positive	Weakly positive
RBC study	Nucleated RBC	Large number of spherocytes with no nucleated RBC
Exchange transfusion	More frequently required	Less frequently required

Abbreviations: DAT, direct agglutination test; HDN, hemolytic disease of newborn; RBC, red blood cell

- Problem not predicted by maternal antibody screening
- Mother blood group usually "O" positive, baby almost always "A" positive
- 15–25% of all maternal-fetal pairs have ABO incompatibility, but only 1% such woman have high IgG antibody
- Hemolysis is more common with anti-A than anti-B
- Affected neonates are DAT (Coomb's) positive but not strongly positive like Rh HDN
- Blood film study shows significant spherocytes but no nucleated RBC like Rh-D incompatibility.

Management of ABO Hemolytic Disorder of Newborn

- Most of the newborns improve with advanced phototherapy without requiring exchange transfusion
- IVIG may be useful as an adjunct therapy.

OTHER CAUSES OF HEMOLYTIC DISORDER OF NEWBORN CAUSING EARLY NEONATAL JAUNDICE

RBC Membrane Defect Disorder

Hereditary Spherocytosis

Hereditary spherocytosis is the most common RBC membrane disorder causing significant jaundice in newborn. It is autosomal dominant but around 25% are due to new nutrition.

Presentation

- Unconjugated hyperbilirubinemia.
- A few develop anemia.

Investigation

- Spherocytosis
- Negative DAT (Coomb's test).

Other RBC Membrane Disorders

- Hereditary eliptocytosis
- Hereditary pyropoikilocytosis.

RBC Enzyme Defect

Glucose-6-phosphate Dehydrogenase Deficiency

- G6PD deficiency is the most common RBC enzyme deficiency causing significant neonatal jaundice
- Jaundice may be high enough to cause kernicterus
- However, only some but not all develop jaundice
- Anemia is usually absent
- Cannot be diagnosed in peripheral blood samples, if no active hemolysis
- Diagnosis confirmed by assaying G6PD on peripheral blood film.

Other RBC Enzyme Deficiency

- Pyruvate kinase deficiency.

NEONATAL JAUNDICE DUE TO HEMOGLOBINOPATHY

Alpha-thalassemia Major

- More frequent in families of Southeast Asian countries
- Usually fatal anemia with hydrops fetalis
- Fetal death usually occurs few hours after birth.

MANAGEMENT

The management of all nonimmune hemolytic anemias have been discussed in "Hemato-oncologic disorder" chapter.

NEONATAL CHOLESTATIC JAUNDICE

The evaluation of neonate with cholestasis is a multistep process that should follow a logical sequence, which helps to differentiate the broad categories of neonatal cholestasis without wasting time with minimum cost. Cholestatic jaundice, which usually appears beyond 2 weeks of age, is potentially life-threatening problem that indicates hepatobiliary dysfunction. They are divided into three broad headings: 1) Infective/inflammatory, 2) metabolic, and 3) obstructive/surgical. However, initial evaluation should focus on establishing the patency of biliary tree causing surgical jaundice.

Among surgical jaundice, Extrahepatic Biliary Atresia (EHBA) is the most important condition. It is important to diagnose EHBA before 2 months, if possible before 1 month, because success of surgery and outcome is dependent on age of surgery. Beyond 2 months, biliary trees are significantly damaged with poor outcome.

Clinically, EHBA is associated with pale stool, deepening jaundice in otherwise normal healthy looking baby. Later, hepatomegaly or hepatosplenomegaly occurs. If surgical jaundice (EHBA) is suspected, than following investigation should be undertaken:

- Use of hepatobiliary tree
- Liver function test (serum ALT, AST, GGT), prothrombin time, serum protein, serum albumin
- HIDA scan
- Liver biopsy.

Other rare causes of surgical jaundice include paucity of bile duct, alagille syndrome (biliary hypoplasia with congenital heart disease) and progressive familial cholestasis.

If neonatal jaundice is suggestive of congenital infection (IUGR, microcephaly, evidence of congenital heart disease, cataract, chorioretinopathy) then TORCH screen (IgM antibody) is more relevant. Septic screen (CRP, culture of body fluids) should be done if acquired sepsis (poor activity, abnormal temperature, poor feeding, etc.) is suspected.

Metabolic screen is more relevant if evidences of inborn error of metabolic are present, like presentation with milk intolerance (diarrhea, vomiting), cataract (suggestive of galactosemia), etc. are present. Urine clinitest for reducing substance should be done for galactosemia. In advanced countries, few metabolic disease (galactosemia, tyrosinemia, maple syrup urine disease, hypothyroid, etc.) are screened after birth. Hypothyroid may cause both unconjugated and conjugated jaundice and, therefore, TSF should be done, if not

screened at birth. If jaundice is associated with meconium ileus than serum immunoreactive trypsin (IRT) should be done to exclude cystic fibrosis, particularly in Caucasian.

Clinical differentiation among the common causes of cholestasis is difficult. There is plethora of hematological, biochemical, serological and microbiological investigations described to help reaching the diagnosis. The common causes of cholestasis are mentioned below:

- Neonatal cholestasis syndrome (surgical jaundice):
  - Bile flow obstruction.
- Intrahepatic cholestasis—persistent:
  - Idiopathic neonatal hepatitis
  - Alagille syndrome (arteriohepatic dysplasia)
  - Intrahepatic biliary hypoplasia or paucity of intrahepatic
  - Bile ducts (nonsyndromic)
  - Byler's disease (progressive familial intrahepatic cholestasis).
- Intrahepatic cholestasis—recurrent:
  - Familial benign recurrent cholestasis associated with:
    - Neonatal sclerosing cholestasis
    - Congenital hepatic fibrosis
    - Caroli's disease.
- Extrahepatic disorders:
  - EHBA
  - Sclerosing cholangitis
  - Choledochal Cyst (CDC)
  - Choledocholithiasis.

BILIARY ATRESIA

From a surgeon's point of view, EHBA is the most important diagnosis which needs to be settled at the earliest.

Diagnosis of Surgical Jaundice, Particularly EHBA

Clinical Presentation

Present usually as full-term, normal birthweight well-looking (not sick appearance) baby during neonatal period. This is in contrast to preterm LBW baby, or sick looking baby or IUGR baby associated with congenital TORCH infection.

- Persistent jaundice from second week of life
- Pale stool and dark urine (Figs 132A to C)
- Hepatomegaly and late splenomegaly.

Investigations

- Increased conjugated (direct) bilirubin (>100 μmol/L)
- Increased alkaline phosphatase
- Increased gamma glutamine (>100 IU/L)
- Prothrombin time and albumin normal in early stage.

Ultrasonogram

- Hepatobiliary tract in large liver and absent or contracted gallbladder after 4 hours fast. Biliary dilatation is not seen
- CDC can be excluded by ultrasonogram.

Hepatobiliary Scan

Using technician 99m labeled hepatobiliary iminodiacetic acid (HIDA) scan. Following phenobarbitone pretreatment usually demonstrates good hepatic uptake, but absent or reduced excretion into the intestine within 24 hours.

Other Imaging

- *Magnetic resonance cholangiopancreaticography (MRCP)*: It is a promising noninvasive method for diagnosing EHBA. However, there are limitations of MRCP for differentiating severe intrahepatic cholestasis from EHBA because the ability of MRCP to identify extrahepatic bile ducts depends on bile flow.
- *Endoscopic retrograde cholangiopancreaticography (ERCP)*: ERCP has been proposed for visualization of biliary tree. However, its use in children is limited as it requires considerable technical expertize.

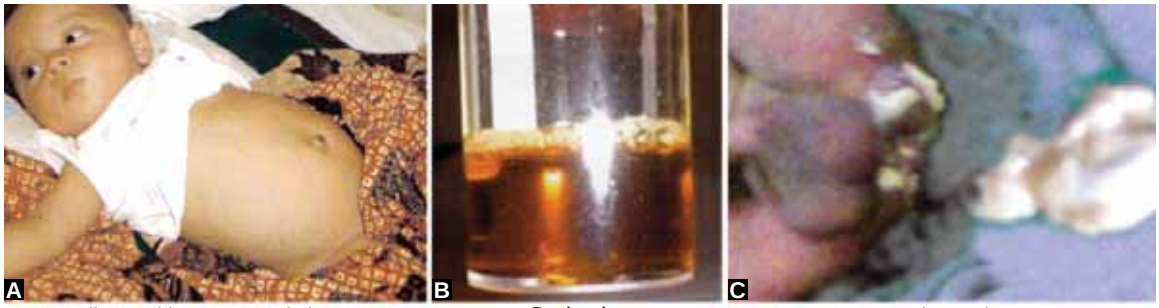
Liver Biopsy

Liver biopsy is considered by some as the most accurate diagnostic test for differentiating biliary atresia from other causes of neonatal cholestasis. Liver histology obtained by percutaneous biopsy shows portal tract fibrosis, cholestasis and proliferation of biliary ductules.

The diagnosis is usually confirmed at laparotomy, with or without cholangiography, when the atresia biliary tree is evident.

Management

Early diagnosis through public and professional education is required for early appropriate referral. Surgery is done before 8 weeks of age. Surgical management is done in an attempt to restore biliary flow (the Kasai portoenterostomy and liver transplantation, if necessary). Medial management consists of antibiotics, ursodeoxycholic acid to encourage bile flow, fat soluble vitamin and nutritional support.



Jaundice and hepatomegaly in non-sick looking baby | Dark urine | Pale stools

Figs 132A to C: Clinical features of biliary atresia: (A) Jaundice and hepatomegaly in non-sick looking baby; (B) Dark urine; (C) Pale stools

Prognosis

Over half of the infants undergoing portoenterostomy will clear the jaundice and have greater than 80% chance of good quality of life. Children developing cirrhosis and portal hypertension require liver transplantation which provides 90% chance of achieving normal life.

EVALUATION OF OVERWEIGHT TERM NEONATES

INTRODUCTION

The infant is large for gestational age (LGA), if birthweight is more than 4,000 g. The newborns birthweight is two standard deviations above the mean or above the ninetieth percentile.

CAUSE

- Maternal causes:
  - Maternal diabetes mellitus [infant of diabetic mother (IDM)]
  - Large parents (mother), large baby.
- Intrinsic fetal diseases:
  - Transposition of great vessels
  - Beckwith-Weidmann syndrome
  - Erythroblastosis fetalis
  - Some post-term infants.
- What complications can this infant experience?
  - Perinatal asphyxia due to difficult delivery
  - Birth trauma due to shoulder dystocia, if delivered vaginally:
    - Fractured clavicle
    - Depressed skull fracture
    - Brachial plexus palsy.
- IDM syndrome and complications
- Neonatal hypoglycemia: Mainly in first 48 hours, often symptomatic. It is due to hyperinsulinemia due to placental transfer of elevated maternal glucose and low plasma glucagon.

CLINICAL INDICATORS OF NEONATAL HYPOGLYCEMIA IN INFANT OF DIABETIC MOTHER

- Maternal diabetes
- Big baby (Fig. 133)
- Delivery by lower uterine cesarean section (LUCS)/ preterm delivery/premature rupture of membranes (PROM)
- Reluctance to feeding
- Delayed feeding/poor feeding
- Respiratory distress
- Jitteriness/tremor/convulsion
- Metabolic complications of IDM:
  - Hypoglycemia
  - Hypocalcemia
  - Hypothermia
- Cardiac complications:
  - Transposition of great arteries (TGA)
  - Ventricular septal defect (VSD)
  - Atrial septal defect (ASD)
  - Truncus arteriosus.
  - Double outlet right ventricle
  - Coarctation aorta

Fig. 133: Infant of diabetic mother with macrosomia

  - Cardiomegaly
  - Heart failure.
- Central nervous system:
  - Lumbosacral agenesis
  - Neural tube defect—Anencephaly.
- Renal:
  - Hydronephrosis
  - Renal agenesis and dysplasia
  - Renal vein thrombosis (due to polycythemia)
  - Flank mass
  - Hematuria.
- Gastrointestinal tract:
  - Small left colon syndrome
  - Duodenal/anorectal atresia.
- Blood:
  - Polycythemia: High hematocrit causes hyperviscosity (it causes poor blood flow in small vessels)
  - Hyperbilirubinemia.
- Respiratory:
  - Respiratory distress syndrome (RDS)
  - Transient tachypnea of newborn (TTNB)
  - Birth asphyxia.

TREATMENT

- Antenatal:
  - Regular antenatal checkup
  - Good glycemic control
  - Regular checkup of blood sugar during pregnancy; treatment with insulin, if needed
  - First trimester management is mandatory due to period of organogenesis: congenital malformation intrauterine device (IUD)/abortion
  - Early USG is mandatory to diagnose congenital malformation.
- During delivery management:
  - Baby should be managed by pediatrician (neonatologists)
  - Large baby with symptoms should be kept under close observation for 72 hours
  - Resuscitation of the baby: Assessment of consciousness, vital signs (pulse, respiration, temperature, blood pressure)

- Capillary refilling time and at the same time, ABC and apnea management:
  - Tactile stimulation
  - Oxygen (O_2) inhalation
  - Bag mask ventilation
  - Mechanical ventilation
  - Injection aminophylline
  - Continuous positive airway pressure (CPAP), if indicated.

- Postnatal management: Treatment goal is to maintain a blood glucose level of atleast 45 mg/dL (2.5 mol/L):
  - Asymptomatic cases: Ensure early feeding, even through N/G tube. Breastfeeding preferable, if formula milk is not available
    - Normoglycemic, high-risk infants: Oral/gavage feeding—2–3 hourly for 24–48 hours
    - Hypoglycemic and high-risk infants [prematurity, small for gestational age (SGA), delayed feeding, large for gestational age (LGA), IDM, erythroblastosis fetalis, sepsis, shock, birth asphyxia, hypothermia, respiratory distress]: Oral/NG
      i. IV infusion: 10% dextrose 6 mg/kg/min
      ii. Early initiation of feeding: Hourly until blood glucose level is normal.
    - IDM baby should have glucose monitoring within 1 hour of birth, irrespective of symptoms, then hourly for next 6–8 hours, then 4–6 hourly until 24 hours of life and then 12 hourly for upto 72 hours of life.
- Parenteral glucose replacement:
  - Symptomatic/poor response to oral feeding/ documented hypoglycemia:
    - Blood glucose of 1.4–2.5 mmol/L, if patient is asymptomatic; only IV glucose maintenance 4–8 mg/kg/min and NG feeding
    - 1.4–2.5 mmol/L, if patient is symptomatic; IV bolus: 200 mg/kg (2 mL/kg), 10% dextrose:
      i. 1 mL/min.
      ii. 4 mL/kg, 10% dextrose, if convulsion.
  - Maintaining continuous infusion of 10% dextrose, 6–8mg/kg/minute, and increase rate to maintain blood glucose more than 50 mg/dL (2.7 mol/L)
  - Blood glucose less than 1.4 mmol/L IV bolus, whether symptomatic/asymptomatic to prevent seizure.
- Emergency glucose replacement:
  - 5–10 mL/kg of 10% dextrose IV over 20 minutes
  - Injection hydrocortisone (5 mg/kg/day) IV in divided dose may be given in difficult cases
  - Consider NICU admission and glucagon administration, if still hypoglycemia persists.
- Treatment of other complications:
  - Hypocalcemia with less than 7 mg/dL injection, 10% calcium gluconate IV—1–2 mL/kg slowly with monitoring
  - Hyponatremia: Fluid restriction (20%)
  - Hyperbilirubinemia: Phototherapy
  - Cardiomyopathy, heart failure, supportive:
    - Fluid and salt restriction
    - O_2 inhalation.
  - Hypertrophic cardiomyopathy: Propranolol
  - Congestive cardiac failure (CCF): Diuretics, digoxin
  - TTNB: Supportive
  - RDS: Self-limiting disease, supportive treatment:
    - Airway clearance
    - O_2 inhalation
    - Maintenance of temperature and nutrition.
      i. Specific treatment for RDS: Surfactant via ET tube
      ii. Perinatal asphyxia: The main treatment is proper resuscitation. In addition, other supportive treatments include:
  - O_2 inhalation and maintain body temperature
  - Breastfeeding, if baby is able to suck and swallow, if not, then N/G tube feeding with EBM
  - IV fluid: 10% dextrose in aqua (D/A)
  - Phenobarbitone: If convulsion, 20mg/kg IV as loading dose over 20 minutes, followed by 4–5 mg/kg once a day
  - If IV access is not possible, give per rectal diazepam (0.5 mg/kg/dose) as a stat dose
  - Resuscitation:
    - Drying and warming the baby
    - Observe: Activity/heart rate (HR)/color/respiration/ reflex irritability (APGAR score)
    - Opening the airway: Positioning of head/neutral position/suction
    - Establish breathing:
      i. Tactile stimulation
      ii. Face mask ventilation
      iii. Mouth-to-mouth breathing.
  - Maintain circulation: By chest compression
  - Intubation, if needed
  - Drugs
  - $NaHCO_3$ (only after establishment of respiration)
  - Adrenaline and dextrose, if required.

HYPOGLYCEMIA (NEONATAL)

DEFINITION

Hypoglycemia is a condition in which the blood glucose is less than 2.6 mmol/L in general. However, there is a considerable debate as what constitute hypoglycemia with definition based on:

- In diabetic patient, cut-off point is 3.5 mmol/L
- To achieve normal neurodevelopmental outcome, neonatal blood glucose less than 3.4 mmol/L should be avoided
- Symptomatic hypoglycemia is less than 1.5 mmol/L
- Most would accept threshold of 2.4–2.6 mmol/L in otherwise normal neonate
- Currently, international consensus suggests blood glucose of 2.2 mmol/L as an "action threshold" for neonates.

PHYSIOLOGY: GLUCOSE HOMEOSTASIS

Excess glucose is stored in liver as glycogen under the influence of insulin and released to maintain blood sugar by:

- Glucagon
- Cortisol
- Growth hormone
- Adrenalin.

Pathways involved in glucose homeostasis:

- Hormone response
- Glycogen breakdown
- Gluconeogenesis
- Fatty acid oxidation
- Ketone body synthesis
- Ketone utilization.

Children and adults are obligate utilizer of glucose for brain metabolism. However, infants and young children also utilize ketone bodies from free fatty acids (FFAs) as an alternate brain fuel source. Normal term-babies may have blood glucose less than 2.6 mmol/L, particularly in first 24 hours, in breastfed baby. But they use ketone bodies as alternate fuel. Therefore, blood glucose analysis should not be performed routinely on healthy term baby.

Babies are at risk of developing clinically relevant hypoglycemia in following conditions:

- Preterm.
- IUGR (SGA).
- Infections (sepsis).
- Hypothermia.
- Hypoxia ischemia.

- Hyperinsulinism:
  - Infant of diabetic mother (usually transient)
  - Hemolytic disease of newborn
  - Transient neonatal hyperinsulinism (SGA, prematurity, maternal diabetes)
  - Beckwith-Wiedemann syndrome
  - Persistent hyperinsulinemic hypoglycemia
  - Insulinoma (islet cell adenoma).
- Endocrine disease:
  - Pituitary: GH deficiency
  - Adrenal: Congenital adrenal hyperplasia
  - Congenital adrenal hypoplasia.
- Carbohydrate metabolism defect:
  - Glycogen storage disease
  - Galactosemia.
- Amino acid metabolism defect:
  - Tyrosinemia.
- Fat oxidation defect
- Liver failure.

Pathophysiology of Decreased Glucose in Various Conditions

In Preterm and SGA/IUGR Babies

- Decreased glycogen store
- Decreased gluconeogenesis
- Increased insulin (transient)
- Decreased counter regulatory hormone (glucagon, adrenalin), particularly in SGA/IUGR.

In Endocrine Disorders

- Reduce insulin counter regulatory hormones.
- Cortisone deficiency, hypopituitarism, adrenal insufficiency.
- Growth hormone deficiency.

Metabolic Disease

Produce hypoglycemia by impairment of:

- Glycogenolysis (glycogen storage disease)
- Gluconeogenesis (impairment of conversion of glucose from nonglucose monosaccharide, like galactosemia or from amino acid like tyrosinemia)
- Impaired ketogenesis and ketone utilization
- Impairment of liver function.

Ketotic Hypoglycemia

Not found in neonate, onset at 18 months to 5 years.

Hypoglycemia Due to Increased Glucose Utilization

- Congenital hyperinsulinism:
  - Beckwith-Wiedemann syndrome.

Hyperinsulinemia

- Can be transient or permanent
- *Genetic*: Mutation of gene (HF-4 α-gene)
- *Other cause*: Insulinoma (islet cell adenoma), persistent hyperinsulinemic hypoglycemia.

CLINICAL FEATURES

- Asymptomatic
- Symptomatic.

Symptomatic Cases

Symptomatic cases are divided into:

- Counter regulatory hormone
  - Adrenergic: Epinephrine and norepinephrine
  - Glucagon.
- Due to neuroglycopenia:
  - Adrenergic symptoms: Sweating, pallor, palpitation, tremor, jitteriness tremulousness
  - Glucagon related symptoms: Hunger, vomiting.
- Neuroglycopenia:
  - Lethargy, apathy, high-pitched cry
  - Irritability
  - Seizure: Coma
  - Tachypnea, apnea, cyanotic episode
  - Hypotonia
  - Poor feeding.

INVESTIGATIONS

Other than blood and serum glucose estimation, investigations should be done if hypoglycemia is severe and/or persistent. History taking and clinical examination may guide further investigation for hypoglycemia. Relevant history taking includes prematurity, SGA, maternal diabetes, which may cause transient hypoglycemia. Relevant physical examination includes macrosomia (infant of diabetic mother, Beckwith-Wiedemann syndrome), jaundice with cataract (galactosemia), persistent jaundice with micropenis (hypopituitarism), hepatomegaly (glycogen storage disease), ambiguous genitalia (congenital adrenal hyperplasia), etc.

Investigations include (according ketonuria present or absent) (Table 57):

- Blood:
  - Glucose
  - Electrolyte
  - Cortisol
  - Insulin plus c-peptide

Table 57: Key investigation is checking urine for ketones

Ketonuria absent	Ketonuria present
• Hyperinsulinism (genetic, insulinoma) • Fatty acid oxygenation defect • Liver failure • Galactosemia • Carnitine deficiency	All others, including glycogen storage disease, hypopituitarism, adrenal insufficiency, ketotic hypoglycemia

  - Acylcarnitines
  - FFA
  - Lactate liver enzymes
  - Growth hormone
  - β-hydroxybutyrate
  - Ammonia
  - Galactose-1 phosphate uridyl transferase.
- Urine:
  - Ketone (dipstick)
  - Clinitest (nonglucose reducing substance)
  - Clinistix for glucose: Clinitest positive but clinistix negative is suggestive of galactosemia
  - Organic acid.

Algorithm of diagnostic approach and treatment of neonatal hypoglycemia has been given in Flow chart 12.

TREATMENT OF HYPOGLYCEMIA

Determine Babies at Risk of Hypoglycemia

If risk factors are present:
- Early and frequent enteral feeding
- Check blood sugar before second/third and fourth week until there has been at least two blood sugar above 2.6 mmol/L.

If sugar is less than 1.5 mmol/L:
- Admit the baby preferably in NICU, confirm hypoglycemia with laboratory blood glucose estimation, give IV 10% glucose 2 mL/kg bolus, followed by an infusion. Initial infusion rate 3.6 mL/kg/h 10% glucose which is equivalent to 6 mg/kg/min
- Check glucose after 15 minutes initially and then frequently until stable, aiming for glucose level 3–4 mmol/L.

If sugar is 1.5–2.5 mmol/L:
- Feed immediately and recheck blood sugar after 30 minutes
- If blood sugar is still low, consider admission and IV glucose.

Treatment of Persistent and Severe Hypoglycemia

In persistent or severe hypoglycemia, or if glucose requirement is high, (>10 mg/kg/min) to maintain normal blood sugar then consider hyperinsulinism. Further treatment with diazoxide or somatostatin analog may be required. Refer to local endocrine metabolic team for further management, if hyperinsulinism is suspected.

Infants of diabetic mother with hypoglycemia: Neonatal hypoglycemia occurs mainly in first 48 hours, often symptomatic. It is due to hyperinsulinemia due to placental transfer of elevated maternal glucose and low plasma glucagon.

CLINICAL INDICATORS OF NEONATAL HYPOGLYCEMIA—INFANT OF DIABETIC MOTHER

- Maternal diabetes
- Big baby
- LUCS/preterm delivery/PROM
- Reluctance to feeding
- Delayed feeding/poor feeding
- Respiratory distress
- Jitteriness/tremor/convulsion.

Treatment goal is to maintain a blood glucose level of atleast 2.6 mmol/L.

Asymptomatic Cases

Ensure early feeding, even through N/G tube-breastfeeding formula milk:
- Normoglycemic, high-risk infants; oral/gavage feeding—2–3 hourly for 24–48 hours.
- Hypoglycemic and high-risk infants (prematurity, SGA, delayed feeding, LGA, IDM, erythroblastosis fetalis, sepsis, shock, birth asphyxia, hypothermia, respiratory distress): Oral/NG:
  - IV infusion: 10% dextrose 6 mg/kg/min
  - Early initiation of feeding: hourly until blood glucose level is normal
- IDM baby should have glucose monitoring within 1 hour of birth, irrespective of symptoms, then every hourly for next 6–8 hours, then 4–6 hourly until 24 hours of life and then 12 hourly for upto 72 hours of life.

PARENTERAL GLUCOSE REPLACEMENT

- Symptomatic/poor response to oral feeding/documented hypoglycemia:
  - Blood sugar 1.4–2.5 mmol/L, if patient is asymptomatic, only IV glucose; maintenance 4–8 mg/kg/min + NG feeding
  - 1.4–2.5 mmol/L, if patient symptomatic; IV bolus 200 mg/kg (2 mL/kg), 10% dextroseat 1 mL/min:
    - 4 mL/kg, 10% dextrose, if convulsion
- Maintaining continuous infusion of 10% dextrose, 6–8 mg/kg/min and increase rate to maintain blood glucose to more than 50 mg/dL (2.7 mmol/L)
- Blood glucose less than 1.4 mmol/L, IV bolus whether symptomatic/asymptomatic to prevent seizure.

EMERGENCY GLUCOSE REPLACEMENT

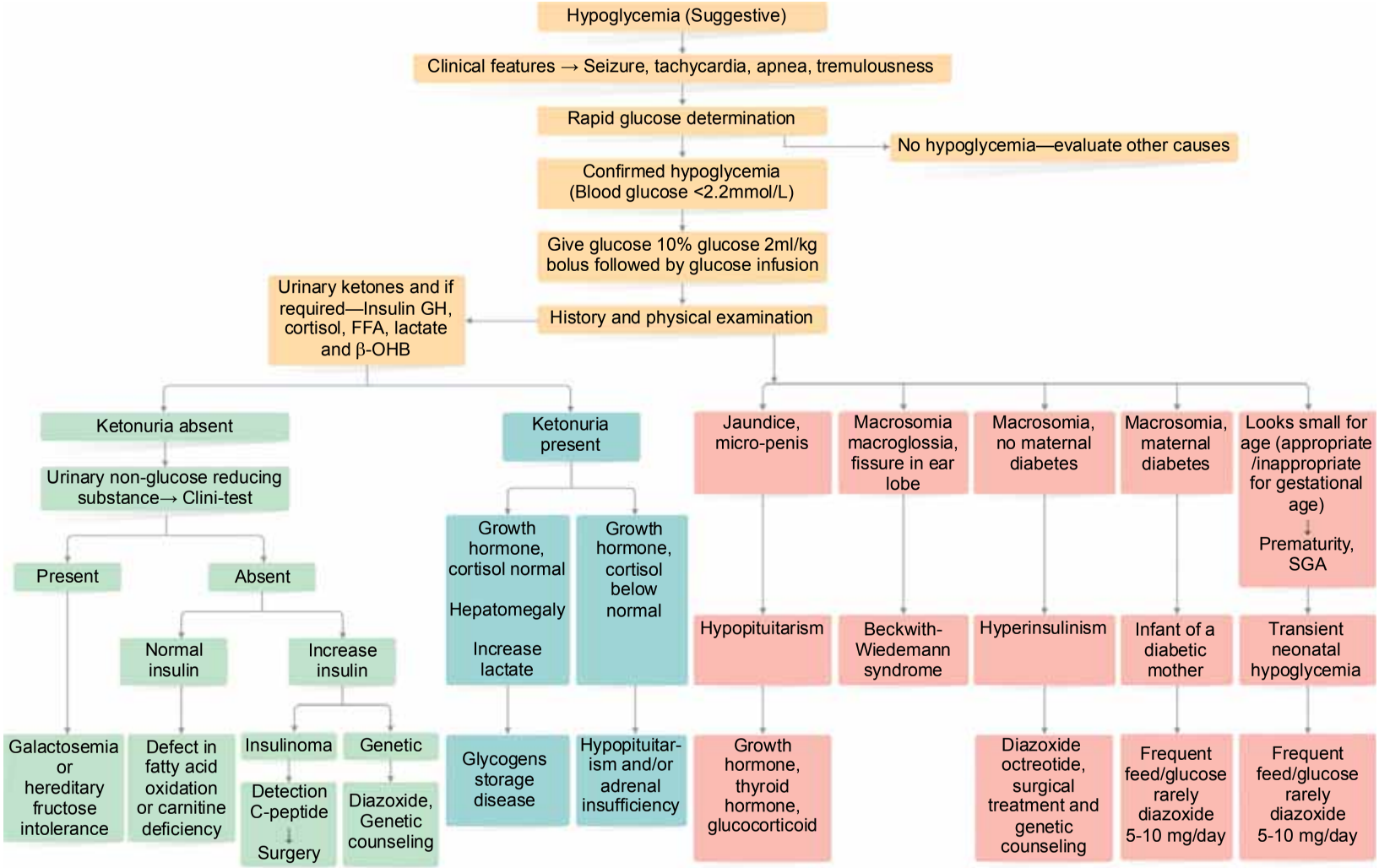
- 5–10 mL/kg of 10% dextrose IV over 20 minutes
- Injection hydrocortisone (5 mg/kg/day) IV in divided dose may be given in difficult cases
- Consider NICU admission and glucagon administration, if hypoglycemia still persists.

NEONATAL CONVULSION

PRESENTATION

- Neonate presented with:
  - Abnormal deviation/jerky movements of the eyeball
  - Repetitive blinking
  - Stare look
  - Fluttering of the eyeball
  - Drooling
  - Sucking or other orofacial movement—chewing, lip smacking, tongue thrusting
  - Unusual limb movements—cycling, swimming, paddling, etc. (Fig. 134)
  - Tonic posturing of limbs
  - Focal/multifocal clonic movements
  - Apnea.

Flow chart 12: Algorithm for management of hypoglycemia (neonatal)



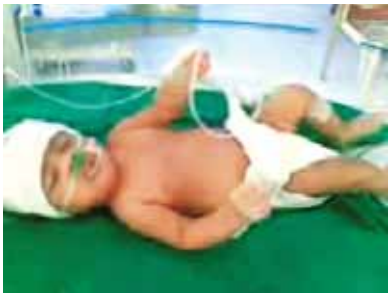


Fig. 134: Unusual limb movements of neonatal

DIAGNOSIS (TABLE 58)

Common causes of neonatal convulsion are:

- Perinatal complications:
  - Birth asphyxia (perinatal asphyxia)
  - Hypoxic ischemic encephalopathy
  - Birth trauma
- Hypoglycemia
- Hypocalcemia
- Sepsis/meningitis
- Intracranial hemorrhage—such intraventricular hemorrhage (IVH)
- Dyselectrolytemia
- Neonatal tetanus.

CONVULSION

Convulsion is a sudden, violent, disorderly discharge of brain cells. Neonates do not show grandmal seizures as central to peripheral connections are not yet completed. Difference between a convulsion and jitteriness has been discussed in Table 59.

Table 58: Differential diagnosis of newborn (neonate) presenting with lethargy, unconsciousness or convulsion

Diagnosis or underlying cause	Points in favor
Birth asphyxia or perinatal asphyxia	• Onset in first 3 days of life
HIE	• History of difficult delivery: Abnormal presentations or instrumental delivery, cord around the neck, H/O difficult resuscitation, H/O prolonged and difficult labor, delayed cry
Birth trauma	• Presence of birth injury
Intracranial hemorrhage including IVH	• Onset in first 3 days of life in a low birthweight or preterm infant: <28 weeks, 90% chance of IVH; <30 weeks, 70–80% chance of IVH
	• H/O birth trauma/difficult labor may be present
	• Excessive cry, convulsion
	• O/E: Pale (suddenly), bulged fontanel (↑ ICP), apnea, excessive cry, ↓ moro reflex, shock
Hypoglycemia	• Feeding history: H/O delayed feeding/no feeding at all
	• Maternal history of diabetes mellitus (IDM); GDM
	• Reluctant to feeding, excessive sweating
	• Big baby, jitteriness/tremor/convulsion
	- O/E: Plump and plethoric, LGA/SGA, tachypnea/Apnea, lethargy, poor sucking
Hemolytic disease of the newborn, kernicterus	• Onset in first 3 days of life
	• Jaundice develops within first 24 hours of life
	• Pallor (develops within 4–5 hours of life
	• May present with H/O jaundice of previous child
	• H/O intrauterine deaths, abortion in mother with Rh
	• Hepatosplenomegaly, ascites, growth failure, heart failure
Meningitis	Lethargy, apneic episodes, convulsions, high pitch cry, tense/bulging fontanel (↑ ICP); unconsciousness or convulsion. Onset usually at or after 3 days of life.
Sepsis	Reluctant to eat, vomiting, less active, lethargy, fever/hypothermia, any evidence of sepsis, e.g., rash, shock, seriously ill, with no apparent cause. Onset usually at or after 3 days of life. H/O PROM >18 hours, maternal history of fever
Neonatal tetanus	Onset at age 3–14 days, irritability, difficulty in breastfeeding, trismus, muscle spasms, convulsion, no maternal history of TT immunization, possible history of TT immunization, possible history of unclean delivery and unhealthy cord cutting, possible history of application of: cow dung, ash, etc., in the cord
Dyselectrolytemia	Onset 0–10 days of life, possible history of prolonged fasting, reduced apetite, vomiting, therapy, convulsion
Hypocalcemia	Onset in: 0–10 days of life, history of prolonged fasting, reduced appetite, prolonged parenteral nutrition without supplementation of calcium
Hypomagnesemia	Onset in is usually after 3 days of life. History of prolonged fasting/parenteral nutrition without supplementation

Abbreviations: HIE, hypoxic ischemic encephalopathy; H/O, history of; IVH, intraventricular hemorrhage; O/E, on examination; ICP, intracranial pressure; IDM, infants of diabetic mother; GDM, gestational diabetes mellitus; LGA, large for gestational age; SGA, small for gestational age; PROM, premature rupture of membranes

INCIDENCE

- In neonates: About 1%
- In childhood: 5–10%.

INDICATION OF CNS INSULT

Insult of central nervous system is indicated by symptom, as well as, cause of brain damage.

ETIOLOGY AND ONSET OF NEONATAL CONVULSION

Etiology and time of onset of convulsion is given in the Table 60.

INVESTIGATION

First-line

- Septic screening: CBC, CRP, blood culture and sensitivity (C/S), CSF study and possible urine C/S (by suprapubic aspiration)
- Blood glucose
- Serum Ca, Mg
- Serum electrolytes
- Serum bilirubin (if icteric)
- USG of brain.

Table 59: Difference between convulsion and jitteriness

	Convulsion	Jitteriness
Abnormalities of gaze, extraocular movements	Present	Absent
Stimulus sensitive	No	Yes
Can be stopped by flexion of affected limb	No	Yes
Dominant movement	Clonic/jerking irregular	Tremor
Nature	Generalized	Focal
When touched	No change of convulsion	Stops

Second-line

- TORCH screening
- EEG
- CT scan of the brain.

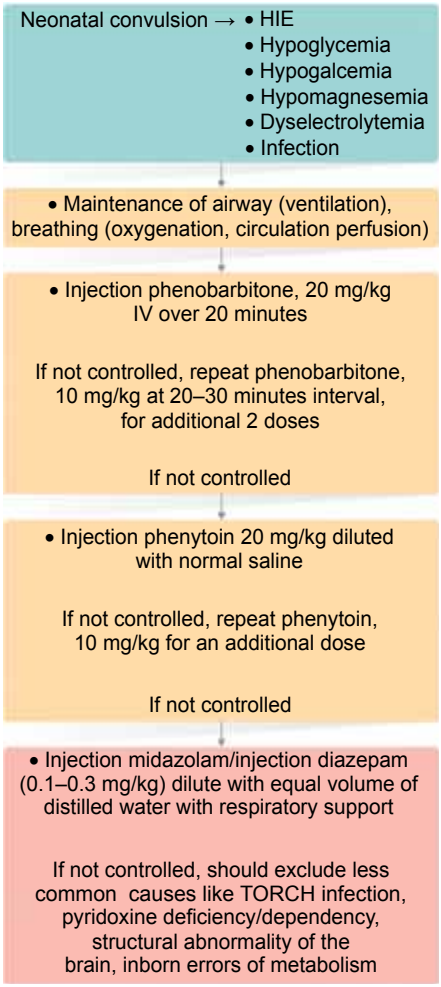
MANAGEMENT (FLOW CHART 13)

- Turns the patient in semiprone position with head downwards, maintenance of airway- by clearance of secretion, breathing is maintained by oxygen inhalation, if needed intubation and positive pressure ventilation, assessment of circulation (perfusion) by monitoring of heart rate, capillary refilling time (CRT) and blood pressure. Oxygen saturation may be measured by pulse oxymetry and arterial blood gas (ABG) may be measured, if facility is available.
- Urgent IV line, preferably two, one for drugs and one for fluid and nutrition. If IV line is delayed, per rectal diazepam. IV line is maintained with 10% dextrose with maintenance of electrolytes.
- Anticonvulsant:
  - Injection Phenobarbitone: 20 mg/kg IV slowly over a period of 20 minutes. If convulsion is not controlled after this loading dose, repeat dose of injection phenobarbitone 10 mg/kg IV every 20–30 minutes till a dose of 40 mg/kg is reached.
  - If injection phenobarbitone fails to resolve seizure, or if there are adverse effects like respiratory depression, hypotension, bradycardia, then injection phenytoin (injection fosphenytoin may be used). 20 mg/kg IV diluted with normal saline slowly over a period of 20 minutes should be given. A repeat dose, if injection phenytoin 10 mg/kg IV may be tried in refractory seizures.
  - Injection diazepam 0.3 mg/kg or injection midazolam (0.1–0.2 mg/kg IV slowly after dilution with equal volume of distilled water (with respiratory support). Injection diazepam is usually avoided because of the risk for apnea and kernicterus.

Table 60: Etiology and time of onset

Etiology	Time of onset of convulsion		
	0–3 days	4–10 days	> 10 days
Perinatal complication	+ (onset in first 3 days of life)	+	+
Intracranial hemorrhage	+ (onset in first 3 days of life)		
Hemolytic disease of the newborn, kernicterus	+	+	+
Hypoglycemia	+		
Hypomagnesemia		+	
Infections (meningitis, septicemia, encephalitis)		+	+
Neonatal tetanus (3–14 days)		+	+
Hyponatremia	+	+	
Hypernatremia	+	+	
Hyperbilirubinemia		+	+
Pyridoxine deficiency/dependency	+	+	+
Congenital cerebral malformations	+	+	+
Inborn errors of metabolism–Amino acid/organic acid abnormalities		+	+

Flow chart 13: Management of neonatal convulsion (algorithm)



- Simultaneously find out the underlying causes like HIE, hypoglycemia, hypocalcemia, hypomagnesemia, dyselectrolytemia, infection, kernicterus, etc. and treated accordingly.
- Injection pyridoxine: 25 mg IV/IM, two doses of 12 mg, is reserved as last resort of therapeutic trial (normal investigations). Can be given orally.
- If seizures fail to control than less likely causes of neonatal seizure like inborn error of metabolism, structural abnormality of brain, congenital infections (TORCH) will be considered.
- Treatment of cerebral edema, if present:
  - Fluid restriction
  - IV mannitol (5 mL/kg of 20% solution over 30–60 minutes).
- For maintenance of anticonvulsant action: Injection phenobarbitone is used in a dose of 3–8 mg/kg/day. If phenytoin is also needed for the acute episodes, then this drug is also used for maintenance (3–8 mg/kg/day). The maintenance dose begins 12 hours after loading dose and give in a 12-hourly divided dose IV or orally.

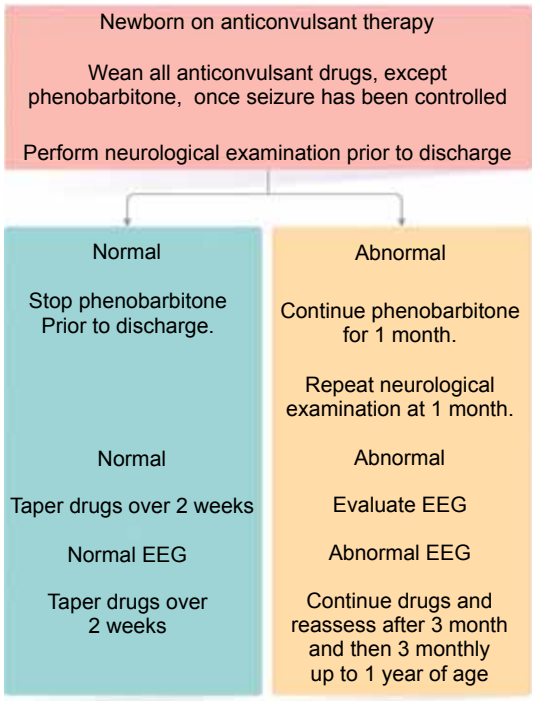
When to Discontinue Anticonvulsant Drug

Once seizure has been controlled, all anticonvulsant drugs except phenobarbitone will be discontinued. Prior to discharge, neurological examination will be performed. If neurological examination is normal then phenobarbitone will also be discontinued. But, if neurological examination is abnormal, phenobarbitone will be continued and the baby will be reassessed after 1 month. After 1 month, if neurological examination is normal, phenobarbitone will be discontinued over 2 weeks. But, if neurological assessment is abnormal, an EEG is obtained. If EEG is normal, phenobarbitone will be tapered and discontinued. If EEG is abnormal, then the infant is reassessed in the same manner at 3 months and then 3-monthly till 1 year of age.

Weaning and Duration of Anticonvulsant Therapy

Flow chart 14 describes the weaning and distribution of anticonvulsant therapy.

Flow chart 14: The weaning and distribution of anticonvulsant therapy



VITAMIN K DEFICIENCY BLEEDING (HEMORRHAGIC DISEASE OF NEWBORN)

INTRODUCTION

Vitamin K deficiency bleeding (VKDB) has replaced the previous term of hemorrhagic disease of newborn. This is because vitamin K deficiency not only occurs in newborn period but continue to occur beyond neonatal period (late VKDB) and hemorrhage during newborn period also occur other than vitamin K deficiency.

VITAMIN K DEFICIENCY BLEEDING

The relationship of vitamin K administration and abolishment of symptomatic prothrombin deficiency in newborn was observed in 1939. With better understanding of such relationship after

so many years, VKDB however, has never gone away but is merely rediscovering at the time of progressive trend toward exclusive breastfeeding. The latter has long been recognized as an important factor for neonatal hypoprothrombinemia.

ETIOLOGY AND PATHOGENESIS

- Newborn babies are born with relatively less vitamin K reserve
- Breastfed babies are at increased risk of VKDB (formula milk are fortified with vitamin K), if vitamin K prophylaxis is not given
- Underlying latent liver disease may present as jaundice after 3 weeks of age. Proportion of conjugated bilirubin, rather than total bilirubin estimation, is helpful at the time of bleeding or apprehending bleeding in early neonatal period
- Neonatal cholestasis (biliary atresia, cystic fibrosis, congenital TORCH) is more associated with VKDB. Pale stool and high color urine are suggestive of cholestasis
- Preterm infants are at risk to develop VKDB (evidence, however, is not strong)
- Maternal risk factor: Maternal drugs ingestion affecting synthesis of vitamin K dependent clotting factors like anticonvulsant, rifampicin, INH and anticoagulants.

PRESENTATION

Although arbitrary, helps in considering etiology and prophylaxis:

- *Early onset*: Onset within 24 hours of birth. More associated with maternal ingestion of drugs affecting vitamin K metabolism like anticonvulsant.
- *Classical*: Onset 1–7 full days after birth. Usually who are breastfed and have not received vitamin K prophylaxis.
- *Late*: Onset after 7 days to over weeks, usually upto 8 weeks. Unexpected intracranial bleeding is an important manifestation of late VKDB, not given vitamin K prophylaxis.

CLASSIFICATION ACCORDING TO DIAGNOSIS

- *Confirmed:* Appropriate history of bleeding, documented prothrombin time or International Normalized Ratio (INR) at least twice the control value, normal or raised platelet count, no evidence of infection or disseminated intravascular coagulopathy (DIC).
- *Probable:* Appropriate history of bleeding, diagnosis other than VKDB, unlikely but lacking full laboratory confirmation.

TYPES OF BLEEDING

Subcutaneous bleeding, like bruises (Fig. 135), GI bleeding, hematemesis, melena, nasal bleeding, hematuria, intracranial bleeding.

Warning Bleeds

Warning bleeds may precede more serious bleeds. It includes bruises, nasal bleed, oozing from scratches, umbilical oozing, etc.

INVESTIGATION

- Full blood count, platelet count, prothrombin time, Activated Partial Thromboplastin Time (APTT), liver function test, serum ALT, AST and serum bilirubin.

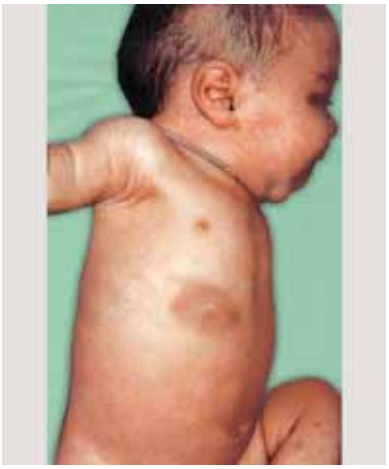


Fig. 135: Bruises in a vitamin K deficiency bleeding disorder

- If facilities are available, serum concentration of vitamin K, serum undercarboxylated prothrombin (PIVKA-II) can also be assessed.

MANAGEMENT

Prophylaxis

All babies should receive vitamin K prophylaxis, particularly breastfed babies. Either single IM dose or multiple oral doses required.

Oral Vitamin K (Oral Phytomenadione Mixed Micellar)

- 2 mg oral dose—three doses
- First dose at birth, second dose at 1 week, third dose at 4–6 weeks.

Intramuscular Vitamin K (Intramuscular Phytomenadione Mixed Micellar)

Once, only at birth; birthweight more than or equal to 2.5 kg, 1 mg/kg, birthweight less than 2.5 kg, 0.4 mg/kg.

Intramuscular or Oral Vitamin K

Intramuscular is preferable to oral vitamin K for the following reasons:

- Supply and compliance with second and third dose of oral vitamin K may be a problem
- Intestinal absorption of oral mixed micellar K [konakion mixed micellar (mm) is unreliable in infants with conjugated hyperbilirubinemia (cholestatic jaundice)
- IM prophylaxis is more useful to protect who are sick, preterm and born to mothers taken vitamin K antagonistic drug like anticonvulsant.

Disadvantages of Intramuscular Vitamin K

- Possible theoretical risk (statistically insignificant) of acute leukemia in future cannot be ruled out.
- *Intravenous dose of vitamin K*: Not recommended as depot effect of IM injection is not obtained. If given IV, frequent dose is required.

TREATMENT DURING ACTIVE BLEEDING

Threshold for treatment:

- No treatment in mild case
- Treatment is required if significant bleeding occurs:
  - Baby is unwell
  - Baby in first week of life in preterm baby.
- Phytomenadione vitamin K: It may have to be given repeatedly
- Fresh frozen plasma (FFP): Start with 15 mL/kg
- Cryoprecipitate: If fibrinogen remains low (<0.8 g/L) despite FFP
- Specific factor concentrate: If specific deficiency found.

CONGENITAL HEART DISEASE IN NEWBORN

(Discussed in detail in Cardiology Chapter).

CONGENITAL HEART DISEASE IN NEWBORN

Fetal Circulation and Changes at Birth

When considering the consequences of congenital heart defects and their management, a basic understanding of fetal cardiovascular physiology and the changes that occur at birth are essential.

Fetal Circulation

Fetal circulation differs from postnatal circulation in three important ways:

1. Oxygenated blood enters the circulation from placental transfer.
2. Due to high pulmonary vascular resistance, pulmonary blood flow accounts for less than 20% of total cardiac output.
3. Five fetal vascular structures exist to direct blood flow:
   - Ductus arteriosus connects the pulmonary artery to the aorta, thereby diverting fetal blood flow away from the fetal lungs, thereby shunts lungs from right to left
   - Foramen ovale is a communication between the two atria, which also diverts blood returning to the right atrium to left atrium through the septal wall
   - Umbilical arteries and umbilical vein carry deoxygenated blood to and oxygenated blood away from the placenta, respectively
   - Ductus venosus receives oxygenated blood from the umbilical vein and directs it to the inferior vena cava and right atrium, thereby bypassing the liver.

Circulatory Changes at Birth

The following changes occur after birth:

- Pulmonary vascular resistance falls as the lungs inflate which allows greater pulmonary blood flow and an increase in oxygen tension
- Due to increased blood flow and increased pulmonary venous return, the right atrial pressure increases, causing the flap valve of the foramen ovale to close, which separates the right and left atria
- The ductus arteriosus closes soon after birth due to increased oxygen tension which constricts smooth muscle surrounding the ductus. Complete closure of the ductus takes place usually within 60 days after birth.

CLINICAL SIGNIFICANCE OF PHYSIOLOGICAL CHANGES OF THESE STRUCTURES

Duct-dependent Congenital Heart Disease (Figs 136A to C)

- Certain type of Congenital Heart Disease (CHD) may show deterioration of clinical condition after closure of ducts, on which their circulation was dependent, like transposition of great arteries
- On the contrary, failure of physiological closure of duct may also deteriorate some CHD, like patent ductus arteriosus.

CLASSIFICATION OF CONGENITAL HEART DISEASE

Flow chart 15 shows the classification of congenital heart disease.

Approach to Case Scenarios and Evaluation of Central Cyanosis

Peripheral cyanosis is very common, especially in newborn babies, and is of no significance. Perioral cyanosis is particularly common in older children who are cold, especially after swimming, and again is of no importance. Central cyanosis is recognized as a purple or blue tinge to the lips and tongue. It is clinically detectable when the amount of deoxygenated hemoglobin in arterial blood exceeds 5 g/dL. It is therefore readily recognized in a newborn baby with a high hemoglobin but less noticeable in an anemic child. Pulse oxymetry is very useful if there is doubt about the presence of cyanosis. There

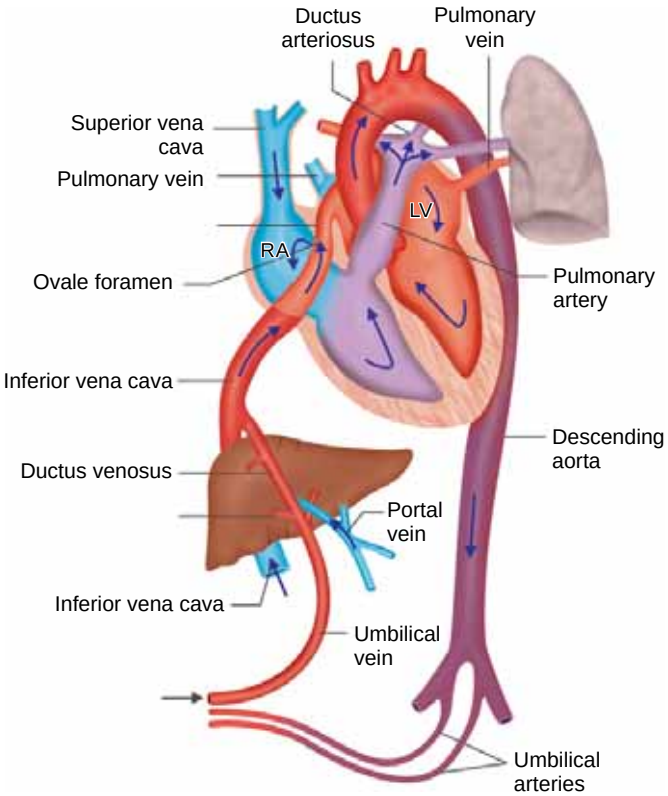


Fig. 136A: Fetal circulation

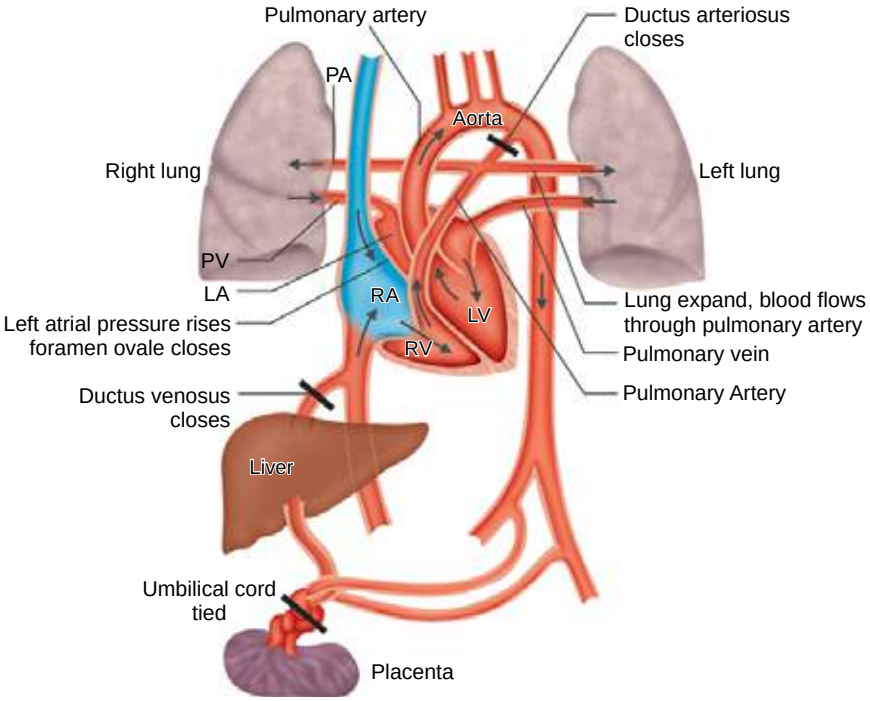


Fig. 136B: Circulatory changes at birth normal heart

Abbreviations: LV, left ventricle; LA, left auricle; PA, pulmonary artery; PV, pulmonary vein; RA, right auricle; RV, right ventricle

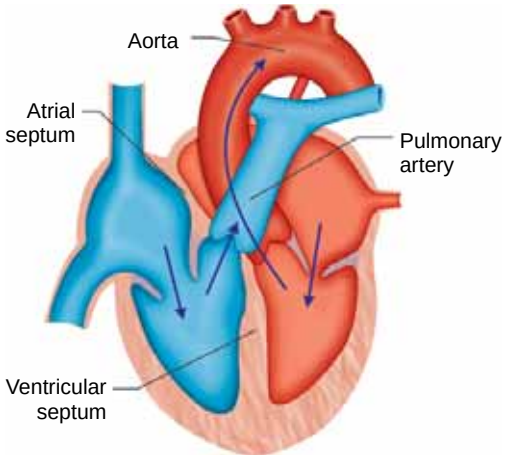


Fig. 136C: Normal heart

are other causes of central cyanosis besides heart disease in the newborn period (Table 61); the following should be considered:

Clinical Problem and Likely Systemic Disorder

- The baby looks ill and has obvious respiratory difficulty
- Arterial blood gases show a low.
- PO_2 and PCO_2 may be normal or raised. A nitrogen washout test produces a rise in PO_2 to a level usually above 100 mg Hg (14 kPa)
- The Chest X-ray (CXR) shows a normal heart size and abnormal lung field.

Clinical Disorder: Pulmonary Disorder

- Hyaline membrane disease
- Pneumonia, and
- Meconium aspiration

} May result in central cyanosis

Clinical Problem and Likely Systemic Disorder

- There is a history of cerebral insult, such as birth trauma
- It may be apparent from inspection that the baby is under ventilating with slow, shallow breathing
- Arterial blood gases show a low PO_2 and a high PCO_2. A nitrogen washout test produces a rise in PO_2
- The baby may exhibit other neurological abnormalities, e.g. convulsion.

Clinical Disorder: Cerebral Disorder

- Control of respiration may be affected by drugs, immaturity, trauma or asphyxia. Hypoventilation may occur with resulting cyanosis.

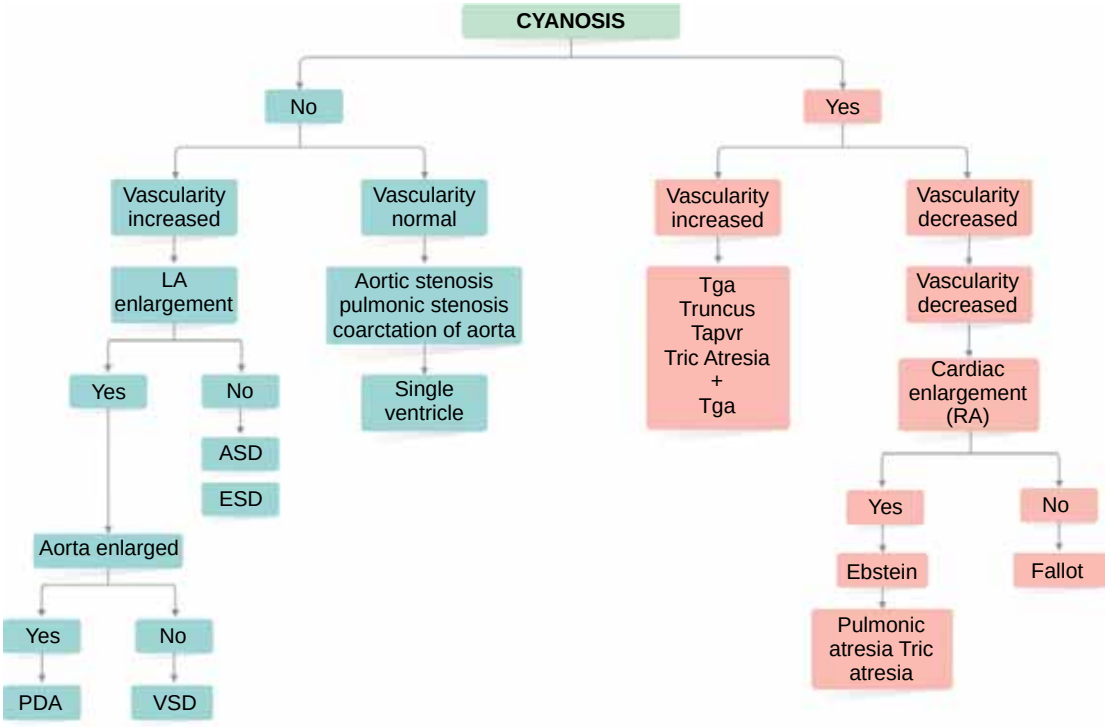
Clinical Problem and Likely Clinical Diagnosis

- Clinically reveals a baby with central cyanosis
- Arterial blood gases show a low PO_2 and normal PCO_2. The PO_2 of preductal blood is frequently more than 5 mm Hg higher than that of postductal blood. Simultaneous transcutaneous PO_2 measurements from the right chest and the lower abdomen may show this, arterial PO_2 changes little with 100% O_2
- Auscultation reveals a loud pulmonary second sound.

DIAGNOSIS

Persistent pulmonary hypertension, also called persistent transitional or fetal circulation, is the most difficult condition to distinguish from cyanotic CHD and referral to a cardiac center may be necessary. After birth, the pulmonary vascular resistance remains high so that the right-sided pressures (in the right atrium, right ventricle and pulmonary artery) are high. Blood shunts from right to left through the normal fetal channels of the foramen ovale and the ductus arteriosus, resulting in central cyanosis. The phenomenon is seen in babies with severe lung

Flow chart 15: Classification of congenital heart disease



Abbreviations: ASD, atrial septal defect; VSD, ventricular septal defect; PDA: patent ductal arteriosus; TGA: transposition of great arteries; TAPVR: total anomalous pulmonary venous return; Tric atresia: tricuspid atresia; ECD: endocardial cushion defect; LA, left atrium; RA, right atrium

Table 61: Difference of central cyanosis—respiratory cause and cardiac cause

Cardiac problem	Respiratory problem
1. Hyperoxia test—PO_2 < 100 mm Hg	PO_2 >150 mm Hg
2. No respiratory distress, except in TAPVR (obstructed), mixers have shallow tachypnea	Respiratory distress, abnormal X-ray
3. Normal or low PCO_2	Respiratory acidosis- PCO_2 highly increased
4. Weak pulses or differential pulses	Normal pulse
5. Single second heart sound	TR murmur
6. No risk factors or respiratory distress	Meconium stained amniotic fluid, prolonged rupture of membrane
7. Tachypnea: RR around 40–60/min, usually	Tachypnea RR usually > 80/min

Abbreviations: TAPVR: total anomalous pulmonary venous return; TR, tricuspid regurgitation; RR, respiratory rate

disease, especially hyaline membrane disease, and meconium aspiration and group B hemolytic streptococcal pneumonia. It is also seen in the absence of lung disease in babies who are small for dates, asphyxiated at birth or polycythemic. Echocardiography is useful because it demonstrates an anatomically normal heart with a right to left shunt at atrial level after peripheral contrast injection or on Doppler assessment.

APPROACH TO CASE SCENARIOS

Suspected heart disease from symptoms (in neonates):

- Cyanosis (Fig. 137)
- Tachypnea

Fig. 137: Infant with cyanosis due to congenital cyanotic heart disease

- Murmur
- Weak pulses
- Shock
- Dysmorphic features
- Hypotension
- Cardiomegaly
- Acidosis
- Other congenital malformations.

Management Guidelines of Congenital Cyanotic Heart Disease in Newborn

- Prostaglandin E (PGE)—to keep ductus open:
  - To increase pulmonary blood flow in right sided obstructive lesions
  - To increase systemic blood flow in left sided obstructive lesions.

It may help in dextraposed transposition of great arteries (D-TGA) but it may harm the patient with TAPVR and mixing lesions

- To keep oxygen saturation between 75—85% and PO_2 30–50 mm Hg
  Additional oxygen can be given in associated pulmonary disease and in obstructive TAPVR. It will not help in right-sided obstructive lesions and simple D-TGA, while it will hurt patients with hypertrophic left heart syndrome as it will increase pulmonary blood flow but decrease systemic circulation
- Correction of any metabolic acidosis, seen mainly in left-sided obstructive lesions, if $NaHCO_3$ is used. It may need ventilation to blow off CO_2
- Volume and inotropic support: Aim is to maintain systolic BP of 55–80 mm Hg. Minor perfusion, pH, urine output and body temperature
  Volume: Normal saline or 5% albumin 8–10 mL/kg
  Inotrope: Dopamine 5–10 µg/kg/min, with or without dobutamine, to maintain myocardial contraction
- Maintenance of airway and breathing intubation, if necessary, but never hyperventilation, maintain normal pH and PCO_2.
- Counseling and psychological support.

CLINICAL PROBLEM (TABLE 62)

- The baby looks well, with no respiratory difficulty
- There may or may not be a heart murmur
- The second heart sound is usually single
- ABGs show low PO_2 and normal PCO_2. After the infant has been breathing oxygen (90% or more) for 10 minutes, the arterial O_2 is unchanged or has slightly increased (not above 100 mm Hg, 14 kPa)
- A CXR shows no lung disease.

DIAGNOSIS

Cyanotic Congenital Heart Disease

- The underlying lesion responsible for the cyanosis can often be deduced from the age at presentation, the CXR and the ECG. The echocardiogram is diagnostic in all cases.

Differential diagnosis of congenital heart disease is given in Table 63.

Cyanotic Heart Diseases Presenting in the First Week of Life

The important lesions are:

- Transposition of the great arteries
- Tricuspid atresia
- Pulmonary atresia
- Total anomalous pulmonary venous drainage with obstruction to the common pulmonary vein
- Ebstein's anomaly.

Transposition of the Great Arteries (Fig. 138)

Cyanosis develops when the foramen ovale and ductus arteriosus start to close. In the absence of a VSD, this often occurs within the first 24 hours. Although, the infant is usually well initially, the increasing cyanosis leads to acidosis and death, if no treatment is given.

Clues to diagnosis:

- Clinical findings:
  - Central cyanosis
  - Mild tachycardia
  - Loud single second heart sound
  - No murmur.
- CXR:
  - "Egg on side" appearance
  - Develops outside neonatal period
  - Pulmonary vascular markings are normal or increased.
- ECG:
  - Superior axis with left ventricle hypertrophy
  - Right ventricular hypertrophy (RVH)—normal in newborn.
- ABG:
  - O_2 saturation decreases acidosis.

TREATMENT

Affected infants may show some improvement in arterial PO_2 with PGE but urgent balloon septostomy may be needed to allow mixing of atrial blood. Transfer to a cardiac center should take place at once. The operation of choice is now the arterial switch procedure which is usually carried out at a few days of age. For complicated cases and with late presentation, diversion of systemic and pulmonary venous returns using a baffle is carried out in older infants (Mustard operation).

Table 62: Difference between cardiac and noncardiac disease in a cyanotic newborn

Points	Cardiac cause	Respiratory cause
Tachypnea	Usually in and around 60/min	Usually more than 80/min
Respiratory distress	Present or may be absent. No respiratory distress except in TAPVR (obstructed) mixer have shallow tachypnea	Prominent respiratory distress
Hyperoxia test	No response, PO_2 <100 mm Hg	Response. PO_2 >150 mm Hg
Weak pulses or differential pulses	Present	Absent (normal pulses)
Heart sound and added sound	Single second heart sound	TR murmur
ABG	Normal or low PCO_2	Respiratory acidosis (increased PCO_2)
Risk factors	No risk factors or respiratory distress	Meconium stained amniotic fluid, prolonged rupture membrane

Abbreviations: TAPVR, total anomalous pulmonary venous return; ABG, arterial blood gas

Table 63: Evaluation of clinical signs, blood gas analysis, X-ray and ECG to narrow down differential diagnosis

Evaluation	Cardiac problem/others	Cause and manifestations
Bedside physiologic evaluation	• No or minimal communication between systemic and pulmonary circulation • Common mixing situations • Right-sided obstructive lesions • Left-sided obstructive lesions	• D-TGA: deep cyanosis • TAPVR, truncus: minimal cyanosis • Pulmonary and tricuspid atresia, TOF: moderate cyanosis • AS, coaorta, interrupted aortic arch: No cyanosis
Saturational evaluation	• Deeply cyanosed, saturation <70% • Cyanosed, saturation (70–80%) • Mild cyanosis, saturation (80–90%) • Differential saturation	• D-TGA, obstructed TAPVC • Tricuspid atresia, TOF, pulmonary atresia • Hypoplastic left heart, TA, interrupted aortic arch • Right arm > lower lumb: coaorta, PPHN • Leg > arm: Coaorta with D-TGA
X-ray evaluation	• Increased pulmonary blood flow • Decreased pulmonary blood flow	• TAPVR, D-TGA, truncus, hypoplastic left heart • Tricuspid atresia, Ebstein anomaly, pulmonary atresia, TOF
ECG evaluation	• Left axis deviation • Right atrial enlargement • No ventricular forces • Right ventricular enlargement	• Atrioventricular septal defect, tricuspid atresia • Ebstein's anomaly, TA, P. atresia with intact ventricular spectrum • Hypoplastic left heart, dextrocardia • TOF, P. atresia with VSD, hypoplastic left heart

Abbreviations: AS, aortic stenosis; COA, coarctation of aorta; D-TGA, dextraposed transposition of great arteries; P. atresia, pulmonary atresia; TAPVR, total anomalous pulmonary venous return; TOF, tetralogy of Fallot; TA, tricuspid atresia; VSD, ventricular septal defect

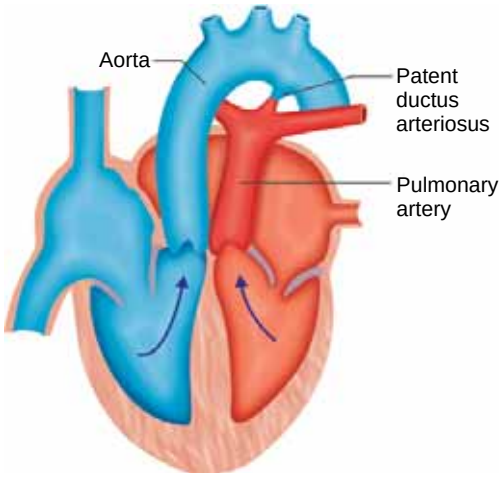


Fig. 138: Transposition of the great arteries

Tricuspid Atresia (Figs 139A and B)

There are a number of variants of this condition but the presentation is usually with central cyanosis in the early newborn period. The diagnosis is made on echocardiography, although cardiac catheterization is carried out later in childhood before definitive surgery.

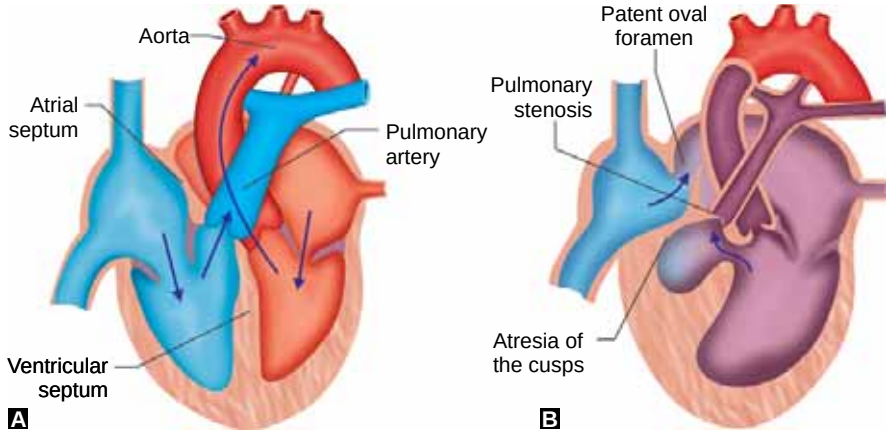
- PGE will reverse the cyanosis and allowed unhurried transfer to a cardiac center at a convenient time
- A systemic to pulmonary anastomosis, an artificial patent ductus is then created
- The definitive operation is the creation of a right atrial to pulmonary arterial anastomosis with a valve-conduit (Fontan procedure).

Clues to Diagnosis

- Clinical findings:
  - Central cyanosis
  - No tachycardia
  - Single second heart sound
  - Presence or absence of soft systolic murmur.
- CXR:
  - Small heart
  - Oligemic lung fields.
- ECG:
  - Superior QRS axis [S wave > R wave, in arteriovenous fistula (AVF)]
  - Reduce right ventricular (RV) forces.

Treatment in short:

- PGE- will reverse cyanosis
- Systemic to pulmonary artery anastomosis



Figs 139A and B: (A) Normal heart, (B) Tricuspid atresia. Note the small right ventricle and the large left ventricle

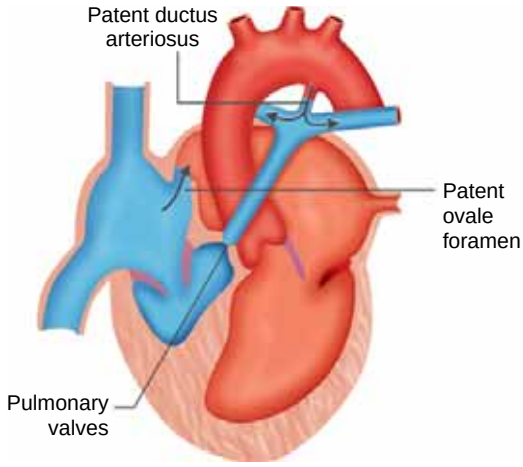


Fig. 140: Pulmonary valvular atresia with a normal aortic root. The only access route to the lungs is by way of a patent ductus arteriosus

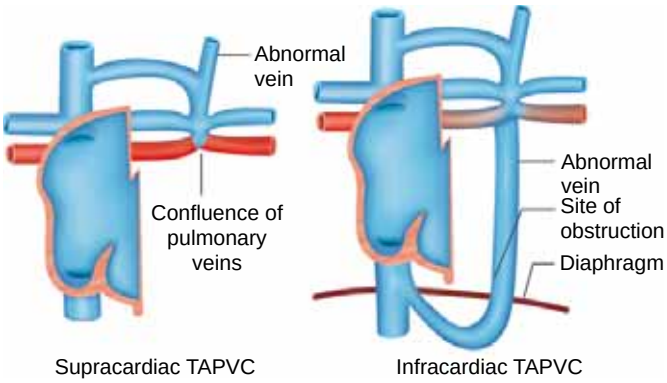


Fig. 141: Total anomalous pulmonary venous connection

- Pulmonary atresia (without a ventricular septal defect)
- The right ventricle is thick walled but the cavity and the tricuspid valve are often small (Fig. 140).

Clues to Diagnosis

- Clinical findings:
  - Severe central cyanosis (early neonatal period)
  - Single second heart sound
  - No murmur.
- CXR:
  - Prominent right atrium
  - Mild cardiomegaly
  - Oligemic lung fields.
- ECG:
  - Right atrial hypertrophy
  - Normal axis
  - Reduced RV and increased LV forces.

Treatment:

- PGE-will reverse cyanosis
- Pulmonary valvotomy
- Surgical: Systemic to pulmonary anastomosis in neonatal period [modified Blalock-Taussig (BT) shunt].

Total Anomalous Pulmonary Venous Drainage

- Total anomalous pulmonary venous drainage (TAPVD) (Fig. 141): The supracardiac and cardiac types present with heart failure, failure to thrive and minimal or no cyanosis. In the infracardiac type, where the common pulmonary vein passes below the diaphragm and drains into the portal or systemic venous system, the pulmonary venous return is obstructed. The pulmonary veins are congested, there is pulmonary hypertension and pulmonary edema.
- Symptoms develop in early infancy, often in the newborn period, with a combination of central cyanosis and respiratory distress. Always consider the diagnosis in any cyanosed infant with respiratory difficulty.

Clues to Diagnosis

- Clinical findings:
  - Central cyanosis with respiratory distress
  - Tachypnea and recession
  - Frequent respiratory tract infection
  - No murmur
  - Hepatomegaly
  - Failure to thrive (FTT).
- Chest X-ray:
  - Small heart
  - Streaky hilar shadows
  - Hazy lung fields (edema).
- Electrocardiogram
  - Often normal.

Treatment

- Surgical correction. Without surgery death is inevitable.

Ebstein Anomaly (Fig. 142)

- The leaflets of the tricuspid valve are deformed and are displaced distally towards the apex of the right ventricle. Thus the right atrium is large, the RV is small and there may be tricuspid regurgitation (TR). There is usually an associated ASD and there may be an accessory atrioventricular conduction pathway (Wolff-Parkinson-White syndrome). The severest form results in intrauterine death, the milder forms are asymptomatic and compatible with normal life expectancy, but those in between present with symptoms
- Central cyanosis can develop in newborn period
- FTT
- Reduced exercise tolerance.

Clinical Clues to Diagnosis

- Clinical findings:
  - Central cyanosis
  - FTT
  - Soft systolic and diastolic murmurs
  - Added sounds.
- CXR:
  - Cardiomegaly
  - Large RA shadow
  - Oligemic lung fields.
- ECG:
  - Tall P waves
  - Prolonged PR interval
  - Right bundle branch block.

Treatment:

Surgical correction.

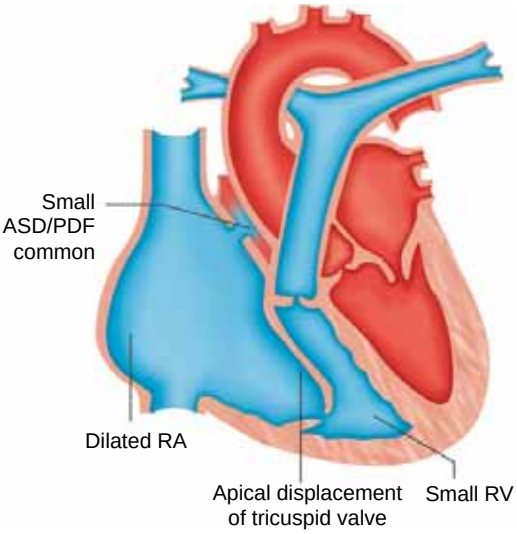


Fig. 142: Ebstein anomaly

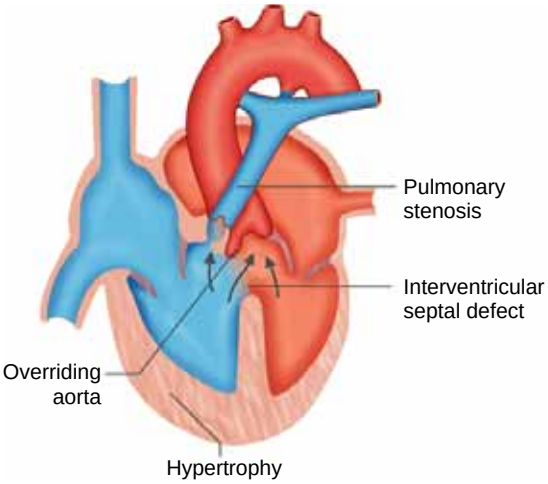


Fig. 143: Tetralogy of Fallot. The four components of the defect: Pulmonary stenosis, overriding aorta, interventricular septal defect and hypertrophy of the right ventricle

Cyanotic Heart Disease Presenting after the First Week of Life

- Tetralogy of Fallot (TOF)
- TGA with shunt.

Tetralogy of Fallot (Fig. 143): This is the commonest cyanotic congenital heart lesion presenting outside the immediate newborn period. Its severest form, pulmonary atresia with a VSD, will result in central cyanosis at a very early age. There is a large subaortic VSD with the aortal overriding both ventricles, pulmonary valve, and infundibular stenosis and right ventricular hypertrophy.

Clinical Clues to Diagnosis

- Classical presentation of TOF:
  - Central cyanosis (late onset, usually after infancy)
  - Clubbing (after infancy)
  - Conjunctival congestion
  - Cyanotic spells
  - Single S_2 sound
  - Pulmonary ejection systolic murmur

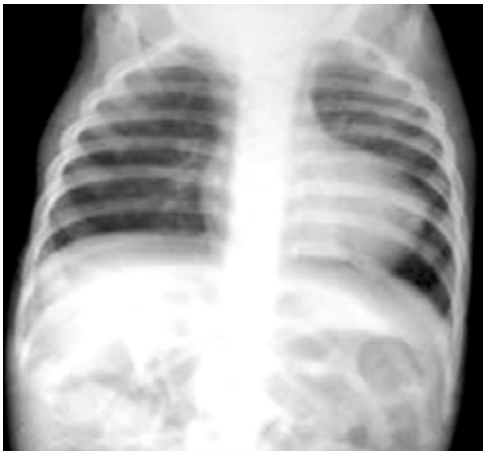


Fig. 144: X-ray showing upward tilted apex of heart with oligemic lung field characteristic of TOF

- CXR (Fig. 144):
  - Boot shaped heart (apex telt up)
  - RVH and small pulmonary artery
  - Oligemic lung field (increased lucency of lung field and there is no vascular markings).
- ECG:
  - Right axis deviation
  - RVH.

Treatment:

Medical management:

- Treatment of cyanotic spells: It includes:
  - Keeping the baby in knee-chest position
  - Nothing peroral (NPO)
  - IV infusion
  - Oxygen inhalation by mask or hood (4–8 L/min)
  - Injection morphine (0.1 mg/kg IV)
  - Injection propranolol (0.1 mg/kg IV)
  - Injection sodium bicarbonate (1 mL/kg IV)
  - Patient should be kept calm
  - Avoidance of unnecessary sampling and handling
- Treatment at home:
  - Oral iron supplement to correct relative iron deficiency and to avoid cyanotic spell
  - Oral propranolol (1 mg/kg/dose) 4 hourly to prevent recurrence of cyanotic spells
  - Ensure intake of more fluids to avoid dehydration, hemoconcentration and thromboembolism, so dehydration should be treated promptly.
- Surgical treatment: Treatment is surgical—either total correction of the defects or (if symptoms occur in early infancy) a palliative shunt surgery (systemic to pulmonary anastomosis). The latter, the modified BT procedure, is creation of an artificial ductus arteriosus which improves pulmonary blood flow until a total correction is performed.

Indication of palliative shunt surgery:

- Small infants with severe cyanosis, or
- Frequent severe hypoxic spells whose complete correction is too risky
  - Total correction: by 2 years of age.

Hypoplastic left heart syndrome (Fig. 145): The term is used to describe a group of disorders associated with under development of left side heart structures. The left heart is

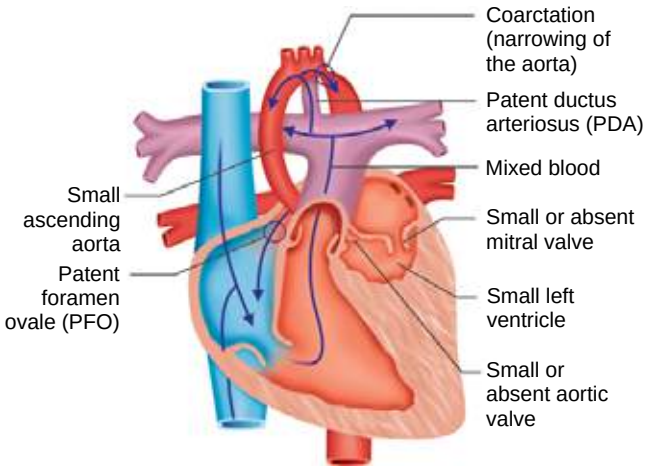


Fig. 145: Hypoplastic left heart syndrome

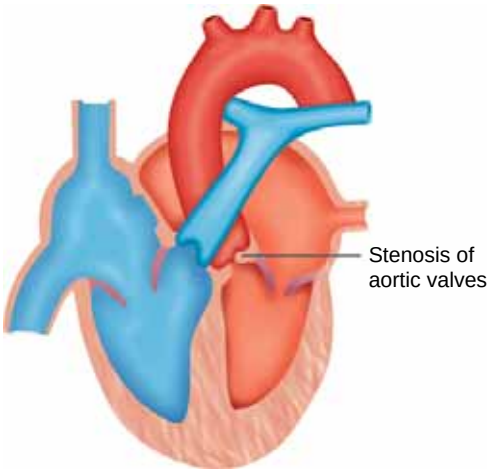


Fig. 146: Aortic vulvular stenosis

small, characterized by hypoplasia or atresia, hypoplasia of the ascending aorta and coarctation with endocardial fibroelastosis. Consequently, the left ventricle becomes less functional, and right ventricle maintains both pulmonary and systemic circulation. The latter is achieved by pulmonary venous blood passing through ASD or patent foramen ovale or via retrograde flow though PDA. Right ventricle is dilated and hypertrophied with a large pulmonary artery.

Presentation: Presents at early days of life, as duct closes, as it is duct dependent.

- Cyanosis and heart failure.
- Poor perfusion, metabolic acidosis, weak femoral pulses, active precordium
- Sick looking child
- Heart sounds: Loud single S2, gallop rhythm
- CXR: Cardiomegaly, increased pulmonary vascularity
- ECG: Small LV forces, right access radiation, right ventricular hypertrophy and right atrial enlargement.

Management: Start a prostaglandin infusion to maintain ductal patency and systemic blood flow:

- Inotropic support may be required if right ventricular function is impaired
- Intubation and ventilation may be required if pulmonary blood flow becomes too great
- These babies will need to be transported shortly after birth to centers that performs surgery for this condition.

Surgical repair: Surgery aims to convert the right ventricle into the systemic ventricle:

- Initially, Norwood procedure, followed by the Glenn or Hemi-Fontan procedures in infancy
- Finally, the Fontan procedure in early childhood
- Heart transplantation may be required.

Prognosis:

- Long-term outcome is as yet uncertain
- Mortality is highest for the first stage (Norwood procedure) and decreases thereafter.

Truncus arteriosus: Discussed in pediatric cardiology chapter

Congenital acyanotic heart disease presenting in neonatal period:

patent ductal arteriosus: Discussed in neonatology and pediatric cardiology chapter

Aortic stenosis (Fig. 146):

(Also discussed in pediatric cardiology chapter)

Presenting in neonatal period: In most of the cases, aortic stenosis (AS) is asymptomatic in neonatal period. However, in few cases, AS can present with collapse in neonatal period.

Clinical features: Symptomatic babies may present with loss of pulses, acidosis and shock. When the ductus arteriosus closes, usually they are asymptomatic.

Heart sound: Ejection systolic murmur in aortic area (right upper sternal edge) radiating into the carotids with a carotid thrill.

- CXR: Normal
- ECG: Left ventricle hypertrophy.

Management: In severe case, start a prostaglandin infusion to maintain a ductal patency and systemic blood flow.

Definitive treatment: Treatment is with transcatheter balloon angioplasty in most cases; all will eventually require aortic valve replacement.

Coarctation of the Aorta (Discussed in detail in cardiology chapter):

Aortic coarctation is common and accounts for 10% of CHD cases. It is more common in males and is strongly associated with Turner's syndrome. and additional cardiac defects are common. There is a narrowing of the lumen of the aorta, usually at the arterial duct (Fig. 147).

Clinical features

- In mild infants may be asymptomatic and present in childhood or even as adults
- Symptoms manifest when the duct begins to close in the first week of life. The degree of coarctation together with the patency of the ductus arteriosus determines the severity of symptoms
- Tachypnea and tachycardia may be present due to left ventricular failure. This is due to aortic obstruction causing an increase in left ventricular afterload that results in poor distal perfusion
- Lower limb cyanosis may be present due to right to left shunt across the duct
- Hepatomegaly may be present due to right heart failure
- Asymmetric blood pressure with higher blood pressure proximal to the obstruction and lower blood pressure distally that can be observed
- Pulse: bounding and brachial pulses with weak femoral pulse

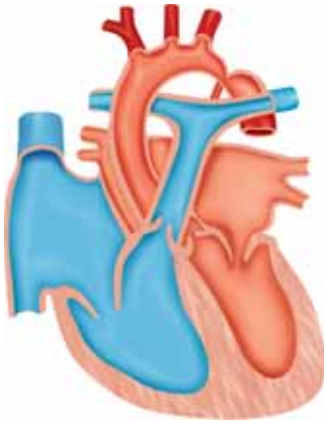


Fig. 147: Coarctation of the aorta

- Shock and metabolic acidosis, and eventually collapse
- Active precordium
- Heart sounds: Gallop rhythm and systolic murmur
- ECG: Findings of symptomatic coarctation aorta in newborn is different from that of child and adult. The 12-lead electrocardiogram will show marked right axis deviation and significant reduction in left ventricular forces in the lateral chest leads
- Echocardiograph: With apical four-chamber view may show dilated right atrium (RA), dilated hypertrophied right ventricle (RV), left atrium (LA), and left ventricle (LV)
- CXR: Cardiomegaly, increased pulmonary vasculature.

Management:

- Start prostaglandin infusion early to maintain ductal patency and systemic blood flow
- Heart failure should be managed by reopening the duct and may require inotropic support.

Surgical repair: Surgical repair involves resection of the coarctation and ductal tissue with an end-to-end anastomosis.

Cardiac arrhythmia (supraventricular tachycardia): Discussed in pediatric cardiology chapter.

HEART FAILURE DURING NEONATAL PERIOD

Definition

Heart failure (HF) results when cardiac output is insufficient to meet the metabolic demands of the body. The largest HF burden comes from children born with congenital malformations. It has been estimated that 15–25% of children who have structural heart disease, develop HF.

- The diseases implicated are very different in the first week of life to those after this time
- Up to 7 days, most infants with HF have an obstructed left heart, especially with duct dependent lesions (coarctation aorta and AS)
- After 7 days, this is most likely to be due to left to right shunt (PDA).

Causes of Heart Failure (Cardiac Causes)

First Week

- Coarctation of aorta (CoA)
- Critical AS (duct-dependent)/aortic atresia
- Interrupted aortic arch
- Hypoplastic left heart syndrome (HLHS)
- Total anomalous pulmonary venous connection (TAPVC)
- Arrhythmias (supraventricular tachycardia)
- Arteriovenous malformation
- Myocardial disease (ischemia, myocarditis, cardiomyopathy).

Second to Fourth Weeks

- VSD (clinical features of VSD rarely occurs during first few weeks of life due to increased pulmonary vascular resistance)
- Atrioventricular septal defect
- Common mixing:
  - Transposition of great arteries (TGA) + VSD + PDA
  - Truncus arteriosus.

Symptoms and Signs of Heart Failure

General

- Feeding difficulty
- Tachypnea, breathlessness is the major feature of heart failure
- Respiratory distress
- Excessive weight gain
- Hepatomegaly
- Fine crepitations on chest auscultation.

Cardiovascular

- Sweating
- Tachycardia
- Hyperdynamic precordium
- Heart murmur and gallop rhythm
- Cardiomegaly and increased pulmonary vascularity on CXR
- Mottled, clammy, cool skin
- Poor peripheral perfusion
- Acidosis and shock
- Collapse and death (if ductal patency is not maintained).

Management

Acute Heart Failure

- Resuscitate, as appropriate
- Consider commencing a prostaglandin infusion even before an exact diagnosis has been made, if there is suspicion of a duct-dependent lesion
- Preload reduction by furosemide IV 1 mg/kg, 6–12 hourly
- Correct anemia, if present
- Maintain adequate oxygenation
- Fluid restriction to two-thirds of maintenance, if PDA
- Consider inotropes, if there is evidence of myocardial dysfunction
- Reduction after load with an (angiotensin-converting enzyme) ACE inhibitor
- Discuss with a cardiologist early, if cause unknown.

Inotropes: Augmenting contractility by inotropic drugs like digitalis improves cardiac output. In infants and children, only digoxin is used. It has a rapid onset of action and is eliminated quickly. It is available for oral and parenteral administration. Digoxin dose is 0.04 mg/kg followed by maintenance of one-fourth fraction of digitalizing dose.

Digitalis is used with caution in the following situations:

- Premature neonates
- CCF due to myocarditis

- Intensely cyanotic patients
- CCF associated with a large heart.

Patient receiving combined treatment with digoxin and frusemide should preferably receive PO potassium chloride 1–2 mEq/kg/day in divided doses.

Correcting the Underlying Cause

Last, but not the least, correction of the underlying cause has the biggest impact on survival. As treatment is initiated, it is important to obtain the basic information required to identify the cause of CCF. The approach should be systematic. Noninvasive tests (especially echocardiography) allow identification of the cause in virtually all children with suspected heart disease, catheterization with angiocardiography is seldom necessary.

NEONATAL SURGICAL CONDITIONS

DUODENAL ATRESIA

Etiopathogenesis

- A congenital discontinuity of duodenum in the region of ampulla of Vater
- Incidence: 1 in 6,000 live births
- More commonly associated with Down's syndrome (30%).

Clinical Features

- Antenatal history of polyhydramnios
- Look for facial dysmorphism of Down's syndrome and other anomalies of trisomy 21
- Bilious vomiting within hours of birth
- Distended stomach and duodenum
- Visible gastric peristalsis.

Investigations

- X-ray abdomen: Double bubble sign of gas distending stomach and duodenal (Fig. 148)
- Biochemical test: Serum electrolytes, karyotype study, if signs of trisomy 21.

Management

- Stop enteral feeding and start IV maintenance
- Insert NG tube, aspirate hourly
- Correction of electrolyte and acid base disturbance.

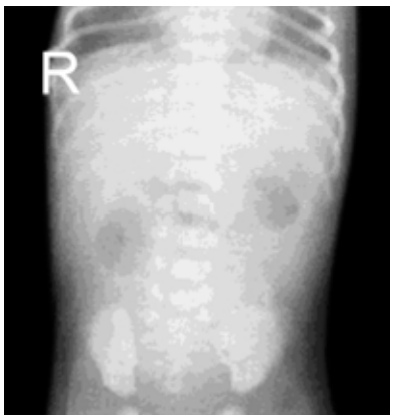


Fig. 148: Double bubble shadow on plain X-ray abdomen in duodenal atresia

Surgical Management

Early definitive surgical treatment is required by anastomosis of healthy duodenal segment.

Prognosis

Usually good, unless not associated with other medical problems.

SMALL BOWEL ATRESIAS (JEJUNAL AND ILEAL ATRESIA)

Vascular cause: Intrauterine mesenteric infarction and subsequent absorption of a segment of bowel to leave a small bowel atresia (Fig. 149).

Clinical Features

- Bile stained vomiting, shortly after birth
- Abdominal distension.

Investigations

- *Plain X-ray abdomen*: Multiple fluid level with dilated bowel loops. Peritoneal calcification may be present (Fig. 150).
- *Biochemical test*: Serum immunoreactive trypsin (IRT) at birth and sweat test at appropriate age to exclude CF as 15% of CF present as meconium ileus, which mimics small bowel atresia.

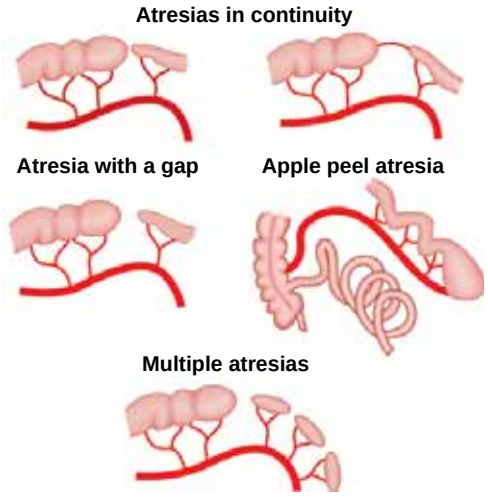


Fig. 149: Types of small bowel atresia

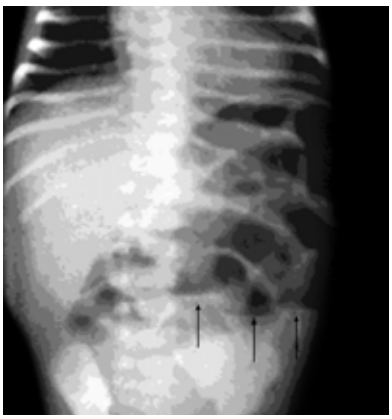


Fig. 150: Plain X-ray abdomen showing multiple dilated bowel loops with fluid level in ileal atresia

Management Surgical

Same as duodenal atresia. End-to-end anastomosis.

Prognosis

Depends on length of the remaining small bowel. May develop short gut syndrome with malabsorption syndrome.

MALROTATION AND VOLVULUS (FIGS 151A TO C)

Definition

Malrotation is the congenital malposition of bowel resulting from the failure of normal rotation during embryogenesis that predisposes to volvulus.

Volvulus is the twisting of the bowel and its mesentery which obstruct blood flow and results in infraction of bowel.

Epidemiology

- More common in males than females
- Other anomalies, like diaphragmatic hernia, Hirschprung's disease, etc. may coexist.

Clinical Features

Presents commonly in first month of life with:

- Bile stained vomiting
- Abdominal distension
- Rectal bleeding
- Circulatory collapse.

Investigations

Plain X-ray Abdomen

- May appear similar to duodenal atresia with a double bubble sign and absence of gas elsewhere in the abdomen
- Upper GI contrast study: It confirms the diagnosis showing contrast material in duodenum failing to cross the midline of abdomen
- If there is a volvulus, contrast is obstructed and forms a cork's screw pattern.

Management

- Resuscitation, as appropriate.
- Immediate laparotomy to untwist the volvulus and resection of nonviable bowel.

Prognosis

- Frequently, there is a massive intestinal necrosis and the child may be left with short gut.

ANORECTAL ANOMALIES

Introduction

Anorectal anomalies consist of wide range of defects with variable severity.

Epidemiology

- Incidence: 1 in 5,000 live births
- About a half will have another anomaly
- Vertebral, anal, cardiac tracheal, esophageal, renal, limb (VACTERL) association consists of genitourinary, skeletal and GI defect, in association with anorectal anomaly.

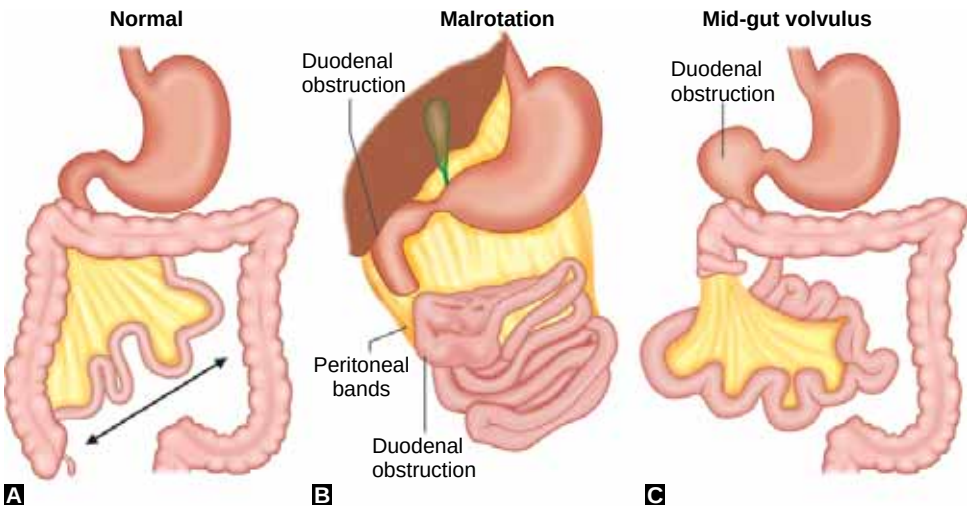
Types

Low Variety

- Rectum terminates close to perineal skin
- Imperforate anus, rectal stenosis
- Anterior anus in girls.

High Variety

- Rectum terminates in pelvis
- Anal stenosis, anal membrane, perineal fistula, rectourethral fistula in boys, retrovestibular in girls, retrovesicular fistula, cloacal malformations.



Figs 151A to C: Diagrammatic picture of malrotation and volvulus: (A): Broad stable base. Cecum in RIF and duodenojejunal flexure to left of midline (B): Cecum lying to the left of the duodenal and the peritoneal bands crossing anterior to the duodenal which predisposes to volvulus of midgut; (C): Volvulus around the base of midgut causes bowel obstruction and infarction of the midgut

Examination

In Male (Fig. 152)

- No anal opening
- Opening on perineum
- Meconium may be seen running subcutaneously along the raphe of midline.

In Female

- Anterior anus most common presentation
- Rectovestibular fistula.

Various types of anorectal malformation in females are shown in Figure 153.

Investigations

X-ray pelvis in lateral prone

- Taken 24 hours of birth with pelvis tilted up and radiopaque marker placed over anal dimple. It reveals the position of rectal gas. Short distance between rectal gas shadow and anal maker reflex low variety while long distance suggests high variety of anorectal anomaly (Figs 154 and 155).

Management

Low Variety

Anal dilatation followed by anoplasty in newborn period.

High Variety

- Initial defunctioning colostomy proximal to the defect.
- Definitive surgical intervention few months later with posterior sagital anorectoplasty.

Prognosis

Constipation

Constipation with fecal incontinence, particularly in high variety.

HIRSCHSPRUNG'S DISEASE

Introduction

Hirschsprung's disease is a congenital disease of distal bowel, where bowel obstruction requiring surgery occurs due to congenital absence of involved bowel innervation.

Pathology

Congenital absence of ganglion cells in the rectal mucosa, extending proximally, resulting in the absence of coordinated bowel peristalsis and functional intestinal obstruction.

Pathogenesis

Failure of migration of neural crest cells down the gut during embryogenesis.

Type—According to Length Affected

- Short segment disease (7%): Rectal and sigmoid colon
- Intermediate segment disease (15%): Extend up to transverse colon
- Long segment disease (8–10%): Enter colon and terminal part of ileum.

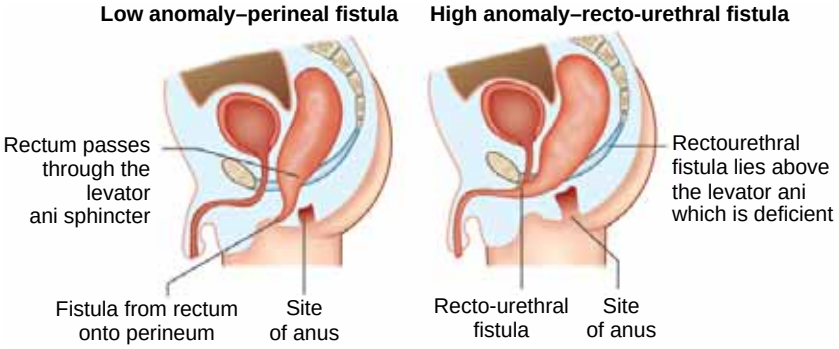


Fig. 152: Male anorectal malformations

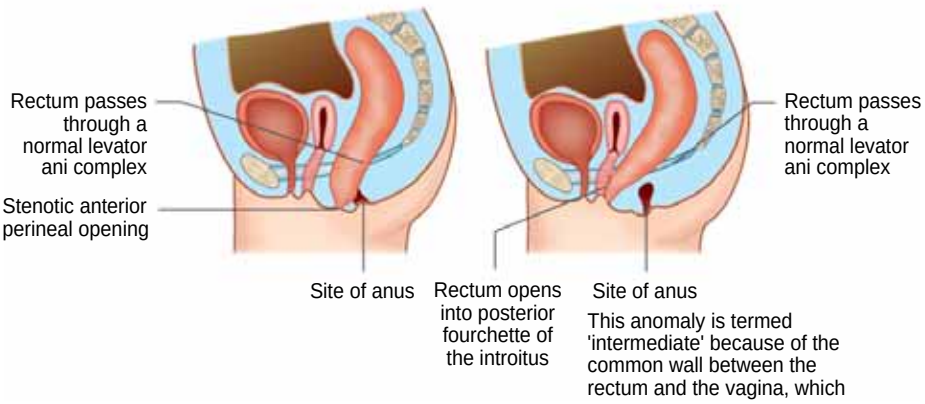


Fig. 153: Female anorectal malformations

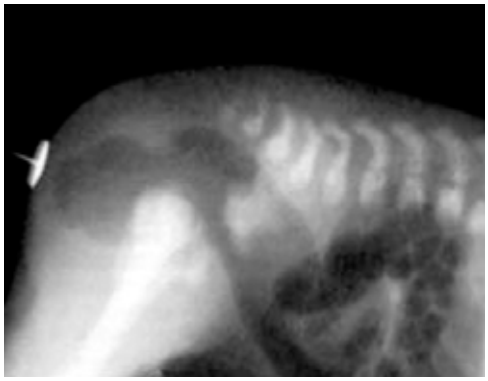


Fig. 154: Lateral prone X-ray of a newborn showing low variety anorectal anomaly. *Note* the short distance between rectal gas shadow an anal marker

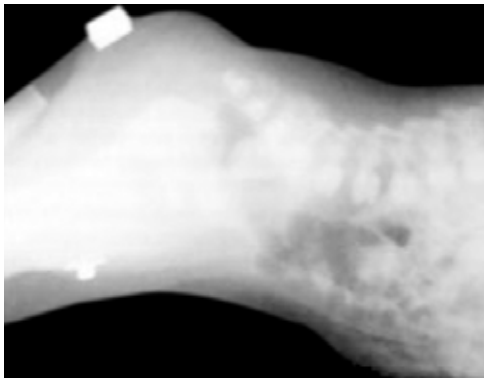


Fig. 155: Lateral prone X-ray of a newborn showing high variety anorectal anomaly. *Note* the long distance between rectal gas shadow an anal marker

Epidemiology

Incidence

- 1 in 5,000 live births
- Male to female (M:F) ratio: 4:1
- Associated with Down's syndrome, Warrensburg's syndrome.

Clinical Features (Typical)

- Delayed passage of meconium (>48 hours in term babies)
- Progressive abdominal distension (Fig. 156)
- Bilious vomiting
- Poor feeding.

Rectal Examination

Rectal examination shows contracted anorectum with explosive passage of stool and flatus.

Investigations

Plain X-ray Abdomen (Fig. 157)

- Multiple dilated bowel loops.
- Absence of rectal gas.
- If enterocolitis: Bowel wall thickening, mucosal irregularity with fluid levels.
- Contrast study: Transition zone with proximal dilatation (Fig. 158).

Fig. 156: Gross abdominal distension in a two-month-old infant with Hirschsprung's disease

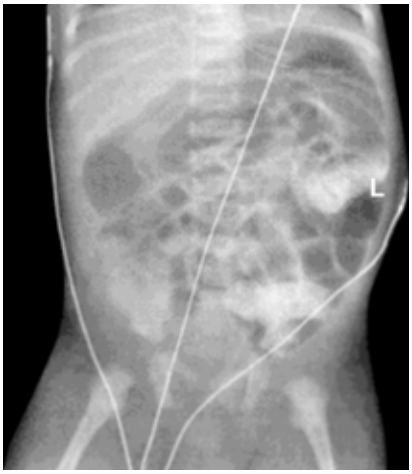


Fig. 157: Plain X-ray abdomen showing distended bowel loops with absence of air in rectum

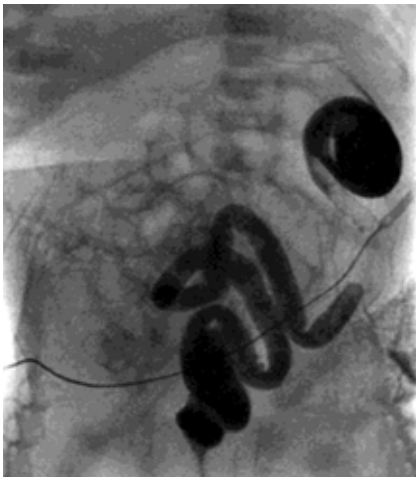


Fig. 158: Contrast study showing transition zone and proximally dilated bowel

Suction Rectal Biopsy

Site of biopsy is 2 cm above anal canal. No ganglion cell in submucosal.

Anorectal Manometry

Rarely used, shows raised rectal resting pressure.

Management

Three-stage Surgery

- Initial defunctioning colostomy with multiple biopsies to confirm the site of transition zone

- Pull through operation to bring healthy bowel down to anus
- Closure of colostomy.

Single-stage Surgery

Many surgeons now perform a single pull through operation during neonatal period with rectal washout.

Prognosis

- 75% will achieve good bowel control by adulthood
- Complications, which may occur, include fecal incontinence, constipation and enterocolitis.
- Associated with Down's syndrome may have protracted course.

ANTERIOR ABDOMINAL WALL DEFECTS

Gastrochisis

Abdominal viscera, including stomach, small bowel, colon, ovaries/testis prolapse through a congenital defect on the right side of umbilicus.

Epidemiology and Pathogenesis

- Incidence of 1 in 7,000 live births
- Occurs equally in males and females
- Association with young maternal age
- The bowel is eviscerated and not covered by a sac (Fig. 159).

Clinical Features

- Most cases are identified by antenatal USD
- There is no sac covering the gut
- Appearance varies with normal looking gut to be covered in thick fibrin like shell.

Management

Immediate:

- Cover the exposed bowel with cellophane or preformed plastic sheath
- Insert NG tube, aspirate frequently and leave on free drainage
- Nothing by mouth.
- Start IV maintenance
- Start IV antibiotic
- Monitor and correct dyselectrolytemia.

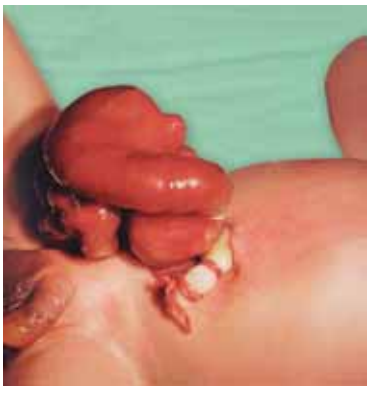


Fig. 159: Gastrochisis showing prolapsed bowel with no covering sac

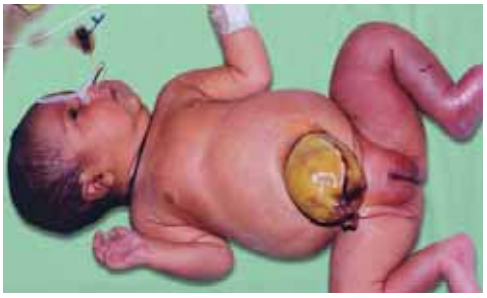


Fig. 160: Exomphalos showing prolapse of gut within an amniotic sac

Surgery:

The defect requires surgical closure as early as possible.

Outcome

- 90% survival
- Nevcotizing enterocolitis (NEC) as a complication.

Exomphalos (Omphalocele)

It is a congenital umbilical defect with prolapse of gut within an amniotic sac outside the abdominal cavity (Fig. 160).

Epidemiology

- Incidence: 1 in 5,000 live births
- Occurs equally in males and females
- Associated condition:
  - Beckwith-Wiedemann syndrome
  - Trisomy 13, 18 and 21
  - 40% will have other congenital defect.

Two types of exomphalos depending of size.

1. Exomphalos major: defect more than 5 cm diameter
2. Exomphalos mino: Defect less than 5 mm diameter.

Management

- Nothing by mouth
- Insert NG tube
- IV infusion
- Monitor blood glucose for hypoglycemia associated with Beckwith-Wiedemann syndrome
- Upper GI contrast study
- Echocardiography and karyotype.

Surgical Treatment

Closure of the defect in one or more steps.

Prognosis

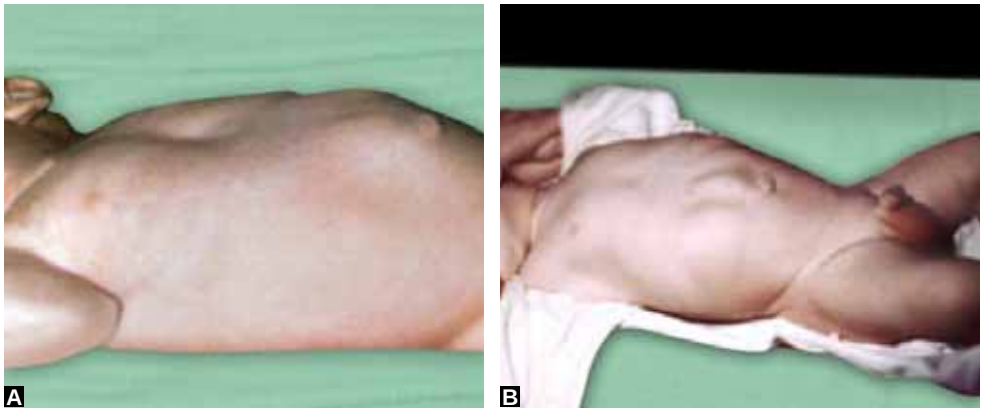
Prognosis depends on associated malformations.

Idiopathic Hypertrophic Pyloric Stenosis (Figs 161A and B)

Epidemiology and Pathophysiology

Incidence: 3 in 1,000 live births, more in weight in dark skin race.

- Boys are more commonly affected then girls, M:F ratio is more than 4:1



Figs 161A and B: (A) Visible mass (frequently better felt) of idiopathic hypertrophic pyloric stenosis; (B) Visible peristalsis seen in idiopathic hypertrophic pyloric stenosis

- Hypertrophy of circular muscle pylorus, which feels like tumor
- The cause remains unknown
- Genetic predisposition may run in families
- Triggering factor: Prokinetic, like erythromycin, is a triggering factor.

Clinical Features

- Presents between 3–8 weeks of age
- Projectile nonbilious vomiting, following feed
- Characteristically hungry after feed
- Constipation
- Visual peristalsis from left to right
- Unconjugated hyperbilirubinemia
- Dehydration, malnutrition (wasting)
- Hypochloremic, hypokalemic metabolic alkalosis.

Diagnosis

Test feed:

- Palpation of right upper quadrant of abdomen reveals an olive like tumor after feed (Fig. 162)
- Visible peristalsis may become more obvious after feed
- USD: Confirmed by ultrasonogram of abdomen. Occasionally barium meal
- Blood gas and serum electrolytes: Hypochloremic, hypokalemic alkalosis (decreased pH, Cl^-, K^+, increased HCO_3)
- Urine analysis: Inspite of metabolic alkalosis, there will be paradoxical aciduria with decreased urine pH (Figs 163A and B).

Management

- Stop oral feeding and start IV infusion
- Rehydrate and correct the alkalosis before surgery
- IV fluid should be started: 0.45% saline with 5% dextrose and 20 mmol/L potassium chloride at 120 mL/kg/day
- Surgical treatment with Ramstedt's pyloromyotomy (Fig. 164)
- Postoperatively, feeding is reintroduced within 24 hours, despite transient vomiting.

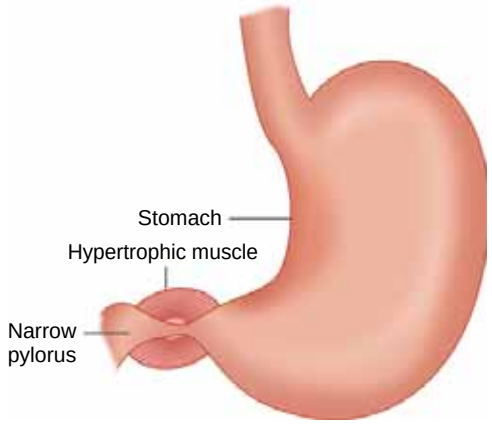
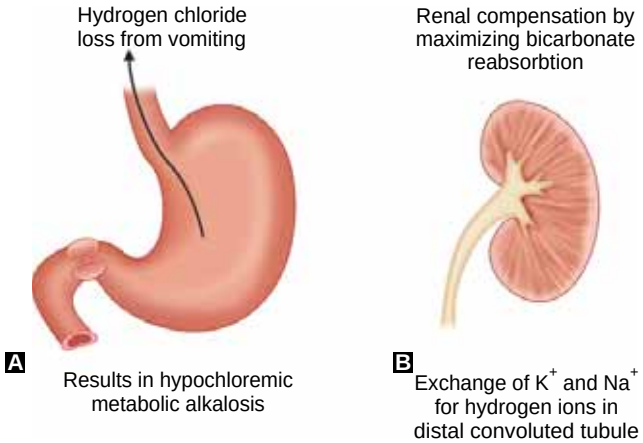


Fig. 162: Gross pathology of hypertrophic pyloric stenosis



Figs 163A and B: Mechanism of (A) hypochloremic, hypokalemic metabolic alkalosis and (B) paradoxical aciduria

Fig. 164: Ramstedt's operation

SOME USEFUL DRUGS USED IN NEONATOLOGY

(See also Therapeutic Medicine Chapter)

EMERGENCY DRUGS

Digoxin

Oral Dose

- Neonate under 1.5 kg: initially 25 µg/kg in three divided doses for 24 hours, then 4–6 µg/kg daily in 1–2 divided doses
- Neonate, 1.5–2.5 kg: Initially 30 µg /kg in three divided doses for 24 hours, then 4–6 µg /kg daily in 1–2 divided doses
- Neonate over 2.5 kg: Initially 45 µg /kg in three divided doses for 24 hours, then 10 µg /kg daily in 1–2 divided doses
- Child, 1 month to 2 years: Initially 10 µg /kg in three divided doses for 24 hours, then 10 µg /kg daily in 1–2 divided doses
- Child, 2–5 years: Initially 35 µg/kg in three divided doses for 24 hours, then 10 µg /kg daily in 1–2 divided doses
- Child, 5–10 years: Initially 25 µg/kg in three divided doses for 24 hours, then 6 µg/kg daily in 1–2 divided doses
- Child, 10–18 years: Initially 0.75–1.5 mg in three divided doses for 24 hours, then 62.5–250 µg/kg daily in 1–2 divided doses.

Digoxin—by Intravenous Infusion—Used in Acute Condition

- Neonate under 1.5 kg: initially 20 µg/kg in three divided doses for 24 hours, then 4–6 µg/kg daily in 1–2 divided doses
- Neonate, 1.5–2.5 kg: Initially 30 µg/kg in three divided doses for 24 hours, then 4–6 µg/kg daily in 1–2 divided doses
- Neonate, over 2.5 kg: Initially 35 µg/kg in three divided doses for 24 hours, then 10 µg/kg daily in 1–2 divided doses
- Child, 1 month to 2 years: Initially 35 µg/kg in three divided doses for 24 hours, then 10 µg/kg daily in 1–2 divided doses
- Child, 2–5 years: Initially 35 µg/kg in three divided doses for 24 hours, then 10 µg/kg daily in 1–2 divided doses
- Child, 5–10 years: Initially 25 µg/kg (maximum 500 µg) in three divided doses for 24 hours, then 6 µg/kg (maximum 250 µg daily) in 1–2 divided doses
- Child, 10–18 years: Initially 0.5–1 mg in three divided doses for 24 hours, then 62.5–250 µg/kg daily in 1–2 divided doses (higher doses may be necessary).

Administration: For IV infusion, dilute with 0.9% NaCl solution or 5% glucose, loading doses should be given over 30–60 minutes and maintenance doses over 10–20 minutes.
Source: Paediatric Formulary Committee. BNF for children 2010–2011. London: Pharmaceutical Press; 2010.

Adrenaline (Epinephrine)

Presentation: 1 mg/mL (1:1000 concentration).

Uses: As a part of newborn resuscitation, cardiopulmonary resuscitation.

Dosage: 0.1–0.3 mL/kg/dose of 1:10,000 dilution, repeat every 3–5 minutes, if necessary.

Route: IV or endotracheal route.

Direction for use: Take 0.1 mL in bacillus Calmette-Guérin (BCG) syringe. Dilute with 0.9 mL distil water (10 × dilution). The resultant concentration is 1:10,000 solution.

Dopamine Hydrochloride

Presentation: 40 mg/mL.

Uses:

- Cardiovascular shock
- Septic shock (shock with peripheral vasodilatation)
- Decreased cardiac output and vasoconstriction
- To promote urinary output in oliguric phase in acute renal failure (low dose)
- To correct the hemodynamic imbalance due to acute hypotension.

Dosage: Dose dependent activation of adrenergic and dopaminergic receptors.

- Neonates: Initially 3 µg/kg/min, adjusted according to response (maximum 20 µg/kg/min)
- Child, 1 month to 18 years: Initially 5 µg/kg/min, adjusted with according to response (maximum 20 µg/kg/min).

Actions:

- At low dose (0.5–3 µg/kg/min): Activates dopaminergic receptors in renal, mesenteric and cerebral circulation, and increases blood flow
- Dose of 3–7.5 µg/kg/min: Stimulates receptors in heart and peripheral circulation that increases cardiac output
- Dose greater than 7.5 µg/kg/min: Stimulates receptors in systemic and pulmonary circulation and causes vasoconstriction.

Route: IV infusion. Neonatal intensive care, dilute 30 mg/kg body weight to a final volume of 50 mL with infusion fluid; an IV infusion rate of 0.3 mL/h provides a dose of 3 µg/kg/min.

Dobutamine

Presentation: Strong sterile solution, containing dobutamine (as hydrochloride) 12.5 mg/mL, available in 5 mL and 20 mL ampule.

Uses: Inotropic support in low cardiac output states, after cardiac surgery, cardiomyopathies, septic shock and multiple organ failure, systolic dysfunction (not to use in diastolic dysfunction).

Dosage

- Neonate: Initially 5 µg/kg/min, adjusted according to response to 2–15 µg/kg/min (maximum 20 µg/kg/min)
- Children: 1 month to 18 years: Initially 5 µg/kg/min, adjusted according to response to 2–20 µg/kg/min.

Action: Causes dose dependent actions:

- Increase in stroke volume with decreased cardiac filing pressure
- Proportionate decrease in systemic vascular resistance, so blood pressure remains same.

Route: IV and for continuous IV infusion. Neonatal intensive care, dilute 30 µg/kg body weight to a final volume of 50 mL with infusion fluid; IV infusion rate of 0.5 mL/hr provides a dose of 5 µg/kg/min.

Furosemide

Presentation: Injection 20 mg/2 mL ampicillin. Tablet: 40 mg

Uses: To reduce preload and causes diuresis.

Action: Pulmonary venous vasodilatation and diuresis and reduce preload.

Route: IV, oral.

Dosage: IV: 0.5–1 mg/kg/dose.
Oral: Up to 2 mg/kg/dose.

Aminophylline

Presentation: Injection 250 mg in 10 mL ampoules

Uses: Apnea.

↓

Neonatal

Dosage: Loading dose: 0 5–5 mg/kg/IV.

Maintenance: 1–2 mg/kg/dose 8 hourly.

Continuous IV infusion: 0.5–1 mg/kg/hr.

Route: IV/oral.

Direction for use: Take 0.1 mL of solution in 1 mL syringe. Dilute with 0.9 mL of water to make 1 mL for injection. Resultant concentration is 2.5 mg/mL; administration over 20 minutes.

Compatible: 5% dextrose, normal saline.

Incompatible: Sodium bicarbonate.

Caution: Never use IM route.

Calcium Gluconate

Presentation: 9 mg/mL.

Uses: Treatment of low blood calcium level.

Dosage: 1–2 mL/kg/dose every 6–8 hourly.

Route: IV route (infusion or bolus)

Directions of use: To be diluted in equal amount of distilled water.

- Inject very slowly while monitoring heart rate. If there is bradycardia, discontinue the injection
- Take care to avoid extravasation, if being given as infusion, as it may cause sloughing of skin.

Prostaglandin

Presentation: 500 µg/mL.

Uses: Maintaining patency of the ductus arteriosus in duct dependent cardiac lesions.

Dosage: By continuous IV infusion. Neonates initially 5 ng/kg/min (0.005 µg/kg/min), adjusted according to response in steps of 5 ng/kg/min, maximum 100 ng/kg/min.

Action: Vasodilatory action.

Side-effects: Apnea, particularly in neonates less than 2 kg. It is dose related cutaneous vasodilatation, hypotension, jitteriness, flushing, bradycardia, tachycardia, cardiac arrest, edema, diarrhea, fever, convulsion, DIC, hypokalemia, gastric outlet obstruction due to antral hypertrophy, respiratory depression.

Indometacin

Indication: Medical closure of patent ductus arteriosus within 2 weeks of birth.
Mechanism of action: Inhibition of prostaglandin synthesis.
Route: IV infusion over 20–30 minutes (orally when IV preparation not available).
Dosages: Neonate under 48 hours: Initially 200 µg/kg as a single dose followed by (if urine output adequate) two doses of 100 µg/kg at interval of 12–24 hours. Course may be repeated after 48 hours, if necessary.

- Neonate 2–7 days: Initially 200 µg/kg as a single dose followed by (if urine output adequate) two doses of 200 µg/kg at interval of 12–24 hours; course may be repeated after 48 hours, if necessary
- Neonate over 7 days: Initially 200 µg/kg as a single dose followed by (if urine output adequate) two doses of 250 µg/kg at interval of 12–24 hours; course may be repeated after 48 hours, if necessary.

Side-effects: Focal ischemic gut, perforation and GI hemorrhage, renal failure.

Phenobarbitone

Presentation:

- Injection: 200 mg/mL.
- Tablet: 30 mg, 60 mg.
- Syrup: 20 mg/5 mL.

Uses: Neonatal convulsion, all forms of epilepsy, except absence seizures.

Dosage: 20 mg/kg/IV slowly over a period of 20 minutes. If seizure is not controlled after this loading dose, repeat dose of injection phenobarbitone 10 mg/kg/IV every 20–30 minutes till a dose of 40 mg/kg is reached.

Maintenance dose: 2.5 to 5 mg/kg once or twice daily, IV or orally.

Side-effects: Respiratory depression, hypotension, bradycardia, drowsiness, lethargy.

Phenytoin

Presentation:

- 100 mg/2 mL (phenytoin), 150 mg/2 mL (fosphenytoin)
- Suspension: 30 mg/5 mL
- Fosphenytoin is a prodrug of phenytoin.

Uses: Neonatal convulsion, all forms of epilepsy except absence seizures. Effective for tonic-clonic, partial and neonatal seizures, but it may worsen myoclonus.

Dosage: 20 mg/kg/IV loading dose diluted in neonatal saline, slow infusion over 20–30 minutes. Maintenance dose 2.5–5mg/kg, twice daily.

Side-effects: Coarse facies, acne, hirsuitism and gingival hyperplasia.

Diazepam
(For Detail See Therapeutic Medicine Chapter)

Presentation:

- Tablet: 5 mg
- Injection: 10 mg/2 mL
- Suppository: 10 mg.

Uses: Status epilepticus, febrile convulsion, convulsions caused by poisoning.

Dosage: IV injection (given with caution):

- Neonate: 300–400 µg/kg repeated after 10 minutes, if necessary
- Child: 1 month to 12 years: Same dose
- Per-rectum: 1.25–2.5 mg repeated once in 10 minutes, if necessary (neonate)
- Per rectal: 0.5 mg/kg, then 0.25 mg/kg in 10 minutes, if needed
- Sedation: Oral: 0.2–0.3 mg/kg (maximum 10 mg).

Side-effects:

- Apnea, kernicterus (in neonates)
- Hypotension, bradycardia, cardiac arrest (with IV dose), drowsiness, ataxia, confusion, blurred vision, diplopia, sweating, dry mouth, increased or decreased appetite, physical and psychological dependence.

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2 Clinical Genetics

HUMAN GENOME PROJECT

Genetics is the study of heredity. It is the study of genome and its functions that seeks to understand the structure and function of the entire genetic complement of an organism based on the knowledge of the organism's entire DNA sequence.

The human genome project, culminating the first publication of the human genome sequence, in 2001, together with the development of genetic databases, has resulted in an explosion of knowledge about the basis of genetic diseases. It is now estimated that the human genome contains 30,000–35,000 genes, although the function of many of these genes remains unknown. Clinical application of these advances is available to families through specialized genetic centers that offer diagnosis, investigation, counseling and antenatal diagnosis for an ever widening range of disorders (Fig. 1).

Gene therapy trials are also underway, bringing hope of improved treatment in the future.

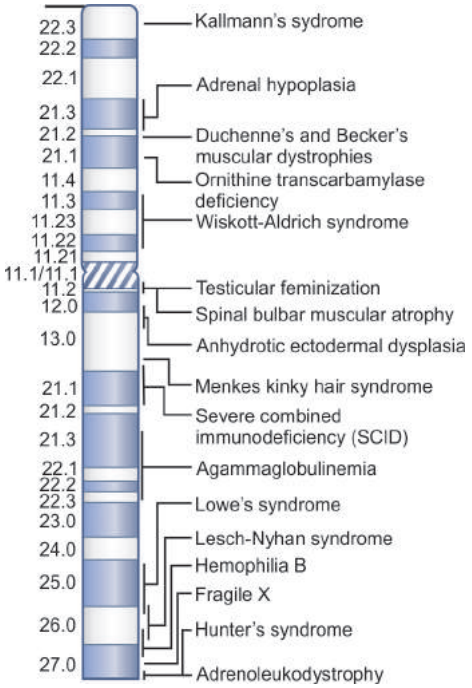


Fig. 1: Structure of a gene showing genes responsible for different diseases

GENETIC COUNSELING

What is Genetic Counseling?

It is the process through which a person, who is likely to acquire or transmit a genetic disorder, is told about the nature of genetic disorder and the probability of acquiring or transmitting the disorders to his/her offspring, and the way by which he/she can ameliorate the disease.

GENETIC DISORDERS

Genetic disorders are classified as:

- Single mutant genes disorder (Mendelian inheritance):
  - Recessive
  - Dominant
  - X-linked
- Chromosomal disorder
- Multifactorial diseases.

Genetic disorders are:

- Common with 2% of live-born babies having a significant congenital malformation and about 5% a genetic disorder
- Burdensome to the affected individual, family and society, as many are associated with severe and permanent disability.

Autosomal Recessive Inheritance

Characteristics of Autosomal Recessive Inheritance

- The disease characteristically appears only in siblings, the parents and other relative are normal

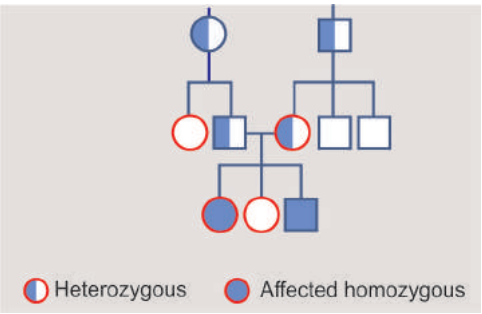


Fig. 2: Pedigree of autosomal recessive disorders

- The risk of affected person is 1 in 4 or 25%
- Consanguinity is more likely in rare recessive disorders. In the more common conditions, parents are usually unrelated
- Both sexes are affected
- Generally, autosomal recessive (AR) mutation affects enzyme synthesis, leading to inborn error of metabolism and neurometabolic disorders
- A classical pedigree is shown in Figure 2.

Examples of AR diseases are:

- Congenital adrenal hyperplasia
- Cystic fibrosis (CF)
- Friedreich's ataxia

- Galactosemia
- Glycogen storage diseases
- Hurler's syndrome
- Oculocutaneous albinism
- Phenylketonuria (PKU)
- Sickle cell disease
- Tay-Sachs disease
- Thalassemia
- Werdnig-Hoffmann disease [spinal muscular atrophy (SMA) type I].

If individual carries a few abnormal genes, the possibility of marrying someone carrying the same abnormal gene is considerably increased by marrying a relative, particularly first cousin. This is due to the first cousin share one-eighth of their genome with each other.

How to calculate the probability of acquiring the disease from genetic pedigree in autosomal recessive inheritance?

- Carrier state of an AR disorder in a population can be obtained from the disease incidence in the community
- If marriage is nonconsanguineous, the risk of the spouse carrying the same gene depends on the frequency of that gene in the population, and the carrier frequency can be obtained from square root of incidence of the disease in the community from the formula: $2 \times 1/\sqrt{\text{incidence}}$. For example, if incidence of cystic fibrosis (CF) is 1 in 2,500, in a country, then the carrier frequency is $2 \times 1/\sqrt{2500} = 1/25$, i.e. 1 per 25 person in the population is a carrier of CF
- On the other hand, if the carrier state is known, then the probability of having a diseased child can also be obtained. For example, the chance of a person of CF to marry another CF carrier is 1 in 25, and as per characteristics of AR, the chance of a diseased child is 1 in 4. Therefore, the overall probability is $1/25 \times 1/25 \times 1/4$, i.e. 1 in 2,500
- Parents of the affected child have one chance (instead of 1 in 25 or 1/25) of inheriting the gene (Fig. 3, B1 and B4)
- Grandparents, uncles/aunts of affected child have half a chance of inheriting the gene (Fig. 3, A1 and A2, and B2 and B5)
- The other siblings of diagnosed child (affected child) have two-thirds chance of carrying the mutant genes (Fig. 3, C2)
- The affected child obtains two for carrier gene (Fig. 3, C1)
- First cousin of affected child has one-fourth risk of carrying the gene (Fig. 3, D1)

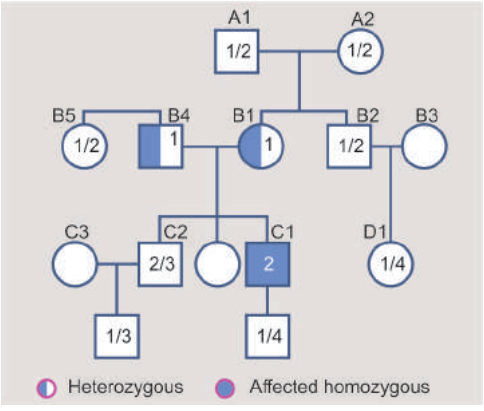


Fig. 3: Pedigree of autosomal recessive disorder. Risk of carrier frequency are given inside the circle (female) and in the box (male)

- The carrier state of inheritance of the gene is shown in Figure 3.

Data Interpretation

In Figure 3, if B2, who caries half chance of inheriting the genes, marries an unrelated woman (whose likely frequency of inheriting a genetic disease like CF is 1 in 25), then the likelihood of having an abnormal child is $1/2 \times 1/25 \times 1/4 = 1/200$, which is high in comparison to normal incidence of the disease (CF) of 1 in 2,500.

If sibling of affected child like C2 (carrier, 2/3) marries his first cousin D1 (carrier, 1/4) then the likelihood of having affected offspring is even higher, i.e. $2/3 \times 1/4 \times 1/4 = 1/24$.

However, if the cousins marriage occur, when the index individuals are not siblings of affected child, then chances of having affected child is relatively lower, i.e. if D1 marries offspring of B4 and B5 (not shown in the figure) then the chance of affected child is $1/4 \times 1/4 \times 1/4 = 1/64$.

When parents do not come of a genetic disease family, or such condition is not known in the family, and if they happen to be the first cousin, then the carrier rate is higher then the normal population (carrier, 1/8). This is because first cousin shares one-eighth of the total genetic complement.

The chance of inheriting the AR disorder from the affected family should also be interpreted on the basis of practicability, depending on severity, longevity and organ involved from disease. For example, if the affected child with CF in the pedigree carrying carrier frequency of two marries unrelated woman, then the probability of having an abnormal child is $2 \times 1/25 \times 1/4 = 1/50$. However, a male child with CF frequently has azoospermia and cannot produce child. Therefore, the probability of having such an affected child does not arise.

Autosomal Dominant Inheritance

Characteristics of Autosomal Dominant (AD) Inheritance

- Usually milder than the recessive, but more frequent than recessive
- Usually involves structural or nonenzymatic proteins like connective tissue disorders, such as Marfan syndrome
- Each child of either sex born to one of the affected parent has fifty-fifty chance or half chance of inheriting the gene
- There may be clinical variation in the affected offspring
- Homozygotes for the dominant gene usually die prenatally as in the case of achondroplasia
- Normally, an affected person has affected parents with an exception of new mutation
- Both sexes are affected and there may be considerable variation in the clinical severity of the disease

Examples of AD diseases are:

- Achondroplasia (Fig. 4)
- Ehlers-Danlos syndrome
- Familial hypercholesterolemia
- Huntington's disease
- Marfan's syndrome
- Myotonic dystrophy
- Neurofibromatosis
- Noonan's syndrome
- Osteogenesis imperfecta
- Otosclerosis

Fig. 4: A 10-year-old child with achondroplasia and her phenotypically normal parents. An example of autosomal dominant condition with new mutation

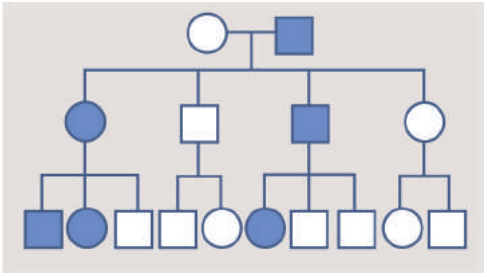


Fig. 5: Pedigree of autosomal dominant diseases

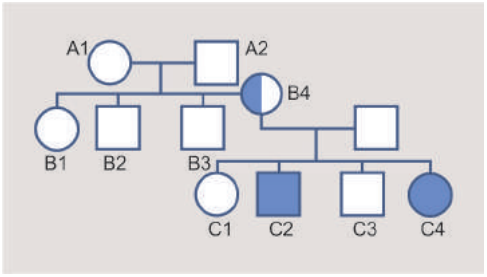


Fig. 6: An affected female (B4), whose parents (A1, A2) are phenotypically normal; an example of spontaneous mutation. Offspring of B4 are affected, one male (C2) and one female (C4) characteristics of autosomal dominant inheritance. Although mother was affected by spontaneous mutation, she had transmitted the disease in autosomal dominant fashion affecting the 50% of her children, and affecting both male and female offspring equally. This is typically seen in achondroplasia

- Polyposis coli
- Tuberous sclerosis.

The pedigree of AD disease is shown in Figure 5. The Figure 6 shows the pedigree of AD inheritance with new mutation.

X-linked Recessive Inheritance

Characteristics of X-linked Recessive Inheritance

- The trait is normally passed from a carrier female to her male offspring
- Sons have fifty-fifty chance of inheriting the gene and, therefore, developing the disease
- Daughters have a fifty-fifty chance to become a carrier like mother
- An affected male cannot transmit the disease to his sons, but all his daughters will be carrier. However, this applies to X-linked disease, when an affected male can survive into adulthood and capable of reproduction
- Daughters of affected males can pass the disease to their sons

In some X-linked diseases, females may show some clinical evidence of the disease. This is explained by the inactivation of X chromosome just after formation of zygote called Lyon hypothesis, which was proposed by Dr Mary Lyon.

Examples of X-linked recessive inheritance are:

- Hemophilia A and B
- Duchenne's and Becker's muscular dystrophies
- Diabetes insipidus
- Fragile X syndrome
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Hunter's syndrome (mucopolysaccharidosis type II)
- Color blindness (red-green)
- Hypophosphatemic rickets.

In Figure 7, pedigree demonstrates the X-linked recessive inheritance.

X-linked Dominant Inheritance

Characteristics of X-linked Dominant Inheritance

- Diseases are common in females usually, and more severe or lethal in males
- Both sons and daughters have fifty-fifty chance of inheriting the gene from an affected female and, therefore, developing the disease
- An affected male will transmit the disease to all of his daughters but none of his sons.

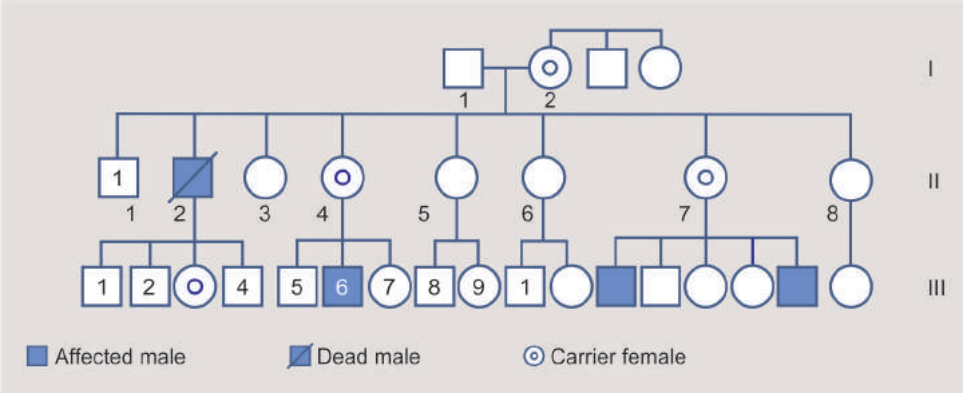


Fig. 7: Pedigree showing X-linked recessive inheritance. Pedigree showing carrier mother (in circle) in first generation (I) On the next generation (II), one affected male (2) and two carrier females (4 and 6). The third generation (III), showing no male to male transmission of the disease (1, 2 and 4), whereas the female child became carrier

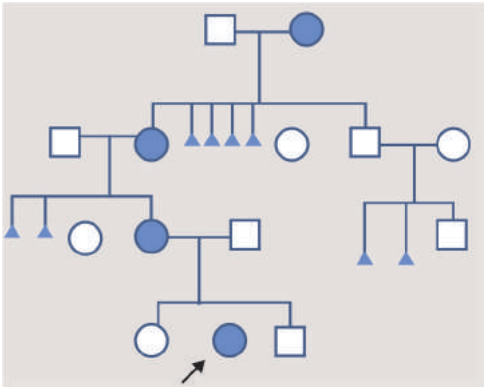


Fig. 8: Pedigree showing X-linked dominant inheritance

Examples of X-linked dominant inheritance are:
- Variant of vitamin D-resistant rickets
- Rett's syndrome
- Incontinentia pigmenti

In Figure 8, pedigree demonstrates X-linked recessive inheritance.

GENETIC TESTING

Clinical Test

Screening Test

Population may be screened for carrier detection or affected status. Neonatal screening is done in some advanced countries for PKU, sickle cell disease.

Diagnostic Test

Diagnostic test is useful for confirmation of a diagnosis suspected on a clinical ground.

Carrier Test

Carrier test is undertaken to determine the risk to offspring, but the result has no implication for the health of the individual.

Predictive Test

Predictive test is undertaken in a normal individual, who is at risk of developing familial disease in future. However, ethical consideration may arise in such condition.

Preimplantation Genetic Diagnosis

In *preimplantation genetic diagnosis (PIGD),* embryos are generated by in vitro fertilization at the 8–16 cell stage, a single cell is removed to test for a specific genetic disorder. Techniques used are:

Karyotyping

A karyotyping is a photomicrograph of an individual's chromosomes arranged in a standard format showing the number, size and shape of each chromosome.

Mutation Analysis

Mutation analysis involves direct analysis of DNA for specific detection of disease is increasingly available. Amplification of the DNA using polymerase chain reaction (PCR) is frequently the first step.

Fluorescent In Situ Hybridization

Fluorescent in situ hybridization (FISH) is the annealing of the specific single stranded DNA probes to complementary sequences in immobilized chromosomes in situ. Because the probes are visualized by labeling the probes with a fluorescent dye, the procedure is termed as FISH. FISH is useful in the detection of microdeletion syndrome, trisomy detection and rapid sexing.

Selected Chromosomal Disorders

Few of the selected chromosomal disorders have been discussed below.

Down's Syndrome

Down's syndrome is the most common and best known human chromosomal disorder. The overall incidence is approximately 1 in 1,000 live births, but markedly varies with increasing maternal age (Table 1).

Causes: Majority (90%) of the babies are born with Down's syndrome usually due to nondisjunction during maternal oogenesis, 2% are as a result of Robertsonian translocation and 2% are mosaic with a normal cell line as well as trisomy cell line.

Clinical features (Figs 9A to E): Usually present at birth with gastrointestinal (GI) system defect, like duodenal atresia, Hirschsprung's disease, trachea esophageal fistula, imperforated anus.

Facial features: A small, low-set ears, upwardslanting eyes, prominent epicanthic folds, brush fields spots apparent in eyelids (white spot in the iris), flat facial profile, small oral cavity with protruding tongue, short nose with depressed nasal bridge, brachycephaly.

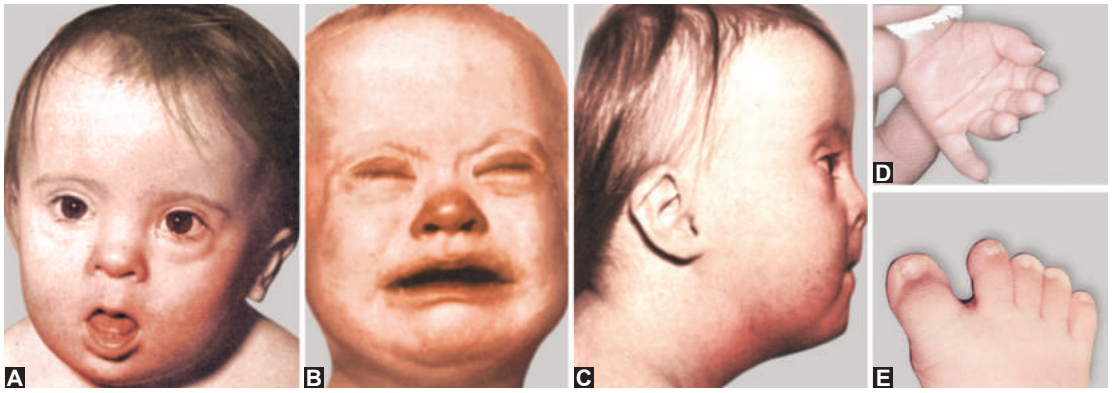
Other features:
- Hypotonia
- Single palmar crease
- Fifth finger clinodactyly.

Associated defects other than gastrointestinal defects:
Cardiac
- 40–50% have congenital heart disease, like endocardial cushion defect, ventricular septal defects (VSD), atrial septal defect (ASD), Fallot's tetralogy and isolated posterior descending artery (PDA)
- About 70% of all endocardial cushion defects are in Down's syndrome patients.

Eyes
- Congenital cataract
- Glaucoma

Table 1: Likely incidence of Down's syndrome with increasing maternal age

Maternal age	Incidence
20	1 in 1,530
30	1 in 900
35	1 in 385
37	1 in 225
40	1 in 109
44	1 in 41



Figs 9A to E: Photograph showing characteristics dysmorphic faces, hand and feet of Down's syndrome: (A) Upslanting eyes, small mouth with protrusion of tongue; (B) Upslanting eyes usually more obvious on crying; (C) Flat face and occiput (brachycephaly sparse hair); (D) Simian crease and clinodactyly of fifth finger; (E) Wide gap between first and second toes

Genitourinary system
- Hypospadias
- Cryptorchidism

Hematological
- Iron deficiency anemia
- Leukemia

Endocrine
- Acquired hypothyroidism
- Deafness: Both sensorineural and conductive

Orthopedic
- Developmental hip dysplasia
- Atlantoaxial dislocation
- Increased risk of infection.

Diagnostic investigation: A clinical diagnosis requires cytogenetic studies, including karyotyping of the infant. In translocated Down's syndrome, parents also need karyotyping.

Fluorescent in situ hybridization test or quantitative fluorescence PCR (QFPCR) may provide rapid diagnosis.

Prenatal screening: Screening is offered to women of all ages.
- A nuchal translucency scan is done at 11–13 weeks of pregnancy
- Maternal serum markers like serum alpha fetoprotein, unconjugated estriol, total human chorionic gonadotropin (hCG) can be measured between 10 weeks and 14 weeks of gestation.

Prenatal diagnostic tests: Diagnostic test should be done in suspected screening population. Initial screening test include:
- Chorionic villus sampling (CVS)
- Amniocentesis after 15 weeks of gestation followed by QFPCR or full karyotyping.

Management:
- Genetic counseling by a pediatrician or better by clinical geneticist, if available, should be offered. Recurrence risk for trisomy 21 is 1% and de novo translocation is 2–3%. For a Robertsonian carrier parent, the theoretical risk of recurrence rate 10–13% for carrier mother and 2–3% in carrier father
- Refer for a detailed cardiac assessment, hip ultrasound and audiology.

Investigation: The investigations include
- Cardiac echo
- Thyroid function test
- Immunoglobulin level
- Ophthalmological examination
- Hearing test.

Medical follow-up:

Central nervous system
- Moderate to severe learning difficulty occurs, but cognitive development is variable.

Psychiatric disorder
- Psychiatric disorder can occur in some children, like autism, attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder and Alzheimer like dementia, may develop early
- Many children need speech and language therapy.

Eye
- Strabismus, blepharitis, cataract should be corrected and annual ophthalmological and audiological evaluation should be done.

Endocrine
- Short stature, obesity, hypothyroidism, diabetes, decreased fertility should be addressed properly.

Skeletal
- Atlantoaxial instability can lead to spinal cord compression and acquired hip dislocation.
- Cervical radiography to detect atlantoaxial instability at 3 years.

Hematological follow-up
- Acute myeloid leukemia is as common as acute lymphoblastic leukemia. Blood should be checked, if suspected.

Respiratory tract ENT
- Obstructive sleep apnea
- Dental problem
- Chronic otitis media
- Hearing loss.

Long-term follow-up should ideally be by a multidisciplinary team led by a pediatrician with special expertise, such as a developmental pediatrician working in a child developmental center. Physiotherapy to improve tone and posture is often required.

Prognosis: Outlook is much improved with better integrity and longevity. Majority can live semi-independently with supervision. Congenital heart disease is the main cause of early mortality.

Alzheimer's like dementia may occur in Down's syndrome.

Edwards Syndrome

Other name of Edwards syndrome is trisomy 18.

Etiology:

- 95% are due to meiotic nondisjunction
- 5% are due to translocation or mosaics.

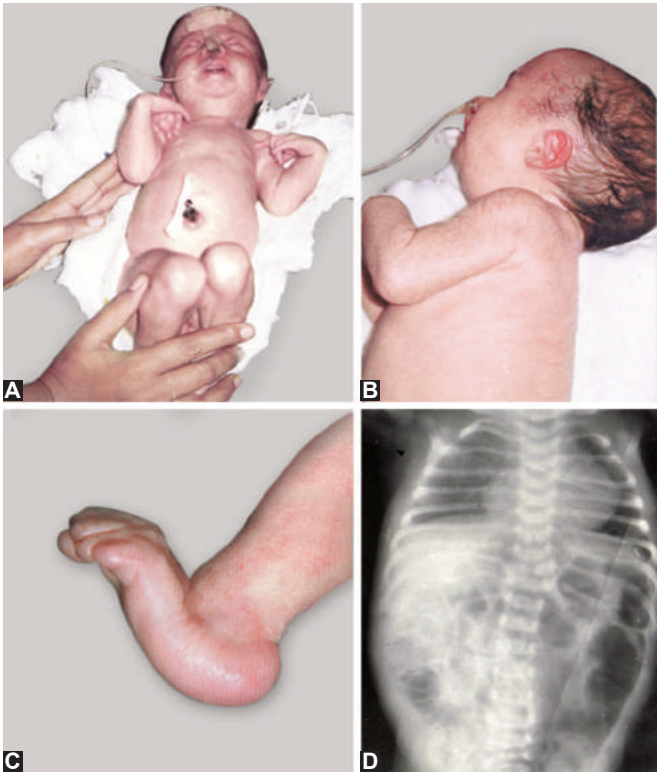
Clinical features (Figs 10A to D):

- Intrauterine growth retardation
- Dysmorphic and characteristic features
  - Micrognathia
  - Narrow palpebral fissures
  - Prominent occiput
  - Ptosis
  - Hyperflexed wrist
  - Ocular hypertelorism
  - Microcephaly
  - Cleft lip/palate
  - Low set or malformed ear
- Skeletal abnormalities
  - Rocker bottom feet
  - Over-riding fingers
  - Clenched fist
  - Hemivertebrae.
- Cardiac and renal anomalies.

Diagnosis: Prenatal diagnosis is by triple test and targeted ultrasonography.

Prognosis

- 50% die in utero
- For live-born children; 50% live up to 2 months.



Figs 10A to D: Clinical features of Edwards syndrome. (A) A baby with Edwards syndrome showing hyperflexion at wrist and overlapping of finger; (B) Same child having prominent occiput; (C) Rocker bottom feet; (D) X-ray of this baby showing hemivertebra and cardiomegaly due to congenital heart disease

Turner Syndrome

Incidence: 1 in 2,500 live birth.

Karyotype: 45,XO.

Etiology: In 80% of cases, the paternal X chromosome is missing. Other variants of karyotypes are: Mosaics: 46,XX/45,X or 46,XY/45,X.

Structural abnormalities of the second X chromosome, which may be inheritable, or a ring X chromosome, which may cause a more severe phenotype.

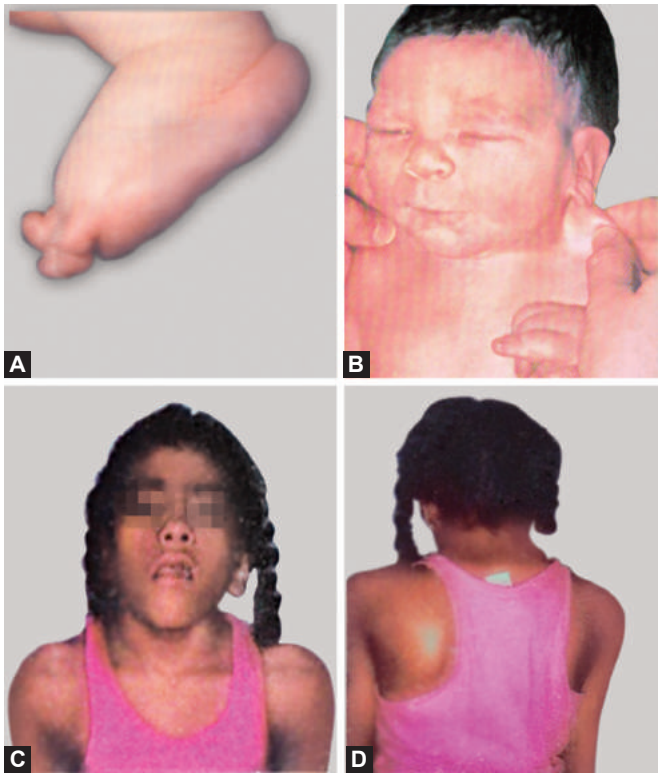
Clinical features (Figs 11 and 12):

Newborn: Phenotypic features of Turner syndrome are:

- Webbed neck
- Low posterior hairline
- Shield chest
- Wide-spaced nipples
- Coarctation of aorta
- Loose folds of skin particularly in neck
- Lymphedema (Bonnevie-Ullrich syndrome).

Childhood:

- Short stature
- Delayed puberty
- Skeletal:
  - Cubitus valgus, short fourth metatarsal or meta–carpal, shield chest, hip dislocation.
- Cardiovascular:
  - Coarctation of aorta, bicuspid aortic valve
- Eyes and ear:
  - Ptosis, strabismus, amblyopia and cataract.



Figs 11A to D: Clinical features of Turner syndrome during newborn and childhood. (A) Edema of feet (Bonnevie-Ullrich syndrome); (B) Loose fold of skin around neck; (C) Webbed neck; (D) Low posterior hairline

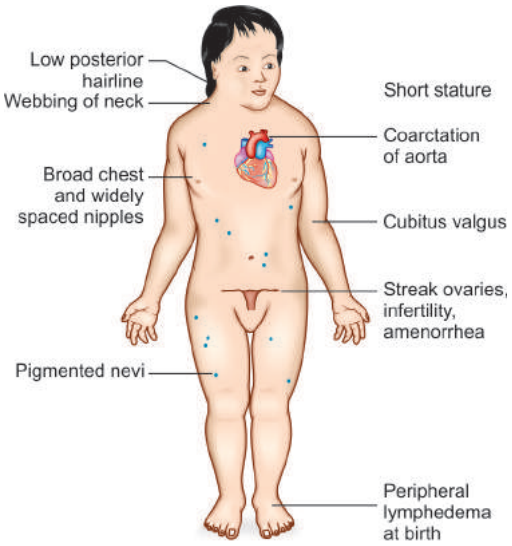


Fig. 12: Characteristic clinical features of Turner syndrome

Treatment (Multidisciplinary approach):

Endocrine

- Growth hormones are given before the epiphyses are fused to increase the adult height
- Estrogen therapy usually started from age 12–15 years
- Monitor thyroid function test every year
- Measure bone density in adolescence as osteoporosis is common
- Screen for diabetes mellitus and prevent obesity

Cardiovascular

- Cardiovascular evaluation by echocardiography
- Corrective surgical intervention should be done for significant cardiac anomalies
- Cardiovascular evaluation should be carried out every 5 years for possible aortic dissection.

Renal

- Turner syndrome is associated with horseshoe-shaped kidney and should undergo ultrasound scan for early detection of Wilm's tumor
- Monitor blood pressure regularly.

Psychosocial

- May require psychosocial support particularly for short stature and infertility.

Klinefelter Syndrome

Klinefelter syndrome is the most common cause of hypogonadism and infertility in males, and the most common sex chromosome aneuploidy in humans. Phenotypic presentation is usually male.

Karyotype:

- 80% have a male karyotype with an extra chromosome X:47,XXY

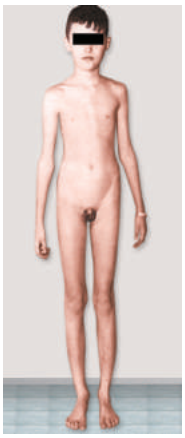


Fig. 13: A 9-year-old XXY child with long leg and small penis

- 20% have multiple sex chromosome aneuploidies (48,XXXY; 48,XXYY; 49,XXXXY), mosaicism (46, XY/47,XXY), or structurally abnormal X chromosomes.

Characteristic clinical features:

- Tall stature due to delayed closure of epiphysis
- Boys with Klinefelter syndrome enter puberty normally, but in mid-puberty, the testis begins to involute (small testis) and the boys develop hypo-gonadotropic hypogonadism with azoospermia and low testosterone level (Fig. 13)
- Secondary sexual characteristics show variable development. There is poor growth of facial and body hair
- Mild behavior and cognitive function impairment may occur.

Prognosis:

Klinefelter syndrome is a leading cause of male infertility. There is increased risk of breast cancer and autoimmune disorder.

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3 Fluid and Electrolyte Balance and Its Disorders

INTRAVENOUS FLUID AND ELECTROLYTE

Ideally fluid, electrolyte and calorie replacement should be given by enteral routes. Maintenance intravenous (IV) fluids do not provide adequate calories, proteins, fat, minerals and vitamins. A patient receiving maintenance IV fluid is receiving inadequate calories and will loss 0.5–1% of body weight each day. It is imperative that the patient does not remain on maintenance therapy indefinitely. This is, however, typically not problematic for a patient receiving IV fluid for a few days. IV fluid should only be given when enteric fluid is not possible or appropriate. This chapter mostly deals with IV fluid and electrolytes involvement assuming infants and children are unable to take oral and enteral fluids.

General Points

Water

- Approximately 80% of the body weight at birth is of water
- This is reduced to 60% by 1 year of age
- Approximately two-thirds is intracellular and one-third is extracellular. Extracellular fluid (ECF) is proportionately greater in neonates (initially two-thirds) and falls as the child grows and cells increase in number
- Adipose tissue stores less water, so postpubertal girls have lower total body water content than boys and prepubertal girls.

Electrolytes

- Within the intracellular compartment:
  - Potassium (K^+) is the principal cation
  - Phosphate (PO_4) and proteins are the main anions.
- Within the extracellular compartment:
  - Sodium (Na^+) is the principal cation
  - Bicarbonate (HCO_3^-) and chloride (Cl^-) are the main anions.

Daily Requirements

Fluid Requirements

Fluid needs can be calculated with the weight of the child using the calculations depicted in Table 1.

Table 1: Daily fluid requirement calculation

Child's weight (kg)	"Maintenance" (mL/24 h)
2–10	100 mL/kg
10–20	1,000 mL plus 50 mL/kg for each kg >10 kg
>20	1,500 mL plus 20 mL/kg for each kg >20 kg
Maximum amounts: Males: 2,500 mL/24 h; females: 2,000 mL/24 h	

- This guide amount is reduced:
  - In neonates: 50 mL/kg/day on day 1 of life, 75 mL/kg/day on day 2
  - After major surgery
  - If child is intubated on humidified ventilation (25–50% reduction)
  - Where fluid is being retained (cardiac failure or renal impairment)
- The amount is increased in the following conditions:
  - With abnormal skin
  - Who are pyrexial or on phototherapy (25% increase)
  - With tachypnea or on nonhumidified mask ventilation.

Electrolyte Requirements

Daily electrolyte requirements have been summarized in Table 2.

Table 2: Daily electrolyte requirements (mmol/kg/day)

Na^+	2–4
K^+	2–3
Ca^{2+}	1
Mg^{2+}	1
Cl^-	3–5
PO_4^{3-}	2–3

- Potassium concentrations should not normally exceed 40 mmol/L for peripherally administered solutions (risk of extravasation injury)
- Avoid giving calcium via peripheral lines unless absolutely essential. Monitor peripheral cannulation sites carefully where calcium is added to fluid as skin burns can result from extravasation.

Fluid Replacement

Ideally all fluids, electrolytes and calorie replacements should be given by the enteral route, and IV fluids should only be prescribed when this is not possible or appropriate (Table 3).

Osmolality and Tonicity

- Osmolality is a measure of the solute concentration, or the number of solute particles present in solution and is independent of the size or mass of the particles
- Tonicity is the effective osmolality and is equal to the sum of the concentrations of all the solutes that have the capacity to exert an osmotic force across a membrane
- Solutes that penetrate freely across a membrane do not exert an osmotic force across it
- When infusing 5% glucose, for instance, the glucose is taken up and metabolized by cells, leaving only electrolyte-free water. Therefore, glucose does not exert significant sustained osmotic force across a membrane. In contrast, sodium exerts more and significant sustained osmotic force across membrane.

Table 3: Composition of commonly used IV fluids

	Serum	0.9% saline	0.9% saline/g5w	0.45% saline	0.45% saline/g5w	0.18% saline/g4w	HS
Na^+	135–145	154	154	77	77	31	131
K^+	3.5–5						5
Ca^{2+}	2.2–2.6						2
Cl^-	95–105	154	154	77	77	31	111
HCO_3^-	24–32						29*
Na^+/Cl^-	1.28–1.45:1	1:1	1:1	1:1	1:1	1:1	1.18:1
Glucose	4–6		50 g/L		50 g/L	40 g/L	
Osmolality (mOsm/kg)	275–295	286	580	142	432	355	276
Calorie/L	-	0	200	0	200	160	
Tonicity		Iso	Iso	Hypo	Hypo	V. hypo	Iso

All values in mmol/L, except Na^+/Cl^- (ratio); osmolality (mOsm/kg); g5w, 5% glucose; g4w, 4% glucose; HS, Hartmann's solution; *As lactate; Iso, isotonic; Hypo, hypotonic; V. hypo, very hypotonic

How to Calculate Osmolality and Tonicity

Plasma osmolality can be estimated by calculation based on the following formula:

Osmolality = $2 \times [Na^+] + [\text{glucose}]/18 + \text{BUN}/2.8$.

If the calculated osmolality is less than the laboratory measured osmolality, then there is another osmotically active substance present, i.e. sugar, mannitol, etc.

Glucose and blood urea nitrogen (BUN) are measured in mg/dL. Division of this value by 18 and 2.8 as shown converts units into mmol/L.

Effective Osmolality also called Tonicity

As mentioned earlier, solutes that penetrate free across a membrane do not exert an osmotic force across it. Urea usually contributes little to the plasma osmolality. Urea is not confined to the extracellular space because it readily crosses the cell membrane and intracellular concentration approximately equals its extracellular concentration. Therefore it is the effective osmolality which determines the osmotic force that is mediating the shift of water between ECF and ICF. The effective osmolality also called tonicity, therefore, can be calculated as follows:

Effective osmolality = $2 \times [Na^+] + [\text{glucose}]/18$.

Few Points on Intravenous Solution

Osmolality

A normal plasma osmolality is 285–295 mOsm/kg. Infusing an IV solution peripherally with a much lower osmolality can cause water to move into red blood cells causing hemolysis. This IV fluid is generally designed to have an osmolality that is either close to 285 or greater. Higher osmolality does not cause problem. Half strength normal saline (0.45% saline) or 0.2 normal saline has lower osmolality. However, if given with 5% dextrose, osmolality can be increased significantly. 0.2 normal saline has osmolality of 68, but 5% dextrose with 0.2 normal saline has osmolality of 472. Therefore, 0.45% saline or 0.2% saline should not be used alone as IV fluid.

On the other hand, higher osmolality (more than plasma osmolality) does not usually create problem. Like 5% dextrose of 0.2 normal saline has osmolality of 472 due to added glucose. But glucose contributes little to osmolality; as mentioned earlier, glucose is taken up and metabolized by cells leaving only electrolyte in serum.

However, in exceptional conditions, it can create problem, for example, in hyperglycemia and in diabetic ketoacidosis (DKA). In such conditions, there will be a shift of water from intracellular to extracellular space. This shift of water in the extracellular space causes dilutional hyponatremia despite elevated plasma osmolality.

Tonicity

Isotonic solution should not only be used for acute volume replacement but also as maintenance solution. Isotonic solution containing glucose, like 5% dextrose in normal saline, is preferred to isotonic infusion without glucose (Hartmann's solution). 0.9% saline (Na^+ = 154 mmol/L) containing 5% glucose is an ideal isotonic solution for infusion. Hypotonic solutions are 5% dextrose or 10% dextrose or 5% glucose + 0.45% normal saline or 4% glucose with 0.18% saline. They are currently not recommended for IV maintenance to avoid risk of hyponatremia.

Hyponatremia and Its Consequences Associated with Hypotonic IV Infusion

Sodium chloride 0.45% (Na^+ = 77 mmol/L) with 5% glucose or 0.18% saline (Na^+ = 31 mmol/L) with glucose not only containing less sodium as compared to 0.9% (Na^+ = 154 mmol/L) saline with or without glucose but also aggravating dilutional hyponatremia which may occur when given in unrecognized stressful clinical conditions like respiratory disease, dehydration, intracranial lesions like meningitis, etc. due to inappropriate Antidiuretic Hormone (ADH) secretion in such conditions. Hyponatremia may cause acute neurological problems with significant morbidity and mortality.

KCl Administration

20 mEq/L of KCl should be given in maintenance fluid to prevent hypokalemia.

Managing Fluids and Electrolytes

- 0.9% saline or 0.9% saline with 5% glucose has become the fluid of choice for maintenance and deficit replacement in most cases.
- Hartmann's solution although isotonic but does not contain glucose, therefore, not ideal for IV maintenance solution

- Previous use of 0.45% saline with 5% glucose (half normal with glucose) or 0.18% saline with 4% glucose (quarter normal with glucose) has been declined with concerns about hyponatremia
- Preterm and newborn infants may be an exception to this rule as they have limited ability to excrete Na^+. They may be managed with 10% glucose, added electrolytes and regular monitoring
- However, many centers have not yet adopted the practice of giving isotonic infusion (0.9% saline with 5% glucose) as maintenance fluid
- If 0.45% saline with 5% glucose or 0.18% solution with 4% glucose has to be given, it should be infused at reduced rate to avoid risk of water intoxication
- Glucose content of fluid can be adjusted to the needs of the child
- 20 mEq/L of KCl can be administered to prevent hypokalemia associated with IV infusion.

Fractional Excretion of Water and Sodium

- The fractional excretion of water (FEH_2O) is the fraction of the glomerular filtrate volume that appears as urine, expressed as a percentage
- The fractional excretion of sodium ($FENa^+$) is the fraction of the sodium filtered by the glomeruli which appears in the urine, expressed as a percentage
- Values depend upon water intake, ADH levels, the renin/angiotensin system, renal health and maturation, medications and other factors
- Children with healthy kidneys can lower both FE values to less than 1%
- In renal hypoperfusion, the $FENa^+$ is less than 1%
- In intrinsic acute renal failure (ARF), it is greater than 2.5%
- Recent use of diuretics makes interpretation of FE values difficult
- Together, urinary sodium concentration, urinary osmolality, $FENa^+$ and FEH_2O can be interpreted to understand a patient's fluid and electrolyte status
- Urinary sodium concentration cannot be interpreted alone, as sodium and water excretion may vary together or independently.

Calculation of FEH_2O and $FENa^+$

$FEH_2O = (PCr/UCr) \times 100$
$FENa = [(UNa/PNa) \times (PCr/UCr)] \times 100$
PNa = Plasma sodium, mmol/L
UNa = Urine sodium, mmol/L
PCr = Plasma creatinine, µmol/L
UCr = Urine creatinine, µmol/L
(UCr often reported in mmol/L, may need multiplication by 1,000).
The fractional excretion values are expressed as a percentage.

Intravenous Fluids—a Few Points and Some Fallacies and Myths

Sick infants and small children are particularly susceptible to increased ADH secretion as part of the "stress response"

- This is not "inappropriate" ADH syndrome but an evolutionary physiological response to real or potential hypovolemia (e.g. following surgery or trauma), when the body needs to retain fluid
- Obviously evolution did not anticipate the advent of IV fluid therapy. Combined *increased* ADH secretion and prescribed hypotonic IV maintenance fluid result in iatrogenic hyponatremia which becomes a major problem with a significant associated mortality.

Very hypotonic; hypotonic; isotonic; or hypertonic fluids as IV maintenance and their possible consequences

- Very hypotonic fluids are associated with hyponatremia whereas the moderately hypotonic and the isotonic fluids appear to be safer
- Isotonic solutions should be prescribed for "maintenance fluids" in most cases
- If hypotonic fluids are prescribed, the child should be reviewed regularly, particularly if they are, or have recently been sick.

The frequently used formulae for IV fluid prescription may in fact be an overestimation of actual requirement

- This calculation is based on calorie consumption (1 mL of fluid for every kCal consumed) which itself is based on the child's weight
- 80% of energy expenditure occurs in the major organs which account for less than 10% of the body weight. The assumption that increase in weight results in a direct proportional increase in energy expenditure is incorrect. Energy expenditure and hence fluid requirements may be overestimated, particularly in obese children
- Sick children consume significantly less energy than healthy children due to inactivity.

All these factors have implications for hospitalized children:

- Intravenous maintenance should be isotonic (preferably 0.9% saline with 5% glucose or Hartmann's solution/Ringer's lactate) or moderately hypotonic (0.45% saline with glucose 2.5% or 5%)
- All very hypotonic IV fluids are restricted to specialized use only
- All additional losses, e.g. Nasogastric (NG) losses or excessive diarrhea/stoma losses should be replaced with 0.9% saline
- The volume of maintenance fluid prescribed should be restricted in all cases where ADH secretion is raised [e.g. postoperatively, central nervous system (CNS) and lung pathology]. Prescribe 66–75% of full maintenance (based on body weight).

PICU patients have even more reasons to restrict IV fluid prescriptions

- Children are extremely inactive (sedated and paralyzed)
- Mechanical ventilation reduces work of breathing and therefore calorie consumption
- Insensible loss is reduced through humidification of inspired gases
- Antidiuretic hormone secretion is induced by positive pressure ventilation, lung pathology, CNS insults, and other common situations in pediatric intensive care unit (PICU)
- This means that children on ventilators should be restricted to 50–75% of normal IV maintenance fluids (calculations based on their weight).

Note: This does not apply to children with large fluid requirements, e.g. burns, sepsis, etc. or to NG feeding prescriptions.

Fluid Deficits and Rehydration

- Shock states or ongoing losses of body fluids should be treated initially with normal saline, plasma expanding colloids or 4.5% human albumin solution. Further losses may necessitate the use of blood products
- A fluid deficit is estimated by weight or clinical examination, and the deficit added into maintenance fluids for replacement at a rate which is governed by the extent of the deficit and its cause
- Fluid deficit is most accurately gauged by a change in weight
- Where weighing is impossible or no recent weight is available for comparison, a clinical estimate of dehydration may be made
- This is expressed as the number of mL of water lost per 100 g of body weight or the percentage of dehydration
- Rates of rehydration need careful recalculation and adjustment in each child.

Clinical Estimation of Dehydration

- *Five percent dehydration*: Reduced skin turgor, sunken eyes and/or fontanel, dry mucous membranes, decreased peripheral perfusion, irritability, oliguria, pyrexia
- *Ten percent dehydration*: Lax skin, poor perfusion, drowziness, anuria
- Using this estimate, the child's fluid deficit can then be calculated:

Deficit in liters = [Weight (kg) × % (Dehydration)]/100.
A 5% dehydration in 10 kg child is:

$$\text{Deficit in liters} = \frac{10 \times 5}{100} = 0.5 \text{ L or } 500 \text{ mL}.$$

Rate of Deficit Replacement

- Shock needs to be addressed swiftly (20 mL/kg of 0.9% sodium chloride)
- Severe dehydration (10% or more) should be corrected quickly:
  - In infant less than 12 months, 100 mL/kg Ringer's lactate, cholera saline or 0.9% sodium chloride should be given in 6 hours of which 30 mL/kg in first hour followed 70 mL/kg in next 5 hours
  - In child of 12 months to 5 years with severe dehydration is corrected in 3 hours by giving 100 mL/kg fluid of which 30 mL/kg is given in 30 minutes followed by 70 mL/kg in next 2½ hours.
- In moderate dehydration (some dehydration 5–9%), fluid deficit in liter [weight (kg) × % (dehydration)]/100 is given over 6 hours (approximately 75 mL/kg)
- In all above cases, enteral fluid (or saline) can be given orally or by NG tube, if facilities for IV are not available or not appropriate
- In hypernatremia and hyponatremia, 48–72 hours may be needed for deficit replacement. This is necessary to avoid neurological complications caused by rapid changes in serum Na^+. However, severe hyponatremia will require quick correction.

Severe Dehydration

- Children who are greater than or equal to 10% dehydrated are prone to complications such as renal and cerebral venous sinus thrombosis
- These complications should be remembered when the expected responses in urine output or conscious level are not obtained with fluid therapy
- Appropriate further examination and investigation should be undertaken.

Colloids and Its Advantage in Clinical Practice

Colloids are aqueous electrolyte solutions containing large molecules-proteins in the case of human albumin solution (molecular weight of 68,000 Daltons) and gelatins in gelofusine and hemaccel (molecular weight of 30,000 Daltons). The large molecules leak slowly from the circulation through the capillary endothelium and therefore these solutions exert a colloid osmotic (oncotic) pressure. The advantage of colloids is that they stay in the circulation longer and thus less is needed to resuscitate the intravascular space when compared to crystalloids. In theory, they should also cause less edema. Best use in clinical practice is in dengue shock syndrome refractory to crystalloid solution infusion.

Human albumin solution 4.5% is a heat-sterilized human blood by-product that has a half-life of 16 hours in the circulation. Gelofusine and hemaccel persist for less time in the circulation but for longer than crystalloids. All three solutions contain plasma-like concentrations of sodium and chloride. Larger molecular solutions such as hespan and pentaspan as well as dextran should be avoided.

Crystalloids versus Colloids

Whilst it is standard practice to prescribe maintenance IV therapy with crystalloid solutions, there is controversy regarding the suitability of colloids in resuscitating patients with hypovolemia and sepsis. Proponents of colloid point to their efficiency (less required for the same effect) and physiological effect. Opponents point to their cost (colloids are considerably more expensive) and lack of evidence base. However, most intensivists use a combination of both depending on the situation—often starting resuscitation with IV crystalloids, e.g. at 20 mL/kg, and introducing colloids if more aggressive resuscitation is required (5–10 mL/kg). Postoperative cardiac patients are often treated with colloid IV and many intensivists use human albumin for meningococcal sepsis.

Monitoring Fluid Therapy

The key to effective and safe practice in fluid and electrolyte therapy is careful documentation and regular monitoring of the following:

Clinical Parameters

- *Weight:* Remember individual weighing-scales differ in accuracy
- *Fluid balance:* Intakes-outputs all need to be charted
- *Perfusion state:* pulse and central capillary refill time
- *Conscious level:* Glasgow Coma Score (GCS) should not drop
- Hydration state
- Cannulation sites.

Laboratory Parameters

- *Serum electrolytes:* Especially where supplements are given
- *Serum urea and creatinine:* Rising values alert to renal impairment
- *Hematocrit:* A marker of intravascular status, if no bleeding

- Blood glucose
- *Urine electrolytes:* Urine Na^+ and CI^- less than 20 mmol/L in hypovolemia.

Fluid Losses

- Losses incurred such as hemorrhage, and capillary leak.
- Losses from the gastrointestinal (GI) tract will depend on their origin and may require specific replacement intravenously (Table 4).

Table 4: Composition of gastrointestinal (GI) fluids (mmol/L)

Fluid	Sodium	Potassium	Chloride
Gastric	20–80	5–20	100–150
Pancreatic	120–140	5–15	40–80
Biliary/upper small intestine	100–140	5–15	80–130
Ileostomy	40–140	5–15	20–120
Diarrheal	10–90	10–80	10–110

- Fluid balance fluctuates rapidly and widely in seriously ill patients
- Carefully measured input (IV and enteral) and output (urine, drain losses, GI losses) values must be recorded hourly
- Insensible losses are often overlooked:
  - Important as children have a ↑surface area to body weight ratio
  - Come from skin and respiratory tract
  - Vary with the patient's temperature, dimensions and ventilation (humidification of inspired gases ↓respiratory losses by 80%)
- 10–30 mL/kg/day (300 mL/m^2/day) is a reasonable estimate of insensible losses

ELECTROLYTE IMBALANCE

Hyponatremia: Na^+ <130 mmol/L

- Causes are as follows:
  - *Sodium loss*: Diarrhea particularly associated with cholera, burns, adrenal failure including Congenital Adrenal Hyperplasia (CAH), hypothyroidism; thiazide diuretics.
  - *Water gain*: Syndrome of inappropriate ADH secretion (SIADH); edema, e.g. congestive cardiac failure (CCF), liver failure; oliguric renal failure, e.g. acquired excessive IV rehydration; psychogenic polydipsia (very dilute urine and dilute plasma).
- Syndrome of inappropriate secretion of ADH:
  - Low serum sodium (and often urea and creatinine)
  - Plasma osmolarity less than 280 mOsmol/kg
  - Inappropriately concentrated urine greater than 100 mOsmol/kg
  - Elevated urine sodium greater than 20 mEq/L.

Causes of Hyponatremia in PICU (Table 5)

- Causes of hyponatremia can be grouped by assess-ment of ECF volume status and urine Na^+
- Measurement of FEH_2O and $FENa^+$, and urinary osmolality help in the diagnosis
- More than one cause may coexist [e.g. SIADH and cerebral salt wasting (CSW) in head injury]
- SIADH.

Clinical Features

May complain of nausea, headache, lethargy with progression to confusion. Seizures occur if sodium falls below 120 mmol/L.

- Evidence of shock associated with dehydration in diarrheal disease, adrenal insufficiency including CAH.

Other clinical features depend on the cause.

Management of Hyponatremia

- Assess the hydration status
- Evidence of adrenal insufficiency such as hyper-pigmentation, ambiguous genitalia.

Investigations

- Blood-urea and electrolytes, glucose, plasma osmolality (normal = 275–295 mOsm/kg)
- Urine-dipstick (expected specific gravity >1.005) and osmolality (expected >750 mOsm/kg); 24-hour urinary collection for urinary sodium.

Treatment

- Depends on specific cause and severity of hyponatremia
- Hyponatremia management associated with diarrhea and dehydration (discussed in chapter Gastroenterology)
- Acute symptomatic hyponatremia, for example, associated with convulsion or shock should be corrected quickly
- Patients who have symptomatic hyponatremia like convulsion, sodium depletion should be corrected quickly as follows: Use 3% sodium chloride, (513 mmol/L or 0.5 mmol/mL). The exact sodium deficit can be calculated (assessing assumed volume of distribution of Na^+ of 60% body weight) using the classical formula
  Na^+ deficit in mmol = Weight (kg) × 0.6 × (125 – Current plasma Na^+). For example, in a 10 kg weight child with hyponatremic convulsion with plasma sodium of 120 mmol/L, the Na^+ deficit to be corrected:
  Na^+ deficit = 10 × 0.6 × 5 = 30 mmol.
  1 mmol of Na^+ is present in 2 mL of 3% Na^+ chloride. 30 mL of Na^+ is present in 60 mL of 3% Na^+ chloride. Therefore, if given quickly within 4 hours, give 3% Na^+ chloride at 15 mL/hour.
  (Discuss with PICU personnel if convulsion occurs with hyponatremia).

Hyponatremia associated with hypovolemic shock—20 mL/kg, 3% sodium chloride should be given quickly (within 4 hours):

Table 5: Causes of hyponatremia in PICU

ECF volume status	Ur Na^+ <20 mmol/L	Ur Na^+ >20 mmol/L
Normal	-	H_2O excess, SIADH, NSAID use, hypoadrenal/thyroid
Increased (edema)	Capillary leak syndrome, low cardiac output, hepatic failure	ARF
Decreased	3rd space loss, GI loss, burns	Polyuric phase of ARF, osmotic diuresis, CSW

Abbreviations: PICU, pediatric intensive care unit; ECF, extracellular fluid; Ur, urine; SIADH, syndrome of inappropriate ADH secretion; NSAID, nonsteroidal anti-inflammatory drug; GI, gastrointestinal; ARF, acute renal failure; CSW, cerebral salt waiting.

- If symptoms are severe that is if child is fitting, give 4 mL/kg 3% sodium chloride over 30 minutes and repeat. If symptoms persist, give 2 mL/kg over 15 minutes and repeat if symptoms persist
- Stop at plasma sodium of 125 mmol/L, or if sodium is increased greater than 0.5 mmol/hour
- Hyponatremia associated with diarrhea with nonsevere dehydration should be preferably corrected by sodium containing Oral Rehydration Salts (ORS)
- Hyponatremia associated with diarrhea due to cholera should preferably be corrected by previous higher sodium containing ORS (sodium of 90 mmol/L) rather currently used hypo-osmolar low sodium (sodium 75 mmol/L) containing ORS.

Treatment of chronic hyponatremia: The neurons adjust to the lower serum osmolality by lowering their own osmolality. Cerebral edema is less severe, but it is the rapid treatment that can cause mortality or central pontine myelinolysis. In such condition, the sodium requirement is determined as follows:

Sodium deficit (mEq) = [Desired Na^+ – Sodium present) × Weight (kg) × 0.6.

If desired sodium is 125 and present sodium is 120 and child weight is 10 kg then sodium deficit is: 5 × 10 × 0.6 = 30 mEq.

It should be corrected slowly over 48 hours.

Treatment of hyponatremia in other conditions:

In PICU:

- Best dealt by taking preventive measures—restrict intake to 50–75% of normal maintenance for patients on positive pressure ventilation and receiving humidified gases
- If hyponatremia is due to water retention (i.e. SIADH), restrict fluid to 25–50% of normal maintenance rather than increased sodium supply
- With severe (or symptomatic) hyponatremia, less than 125 mmol/L fluid restriction alone would take too long to rescue the patient from dangerously low sodium concentrations. Use 3% saline (i.e. 523 mmol/L or 0.5 mmol/mL):
  - The exact sodium deficit can be calculated (assuming a volume of distribution of Na^+ of 60% body weight) using the classic formula:

  Na^+ deficit (in mmol) = Weight (kg) × 0.6 × (125 – Plasma Na^+).

Further Management

- Take a detailed history focusing on precipitating factors—water excess, chest infection, habitual juice drinking and head injury
- Examine the child with particular attention to hydration state, perfusion and neurological system.

Hypernatremia: Na^+ >150 mmol/L

- Results from either:
  - Water deficiency (more than sodium loss)
  - Sodium excess (more than water gain).

Causes (Table 6)

- Loss of water (more than sodium):
  - Gastrointestinal water loss (osmotic diarrhea, gastroenteritis in bottle fed infant)
  - Insensible water loss (fever, hyperventilation, burns)

Table 6: Causes of hypernatremia in PICU (all figures in mmol/L)

Urine sodium	Urine osmolality		
	<800	Variable	>800
< 20	-	-	GI water loss
Variable	Diabetes insipidus	-	↓Water intake
>20	Hyperglycemia	-	-
>75	-	↑Na^+ intake	-

  - Diuretic therapy (osmotic diuretic, loop diuretic)
  - Hyperglycemia (osmotic diuretic)
  - Renal disease
  - Diabetes insipidus
- Sodium excess (more than water):
  - Excess ingestion—including salt poisoning, iatrogenic (IV fluids with high sodium or salt containing drugs or hyperosmolar oral saline). Currently low osmolar ORS is used in diarrhea to prevent hypernatremia
  - Near-drowning (seawater)
  - Cushing's syndrome
  - Conn's syndrome.

Clinical Features

- Targeted history focusing on causes (diarrhea and vomiting, head injury, thirst and polyuria, milk formula use) and any neurological symptoms
- Weakness, confusion progressing to seizure, coma
- Clinical signs of dehydration may be masked as ECF volume is protected by the high Na^+.

Investigations

- Blood-urea and electrolytes, glucose, plasma osmolality (normal = 275–295 mOsm/kg)
- Urine-dipstick and osmolality. If less than 750 mOsm/kg, concurrent with plasma osmolality greater than 295 mOsm/kg, this is diagnostic of diabetes insipidus.

Management

- Cautious rehydration using ORS or with 0.9% saline or 0.45% IV saline. Aim for a slow fall of Na^+ at 0.25 mmol/L/hour.
- Rehydration over 48 hours, using ORS or IV fluids. For example, for 12 kg child with 5% dehydration:
  - Maintenance fluids in 48 hours = 1,100 mL/24 hour (up to 10 kg, 100 mL/kg and 50 mL/kg for each kg after 10 kg)
  - Fluid deficit = 5% of 12 kg = 600 mL or 0.6 L (50 × 12 in mL or weight in kg × percentage of dehydration/100 in liter)
  - Replace 2-days maintenance with deficit over 48 hours: (1,100 + 1,100 + 600 = 2,800 mL in 48 hours, i.e. 58.3 mL/hour) at 14 drops/minute in normal drop or 56/minute in microdrop (1 mL = 15 drop or 60 microdrop). One drop in normal burette in IV infusion = 4 drops in microburette. If the child is taking some fluid orally then adjust IV fluid accordingly (see also in Gastroenterology chapter).
- Check urea and electrolyte every 4 hours. Aim to reduce sodium by no more than 10 mmol/L every 24 hours.
- Specific replacement of ADH is indicated for central or neurogenic diabetes insipidus.
- Resistance to replacement therapy suggests a nephrogenic cause.

Hypokalemia: Serum K^+ <3.5 mmol/L

- Ensure that sample is the not contaminated.
- If K^+ is less than 2.5 mmol/L, the Electrocardiogram (ECG) changes normally evident (ST depression + U waves).

Causes

- Inadequate intake (typically in PICU patient in IV fluids).
- Potassium loss:
  - Gastrointestinal (diarrhea most important cause)
  - Diuretic therapy
  - Hyperglycemia (osmotic diuretic)
  - Renal disease
  - Low Mg^{2+} can cause hypokalemia and hypocalcemia.
  - Cushing's syndrome
  - Conn's syndrome
- Movement of potassium into cells:
  - Acidosis correction
  - Insulin use
  - Beta-2 (β_2) agonist use.

Clinical Features

- Weakness, cramps, hypotonia, abdominal distension due to weakness of abdominal muscle and ileus (decreased peristalsis), hyporeflexia and lethargy.

Investigations

- Blood-urea electrolyte
- ECG provides better index of tissue potassium status of body than serum potassium level (ST depression, increase QT interval, presence of U wave) (Fig. 1)
- Blood gas analysis.

Management

- Assess for alkalosis associated with hypokalemia by blood gas analysis. Where present, this should also be treated—KCl therapy may be used as a source of both K^+ and Cl^- in the setting of diuretic-induced alkalosis
- Assess need for urgent correction of deficit:
  - Is the child symptomatic (cardiac arrhythmia, severe muscle weakness or illness)?
  - Or at risk (congenital heart disease, myopathy, severe illness)?
- Urgent replacement—use high strength KCl via a central line in aliquots of 0.5 mmol/kg over 1 hour then recheck K^+.

Injection of magnesium sulfate: In refractory hypokalemia as found in severe malnutrition with abdominal distension, injection of 50% magnesium sulfate intramuscular (IM) can improve hypokalemic status (0.3 mL/kg IM on 1st day and 0.1 mL/kg on 2nd and 3rd day in severe malnutrition).

Do not give boluses of potassium solutions.

- Nonurgent enteral supplements (preferred) and/or parenteral replacement by peripheral IV with K^+ additives in maintenance fluid (maximum concentration 40 mmol/L)
- Elucidate cause by considering depletion (diet, renal or gut loss) or redistribution (alkalosis, thyrotoxicosis and familial paralysis).

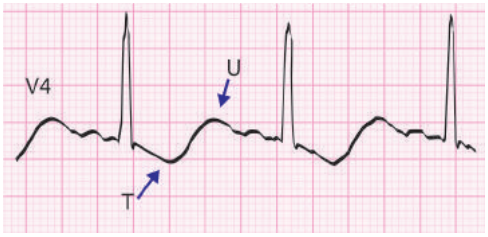


Fig. 1: ECG changes in hypokalemia

Hyperkalemia: Serum K^+ >5.5 mmol/L

- Normal ranges for K^+ are higher in infants who also tolerate hyperkalemia better than older children
- Ensure that the sample is not hemolyzed
- Stop exogenous administration of K^+
- Elucidate causes: Consider sources of and evaluate renal function.

Causes

- Excess K^+ [Total Parenteral Nutrition (TPN), blood transfusion, supplements]
- Acute renal failure
- Cell destruction:
  - Tumor lysis syndrome
  - Rhabdomyolysis
  - Acute burns
  - Trauma—crush injuries
- Congenial adrenal hyperplasia
- Addison's disease
- Drugs
- Movement of potassium out of cells
- Hemolysis during/after sampling—artifactually high K^+
- Acidosis
- Insulin deficiency (DKA) but total body sodium often depleted.

Clinical Features

- Tingling, numbness
- Cardiac arrhythmia (ectopic beat, drop beat, asystole).

Investigations

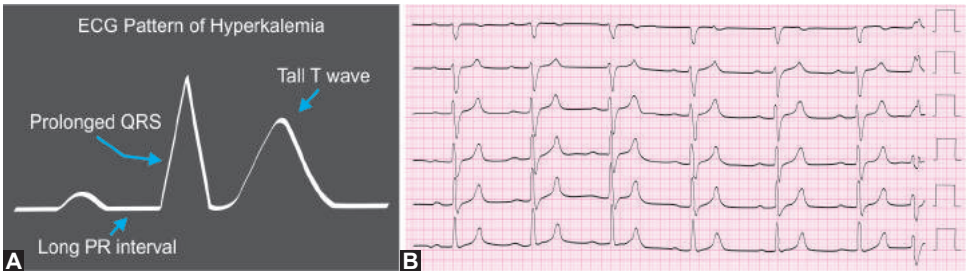
- Blood, electrolyte, urea and creatinine
- Hyperkalemia necessitates ECG monitoring—if K^+ greater than 6.5 mmol/L—ECG changes normally evident (long PR, tall peaked T waves and wide QRS) (Figs 2A and B)
- Urgent blood glucose and arterial blood gas (ABG).
- If evidence of increased tissue destruction, order for creatine kinase (CK), uric acid, PO_4, calcium.

Treatment

- Stop all IV and oral fluid containing K^+
- If arrhythmia present, give calcium gluconate 10%; 0.5–1 mL/kg over 5–10 minutes.

If no arrhythmia, treatment can be combined as follows:

- Nebulize salbutamol 2.5 mg for less than 5 years old children, 5 mg to greater than 5 years old children or with salbutamol IV 4 µg/kg over 10 minutes (shifts K^+ into cells)
- Sodium bicarbonate 8.4%; 1–2 mmol (mL)/kg over 30 minutes
- Glucose and insulin:



Figs 2A and B: (A and B) ECG changes of hyperkalemia (prolonged PR interval, broad QRS and tall peaked T wave)

- Bolus 0.1 units/kg insulin with 2 mL/kg of 50% glucose
  or
- Infuse 1 g/kg/hour glucose (i.e. 5 mL/kg/hour-20% glucose or 10 mL/kg/hour-10% glucose) with insulin infusion 0.1 unit/kg/hour
- Monitor blood-glucose every 15 minutes for first hour, then hourly thereafter
- Watch for late hypoglycemia

- Calcium resonium 1 g/kg orally or rectally with oral lactulose.

Calcium, Magnesium and Phosphate

These ions affect cardiac function and need to be monitored closely in the perioperative period of cardiac surgical cases. They are also important for skeletal system repair and growth.

Plasma Forms of Calcium and their Clinical Significance

Three main fractions:
1. Ionized (50%)
2. Albumin bound (40%)
3. Complex to phosphate citrate, etc (5–15%).

- Total Ca^{2+} lab values, corrected for albumin, should be 2.0 mmol/L
- Ionized Ca^{2+} (normal = 1.0–1.5 mmol/L) is not age or albumin dependent. It is affected by acid-base status (↑ by acidosis and ↓ by alkalosis).

Use ionized Ca^{2+} as the guide to treatment rather than total or corrected total calcium—threshold for IV calcium supplementation should be less than 0.7 unless symptomatic.

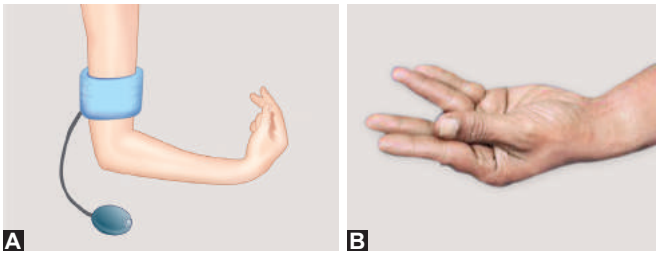
Hypocalcemia

Causes

Neonatal:
- Prematurity, infant of diabetic mother, RDS, birth asphyxia
- Transient neonatal hypoparathyroidism
- Maternal osteomalacia
- Maternal hyperparathyroidism
- Persistent idiopathic hypoparathyroidism
- DiGeorge syndrome
- Congenital hypomagnesemia with secondary hypocalcemia.

Older children:
- Vitamin D deficiency:
  - Nutritional rickets
  - Anticonvulsants
  - Renal rickets, ARF

Fig. 3: Eliciting Chvostek's sign



Figs 4A and B: Carpal spasm following inflation of sphygmomanometer

  - Vitamin D dependent rickets
  - Nephrotic syndrome
- Hypomagnesemia
- Acute pancreatitis.

Clinical Features

- Likely to be triggered as a result of a convulsion or the presence of tetany, the clinical hallmark of hypocalcemia.
- Difficult to give an exact figure at which emergency intervention is required but serum calcium concentrations below 1.7 mmol/L (ionized calcium < 0.7 mmol/L) are likely to be associated with problems. Clinical presentation includes the following:
  - *Neuromuscular*: Paresthesia, tetany, convulsion, myopathy, laryngospasm (hypocalcemic stridor)
  - Positive Chvostek's sign characterized by twitching of the facial muscle in response to gentle tapping over facial nerve anterior to earlobe (Fig. 3).
  - *Positive Trousseau's sign*: Carpal spasm following inflation of sphygmomanometer over upper arm above systolic BP (Figs 4A and B).

Management

- Get adequate venous access in a large vein. IV calcium is very corrosive and may cause serious extra—vasation injury
- Commence slow IV injection of 10% calcium gluconate (1–2 mL/kg equivalent to 9–18 mg elemental calcium/kg or 0.225–0.45 mmol/kg) over 3 hours with ECG monitoring
- Repeat every 6–8 hours whilst symptoms persist
- May need longer continuous infusion as total body calcium may be low

- Maintenance therapy with oral calcium (50–75 mg/kg/day of elemental calcium) and at the same time, start treatment with oral vitamin D (calciferol) 1,500 IU/day in neonates or 3,000 IU/day in older children
- Do not use 1α-hydroxyl-cholecalciferol at this stage or until definitive diagnosis has been made
- Low Mg^{2+} can cause hypocalcemia. Treatment with Mg^{2+} to prevent recurrence of hypocalcemia is done. Dose 0.2 mL/kg of 50% magnesium sulfate IV over 30 minutes. Repeat, if necessary.

Calcium chloride and gluconate formulations contain different amounts of Ca^{2+}. Both are irritant to veins (gluconate milder).

Hypercalcemia

Causes

- Hyperparathyroidism (primary, tertiary but not secondary)
- Idiopathic infantile hypercalcemia
- Vitamin D intoxication
- Vitamin A intoxication
- Milk alkali syndrome
- Prolonged immobilization (after fracture of long bones).

Some syndromic conditions:

- Williams syndrome (Fig. 5)
- Hypophosphatasia.

Clinical Features

- Constipation
- Nephrocalcinosis (Figs 6A and B)

Fig 5: A child with Williams syndrome

- Failure to thrive
- Renal calculi
- Polyuria (nephrogenic diabetes insipidus)
- Metastatic calcification
- Supravalvular aortic stenosis in Williams syndrome.

Investigations

- Full blood count (FBC), blood film, serum calcium (total), phosphate and venous bicarbonate
- Blood urea, creatinine
- Ionized calcium
- Parathyroid hormone (PTH)
- Liver function test including albumin and alkaline phosphatase (ALP)
- ECG: Short QT
- Imaging: Ultrasound of kidney for nephrocalcinosis.

Other investigations: As indicated, e.g. formal glomerular filtration rate (GFR), blood gas, etc.

Treatment

- Volume expansion, e.g. 3 L/m^2/24 hour IV solution Loop diuretic (Furosemide 1 mg/kg IV 6–8 hourly)
- Corticosteroid in chronic hypocalcemia
- Calcitonin infusion, 5–10 units/kg IV followed by 4 units/kg IV
- Bisphosphonate, e.g. pamidronate infusion in hypercalcemia of malignancy.

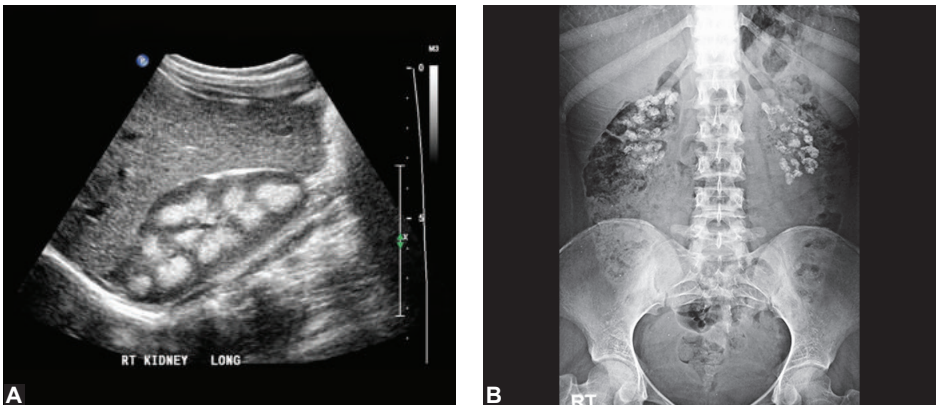
Magnesium: State of magnesium in plasma and their clinical significance

- Normal plasma Mg^{2+} (0.7–1.0 mmol/L)
- Mg^{2+} and Ca^{2+} absorption are linked
- Low Mg^{2+} levels are proarrhythmic
- Ionized fraction is the active fraction (like calcium) but not routinely measured in most centers.

Hypomagnesemia

Magnesium less than 0.6 mmol/L. Clinically concerning when it is under 0.3 mmol/L as it impairs the release of PTH, resulting in hypocalcemia. Secondary hypokalemia can also arise, especially with renal disease. Symptoms of isolated hypomagnesemia resemble those of hypocalcemia, but arrhythmias are unlikely if there are no cardiac anomalies.

Intravenous magnesium sulfate is given in infusion in the management of acute severe asthma as bronchodilator, but it



Figs 6A and B: Ultrasonogram of abdomen and plain X-ray abdomen showing nephrocalcinosis respectively

is not clear whether such patients are magnesium deficient or not.

Causes

- *Decrease intake:* Severe malnutrition, particularly associated with hypokalemia.
- *Gastrointestinal loss:* Vomiting, diarrhea, protracted inanition, malabsorption conditions, e.g. celiac, cystic fibrosis (CF), inflammatory bowel disease (IBD).
- *Renal loss:* tubular disease, e.g. nephritis, Bartter's, Gitelman's; osmotically active agents, e.g. glucose, mannitol; medications, e.g. diuretics (loop and thiazides); nephrotoxic, e.g. amphotericin, cyclosporine.
- Acute renal failure (polyuric phase).
- Endocrine causes, i.e. hypoparathyroidism and hyperthyroidism.

Clinical Features

- Resembles those of hypocalcemia, but arrhythmia is unlikely
- Symptoms include the following:
  - Seizures, particularly in neonates
  - Stridor secondary to laryngospasm—may need intubation
  - Neuromuscular, e.g. tingling in hands, around mouth; carpopedal spasm and Chvostek's sign.

Investigation

ECG: Stinted T waves prolongation of ST.

Management

- If urgent, give 0.2 mmol/kg IV over 10 minutes (0.1 mL/kg of 50% magnesium sulfate diluted 5% with 0.9% saline)
- Neonates may be given 0.4 mmol/kg, appropriately diluted and given slowly
- In severe acute asthma:
  - 0.1 mL/kg in IV infusion for 20 minutes, followed by 0.06 mL/kg/hour until severity decreases
- In severe malnutrition:
  - 0.3 mL/kg IM on 1st day, followed 0.1 mL/kg/day on 2nd and 3rd day (useful in improving hypokalemic condition causing abdominal distension and feeding difficulty)
- Smaller doses of 0.1 mmol/kg are used in treating torsade de pointes [polymorphic ventricular tachycardia (VT)], pulmonary hypertension and acute severe asthma (nebulized or IV).

Hypermagnesemia

- Rarely seen except in renal failure and when given therapeutically
- Leads to muscle weakness and coma but not until very high levels are reached—often increase to 2–3 mmol/L in setting of Mg^{2+} treatment for pre-eclampsia, asthma, etc.

Low Phosphate Level

- Serum PO_4 varies with age and acid-base status (↑ in infancy and acidosis)
- Keeping level greater than 1.0 mmol/L helps cardiac function and bone growth
- Decrease phosphate results in poor bone mineralization causing osteopenia of prematurity in preterm babies, rickets in children and osteoporosis in adults
- Decrease in phosphate occurs in:
  - Nutritional rickets due to secondary hyperparathyroidism
  - Osteopenia of prematurity
  - Starvation/poor intake
  - Critical illness
  - Diuretic and renal replacement therapies
  - Parenteral nutrition
  - Hyperparathyroidism.

Clinical Features

- Decreased linear bone growth with pathological fracture
- Muscle weakness (rarely apparent clinically)
- Cardiac dysfunction.

Treatment

- Low levels are treated with 0.5 mmol/kg over 10 hours (over 1 hour if urgent) as 1 mL/kg of 13.6% potassium acid phosphate diluted × 10 with 0.9% saline (this also gives some dose of potassium)
- In osteopenia of prematurity, oral supplementation is given: Prescribe phosphate (joulic solution) in Very Low Birth Weight (VLBW) less than 1,500 g baby with ALP greater than 500 IU/L and plasma phosphate less than 1.8 mmol/L. In a breastfeed baby, 1.5 mmol/kg/day orally for 6 months corrected age.

High Phosphate Level

Causes

Causes of decreased excretion:
- Renal insufficiency (most important cause)
- Hypoparathyroidism or pseudohypoparathyroidism
- Increased intake:
  - Cow's milk intake
  - Vitamin D intoxication.

Other causes:
- Tumor lysis syndrome
- Acute hemolysis
- Rhabdomyolysis.

Clinical features of hypocalcemia (↑ phosphate precipitates calcium as calcium phosphate salts).
- Tetany, paresthesia, convulsion and muscle weakness.

Clinical features due to deposition of calcium phosphate salts in various organs

Eye:
- Photophobia, visual impairment.

Treatment

Treatment of underlying conditions: Treatment of renal failure, etc.

Phosphate binders: They are used to prevent intestinal calcium absorption.

Calcium carbonate and calcium acetate are most commonly used. Phosphate binders can decrease absorption 30–40% particularly if given before meal.

Urea and Uric Acid

Urea is created to remove ammonia, a toxic by-product of protein catabolism that is not readily excreted. Uric acid is generated by purine metabolism, e.g. the breakdown of DNA. Uric acid is measured as urate, its salt form.

Both urea and uric acid are toxic if they accumulate.

Elevated urea is greater than 6 mmol/L.

Urea is soluble in water so is easily excreted by the kidney, thus high levels of urea seldom arise in isolation, and usually reflect impaired renal function, secondary to reduced GFR. Persistently high levels will cause itching and GI irritation, such as vomiting and nausea.

Causes

- Increased production. GI: Upper GI bleed, high protein diet; medications: Steroids, diuretics.
- Impaired excretion. Renal: prerenal (dehydration); renal (renal failure); postrenal (obstruction, e.g. urethral valve, stone).

Treatment

- Renal failure
- Assess hydration. Rehydrate, if necessary
- Review medication.

High Uric Acid

Urate is greater than 0.35 mmol/L. Uric acid becomes soluble in water at high concentration. Crystals are deposited in the kidney causing renal stones; in the joints causing gout and ultimately in the nerves with resultant neuropathies. Precipitation is exacerbated by dehydration or acidosis.

Causes

- Increased cell turnover: Malignancy, cyanotic heart disease, hereditary anemia and psoriasis.
- Associated syndromes: Lesch-Nyhan (X-linked, progressive developmental delay and spasticity, self-mutilation especially biting), Down's syndrome; glycogen storage disorders I, III, IV, V.

Treatment

- Increasing fluid intake IV rehydration
- Allopurinol 5 mg/kg/dose bd to qds PO (maximum 600 mg/day) to reduce production; probenecid 10 mg/kg/dose qds PO to increase excretion
- Consider alkalinization of urine.

Edema

Mechanisms of Edema

Movement of fluid across the capillary wall endothelium depends on:

- The nature of the molecule, i.e. its size, charge, water and fat solubility
- The balance of forces across the capillary wall
- The permeability of the capillary wall.

Water and water-soluble molecules (NaCl, glucose) pass across the capillary membrane with greater ease than large molecules such as proteins (albumin) or gelatins (gelofusine). This movement produces a low protein filtrate that is referred to as interstitial fluid. This is the ECF that sits in outside the vascular compartment.

The balance of forces affecting fluid distribution across the capillary depends on the balance between hydrostatic forces [capillary hydrostatic pressure (P_c)—interstitial fluid hydrostatic pressure (P_i)], forcing fluid out of the capillary and the osmotic forces [capillary colloid osmotic pressure (π_c)—interstitial fluid colloid osmotic pressure (π_i)], sucking fluid into the capillary. Thus:

$$\text{Flow of fluid} = k\,[(P_c - P_i) - \sigma\,(\pi_c - \pi_i)]$$

Where k is a filtration coefficient and σ is the coefficient that represents the permeability of the endothelium.

Capillary hydrostatic pressure falls from approximately 30 mm Hg at the arterial end (forcing fluid out of the capillary) to about 15 mm Hg at the venous end of the capillary. The pulmonary circulation has lower capillary pressures. These pressures are also slightly lower in infants and smaller children. Capillary colloid osmotic pressure (oncotic pressure) is generated by the "pull" of intravascular protein and is normally 25 mm Hg. Interstitial colloid osmotic pressure is about 10 mm Hg.

In health, the volume of fluid leaving the capillary exceeds that absorbed by a small amount. This excess is absorbed by the lymphatics.

When capillary filtration exceeds lymphatic drainage, there is an excess of interstitial fluid and edema that result. In intensive care unit (ICU), this is commonly seen in the peripheral subcutaneous tissues, the lungs (pulmonary edema), in the pleural space (effusion), and abdominal (ascites) and pericardial spaces. Edema may not only reflect disease severity but also impairs oxygen and nutrient delivery from the capillary to the cell.

From Starling's equation, we can see that edema may result from three causes:

1. Increased capillary pressure (P_c), e.g. in right heart failure, fluid overload or in dependent edema
2. Decreased colloid osmotic pressure (π_c); when there is a fall in plasma protein, e.g. malnutrition (↓intake), nephrotic syndrome (protein loss), hepatic failure (reduced synthesis).
3. Increased capillary permeability (↓σ); in diseases of inflammation circulating cytokines can cause massive and widespread capillary leak, e.g. dengue shock syndrome, meningococcemia, sepsis. In these conditions, the edema is usually high in protein content (>30 g/L), i.e. exudative type. Fluid may leak from capillary to body cavity, i.e. abdominal cavity causing ascites, pleural cavity causing pleural effusion.

Pulmonary Edema

Pulmonary edema occurs when pulmonary lymphatics become exhausted—initially interstitial edema occurs but this

progreses to alveolar edema with accompanying reduction in compliance and intrapulmonary shunting. Classic signs are dyspnea and hypoxemia.

Pulmonary edema may be either:

- *Cardiogenic*: Myocardial dysfunction or inadequate emptying of left ventricle or atrium leads to subsequent increase in left ventricular end-diastolic pressure, left atrial pressure and pulmonary venous pressure resulting in increased pulmonary capillary pressure and pulmonary edema.
- *Noncardiogenic*: This is mainly due to increased capillary permeability and is seen in Acute Respiratory Distress Syndrome (ARDS) and pneumonia.

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4 Acid-Base Balance and Disturbance

INTRODUCTION

Acid-base disorders are common in pediatric intensive care unit (PICU) patients. Acidosis both metabolic and respiratory, are the hallmarks of multiple organ failure and seen in sepsis, trauma, and postoperative patients (particularly cardiac surgery) as well as in renal, metabolic and endocrine conditions. Both respiratory and metabolic alkaloses also occur with regularity in PICU. Thus it is important that the intensivist not only understands the underlying processes involved in acid-base disorders but can also apply this to managing conditions properly. This is vital as there is compelling research base evidence that misinterpretation and consequent mismanagement of acid-base disorder is common in hospital medicine.

DEFINITIONS

- Acidosis is an abnormal process or condition which lowers the arterial pH if there is no compensatory response
- Alkalosis is an abnormal processes condition which raises the arterial pH if there is no compensatory response
- Acidemia is arterial pH lower than 7.35. It can cause hyperkalemia as potassium exits cells to preserve trans-membrane potential
- Alkalemia is arterial pH greater than 7.45. It is associated with hypokalemia due to potassium movement into cells
- In mixed acid-base disorders, coexisting disorders may have opposite effects on pH. Generally the most severe disorder dictates the pH.

pH AND HYDROGEN IONS

Hydrogen ion concentration $[H^+]$ is expressed in nmol/L, i.e. a millionth of a mmol. Thus, the concentration of Na^+, Cl^-, K^+ and other strong ions are a factor of a million times more concentrated in extracellular fluid (ECF) and intracellular fluid (ICF) than H^+. Due to the scale of this, the $[H^+]$ is routinely expressed as the negative logarithm of $[H^+]$.

- pH 7.4 corresponds to $[H^+]$ 40 nmol/L
- The normal range for pH is 7.35–7.45 ($[H^+]$ 45–35 nmol/L), i.e. the change in $[H^+]$ is only 10 nmol/L. This is an indication of how tightly controlled $[H^+]$ is in normal daily processes, e.g. exercise.
- Due to the logarithmic nature of pH, at the acidotic end of the scale, the change in $[H^+]$ is much higher than at the alkalotic end, i.e. pH 7.1 = 80 nmol/L $[H^+]$; pH 7.7 = 20 nmol/L. A drop in pH from 7.4 to 6.8 involves a 6-fold increase in $[H^+]$.

PHYSIOLOGICAL PRINCIPLES

Acid Production

As fire makes smoke, so metabolism makes acids. Acids are primarily:

- Respiratory acid: CO_2 which is excreted via the lungs. This combines with H_2O to produce H_2CO_3 which dissociates into HCO_3^- and H^+ ions
- Metabolic acid: Fixed organic acids (not excreted by lungs), which dissociate into anions (A^-) and H^+ ions, are excreted in the urine
  - Lactate from carbohydrate metabolism
  - Ketoacids (acetoacetate and β-hydroxybutyrate) from fat metabolism
  - Phosphates and sulfates from protein metabolism.

Acid-Base Regulation

For acid-base balance, the amount of acid excreted must equal the acid produced. The body has three processes to regulate acid-base balance:

1. Buffer
2. Ventilatory
3. Renal
   - Immediate buffering: The body has a huge capacity to buffer via the process: $A^- + H^+ \rightarrow HA$. Thus, a 1 mmol/L fall in A requires 10^6 nmol/L (1 mmol/L) of H^+ ions to be "mopped" up by another buffer. The main buffers are bicarbonate (HCO_3^-), plasma proteins, hemoglobin and phosphates
   - Immediate respiratory response: H^+ ions stimulate chemoreceptors to increase ventilation, and more CO_2 is excreted (lowering $PaCO_2$) as follows:
     $H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$
   - Slow renal response: The kidney reabsorbs filtered HCO_3^- ions (raising plasma HCO_3^-) and excretes fixed acids in response to respiratory acidosis. This response takes between 12 hours to several days (acute or chronic renal response).

Simple and Mixed Acid-Base Disturbances

A simple acid-base disturbance denotes the presence of one primary process, coupled with its appropriate physiologic response. For example, in primary respiratory acidosis with $PaCO_2$ of 50 mm Hg, plasma HCO_3^- generally increases appropriate by 2–3 mEq/L in an attempt to balance acidemia, caused by increased $PaCO_2$ (partially compensated).

A mixed acid-base disturbance refers to coexistence of two or more primary processes. These processes may have additive

or nullifying effect on plasma acidity. For example, if in above condition of $PaCO_2$ 50 mm Hg, plasma HCO_3^- decreases instead of increasing, then metabolic acidosis together with respiratory acidosis have taken place, for example such conditions occur in respiratory distress syndrome (RDS), cystic fibrosis, unresponsive or untreated acute severe bronchial asthma.

METABOLIC ACIDOSIS

"Acid" derives from the Latin word "acidus", which means sour.

Examination of Acid-Base Status

There are three accepted models for quantifying acid-base status in common use:

- $HCO_3^-/PaCO_2$ relationship, i.e. Henderson-Hasselbalch equation
- BE and AG calculation
- Stewart's quantitative approach, i.e. strong ion difference (if indicated and available).

Bicarbonate/$PaCO_2$

- CO_2 is directly measured in blood gas analyzers
- CO_2 combines with water to form carbonic acid which can dissociate:
  $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$
- HCO_3^- is not directly measured but is calculated from the Henderson-Hasselbalch equation:
  $pH = pK + Log_{10}[HCO_3^-]/[CO_2]$
  where K is the equilibrium constant (6.1)
- The normal range for HCO_3^- concentration is 18–26 mmol/L but can be lower (12–16 mmol/L) in preterm babies.

Base Excess

- The BE is a single calculated variable that is used to quantify the metabolic (nonrespiratory) component of a patient's acid-base status
- Base excess is defined as the quantity of alkali (HCO_3^-) required to titrate blood to a pH of 7.4 with a fixed $PaCO_2$ of 5.3 kPa (i.e. normal) at 37°C. In practice, this is calculated from the Siggaard-Andersen nomogram by most modern blood gas analyzers
- A negative BE (base deficit) implies metabolic acidosis.
- A positive BE implies metabolic alkalosis.

Anion Gap

This is a parameter used to establish the cause of a patient's metabolic acidosis, i.e. the underlying problem is:

- Secondary to accumulation of unmeasured anions and thus H^+ ions, i.e. raised AG.

  or

- Secondary to accumulation of chloride ions (Cl^-), i.e. normal AG.

$$AG = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$$

- Normal AG is 8–16 mmol/L. If this is clearly raised, i.e. more than 20 mmol/L, then this represents significant unmeasured anions in plasma/ECF.

Causes of metabolic acidosis with increased AG (due to unmeasured anions):

- Shock status (lactic acidosis from septic shock, hypovolemic shock)
- Diabetic ketoacidosis (increase ketones)
- Renal failure (increase SO_4^{2-} and PO_4^{3-} accumulation).
- Poisons, e.g. ethanol, methanol, salicylates, ethylene glycol
- Metabolic disorders: Inborn error of metabolism like organic acidemia, fatty acid oxidation defect. A useful aide to remember is MULEPACK for different causes of metabolic acidosis with increased AG.
  - M = Metabolic defects, e.g. organic acidemia, fatty acid oxidation
  - U = Uremia
  - L = Lactic acidosis: Tissue ischemia in shock (hypovolemic or septic shock)
  - E = Ethanol, methanol
  - P = Paraldehyde
  - A = Aspirin
  - C = Carbon monoxide
  - K = Ketones in diabetic ketoacidosis (DKA)

Normal AG metabolic acidosis occurs in following conditions. This is commonly due to the loss of HCO_3^- from the gut or kidney, or impaired acid secretion by the kidney.

- Diarrhea (most frequent cause in children)
- Type I (distal) renal tubular acidosis (RTA): Inability to excrete hydrogen ion, urine pH is always high (>6.5); caused by a variety of medications or is inherited; often associated with hypokalemia and hypercalciuria
- Type (proximal) II RTA: Impaired reabsorption of HCO_3^- from proximal tubule, usually associated with other proximal tubular dysfunction such as phosphaturia or glycosuria (Fanconi syndrome)
- Type IV (hyperkalemic) RTA: Inadequate aldosterone production or inability to respond to it, seen in acute pyelonephritis or obstructive uropathy.

Approach to Diagnosis and Management of Metabolic Acidosis

Clinical Assessment

History:

A thorough history is important. One will need to identify any symptoms of fever, flank pain and vomiting (pyelonephritis), lethargy, or altered mental state (metabolic disease, sepsis or poisoning). Then specific question should be asked about the gastrointestinal symptoms particularly of diarrhea and renal tracts, and growth. Lastly, there may be a significant family history of renal disease, kidney stones or early infant death.

Examination

A full examination is needed (Fig. 1). Assess:

- Cardiovascular system: Warm, flushed skin or cold clamming extremities, increased pulse rate, decreased blood pressure
- Respiratory system: Tachypnea, deep rapid respiration in absence of clinical respiratory features like cough and no added sound on chest auscultation (suggestive of renal failure, DKA)
- Hydration:
  - Significant dehydration associated with diarrheal disease and DKA
  - Severe dehydration, deep rapid breathing with abdominal pain is suggestive of DKA.

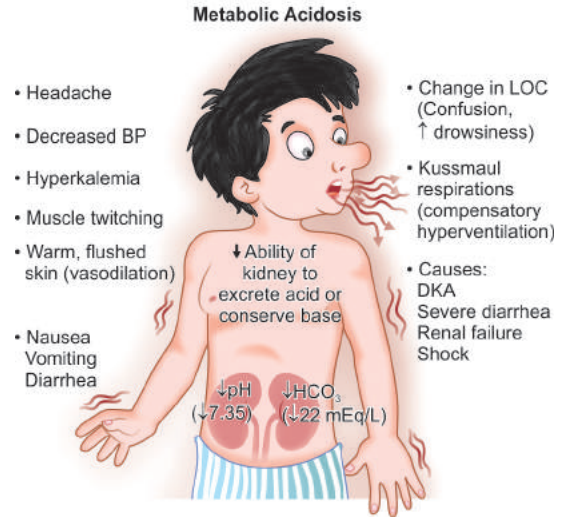

Fig. 1: Clinical features of metabolic acidosis

- CNS: Altered sensorium in sepsis, poisoning and metabolic disorder associated with metabolic acidosis
- Abdomen
- Growth: Usually retarded in renal failure, untreated diabetes mellitus

1. Confirm diagnosis (blood gas analysis):
   - Arterial pH less than 7.34
   - Base excess less than 3 mmol/L
   - $PaCO_2$ appropriate for acidosis, i.e. it is usually low when hyperventilatory compensation occurs but is often high if there is also a respiratory acidosis component or normal in ventilated paralyzed patients.
2. Check blood and urine:
   - Measure serum Na, K, Cl, urea, creatinine, lactate, glucose and albumin
   - Check urine for pH, ketones
   - Imaging: Renal ultrasound scan looking for nephrocalcinosis (type I RTA)

   Once diagnosis of metabolic acidosis is confirmed, attempt to identify the underlying cause by calculation of corrected AG.
3. AG more than 16—consider clinical context and treat cause:
   - Lactic acidosis: Does this fit with clinical context, e.g. hypotension, fluid/blood loss, myocardial dysfunction, septic shock, seizures, etc.
   - Ketoacidosis (↑ blood sugar)
   - Renal failure (↑ urea, creatinine)
   - If none of these, consider underlying metabolic disease or poisoning.
4. AC less than 16— consider clinical context and treat cause:
   - HCO_3^- loss from gastroenteritis (GIT).
   - HCO_3^- loss from kidneys (RTA).
   - Check chloride, whether it is raised.
   - Excess chloride from drugs, infusions.

Treatment

- Most metabolic acidoses seen in PICU are lactic acidosis with normal plasma lactate. This only rises in more severe cases, secondary to shock (reduced oxygen delivery) or seizures (↑oxygen consumption) and improves with attention to fluid resuscitation and oxygen.
- Aim for target pH more than 7.25, if possible. Consider ventilatory support if pH less than 7.2.
- Maintain supportive measures and organ support even in the absence of diagnosis until pH improves.
- Consider HCO_3^- therapy if indicated.

Monitoring

Ensure the airway breathing circulation (ABC). Then, the form and type of monitoring will be dictated by the patient's condition. Start with continuous pulse oximetry and ECG monitoring, and intermittent BP monitoring. Follow hourly output.

Therapy

Correction of Dehydration

If the patient is dehydrated then this problem should be treated with oral or IV replacement. This alone may improve serum HCO_3^-. Other interventions if required are follows:

- Inotropes in persistent hypotension after fluid resuscitation
- Identify the underlying cause and treat accordingly (antibiotic in sepsis)
- The use of buffers is common but lacks consensus on indications and possible benefits
- Sodium bicarbonate ($NaHCO_3$) may worsen intracellular acidosis, hypokalemia and hypocalcemia. It may increase the risk of cerebral edema in diabetic ketoacidosis.

However, HCO_3^-/alkali therapy may be used for specific metabolic disorders.

Metabolic Acidosis with Increased AG

- Identify the cause and treatment; IV $NaHCO_3$ is only given as last resort (child must be able to excrete the CO_2 generated)
- Sodium bicarbonate 8.4% (1 mmol/mL) is commonly used and may be indicated in:
  - Severe acidosis (pH <7.1) and hypotension when inotropes appear to be ineffective due to receptor dysfunction
- Sodium bicarbonate should not be given as rapid bolus but as slow infusion (i.e. 1–2 mL/kg/hr of 8.4% $NaHCO_3$ = 1–2 mmol/kg/hr) and titrate to effect, i.e. target pH more than 7.2
- Estimate the deficit = (20 – [HCO_3^-]) × weight (kg) × 0.5 mmol
- Replace over 24–48 hours with oral supplements
- Tham (tromethamine) is a sodium-free buffer that does not generate CO_2. Despite its attractive qualities, it has not yet been shown to have clinical advantages over $NaHCO_3$. It has also been linked with the adverse effects of hyperkalemia, hypoglycemia and apnea.

Metabolic Acidosis with Normal Anion Gap

This indicates HCO_3^- loss. Diarrhea is the most common cause; acidosis is corrected by fluid and electrolyte correction by oral rehydration salt or in severe rehydration by IV polyelectrolyte solution. Usually do not require extra IV $NaHCO_3$.

Other causes of metabolic acidosis with normal AG are:

- Distal or proximal RTA: Treatment includes HCO_3^- supplementation
- Hyperkalemic RTA: Correct serum HCO_3^- and increased fluids to improve sodium delivery to the distal tubule (this will enhance potassium secretion).

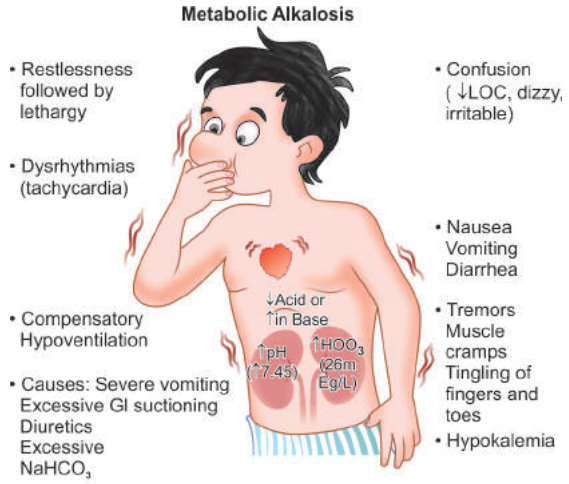

Fig. 2: Clinical features and etiology of metabolic alkalosis

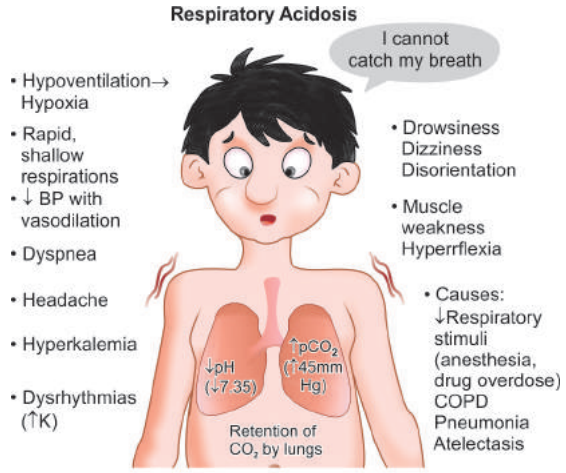

Fig. 3: Etiology and clinical features of respiratory acidosis

METABOLIC ALKALOSIS

Causes

- Often results from chloride depletion (secondary to vomiting or loop diuretic therapy)
- It is rarely due to alkali administration, laxative, or diuretic abuse
- Both severe vomiting and diuretics can cause hypokalemia and an aggravating "paradoxical aciduria" which worsens the alkalosis as seen in pyloric stenosis. Clinical features and etiology of metabolic alkalosis are shown in Figure 2.

Treatment

- Standard rehydration with 0.9% normal saline and potassium supplementation is usually an adequate therapy
- Some causes of chloride depletion are resistant to replacement therapy such as renal tubular defects (Bartter syndrome should be treated with indomethacin)
- Administration of acid is very occasionally needed for metabolic alkalosis:
  - 0.5 mL/kg of 5.35% ammonium chloride into a central vein over 1 hour (do not give in liver impairment)
  - In liver impairment, use 5 mL/kg of 100 mmol/L hydrochloric acid into a central vein over 1 hour.

RESPIRATORY ACIDOSIS AND RESPIRATORY ALKALOSIS

When an increase or decrease in $PaCO_2$ initiates a disturbance, it is referred to as respiratory acidosis or respiratory alkalosis. Also consider primary clinical conditions as respiratory disorders like pneumonia, asthma, bronchiolitis, etc.

Acid-Base Balance Involving Respiratory System

1. Acid-base disorders involving primary respiratory diseases (pneumonia, bronchial asthma, etc.) with hyperventilation causing respiratory alkalosis (↓pCO_2) due to washing out of CO_2
2. Acid-base disorders due to hypoventilation associated with primary lung function and hypoventilation due to CNS depression. It results in respiratory acidosis (↑pCO_2) due to CO_2 retention
3. Obstructive airway disease (severe acute bronchial asthma as late finding, severe pneumonia; retention of CO_2 cause ↑pCO_2 with respiratory acidosis)
4. Respiratory functions in primary metabolic disorders (metabolic acidosis like diabetic ketoacidosis and metabolic alkalosis like hepatic failure). In metabolic acidosis, hyperventilation washout CO_2 in an attempt to compensate metabolic acidosis. In metabolic alkalosis, hypoventilation occurs, retaining CO_2 in an attempt to compensate metabolic alkalosis.

Respiratory Acidosis

Step 1: Confirm the pH (<7.35)
Step 2: Determine the $PaCO_2$ (≥5.3 kPa or >40 mm Hg)
Step 3: Increased BE. Slightly high (2–3 mmol higher HCO_3^- than normal) in acute condition. In chronic condition, kidney gets more time to conserve more HCO_3^- (↑BE), to compensate acidemia and pH almost become normal (compensated respiratory acidosis)
Step 4: Clinical condition: Primary clinical condition should be respiratory, like pneumonia, bronchiolitis or hypoventilation due to primary respiratory condition or CNS depression.

Remember if $PaCO_2$ increases, BE also increases and if $PaCO_2$ decreases, BE also decreases as a compensatory mechanism (Fig. 3).

Causes of Respiratory Acidosis (Following Steps are Essential Characteristics)

Any process (other than alkalemia) that produces alveolar hypoventilation results in respiratory acidosis. The causes are:

Central Nervous System Disease

- Sedative overdose
- Narcotic poisoning
- Respiratory arrest secondary to brain damage due to intracranial lesion
- Brain tumor

Pulmonary Diseases

- Primary alveolar hypoventilation in late complicated acute bronchiolitis, life-threatening bronchial asthma due to exhaustion

- Acute airway obstruction (foreign body obstruction)
- Acute obstructive lung diseases (late stage of severe acute bronchial asthma)
- Chronic obstructive pulmonary disease
- Severe and very severe pneumonia (pneumonia usually causes respiratory alkalosis due to hyperventilation)
- Severe pulmonary edema
- Tension pneumothorax
- Respiratory muscle disorders like Guillain-Barré syndrome (GBS), poliomyelitis, myopathies, spinal muscular atrophy
- Restrictive disease of thorax (scoliosis, pectus excavatum).

Acute versus Chronic Respiratory Acidosis

Most of the acute respiratory acidoses are short-lived with short lived increased $PaCO_2$. There is a small secondary increment of HCO_3^- (2–3 mEq/L), and pH still remains low (acidic).

In chronic respiratory acidosis (most often the consequence of chronic obstructive lung disease), secondary renal responses result in more marked increase in plasma HCO_3^- concentration. The mean increment in HCO_3^- concentration in an individual fully adapted to chronic hypercapnia is approximately 0.4 mEq/L for each mm Hg increment in $PaCO_2$. The coexistence of metabolic acid-base disturbance in patients with primary respiratory acidosis can be assessed by determining whether the level of plasma HCO_3^- concentration corresponds to the level anticipated for the observed degree and duration of hypercapnia.

Example

A child with long-standing chronic lung disease (cystic fibrosis) has a $PaCO_2$ of 55 mm Hg, pH 7.34 and plasma HCO_3^- concentration of 30 mEq/L. The increment above normal $PaCO_2$ is approximately 15 mm Hg (55–40 mm Hg). Thus one might anticipate an increment in plasma HCO_3^- concentration of approximately 6 mEq/L just on the basis of chronic hypercapnia (15 × 0.4 mEq/L). The increment in HCO_3^- concentration will make serum HCO_3^- (considering mean serum HCO_3^- as 24 mEq/L) level to be (24 + 6) 30 mEq/L, which is called partially or completely compensated (if pH becomes normal) respiratory acidosis. This sort of compensated respiratory acidosis may also be found in chronic obstructive airway disease in adult and sometimes in persistent (moderate to severe) asthma in children. Compensatory respiratory acidosis is unusual in acute respiratory conditions. If HCO_3^- level increases more than 30 mEq/L, than independent process also works, which is an evidence of mixed acid-base disturbance in which an element of metabolic alkalosis is present (the respiratory acidosis + metabolic alkalosis).

Mixed Respiratory Acidosis with Metabolic Acidosis

This is not an uncommon mixed acid-base disturbance, where two primary mechanisms work. Important steps are:

Clinical settings

+

Step 1: Confirm the pH (<7.5)

Step 2: Confirm the $PaCO_2$ (>5.3 kPa or >40 mm Hg)

Step 3: High negative BE (base deficit) and decreased HCO_3^- instead of usual increased BE and increased HCO_3^- found in chronic respiratory acidosis with its appropriate physiological response.

Clinical settings associated with mixed respiratory and metabolic acidosis with Type 2, respiratory failure ($\downarrow pO_2$, $\uparrow pCO_2$) are found in severe complicated acute bronchiolitis, final stage of acute severe bronchial asthma, cystic fibrosis, respiratory distress syndrome, etc. In both acute severe bronchiolitis and acute severe bronchial asthma, initially there is decreased pO_2 and decreased pCO_2 due to hyperventilation and respiratory alkalosis follows. As bronchial obstruction and hypoventilation finally occur due to exhaustion, pCO_2 increased. If increased pCO_2 and decreased pO_2 are not corrected timely by assisted ventilation, respiratory acidosis takes place. If respiratory acidosis and hypoxemia continue then anaerobic glycolysis and lactic acidosis take place causing metabolic acidosis. Serum HCO_3^- then falls inappropriately to increased pCO_2 and decreased pH. Here increased pCO_2 is associated with decreased HCO_3. Such clinical setting sets in mixed respiratory and metabolic acidosis.

Example

A 1-year-old child with acute severe bronchiolitis, developed type II respiratory failure with pO_2 of 50 mm Hg and pCO_2 60 mm Hg, serum HCO_3^- of 12 mEq/L and pH of 6.9. A rise of pCO_2 of 20 (60–40 mm Hg) is supposed to increase serum HCO_3^- to 20 × 0.4 = 8 mEq/L, that is serum HCO_3^- is expected to be (24 + 8) = 32 mm Hg. However, serum HCO_3^- (base deficit) was found to be 12 mEq/L. This indicates another primary process (here lactic acidosis due to hypoxia) working in opposite direction to make acidemia worse.

Practice

A 4-day-old preterm newborn baby presented with respiratory distress, since birth with pO_2 of 55 mm Hg and pCO_2 60 mm Hg. His HCO_3^- level is 8 mEq/L and pH is 6.9. X-ray shows air bronchogram.

1. What is his respiratory status?
2. What is the most likely clinical diagnosis?
3. What is the acid-base status?

Answers:

1. The baby has developed type II respiratory failure ($\downarrow pO_2$ and $\uparrow pCO_2$)
2. Most likely, diagnosis is respiratory distress syndrome (RDS) as evidenced by air bronchogram on chest X-ray
3. Mixed respiratory acidosis and metabolic acidosis.

Explanation:

pH: Less than 7.4 (Acidemic).

pCO_2: More than 40 mm Hg respiratory acidosis as primary clinical setting is respiratory problem (RDS)

Plasma HCO_3^-: Decreased instead of physiological response of increased HCO_3^-.

pCO_2 is 20 mm Hg (60–40 mm Hg) more than normal. In simple respiratory acidosis, there will be increase of 2–3 mEq/L of serum HCO_3^- in acute hypercapnia (within few hours) and 0.4 mEq/L for each mm Hg increase of pCO_2 in chronic hypercapnia. If condition continues further (chronic), 8 mEq/L (20 × 0.4) increase in serum HCO_3^- above normal is expected. If normal mean serum HCO_3^- is considered to the 24 mEq/L than HCO_3^- is expected to be 32 mEq/L (24 + 8). However, the baby had serum HCO_3^- of 8 mEq/L which indicates another primary process, which has inappropriately decreased serum HCO_3^-. Here, prolonged hypoxia has caused tissue hypoperfusion

and lactic acidosis. Therefore mixed respiratory acidosis with metabolic acidosis occurred instead of respiratory acidosis with usual physiological compensated (partially or completely) metabolic alkalosis.

Respiratory Alkalosis

Clinical conditions: Pneumonia, bronchial asthma, bronchiolitis associated with hyperventilation (Fig. 4). Although respiratory disorders, like pneumonia, bronchial asthma, bronchiolitis commonly cause respiratory alkalosis, very severe pneumonia, acute severe bronchiolitis and untreated or medically unresponsive acute severe bronchial asthma (hypoventilation due to exhaustion and severe bronchial obstruction), may eventually cause respiratory acidosis due to CO_2 retention.

Step 1: Confirm the pH (>7.45)
Step 2: Determine the $PaCO_2$, it should be less than 4.5 kPa or 33 mm Hg
Step 3: Increase in plasma HCO_3 (↓BE)

Degree of decreased BE depends on acute or chronic clinical condition. In acute clinical condition (acute respiratory alkalosis), there will be slight fall in decreased BE (↓HCO_3^-). However, in prolonged clinical condition (chronic lung disease), kidney gets more time to adjust HCO_3^- (excretes ↓HCO_3^-) and pH may become almost normal (compensated respiratory alkalosis).

Example of Acute versus Chronic Respiratory Alkalosis

Many respiratory diseases causing respiratory alkalosis, like pneumonia and bronchial asthma, are short-lived. In this instance, the acid-base disturbance is manifested by primary decrement in $PaCO_2$ (due to primary hyperventilation and tachypnea) and a small secondary physiological decrement in HCO_3^- concentration that results from the titration of nonbicarbonate tissue buffers. A decrement of only 3–4 mEq/L (considering mean serum HCO_3^- 24 mEq/L as normal) may be expected to occur with several minutes after $PaCO_2$ is lowered to 20–25 mm Hg.

Less commonly if respiratory alkalosis lingers enough (a few days or more), renal adjustment in HCO_3^- concentration occurs, e.g. in patients with hepatic insufficiency, chronic hyperoxic states, chronic salicylate poisoning, etc. When secondary renal adjustments are fully established and a new steady state is maintained, the average reduction in plasma HCO_3^- is approximately 0.5 mEq/L for each mm Hg reduction of $PaCO_2$.

For example, if $PaCO_2$ is 20, than fall in HCO_3^- will be 40–20 × 0.5 = 10 mEq/L, plasma HCO_3^- will be 24–10 = 14 mEq/L.

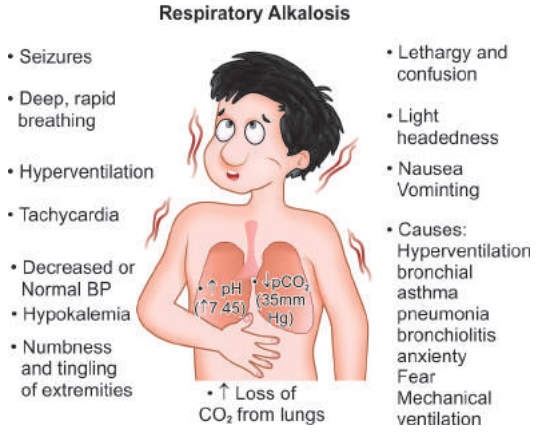

Fig. 4: Etiology and clinical features of respiratory alkalosis

Pulmonary Function in Primary Metabolic Acid-Base Disturbance

Lungs also play secondary important role by increasing or decreasing ventilatory rate in primary metabolic acidosis or alkalosis. In metabolic acidosis, there will be hyperventilation with CO_2 washout (↓pCO_2), and in metabolic alkalosis, there will be hypoventilation, with CO_2 retention and increased $PaCO_2$.

In metabolic acidosis for each mEq/L, reduction of HCO_3^- there will be a fall of pCO_2 of 1.0 to 1.3 mm Hg through hyperventilation. For example, if serum HCO_3^- is 12 mEq/L, then decrease of pCO_2 will be 14.4 (12 × 1.2), considering mean serum HCO_3^- as 24 mEq/L. Therefore anticipated pCO_2 will be 25.6 mm Hg (40–14.4 mm Hg), considering mean normal $PaCO_2$ as 40 mm Hg. This is primary metabolic acidosis with appropriate physiological response, which tends to compensate acidemia.

However, lungs may also act as another primary process in addition to metabolic disturbance. Like mixed metabolic acidosis with respiratory alkalosis, when lung hyperventilates disproportionately. This commonly occurs in Gram-negative septicemia.

Examples of Mixed Metabolic Acidosis and Respiratory Alkalosis

A child with Gram-negative septicemia with shock found to have rapid deep respiration. Arterial blood studies revealed a $PaCO_2$ of 15 mm Hg, a pH of 7.35 and a plasma HCO_3^- of 8 mEq/L. Plasma HCO_3^- is 16 mEq/L below normal (24–8 mEq/L); as a result of metabolic acidosis, presumably as the result of lactic acid over production. Thus one might expect a reduction of $PaCO_2$ of approximately 19 mm Hg just as the result of physiologic response to this degree of metabolic acidosis (16 mEq/L × 1.2 = 19 mEq/L). However, the observed reduction of pCO_2 is 25 mm Hg (40–15), instead of anticipated reduction of $PaCO_2$ of 19 mm Hg. This discrepancy between the observed and expected degree of pCO_2 signifies an independent process stimulating ventilation and thus evidence of mixed disturbance in which metabolic acidosis and respiratory alkalosis coexist. This condition may be found in Gram-negative septicemia.

Management of Respiratory Acidosis

- Usually occurs secondary to respiratory failure, e.g. ventilation perfusion abnormalities, low compliance, increased airway resistance, decreased respiratory drive, airway obstruction, increased dead space
- In chronic setting, metabolic compensation (provided renal function is adequate) usually normalizes pH
- Pay attention to ABCs, i.e. intubate and ventilate if necessary and treat underlying cause of respiratory failure
- Heparin contamination of a gas sample can lower $PaCO_2$ and HCO_3^- measurements and can mask renal compensated respiratory acidosis.

Management of Respiratory Alkalosis (pCO_2 <25 mm Hg)

Disorders of high pH are classified into those resulting from excess removal of CO_2 (respiratory alkalosis), and those resulting from loss of nonvolatile acids or accumulation of buffer (metabolic alkalosis). Respiratory alkalosis can occur due to:

- Hyperventilation from different causes leading to respiratory alkalosis (pneumonia, bronchiolitis, bronchial asthma)
- Other causes include anxiety, hysterical hyperventilation and central hyperventilation from brain injury, encephalopathy, encephalitis, salicylate toxicity, hypoxia
- Also commonly occurs in ventilatory support from excessive minute volume when a patient is initially intubated and ventilated. It can be minimized from monitoring early arterial gases or from use of $EtCO_2$ monitoring-severe hypocapnia. Respiratory alkalosis from overventilation can significantly reduce brain perfusion and aggravate cerebral ischemic injury.

Clinical Features of Respiratory Alkalosis

In addition to hyperventilation symptomatic respiratory alkalosis appear only in acute severe respiratory alkalosis which are one or more of the followings:

- Tingling around mouth and fingers
- Parasthesias, numbness
- Tetany and convulsion due to decrease in ionic calcium commonly found in hysteric hyperventilation.

Treatment

- Treatment consists of treating specific underlying causes
- Check oxygen saturation to exclude hypoxia
- Try to find the source of anxiety and take steps accordingly
- If occurs in patients on ventilators due to excessive minute volume then measures to be taken include reducing minute volume and/or introducing dead space into the ventilator circuit.

KEY POINTS OF ACID-BASE DISTURBANCE AS A WHOLE

- Regulation of normal extracellular pH (7.4) and intracellular pH (7.0) is vital for organ function in the long-term
- Apart from primary metabolic disorders, most acid-base disorders in PICU should be viewed as a complex physiological response to an underlying pathological abnormality
- Despite some controversy in mechanisms, it is best to approach acid-base disorders via the principles of:
  - pH
  - $PaCO_2$ relationship (Henderson-Hasselbalch equation) to pH
  - Calculation of the base excess (BE)
  - Anion gap (AG)

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5 Growth and Development

The characteristics of children which most clearly distinguish them from adults are that they are growing and developing. Adults do not grow, except in girth and most of them are degenerating. The processes of growth and development start from conception and are influenced by a wide variety of genetic and environmental variables. Growth may be affected by disease, it may also affect the manifestations of disease.

CHILDHOOD GROWTH

Growth consists of three phases superimposed upon each other, each of which is under different controls— nutritional and hormonal.

Infantile Phase

Growth is predominantly under nutritional control. Children with congenital growth hormone (GH) deficiency usually have normal birthweight and length.

Childhood Phase

Childhood phase is under hormonal control, predominantly GH and thyroid hormone. Nutritional factors also play a role. There is a steady and decelerating growth curve which starts at around 2–3 years of age and continues until puberty. By the 8th year of birth, most children achieve three-quarters of their adult height.

Malnutrition is associated with a GH-resistant state with elevated serum GH, but abnormal pulsatility of Insulin-like Growth Factor-1 (IGF-1) and GH receptor. GH in infancy is determined by nutrition. During the first year of life, infant grows more rapidly than any other period in extrauterine life. By 2 years of age, a child is roughly half of adult height indicating that 50% of growth has already occurred.

Puberty Phase

Puberty phase is under the control of GH, and sex hormone acting synergistically. Height velocity may double during pubertal growth spurt; increasing trunk length is predominant. These last from adolescent onward and have different timing and strength in two sexes.

It is the phase of growth which accounts for the sex differences in the final height of around 14 cm between males and females. While girls enter their growth spurt earlier, the peak height velocity is not as great as in boys. The same sex steroids cause fusion of the epiphyseal growth plate and a cessation of growth, so final height is reduced if puberty is early.

PHYSIOLOGY OF GROWTH

After initial infantile period, GH is the main factor involved in growth. GH is secreted in a pulsatile fashion with pulses approximately every 180 minutes. The largest pulses are at the night time.

The most important regulators of GH are hypothalamic hormones, growth-hormone-releasing hormone (GHRH) which is stimulatory and somatostatin which is inhibitory. GHRH and somatostatin, in turn, are regulated by feedback from blood GH and IGF-1 concentrations.

EFFECTS OF GROWTH HORMONE

Direct Effects

- Opposes insulin, being lipolytic in fat and causing gluconeogenesis in muscle
- Stimulates duration and multiplication of chondrocytes promoting long bone growth.

Indirect Effects

- In the liver, it promotes the synthesis and secretion of peptide IGF-1, and other tissues stimulate bone growth, protein synthesis and muscle.

  Other hormones involved in growth are:

Sex Steroid

Increasing level of sex steroid in puberty stimulates growth by increasing endogenous GH secretion and may also have a direct effect in IGF-1 production.

Thyroxine

It plays an important role in controlling growth in part by regulating GH secretion.

Growth Factors

Insulin-like growth factors: IGF-1, IGF-2 and IGF-3 have a high sequence similarity to insulin and form part of a system referred to as GH-IGF axis.

POSTNATAL GROWTH

An infant continues to grow in weight, height and in head circumference (HC) with alteration of body proportion. At birth, the upper and lower segment of body proportion is 1.7:1, at 2 years of age it becomes 1.46:1 and at 10 years of age it becomes 1:1. The growth pattern during childhood is not similar in all stages of development. Weight and height increase relatively rapidly in the early months of life and at puberty,

Table 1: Growth in infancy and increment of growth parameters per day

Age	Weight (g)		Length (cm)	Skull circumference (cm)
At birth	3,100–3,400		50	34–35
Birth–3 months (increment/day) At 3 months	25–30 g/day increment = 5.5 kg		3.5 cm/month = 60 cm	2 cm/month = 40 cm
3–6 months	20 g/day	400 g/month	2.0 cm/month	1 cm/month
6–9 months	15 g/day		1.5 cm/month (9 months = 70 cm)	0.5 cm/month
9–12 months	12 g/day	300 g/month	1.3 cm/month (12 months = 73–75 cm) 4 years = 100 cm (doubles) 13 years = 150 cm (triples)	0.3 cm/month (12 months = 46–47 cm) 24 months = 48 cm 7 years = 50 cm 12 years = 52 cm

*Birthweight recovers its initial losses by 10–15 days postnatally. It doubles by 5 months and triples by 12 months

The pattern of stature (length/height) gain during period of growth and velocity curves for girls and boys.
Easy formula for approximate height from 2–12 years: Age in years × 6 + 77 cm, for example, 5 years child = 5 × 6 + 77 = 107 cm. Another formula for approximate height from 4 years to 10 years is 100 + 6 cm for each year after 4 years. For 7-year-old child expected height = 100 + 18 = 118 cm.

but at a very constant rate in between. For the first 3 months, weight increases at 25–30 g/day, length increases at velocity of 3.5 cm/month and HC increases at the rate of 2 cm/month. The growth velocity then declines and child weight increases at 20 g/day, length increases by 2.0 cm/month and HC increases by 1 cm/month for up to 6 months and continues to decelerate until puberty. The circumference of the head is half of its total growth in the 1st year of life (Table 1). Sexual development is concentrated into two episodes, at the 6th week of embryonic life and at puberty.

Growth is traditionally estimated by weight and height (length in babies) and this is sufficient for most purposes.

In clinical medicine, other measurements including sitting height (which reflects body proportions), span, skin fold thicknesses and skeletal age by X-ray, may be needed to elucidate particular problems.

CHILDHOOD GROWTH

Early childhood is in between 1 and 5 years of age (GH controlled).

Head

There is a striking decline in the growth rate, e.g. neural (brain or head), which increases by 35% (35 cm to 46–47 cm) from birth to 1 year of age, increases by about 10% through the 5th year, most of it occurs between 1 and 2 years of age (at 5th year, 50.7 cm in the USA, and 50.3 cm in affluent Indians).

Length

Measurement in erect or supine position, between 2 and 5 years of age may have difference of 2 to 1 cm, supine length being more than height (standing). The child gains 1 cm/month between 1 and 2 years of age, about 6 cm/year between 2 and 6 years of age.

HEIGHT

Mid-parental Height

From 2 years of age, there is a strong correlation between:

- A child's centile position for height, and their final height centile.
- A child's centile position and their parents' height centiles.

As adult males are on an average 14 cm taller than adult females, Mid-parental Height (MPH) for a boy is calculated as follows:

$$\text{MPH for a boy} = \frac{\text{Father's height (cm)} + \text{Mother's height (cm)}}{2} + 7$$

For a girl, 7 cm is deducted rather than added.

The target centile ranges (TCRs) (±2SD) are ±10 cm of MPH for a boy and ± 8.5 cm of the MPH for a girl.

Height Velocity (Fig. 1)

Growth is not a continuous process but has a number of superimposed phases.

1. *Weeks:* Growth spurts with intervening growth arrest (saltation and stasis).
2. *Months:* Seasonal variation in growth (usually faster in spring and summer compared with autumn and winter).
3. *Years:* Long-term variation over a number of years.

Mean Height Velocity

A mean height velocity on the 50th centile will cause a child to grow parallel to the 50th centile for height.

WEIGHT

Weight Gain

At 1 year, a child's weight becomes three times of his birth weight. At 2 and at 3 years of age, the child's weight becomes 4 and 5 times of child's birth weight, respectively. A child is expected to gain weight 8 g/day between 1–3 years and 6 g/day between 3–5 year. A simple way of expected weight of a child from 1–5 years is provided in Table 2.

Weight Velocity

The term centile crossing rather than "weight velocity" is usually used especially in infants. The phenomenon of regression to the mean means that children born larger for dates tend to catch down, whilst the small for dates catch up.

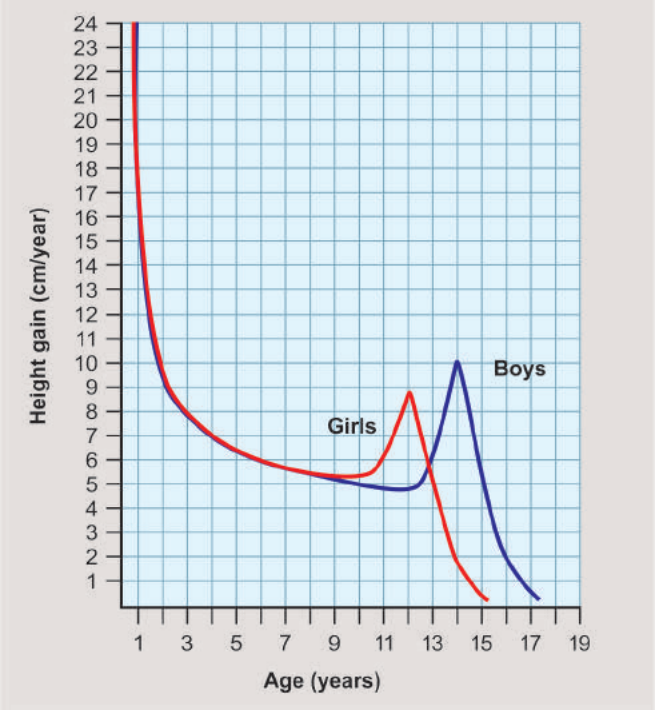


Fig. 1: Curves showing growth velocity of boys and girls. It shows that adult males are taller than females as they have a longer childhood growth phase, their peak height velocity is higher and their growth ceases later

Table 2: Expected weight at age; as multiple (times) of birthweight

Age (years)	Multiple of birthweight	Velocity
1 = 3×	Birthweight	8 g/day 1–3 years 6 g/day 3–5 years
2 = 4×	Birthweight	
3 = 5×	Birthweight	
5 = 6×	Birthweight	

Fifty percent of children cross at least one centile line between 6 weeks and 12–18 months. Five percent of children cross two centile line. Pubertal assessment is also required for growth which is discussed in Endocrinology chapter.

When interpreting measurements of growth and development, it is important to distinguish between normal and average. It is useful to known the average weight of a 1-year-old, the average age at which a child walks unaided, and the average head circumference of a newborn baby. It is also vital to know how far removed from average a measurement can be and yet remain within the range of normal. For each parameter, there is a distribution curve, and this can be indicated on standard record charts by showing centiles (percentiles) or standard deviations as well as averages. The 3rd and 97th centiles approximate to ±2 standard deviations. About 3% of normal children will be below the 3rd centile and another 3% above the 97th centile. In normally proportioned children, whether large, average or small for their age, the height and weight will occupy similar positions on centile charts. Much more can be learnt from serial observations of height, weight or head circumference than from a single measurement. The normal ranges for these are given in growth chart appendices (Fig. 2).

The grades of malnutrition are according to Gomez's classification, weight ranges as percentage to 50th centile (Table 3).

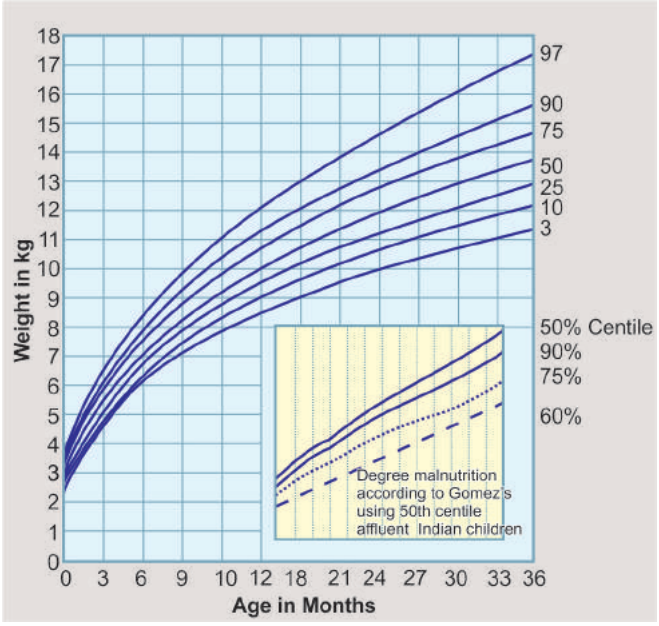


Fig. 2: Weight for age curve, birth to 3 years of age. Single measurement of a child can be put on this percentile weight for age, to assess the line he/she is following, how close he/she is to the 50th centile line

BONE AGE

Although GH secretion continues throughout the life, final height is achieved in the mid to late teens when bony epiphyses fuse under the influence of estrogen. As the hand and wrist contain numerous epiphyses, a radiograph of the nondominant hand enables a "bone age" to be calculated, which is an estimate of the "biological" rather than the "chronological" age. By quantifying the years of remaining growth, it also enables an estimation of final height to be made.

Several different methods are used to estimate the bone age with Tanner and Whitehouse methods being the most common.

GROWTH DISORDERS

There are a number of different factors that affect growth. These are as follows:

- Environmental:
  - Nutritional
  - Malnutrition
  - Socioeconomic
  - Poverty
- Birth size:
  - Small for gestational age
  - Intrauterine growth retardation
- Chronic illness:
  - Cardiovascular: Chronic heart failure
  - Respiratory: Asthma, cystic fibrosis
  - Renal: Chronic renal failure
  - Gastrointestinal: Coeliac disease, inflammatory bowel disease
- Familial:
  - Familial height: Familial short stature
  - Familial growth pattern: Constitutional delay of growth and puberty
- Endocrine:
  - Thyroid hormone: Hypothyroidism

Table 3: Fiftieth (100%) centile of weight for age in children between 3 and 72 months and weight range for malnutrition according to deviation from 50th (100%) centile weight

Approx. weight for age (kg)			Approx. weight range for malnutrition		
Age in months	**50th (100%) centile**	**Normal >90%**	**Grade I 90–75%**	**Grade II 75–60%**	**Grade III <60%**
3	5.7	5.1	5.1–4.3	4.3–3.4	3.4
6	7.4	6.7	6.7–5.6	5.6–4.4	4.4
9	8.5	7.7	7.7–6.4	6.4–5.1	5.1
12	9.3	8.4	8.4–7.0	7.0–5.6	5.6
18	10.7	9.6	9.6–8.0	8.0–6.4	6.4
24	11.9	10.7	10.7–8.9	8.9–7.1	7.1
30	12.9	11.6	11.6–9.7	9.7–7.7	7.7
36	13.8	12.4	12.4–10.4	10.4–8.3	8.3
42	14.6	13.1	13.1–11.0	11.0–8.8	8.8
48	15.4	13.9	13.9–11.6	11.6–9.2	9.2
54	16.2	14.5	14.5–12.2	12.2–9.7	9.7
60	17.1	15.4	15.4–12.8	12.8–10.3	10.3
66	18.1	16.3	16.3–3.8	13.8–10.9	10.9
72	19.2	17.3	17.3–14.4	14.4–11.5	11.5

Source: Reproduced from Gomez et al. Trop Ped Env Ch. Hlth. 2;77. Followed by National Nutrition Monitoring Bureau of India

  - Growth hormone: GH deficiency
  - Corticosteroid: Cushing's syndrome
  - Sex steroids: Precocious puberty
- Genetic:
  - Turner syndrome
  - Noonan syndrome
  - Russel-Silver Syndrome (RSS)
- Psychological factors:
  - Psychological deprivation.

CHILD DEVELOPMENT

(Also discussed in Vision and Hearing of Neurology Chapter)

Normal development follows a recognized sequence and the range of expected ages of milestones at which particular development skills are attained is well- established. The infant is a dynamic, ever-changing being who undergoes an orderly and predictable sequence of neurodevelopmental and physical growth. It is an exciting period of first smile, first successful grasp, first evidence of separation anxiety, first word, first step and first sentence.

Domains of Development

Development is assessed in four groups or domain, though there is a considerable overlap. The domains are:

1. Gross motor (Table 4):
   - Sitting, walking and running
2. Fine motor and vision (Table 5):
   - Hand skills, visual development
3. Speech, language and hearing (Table 6):
   - Both verbal and nonverbal communication skills, hearing development
4. Social behavior and play (Table 7):
   - Feeding, toileting, dressing and social relationship.

Neurodevelopmental sequences can be viewed broadly in terms of the traditional developmental milestones. Developmental milestones provide a systematic approach by which to observe the progress of the infant over time (Tables 4 and 5). It is important to analyze all milestones within the context of the child's history, growth and physical examination as part of an ongoing surveillance program.

There are some generalizations about neurodevelopmental maturation over time:

- Responses to stimuli proceed from generalized reflexes involving the entire body, as seen in the newborn (and fetus), to discrete voluntary actions that are under cortical direction.
- Development proceeds from cephalic to caudal and proximal to distal.
- Developmental progression is from dependence to independence.

Building and copying with blocks: Small wooden 1 inch cubes are the best. The child will copy a tower of 4 cubes at 1 year and 6 months of age (Table 8).

Copying: A child will copy the following shapes with a pencil:

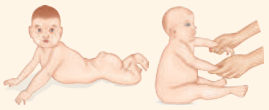
| Or ____	At 2 years	□	At 5 years
O	At 3 years	△	At 6 years
+	At 4 years	◇	At 7 years

Developmental Assessment

Developmental examination is the part of a multistep process of early identification and management of developmental impairments. The four main components of this examination are:

1. Eliciting concerns
2. Gathering information on social and biological risk factors
3. Making structured observations of spontaneous and elicited behavior
4. Interpreting findings with knowledge both of the features which raise significant concerns and of common behavioral phenotypes of developmental disorders.

Table 4: Developmental milestones in gross motor

Age	Milestones	Picture
3 months	Lifts head and shoulders off floor in prone position Little or no head lag on pull to sit	
6 months	Prone: Weight borne on hands with extended arms, chest and upper part of the abdomen therefore being off the couch Sits (supported) for a few minutes Rolls front to back and usually back to front	
8 months	Sits independently without support	
10 months	Crawls, pulls to stand	
11 months	Sitting position with pivoting	
12–14 months	Walks independently	
18 months	Squats to pick up objects, kicks a ball	
2 years	Runs and jumps	
3 years	Stands on one leg momentarily	
4 years	Hops	

Assessment of development needs domain specific enquiry such as:

- Do you have any concern about how your child talks and makes speech sounds?
- Do you have any concern about how your child understands what you say?
- Do you have any concern about how your child uses his or her hands to do things?
- Do you have any concern about how your child walks or runs?
- Do you have any concern about how your child behaves?
- Do you have any concern about how your child gets along with others?

Table 5: Developmental milestones in fine motor and vision

Age	Milestones
3 months	Watches own hands, fixes and follows objects through 90° laterally
4 months	Reaches and grasps an object, holds with palmar grasp
6 months	Palmar grasp at 6 month (Fig. 3) Transfers objects between hands
9 months	Scissors grasp
12 months	Mature pincer grasp, bangs bricks in imitation
15 months	Builds tower of 2 cubes
18 months	Builds tower of 3 cubes Scribbles to and fro
2 years	Builds tower of 6–8 cubes Circular scribbles
3 years	Copies a 3-cube bridge Draws circle
3 years and 6 months	Copy a train
4 years	Draws a "+" sign Draws a person with head, body and legs Builds 6 bricks steps
5 years	Draws a "square" sign

Fig. 3: Palmar grasp at 6 months, scissors grasp at 9 months, pincer grasp at 12 months

Table 6: Average milestones of speech, language and hearing

Age	Comprehension	Expression
3–6 months	Responds to speech	Babbling, cooing
9 months	Responds to name imitates Lip smacking	Babbles with two syllable
12 months	Plays "peek a boo", waves	Imitates. Points 1–2 words
18 months	Understands simple commands, objects by name	6–20 words
2 years	Understands two-word commands	50 words Joins two words Joins in nursery rhymes
2.5 years	Asks questions	200 words Uses pronouns
3 years	Understands three word command Understands prepositions	Tasks in short (3–4 words) sentences Asks "what" and "who" questions
4 years		Asks "why", "when", "how" question Counts up to 20 by rote

Table 7: Average social behavior and play milestones

Age	Milestones
6 weeks	Smiles in response
3 months	Expresses pleasure on cuddling
9 months	Stranger awareness
12 months	Helps with dressing, wave bye-bye, plays peek-a-boo
18 months	Takes off socks, hat, spoon-feeds self
2 years	Plays alongside other children
3 years	Eats with fork and spoon, joins in make-believe play
4 years	Can dress and undress, except for shoe laces

Table 8: Building and copying with blocks	
3 cubes	
At 2 years a tower of 6–8 cubes	
At 3 years a "bridge" is copied	
At 3 years and 6 months a "train"	
At 4 years "steps"	

- Do you have any concern about how your child does things for himself or herself?
- Do you have any concern about your child's learning?
- Do you have any concern about your child's hearing or vision?
- Do you have any other concerns?

Clinical assessments of development along with neurological assessment in neonate and infant are discussed in the chapter Pediatrics Neurology.

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6 Nutrition and Its Disorders

NUTRITION

Nutrition is the provision to cell and organisms of materials necessary in the form of food to support life. Nutritional status reflects the balance between supply and demand and the consequence of any imbalance. Our nutrients are composed of complex chemical substances and generally grouped in to two categories, macronutrients and micronutrients. The macronutrients are needed in large quantities and are composed of protein, carbohydrates and fats and are required for building body's structure, while micronutrients consist of vitamins and minerals and are required in little quantities. Micronutrients are important for metabolism and body's immunity.

NUTRITIONAL REQUIREMENTS

Energy Metabolism During Growth and Growth Failure

In order to maintain the body weight, energy intake must equal the energy expenditure. For growth to occur in children, energy intake must be greater than energy expenditure. Conversely, weight loss is achieved by increasing energy expenditure or decreasing energy intake. The energy content of food is usually expressed in kilojoules (kJ) or kilocalories (kcal). A calorie is defined as the energy needed to heat 1 g water by 1°C; 1 kcal is equivalent to 4.184 kJ.

Energy Balance

Total energy expenditure is made up of:

- Basal metabolic rate (BMR) 50–75%
- Physical activity 20–40%
- Diet-induced thermogenesis (DIT) 10%
- Growth, injury, and fever will increase energy expenditure.
- Basal metabolic rate is the amount of energy expended by the body to maintain normal physiological functions
- Energy metabolism is sustained by the oxidation of fatty acids, carbohydrate, and amino acids to carbon dioxide and water, with the release of some heat
- For clinical purposes, indirect calorimetry (measurement of oxygen consumption and carbon dioxide production) is used to determine metabolic rate.

Nutrient Requirements for Healthy Children

- Dietary reference value (DRV) is a term used to cover lower reference nutrient intake (LRNI), estimated average requirement (EAR), reference nutrient intake (RNI) and safe intake
- Recommended daily amount (RDA): The average amount of the nutrient which should be provided per head in a group of people if needs of practically all members of the group are to be met
- Requirement: The amount of a nutrient that needs to be consumed in order to maintain normal nutritional status
- Estimated average requirement: The mean requirement of a nutrient for a population or group of people; on average 50% will consume more and 50% less than the EAR
- Reference nutrient intake: Two SDs (standard deviations) above EAR; at this level intake will be adequate for 97.5% of the group
- Saturated fatty acids should be 11% of total dietary energy
- Essential fatty acids: Linoleic acid should be a minimum of 1% total dietary energy and α-linolenic acid a minimum of 0.2% total dietary energy
- There are no specific recommendations for non-starch polysaccharides (NSP) or fiber in children, but the "age + 5" rule is commonly used, e.g. a 4-year-old child should have a daily intake of 4 + 5 = 9 g of NSP.
- A rough estimate of energy requirement from one year of age is '1,000 + 100 for each year of life, e.g. a 7-year-old requires 1,000 + 700 = 1,700 kcal/day.
- Nutritional needs of sick children will vary, and increased demands from infection, sepsis, inflammation etc. may be offset by decreased energy expenditure.

Some nutrient requirements in childhood are mentioned in Table 1.

NUTRIENTS

Carbohydrates

Carbohydrates are the main source of energy, and contribute 55–60% of total energy intake. Carbohydrates are of two types: a) simple carbohydrates and b) complex carbohydrates. Simple carbohydrates are mono-saccharides and disaccharides (glucose, fructose, lactose etc. present in honey fruits, milk, etc.) and complex carbohydrates are composed of oligosaccharide and polysaccharides, present in cereals, pulse, vegetables, lentils, etc. Glucose is the quick source of energy and is derived from sugar and breakdown of starch present in diet. Unused glucose is converted to glycogen in the liver and muscle, while excess glucose and carbohydrates are converted to fat. Lack of carbohydrate will cause ketosis and breakdown of protein. One gram of carbohydrate yields 4 kcal of energy.

Proteins

Protein is the second most abundant substance of the body and most important nutrient relevant to global under five mortality of developing countries. Protein is required for synthesis of body's tissue, enzymes, plasma proteins, hemoglobin (Hb)

Table 1: Some nutrient requirements in childhood

Age	Weight (kg)	Fluid (mL/kg)	Energy (kcal/day)	Protein (g/day)	Na (mmol/day)	K (mmol/day)	Vitamin C (mg)	Ca (mmol/day)	Fe (µmol/day)
			EAR	RNI	RNI	RNI	RNI	RNI	RNI
Males									
0–3 m	5.1	150	545	12.5	9	20	25	13.1	30
4–6 m	7.2	130	690	12.7	12	22	25	13.1	80
7–9 m	8.9	120	825	13.7	14	18	25	13.1	140
10–12 m	9.6	110	920	14.9	15	18	25	13.1	140
1–3 y	12.9	95	1,230	14.5	22	20	30	8.8	120
4–6 y	19	85	1,715	19.7	30	28	30	11.3	110
7–10 y	-	75	1,970	28.3	50	50	30	13.8	160
11–14 y	-	55	2,220	42.1	70	80	30	25	200
15–18 y	-	50	2,755	55.2	70	90	40	25	200
Females									
0–3 m	4.8	150	515	12.5	9	20	25	13.1	30
4–6 m	6.8	130	645	12.7	12	22	25	13.1	80
7–9 m	8.1	120	765	13.7	14	18	25	13.1	140
10–12 m	9.1	110	865	14.9	15	18	25	13.1	140
1–3 y	12.3	95	116	14.5	22	20	30	8.8	120
4–6 y	17-2	85	1545	19.7	30	28	30	11.3	110
7–10 y	-	75	1740	28.3	50	50	30	13.8	160
11–14 y	-	55	1845	42.1	70	70	35	20	260
15–18 y	-	50	2110	45.4	70	70	40	20	260

Abbreviations: EAR, Estimated average requirement; RNI, Reference nutrient intake

Reproduced from Aggett PJ, Bresson J, Haschke F, et al. Recommended Dietary Allowances (RDAs), Recommended Dietary Intakes (RDIs), Recommended Nutrient Intakes (RNIs), and Population Reference Intakes (PRIs) are not "recommended intakes." J Pediatr Gastroenterol Nutr. 1997;25:236-41.

and hormones. It is also alternate source of energy for the body. Proteins are made up of 20 amino acids, some of which are essential amino acids which cannot be synthesized in the body. Essential amino acids are leucine, isoleucine, lysine, methionine, phenyl alanine, threonine, tryptophan, and valine. Food proteins differ in their nutritional quality depending upon their amino acid profile and digestibility. For example, pulses are rich in lysine, an essential amino acid, but lack in sulfur-containing amino acid methionine. On the other hand, cereals are deficient in lysine. Therefore if cereals are taken in combination with pulses, the requirement of essential amino acid can be met, even without taking any animal protein, the costly proteins.

Generally, animal proteins have a higher biological value (BV) than plant protein. Egg protein (egg albumin, present in egg white) has the highest BV and net protein utilization (NPU). That is the basis of offering egg albumin in food recipe of malnourished children.

Protein requirement: Nearly, 8–12% of total body energy should come from protein. A protein intake of 8% is sufficient if protein come mainly from animal sources. Protein yields 4 kcal energy/g.

Fats

Fats are major source of energy. It is a major structural element of cell membrane, hormones, and carriers of fat soluble vitamin (A, D, E and K) and of biosynthesis of prostaglandins. The fats in human body or in our food are in the form of triglycerides, fatty acids, cholesterol and phospholipids. Fats are in the form of liquid or solid depending upon presence of saturated or unsaturated fatty acids. Saturated fats tend to solidify while unsaturated or polyunsaturated fatty acids (PUFA) stay in liquid form (soya oil). About 25–30% of energy intake should come from fat. Fat provides 9 kcal of energy per gram, which is more than double than that of carbohydrates and proteins. This is the basis of adding few spoon of edible oil in diet (F-75 or F-100) of severely malnourished children.

Triglycerides (TG) are divided into long chain triglyceride (LCT, >12 carbon length) and medium chain triglyceride (MCT, 6–12 carbon length). MCT are immediate source of energy as they are transported directly from small intestine to liver by portal veins. They promote fat burns, spare muscle glycogen, increase metabolism and decrease cholesterol. It is present in coconut oil, palm oil and butter. It is used in diet (comminuted chicken soup) of malnourished children associated with diarrhea in particular. Also used in cystic fibrosis, epilepsy, gall stone, etc. Long chain fatty acids on the other hand provide essential fatty acids, which require carnitine for its utilization.

Essential fatty acids (EFA) (linoleic acid, γ-linolenic acid and arachidonic acid) have to be supplied through dietary

fat. Linoleic acid together with eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) are omega-3 fatty acids, which are required for grey matter development of children. Omega-3 fatty acids fed children demonstrated better cognitive development than those who are not fed with these fatty acids. Deficiency of EFA leads to growth failure, diarrhea, alopecia, decreased calcium absorption and decreased bone growth.

Consequences of Undernutrition

The multisystem consequences of undernutrition include:

- Growth failure
- Impaired gastrointestinal function
  - Hypochlorhydria
  - Reduced mucosal function
  - Pancreatic exocrine impairment
- Immunodeficiency
  - Impaired cell-mediated immunity
  - Anergy
- Respiratory dysfunction
  - Reduced respiratory force and minute volume
    Myocardial dysfunction
    Reduced muscle mass
    Increased operative morbidity/mortality
    Delayed wound healing
    Impaired intellectual development
    Altered behavior
  - Apathy
  - Depression.

Nutritional Assessment

Nutritional status reflects the balance between supply and demand and the consequences of any imbalance. Nutritional assessment is therefore the foundation of nutritional care for children. When judging the need for nutritional support an assessment must be made both of the underlying reasons for any feeding difficulties, and of current nutritional status. This process includes a detailed dietary history, physical examination, anthropometry (weight, length, head circumference in younger children) with reference to standard growth charts, and basic laboratory indices when possible. In addition, skin fold thickness and mid-upper arm circumference measurements provide a simple method for estimating body composition.

MALNUTRITION

There is no universally agreed definition of malnutrition in children but different criteria are commonly used. In addition to protein-energy malnutrition (PEM), other nutrients such as iron, zinc and cooper may be deficient in malnutrition.

Malnutrition is a global problem that varies from undernutrition to overnutrition. It has been defined as failure of the body to obtain the appropriate amount of proteins, energy, vitamins and other nutrients it needs to maintain healthy tissue and organ function. The preventable malnutrition associated death of 5.6 million children each year is a "humanitarian disaster" that cannot be allowed to continue.

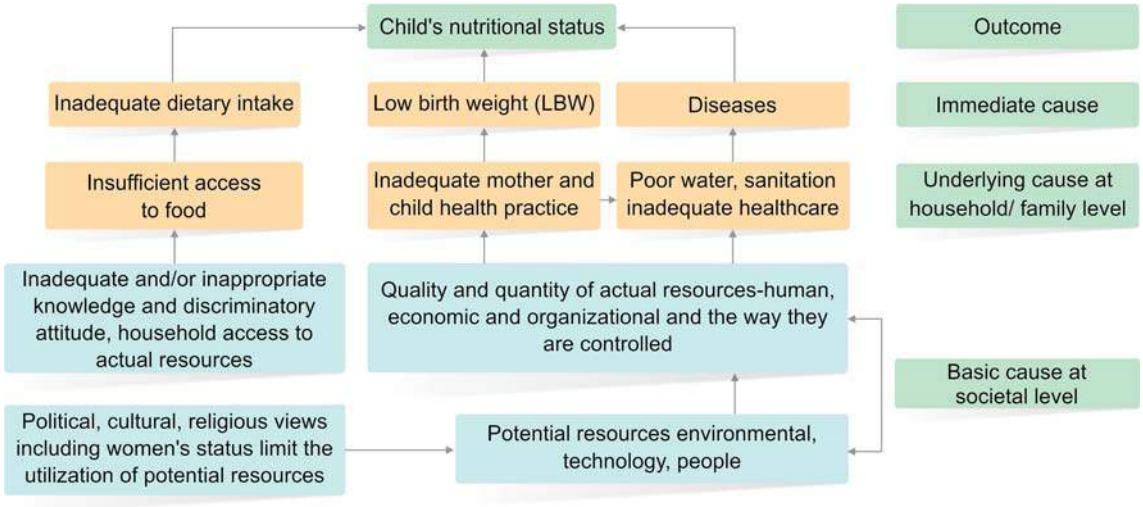
Recent "Data on Disability Adjusted Life Years" (DALYs) approach shows that undernutrition remains the single leading cause of health loss in the world today. Malnutrition in early childhood can result in short stature and impaired neurological development that will increase the risk of morbidity and mortality and impairs performance at school and ultimately the ability to contribute to the society in adult life.

Child survival is firmly back in the spotlight. Improved nutrition is essential to economic development and also to achieving probably all of the millennium development goals (MDG) as well as goal for reducing under 5 mortality by the year 2015. Malnutrition is a global problem and can be of macronutrients deficiency such as proteins and calories or micronutrients such as vitamins and minerals. Despite different development programs and priority in several health and other programs, malnutrition remains a perennial problem in many developing countries.

Underlying Determinants of Malnutrition (Etiology)

Etiology of malnutrition is multifactorial as shown in the Flow chart 1. The important immediate causes of malnutrition are inadequate dietary intake (deprivation), disease, particularly infectious disease and low birth weight (LBW) particularly intrauterine growth restriction (IUGR). Undernutrition makes children vulnerable to disease particularly infectious diseases. On the other hand, children are likely to develop undernutrition following suffering from diseases like

Flow chart 1: Etiology of malnutrition



pneumonia, diarrhea, measles, tuberculosis, etc. (Figs 1 and 2). There are two well known vicious cycles involving malnutrition infection → malnutrition, and malnutrition → diarrhea → malnutrition. LBW associated IUGR may not show catch up growth and do not get weight properly and may remain under nourished. Food refers to food security at household level; it is sustainable access to safe food of sufficient quality and quantity, paying attention to energy, protein and micronutrients. Health includes access to preventive and curative health service to all community members as well as hygienic and sanitary environment, an access to safe drinking water. For prevention of birth of LBW babies, adequate nutrition and healthcare of pregnant mother is essential. Care of nursing mother or caregiver is also essential for achievement of optimal child nutrition. Care refers to process taking place between caregiver and receiver of care. It translates food availability at the household level and presence of health service in to good growth and development of child. Care includes care for women, breastfeeding and complimentary feeding, home health practice, hygiene practice, psychosocial care and food preparation. The factor that determine adequate household food security care are related to resource, their control, and a host of political, cultural and social factors that affect their utilization. Resources include human, economic and organizational resources.

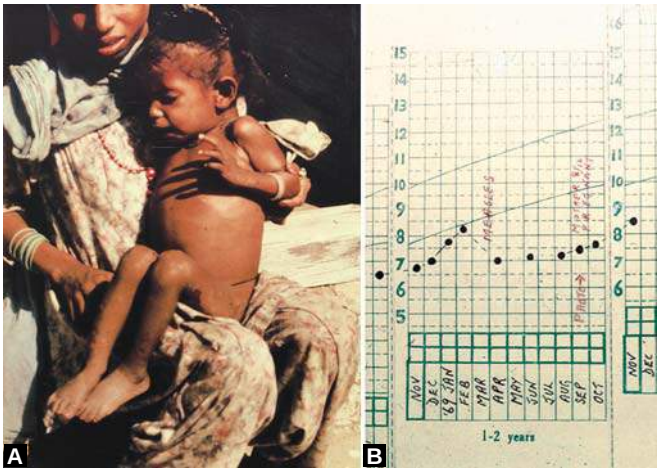
MALNUTRITION: GLOBAL SCENARIO

Food Insecurity and Malnutrition

Severe malnutrition is an important cause of under five deaths in developing countries. Currently, according to International Food Policy Research Institute (IFPRI), USA survey 2011 report still 36% children under 5 are underweight.

In a study of the world population the sample of 191 countries has been taken.

These countries divided by regions of world as—East Southern Africa, West Africa, East Asia and Pacific, South Asia, Eastern Europe and Central Asia, Europe, Middle East, North Africa, North America, and South America. The results show that the highest mean rate of child malnutrition was found in South Asia region (57 children per 100), while the smallest mean rate was found in Europe region (just 1 child



Figs 1A and B: (A) The picture showing severe wasting following measles infection; (B) The growth chart showing initial progressive weight gain followed by weight loss after measles infection followed by again weight gain with protocolized management of severe acute malnutrition (SAM)

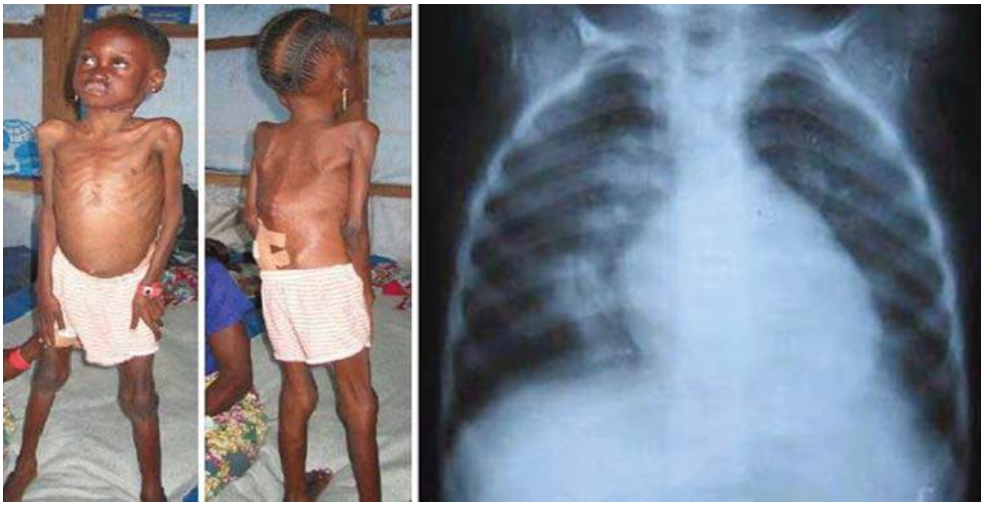


Fig. 2: Picture showing tuberculosis (TB) of spine in a severely malnourished child and chest X-ray showing evidence pulmonary TB

per 100). In West Africa region, the average of child mortality rate per 1000, 172 children, was the highest among all regions in the world, while in Europe was found to be 14 children per 1,000. The results reveal that there were associations between illiteracy rate, unemployment, poverty, fertility rate, family size, food consumption, maternal mortality rate, and child malnutrition and mortality in the whole world regions.

The American Dietetic Association (ADA) supports programs and encourages practices that combat hunger and malnutrition, produce food security, promote self-sufficiency and are environmentally and economically sustainable. Poverty, gender inequality, ethnocentrism, racism, and the lack of political will are key constraints to solving the problems of global hunger and malnutrition. The ADA identifies sustainable development as the long-term strategy to ending world hunger and achieving food security. Sustainable development requires political, economic, and social changes that include empowering the disenfranchised, widening access to assets and other resources, narrowing the gap between rich and poor, and adjusting consumption patterns so as to foster good stewardship of nature. Additionally, because the health status of future generations is related to the well-being of their mothers, achieving food security will also require increased access for women to education, adequate health care and sanitation, and economic opportunities. The Association supports programs and encourages practices that combat hunger and malnutrition, produce food security, promote self-sufficiency, respect local cultures, and are environmentally and economically sustainable.

CLASSIFICATION OF MALNUTRITION

Classification does not define a specific disease but rather clinical signs that may have different etiology.

The assessment of nutrients status is done according to weight for height or length (W/H), height (or length) for age (H/A) and presence of edema. The WHO recommends the use of Z-scores or standard deviation (SD) scores for evaluating anthropometric data, so as to accurately classify individuals with indices below extreme percentile.

Currently older classification depending on presence of under nutrition with edema (Welcome Classification) is also used (Table 2). However, to avoid confusion with clinical symptoms of kwashiorkor, which includes other features the term "edematous malnutrition" is preferred.

Table 2: Welcome classification of malnutrition

Weight for Age	With edema	Without edema
60–80% expected weight for age	Kwashiorkor	Undernutrition
<60% expected weight for age	Marasmic kwashiorkor	Marasmus

WHO Classification of malnutrition depending of weight for height and height for age given in Table 3.

Gomez classification of malnutrition depending upon weight for age is given in Table 4.

A child aged 6–59 months is classified as severely malnourished if she/he has one or more of the following:

- Weight for height median (WHM) <70%
- Weight for height Z-score (WHZ) < –3SD
- Mid-upper arm circumference <110 mm
- Bipedal edema (Kwashiorkor, marasmic kwashiorkor or edematous malnutrition)
- A child <6 months should be classified as severely malnourished if he/she has (i) Visible wasting, (ii) WHM <70% or – 3 SD (iii) Bipedal edema

Calculation of SD Z: Weight for height SD Z and its significance

$$\text{SD Z-score} = \frac{\text{Observed value} - \text{Expected value}}{\text{One Standard deviation (SD)}}$$

For example: A male child of 2 years old having weight 5 kg, height 87 cm.
His expected median weight at this height is 12.39 kg while one standard deviation weight for this height (W/H) is 1.2 kg.

$$\text{So SD Z-score will be} = \frac{5 - 12.39}{1.2}$$

$$= -6.1$$

Calculation of Z-score is a measure to assess the degree of severity of severe acute malnutrition and also helps to assess the prognosis, duration of management of severely malnourished child. For example, a severely malnourished child having WHZ score of – 6.1 is more severely wasted than a malnourished child for WHZ score of – 4.5, although both of them are suffering from SAM according to definition. The duration of management of a child having WHZ score –6.1 is expected to be more and prognosis is expected to be more guarded than the child having WHZ score of –4.5

Bangladesh has adopted the new World Health Organization (WHO) Growth Reference Standard (GRS)

Table 3: WHO classification of malnutrition

	Under Nutrition				Over Nutrition	
	Severe malnutrition	**Moderate malnutrition**	**Mild malnutrition**	**Well nourished**	**Over weight**	**Obese**
Symmetrical edema	Yes	No	No	No	No	No
Weight for height (SD)	< –3 SD (<70%) severe wasting	–2 SD to –3 SD (70–79%) Moderate wasting	–1SD to –2 SD (80–89%) Mild wasting	+2 SD to –1 SD (90–120%)	+2 SD to +2.9 SD (121–129%) Over weight	>+3.0 SD (>130%) Obese
Height for Age	< –3SD (<85%) Severely Stunted	–2 SD to –3 SD (85–89%) Moderately stunted	–1 SD to –2 SD (90–94%) Mildly stunted	+2 SD to – 1 SD (95–110%)	>+2 SD > (110%) Tall	

Table 4: Gomez classification of malnutrition	
Weight for age (Median)	**Nutritional status**
>90	Normal nutritional status
75–89	1st degree malnutrition
60–74	2nd degree malnutrition
<60	3rd degree malnutrition

Indian Academy of Paediatrics (IAP) divides underweight children in five groups. Children below 50% weight for age are graded intravenous (IV) or very severely malnourished.

Depending on duration, undernutrition is divided into acute and chronic. In acute malnutrition (non-edematous) weight for age and weight for height are reduced significantly, while height is not affected significantly. If malnutrition continues for a long time (chronic), height for age is also significantly decreased causing significant stunting. As height is reduced significantly in chronic malnutrition, weight for newly achieved reduced height (weight for height) may not be significantly decreased. Therefore, uncomplicated chronic malnutrition occurring over long time usually characterized by significant stunting but insignificant wasting. However, the stunted children may become suddenly wasted due to loss of weight, due to acute stress like acute infections and consequently the child becomes both wasted and stunted (acute on chronic). In facility based care, it is not uncommon to find severe chronic malnutrition with significant stunting (↓ H/A and ↓ W/A) complicated by various medical conditions leading to significant wasting (↓W/H) along with significant stunting. Therefore, in facility based care, which is primarily designed to treat children suffering from SAM with significant wasting (↓W/H), a significant number of children are also admitted who had chronic malnutrition (↓H/A) but later developed sudden wasting due to loss of weight due to acute stress (infection or other environmental).

PATHOGENESIS OF MALNUTRITION

Mild to moderately malnourished children, which constitute great portion of malnourished children, if not managed properly at community level with adequate protein and energy dense diet, undergo severe under nutrition, initially in the form of wasting (severe wasting or severe nonedematous malnutrition). Severely malnourished (nonedematous) children, who are immune-compromised suffer from recurrent infections, both clinically and subclinically. In response to recurrent infection, liver produces increased active phase proteins in the form of increased C-reactive protein (CRP), α-1 acid protein, α-1 antitrypsin, macroglobulin, etc. at the cost of producing albumin in liver. As serum plasma albumin is decreased, plasma colloidal oncotic pressure is decreased; consequently more fluid is lost from intravascular to extravascular space, giving rise to edema and edematous malnutrition.

However development of edema does not depend solely on decreased serum albumin. In normal healthy children, there is balance between oxidant and anti-oxidant. In malnourished children, there is oxidative stress and free radical-induced damage of tissue and antioxidants like zinc, β-carotene, tocopherol, etc. are decreased. Therefore net increase of oxidants cause ongoing oxidative stress induced tissue damage and tissue damage induced edema. Through Fenton reaction and lipid per oxidation in the presence of free iron, cell membrane and tissue are chemically damaged. Consequently increased free radical-induced tissue damage also contributes to tissue edema.

Edematous malnutrition is also associated with increased antidiuretic hormone (ADH), which causes fluid retention which further aggravates edema. Increased serum ferritin, associated with edematous malnutrition, also act as ADH, which also contributes to edema.

Serum protein takes long time to decrease in severe malnutrition and is not sensitive and early indicators of PEM.

In severely malnourished children serum albumin is initially decreased due to decreased protein intake and serum globulins are increased (albumin-globulin ratio is altered) maintaining normal total serum protein. If malnutrition status continues for long time without dietary intervention, total serum protein is finally also decreased. Serum albumin is not the earliest biochemical indicator of PEM. Decreased serum transferrin, serum pre-albumin and serum retinol binding protein (RBP) are sensitive and early indicators of severe PEM.

Both blood urea and serum transferrin in PEM are increased early (in terms of days) with increased dietary intake of protein enriched diet in malnourished children. Serum total protein and albumin take long time (in terms of weeks) to increase in response to dietary intervention. Therefore serum transferrin estimation rather than serum albumin is an early indicator of dietary response of protein intake in malnourished children.

Serum creatinine and urine creatinine in particular, indicate endogenous protein (skeletal muscle and white muscle fibers) contents.

In severe malnutrition urinary creatinine height indices (CHI) is decreased as follows:

$$\text{CHI} = \frac{\text{24 hour urine creatinine}}{\text{24 hour urine creatinine of normal child with same height}}$$

Range 0.25–0.75 in kwashiorkor and 0.33–0.85 in marasmus, recovered value is 1.

Various hormonal and biochemical changes occur in malnutrition some are increased and some are decreased. Some important hormonal and biochemical changes are given in Table 5.

Significant pathological changes occur in various system of the body. Some important pathological changes of clinical significance are mentioned in Table 6.

Table 5: Status of hormones and biochemical indices in severe protein energy malnutrition	
Parameter increased	**Parameter decreased**
Serum growth hormone	Somatostatin
Serum cortisol	IGF-1 and IGF-2
Serum ADH	Serum insulin
CRP	Serum T4 and TSH
α 1 antitrypsin	Serum albumin and prealbumin
α 1 acid protein	Serum retinol binding protein (RBP)
Serum ferritin	Serum transferrin
Serum globulin	
Abbreviations: IGF, insulin-like growth factor; ADH, antidiuretic hormone; CRP, C-reactive protein; TSH, thyroid stimulating hormone	

Table 6: Pathological changes in malnutrition

Upper GIT	Mucosa flat atrophy
Small Intestine	Mucosal and villous atrophy
Pancreas	Exocrine secretion depressed Endocrine less affected
Lymphoreticular system	Thymus atrophied Lymphocyte proliferation depressed
CNS	Head circumference and brain growth retarded
CVS	Myocardial function decreases due to myocardial structural changes Degeneration of myocardial cells with formation of Aschoff cell

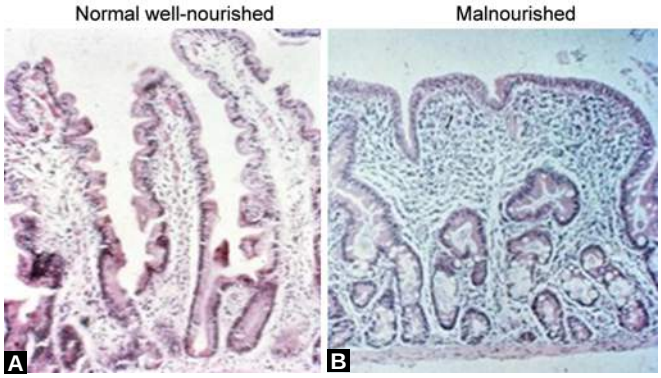
Abbreviations: GIT, gastrointestinal tract; CNS, central nervous system; CVS, cardiovascular system.

Some important pathological changes in various system in malnourished children are given in Figures 3 to 5.

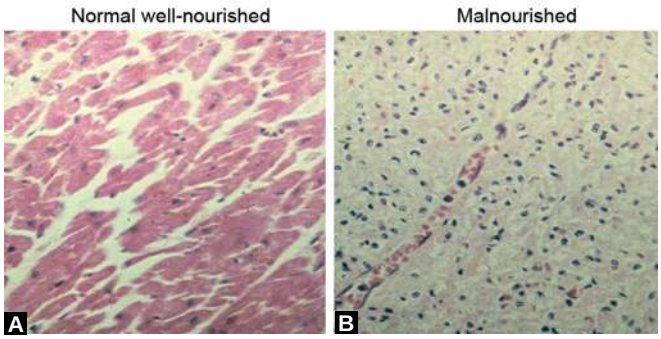
Clinical Significance of Pathological Changes

Mucosal and villous atrophy (Figs 3A and B) is an important cause of frequent and persistent diarrhea and malabsorption in severely malnourished children. This is also the basis of offering initial low volume and low calorie (F-75) diet to severely malnourished children instead of initial high calorie (F-100) diet and high protein diet. Mucosal atrophy is more pronounced in edematous malnutrition. This is one of the basis of offering low volume diet (9 mL/kg/feed) in edematous malnutrition in comparison to non-edematous (11 mL/kg/feed) malnutrition.

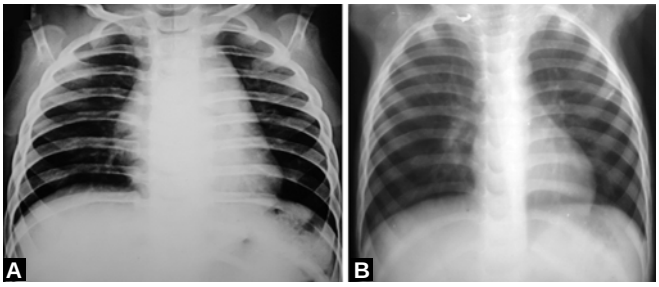
Heart muscle in malnourished children also undergoes degeneration and atrophy (Figs 4A and B), therefore heart muscle cannot cope with initial sudden increase in protein, calorie and fluid intake.



Figs 3A and B: (A) Histology of normal villous of gut mucosa epithelium; (B) Submucous villous atrophy in malnourished child



Figs 4A and B: (A) Histological slide of heart muscle showing normal heart muscle cells in well-nourished child; (B) Degenerated cells showing Aschoff cells in malnourished child



Figs 5A and B: (A) Chest X-ray of normal well-nourished child showing prominent thymic shadow; (B) Atrophic thymic shadow in malnourished child evidenced by narrow superior mediastinum

Decreased pancreatic exocrine secretion contributes to malabsorption and food intolerance in malnourished children.

Thymic atrophy: Evidence of lymphoreticular depletion and impaired cell-mediated immunity (CMI) in severe malnutrition can be seen on X-ray chest. Normally infants have large corrugated margined thymic shadow. In malnourished children, due to thymic involution thymic shadow cannot be seen and X-ray chest shows only narrow stalk of superior mediastinum instead of normal prominent thymic shadow of healthy infant (Figs 5A and B).

Due to qualitative and quantitative reduction of T lymphocytes, CMI is impaired. This is clinically evidenced by anergy to tuberculin test, in spite of presence of active tuberculosis in children. More scientifically it can be tested by impaired CMI with *Candida albicans* antigen test which will be similarly nonreactive.

Central nervous system: Head circumference diminishes in severe PEM. CT scan/MRI of brain shows atrophy. There are also dendritic arborization defect in brain. Consequently, children may have developmental, learning and cognition problems when they are grownups.

CLINICAL FEATURES OF MALNUTRITION

Depending upon severity, duration of PEM presence of edema, dermatoses and associated other nutritional deficiencies and complications associated with malnutrition, the presentation will be different.

Edema in all malnutrition is graded using the classification as given in Table 7.

Clinical Features of Malnutrition in Children

In severe acute undernutrition weight for age and weight for height are significantly reduced, but height for age usually remains normal, as linear growth retardation or stunting due to undernutrition takes longer time to affect linear growth adversely. If acute malnutrition is not managed appropriately and undernutrition is prolonged, height for age eventually significantly reduced, and the child becomes both wasted and stunted (Fig. 6). Similarly in acute edematous

Table 7: Grading of edema

Grade of edema	Definition
Grade +	Mild both feet, ankle
Grade ++	Moderate, both feet plus lower legs, hands or lower arms
Grade +++	Severe. Generalized edema including both feet, legs, hands, arms and face

malnutrition (Kwashiorkor), weight for age and weight for height usually remain normal due to excessive fluid retention (Fig. 7). However, if it continues for long time (severe chronic malnutrition with edema), height for age is also significantly reduced (stunted) and the child will show evidence of wasting in some parts of the body (thigh, scapular region) in addition to edema, in other parts of body like ankle edema (Fig. 8). This child's weight for age and weight for height may also be reduced in spite of edema (chronic edematous malnutrition).

Dermatoses of malnutrition include hypopigmentation or hyperpigmentation, desquamation, ulceration, spreading over limbs, thigh, groin and genitalia.

The skin lesions may look like mosaic of floor called crazy pavy dermatosis or pigmented lesion may become confluent followed by flaking of skin called flaky paint dermatosis (Fig. 9).

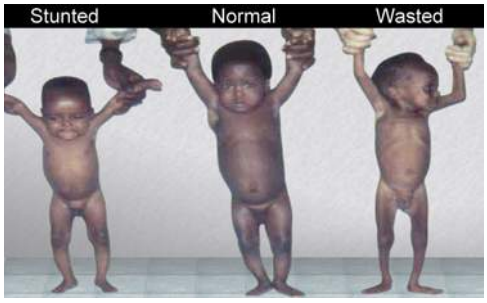


Fig. 6: Child with wasting and stunting are compared with normal one

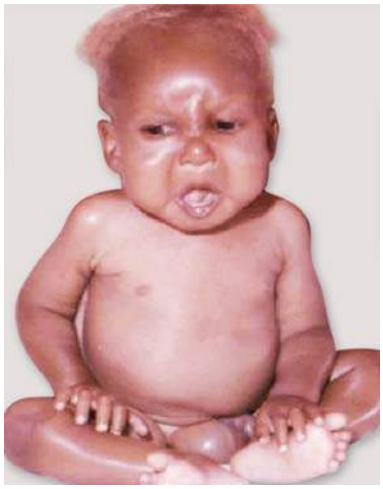


Fig. 7: A child suffering from kwashiorkor

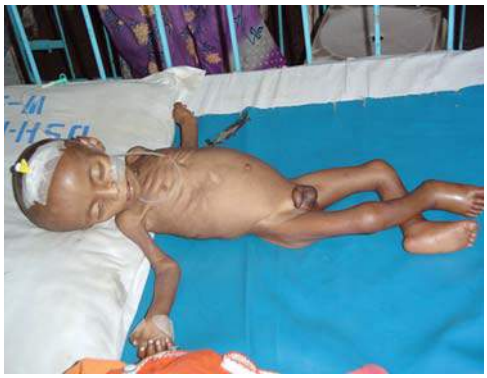


Fig. 8: Child suffering from severe wasting and ankle edema (Marasmic kwashiorkor)

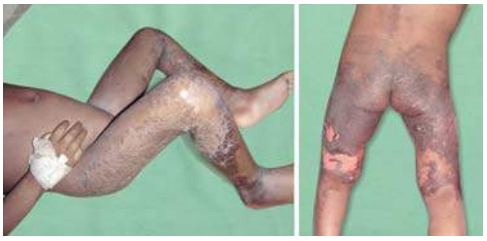


Fig. 9: Flaky paint dermatoses

Severe dermatoses, which include ulcer, fissures and exudative lesion may resemble burn.

All dermatoses may be complicated with secondary infection including *Candida*.

Hair may be depigmented, lusterless. A flag sign is the alternate bands of hypo- and normally pigmented bands of hair, when growth occurs in spurts.

A severely malnourished child quite often presents with diarrhea, dehydration, pneumonia with respiratory distress, septicemia, loss of appetite, vomiting, etc. and will require facility based treatment.

Difference between Edematous (Kwashiorkor and Marasmic Kwashiorkor) and Non-edematous (Marasmus) Malnutrition

The characteristic difference between edematous and non-edematous malnutrition are shown in the Table 8. However such clinical features are not always consistent distinguishing features between edematous and non-edematous malnutrition. For example, liver enlargement may occur in marasmus and may be absent in kwashiorkor. A marasmic child may be more anorexic, while kwashiorkor child appetite may be reasonably preserved. Although edematous malnutrition develops usually in the second year of life usually after development of wasting (marasmus), it may occur below six month of age without going through the phase of wasting (marasmus). It can occur below 6 months age in a non-breastfed infant, taking diluted milk formula or diluted milk formula mixed with rice powder, which makes infant's feed low in protein and energy. The child may look paradoxically plump and healthy due to hypoproteinemia, so called barley baby, much to the satisfaction of parents despite PEM (Fig. 10).

Clinical features of malnutrition with or without edema and with or without dermatosis are summarized in Table 9.

MANAGEMENT OF SEVERE ACUTE MALNUTRITION

Achieving the Millennium Development Goal (MDG) of a two-third reduction in childhood mortality will not be possible if SAM is not addressed properly. Cost-effective, high impact approaches now exists. In order for these to reach their potential, the treatment of SAM should become more centered to the healthcare agenda in developing countries among policy makers.

Severe acute malnutrition, particularly associated with complications is an important cause of under five mortality in developing countries. Faulty case management and weak health system, inappropriate treatment strategies, inadequately trained staffs, lack of support lead to high case fatality of severe malnutrition.

Table 8: Difference between edematous and non-edematous malnutrition

Clinical features	Non-edematous (Marasmus)	Edematous (Kwashiorkor)
Edema	Absent	Present
Age of onset	Usually below 1 year	Usually after 1 year
Occurrence	More common	Less common
Activity	Active	Apathetic
Appetite	Good	Poor
Hepatomegaly	±	+
Initial therapeutic food	More 11 mL/kg/feed 2 hourly or 130 mL/kg/day	Less 8 mL/kg/feed 2 hourly or 80–100 mL/kg/day
Dermatosis	±	+
Infection	Less prone	More prone
Recovery	Recover early	Long to recover
Mortality	Less	More

Table 9: Clinical features of undernutrition in children

	Edema	Wasting	Dermatosis	Reduced weight for age	Reduced height for age	Reduced weight for height
Severe acute malnutrition (SAM)						
Marasmus (acute)	0	++	0	++	0	++
Kwashiorkor (acute)	++	0	±	±	0	±
Severe chronic malnutrition (SCM)						
Marasmus (chronic) (Chronic wasting and stunting)	0	++	0	+++	++	+++
Kwashiorkor (Chronic)	++	+	±	++	++	++
Chronic mild malnutrition (Nutritional dwarfism)	0	0	0	++	++	±

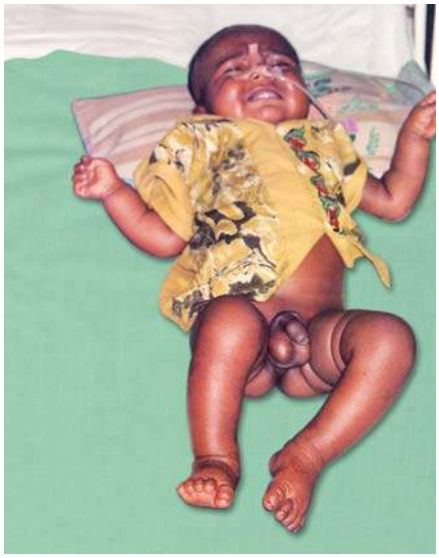


Fig. 10: An apparently plump healthy looking non-breastfed infant with edematous malnutrition who took diluted milk and rice powder

In order to maximize coverage and access to therapeutic care for severely malnourished children, an approach that combines the following components is most appropriate which include:

- Management of SAM with complication at facility level
- Management of SAM without complication at community level.

Underlying Conditions and Management Strategy of SAM and Chronic Malnutrition

Severe acute malnutrition characterized by severe wasting (Fig. 11) is an unstable condition resulting from absolutely short duration of nutritional deficit that is often complicated by concurrent infective illness. The child with SAM has a limited ability to respond to stresses (infectious and environmental), is highly vulnerable to infectious disease and has a high mortality rates. It is thus vital to treat SAM proactively with short duration, highly intensive treatment regimen, aiming to rehabilitate the child in a few weeks. By contrast, chronic malnutrition characterized by significant stunting is relatively stable condition is the result of slow progression of prolonged episodes of undernutrition, both of the pregnant mother and of the young infant, importantly during the first two years of life. The stunted child in comparison to SAM gets more time to adjust and adapt with stresses associated with gradual nutritional deterioration. The child's weight for age and height for age is decreased. Since height is decreased, weight for height is not significantly affected and the child looks small, underage, may be active and playful, so called nutritional dwarfism.

This prolonged etiology of chronic malnutrition is best addressed through long-term preventive programs, targeting maternal health and nutrition, prior to and during pregnancy and infant health and nutrition in the first two years of life. These differences in etiology, diagnoses and treatment make it important to differentiate clearly between the two conditions.

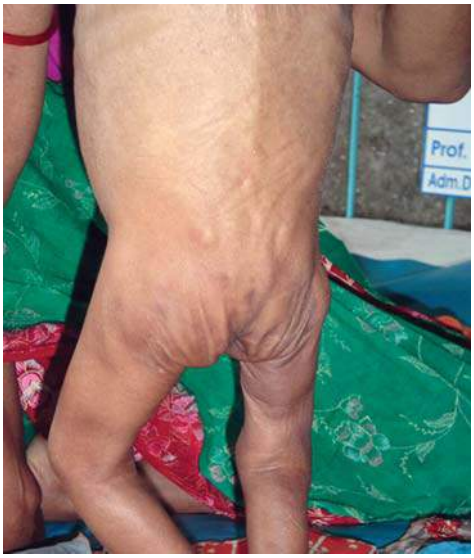


Fig. 11: Marked wasting of buttocks so called baggy pant wasting

However, a significantly nutritionally stunted child may become significantly wasted suddenly (acute on chronic) due to diseases, acute dietary insufficiency, etc. In that case, chronically malnourished children becoming severely wasted (W/H <70% or < –3SD) will qualify for receiving treatment of SAM in facility-based care. This is why in facility-based care, which is primarily designed to treat children suffering from SAM (characterized by severe wasting), it is not unusual to find significantly stunted children who have also developed sudden wasting due to acute stress like acute infections, so called acute on chronic malnutrition.

Management of Severe Acute Malnutrition in Facility-Based Inpatient Care

General Principle for Routine Care

The general principles of management of SAM are derived on the basis of following physiological and metabolic conditions of severely malnourished children.

- Reductive adaptation: This is physiological and metabolic slow down in order to preserve energy. This mechanism is relevant to hypothermia, hypoglycemia and initial low calorie therapeutic food in malnourished children.
- Not to use diuretics for edema: Use of diuretics may aggravate already existing intravascular hypovolemia, leading to hypovolemic shock. Diuretics may cause further potassium loss of potassium depleted malnourished children.
- Avoid initial intake of high protein and high calorie diet: Death may occur if high protein and high calorie diet is given early, as due to reductive adaptation theory, cardiovascular and gastrointestinal (GI) system cannot cope with sudden increase in proteins, calorie and fluid intake. Heart muscle of malnourished children (Fig. 4) undergoes degeneration and GI system is associated with subtotal villous atrophy (Fig. 3). The malnourished children may develop heart failure, loose motions and vomiting from food intolerance and malabsorption, with increased case fatality, associated with initial high calorie and high protein therapeutic food.
- Minimum use of intravenous fluid: Intravenous fluid may be administered only for 2 hours and slowly in shock only. IV fluid may cause heart failure due to fluid overload in severely malnourished children.
- Low sodium and high Potassium containing fluid: In spite of low serum sodium in malnourished children, there is sodium retention and decreased tissue potassium which is not always reflected in serum electrolytes level. This is the basis of providing half strength polyelectrolyte solution (cholera saline) to malnourished children with diarrhea and shock. Oral rehydration saline for malnourished children (ReSoMal) similarly contains low sodium and high potassium.
- Frequent feeding: Due to reductive adaptation and loss of appetite, malnourished children are vulnerable to hypoglycemia. This is the basis of 2 hourly feeding, including feeding at night for PEM children. Similarly ReSoMal also contain high sugar than previous conventional ORS.
- Give antibiotics empirically: Since the severely malnourished children are immunocompromised, they are prone to develop intercurrent infection, some of which are clinically obvious like pneumonia, gastroenteritis, etc. for which admission in facility- based care are sought. However, some are not clinically obvious. Since infections in malnourished children are catastrophic, SAM children are given routine broad spectrum antibiotics on admission.
- Iron should not to be given immediately: Iron is less utilized in malnourished children for synthesis of hemoglobin. The free unused iron acts as a free radical which promotes bacterial growth and oxidative tissue damage. Iron in malnourished children is converted to ferritin, which acts as antidiuretic hormone and helps in developing edema. There is evidence to suggest that increased ferritin is associated with increased case fatality in malnourished children.

The 10 steps in the management of children with SAM and are divided into two parts.

1. Initial stabilization phase (containing 7 steps)
2. Rehabilitation phase (containing 3 steps)

Initial Stabilization Phase: There are seven steps in initial stabilization phase, where life-threatening conditions are identified and treated and specific deficiency is corrected and which is usually achieved in 1st week.

Seven steps are the following:
Step 1: Treat/prevent Hypoglycaemia
Step 2: Treat/prevent Hypothermia
Step 3: Treat/prevent Dehydration
Step 4: Correct electrolyte imbalance
Step 5: Treat/prevent Infection
Step 6: Correct Micronutrient deficiency
Step 7: Start cautious feeding including breast feeding
Rehabilitation phase: Usually achieved in 2–6 weeks.

Three stages of rehabilitation are following:
Step 8: Achieve catch up growth
Step 9: Provide sensory stimulation and emotional support
Step 10: Prepare for discharge and follow up regularly.

STEPS OF MANAGEMENT

Initial Stabilization Phase

Step 1: Hypoglycemia

- Blood glucose
  Less than 3 mmol/L or 54 mg/dL

- Clinical features: Lethargy, hypothermia, altered level of consciousness
- Management
  - If the baby is conscious
    - 50 mL of 10% glucose orally or by nasogastric (NG) tube
    - F-75 diet half hourly for 2 hours (giving one-quarter of 2 hourly feed)
    - Keeping the child warm
    - Antibiotics
    - Two hourly feed, day and night
  - If the child is unconscious
    - Intravenous 10% glucose (10 mL/kg) followed by 10% glucose 50 mL by NG tube, followed by F-75 diet as mentioned above.

Blood sugar should be carefully monitored. If blood sugar is persistently less than 3 mmol/L, in spite of above management more severe underlying cause including septicemia should be considered and appropriate management and if possible, referral to a higher facility should be done.

Step 2: Hypothermia

- Rectal temperature less than 35.5°C, axillary less than 35°C
- Co-exists with hypothermia and sepsis
- Re-warm the child
  - Cover the child with warm blanket and increase the ambient temperature with safe heat source, or put the baby on mother's bare chest (skin to skin) and cover them, the Kangaroo mother care
  - Start antibiotics and 2 hourly feed.

Step 3: Diarrhea and Dehydration

It is difficult to estimate dehydration in severely malnourished children as positive skin pinch sign and sunken eye may occur due to loss of fat and muscle wasting without dehydration. Similarly dehydration may be overestimated in edematous malnutrition. Therefore, it is assumed that malnourished children with diarrhea have dehydration. Clinical assessment of dehydration in severe PM are shown in Figures 12 and 13.

Dehydration correction oral solution for malnourished children called ReSoMal contains low sodium and high potassium (Table 10). Correction of dehydration is done in the following manner:

- Give ReSoMal 5 mL/kg every 30 minutes for 2 hours. Then 5–10 mL/kg/hour every alternate hour for 4–6 hours

Table 10: Composition of oral rehydration salts solution for severely malnourished children (ReSoMal) showing low sodium and high glucose and potassium content

Component	Concentration (mmol/L)
Glucose	125
Sodium	45
Potassium	40
Chloride	70
Citrate	7
Magnesium	3
Zinc	0.3
Copper	0.45
Osmolarity	300

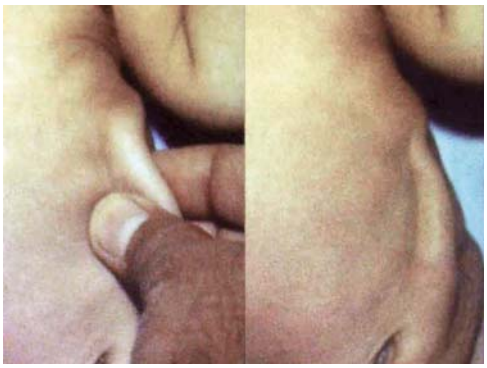


Fig. 12: Technique of skin (full thickness) pinch to assess dehydration in malnutrition

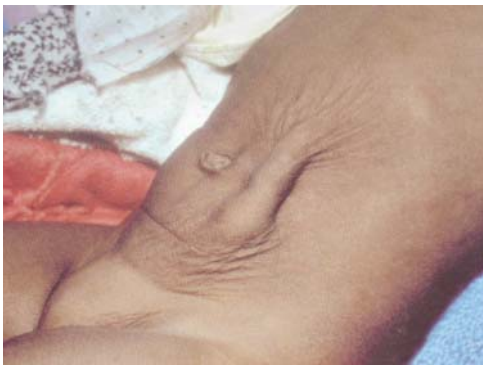


Fig. 13: Skin pinch (full thickness) goes back very slowly in a malnourished child with diarrhea

- F-75 in alternate hour
- If diarrhea is severe modified/ Hypo-osmolar WHO ORS, containing more sodium (75 mmol sodium/L) than of ReSoMal (sodium 45 mmol/L) may be used to prevent symptomatic hyponatremia.

Signs of overhydration (due to injudicious use of fluid resuscitation)

- Increasing pulse rate
- Increase respiratory rate
- Edema (puffy face)
- Distended neck veins.

A positive skin pinch sign may be found in malnourished child due to loss of subcutaneous fat, even without dehydration. So a full thickness skin pinch (Figs 12 and 13) is required to assess dehydration.

Step 4: Correct Electrolyte Imbalance

Severe acute malnutrition children have excess body sodium with low tissue potassium and magnesium. Serum electrolytes do not reliably reflect tissue electrolytes contents rather it may act as supporting role of clinical dyselectrolytemia.

Treatment

Until stabilization introduce:

- Extra potassium 3–4 mmol/kg/day
- Extra magnesium 0.4–0.6 mmol/kg/day
  When rehydrating, give low sodium rehydration fluid (ReSoMal)
- Prepare food with less salt
- Do not treat edema with diuretics

Symptomatic tissue potassium deficiency may be associated with ileus and abdominal distension, which aggravates feeding difficulty. Intramuscular magnesium injection help improving body potassium utilization, thereby improving abdominal distension and feeding difficulty. Injection 50% magnesium sulfate 0.3mL/kg intramuscular (IM) should be given on 1st day and 0.1 mL/kg on 2nd and 3rd day.

Step 5: Treat and Prevent Infection

Signs of infection such as fever are absent and subacute bacterial infections are common in malnourished children which may be asymptomatic. Therefore, routine broad-spectrum antibiotics are used on admission. Early use of antibiotics also:

- Improves nutritional response to feeding
- Prevents shock
- Reduce mortality.

First-line treatment:

With no complication (WHO guidelines) oral amoxycillin 15 mg/kg 8 hourly for 5 days.

If the child is severely sick with lethargy or complication IV/IM ampicillin (50 mg/kg) 6 hourly for 2 days, then oral amoxycillin 15 mg/kg 8 hourly for 5 days and IV/IM gentamicin 7–8 mg/kg once daily for 7 days.

Second-line treatment:

If the child does not improve with first-line of treatment within 48 hours or deteriorates after 24 hours or if the child present with septic shock or meningitis, then inject IV/IM Ceftriaxone injection 100 mg/kg/day along with injection Gentamicin (IV/IM) for 5 days.

Step 6: Correct Vitamin A and other Micronutrient Deficiency

Severely malnourished children are at high-risk of blindness due to Vitamin A deficiency. Thus vitamin A should be given to all severely malnourished children on Day 1, unless there is definite evidence that a dose has been given in the past month. Additional doses are given if:

- The child has visible clinical signs of vitamin A deficiency like Bitot's spots, corneal opacity (Fig. 15) or corneal ulceration
- The child has signs of eye infection (pus, inflammation) that may hide the signs of vitamin A deficiency or
- The child has measles now or has had measles in the past 3 months

The addition doses (Table. 11) are given on D2 and at least 2 weeks later on D14. Other vitamin deficiencies either occult or showing their clinical feature like angular stomatitis (Fig. 14) are frequently associated with severe malnutrition. Therefore multivitamins (not containing iron initially) in the form of drops containing water soluble and fat soluble vitamins should be given daily. Vitamins and minerals for malnourished children if available as combined mineral and vitamin (CMV) can be used in preparing food. Other micronutrient including folic acid, zinc, cooper and later iron should also be given in appropriate dose. Appropriate timing and doses of vitamin A and other micronutrients are mentioned in Table 11.

Calcium is also added in therapeutic food. Although calcium and vitamin D deficiency are also associated with

Table 11: Doses and timing of micronutrient supplement offered to severely malnourished children

Vitamin A orally on D1,D2,D14 (If not received within one month) in following dose according to age	
<6 months of age	50,000 IU
6–12 months of age	100,000 IU
>12 months of age	200,000 IU
Give daily at least for 2 weeks	
• Multivitamin supplement (without iron)	
• Folic acid: Give 5 mg on day one	1 mg/kg/day
• Zinc	2 mg/kg/day
• Copper	0.3 mg/kg/day
• Iron	3 mg/kg/day
But only given when child is gaining weight (start at rehabilitation	

Fig. 14: Evidence of avitaminosis (angular stomatitis) in severely malnourished child contributing feeding difficulty. Discoloration of lip is due to gentian violet application

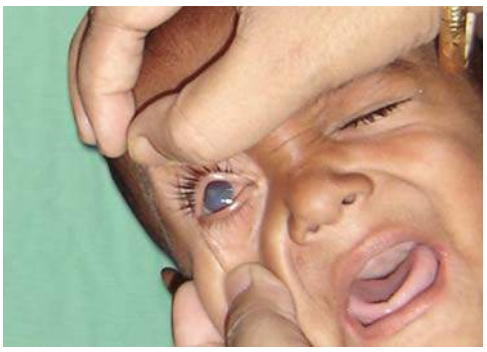


Fig. 15: Corneal opacity due to vitamin A deficiency (VAD) in a malnourished child

severe malnutrition, clinical rickets is very unusual (Fig. 16). This is because rickets occurs due to mineral deficiency in growing bone. Calcium and vitamin D supplement are essential during rehabilitation phase of malnutrition when the child grows rapidly.

WHO recommended therapeutic diet:

- F-75 (100 mL containing 0.9 g protein and 75 kcal energy)
- F-100 (100 mL containing 2.9 g protein and 100 kcal energy)
- Prepared from milk powder, sugar, soybean oil
- Combined minerals and vitamins (CMV if available) or electrolytes/mineral solution if CMV not available commercially.

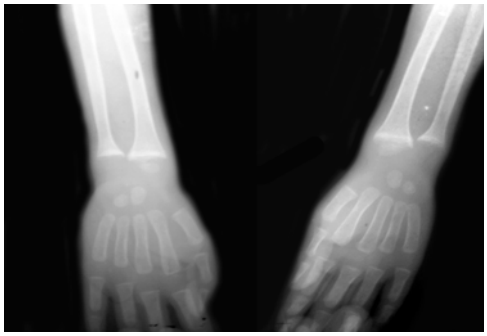


Fig. 16: Radiological evidence of rickets in PEM: A rare presentation in severe malnutrition with cupping and fraying of long bones

Frequency of feeding during the acute phase:

- Start with therapeutic feed every 2 hours (12 feeds in 24 hours)
- Night feeds are extremely important.

Step 7: Start cautious feeding including breastfeeding

Start feeding with F-75 containing 75 kcal and 0.9 g protein/100 mL feed from cup/spoon/syringe.

The following Table 12 is the usually recommended schedule:

For children with severe edema, the volume/feed and volume/day (100 mL/kg/day) are reduced until edema disappears. If intake is less than 80 kcal/kg/day, give remaining by NG tube.

In rare cases with feeding difficulty and food intolerance continuous slow feeding may be required with feeding pump as shown in Figure 17.

Breastfeeding

- Breastfeeding is encouraged in between feeds
- Required amounts of therapeutic diet are ensured even if the child is breastfed, that is required amount of F-75/ F-100 diet are not curtailed if the child breast- feeds.

Treatment of Associated Conditions

Emergency Management of Shock

Severe dehydration/dehydration shock and septic shock are difficult to differentiate on clinical signs alone. Signs of septic shock may include:

- Signs of shock but without history of watery diarrhea. Do not drink eagerly like severe dehydration
- Hypothermia or hypoglycemia

Diagnosis of shock is based on following criteria:

- Lethargy and unconscious
- Cold clammy hands and feet plus either of the following:
  - Slow capillary refill time (>3 sec), or
  - Weak fast pulse (>160/min in 2–12 months of age, >140/min in 1–5 years of age).

Treatment of shock

Six important components:

1. Give oxygen.
2. Give sterile 10% glucose (5 mL/kg) IV route.
3. Keep the child warm.
4. Give an antibiotic.
5. Give IV fluid at 15mL/kg over 1 hour. Use Ringer's lactate with 5% dextrose or half strength normal saline with 5% dextrose.

Table 12: Recommended schedule

Days	Frequency	Vol/kg/feed	Vol/kg/day
1–2	2 hourly	11 mL	130 mL
3–7	3 hourly	16 mL	130 mL
8+	4 hourly	22 mL	130 mL

Fig. 17: A malnourished child getting slow continuous measured feeding by feeding pump

6. Measure and record pulse and respiration rate every 30 minutes.

   If the shock is due to severe diarrhea: Use half strength cholera saline (15 mL/kg for first 2 hours to prevent symptomatic hyponatremia).

If there are signs of improvement after 1 hour (pulse and respiratory rate decreasing):

- Repeat IV fluid 15 mL/kg for 1 hour (total 2 hour).
- Switch to oral or NG rehydration with ReSoMal 10 mL/kg/hr in alternate hours with F-75 diet.
- Continue feeding with F-75 diet.

If the child fails to improve (pulse and respiratory rate remains high) after 1 hour, assume septic shock. In this case:

- Give maintenance IV fluid (3 mL/kg/hour) while waiting for blood.
- Transfuse whole blood at 10 mL/kg slowly over 3 hours
- Stop infusion if signs of overhydration appears (pulse suddenly increases by >25/min or respiration rate increases by >5/min from existing condition).

Anemia in Malnourished Children

Anemia, particularly iron deficiency (ID) is commonly associated with severe PEM. In majority of cases, normocytic normochromic anemia is common. However associated vitamin and mineral deficiencies, including ID and ongoing sepsis may modify the picture. The normocytic normochromic anemia in severe PEM is associated with decrease in circulatory erythrocytic mass. The metabolic changes in red blood cell, decrease in erythrocytes, and fall in erythropoietin production cause erythroid hypoplasia with increase in myeloid/erythroid ratio. However, associated ID may cause iron deficiency anemia (IDA). The incidence of IDA is variable and depends on number of factors such as dietary habits, parasitic infestation, chronic blood loss, etc.

Although majority of hypochromic microcytic anemia are due to ID but other conditions like ongoing infection is frequently associated with PEM. Infection decreases Hb synthesis and iron is less utilized for Hb synthesis and it is eliminated rapidly from blood to reticuloendothelial system in the form of ferritin. Characteristically in IDA serum iron (SI) is decreased with increase of total iron binding capacity (TIBC) and decrease in serum ferritin. However, in anemia with severe PEM, SI though less, TIBC is also less and serum ferritin may be increased.

Not only iron is unutilized in PEM, the unaltered ferrous ion catalyzes the reaction of superoxide and hydrogen peroxides (H_2O_2) to produce highly reactive hydroxyl (OH) ion through Fenton reaction, which is capable of producing chemical injury to cell membrane. Lipid per oxidation has been proposed as the primary mechanism for cellular dysfunction and tissue injury. In malnourished children, oxidative process overwhelms the antioxidant protection. These facts are the basis of withholding of iron supplementation in the early phase of management of severely malnourished children. In mild to moderate anemia, iron should be given for 3 months to replace the iron store, but this should not be started until after the initial stabilization phase has been completed.

Emergency Treatment of Severe Anemia

A blood transfusion is required

- If Hb is less than 5 g/dL
- If Hb is between 5 g/dL and 7 g/dL with respiratory distress.

Transfuse:

- Whole blood 10 mL/kg slowly over 3 hours
- Furosemide 1 mg/kg at the start of transfusion.

If signs of cardiac failure appear, transfuse. Packed cell 5–7 mL/kg body weight rather than whole blood.

Vitamin A Deficiency

Vitamin A on day 1, 2 and 14. If there is corneal clouding or ulceration

- Chloramphenicol or tetracycline eye drop
- Atropine eye drop
- Cover with eye pads soaked in saline solution and bandage.

Dermatosis

- Apply gauze soaked in 1% potassium permanganate solution over affected area and keep it for 10 minutes twice daily
- Omit nappies so that perineum can remain dry
- Zinc oxide paste/ointment
- Antifungal (Clotrimazole) twice daily for candidiasis, oral nystatin (100,000 IU), four times daily for oral candidiasis, which also acts as reservoir for gut and skin candidiasis. Figure 18 shows before and after treatment of both edema and dermatoses.

Helminthiasis

Helminthiasis is frequently associated with malnourished children. Anthelmintic given during rehabilitation phase.

- Single dose of 200 mg of albendazole, if age is more than 3–23 months, 400 mg of age is more than 24 months
- 100 mg of mebendazole twice daily for 3 days for children more than 24 months.

For Giardiasis:

- Metronidazole (7.5 mg/kg, 8 hourly for 7 days.)

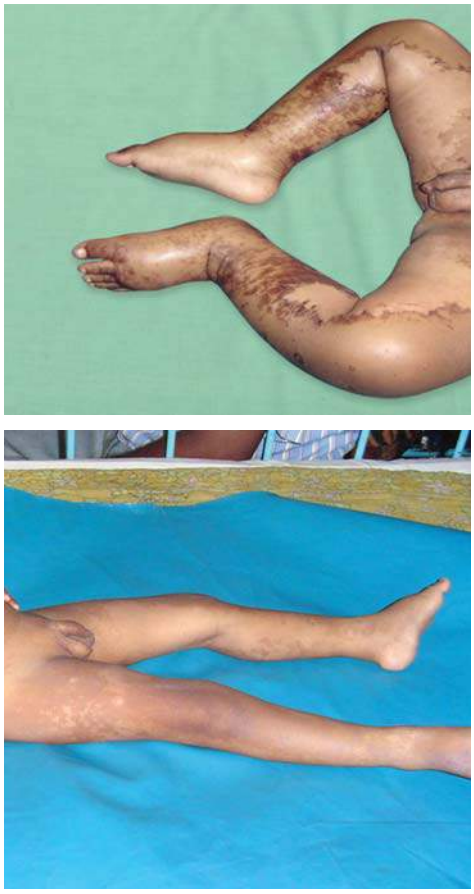


Fig. 18: Disappearance of both edema and dermatoses in malnutrition after protocolized management of SAM including skin treatment with zinc oxide and potassium permanganate

Tuberculosis

If tuberculosis is suspected due to contact with adult TB patient, chronic cough (>2 weeks), chest infection not responding to conventional antibiotics, perform a Mantoux test. In malnourished children the interpretation of Mantoux test is made with caution. It may be false negative or mildly positive (if induration <5 mm) in spite of presence of active tuberculosis due to impaired cell-mediated immunity.

Continuing Diarrhea and Dysentery

Loose or poorly formed stool are frequently associated with malnourished children, particularly in rehabilitation phase requiring no treatment provided the child is not sick and weight gain is satisfactory. Similarly food intolerance like lactose intolerance, milk protein allergies, etc. are frequently over diagnosed in malnourished children. Rarely diarrhea is due to lactose intolerance. Treat only if continuing diarrhea is preventing general improvement. In that case, substitute normal milk with non-milk formula (Rice, suji, comminuted chicken soup) [see annex].

Osmotic diarrhea

Some malnourished children cannot tolerate high osmolar diet during rehabilitation phase (F-100). In that case, low osmolar cereal based F-75 diet should be continued for long time and F-100 should be gradually introduced.

Persistent diarrhea

Diarrhea associated with severe malnutrition is a special entity and require special approach. Persistent diarrhea commonly associated with severely malnourished children not only responsible for treatment failure with poor weight gain, but also associated with high mortality. It should be treated with easily digestible protein and energy rich diet (Rice, suji, comminuted chicken soup, elemental and pre-elemental diet, etc.), together with appropriate micronutrients (Zinc, vitamin A, copper, potassium) and appropriate antibiotics when required.

HIV/AIDS

It may hinder recovery and may be associated with food intolerance (like lactose intolerance) and persistent diarrhea. Lactose-free diet may be tried.

Pneumonia

Pneumonia is one of the most frequent medical complications contributing to increased case fatality. Characteristic clinical features of pneumonia (tachypnea, lower chest in drawing, cough) may not be evident due to poor host response associated with poor intercostal, subcostal and diaphragmatic muscle mass. For a given sensitivity and specificity they produce five breaths fewer respiratory rate than well-nourished children. A number of children do not have fever and X-ray chest finding may not be conclusive. Therefore, high index of clinical suspicion of pneumonia should be adopted with mild cough and suboptimal tachypnea and even when characteristic WHO defined features of pneumonia are absent. Failure to recognize the above facts may cause failure to diagnose pneumonia early in malnourished children and also can delay timely treatment for pneumonia which may be potentially catastrophic.

Rehabilitation Phase

Step 8: Achieve catch-up growth

Signs of entrance to the rehabilitation phase are return of appetite (Fig. 19) and loss of edema in edematous malnutrition

- It should be gradual and takes usually 1 week.
  Recommended food: F-100 (every 10 mL containing 100 kcal energy and 2.9 gram of protein)
  To change from starter (F-75) to catch-up formula:
- Replace F-75 with same amount of F-100 every 4 hours for 48 hours
- Increase each successive feed by 10 mL until some feed remains uneaten
- The point when some remains unconsumed after most feeds is likely to occur when intake reach about 30 mL/kg/feed (200 mL/kg/day)

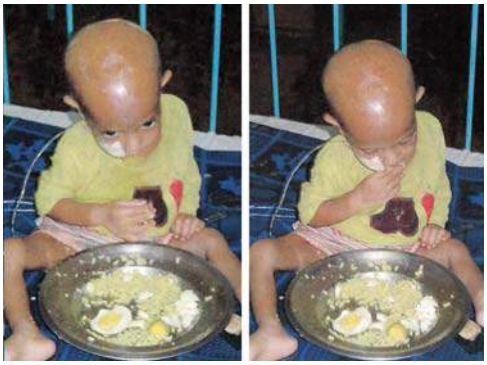


Fig. 19: A malnourished child in rehabilitation phase showing return of appetite

Fig. 20: Psychosocial stimulation through low cost toys required during rehabilitation phase

- In place of F-100 diet, non-milk formula like khichdi, haluva, modified porridge or modified family food can be used, provided they have comparable energy, protein and micronutrient concentration.

Step 9: Sensory stimulation and emotional support

- Tender loving care
- A cheerful, stimulatory environment (Fig. 20)
- Toys made of locally available discarded materials
- Physical activity as soon as the child is well enough
- Parental involvement when possible, comforting, bathing, play and to be continued at home.

Step 10: Prepare for discharge and follow-up regularly

Criteria for discharge from inpatient care in areas where there is no community-based outpatient care:

Child factor

- Weight for height median (WHM) more than 80% or more than WHZ more than –2 SD
- Edema has resolved
- Good appetite and gaining weight
- Child has been provided with appropriate micronutrients. List out of the fundamental rights and duties of the citizens of India.

Mother factor

- Mother can prepare appropriate food and feed for child
- Has financial resources to feed the child
- Can recognize danger sign and early access to hospital for urgent re-admission
- Can be visited weekly.

Failure to respond to treatment

Indicators:

- High mortality (Table 13)
- Poor weight gain.

Table 13: High mortality

Unacceptable	>20%
Poor	11–20%
Moderate	5–10%
Good	<5%

Death occurring within 24 hours of admission

Consider untreated or delayed treatment of sepsis, pneumonia, severe anemia, hypothermia, incorrect rehydration fluid, overuse of IV fluids. Table 14 summarizes the causes of death of severely malnourished children at different stages after admission in facility based care.

Within 72 hours

Low volumes to high volume feed or feeding with wrong formula (Table 14).

Table 14: Likely causes of death of severely malnourished children at different stages after admission in facility-based care

Death Occurring at night:	Hypothermia Not covered with blanket Draught coming from nearby window/door No night feed
Death during rehabilitation	Too rapid treatment with F-100 diet
After 7 days	Consider hospital acquired sepsis Persistent diarrhea among malnourished children is associated with high mortality

Weight gain is considered poor, moderate and good on the basis of weight gain in gram/kg/day as mentioned in Table 15.

Table 15: Status of weight gain during rehabilitation phase

Poor	<5 g/kg/day
Moderate	5–10 g/kg/day
Good	>10 g/kg/day

If weight gain is poor, then major changes of management and overhauling of department of nutrition will be necessary.

Undiagnosed infections [(TB, asymptomatic urinary tract infection (UTI)] may also be considered.

Other factors involved in poor weight gain are:

- Inadequate feeding, particularly night feed, wrong feeding technique and wrong preparation of food
- Specific nutrient deficiency, particularly not providing zinc and potassium to diet. Zinc and potassium particularly required during catch-up growth, as growing muscles require zinc and potassium
- Psychological problems and psychosocial problem are frequently associated with malnourished children. They are quite often emotionally deprived due to dysfunctional family unit and functionally single parent family. The psychological problems are characterized by stereotyped movements, rocking, rumination, etc. Treat by providing extra care, love and attention (Fig. 21).

Fig. 21: A minor girl is looking after her malnourished brother due to non-availability of her adult parents: A frequent psychosocial problem associated with SAM

COMMUNITY-BASED MANAGEMENT OF ACUTE MALNUTRITION

Role of Community- based Management of Severe Malnutrition

Where sufficient resources are made available, the WHO inpatient medicalized treatment model for SAM can achieve low case fatality rate (CFRs). However, exclusive inpatient treatment strategies are resource intensive, requiring large number of skilled staff. As the prevalence of SAM is highest in resource poor environment, there is usually substantial mismatch between the large numbers of patients requiring treatment and small number of skilled staff and limited resources available to treat them. The HIV/AIDS has further aggravated in sub Saharan Africa.

Community-based management (CBM) compliments the existing WHO inpatient protocol.

A growing number of countries and international relief agencies have adopted a community-based model for the management of acute malnutrition called community-based therapeutic care (CTC).

The WHO also recommends treatment of uncomplicated SAM at community level. The model provides a framework for an integrated public health response to acute malnutrition, treating most patients with SAM solely as outpatient and reserving inpatient care for the few with SAM associated with complications. The model also aims to integrate treatment with various other interventions designed to reduce the incidence of malnutrition and improve public health and food security. Program designed attempts to take into account the socioeconomic factors particularly poverty, high workload of women and factors that contribute to late presentation of cases of SAM. The design minimizes the cost of families and maximizes access to treatment. The decentralized design also means that in non-emergency situation, there are few cases of SAM at any one access point and the quantities of ready to use therapeutic food (RUTF) required to treat SAM are therefore small.

Severe acute malnutrition is classified on the basis of whether there is co-existent life-threatening complications. Children presenting with SAM complicated by life-threatening illness receive inpatient care according to WHO treatment protocol. Those with SAM but without life threatening complications are treated through weekly or fortnightly therapeutic program.

Management of SAM with and without complication is shown in Figure 22.

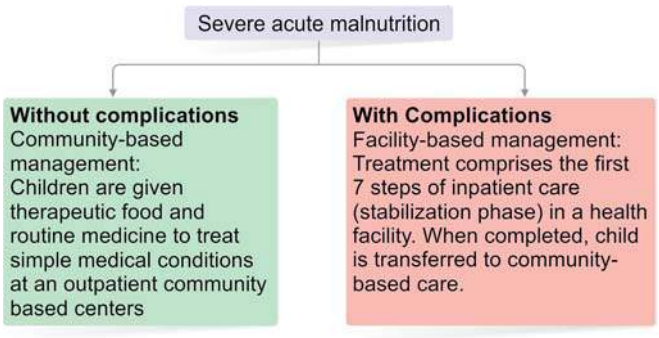
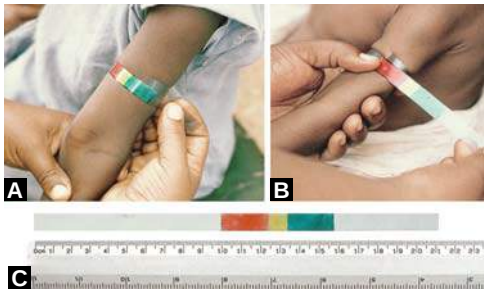


Fig. 22: Management of SAM with or without complication



Figs 23A to C: Assessment of malnutrition in community using mid-upper arm circumference (MUAC). (A) Well nourished child's MUAC falls in green zone; (B) Whereas malnourished child's MUAC in red (< 110 mm) zone; (C) and Measurement scale

Fig. 24: Preparation of ready to use therapeutic food (RUTF)

The key components of community-based management are:

- The introduction of technique to engage community to promote early presentation and compliance
- Handing over the identification of SAM to community through use of mid-upper arm circumference (MUAC) (Fig. 23)
- The development of RUTF based on local capacity.

This model can easily be implemented and resourced even in impoverished environment.

In outpatient therapeutic program, they receive a ration of take home RUTF to provide energy of 200 kcal/kg/day, a course of oral broad-spectrum antibiotic, folic acid, anthelminthic, and if appropriate anti-malarial.

Ready to Use Therapeutic Food

Development of RUTF has greatly eased the difficulties associated with providing a suitable energy high-nutrient dense food that is safe to use in outpatient program. RUTF is an energy dense food enriched with minerals and vitamins with similar nutrient profile but greater energy and nutrient density than F-100, the diet recommended by WHO in the recovery phase of treatment of SAM. The original RUTF recipes contain five ingredients: (1) Peanut-butter; (2) vegetable oil; (3) powdered sugar; (4) dried skimmed milk; (5) a vitamin mineral mix. In contrast to water-based F-100, RUTF is an oil-based paste with extremely low water activity. As a result RUTF food does not grow bacteria, allowing it to be kept unrefrigerated in simple packaging for several months. As the food is eaten uncooked, heat labile vitamins are not destroyed and labor, fuel and water demands on poor household are minimized. The production process is simple and is RUTF can be made from local crops with basic technology that is readily available in developing countries (Fig. 24).

The development of RUTF food has allowed much of the management of SAM to move out of the hospital by shortening of duration of inpatient treatment; the move towards using RUTF food in the recovery phase of treatment reduces the resources to treat SAM which improves cost effectiveness.

Currently imported, commercially-produced RUTF are used. Therefore, RUTF needs to be more easily accessible and affordable for the approach to be sustainable. Local production of RUTF needs to be promoted for increased access and availability to RUTF through reducing cost.

Home-based Nutrient-dense Foods

There is some merit in arguments on emphasis of wide use of RUTF in impoverished communities of developing countries, considering:

- The cost of imported RUTF
- It also presents an opportunity for commercialization of malnutrition through multinational companies' product-based nutrition therapy.

Home-based nutrient-dense food has been found to be cost effective and has been recommended during rehabilitation phase of treatment for malnutrition in areas where follow-up is possible.

The WHO recommends treatment of uncomplicated severe malnutrition at home. Mother of children should be taught how to prepare high calorie cereal milk (HCCM). It can be prepared by mixing 100 mL of milk fortified with 15 gm flour of other cereals (food grains) of mothers' choice, 5 mL of oil and 2 teaspoonful of sugar, cooked to porridge like consistency. Two such servings of HCCM made with 100 mL of milk can be given at home. HCCM found very useful homemade food in South India.

Commercially available nutrient-dense food is expensive. RUTF itself is used in acute phase of rehabilitation and prescribed as therapeutic item not as food. Therefore locally made RUTF in the community based treatment of childhood malnutrition is feasible and desirable. The success of home-based treatment of severe malnutrition will require the provision of homemade nutrient-dense food supplement which can be safely stored and administered without much preparation by caregiver.

COMMUNITY-BASED MANAGEMENT FOR ACUTE MALNUTRITION (CMAM)

Community-based management for acute malnutrition is shown in the Figure 25.

Community Outreach Activities

Children with acute malnutrition (Fig. 26) will be identified in the community and at household level using MUAC tapes (Fig. 27) and simple techniques are used to identify nutritional

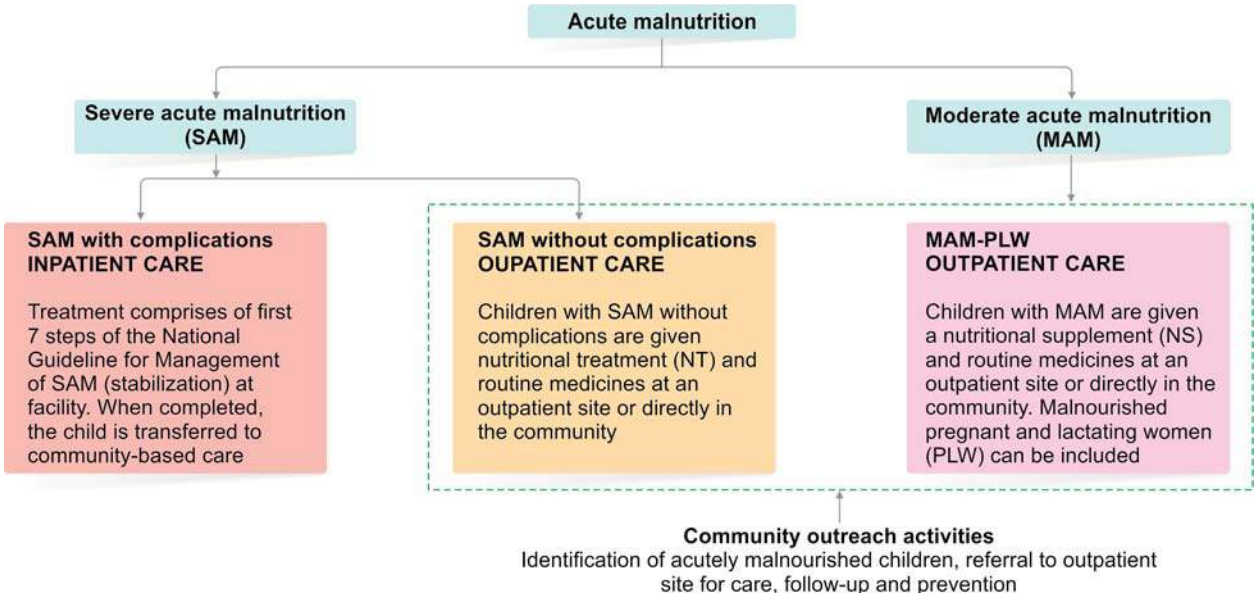


Fig. 25: Components of community-based management of acute malnutrition

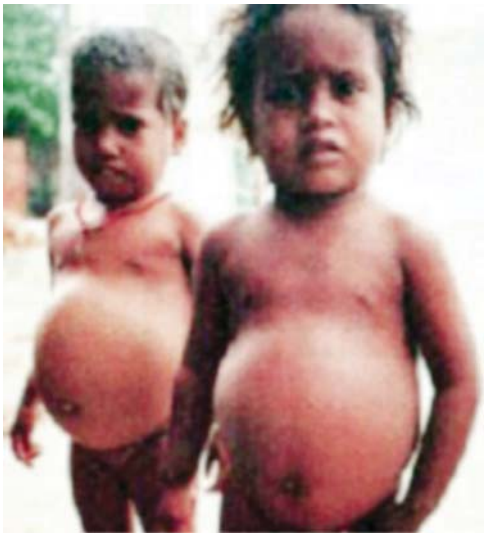


Fig. 26: Two malnourished children in the community with evidence of wasting and abdominal distension

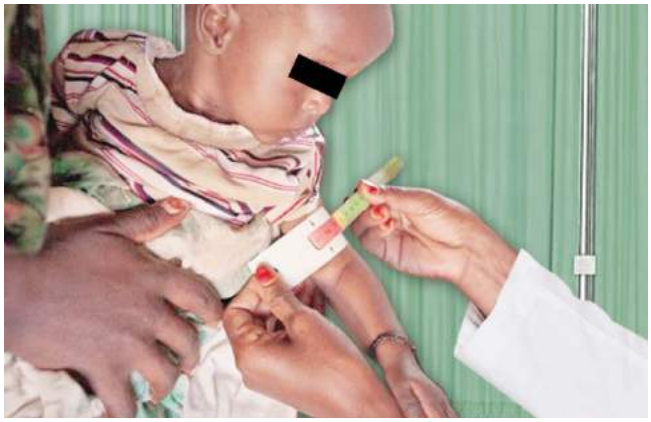


Fig. 27: Assessment of MUAC (<11.5 cm, red zone) for enrolment criteria of CMAM of SAM

edema and visible wasting. Identification and referral of children with acute malnutrition and acutely malnourished PLW at community outpatient site are given in Table 16. Caregivers of children with SAM will be given a referral slip and asked to go to the outpatient site on a certain day. Children with MAM and acutely malnourished PLW may also be included in a community-based program. Enrolment criteria for inpatients care and community based management of SAM, MAM an acutely malnourished pregnant and lactating woman (PLW) are provided in Table 17. Some children with SAM will require follow-up at home. CHWs follow-up with children who are absent, who have defaulted or have other problems with their treatment and recovery.

Community-based Management of SAM without Complications

Children with (SAM) with appetite and without complications will be given nutritional treatment (NT) and routine medicines. The children and their caregivers will come to a designated outpatient site every week for a medical check-up and to receive NT. The management of children with SAM at the outpatient site is the responsibility of a designated service provider. In some cases, a trained CHW will directly manage the child at the community level without referral to a designated outpatient site.

Inpatient Care for SAM with Complications

Children with SAM who do not have appetite and/or with complications and severely malnourished infants less than 6 months will be treated in inpatient care until stabilized.

Community-based Management of MAM and Pregnant and Lactating Woman

Children with MAM may be managed at the community level using energy and nutrient-dense local foods or NS which will be provided every two weeks at the outpatient site. Acutely

Table 16: Identification and referral of children with acute malnutrition and acutely malnourished PLW at community outpatient site

Target group	Finding	
6–59 months		• Refer to outpatient site **CHW providing direct treatment** • Determine complications • Refer to inpatient care if SAM with complications • Provide nutritional treatment (NT) and medical care for SAM without complications
6–59 months	Bilateral pitting edema (any grade)	• Refer to outpatient site **CHW providing direct treatment** • Refer to inpatient care
6–59 months	MUAC 11.5 cm – <12.5 cm (Yellow)	• Refer to outpatient site **CHW providing direct treatment** • Provide nutritional supplement (NS) and medical care for MAM/or practical guidance on use of local foods
Pregnant and lactating women	MUAC <21cm	• Refer to outpatient site **CHW providing direct treatment** • Provide nutritional supplement (NS) and medical care for/or practical guidance on use of local foods
Infants <6 months*	• Visibly wasted infants • Infants with edema • Infants too weak or feeble to suckle with failure to gain weight	• Refer to outpatient site for evaluation • Refer to inpatient care

Abbreviations: CHW, community health worker; SAM, severe acute malnutrition; MAM, moderate acute malnutrition; MUAC, mid-upper arm circumference.

Table 17: Enrolment and discharge criteria for community-based management of SAM, MAM and acutely malnourished PLW

ENROLMENT CRITERIA		
Inpatient care	**Community-based management (outpatient care)**	**Community-based management (outpatient care)**
SAM with complications (children 0–59 months)	SAM without complications (children 6–59 months)	MAM (children 6–59 months) and acutely malnourished PLW
• Bilateral pedal edema (any grade) OR • Marasmic-Kwashiorkor MUAC <11.5 cm with any grade of edema OR • MUAC <11.5 cm with any of the following complications: – No appetite/unable to eat – Persistent vomiting (>3 per hour) – Fever >39°C or 102.2°F (axillary temperature) – Hypothermia <35°C or 95°F (axillary temperature) – Rapid breathing as per IMCI guidelines for age: >60/min for children <2 months >50/min for children 2–12 months >40/min for children 12–59 months • Dehydration based primarily on a recent history of diarrhea, vomiting, fever or sweating, not passing urine for last 12 hours and on recent appearance of clinical signs of dehydration as reported by the caregiver	• MUAC <11.5 cm **And all of following:** • Presence of appetite • Without medical problems or any complications	• MUAC 11.5 cm–<12.5 cm **And** No bilateral pedal edema **And all of following:** • Presence of appetite • With or without medical complication – Pneumonia (not severe pneumonia or very severe disease) – Diarrhea with no dehydration
• Severely pale (severe palmer pallor) with or without difficulty in breathing • Very weak, apathetic, unconscious, fitting/convulsions • Conditions requiring IV infusion or NG tube feeding **Infants < 6 months:** Severe malnourished Infants <6 months who are visibly wasted and or unable to breastfeed		**Pregnant women** MUAC <21 cm **Lactating women with** Infant is under 6 months **And** MUAC <21 cm

Abbreviations: SAM, severe acute malnutrition; NG, nasogastric; MAM, moderate acute malnutrition; MUAC, mid-upper arm circumference

malnourished PLW with infants less than 6 months can also be included in a community-based program where resources and capacity are sufficient.

Basic supplies for community outreach activities

- Mid-upper arm circumference tapes
- Referral slips in duplicate copy
- Home visit form and checklist
- Key messages for caregivers of children with SAM and MAM
- IEC materials on prevention of acute malnutrition.

BASIC REQUIREMENTS FOR COMMUNITY- BASED MANAGEMENT OF SAM

Who will Manage Community-based SAM?

The outpatient site/community outreach site is managed by a designated service provider. This may be a skilled trained health worker or a trained CHW.

Direct management of SAM cases in the community can be managed by a trained CHW. This delivery mechanism ideally

requires one trained dedicated CHW for an average of 200 households to ensure a manageable caseload.

Where the Community-based SAM will be Managed?

An outpatient site/community outreach sites can be operated at any of the following: Satellite/Outreach Clinic, Community Clinic, Union Health and Family Welfare Center (UHFWC), Union Sub-Center, UHC outdoor facility, NGO static clinic, mobile clinic, outdoor facilities of secondary and tertiary hospitals and other community-based outreach sites.

Nutritional Treatment for SAM without Complications

Nutritional treatment is a specialty prepared and pre-packaged dietary treatment for SAM without complications. Nutritional treatment is oil-based energy-dense mineral/vitamin enriched nutritious food. It contains 450–550 kcal/100 g of which fat is 45–60% of total energy and protein (including milk products) is 10–12% of total energy. It has similar nutrition contents as F100, which is recommended by the World Health Organization (WHO) for the treatment of severe acute malnutrition in recovery phase. Multi-micronutrient content of NT is equivalent to F100. NT does not require any mixing or cooking, therefore, there is minimal chance to microbiological contamination. NT is soft and crushable with smooth homogenous texture. It can be consumed directly from the packet. It has a very little water content and therefore can be safely stored at home in a dry place without risk of contamination. As it does not require cooking, loss of micronutrients by heat is minimal.

Nutritional treatment for SAM without complications should be sought from prequalified supplier in order to ensure that recommended international and national quality and safety standard (including packaging) of such food are adhered to at all time. NT for SAM without complications can be imported or procured locally wherever possible. Locally produced NT, made of local food ingredients, meeting international and national standards for quality, safety and cost, is preferred for community-based management of SAM.

The amount of NT given is based on weight (175–200 kcal/kg/day).

Nutritional treatment should be given after breastfeeding. No other foods (other than breast milk) should be given for at least one week. After one week, additional home foods may be given AFTER breastfeeding and NT if the child still has appetite. Plenty of safe drinking water should be available to children taking NT. Where NT is not available, children with SAM without complications should be referred to the UHC.

Following the initial phase of treatment, children may be managed at home. Mothers and caregivers will be advised on the preparation of high energy nutrient dense foods. Animal protein should be added to foods prepared at home. Milk products should also be added where possible. A multi-micronutrient supplement must also be included.

Following the initial phase of treatment, children may be discharged from community management of SAM. The discharge criteria from inpatient care in the community (without complication) or with medical complications in facility based health complex and from outpatient care of community based management of MAM and acutely malnourished PLW in mentioned in Table 18. Simple techniques for discharge criteria like measurement of MUAC (Fig. 28) can be used in community based outpatient management (Table 18).

Nutritional Management of Moderate Acute Malnutrition at Community Level

The nutritional management of MAM aims to provide additional energy and nutrient density to the existing home-based diet to support catch up growth. This means adding at least 25 kcal/kg/day over and above the energy requirements of a well-nourished child. This should be done by encouraging increased intake of home food. The staple cereal (rice) should be fortified with micronutrient powder and animal source of

Fig. 28: MUAC more than or equal to 12.5 cm (green zone) for discharge criteria after CMAM

Table 18: Discharge criteria for community-based management of SAM, MAM and acutely malnourished PLW

DISCHARGE CRITERIA		
Inpatient care	**Community-based management (outpatient care)**	**Community-based management (outpatient care)**
Transfer to outpatient site (6–59 months children) when: • Appetite returned • Medical complications controlled/resolved • Edema resolved	• MUAC >11.5 cm for two consecutive visits **AND** • 15% weight gain from admission (or edema free lowest weight) **AND** • No sign of severe illness as per IMCI protocol/clinically well **Transfer to community-based management of MAM where possible**	Children 6–59 months • MUAC >12.5 cm for two consecutive visits **Pregnant and lactating women** • MUAC >21 cm **AND** • Infant completed 6 months

Abbreviations: MUAC, mid-upper arm circumference; IMCI, integrated management of illness; MAM, moderate acute malnutrition

Fig. 29: Group feeding of children (Nutritional treatment) of MAM in a community

food (fish, egg, milk, etc.) included in the diet. De-worming should be done at least 6 monthly intervals. Intercurrent infections should be appropriately treated. Hygiene should be promoted to prevent infection.

Children with MAM living in extremely food insecure conditions where the caregivers may not be able to provide the additional food will require an NS. The NS should ideally provide 700–1000 kcal/child/day with 25–30% of energy from fat and 10–12% of energy from protein (Fig. 29).

ENROLMENT IN COMMUNITY-BASED MANAGEMENT OF MAM

Target Group

Children with MAM aged 6–59 months with appetite (ability to eat) and without medical complications who meet the enrolment criteria. Detailed enrolment criteria for community--based management of MAM has been provided in Table 19.

Other cases such as:

Children discharged from SAM: Children who have completed treatment for SAM should continue treatment as MAM.

Table 19: Enrolment criteria for community-based management of MAM

Category	Criteria
Children 6–59 months	• MUAC >115 mm to <125 mm (>11.5cm to <12.5 cm) **AND** • No edema **AND** • Presence of appetite With or without infection, like: • Pneumonia (not severe pneumonia or very severe disease) • Diarrhea with dehydration (No danger signs according to IMCI protocol)
Other reasons for enrolment	
Discharged from SAM	Child is transferred to MAM after completion of treatment for SAM in the outpatient program
Return after default	Children who return after default (absent more than two visits)

Abbreviations: MUAC, mid upper arm circumference; IMCI, integrated management of illness; MAM, moderate acute malnutrition; SAM, severe acute malnutrition

Return after default: Children who return after defaulting (absent more than 2 weeks) are readmitted if they still fulfill the admission criteria.

Follow-up visits "every two weeks until" discharge

Children and their mothers/caregivers will have an appointment every two weeks at the outpatient site or with the CHW if managed directly at the community level. At each visit, the child will be assessed and counseled on the use of energy/nutrition-dense local foods. If available, receive the NS.

- At each visit the MUAC and weight is measured and edema is assessed
- Children with danger signs should be referred to the nearest health facility
- If the child has not gained weight after two to three weekly visits or if the child is losing weight, refer him/her for a medical check-up at the nearest inpatient care or health facility.
- Children who are enrolled as MAM and then deteriorate or develop edema should be transferred to the program for SAM.

BODY COMPOSITION

Body composition (distinguishing fat and fat-free mass) and growth are key components of health in both individual and population. The ongoing epidemic of obesity in children and adults has highlighted the importance of body fat for short-term and long- term health. However, other components of body composition like lean mass, total body water (TBW) are now understood to be important health outcome in infants and children.

Measurement such as weight and length provide useful but incomplete data leading to growth and nutritional status of a child. Thus more detailed assessment of body composition is being sought by those interested in pediatrics, nutrition, growth and development.

Estimates of body composition based upon simple straight forward anthropometric measurements have been available for many years. The majority of these methods rely on the ability of measurements of subcutaneous fat folds or skin folds in selected sites to predict accurately total body fatness. It has been never thought whether this approach was perfect and there are many problems associated with the model that are not easy to overcome. It has been shown that it is not possible in infants to predict total body fatness from measurement of skin fold thickness to an appropriate level of accuracy, and equations derived for use in childhood and adolescent are extremely population specific.

Body mass index (BMI) calculated as weight/ height^2 is also used as an index of relative weight often expressed as SDs to take into account age and sex. In adults BMI is predictive to clinical outcome such as type 2 diabetes, however, its predictive value in children and adolescent is less clear. BMI is a global index of nutritional status—used, for example, to categorize both over weight and obesity and eating disorders in combination with psychological criteria but its relation with body composition per se is controversial.

Although correlated with percent fat, BMI cannot distinguish fat and lean mass and there is two-fold range of variation in fatness for a given BMI value in individual children.

Body mass index may be particularly misleading in hospitalized children, where children are apparently

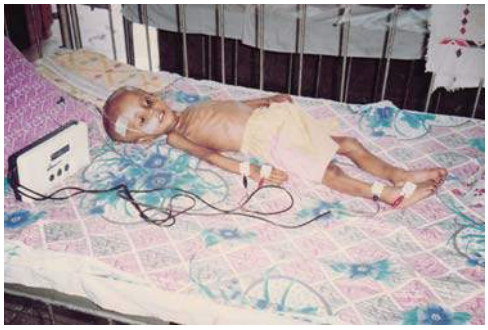


Fig. 30: Body composition analysis by bioelectric impedance (BIA) in a malnourished child using tetrapolar portable body composition analyzer

malnourished in terms of BMI, actually have an increase in relative body fat and a severe disease in lean tissue. This may be important for their nutritional management as the low BMI may lead to inappropriate over feeding.

There are numerous techniques that are used to assess body composition. The majority use a two compartment model, i.e. divides the body into fat and fat free mass. Nevertheless, such techniques are not easily applied in children because of either practical or ethical consideration, e.g. underwater weighing to assess body density and hence body fat mass used to measure body composition in adults is clearly not acceptable to young children.

The various methods used for assessment of body composition:

- Bioelectric impedance
- Assessment of TBW by isotope either hydrogen or oxygen in the form of water and apply a standard dilution principle
- Dual energy X-ray absorptiometry.

However, body composition analysis by bioelectric impedance (BIA) has become extremely popular in recent years. It can measure fat mass and fat-free mass or lean mass in obese children directly by portable bio-electric impedance analyzer machine of various models using a tetrapolar electrodes, placing two electrodes in right lower limbs and two in upper limbs (Fig. 30). According to recognized procedure an electric impulse of 800 mA at 50 kHz is passed through the body of the child through the electrodes and reading of the resistance (electric impedance) is recorded. TBW and hence fat- free body mass (FFBM) or lean mass are derived from TBW. Fat mass (FM) and percentage of body solids are calculated simply from percentage of FFBM and percentage of total body water (TBW), respectively.

In malnourished children, TBW hence FFBM may not be derived directly. In that case, a linear regression equation is used to calculate TBW. FFBM or lean mass is obtained using an age specific formula and age specific constant of body density. Percentage fat mass and percentage of body solids are then calculated simply from percentage of FFBM and percentage of BW, respectively.

VITAMIN DEFICIENCIES AND THEIR TREATMENT

Vitamins are essential organic compound that are required in very small amounts (micronutrients) and are involved in fundamental functions in the body such as growth, maintenance of health and metabolism. Because our body cannot biosynthesize vitamins, they must be supplied by the diet or supplement. Recommended daily nutrient intakes of vitamin are provided in Table 20. Vitamin deficiency states are common in many developing countries and are often associated with global malnutrition. In clinical setting, vitamin deficiency may also occur as complication in children with

Table 20: Nutrient intakes for vitamins unit/day

Vitamin	RNI	RNI	RNI	Tolerable upper intake
	0–6 months	7–12 months	1–3 years	
A (µg)*	350	350	400	800 µg/day
D(µg)†	8.5	7	7	25 µg/day (0–24 m)
E (mg)§	0.4 mg/g PUFA3	0.4 mg/g PUFA	0.4 mg/g PUFA¶	10 mg/100 kcal formula
K (µg)	10	10	10	Not given
B_1 (thiamine) (mg)	0.2	0.2/03	0.5	Not given
B_2 (riboflavin) (mg)	0.4	0.4	0.6	Not given
Niacin (equivalents (mg)	3	4/5	8	2 mg/day (1–3 yr)
B_6 (pyridoxine) (mg)	0.2	0.3/0.4	0.5	Not given
B_{12} (µg)	0.3	0.4	0.5	Not given
Biotin (µg)**	Not given	Not given	Not given	7.5/100 kcal
Pantothenate (mg)	1.7	1.7	1.7	1.2/100 kcal
Folic acid (µg)	50	50	70	200 µg/day (1–3 year)
C (mg)††	25	25	30	30 mg/100 kcal

Source: Beattie RM, Dhawan A, Puntias JWL, et al. Paediatric gastroenterology, hepatology and nutrition. Oxford University Press. 2009.

* 1 µg Vitamin A retinol equivalent (RE) = 3.33 IU
† Vitamin D (calciferol); 1 ug = 40 IU
§ Vitamin E, α-tocopherol equivalent, 1 mg = 1 IU
¶ PUFA, polyunsaturated fatty acids
** No daily reference value given for biotin; an intake between 10 µg/day and 200 µg/day considered safe and sufficient
†† Vitamin C as ascorbic acid

various chronic disorder or diseases. Some vitamin deficiency disorders and their treatment are discussed in this chapter.

VITAMIN A

Discussed in detail later in Vitamin A section.

VITAMIN B COMPLEX

Vitamin B_1

Other name: Thiamine.

Sources: Unmilled cereals, pulses, oil seeds, ground nuts.

Functions

- Acts as co-enzyme
- Essential for proper functioning of nervous system.

Deficiency

Beriberi: Manifest in two forms: dry and wet.

- India and Far East: 'Wet beriberi' with acute high output cardiac failure, in breastfed infants of mothers with a diet of polished rice. Coughing, choking and aphonia with laryngeal edema. Drowsiness and meningism.
- Developed countries and older children: 'Dry beriberi'/ Wernicke's encephalopathy presents as encephalopathy in children on long-term total parenteral nutrition. In older children, with a diet based on polished rice, presents with sensory and motor neuropathy.

Investigations

- Trial of supplements
- Blood for transketolase activity.

Treatment

Parenteral intravenous or intramuscular vitamin B (50–100 mg) preparation, then oral supplements. Dietary intake of nuts, peas, beans, pulses, brewer's yeast.

Vitamin B_2

Other name: Riboflavin

Sources: Milk, liver, kidney, meat, butter, eggs, green and yellow vegetables.

Daily requirement: Infant 0.4 mg and children 1.1 mg.

Functions

- Helps in cellular oxidation
- Acts as co-factor for synthesis of certain enzymes
- Helps in metabolism of carbohydrate, protein and fat.

Deficiency

Cheilosis magenta colored tongue and nasolabial seborrhea (Fig. 31).

Treatment

- Riboflavin 20 mg/day
- Add milk, eggs, liver, pulses or legumes to diet.

Vitamin B_6

Other name: Pyridoxine

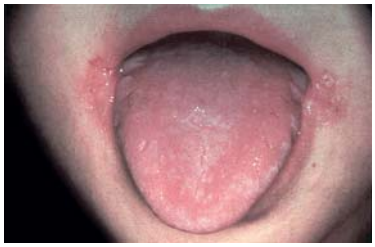


Fig. 31: Cheilosis and glossitis in vitamin B_2 deficiency

Sources: Meat, liver, egg yolk, pulses, vegetables, wheat, nuts.

Daily requirement: Infant 0.2–0.4mg and children 0.5 mg.

Functions

Functions as a coenzyme for many enzymes involved in aminoacid metabolism including aminotransferases, decarboxylases, racemases and dehydratases. Involved in synthesis of neurotransmitters such serotinin.

Deficiency: Convulsion, depression, peripheral neuropathy.

Investigations

- Rapid response to supplements.
- Serum pyridoxal 5-phosphate.

Treatment

- Pyridoxine-dependent seizure: 50–100 mg PO, IM, IV. Maintenance dose: 50–100 mg/day
- Dietary deficiency: 5–15 mg/day for 3–4 weeks then 2.5–5 mg/day
- Drug-induced neuritis: 1 mg/kg/day PO, IM, IV qds.

Vitamin B_{12}

Other name: Cyanocobalamine

Sources: Liver, kidney, meat, cheese, egg, milk, green vegetables usually do not contain B_{12}.

Daily requirement: Infant 0.3 µg and children 0.5 µg.

Functions

- Essential for maturation and production of RBC by synthesizing DNA
- Helps in formation of myelin sheath of nervous fibers.

Deficiency

Megaloblastic anemia: Anemia, yellow tint to skin, glossitis, paresthesia, ataxia and dementia.

Etiology: Ileal resection, vegan diet or intrinsic factor deficiency or abnormality

Neurological manifestation including subacute combined degeneration of spinal cord.

Investigation

Schilling test.

Treatment

- Vitamin B_{12} 1,000 µg m twice weekly until normal Hb, then every 6 weeks.
- In neurological involvement 1 mg vitamin B_{12} should be given IM daily for 2 week then 1mg IM monthly lifelong.

Nicotinic Acid

Sources: Meat, fish, whole milk, cereal, pulses, vegetables and fruits.

Daily requirement: Infant 3–5 mg and children 12 mg.

Deficiency

Pellagra: Characterized by 3Ds (diarrhea, dementia, dermatosis).

Skin: Photosensitive dermatitis with scaling and pigmentation.

Gut: Angular stomatitis and diarrhea

Neurological: Dementia, depression, delirium, peripheral neuropathy.

Etiology

Poor bioavailability on nicotinic acid in maize and low in tryptophan.

Investigations

- Rapid response to supplements
- Urine for N1 methyl nicotinamide and pyridoxine derivatives.

Treatment

- Orally, parenteral vitamin B (100 mg) preparation, four hourly
- Adding pulses, whole meal cereals, meat or fish to diet.

Folic Acid

Sources: Fish, leafy vegetables, liver, kidney, milk, eggs.

Functions

Essential for maturation and production of RBC by synthesis of DNA.

Daily Requirement

Infant 50 µg and children 70–100 µg.

Deficiency

Megaloblastic anemia.

Treatment

5 mg daily orally for several month.

VITAMIN C

Other name: Ascorbic acid.

Sources: Citrus food and green vegetables.

Daily requirement: 20–30 mg.

Functions

- Essential for collagen synthesis of bone cartilage and dentine
- Acts as antioxidant
- Helps in iron absorption
- Required for adrenal gland function.

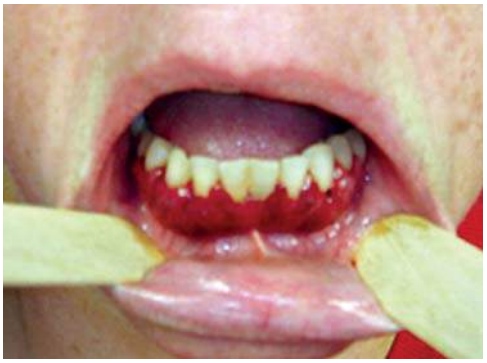


Fig. 32: Gingival hypertrophy in scurvy

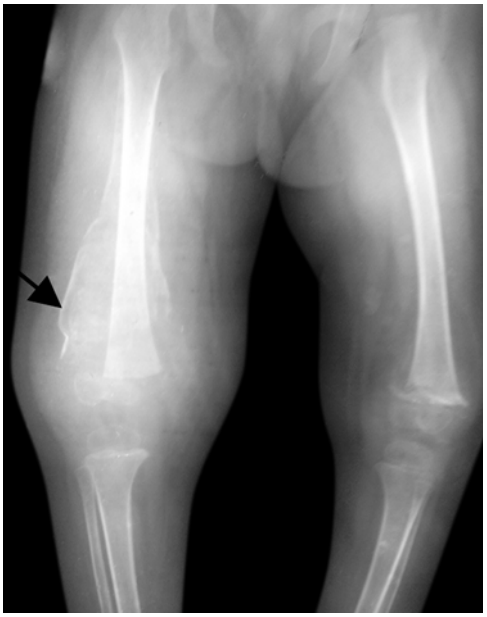


Fig. 33: Bone X-ray of scurvy showing calcified subperiosteal hematoma with ground glass appearance of metaphysis

Deficiency

Scurvy: Gingival hypertrophy (Fig. 32) and around hair follicles and capillaries. Irritability and painful limb swelling causing "pseudoparalysis".

Investigations

- Response to supplements
- Plasma white cell ascorbic acid level
- Bone X-ray: Calcification of sub-periosteal hematoma with ground glass appearance of metaphyses and dense rim, 'smoke-ring' appearance of cortical bone around epiphyses (Fig. 33).

Treatment

Ascorbic acid 500 mg per day for a week, and investigate dietary sources.

VITAMIN E

Other name: Tocopherol.

Sources: Vegetable oil, egg, butter, whole green cereals, nuts, peas.

Daily Requirement: Infant 5 IU and children 9 IU (0.4 mg/g) PUFA.

Functions

Acts as antioxidant.

Deficiency

- Presents with steatorrhea and hemolysis in premature neonates
- Neurological changes: Wide-based gait, spinocerebellar degeneration, ocular palsy.

Investigations

Serum vitamin E level or red cell susceptibility to hemolysis by hydrogen peroxidase.

Treatment

Oral or intramuscular tocopherol supplement.

VITAMIN K

Other name: Naphthaquinone.

Sources: Leafy vegetables, cheese, egg yolk, liver, etc.

Daily Requirement: 10 µg

Functions

Required for synthesis of clotting factors.

Deficiency

- Coagulopathy or hemorrhagic diseases of newborn.
- May affect bone formation.
- Prothrombin time prolonged.
- The normal intestinal flora can manufacture quinines with vitamin K activity.

Etiology: Newborn infants and in children with fat malabsorption.

Treatment

- *Mild case*: 1–2 mg/24 hr orally
- *Severe case*: 5 mg/24 hr parenterally.

VITAMIN A

Vitamin A, one of the fat soluble vitamins (A, D, E and K) controls protein synthesis at either transcriptional or post-transcriptional level. Vitamin A refers generally to all components structurally related to retinol that have biological activity. Carotenoids are provitamin, a substance found in vegetables. Beta carotene is the most effective precursor of vitamin A and a strong antioxidant, which prevents cellular damage.

ABSORPTION AND METABOLISM

Vitamin A is absorbed in esterified form as part of chylomicron. The yellow beta-carotene requires bile salts for absorption and is converted to vitamin A in the intestinal tract. Once absorbed, vitamin A is stored in the liver. The liver releases vitamin A to the circulation, bound to RBP. RBP takes vitamin A to the retina of eye, which is essential for vision, particularly night vision.

PHYSIOLOGIC FUNCTION

There are three main functions of vitamin A

1. Maintenance of vision, particularly night vision.
2. Maintaining of epithelial tissue and differentiation of many other tissues particularly during reproduction and gestation.
3. Immunological role: Vitamin A plays an important role in regulating cell differentiation and thus maintaining epithelial barrier defense and modulating various components of the innate and acquired immunity, help maintain disease resistance and improve healing. Vitamin A deficiency (VAD), results in downregulation of T-cell mediated effectors function. Also VAD influence the Th_1-Th_2 (shift from Th_2 to Th_1) cytokine profile, resulting in greater secretion of proinflammatory cytokines.

Vitamin A deficiency is common among women in the developing countries. Mean serum concentration of vitamin A reserve is about 300 µg during pregnancy among diverse groups of South Asian women in comparison to value of 450–500 µg of better nourished Western population.

Concern about maternal nutrition and VAD has been focused on its adverse effect on fetal and infant vitamin A status, health and survival. Randomized control trial of low dose of vitamin A or carotene revealed low mortality related to pregnancy in Nepal. Trials are on the way to show efficacy of vitamin A supplementation on neonatal sepsis and necrotizing enterocolitis in developing countries, where vitamin A status of newborn is low, which predisposes to neonatal sepsis, an important cause of neonatal mortality.

Burden of Disease Attributing to Vitamin A Deficiency

Published study revealed diarrhea-associated death increased by 24% and measles-associated death increased by 20% due to vitamin A deficiency. Similarly as estimated by DALYs burden of VAD contributes significantly on global disease burden. Nutritional intervention with vitamin A supplementation is cost-effective. Randomized control trial have showed nutritional intervention with vitamin A supplementation, along with breastfeeding, complementary feeding and zinc supplementation can prevent 2.4 million child death per year globally which is 25% of total under five death.

SOURCES OF VITAMIN A

Carrots, dark green leafy vegetables, squash, orange and tomato are good source of vitamin A (Fig. 34). The richest source of

Fig. 34: Foods rich in vitamin A

vitamin A include oil extracted from shark and cod liver. Also goat liver contains vitamin A. Many processed foods and infant formula are fortified with preformed vitamin A.

Clinical conditions which predispose children to vitamin A deficiency

- Undernutrition, particularly severe undernutrition
- Fecal loss associated with recurrent and persistent diarrhea
- In measles, VA falls short of increased demand by epithelial tissue
- Zinc deficiency: RBP is zinc metalloenzymes, which carries retinol to retina, required for dark adaptation
- Maternal vitamin A deficiency, which is frequently prevalent among women in developing countries
- Polished rice as staple food with little or no vegetables or fruits.

CLINICAL FEATURES OF VITAMIN A DEFICIENCY

Ocular

Vitamin A deficiency has public health importance as vitamin A plays an important role in vision, growth, reproduction, cellular differentiation, immunity and maintains epithelial integrity. VAD is one of the most common nutritional deficiencies in developing countries. VAD exerts effects through:

- Direct action on retina and
- Indirectly by increasing vulnerability to infections.

Xerophthalmia

Due to direct effect on retina, it is estimated that 5,000,000 preschool children become blind every year owing to vitamin A deficiency. Associated with malnutrition (blinding malnutrition) it increases the case fatality of SAM (severe acute malnutrition). Defective dark adaptation is the most important and frequent clinical presentation of vitamin A deficiency, resulting in night blindness. The syndrome of VAD consists of Bitot's spot, xerophthalmia, keratomalacia, corneal opacity, hyperkeratosis, growth failure and death (Figs 35 to 38). The deficiency disease in human was called Xerophthalmia (dry eye) because of prominence of the eye sign.

WHO classification of Xerophthalmia shown in Table 21.

Other features include infertility, keratinization of epithelial tissue particularly in the skin (toad's skin), urinary calculus and fetal abnormality.

Laboratory test shows level of serum retinol level of 15 μg/dL or (normal 20–80 μg/dL).

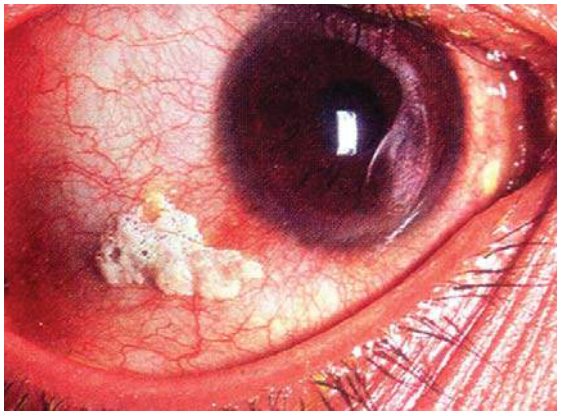


Fig. 35: Bitot's spot

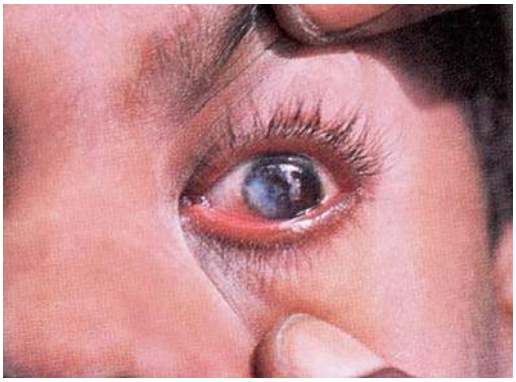


Fig. 36: Corneal ulceration

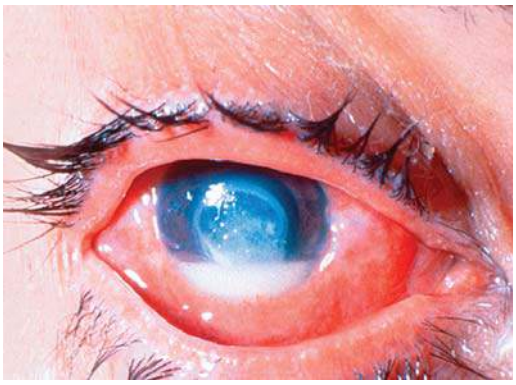


Fig. 37: Infected corneal ulcer with pus in the anterior chamber (hypopyon)

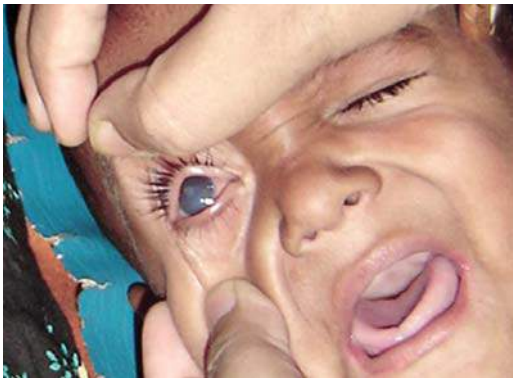


Fig. 38: Corneal clouding

Table 21: WHO classification of xerophthalmia

Primary signs	
X1A	Conjunctival xerosis
X1B	Bitot's spot
X2	Corneal xerosis
X3A	Corneal ulceration (<1/3 of cornea)
X3B	Corneal ulceration (<2/3 of cornea)
Secondary signs	
XN	Night blindness
XF	Fundal change
XS	Corneal clouding

TREATMENT OF VITAMIN A DEFICIENCY

Specific treatment consists of oral administration vitamin A in a dose of 50,000 IU, 100,000 IU and 200,000 IU in children age less than 6 months, 6–12 months, more than 1 year, respectively. The same dose is repeated on next day and 2–4 weeks later.

Parenteral Vitamin A

Parenteral vitamin A (water soluble) can be administered in children with intractable vomiting and malabsorption. The dose is half of oral dose.

In addition, local treatment with antibiotic drop, ointment atropine and padding of eye should be done.

PREVENTION

National Vitamin A Prophylaxis Program

Vitamin A capsule

Vitamin A capsule of 200,000 IU is given to children irrespective of vitamin A status, starting from 6 months (100,000 IU up to 1 year) to 5th birthday (Fig. 39).

It should also be provided in predisposing clinical condition vulnerable to VAD, like severe malnutrition, measles, persistent diarrhea.

Dietary improvement is undoubtedly the most logical and sustainable strategy to prevent VAD. A change in dietary habit and increased access to vitamin A rich foods are required.

Summary

- Responsible for dark adaptation and vision
- Anti-infective property, through its property on maintenance of epithelial tissue, and modulating various component of innate and acquired immunity.
- Carotene, precursor of Vitamin A, is strong anti-oxidant which prevents tissue damage.
- Vitamin A deficiency is associated with increased under five case fatalities from infectious diseases, which include measles, diarrhea and malaria in particular in developing countries. VAD, in association with measles, diarrhea and malaria poses an important global burden in developing countries.

Vitamin A Deficiency Global Perspective

Vitamin A deficiency (VAD) is the single most important cause of childhood blindness in developing countries. It also contributes significantly, even at subclinical levels, to morbidity and mortality from common childhood infections. An estimated 2.8 million preschool-age children are at risk of blindness from VAD, and the health and survival of 251 million others are seriously compromised.

Fig. 39: High potency vitamin A capsule (red 200,000 IU and blue 100,000 IU) are given on Vitamin A Campaign Day

Heightened awareness of the role of vitamin A in human health has led to an international effort to eliminate vitamin A deficiency and its consequences as a public health problem by the year 2000. This is among the important end-of-decade micronutrient goals endorsed by the World Summit for Children (1990), the International Conference on Nutrition (1992), and the World Health Assembly (1993).

Globally, night blindness affects 5.2 million preschool-age children and 9.8 million pregnant women, which corresponds to 0.9% and 7.8% of the population at risk of VAD, respectively.

WHO regional estimates indicate that the highest proportion of preschool-age children affected by night blindness, 2.0%, is in Africa, a value that is four times higher than estimated in South-East Asia (0.5%). This also means that Africa has the greatest number of preschool-age children affected with night blindness (2.55 million), and corresponds to almost half of the children affected globally. A comparable and high proportion of pregnant women affected by night blindness are in Africa (9.8%) and South-East Asia (9.9%), each of which is estimated to have over 3 million pregnant women affected, or one-third of the pregnant women affected globally. The estimates show that the Africa and South-Eeast Asia regions also contain the highest proportions of preschool-age children with biochemical VAD, as indicated by a serum retinol concentration <0.70 μmol/L, with South-East Asia having the greatest number of children and pregnant women affected (Table 22).

Table 22: Population of countries at risk of vitamin A deficiency 1995–2005 globally and by WHO region

WHO region	Preschool-age children[a]		Pregnant women	
	Prevalence[b] (%)	# affected (millions)	Prevalence (%)	# affected (millions)
Africa	2.0	2.55	9.8	3.02
	(0.8–3.2)[c]	(0.99–4.11)	(8.4–11.1)	(2.59–3.44)
Americas	0.6	0.36	4.4	0.50
	(0.0–1.3)	(0.00–0.75)	(2.7–6.2)	(0.30–0.70)
South-East Asia	0.5	1.01	9.9	3.84
	(0.0–2.0)	(0.00–3.75)	(9.5–10.3)	(3.69–4.00)
Europe	0.8	0.24	3.5	0.22
	(0.1–1.5)	(0.04–0.44)	(1.8–5.3)	(0.11–0.33)
Eastern Mediterranean	1.2	0.77	7.2	1.09
	(0.6–1.7)	(0.41–1.12)	(5.2–9.2)	(0.78–1.39)
Western Pacific	0.2	0.26	4.8	1.09
	(0.0–0.4)	(0.02–0.50)	(0.9–8.6)	(0.20–1.97)
Global	**0.9**	**5.17**	**7.8**	**9.75**
	(0.3–1.5)	**(1.97–8.38)**	**(7.0–8.7)**	**(8.70–10.8)**

[a] P opulation subgroups: Preschool-age children (<5 years); Pregnant women (no age range defined).
[b] N umerator and denominator excludes countries with a 2005 GDP ≥US $ 15,000.
[c] 95% Confidence Intervals.
Source: WHO global database on vitamin A deficiency, WHO

GUIDELINES FOR VITAMIN A SUPPLEMENTATION

Children Less than 1 year of age

Colostrums (the secretions from the breast during the first few days after birth) contain high concentration of vitamin A and therefore, all mothers should be encouraged to initiate breastfeeding immediately after birth. Thereafter, exclusive breastfeeding should be continued until the infant reaches seven months of age. Beginning at seven months of age, the child should gradually be given complementary food, including vitamin A rich foods, along with breast milk and other complementary foods. As soon as the child completes his or her first nine months of life, 100,000 IU of vitamin A should be given along with measles vaccination. Vitamin A is significantly reduced in some clinical conditions like night blindness, measles, severe acute malnutrition persistent diarrhea etc. High dose of vitamin A supplementation therefore should be given in such conditions in appropriate dose as mentioned in Table 23.

General Population

Dietary intake of vitamin A is inadequate in the general population of developing countries. The amount of fruits and vegetables currently available in developing countries is estimated to meet only low percent of the population's daily requirement of vitamin A. There is, therefore, a need to expand the production and consumption of green leafy vegetables and yellow/orange colored fruits and vegetables through homestead gardening. By establishing a homestead garden, a poor family can easily grow enough vegetables to meet their own needs and also have a surplus which can be sold in the market to generate additional family income. Examples of vitamin A rich food are given in Table 24.

Table 24: Example of vitamin A rich food in developing countries

Very high amount of Vitamin A	Moderately high amount of Vitamin A
• Goat liver • Yellow squash (*Misti kumra*) • Red amaranth (*Lal shak*) • Mango • Mola fish • Spinach (*Palong shak*)	• Human breast milk • Ripe papaya • Chicken eggs

KEY MESSAGES

- Newborn babies should be given vitamin A-rich colostrums immediately after birth. Exclusive breastfeeding up to 6 months (180 days) and breast feeding should be continued during the first 2 years of life (when the child will have completed 24 months of life) along with complimentary foods.
- After completion of 6 months, vitamin A rich foods such as green leafy vegetables, yellow/orange fruits and vegetables like papaya, fish, eggs, milk, liver and meat should be given along with breastfeeding and other complementary food.
- All children should receive vitamin A supplementation (100,000 IU), when they complete 9 months of age. This should be administered at the time of measles vaccination.
- All children between from 6 months and 11 months should receive vitamin A capsule of 100,000 IU every 6 month and children between 12 month and 59 months should receive a vitamin A capsule of 200,000 IU every 6 months to prevent the serious effects of VAD.
- Children with symptoms of VAD and children suffering from measles, persistent diarrhea or severe malnutrition should receive vitamin A supplementation according to the recommended schedule.
- During pregnancy and lactation, mother should regularly eat green leafy vegetables, fish, eggs, meat and liver.
- Post-partum mothers should receive one 200,000 IU vitamin A supplementation soon after child birth or within 42 days of delivery.
- Green leafy vegetables and yellow/orange fruits and vegetables should also be introduced. All family members' particularly pregnant or lactating women and young children should consume vitamin A rich food regularly.

IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA

Iron deficiency anemia is the most common nutritional deficiency, affecting both developed and developing countries, particularly among preschool children. IDA occurs when there is decrease in total body iron content severe enough to diminish erythropoiesis and cause IDA.

Iron deficiency can occur without anemia even without microcytic hypochromic morphology of RBC. This is because ID has to go through various stages to affect Hb synthesis and to develop anemia. However, ID, without IDA may cause neurological features with listlessness and irritability, mood changes in infants and later cognitive and psychomotor problems. It is therefore important to understand the pathophysiology of various stages of ID.

Table 23: Recommended dose and schedule for vitamin A capsule supplementation for treatment of children with specific medical condition

Medical Condition	Dosage according to age			Dose schedule
	<6 m	6–11 m	12 m or older	
Nightblindness Bitot's spot Xerophthalmia	50,000 IU per dose	100,000 IU per dose	200,000 IU per dose	3 dose (on D1, D2 and D14)
Measles	50,000 IU	100,000 IU	200,000 IU per dose	2 doses (D1 and D2)
Persistent diarrhea Severe anemia Severe Malnutrition*	50,000 IU	100,000 IU per dose	200,000 IU per dose	One dose after each episode

* Discussed in management of SAM

Diminished dietary iron absorption in the proximal small intestine or excessive loss of body iron can result in ID. Iron is essential for multiple metabolic processes, including oxygen transport, DNA synthesis and electron transport. In severe IDA, the iron containing enzymes are low and this can affect immune and tissue function. IDA can result in diminished growth and learning and have serious consequences in children. Numerous dietary constituents make nonheme iron unabsorbable, e.g. phytate, phosphates and tannates.

Healthy newborn infants have a total body iron of 250 mg (approximately 80 parts per million, ppm); decreases to approximately 60 ppm in the first 6 months of life. Body iron is regulated carefully by absorptive cells in the proximal small intestine, which alter iron absorption to match body losses of iron. Breast milk iron content is more bioavailable than cow's milk. Besides this fact, infants who consume cow's milk have more ID because bovine milk has a higher concentration of calcium, which competes with iron for absorption and they may cause GI blood loss due to cow's milk allergy. Multiple intercurrent infections such as hookworm infestation and malaria compounds the problem.

STAGES OF IRON DEFICIENCY

Iron-store Depletion

This is identified using the serum ferritin level and marrow iron stain. A ferritin level less than 20 µg/L and visible iron stores of only 0 to 1+ suggest usable iron stores of less than 100–300 mg. As long as some stores are still available, the SI, TIBC and red cell protoporphyrin levels are within normal limits. Moreover, the patient is not anemic, and red blood cell morphology is normal.

Iron store measurement from marrow iron stain and serum ferritin is given in Table 25.

Table 25: Iron store measurement

Iron stores	Marrow iron stain 0– 4+	Serum ferritin (µg/L)
0	0	<15
1–300 mg	Trace to 1+	15–30
300–800 mg	2+	30–60
800–1000 mg	3+	60–150
1–2 g	4+	>150
Iron overload	---	>150–1000

Iron Deficient Erythropoiesis

Decrease of marrow iron store, serum ferritin and increase in serum TIBC is sensitive to early ID. Iron deficient erythropoiesis is recognized from decrease in SI, percent saturation of transferrin and increase in RBC protoporphyrin. Finally patients in addition develop microcytic hypochromic morphology of RBC and anemia characterized by decreased in Hb. In fact, it is not uncommon to find normal Hb and normal RBC morphology in clinical practice with decreased serum iron (SI), increased TIBC, decreased Ferritin, when ID has not yet reached to the stage of anemia associated with decrease Hb. This clinical condition should be called ID without anemia. However, it has clinical implication too. Usually mild to moderate ID do not produce anemia. Severe ID which may take months to develop, present with anemia.

Similarly while correcting anemia with iron supplement; initially there is brisk rise of reticulocyte count which reach maximum after a 10th day. Hb rises 1 g/week and Hb may become normal within few weeks. But iron supplements should be continued for at least 3 months after correction of blood Hb deficit in order to replenish iron store of reticuloendothelial system.

Iron Deficiency Anemia

At lower Hb levels, both microcytosis and hypochromia become more pronounced. Furthermore, red blood cell production becomes increasingly ineffective, resulting in greater degrees of aniso and poikilocytosis. With very severe IDA, cigar or pencil-shaped red blood cells may be observed. As a rule, *target cells are not seen with ID and when present, they suggest a globin chain production defect, one of thalassemias*. However, this does not exclude the possibilities of ID either alone or in combination with globin production defect.

The several stages of ID including iron store depletion, iron deficient erythropoiesis and IDA are shown in Table 26.

DIETARY SOURCES OF IRON (FIG. 40)

- High iron:
  - Red meat: Beef and lamb
  - Liver, kidney of goat, lamb, etc.
  - Oily fish
- Average iron:
  - Pulses, beans, dark green vegetables, green banana, taro vegetable (Kochu Shak and Kochu Loti), spinach, broccoli, egg yolk
- Food to avoid in excess in toddlers for increased iron bioavailability

Table 26: Laboratory evaluation of iron deficiency

	Normal	Iron-store depletion	Iron deficient erythropoiesis	Iron deficiency anemia
Marrow iron stores	1–3+	0 – 1+	0	0
Serum ferritin (µg/L)	50–200	<20	<15	<15
TIBC (µg/dL)	300–360	>360	>380	>400
SI	50–150	NL	<50	<30
Saturation (%)	30–50	NL	<30	<10
Marrow sideroblast (%)	40–60	NL	<10	<10
RBC protoporphyrin (µg/L)	30–50	NL	>100	>200
RBC morphology	NL	NL	NL	Microcytic/ hypochromic

Abbreviations: TIBC, total iron binding capacity; NL, Nil; SI: serum iron (µmol/L); RBC, red blood cells

Fig. 40: Some dietary sources of iron

  - Cow's milk, tea (tannin inhibits iron uptake)
  - High fiber diet: Phytate inhibits iron absorption
- Food which increases iron absorption

Citrus fruits (vitamin C): Orange, lemon, pineapples, concomitant vitamin A supplementation.

CAUSES OF IRON DEFICIENCY ANEMIA

- Dietary: It is the commonest cause. Exclusive breastfeeding (Breast milk low in iron) more than 6 months without introducing iron-rich weaning complementary food from 6 months
- Infancy and early childhood:
  - Gastrointestinal blood loss from cow's milk enteropathy, blood loss from gastroesophageal reflux disease (GERD), esophagitis, Meckle's diverticulum, worm infestation (hook worm)
- Demand due to rapid growth: Following prematurity or puberty
- Malabsorption of iron
  - Worm infestation
    - Giardiasis
    - Hook worm
  - Celiac disease
  - Tropical sprue
  - Inflammatory bowel disease (IBD) together with fecal blood loss
- Bleeding secondary to drugs
  - Non-steroidal anti-inflammatory diseases
  - Steroids.

PREDISPOSING FACTORS

Children at Risk of Iron Deficiency

- Preterm LBW
  - Anemia of prematurity
- Exclusive breastfeeding more than 6 months without addition of complementary food
- Delayed introduction of iron-containing solid
- Low iron-containing diet
  - Poverty, ignorance, fad diet, strict vegans
- Adolescent female
  - Growth spurts and menstruation.

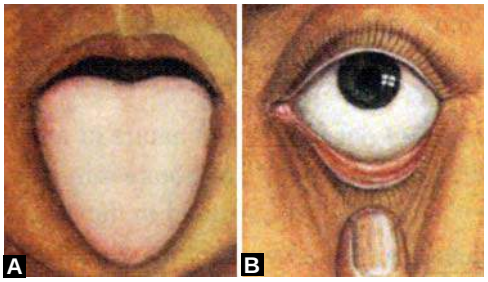
Inadequate intake of iron is common in infants because additional iron is required for the increase in the blood volume during catch up growth of preterm babies around 4–6 weeks of life to build up child's own iron store and in all infant above 6 months of age as breast milk and unmodified cow's milk cannot meet this requirement.

Presentation

- Majority are subclinical and symptoms only develops when ID is severe
- Insidious onset of symptoms of anemia: Pallor (Figs 41 A and B), fatigue, weakness, anorexia, angular stomatitis, glossitis, koilonychia and congestive cardiac failure (CCF) in severe ID
- Pica, i.e. eating unusual items like soil, distemper, wire etc. (Fig. 42)
- Many children particularly in developing countries are presented with coexistent undernutrition and/or failure to thrive (FTT)
- Neurological effects of listlessness and irritability, mood changes, reduced cognitive and psychomotor performances can occur at mild/moderate ID before anemia develops
- Severe IDA may present with
  - Breath holding attack
  - Syncopal attack in children
  - Ischemic stroke (IS).

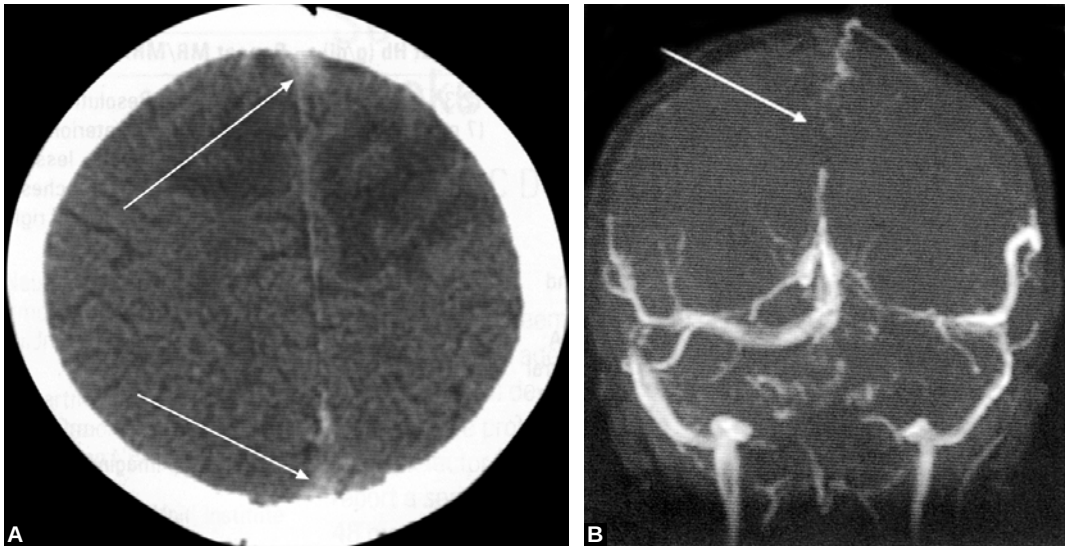
Severe Iron Deficiency Anemia Associated with Ischemic Stroke in Children

Association of IDA and IS in children is a new and serious entity in otherwise normal healthy child with no other risk factors for ischemic brain stroke who may develop ischemic stroke syndrome due to severe IDA. These children with pallor may present with headache, vomiting, irritability, syncopal attack, hemiparesis, seizure and papilledema. Stroke syndrome associated with IDA consists of arterial ischemic stroke (AIS) and cerebral venous sinus thrombosis (CVST). AIS is commonly associated with occlusive intracranial arteriopathy. CVST in contrast, is usually associated with infection and dehydration.



Figs 41A and B: (A) Pale tongue; (B) Pale conjunctiva in iron deficiency anemia

Fig. 42: A child with pallor light lusterless hair and pica, biting the wire due to iron deficiency anemia



Figs 43A and B: CT scan and MRA of a 35-month old child with severe iron deficit anemia presented with seizure and right side hemiparesis. CT scan showing hyperdense thrombus within the superior sagittal sinus (arrow in the image). MRA venography showing lack of flow in the superior sagital sinus (arrow) due to cerebral venous sinus thrombosis (CVST)

Source: Munot P, De Vile C, Hemingway C, et al. Severe iron deficiency anaemia and ischaemic stroke in children. Arch Dis Child. 2011;96:276-9.

Magnetic resonance angiogram (MRA), particularly time-of-flight MRA which is related MR technique provides better diagnosis of AIS and CVST (Fig. 43).

The potential underlying mechanism of stroke syndrome and syncopal attack associated IDA include hypercoagulable state directly related to ID and/or anemia and thrombocytosis and reduced red cell deformability due to microcytosis, both of which result in increased viscosity. Reactive thrombocytosis associated with IDA contribute to hypercoagulable state increasing the risk of thrombosis in venous sinuses. Anemia itself may worsen hypoxia in areas of cerebral perfusion which may also cause syncopal attack.

IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA

Anemia is one of the major public health problem in young children particularly in developing countries where malnutrition and infection are prevalent. Although causes of anemia are multifactorial and interlinked, most anemia in developing countries is thought to be nutrition related. The majority of these children are anemic due to coexisting micronutrient deficiencies. In one of the survey report, the prevalence of anemia is as high as 78% among infant age 6–11 months, and is 64% among young children aged 12–23 months.

Iron deficiency anemia is considered to be the main type of anemia among children. The main etiologies of IDA in these children are hypothesized to be due to poor dietary iron intake, especially during the period of rapid growth. A national 1995-96 reported the diet of children aged 13 years had marked deficits in energy, protein, iron and other nutrients. Usually in developing countries, mothers start supplementary feeding around 3 months of age, with rice based food that lack both iron and protein which contributes to iron deficiency during early infancy and childhood. LBW is another important contributor to IDA as these babies are usually born with low iron stores.

Although ID is considered to be the major cause of anemia in children, there are very few studies to provide strong scientific evidences for underlying causes of anemia, most studies are based on finding Hb level less than 11g/dL but not looking for serum ferritin level. The other critical micronutrients required for red blood cell synthesis like folic acid, copper, vitamin A, vitamin B_{12} needs to be explored to correct anemia. There are evidences to suggest that vitamin A supplementation increases the efficacy of iron supplementation. Abnormal Hb like thalassemia syndrome and Hb E frequently identified in South Asia also contributes to anemia in Bangladesh.

It is well-documented that anemia in younger age affects optimum brain development. To protect the next generation of Bangladesh it is important that IDA be identified and aggressively treated with available low cost short-term supplement. At the same time necessary intervention need to be initiated for poverty alleviation and to improve caregivers knowledge regarding child rearing practices. Further researches to identify other causes of anemia and cost-effective intervention to prevent them, are some important public health priorities.

Diagnosis of Iron Deficiency and Iron Deficiency Anemia

Anemia is clinical condition when Hb concentration in blood is two standard deviation below the mean for the particular age and sex. *According to WHO in children, Hb less than 11 g/dL is considered anemic and serum ferritin level less than 12 μg/L is considered to be ID*. Underlying cause of anemia should be tried to detect and should be treated accordingly. The following investigations should be done:

- Complete blood count (CBC): Hb decreased, MCV decreased (76 fL), MCHC decreased, platelet increases often

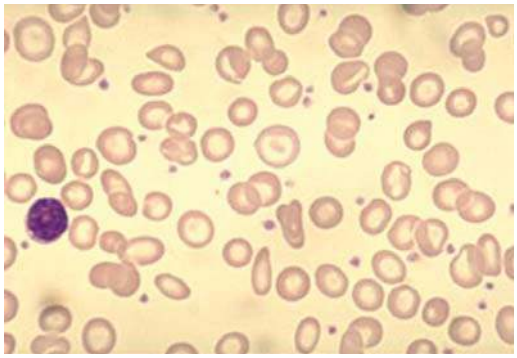


Fig. 44: Blood film microcytic hypochromia with few target cells

- Blood film: Microcytic hypochrommic RBC (Fig. 44) without target cell (late sign of ID)
- Serum ferritin may be low before anemia occurs but treatment with iron supplement helps to improve CNS effects at this point. It may be falsely high in ID due to intercurrent infection. Check CRP, which will be high in infection associated with ID
- Decreased serum iron and increased TIBC (see Table. 27) confirms ID
- Percent saturation decreased
- Increased protoporphyrin.

There are many clinical conditions where RBC morphology is microcytic hypochromic. Serum iron profiles including serum ferritin may be decreased in conditions other than iron deficiency and serum ferritin may be even increased in iron deficiency, if it is associated with recurrent infections. Table 27 will help to diagnose and differentiate iron deficiency from other conditions causing iron deficiency type peripheral blood picture. Characteristics RBC morphology and serum iron profiles in anaemia due to iron deficiency, inflammatory conditions and renal diseases is provided in Table 28.

Other Non-Hematological Investigations

- Magnetic resonance angiogram (MRA) in AIS associated with severe IDA.

All anemic children are not iron deficient, although ID is considered to be a major cause of anemia in young children in developing countries like Bangladesh. On the other hand, ID frequently not associated with anemia (Hb <11 g/dL) as ID has to go through several stages to decrease Hb below 11 g/dL to produce anemia. Therefore, normal serum Hb level does not rule out ID but ID itself can cause health problems like cognitive disorder and learning difficulty without causing anemia.

Few clinical conditions like beta thalassemia, chronic infection and inflammation may have similar RBC morphology and biochemical parameters. In practice beta thalassemia traits which is prevalent in Indian subcontinent present with hypochromia and anemia of varying severity. It is not also uncommon to find β- thalassemia trait and ID both together. Morphologic clue that point to diagnosis of thalassemia includes presence of target cell. A normal cell distribution with indicating uniform microcytosis and microcytic hypochromia occurring out of proportion of severity of anemia is usually found in thalassemia syndrome.

Microcytic hypochromic anemia may occur in chronic inflammations like juvenile idiopathic arthritis which is associated with decreased SI, decreased TIBC but increased serum ferritin (see Table 27).

Red blood cell morphology, SI profiles in IDA, thalassemia trait and inflammation (e.g. Juvenile idiopathic arthritis) are shown in Tables 27 and 28.

Treatment

The cause of anemia should be identified and corrected. Hookworm infestation is a common cause of occult gastro-intestinal blood loss in rural population in developing countries.

Table 27: Diagnosis of microcytic anemia

Tests	Iron Deficiency	Thalassemia (trait)	Inflammation
Smear	Micro/hypo	Micro/hypo with target cells	Variable micro/hypo/normocytic
SI	Low	Normal to high	Normal to high
TIBC	High	Normal	Normal
Percent saturation	<10	30–80	30–80
Ferritin (µg/L)	<15	50–300	50–300
Hb Pattern	Normal	Abnormal	Normal

Abbreviations: SI, serum iron; TIBC, total iron-binding capacity; Hb, hemoglobin

Table 28: Diagnosis of hypoproliferative anemia

	Iron Deficiency	Inflammation	Renal Diseases
Anemia	Mild to severe	Mild	Mild to severe
MCV (fL)	70–90	80–90	90
Morphology	Normo-microcytic	Normocytic	Normocytic
Serum iron	↓ <30	↓ <50	Normal
TIBC	↑ 360	↓ <300	Normal
Serum Ferritin (µg/L)	<15	30–200	115–150
Iron stores	0	2–4+	1–4+

Abbreviations: MCV, mean corpuscular volume

Dietary counseling and treatment of any other causative factors are required to prevent recurrence or failure of therapy. Close follow-up is required to assess for adequate response and correction of anemia, this will help to identify iron therapy failure.

Oral Iron Therapy

Oral iron preparations should be taken on an empty stomach or in between meals for best absorption. About 10–20% patients will develop gastrointestinal side effects such as nausea, epigastric, discomfort, vomiting, and constipation and diarrhea. Enteric-coated preparations have fewer side effects, but are also less efficacious and more expensive. The most effective and economical oral preparation is ferrous sulfate (20% elemental iron). In children, the dose for treatment of anemia is 3–6 mg/kg/day iron. The reticulocyte count increases within 72–96 hours after initiating therapy. After correction of anemia, oral iron should be continued for 4–6 months to replenish iron store.

Home Fortification

Iron fortified "sprinkles" to homemade weaning food have been found effective strategy in reducing ID in developing countries. Sachets containing micro capsulated ferrous fumerate and ascorbic acid in powder form are sprinkled on to homemade complementary food. This strategy has the added benefit over medicinal iron improving in mean corpuscular volume (MCV) with less gastrointestinal side effects.

Parenteral Iron Therapy

Parenteral iron therapy is rarely required. The indications of parenteral iron therapy are limited to conditions such as:

1. Intolerance to oral iron.
2. Malabsorption states.
3. Ongoing blood loss at a rate where the oral replacement cannot match iron loss.

If parenteral iron is indicated, then IV preparations are preferred over IM; iron sucrose IV preparations are safe and effective. They have been used in children with end stage renal disease on dialysis and inflammatory bowel disease. Iron sucrose is administered at a dose of 1–3 mg/kg diluted in 150 mL normal saline as a slow IV infusion over 30–90 minutes.

Dose for parenteral iron: The total dose parenteral iron in milligrams is calculated as follows:

Iron required = Wt (kg) × 2.3 × (15- patient hemoglobin in g/dL) + (500–1000) mg

The total calculated dose is given as divided doses.

Blood Transfusion

As ID is readily corrected with medication, blood transfusion should be avoided in young, stable patients. Red cell transfusions are needed in emergency situations such as in patients where the rate of blood loss exceeds the expected rise of hemoglobin, for urgent surgery, hemorrhage or severe anemia with CCF. In very severe anemia with CCF, transfusions must be given slowly (2–3 mL/kg) with monitoring and diuretic therapy, if necessary.

Thalassemia Trait with Associated Iron Deficiency

There is a popular belief and advice that beta thalassemia trait children should never be prescribed iron supplement and iron-containing diet. However, patient with beta thalassemia trait often associated with concomitant ID should be treated with iron supplement until their iron status become normal.

Iron supplements, even iron rich foods are quite often not offered to iron-deficient thalassemia trait children, which is popularly believed to cause harm in thalassemia trait children. However, it should be offered to thalassemia trait children with coexistent ID to prevent potentially treatable ID related health hazards.

Practice

1. A one year old child presented with mild pallor, irritability and FTT with following blood count and biochemical parameter?
   - WBC 4,000/cumm (Neutrophil 24%, Lympho 72%, Mono 3%, Eosino 1%), Hb 11.5 g/dL
   - Serum ferritin 10 µg/L
   - Blood film: Normocytic normochromic RBCs.

   What is the diagnosis?
   - Iron deficiency anemia: wrong answer
   - Iron deficiency: correct answer.

   Explanation: The child has ID as evidenced by low serum ferritin. However, his Hb still not below critical level (11g/dL) to term him as anemic. The child is, however, failed to thrive and irritable which are clinical features of ID. Therefore, children with ID should be corrected to prevent cognitive disorder.
2. A 2-year old young child blood investigations report showing following features. WBC 5500/cumm, Hb 8.2 g/dL. Blood film microcytic hypochromic RBC.
   - Serum ferritin 8 g/L
   - Hb electrophoresis showed Hb A 92.6%, Hb A2 6.4%, Hb F 1%
   - What is the diagnosis?
   - How will you treat the child?
   - Correct answer: Combined thalassemia trait and IDA.

Management: To provide iron supplement to correct ID, to provide genetic counseling for thalassemia trait.

Explanation of answers: The child is anemic as Hb is less than 11 g/dL, he is iron-deficient as serum ferritin is less than 12 µg/L and having thalassemia trait as there is raised HbA2. Both ID and thalassemia contribute to anemia.
Iron supplement should be given to correct ID.

ZINC

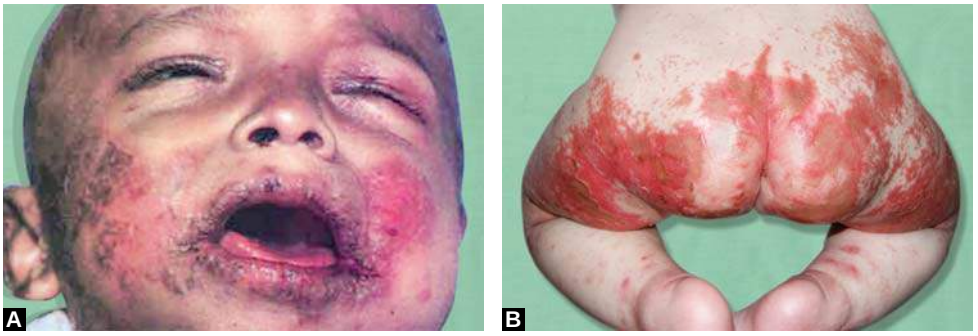
INTRODUCTION

Zinc was used topically by ancient Egyptians in the form of calamine for promotion of wound healing and is mentioned in the Ebers papyrus in 1550 B.C. Over 3,500 years, it is still considered that zinc therapy may promote healing of infectious and non-infectious skin lesion.

Chronic zinc deficiency has been associated with:

- Dwarfism, hypogonadism, dermatitis and alopecia
- Decreased wound-healing, taste and smell
- A disease called acrodermatitis enteropathica (AE) or Danbolt's disease.

Clinical zinc deficiency is prevalent among children in developing countries including Bangladesh. Malnourished children are more vulnerable to zinc deficiency and their



Figs 45A and B: A case of acrodermatitis enteropathica affecting,skin and moist mucocutaneous areas of face (A) and buttock (B)

marginal body zinc further depleted during diarrhea through fecal zinc losses. As high as 159 μmg/kg/day of zinc is lost in diarrhea as against normal fecal loss of 59 μg/kg/ day.

Acrodermatitis enteropathica is a rare inborn error of zinc absorption and represents only tip of iceberg of huge zinc deficiency among the children in the developing world. AE is rare autosomal recessive disorder of zinc absorption associated with decreased level of zinc, diarrhea, bullous-pustular dermatitis of extremities and alopecia.

The classic features of zinc deficiency as seen in AE are:

- Symmetrical, circumorificial, retroauricular and acral dermatitis which may involve also the cheeks, trunk and limbs (Figs 45A and B).
- Failure to thrive
- Anorexia
- Irritability and
- Frequent loose stools.

This florid syndrome is regarded as an acute or severe zinc deficiency, and it easily raises suspicion of zinc deficiency when it is seen. Fortunately treatment with orally administered zinc is effective.

However, it is much more probable that zinc deficiency would be encountered when it presents with subtle subacute form not associated with AE as popularly diagnosed but associated as comorbidity with other clinical conditions such as malnutrition, diarrhea, growth retardation, pneumonia, etc.

ROLE OF ZINC IN CHILD HEALTH

Zinc is a very essential micronutrient and has important role in child health and development. Zinc which is present in more than 100 metalloenzymes has been among the essential micronutrients necessary for growth and prevention of infections. Zinc is essential for protein synthesis, including immunoglobulin and mediators of cell-mediated immunity. Zinc deficient children are vulnerable to infectious disease including diarrhea and pneumonia, even in anthropometrically well-nourished children. Several studies have documented the effect of zinc supplement on growth. Zinc has also the property of improving taste acuity.

Since there is no single assay of zinc that can confidently and comprehensively assess zinc status of human body and there is no single reference range of normal serum zinc level, it is now widely recognized that the best way to demonstrate zinc deficiency is to observe clinical response with zinc supplement in specific conditions suspected of zinc deficiency with appropriate control. Weight gain associated with zinc supplement in comparison to control is useful in this regard.

Zinc has physiological role in normal taste sensation and improves taste acuity. Moreover many cases of zinc deficient and idiopathic hypogeusia have been corrected by zinc supplementation in adult.

Published studies revealed milder form of zinc deficiency is associated with slight growth retardation, poor appetite and impaired taste acuity.

Dietary Intake and Absorption

The intake of zinc by children and adults is about 5 mg/day and 10 mg/day, respectively. Meats are good source of zinc (20–40 mg/g of wet weight in dark meat but less in paler meat such as poultry). Zinc contents are also high in lentils and grains but their bioavailability is decreased due to presence of increased phytate. Iron, phosphate and calcium carbonate also impair zinc absorption. Zinc is absorbed throughout the small intestine and possibly by the colon. The highest absorption is at the jejunum.

Enterocytic uptake of zinc probably involves both specific and non-specific binding mediated processes. Absence of specific *enterocytic mechanism of Zinc uptake* and/or transfer probably underlies the inherited zinc deficiency disease AE**.** Within intestinal enterocyte cysteine-rich intestinal protein (CRIP) that have specific binding sites for zinc may be involved in the mucosal transfer of zinc.

Systemic Distribution and Peripheral Uptake by Tissues

In serum, zinc (at a concentration of 100 ± 20 μg/100 mL of serum or 2×10^{-5} M) is almost all in bound form; approximately 50–60% binds with albumin, 30–40% to an α-2 macroglobulin and the reminder to various amino acids and metalloenzymes.

The uptake of zinc by peripheral cell such as hepatocytes shows carrier-mediated as well as passive diffusional mechanism. Hepatic extraction of recently absorbed zinc is highly efficient and impaired in liver disease. Liver plays an important role in controlling the metabolism of zinc and one important entity in this process is metallothionein.

About 60% of body zinc is distributed in muscle followed by 20–30% in bones. However, the highest concentration of zinc is in the retina of eye and prostate.

Zinc Homeostasis

Strong zinc homeostasis maintains plasma/serum zinc near normal level at adequate and marginary dietary intakes. Homeostasis of zinc metabolism is effected primarily in the intestine and liver. When the body is at risk of zinc deprivation,

the intestinal absorption of exogenous zinc increase. There is reduction in intestinal losses of endogenous zinc arising from intestinal conservation with an upregulation of carrier sites and from a reduction of pancreatobiliary secretion of zinc and increased renal conservation of the element. In early zinc deficiency, the release of zinc from tissue breakdown can maintain the plasma/serum zinc levels within the reference range although the patient has clinical zinc deficiency. For example catabolism only 10 g of muscle with assumed zinc content around 40 µmg (0.6 µmol/g wet weight) would release sufficient zinc to contribute 2 µmol zinc per liter plasma volume.

Intestinal metallothionein mRNA and metallothionein proteins are induced by parenteral zinc. With inappropriate high zinc intakes and increasing body burden, the systemic load is regulated by increased intestinal secretion of endogenous zinc and by reduced mucosal uptake. At high intake of zinc the mucosal transfer of the metal is related inversely to metallothionein.

Due to this strong zinc homeostasis, one cannot confidently and comprehensively assess zinc status of human body from serum zinc level only and therefore should correlate with clinical condition as well.

Properties of Zinc Relevant to Human Health

Zinc is an essential trace element and adequate zinc intake is critical for health:

- It has structural and regulatory role in more than 100 metalloenzymes
- Takes part in gene transcription system that are essential for human metabolism, growth and reproduction
- It is essential for cell-mediated immune system and its deficiency cause reduction of number of T lymphocytes (CD4) and B lymphocytes
- It is an antioxidant and free radicals scavenger.

INFECTION AND ZINC

Zinc and T and B Lymphocytes

Zinc stimulates T lymphocytes both quantitatively and qualitatively. It is necessary for DNA replication by phytohemagglutinin (PHA) stimulated lymphocytes. Lymphocytes are one of the cells activated by zinc. Zinc deficiency is associated with poor immune function particularly in cellular immunity and zinc supplementation of malnourished children improves immune function. Lymphoid atrophy, delayed decreased cutaneous hypersensitivity responses, reduction in number of T_4 helper cells and deficient thymic hormone activity have been described in association with zinc deficiency. However, zinc supplementation in ongoing sepsis in already compromised immune system may not be beneficial.

Serum level of zinc decreases sharply in many infections. Levels slightly below normal seem to be associated with optimal phagocytic function, and low concentrations of zinc may decrease microbial virulence. Brief decreases in serum levels appears to have no detrimental effect on host immunity and may act as a protective measure by decreasing the ability of indigenous or infecting microbes to thrive.

The proposed mechanisms by which zinc stabilizes cell membranes are:

- Zinc may inhibit peroxidation of membrane lipids by forming mercaptides with thiol groups of membrane proteins
- Zinc may bind to and inactivate membrane-regulating enzymes attached to plasma membrane
- Zinc could displace calcium or inhibit calcium uptake by cells requiring calcium for proper functioning of microtubules or microfilaments
- Changes in membrane fluidity associated with zinc binding could also alter membrane function.

High dose of zinc may increase microbiological virulence by:

- Inhibiting PHA induces stimulation of lymphocytes
- Inhibiting phagocytosis by macrophage
- Inhibiting plasma cell stimulation
- By decreasing serum copper which takes part in immunity.

There are two vicious cycles associated negatively with malnutrition.

1. Malnutrition–diarrhea–malnutrition
2. Malnutrition–infectious diseases (which include diarrhea, ALRI/Pneumonia)–malnutrition.

Both diarrhea and acute lower respiratory tract infections (ALRI) (pneumonia) are negatively associated with impaired CMI in another vicious cycle and zinc deficiency is associated with impaired CMI increasing the vulnerability of children to diarrhea and pneumonia. The inter-relationship is given in Figure 46.

Mechanisms and conditions which predispose to dietary and systemic deprivation of zinc:

- Inadequate intake and absorbability:
  - Malnourished states
  - Vegetarianism
  - Delayed absorption in gut
  - Increased phytate in diet (chapatti, rice)
  - Concomitant iron and calcium intake
  - Acrodermatitis enteropathica
- Increased loss
  - Recurrent diarrhea
  - Hepatic disease (biliary obstruction)
- Metabolic complication (TPN)
- Maldigestion and malabsorption
- Increased utilization
  - Rapid tissue synthesis
    - During recovery (rehabilitation phase of severe malnutrition).

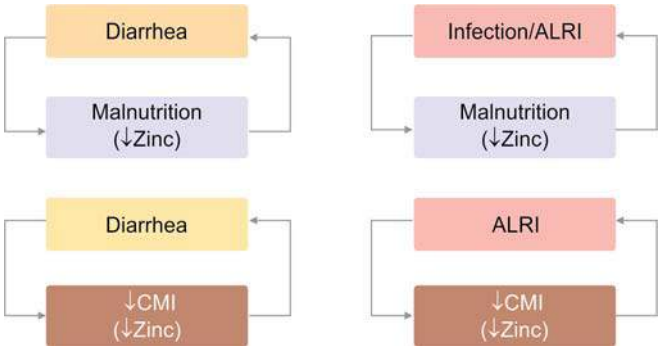


Fig. 46: Inter-relationship of Zinc deficiency, ↓ CMI, Malnutrition, Diarrhea and ALRI

Abbreviations: CMI, cell-mediated immunity; ALRI, acute lower respiratory tract infections

Sources of Zinc

- Meats are good source of zinc (20–40 mg/g wet weight in red meat (Fig. 47) but less in paler meat such as poultry)
- Zinc contents are also high in lentils and grains but their bioavailability is decreased due to presence of increased phytate. The bioavailability of zinc in lentils grains can be increased by soaking, fermenting and sprouting (Fig. 48) of these products
- Although concentration of zinc is less in human breast milk than cow's milk, but bioavailability of zinc is much more in human milk.

Features of Zinc Deficiency

Clinical features are nonspecific and protean and majority of clinical zinc deficiency do not resemble clinical features characteristics of AE. However, most important clinical features relevant to child health and child survival are its association with malnutrition, growth failure and vulnerability to infectious diseases particularly diarrhea and pneumonia. As RBP is a zinc metalloenzyme and retina has higher concentration of zinc, zinc efficiency like VAD cause night blindness. In addition, other clinical features are mentioned in the Table 29.

Table 29: Clinical features of zinc deficiency

Infants
• Anorexia • Failure to thrive, weight loss • Tremor, jitteriness, hoarseness • Dermatitis (periorificial and extensors), vesiculobullous, pustular, hyperkeratotic • Stomatitis, glossitis • Nail dystrophy, paronychia, beaus lines • Fine brittle hair, tapered tips, alopecia • Loose frequent stools, malabsoption (disaccharide intolerance) • Increased susceptibility to infection, impaired immune function
Additionally in older children
• Pica, impaired taste and smell • Height retardation • Depression, mood labiality, impaired cerebration • Neuropsychiatric symptoms, ataxia, dysarthria • Photophobia, night blindness, blepharitis

ZINC AND DIARRHEA

The reduction of child mortality is one of the Millennium Development Goal. The goal is to reduce under five mortality in developing countries by two-thirds between 1990 and 2015.

Over the past decades, significant progress has been made in the understanding of the impact of zinc deficiency on child health and the potential of zinc treatment in reducing childhood morbidity and mortality from infectious diseases.

Fig. 47: Zinc-containing red meat

Fig. 48: Sprouting legume

Zinc is a micronutrient found in foods rich in protein such as red meat, poultry, nuts and dairy products. Zinc stimulates the activity of approximately 100 enzymes in the human body. Its major potential in treating infectious diseases as adjunct therapy is its rapid impact on the immune system, which strengthens the ability of the human body to cope with infections.

Many people living in the developing countries, do not have access to sufficient amounts of zinc-rich foods. This results in zinc deficiency that can lead to growth failure and increased susceptibility to illness and death, especially among young children.

Studies have demonstrated effectiveness of zinc in reducing incidence of diarrhea and pneumonia, the most common cause of death among children in developing countries.

Zinc has already been categorized as a level 1 treatment of diarrhea (level 1 = sufficient evidence of effect) and also a measure to prevent diarrhea and pneumonia.

Changes in gastrointestinal tract during diarrhea:

- Removal of brush border of villi (Figs 49 and 50)
- Subtotal villous atrophy
- Damage of intestinal mucosa with increased access of fluid through intercellular space into the intestinal lumen, increasing stool volume. Damage of intestinal mucosa causing malabsorption of various macro-and micronutrients until damage is repaired
- Rapidity of repairment of damaged intestinal epithelium depends on underlying local intestinal and overall nutritional status and immunity of the host.

Effects of Zinc on GI Tract Pathology with Diarrhea

- Significant reduction in stool volume mediated through its effect on mucosal permeability
- Antioxidant property protects intestinal mucosa from free radical-induced damage during inflammation (gastro-enteritis)
- Rapid repair of damaged intestinal mucosa, maintaining epithelial and tissue integrity through promoting cell growth and suppressing apoptosis.

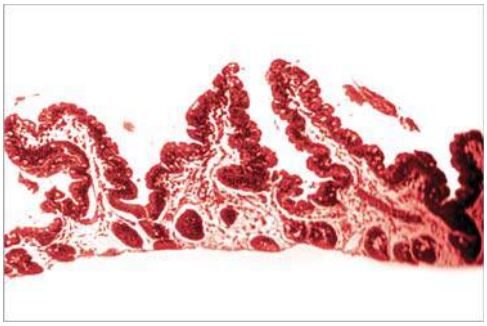


Fig. 49: Normal intestinal mucosa with villi and brush border

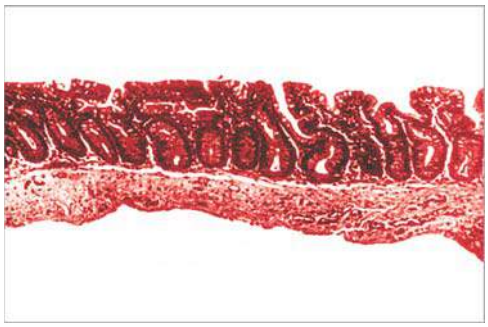


Fig. 50: Removal of brush border of villi in acute diarrhea

Clinical Effect of Zinc in Treatment of Acute Diarrhea

- Short-term effects
  - It reduces stool volume
  - It shortens duration of diarrhea
  - It reduces the severity of diarrhea
  - Prevents growth faltering
  - Increases appetite
- Long-term effects
  - Reduces the incidence and duration of next attack of diarrhea
  - Reduces hospital admission for diarrhea
  - Reduces number and duration of lower respiratory tract infection (LRTI) episodes
  - Reduces hospital admission for LRTI
  - Net gain in length (height).

Is zinc required for treatment in each episode of diarrhea in undernourished children as well as anthropometrically well-nourished children?

- Fecal loss of zinc occurs during every episode of diarrhea at 159 μg/kg/day against 59 μg/kg/day in normal children can make well-nourished children zinc deficient and undernourished children profoundly zinc depleted
- All malnourished children are not zinc deficient; similarly all well-nourished children are not biochemically zinc sufficient
- Anthropometrically, well-nourished children suffering from ALRI was found to be zinc deficient than zinc sufficient well-nourished control
- Even biochemically, zinc sufficient well-nourished or malnourished children can be benefited by zinc supplement during diarrhea due to immunostimulant effect of zinc.

Zinc in Persistent Diarrhea

About 9% of acute diarrhea becomes persistent and significant portion of children who suffer from diarrhea are malnourished.

Persistent diarrhea associated with malnutrition, in particular, carry high risk of mortality and morbidity. During persistent diarrhea, children become zinc depleted due to prolong loss of zinc in diarrheal stool. Published studies suggest zinc supplementation through its effect on intestinal permeability and immune effect can:

- Reduce duration of diarrhea
- Early recovery
- Reduce stool volume
- Prevents fall in body weight
- The above mentioned effects are more significantly found in malnourished children suffering persistent diarrhea.

Role of Zinc in Fetus and Newborn

- Zinc deficiency can cause embryopathy
- Zinc supplementation during pregnancy improve neonatal immune status, early neonatal morbidity and infant infection
- Published study suggests zinc supplementations of babies with LBW can reduce mortality during infancy by a third.

Zinc in Wound Healing and Other Conditions

- Zinc supplement improves and expedites wound healing
- Zinc oxide works as emollient in nappy rash
- Zinc oxide is useful in acne vulgaris and protects skin from sunray's hazardous effects
- Zinc is frequently used in itchy dermatitis
- Zinc deficiency can cause night blindness
- Zinc supplementation can reduce falciparum malaria by a third.

Zinc deficiency: What is the Most Appropriate Intervention?

- WHO recommends zinc only as curative intervention as a part of treatment of severe malnutrition and in the treatment of diarrhea
- Zinc intake is inadequate in developing countries. Correcting this situation will have dramatic impact on mortality and morbidity and modest effect on growth
- However, taking zinc deficiency in isolation is inappropriate
- Zinc intervention by food fortification and supplementation along with existing other health intervention programs will be less disruptive and more integrative
- Use of zinc to treat diarrhea is the more appropriate entry point for zinc supplementation efforts.

Problems Caused by too much Zinc

Although there is no consensus about the toxic dose of oral zinc, in therapeutic dose, it is quite safe in children. However, it is quite often associated with vomiting due to metallic taste. Therefore, in gastroenteritis with vomiting zinc should not be offered initially, rather it should be given when the child has stopped vomiting.

Tolerability of zinc intake in maintenance and therapeutic dose is satisfactory and it is quite safe in children in therapeutic dose.

- Although zinc has a very high therapeutic index, high dose can give rise to following adverse conditions
- Impairment copper absorption
- Immune-suppression
- Increased microbial virulence
- High dose in prolonged duration can cause high mortality when given in severely malnourished children associated with sepsis in particular.

Zinc in Global Perspective

A continuing lack of safe water and adequate sanitation in many parts of the world means that diarrhea remains the leading cause of death among infants and young children in low- and middle-income countries. Every year more than a million children under five years of age succumb to the fluid loss and dehydration associated with the majority of diarrhea-related deaths. It is estimated that 13% of all years lost due to ill-health, disability or early death are caused by diarrhea.

There are two simple and effective treatments for the clinical management of acute diarrhea:

- Use of low concentration oral rehydration salts (ORS)
- Routine use of zinc supplementation, at a dosage of 20 mg/day for children older than 6 months or 10 mg/day in those younger than 6 months, for 10–14 days.

Zinc supplementation has been found to reduce the duration and severity of diarrheal episodes and likelihood of subsequent infections for 2–3 months.

Zinc deficiency is associated with an increased risk of gastrointestinal infections, adverse effects on the structure and function of the gastrointestinal tract, and impaired immune function. Dietary deficiency of zinc is especially common in low-income countries because of a low dietary intake of zinc-rich foods.

VITAMIN D AND RICKETS

In the national and international public health and developmental communities, rickets has been something of a forgotten disease and it tends to be thought of an historic term. However, it has emerged as a public health problem in many developing countries and has also re-emerged in a number of developed countries where it was thought that the disease has been almost eradicated.

THE SIGNIFICANCE OF RICKETS

Unlike other nutritional diseases, rickets can be cured but deformities may not be healed completely. The disease cast a long shadow, affecting communities specially those of the poor, in several ways:

- Reducing the physical capacities and impairing the emotional development of individuals
- Increasing the morbidity and mortality risks of children
- Draining the economic prospects of households
- Reducing the development potentials of communities.

Vitamin D deficiency negatively affects growth and recognized cause of FTT complicating malnutrition. Children affected by rickets are smaller both in weight and height than normal children.

Rickets is a clinical expression of extreme vitamin D deficiency and represents only the tip of iceberg of huge vitamin D deficiency in children and women particularly in the developing world. However, asymptomatic vitamin D deficiency may affect bone health of other-wise apparently healthy looking children and adolescent girl in developing countries in particular and they may not reach pick bone mass as mature adult and at risk of osteoporotic fractures at later life.

DEFINITION: RICKETS, OSTEOMALACIA, OSTEOPOROSIS AND OSTEOPENIA

Rickets is a disorder of growing skeleton due to *inadequate mineralization* of bone as it lays down at the epiphyseal growth plate. There is a characteristic widening of the ends of long bones with characteristics radiological findings.

Osteomalacia occurs when there is inadequate mineralization of mature bones. Both rickets and osteomalacia may be present at the same time.

Osteoporosis is defined by WHO as systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture. In adults it is measured by dual energy X-ray absorptiometry (DXA). Osteoporosis is being increasingly recognized in pediatric practice as a consequence of several factors. These include the complexity of chronic condition and the associated treatment managed by pediatrician. Hereditary skeletal dysplasia like osteogenesis imperfecta are associated with osteoporosis and bony fracture.

The term osteopenia relates to a reduction in the amount of bone tissue and often also used to describe in the reduction in bone density as seen on X-ray or scan in absence of fracture. There are many childhood conditions in which osteopenia has been demonstrated. Osteopenia of prematurity or previously called rickets of prematurity where bone tissue is decreased due to decease accretion of phosphate and calcium of preterm babies during last trimester of pregnancy. Characteristic radiological feature of rickets are usually absent in osteopenia of prematurity.

VITAMIN D DEFICIENCY

Nutritional Rickets

Vitamin D deficiency is the major cause of rickets around the world. Sunlight is the major source of vitamin D, while diet provides less than 10% of body requirement. Vitamin D deficiencies occur in the following conditions:

- Decreased availability of effective sunlight
- Decreased exposure to sunlight
- Decreased amount of skin exposed to sunlight
- Dark skinned people (Decreased bioavailability of sunlight)
- Air pollution blocking ultraviolet (UV) light
- Loss of UV (Protection including sunscreen)
- Living in northern hemisphere
- Intestinal causes
  - Defective production of $25(OH)D_3$
    - liver diseases
  - Increased metabolism of $25(OH)D_3$
    - enzyme induction by anticonvulsants (e.g. phenytoin)
  - Malabsorption.

Treatment: See treatment section.

Vitamin D Dependent Rickets (VDDR) Type I

It is due to the deficiency of the enzyme 25(OH) vitamin D-1-alpha hydroxylase ($VD_3$1A hydroxylase) deficiency. Reduced blood level of calcium normal or low phosphate and elevated alkaline phosphatase are characteristic. Blood level of 25(OH)D_3 are normal but those of 1,25$(OH)_2D_3$ are markedly decreased despite hypocalcemia. Clinical features of VDDR type I are similar to common to vitamin D deficiency but clinical features occur in early infancy mostly in 2nd trimester of life. FTT is an important clinical feature, fits and convulsion may occur due to hypocalcemia. Poor activity and lying supine position mostly occur due to severe muscle and bone pain.

Vitamin D Dependent Rickets Type II

There is end organ resistance to 1,25$(OH)_2D_3$. It is a genetic disorder (Autosomal recessive). This is believed to arise for most part from mutation causing defect in 1,25(OH)D_3 receptor function in 1,25(OH)D_3 target tissues. This leads to virtual abolition of actions of 1,25(OH)D_3, despite its markedly raised levels in circulation. Clinical features of rickets occur at early age. In addition they have high prevalence of sparse hair, alopecia and other ectodermal defects like epidermal cyst, oligodentia etc (Fig. 51). Other characteristics features are seizure and developmental delay particularly motor developmental delay. Alopecia persists in older age, although skeletal problem may improve with age and vitamin D supplement.

Characteristic biochemical features are hypocalcaemia, secondary hyperparathyroidism elevated serum alkaline phosphatase and elevated circulating level of 1,25(OH)D_3. Decrease response to vitamin D analogues is usually observed.

Treatment

High dose of 1,25$(OH)_2D_3$ with 60 µg/kg/day is often successful, although responses are variable.

Vitamin D Deficiency Rickets due to Chronic Kidney Disease

Refractory rickets may occasionally be present with of chronic kidney disease (GFR <30–35 mL/min/1.72 m^2). Rickets occur due to defective production of 1,25$(OH)_2$ D_3 in the kidney. The clinical features of osteodystrophy depend on patients' chronic renal parenchymal pathology and duration of the disease. Biochemical features are characterized by decreased calcium, increased serum phosphate, in addition to increased BUN and increased serum creatinine. Therapy consists of restricting phosphate intake and providing supplement of calcium and active vitamin D analogue.

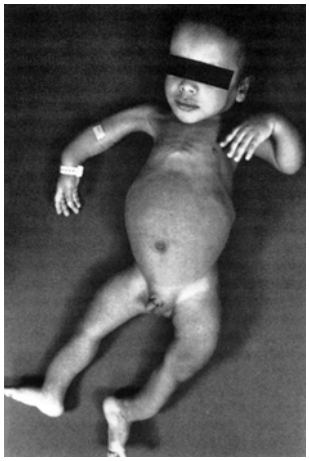
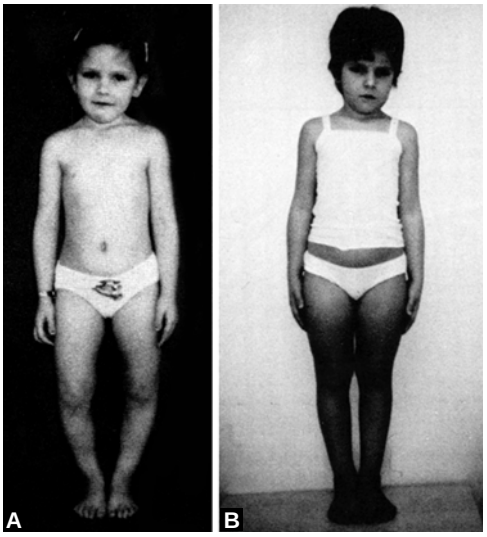


Fig. 51: Vitamin D dependent rickets showing features of chest skeletal deformity with alopecia



Figs 52A and B: (A) A 5-year-old child with familial (X-linked dominant) hypophosphatemic rickets affecting lower limbs in particular; (B) Same child after 7 years treated with phosphate and calcitriol showing improvement of deformity and height

Phosphate Deficiency Rickets

- Increased phosphate loss (renal tubular phosphate loss)
  - Familial (X-linked dominant) hypophosphatemic rickets (Fig. 52)
  - Renal tubular acidosis
  - Fanconi's syndrome (autosomal recessive)
- Decreased store of phosphate
  - Extremely preterm infant with dietary deficiency of phosphorus together with ↓ store of calcium and phosphorus.

Calcium Deficiency (Nutritional) Rickets

- Diet deficient in calcium in unsupervised dairy-free diet
- Decreased bioavailability of calcium (↑ phytate in diet—like chapatti)
- Maternal risk factors
  - Pregnant and lactating mother having low body calcium status.

Vitamin D Metabolism

In most circumstances, sunlight is the most important source of vitamin D. Vitamin D_3 is hydroxylated in liver and again in the kidney to produce 1,25(OH) D_3, the most active form of vitamin D. It is produced following parathormone secretion in response to low plasma calcium (Fig. 53).

Factors influencing endogenous synthesis of vitamin D

- Duration of sunlight exposure
- Amount of skin exposed
- Skin pigmentation
- Latitude

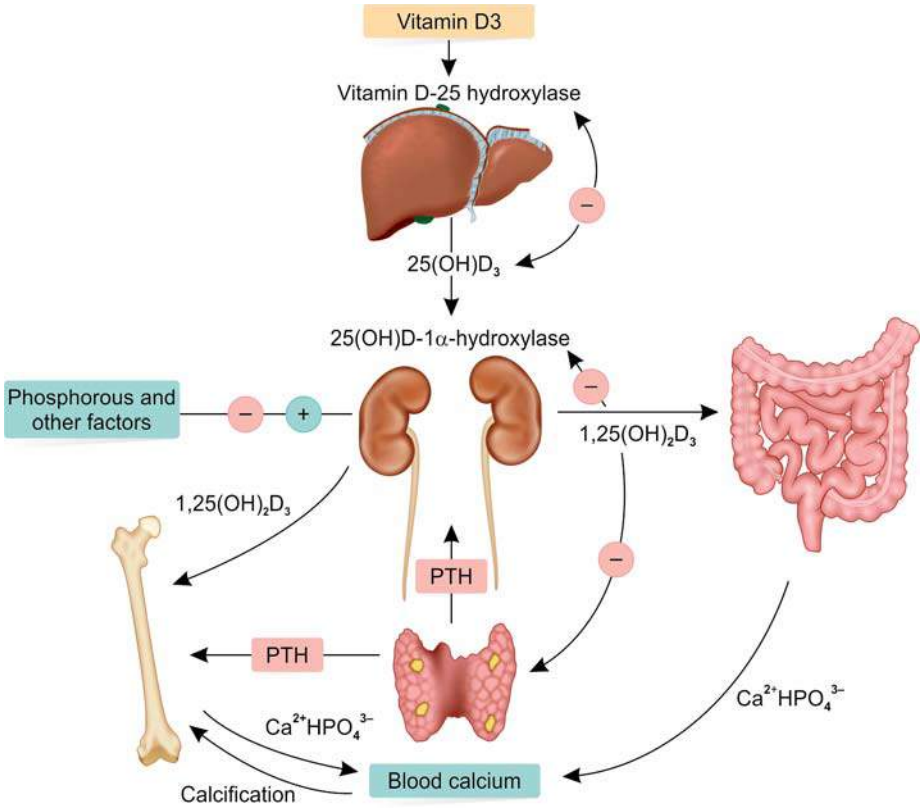


Fig. 53: Vitamin D metabolism

- Season
- Pollution blocking UV light
- UV protector includes sunscreen and glasses.

Physiological reserve of vitamin D in infant depends on

- Maternal reserve of vitamin D during fetal life
- Vitamin D concentration in maternal milk
- Endogenous synthesis from sun exposure.

There are three characteristic stages of disease progression:

1. **Stage 1:** Low plasma calcium/normal plasma phosphate
2. **Stage 2:** Normal plasma calcium due to compensatory hyperparathyroidism
3. **Stage 3:** Low plasma calcium and phosphate-advanced bone disease

Stage 1 and 2 are biochemically evident only. Stage 3 has clinical features.

VITAMIN D DEFICIENCY (NUTRITIONAL RICKETS)

Why children living in abundant sunlight (Asia, Middle East, and Africa) are vulnerable to Vitamin D deficiency?

- Dark pigmented skin synthesizes ten times less vitamin D from sunlight than white skin
- Adolescent girls particularly dark skinned girls of many Asian and African countries have inadequate sunlight exposure due to covering clothes for religious and cultural reasons
- Such women carry low vitamin D status throughout their fertility life, pregnancy and lactation period
- Infants of such women receive less vitamin D from their mother during fetal life and from their mother's milk after birth (Fig. 54)
- Such infants and their mother are seldom taken under sun due to social reasons during few months after child birth
- Many urban children are residing where sunlight exposure is less and seldom get opportunity to play outdoor games (Fig. 55).

EFFECTS OF VITAMIN D DEFICIENCY ON CHILD HEALTH

As mentioned earlier, rickets is a clinical expression of extreme vitamin D deficiency and represents only the tip of iceberg of huge vitamin D deficiency in children and woman particularly of developing world (Fig. 59). In early infancy, vitamin D deficiency usually manifests as nonskeletal clinical features of child health problems. Vitamin D deficiency in early infancy exerts its negative impact on child health through hypocalcemia as clinically manifested by tetany, convulsion, stridor, etc. It also affects growth and development particularly causing delayed motor development, poor dentition, short stature, etc. Clinical features due to early and late effects of vitamin D deficiency are mentioned in Table 30.

Clinical features of rickets occur in untreated extreme vitamin D deficiency and may show one or more of the clinical features shown in Table 31.

Diagnosis

Diagnosis is from history, typical clinical features and characteristic biochemical and radiological features.

History

- Sociocultural: Particularly of clothing practice of adolescent and adult women
- History relevant to exposure to sunlight.

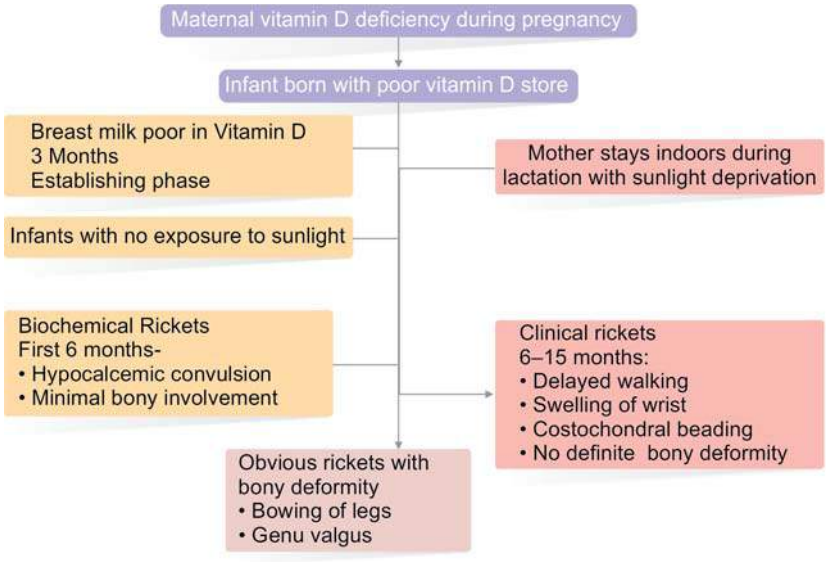


Fig. 54: Sequels of maternal vitamin D deficiency

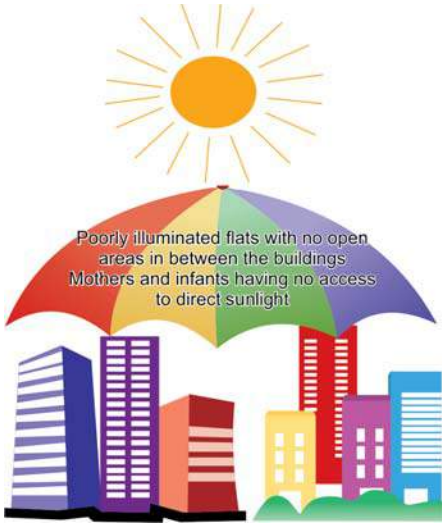


Fig. 55: Urbanization umbrella: A man made factor of rickets

Table 30: Effects of vitamin D deficiency on child health

A. Early effects of vitamin D deficiency
• Tetany, convulsions, stridor, carpopedal spasm (mediated through hypocalcemia) • Hypotonia • Delayed motor development • Poor dentition • Delayed eruption of teeth • Short stature with FTT
B. Late effects of vitamin D deficiency
• Physical disability due to deformity • Short stature • Chest deformity with restrictive lung disease • Affect pelvic shape in women with CPD resulting in obstructed labor

Abbreviations: FTT, failure to thrive; CPD, cephalopelvic disproportion

Laboratory

- Serum calcium is low or normal
- Phosphate low
- Serum alkaline phosphate is increased

Table 31: Clinical features of rickets

- Skeletal deformity (Figs 56 and 57)
  - Swelling of wrist
  - Swelling of costochondral junction (Rickety Rosary)
  - Chest deformity (pectus excavatum, pectus carinatum)
  - Bowing of the long bone
  - Genu varus and genu vulgus
  - Frontal cranial bossing
  - Craniotabes
- Recurrent chest infection with increased occurrence of pneumonia
- Associated with malnutrition, complicates malnutrition

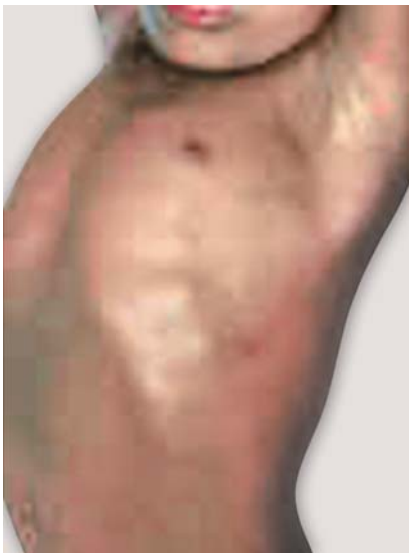


Fig. 56: Rickety rosary

- Serum 25(OH)D_3 is decreased in nutritional rickets
- X-ray of the wrist joints: Show cupping and fraying of the metaphyses and widening of epiphyseal plate (Fig. 58).

Laboratory diagnosis of various types of rickets shown in Table 32.

As discussed earlier rickets represent only tip of iceberg of huge subclinical vitamin D deficiency in developed as well as in developing countries.

Biochemical Vitamin D Deficiency and Rickets

Rickets occur when 1, $25(OH)_2D_3$ below less than 25 nmol/L. However, asymptomatic vitamin D deficiency may affect human health as follows:

Non-ricketic/Non-osteomalacic Clinical Manifestations of Vitamin D Deficiency Particularly in Women

- May affect shape with CPD and obstructed labor
- Adult acquisition of bone mass decreased with increased tendency to osteoporotic fracture

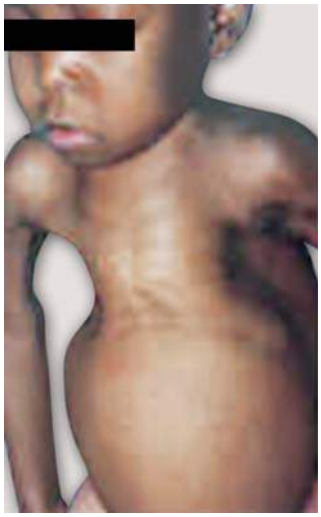
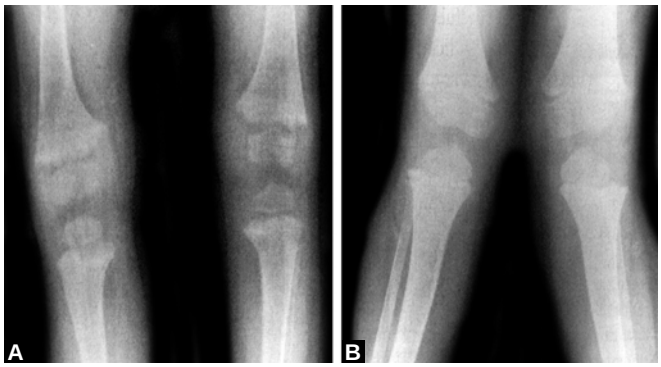


Fig. 57: Chest deformity



Figs 58A and B: (A) X-ray knee joint showing radiograph of the knee with active rickets; (B) Radiograph of knee with healed rickets

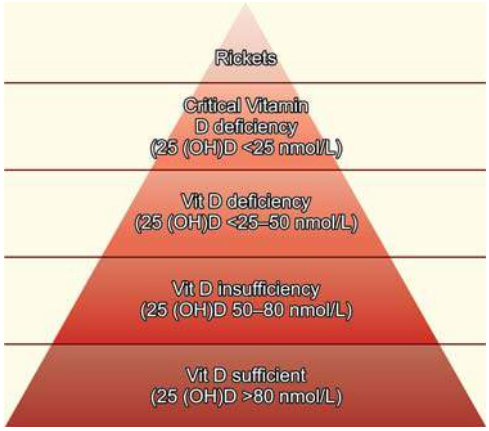


Fig. 59: Various levels of vitamin D deficiency and development of rickets showing rickets in only small proportion of huge asymptomatic vitamin D deficiency

- Negative impact in future vitamin D status on infants that they subsequently bear
- Decreased knee heel length of fetus affected with low gestational 25(OH)D.
- Reduced whole body and lumbar bone mineral contents of child at 9 years associated low gestational 25(OH)D.

Other diseases (nonskeletal) associated with vitamin D deficiency:

- Type I diabetes mellitus
- Iron deficiency anemia
- Cardiomyopathy
- Myopathy with hypotonia
- Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis
- Coronary heart disease in adults
- Cancer (breast, ovary and colon) in adults.

Prevention and Treatment

Prevention

- Education regarding availability of vitamin D
- Vitamin D supplement to exclusive breastfed child particularly of dark skinned mother and child with inadequate exposure to sunlight (breast milk contain negligible vitamin D).
- Outdoor exposure of sunlight of children, adolescent and adult women under privacy if required
- Vitamin D supplement to vulnerable groups with calcium supplementation.

Table 32: Laboratory diagnosis of various types of rickets

Types	Plasma Ca^{++}	Plasma PO_4^{3-}	ALP	25 $(OH)D_3$	1,25 $(OH)_2D_3$	PTH
Vitamin D deficiency (nutritional)	↓	↓	↑	↓	↓	↑
Type I VDDR	↓	↓	↑	← →	↓	↑
Type II VDDR	↓	↓	↑	← →	↑	↑
X-linked hypophosphatemic	↓ or ← →	↓	↑	← →	← →	← → or ↑
Renal rickets	↓	↑	↑	← →	↓	↑

Abbreviations: ALP, alkaline phosphate; PTH, parathyroid hormone; VDDR, Vitamin D dependent Rickets.

Treatment

- Vitamin D_3 (cholecalciferol) in the range of 2000–5000 IU (50–125 µg) daily for at least 4–6 weeks
- If compliance is an issue single high dose of 600,000 IU or over 10 days. (60,000 IU daily for 10 days), followed by maintenance dose of 400 IU daily and oral calcium supplement (50–75 mg/kg/day) should be given.

Healing occur in 2–4 weeks and can be monitored from lowering of alkaline phosphatase, increasing serum Vitamin D level and healing on X-ray, but complete reversal of bony deformity may take years. Swelling of wrist responds most quickly and sensitive indicator of bony response to Vitamin D supplement followed by decrease of swelling of beading of ribs. Deformity in lower limbs may take years to correct by supplement and may require surgical intervention.

Calcium Deficiency and Rickets

Although vitamin D deficiency is probably the final common pathway in the development of rickets, there is evidence that low dietary calcium and high phytate intake play a major role in the pathogenesis of rickets.

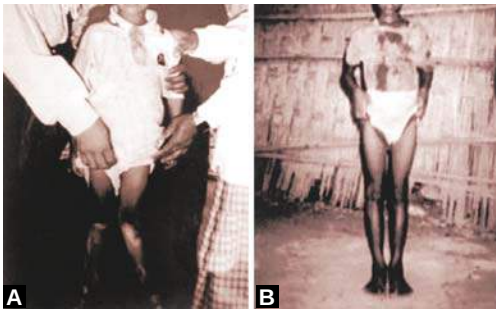
- Causes of calcium deficiency
  - Diet deficient in calcium (non-dairy diet)
  - Decreased bioavailability of calcium (diet rich in phytate)
  - Maternal risk factors
    - Low calcium status throughout the fertility period particularly during pregnancy and lactation.

Calciopenic Rickets and Rickets

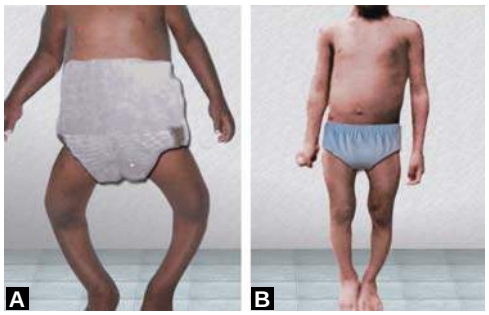
Rickets first identified in South Eastern region of Bangladesh (Chokoria and Cox's Bazar) appeared to be calcium deficiency type as has been described in South Africa and Nigeria. Calcium deficiency is likely to be widespread in impoverish areas of Bangladesh specially affecting children directly as well as via effect of the caregiver who are also calcium deficient along with micro and macronutrient deficiencies. Nevertheless rickets endemic areas are not among the most severely malnourished. Other factors including concomitant vitamin D deficiency are also involved, as evidenced by published study showing mean 25(OH)D of such children were 20 ng/L, lower than cut off point of Vitamin D of 25 ngm/L to develop rickets.

Rickets has emerged as a public health problem during the past two decades. About 5.50 lacs (> half million) children aged 1–15 years suffer from rickets which is preventable. Insufficiency of dietary calcium is thought to be the underlying cause. Calcium deficiency rickets typically present after first year of life, affecting lower limb bones (genu varus and genu vulgus), widening of wrist and beaded ribs (Figs 60 and 61). They carry high risk of developing trauma.

Rickets is increasingly recognized as a failure of health education and health care delivery in many countries. It is not a complex disease, the cause can be clearly identified in great majority of cases. There are major problem in delivering of vitamin D and calcium to many of at risk population but the challenge is one which must be met.



Figs 60A and B: (A) Calcium deficient rickets with bony deformity (genu valgum); (B) Improvement after treatment with calcium and vitamin D supplement



Figs 61A and B: (A) Calcium deficient rickets with bony deformity (genu varus); (B) Improvement after treatment with calcium and vitamin D supplement

Treatment

Treatment with calcium supplementation (380–1000 mg elemental calcium daily) is curative. Severe deformity (>20° angulation) may require surgery and postsurgery bracing along with calcium supplementation (Table 33).

Prevention

- Calcium containing diet and dairy products (cheese, yogurt) crushed fish bones, green leafy vegetables.
- Dietary diversification
- Adding lime stone to rice approximately three finger of lime stone is to be added in 1kg of rice
- Nutritional education.

FAILURE TO THRIVE

DEFINITIONS

Although the concepts of FTT are widely used, no consensus yet exists, regarding specific definition. There is also no agreement on which growth parameters to use and whether to use attained anthropometric values or velocities. Weight is most sensitive indicator in infant and growing children, while height in older children. Thus it seems that static definitions of low attained weight continue to be used despite longstanding recognition of their limitations. Dynamic definition that assess weight velocities and change over time is, however, a preferable definition to attained value. Weight regression to mean over a time is also an acceptable way to define FTT.

Failure to thrive is a state of pediatric undernutrition, quite often defined by low or poor weight gain.

Table 33: Graded treatment proposal for children with calcium-deficiency rickets

Age / Leg Deformity	<6 years	7– 11 years	>11 years
<15°	Nutrition	Calcium tablets	Surgery + Calcium tablets (Pre- and postsurgery) + Bracing (postsurgery)
15 – 30°	Calcium tablets	Calcium tablets ↓ Improvement after 6 months ↓ Yes → Continue → Complete healing ↓ No → Bracing	
>30°		Surgery + Calcium tablets (Pre- and postsurgery) + Bracing (postsurgery)	

Source: Fischer PR, Rahman A, Cimma JP, et al. Nutritional rickets without vitamin D deficiency in Bangladesh. J Trop Pediatr. 1999;45:291-5.

In the context of infants and children, to thrive is generally accepted to be solely an anthropometric term referring to normal weight gain and growth. Adding the word failure implies that an abnormality has to be rectified through some intervention process. There are underlying causes of FTT specific and nonspecific. There is no difficulty in accepting that an infant with celiac disease who is failing to gain weight or child with hypothyroidism whose growth is static are both not 'thriving' in the general sense. In some case, there is effective treatment to rectify the problem. These two examples have a defined diagnosis for which there is clear scientific evidence to explain the pathophysiology. However, not infrequently, the underlying cause of FTT cannot be obtained or the underlying pathophysiology is complex. Consequently management of such disorders are difficult.

Failure to thrive is an indicator of physical or psychosocial problem in early childhood. Failure to find an organic cause for FTT has led to the assumption that neglect must be responsible. FTT is a relative undernutrition state, thus approaching the concept of PEM, a term used to describe primary nutritional deprivation among the children of developing countries, while FTT mainly comprising children in more than 95% of cases are due to not enough food offered or taken.

UNDERLYING CAUSES OF FTT

Specific organic causes of FTT

- Decreased appetite: Psychosocial or secondary to chronic illness
- Infections like UTI, both symptomatic UTI and asymptomatic bacteriuria (controversial)
- Inability to ingest, e.g. structural GI or neurological problems
- Excessive food loss, e.g. GERD, pyloric stenosis
- Malabsorption syndrome (celiac disease, cystic fibrosis)
- Increased energy requirement, e.g. congenital heart diseases.

Non-organic cause:

- Psychosocial deprivation
- Child neglect
- Negative feeding behavior (food refusal)
- Eating disorder.

In infancy, birth weight is a poor guide to correct "genetic potential" and the child may be failure to find his own "level". It is well-practiced prediction that the birth weight of an average healthy infant doubles and trebles by 5 months and 12 months of age, respectively. It is not surprising that parents are concerned if such "normality" is not attained, especially if no explanation can be given for this apparent "FTT". In a well happy child, consider constitutional small stature characterized by normal growth velocity of small stature parents.

Criteria involving behavioral characteristics of the child, mother-child relationship and unsupervised feeding, deprivation are implicated in FTT. Feeding difficulties and disorders like infant sucking problems, temporary infant illness should also be considered. Most importantly behavior of child with asceticism, negatism, competitiveness or a battle of wills particularly with parents and forced feeding by insisting parents may trigger feeding denial and FTT.

MANAGEMENT

- Dietary history including age of onset of FTT and timing of weaning, psychosocial and socioeconomic and sociodemographic history should be carefully taken. Personality of parents, child behavior and quality of mother-child relationship should be observed
- Consider asking dietician to perform detailed dietary history.

Full examination including accurate measurement of growth.

If organic disease is suspected.

Basic investigations:

- CBC, erythrocyte sedimentation rate (ESR), peripheral blood film (PBF), CRP
- Urine RE/ME and C/S
- Stool R/E, M/E and for occult blood
- Serum calcium, phosphate and ALP

Advanced Investigations if indicated

- Liver function test
- Endoscopy of upper GI tract, biopsy
- Esophageal pH manometry
- Sweat test for cystic fibrosis (CF)
- Celiac antibodies for Caucasian children in particular
- Abdominal ultrasound.

If non-organic diseases likely, dietary advice preferably by pediatric dietician. Explore psychosocial problems, family

dynamics, child behavior, parent-child relationship, child neglect, deprivation or possible abuse.

Positive re-enforcement to parents in psychosocial problems.

If FTT still persists:

Admit to hospital for

- Baseline investigations
- Observe response to supervised adequate dietary input
- Adequate growth confirms non-organic cause. Dietetic input, whatever cause, to support nutritional correction/education.
- Explore and support family dynamics
- Identify and correct associated morbidities, e.g. developmental delay.

If FTT occurs at home again:

- Refer to social services.

PROGNOSIS

Majority of non-severe FTT will resolve with no active intervention. Adverse consequences associated with severe FTT, whatever the cause, may be associated with later developmental and behavioral impairment.

Implications for Child Health Practice Relevant to FTT

- Weight monitoring is firmly established among mother and will not be discontinued in child health surveillances. However, it should not be regarded as a reliable screening test for FTT, as weight faltering can occur in normal healthy child, like parent of small stature.
- Given the lack of consensus on the definition of FTT and the most appropriate anthropometric methods to identify it, child health practitioners in both primary and secondary care should avoid diagnostic conclusions based solely on anthropometry.
- Even with weight monitoring using simple anthropometric method based on attained weight, it has proved difficult to ensure in routine practice. More complex methods based on weight velocity or conditional weight gain is likely to present greater quality assurance problems in routine settings.
- In the absence of additional clinical signs of abuse, organic diseases, and severe under nutrition, child health practitioner should be encouraged to adopt a 'wait-and-see' approach for infant who are failing to thrive and avoid inappropriate investigations and referral.
- Infant feeding and thriving are highly emotive aspect of parenting and the child health practitioner should avoid, at all costs, generating unnecessary anxiety and guilt regarding infant weight gain. The search for FTT, as with other conditions, is not neutral and has the potential to do more harm than good.

Despite its established place in pediatrics and child health care, FTT is not a diagnosis and has no universally accepted definition. This does not mean that it should be ignored or abandoned entirely as a clinical concept, but its place in clinical practice needs to be fully informed by recognition of its limitations. Failure to think about FTT will inevitably lead to inappropriate clinical and preventive practice.

SUMMARY

- No consensus definition of FTT
- Failure to grow as expected rate as possible is useful working definition
- Most cases are due to not enough food being offered or taken (non-organic)
- Infant feeding and thriving are highly sensitive and emotive aspect of parenting
- Behavior of child with ascetism or self-denial, unskilled feeding of the parents, quality of mother-child relationship and competition or battle of will of mother in infant feeding are involved in feeding pattern of child with consequent FTT
- In the absence of evidence of organic diseases and severe malnutrition child health providers should adopt a "wait-and-see" approach and avoid inappropriate expensive and invasive investigations and referral.

FEEDING DISORDER (FOOD REFUSAL)

A feeding disorder is diagnosed when, despite persistent attempts by caregivers, a child's behavior results in failure to eat or drink sufficient quantities of food to sustain weight, meet nutritional needs and/or grow. It is a common problem in children and cause of frequent medical visit in pediatric practice. The reported prevalence of feeding problems varies between 2% and 29% in typically developing children. This can happen in a child irrespective of socioeconomic condition, but more frequently observed in a child coming of non-deprived higher socioeconomic family and in urban children. Majority of the cases children are otherwise active and developmentally normal. Most of the time, there is no well-defined organic cause and negative feeding behavior only dominates. Anthropometrically children are initially satisfactory. However, persistent food refusal may subsequently cause failure to thrive. Children exhibiting total food refusal accept only a highly restricted range and quantity of foods or refuse all food, resulting in dependence on liquid oral feedings (e.g. bottle feeds), or in rare extreme cases need enteral nutritional support (nasogastric tube feeding or gastrostomy tube feeds).

While dealing with food refusal, the mechanism of appetite in various phase of child development needs to be understood.

Appetite is governed by following factors in various development:

- 6 weeks of age: Infant regulate feed intake in accordance with energy needs
- 5–6 months: Infant takes feed according to taste and smell of feed. Lack of experience at this stage may mean limited range of tastes accepted
- 12–18 months: Children eat when they feel hungry which depends on their respective energy load. Fear of new foods (neophobia) develops
- Local features of food become important (e.g. biscuit must be whole not broken)
- Around 5 years: Food intake is modified by social rules (e.g. taking vegetables before fish or meat) Neophobic response strengthens but can be overcome by imitations of adults and other children.

Children may refuse food for following reasons:

- Forced feeding
- Over attention and parental anxiety to feed child
- Lack of appetite

- Individual difference in food acceptance (child with negativism, asceticism and frequently engaged in competition in "battle of will" with parents to feed)
- Distaste or disgust at some food (e.g. vegetable, egg)
- Lack of experience of some foods at certain develop-mental stage
- Onset of neophobic response in the second year.

MANAGEMENT

Exclude possible organic cause:

- Take relevant medical, dietary, social and development history, try to understand family dynamics, quality of parent child relationship, parental feeding skill and personality of child and parents
- Observe personality and behavior of parents and children and parent-child interaction during consultation
- A thorough physical examination including anthropometry should be done
- Baseline investigation like FBC, peripheral blood film, stool routine microscopic and urine routine microscopic and culture
- Other investigations if relevant (e.g. SI profile, tuberculin test in chronic febrile illness with FTT).

If there is any underlying organic cause it should be treated accordingly. However, frequently no well-defined organic cause relevant to food refusal is found.

In such cases, management of food refusal are:

- Do not force feed
- Take notice of satiety signal (e.g. closing mouth, turning away from food) (Fig. 62)
- Restrict junk foods
- Do not compare and expect that all children will show similar and satisfactory feeding behavior
- Feed in happy, relaxed environment
- Do not indulge in competition of "battle of will" to feed the child
- Move from mash to "bite and dissolve" foods from 7th month
- Encourage self-feeding as soon as possible, by end of the 1st year (Fig. 63)
- Give encouragement when the child is eating (Fig. 64)
- Do not give attention for not eating
- Take uneaten food away without comment
- Allow the child to be messy at mealtime and to enjoy eating
- Do not use one food as a reward for eating another
- Give frequent small meals
- Offer variety of foods with some favorites
- Try to feed in larger group size (with other family member), if possible with other children (Fig. 65)
- Try to feed during family mealtimes
- Reassure the parents and advise to show patience particularly if the child is physically normal and development wise satisfactory.

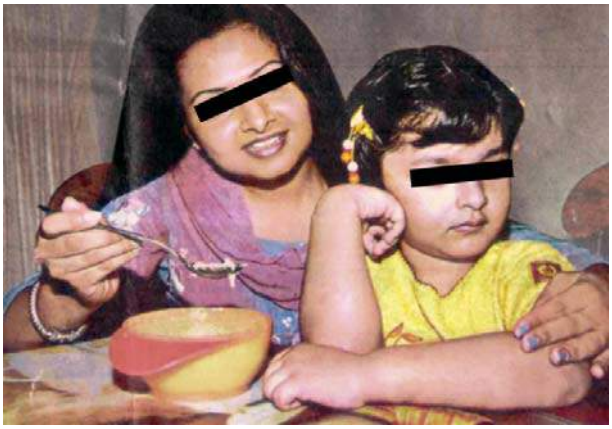


Fig. 62: A child showing food refusal as evidenced by turning away from food

Fig. 64: Children enjoying feeding with self-help and in larger groups

Fig. 63: Self-feeding with encouragement when the child is eating improves feeding behavior

Fig. 65: Food consumption is believed to be increased with eating in larger groups

DEFINITION

Eating disorders are defined as persistence disturbance of eating (± behavior) that impairs physical health or psychosocial functioning or both and that is not secondary to any other medical or psychiatric disorder.

ANOREXIA NERVOSA

Anorexia nervosa (AN) is the third most common chronic illness in teenage girl having a sex ratio of 9:1 (Fig. 66).

Etiology

Often unclear in individual cases.
Common causes are:

- Genetic predisposition
- A perfectionist personality
- Low self-esteem

The pathway into AN is through weight loss, either due to a desire to lose weight or for some other reasons such as depression/anxiety or, sometimes, viral illness.

Diagnostic Features

- Dietary restriction (may be accompanied by vomiting, exercise, laxative abuse, or other weight control methods) leading to significant and unhealthy weight loss (e.g. to less than 85% of expected body weight for height or age) or to stunting of expected growth
- Intense fear of gaining weight even when severely underweight
- Disturbance of experience of weight and shape with feelings of being fat or bloated
- Amenorrhea.

Treatment

The evidence base for treatment is small. Involvement of the family seems to be important. Clearly correction of dangerous weight loss or its secondary complications may be urgent. Otherwise, treatment is likely to be lengthy and to involve attention to anorexic behaviors, to recognizing and not acting on anorexic thoughts and feelings, and to returning to aspects of normal function such as school and home life.

Prognosis

The prognosis for teenagers is generally better than adults with most making a full recovery.

Bulimia Nervosa

- Two to three times more common than AN in adolescents
- Affects girls prominently
- Bulimic symptoms may occur as part of AN or during recovery.

Diagnostic Criteria

- Recent episodes of binge eating
- During bingeing a lack of feeling of control
- Regular use of mechanisms to reduce weight gain from bingeing [e.g. vomit-induction (Fig. 67), laxatives, diuretics, appetite suppressants, excessive exercise]
- Persistent concern with fatness
- Body weight higher than required for the diagnosis of anorexia.

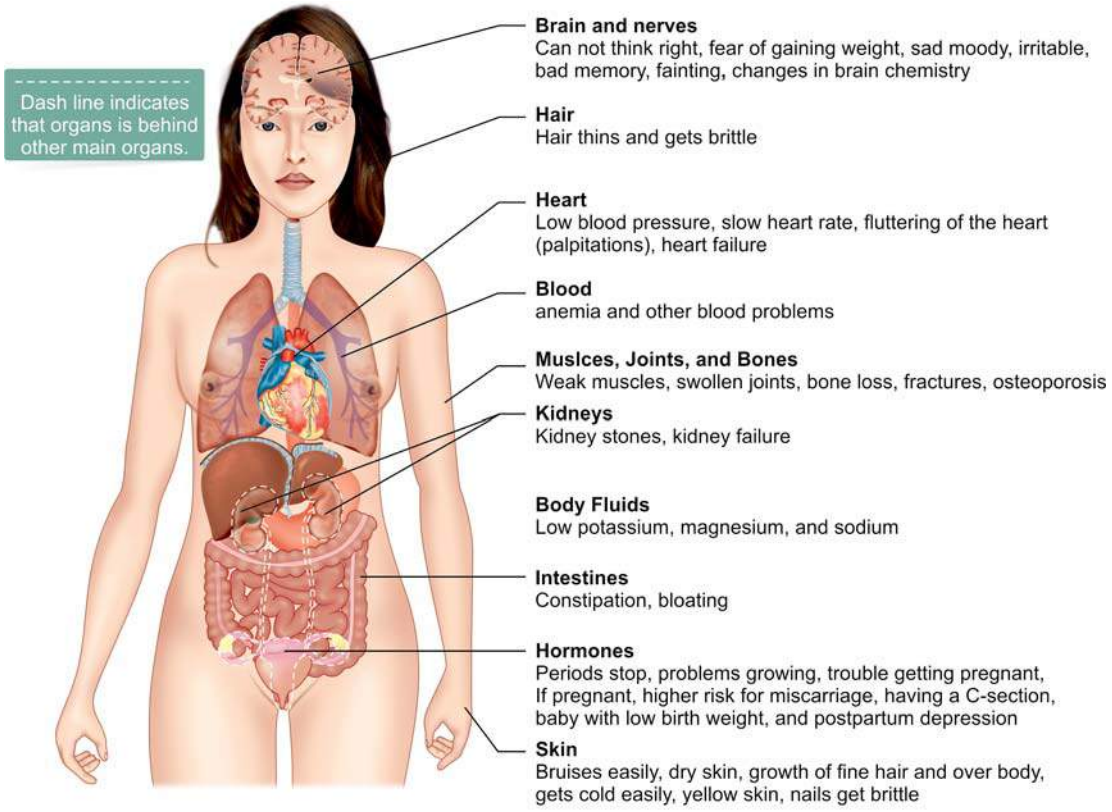


Fig. 66: Anorexia nervosa showing involvement of adverse effects on various organs of body

Fig. 67: Bulimia nervosa showing self-induced vomiting

Repeated vomiting and/or laxative abuse may result in serious electrolyte disturbances, seizures, hematemesis or stomach rupture.

Management

- Assess for concurrent personality disorders
- Cognitive behavioral therapy including educational input about healthy eating, starvation and binging
- Pharmacotherapy, e.g. fluoxetine, rarely used but may reduce food craving.

OBESITY AND OVERWEIGHT: IDENTIFICATION, ASSESSMENT, MANAGEMENT AND PREVENTION

There is no doubt that the prevalence of overweight and obesity is rapidly increasing throughout world with its health hazards. However, it is frequently not well-appreciated by parents and not well-recognized by health care professionals. While under nutrition is an important cause of childhood mortality and morbidity in developing countries, overnutrition and obesity is a growing underemphasized child health problem in many developed as well as developing countries. While health-care providers in developing countries are usually competent in recognizing undernutrition even at grass root level, they are frequently not familiar in recognizing or assessing obesity.

In children and adolescents overweight is defined as a BMI for age greater than 95th centile of a reference population, whereas obese has BMI of 98th percentile. WHO has classified overweight having BMI (Table 34) between 25 and 29.9 and obese having BMI less than 30 [BMI is measured as weight in Kg/h^2 in meter (Fig. 68)].

Obesity is significantly associated with a significant increased risk of cardiovascular and endocrine morbidity which in most cases only manifests as disease in adult life. The increased comorbidities associated with obesity are:

- Hypertension
- Hyperinsulinemia
- Dyslipidemia
- Type 2 diabetes mellitus
- Psychosocial dysfunction
- Exacerbation of conditions such as asthma
- Steatohepatitis.

Table 34: WHO Classification of nutritional status

WHO classification	BMI
Underweight	Below 18.5
Healthy weight	18.5–24.9
Overweight (grade I obesity)	25.0–29.9
Obese (grade II obesity)	30.0–39.0
Morbid /Severe obesity (grade III obesity)	Above 40.0

Fig. 68: An obese child

PATHOGENESIS OF OBESITY, ENERGY BALANCE AND INFLAMMATION

It is well recognized that causes of obesity are complex and multifactorial including genetic, metabolic, psychosocial and hormonal. The main factors contributing to excessive weight gain in children is the impaired balance between energy intake and expenditure. Most of the known genetic causes of obesity primarily play role by augmenting energy intake. Numerous neuroendocrine peptides and cytokines are involved in the pathogenesis of obesity and its associated complications. Research about the pathophysiology and treatment of obesity has been directed to this area in recent years.

Ghrelin is a fast-acting orexigenic hormone, playing role in the short-term energy intake. It is synthesized in gastric fundus. Ghrelin enters the brain through blood stream after being secreted by fundus of stomach. It stimulates growth hormone secretory receptor type 1a (GHS-R1a) in hypothalamus, which stimulates food intake and thereby increasing body weight. Ghrelin is also involved in insulin resistance in children.

In contrast to Ghrelin, obestatin is an anorexigenic hormone which is also synthesized from stomach, suppress food intake. Study demonstrated Ghrelin obestatin ratio is increased in obese children.

ADIPOSE TISSUE AND ADIPOKINES

Adipose tissue is not a passive site of energy storage. The major function of adipocyte is to store and release energy in the form of triglyceride during excess food consumption and starved period, respectively. Leptin, a protein, produced by adipose tissue, plays role in complications of obesity. Leptin was determined as the most sensitive adipokines marker for predicting the accumulation of cardiovascular risk factors and the presence of metabolic syndromes. Elevated serum leptin may also be an indicator of fatty liver disease.

Adipose tissue also produces several other adipokines that are key regulators of inflammation and tissue injury involved in obesity associated complications in children and adults. Increased levels of TNF-α, IL-6, CRP, particularly HsCRP, leads to inflammation and injury in several tissues and organs

including heart. In the heart, these adipokines and cytokines may cause intimal inflammation and proliferation of coronary vessels with early atherosclerosis risk in children.

MEASURES AND CLASSIFICATION OF OVERWEIGHT AND OBESITY

- Body mass index (adjusted for age and gender) is recommended as practical estimate of overweight in children and young people, but needs to be interpreted with caution because it is not a direct measure of adiposity.
- Waist circumference is not recommended as a routine measure but may be used to give additional information on the risk of developing other long-term health problems.
- Bioimpedance can measure both fat mass and FFBM or lean mass can be used in addition. But it is not a substitute of BMI.
- Look for skin changes like acanthosis nigricans (Fig. 69)
- Tailored clinical intervention should be considered with a BMI at or above 91st centile, depending upon the needs of the individual child and family.
- Assessment of comorbidity (hypertension, hyperlipidemia, etc.) should be considered for children with BMI at or above 98th centile.
- Any comorbidity should be managed when they are identified, rather than waiting until the person has lost weight.
- People, who are not ready to change, should be offered the chance to return for further consultation.
- Denial, disbelief, surprise and anger of being fat may hinder obesity management. Stressing the obesity as a clinical term with specific health hazard rather than a question of how you look, may help to mitigate this.

During consultation following steps may be helpful for management:

- Assess the person's view of their weight and the diagnosis
- Explore eating pattern and physical activity level
- Explore belief about eating and physical activity that he/she believes unhelpful
- Assess readiness to adopt change
- Assess confidence in making change

After measurement have been done, further assessment should cover

- Presenting symptoms and underlying causes of overweight and obesity

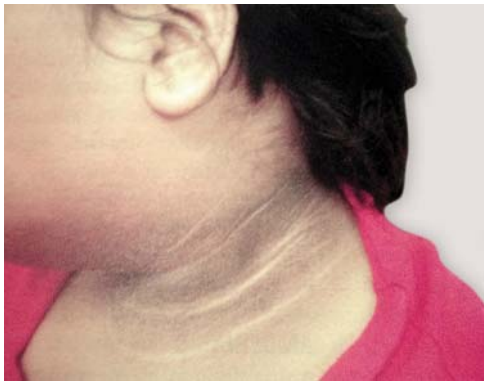


Fig. 69: Acanthosis nigricans (hyperpigmented, hyperkeratotic skin) frequently seen in obese children, often associated with future type 2 diabetes mellitus

- Willingness and motivation to change
- Comorbidities and risk factors
- Psychosocial distress such as low self-esteem, teasing, bullying
- Family history of overweight, obesity and co-morbidities
- Life style (diet and physical activities)
- Environmental, social and family factors that may contribute to overweight and obesity and success of treatment
- Growth and pubertal status

Referral to an appropriate specialist (i.e. a pediatrician) should be considered who are overweight associated with comorbidities or complex needs (e.g. learning or educational difficulties).

In secondary care, following assessment should be done for possible etiology.

- Blood pressure measurement (systolic hypertension in particular)
- Fasting lipid profile (dyslipidemia)
- Fasting insulin and glucose level (insulin-resistant syndrome)
- Liver function (steatohepatitis)
- Endocrine function*

Test results should be interpreted in context to the degree of overweight and obesity, age, comorbidities, family history of obesity and possible genetic and familial metabolic diseases.

MANAGEMENT (TREATMENT)

Management consists of:

- Lifestyle intervention (general and specific), behavioral management
- Dietary management
- Pharmacological intervention, and
- Surgical intervention.

It is desirable to include parents in the management.

Lifestyle Intervention

Multidisciplinary lifestyle intervention, increased physical activities, decreased physical inactivity, and improve eating behavior

When choosing treatment, the following factors should be considered.

- Experience and outcome of previous treatment
- Their level of risk, based on BMI
- Any comorbidity
- Realistic target for weight loss (aim to lose 5–10% of original weight or BMI SDs ≥0.5). The distinction between losing weight and maintaining weight loss and importance of developing skills for both should be appreciated (the change from losing weight to maintenance typically happens after 6–9 months of treatment).

Single-strategy approach to managing weight is not recommended for children.

Parents of overweight and obese children should be encouraged to lose weight if they are also overweight or obese.

Behavioral Intervention

Behavioral intervention, preferably done by trained professional, include

* Endocrine tests are not routinely recommended unless there is other evidence of endocrine diseases or short stature. Many overweight children have cutaneous striae; investigation for Cushings' disease is not recommended unless the patient is hypertensive with growth delay

- Stimulus or impulse control
- Self-monitoring (weight, etc.)
- Goal setting
- Reward for reaching goal
- Problem solving.

Physical Activities

Children and young people should be encouraged to increase physical activities even if they do not lose weight as a result, because of other health benefit exercise can bring, such as reduced risk of type 2 diabetes and cardiovascular disease.

- Children should be encouraged to do at least 60 minutes brisk moderate activity
- Children who are already overweight may need to do more than 60 minutes actively
- Encouraged to reduce physically inactivity, watching television, using computers or playing video games (Fig. 70)
- Cycling, swimming and active outdoor play (football, basketball, etc.) should be encouraged (Fig. 71).

Dietary Advises

Nutrition education is essential. It consists of

- Healthy eating habit, avoidance of junk, fast food (Fig. 72).
- Fat and sugar reduced diet. The diet should contain sufficient protein (15%) and fat not more than 30% and carbohydrate 55%, including 5% sugar
- Should contain fruits and vegetables at libitum
- Dietary change should be individualized, adhere to food preference (of course among healthy food) and allow flexible approach to reducing calorie intake
- Unduly restrictive and nutritionally unbalanced diet should not be used, because they are ineffective in long-term and can be harmful
- A dietary approach alone is not recommended. It is essential that any dietary recommendations are part of a multicomponent intervention
- Any dietary change should be age appropriate and consistent with healthy eating advice
- The total energy intake should be below their energy expenditure. Change should be sustainable.

Pharmacological Intervention

- Pharmacological treatment should be considered only after dietary; exercise and behavioral approach have been started and evaluated
- Drug treatment is not usually recommended for children younger than 12 years of age

Fig. 70: Discourage physical inactivity like TV watching

Fig. 71: Encourage active outdoor play

Fig. 72: Avoid junk food with fat and sugar-enriched diet

- In children younger than 12 years of age, drug treatment may be used under exceptional circumstances like associated sleep apnea, increased intracranial pressure.

Anti-obese Drugs

- *Orlistat (Xenical, Roche)*: Gastric and pancreatic lipase inhibitors
- *Sibutramine*: serotonin and noradrenergic receptor inhibitors
  Side effects: Gastrointestinal side effects, nausea, vomiting, pain abdomen.
  A 6–12 months trial is recommended, with regular review to assess side effects, effectiveness and adherence. There may be rebound weight gain, once medications are stopped.

  Current research about ghrelin in the treatment or prevention of obesity aims the blockage of ghrelin receptors and the use of ghrelin agonists. Ghrelin receptor blockers may prevent recurrent weight gain after weight loss is achieved. Ghrelin agonists may also inhibit the effect of ghrelin by competition on the receptors.
- Metformin: Metformin, a biguanide offers significant potential to intervene to reduce or reverse the metabolic and endocrine changes associated with obesity during puberty. Metformin acts by suppression of endogenous glucose production in the liver, but may also have insulin sensitizing effect of peripheral tissue through intracellular enzyme AMP kinase. It is more effective in overweight hyperinsulimic children.

  However, risk benefit of metformin treatment in the obese children remains largely untested.

Surgical Intervention

- Surgical intervention is not generally recommended in children or young people.

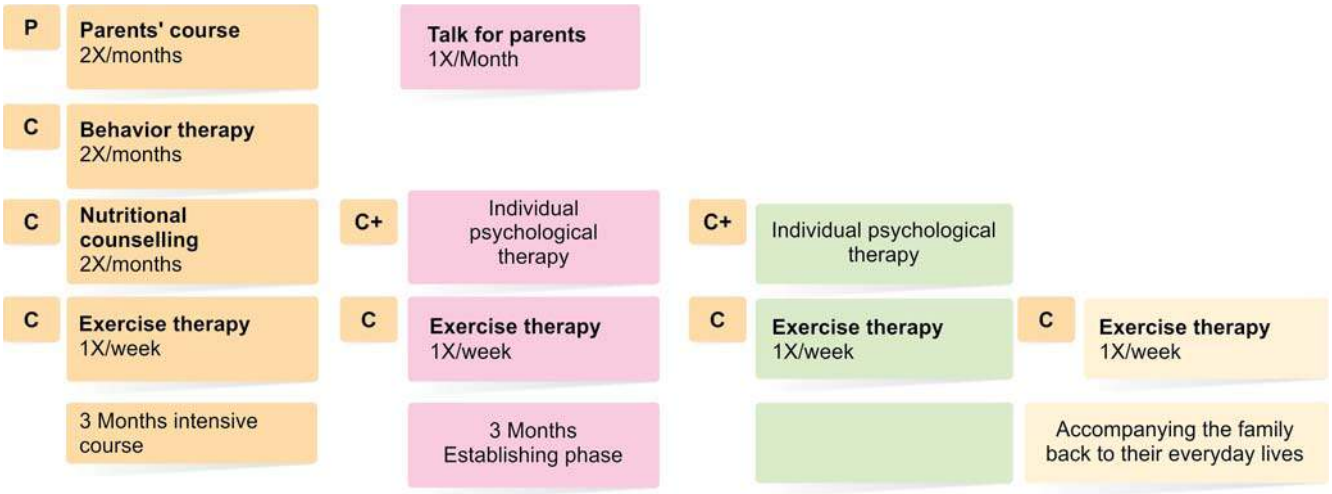


Fig. 73: A model of structure of the outpatient training program (In the model P = Parents, C = Child)

Bariatric surgery (laparoscopic gastric banding, Roux-en-Y gastric bypass, vertical gastric plasty, etc.) can be considered for young people only in exceptional circumstances and if they have achieved physiological maturity and who have a BMI more than 40 or 35 with comorbidity.

EVIDENCE-BASED OUTCOME OF OBESITY MANAGEMENT

Published studies shows an one year of program based on behavior modification of dietary and exercise habits, can bring down BMI SDs more than or equal to 0.5, change in body composition with decrease in fat mass and increase in lean body mass. Improved on BMI more than or equal to 0.25 are associated with decrease in mean SDS waist circumference SDS and key improvement of metabolic risk factors like triglycerides, LDLC, HsCRP (a marker of low grade inflammation linked with increased risk of cardiovascular diseases).

Published studies also demonstrated that multidisciplinary lifestyle intervention effectively improves obesity associated with fatty liver (steatohepatitis) with fall of elevated serum transaminase [serum aspartate aminotransferase–alanine aminotransferase (AST and ALT)].

Psychosocial effects and poor physical health associated with childhood obesity are reversed by proper management of obesity.

Figure 73 provides a model of structure of the outpatient management of obese children.

Prevention

Once obesity has developed, it is difficult to reverse, though not impossible, No magic effective drugs are available to reverse obesity once occurred and drugs are not only without side effects but also costly. Therefore, preventive steps should be taken to prevent obesity.

- Pediatrician should be taught how to more effectively initiate behavioral change in child and family
- Public health approach ensuring healthy eating and physical activity before weight gain occurs
- Parental teaching and family approach is necessary as weight gain can occur very early in life, with which many parents wrongly feel happy.

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7 Gastroenterology

DIARRHEA

INTRODUCTION

The reduction of child mortality is one of the Millennium Development Goals. The goal is to reduce under-five mortality in developing countries by two-thirds between 1990 and 2015. Childhood diarrhea continues to pose big threat to child health and child survival. Though the mortality rate for children under-five suffering from acute diarrhea globally has fallen from 4.5 million deaths annually in 1979 to 1.6 million deaths in 2002, acute diarrhea continues to take a high toll on children in developing countries.

Diarrhea is the passage of watery stools at least three times in a 24-hour period. However, recent change in the consistency of the stool is more important than frequency.

The two main risks of diarrhea are malnutrition and deaths. While dehydration is the most common cause of death, several deaths occur as a result of malnutrition consequent to a series of diarrheal episodes.

CLINICAL TYPES OF DIARRHEAL DISEASE

Four clinical types of diarrhea can be recognized, each reflecting the basic underlying pathology and altered physiology.

1. *Acute watery diarrhea* (including cholera) starts suddenly and lasts several hours or days. The main danger is dehydration; weight loss may occur if feeding in not continued.
2. *Acute bloody diarrhea* (dysentery) is similar to acute watery diarrhea, but associated with gross blood in stool. The main dangers are intestinal damage, sepsis and malnutrition; other complications, including dehydration, may also occur.
3. *Persistent diarrhea* (PD) starts as acute watery diarrhea and lasts for 14 days or longer. The main danger is malnutrition and serious nonintestinal infection; dehydration may also occur.
4. *Diarrhea with severe malnutrition* (Marasmus or Kwashiorkor) carries risk of severe systemic infection, dehydration, heart failure and vitamin and mineral deficiency. It has secured as a separate entity as its management is different. The faulty case management of diarrhea associated with protein-energy malnutrition increases case fatality of malnutrition.

ETIOLOGY OF ACUTE DIARRHEA

- Rotavirus (RV) and enterotoxigenic *E. coli* account for nearly half the total diarrheal episodes. RV is more frequently isolated in children with severe disease than in mild cases.

  Other forms of diarrheagenic *E. coli* like enteroinvasive *E. coli* (EIEC), enterohemorrhagic *E. coli* (EHEC), localized adherent *E. coli* (LA-EC), diffusely adherent *E. coli* (DA-EC), aggregative adherent *E. coli* (Agg-EC). EIEC and EHEC can cause dysentery.
- *Vibrio cholera*
- *Shigella* spp.
- *Salmonella* spp.
- *C. jejuni*
- *Y. enterocolitica*
- *E. histolytica.*

How does diarrhea cause significant physiological disturbances in the body?

Approximately 60% of the child's body weight is present in two fluid compartments: (1) The extracellular fluid (ECF) and (2) intracellular fluid (ICF). Large amount of water and water soluble nutritive substances, such as electrolytes, metabolites and vitamins, are lost from the body during diarrhea episodes. Loss of water from the body causes a reduction or shrinkage in the volume of extracellular compartment. In about half of these cases, the concentration of sodium in the plasma or extracellular compartment remains nearly normal (about 140 mEq/L). Since excessive sodium may be lost in the stools in another 40–45% of cases, there is a relative decline in the serum and ECF sodium level (hyponatremia). Sodium is a major osmotic determinant of ECF. Therefore, the osmolarity of ECF falls causing movement of water from extracellular to intracellular compartment. This causes further shrinkage of the already reduced extracellular compartment volume.

Skin turgor or elasticity is normally maintained by the presence of water and fat in the tissues. Shrinkage of extracellular water in both hyponatremic and isonatremic types of dehydration impairs the skin elasticity. In about 5% of diarrhea cases, serum sodium levels may be elevated to more than 150 mEq/L (causing hypernatremic dehydration). In these patients, the osmotic pressure of ECF is relatively higher. Therefore, water comes from inside the cells to the ECF and, therefore partially masks loss of tissue fluid deficiency clinically.

However, in diarrhea due to cholera, as disproportionately more sodium is lost in stool compared to water, the reduced osmolarity solution may be harmful as it may further aggravate tissue sodium status of the child and may cause symptomatic hyponatremia, including hyponatremic convulsion. In that case, conventional old WHO oral rehydration salt (ORS) containing higher sodium (90 mmol/L) instead of current reduced osmolarity solution with low sodium (75 mmol/L) will be preferable.

DIAGNOSIS

History

Ask the mother or other caretaker about:

- Duration of diarrhea
- Presence of blood in stool
- Presence of fever, cough or other important problems (e.g. convulsion, recent measles)
- Frequency and volume of urine during current illness
- Preillness feeding practice
- Type and amount of fluids (including breast milk) and food taken during the illness
- Drugs or other remedies taken
- Immunization history
- Frequency and volume of urine during current illness.

Physical Examination

First check for signs and symptoms of dehydration.
Look for the following signs:

- General condition; is the child alert, restless or irritable, floppy, lethargic or unconscious?
- Are the eyes normal, sunken, or very sunken and dry?
- Are there tears when the child cries vigorously?

Assessment of Severity of Dehydration

A child's dehydration status should be classified as no dehydration, some dehydration or severe dehydration according to WHO criteria given in Tables 1 and 2.

Table 1: Estimation of fluid deficit

Assessment	Fluid deficit as percentage of body weight	Fluid deficit in mL/kg body weight
No sign of dehydration	<5	<50
Some dehydration	5–10	50–100
Severe dehydration	>10	>100

MANAGEMENT (IN CONFORMITY WITH WHO/IMCI GUIDELINE)

Objectives of Treatment of Diarrhea

Clinical dehydration does not correspond to actual dehydration. Actual dehydration occurs much earlier than clinical signs as shown in the Figure 2. So it is necessary to offer oral rehydration with no sign of dehydration in order to correct actual dehydration and prevent clinical dehydration.

Three important objectives of treatment are:

1. Prevent dehydration, if there is no sign of dehydration
2. Treat dehydration, when it is present
3. Prevent nutritional damage, by feeding during and after diarrhea.

Treatment of Acute Watery Diarrhea

Treatment Plan A

Patients without physical signs of dehydration

Mother should be educated to use increased amount of culturally appropriate home available fluids (Table 3). In addition, they should be given ORS packets for use at home. ORS is appropriate for both prevention and treatment of dehydration. When ORS packets are given to the mother at treatment center or by other healthcare providers, she is less likely to demand or desire antidiarrheal. The mother should be asked to take the child to health worker if the child does not get better in 3 days or develops any of the following danger signs: Many watery stools, repeated vomiting, marked thirst, eating or drinking poorly, fever and blood in stool.

Oral zinc 10 mg/day for child below 6 months of age and 20 mg/day for 10 days should be given as an adjunct therapy.

Plan A: (Used to teach mother):

- Continue to treat child's current episodes of diarrhea at home
- Give early treatment for future episodes of diarrhea

Table 2: Assessment of dehydration in patients with diarrhea

		No dehydration	Some dehydration	Severe dehydration
Look at	Condition*	Well alert	Restless, irritable	"Lethargic or unconscious"* floppy
	Eyes†	Normal	Sunken	Very sunken and dry (Fig. 1)
	Tears	Present	Absent	Absent
	Mouth and tongue‡‡	Moist	Dry	Very dry
	Thirst	Drinks normally, not thirsty	"Thirsty, drinks eagerly"	"Drinks poorly or not able to drink"
Feel	Skin pinch§	Goes back quickly	"Goes back slowly"	"Goes back very slowly" (Fig. 1)
Decide		The patient has no sign of dehydration	If the patient has two or more signs, including one "sign", there is some dehydration	If the patient has two or more signs, including at least one "sign", there is severe dehydration
Treat		Use treatment *Plan A*	Weigh the patient, if possible, and use treatment *Plan B*	Weigh the patient and use treatment *Plan C* urgently

* Being lethargic and sleepy are not the same. A lethargic child is not simply asleep; the child's mental state is dull and the child cannot be fully awakened; the child may appear to be drifting into unconsciousness

† In some infants and children, the eyes normally appear somewhat sunken. It is helpful to ask the mother if the child's eyes are normal or more sunken than usual

‡ Dryness of the mouth and tongue can also be palpated with a clean finger. The mouth may be dry in a child who habitually breaths through the mouth. The mouth may be wet in a dehydrated child with recent vomiting or drinking

§ The skin pinch is less useful in infants and children with marasmus (severe wasting) or Kwashiorkor (severe malnutrition with edema), or obese children

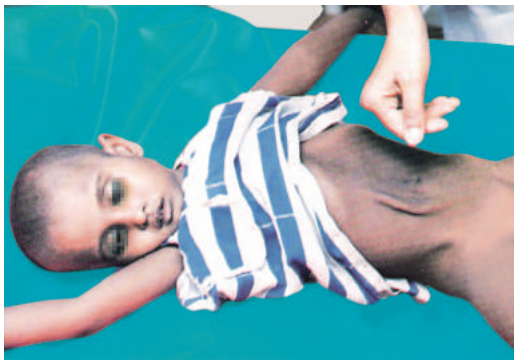


Fig. 1: A child with diarrhea with severe dehydration showing lethargy, sunken eyes and skin going back very slowly by skin pinching

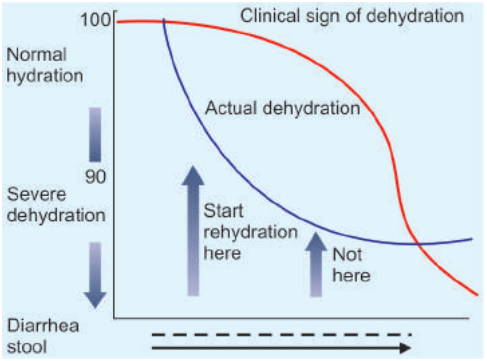


Fig. 2: Showing time of appearance of clinical dehydration and actual (subclinical) dehydration

Table 3: Oral rehydration therapy to prevent dehydration (Plan A)

Age	Amount of ORS or other culturally appropriate ORT fluids to give after each loose stool (mL)	Amount of ORS to provide for use at home (mL/day)
<24 months	50–100	500
2–10 years	100–200	1,000
10 years or more	As much as wants	2,000

- Describe and show the amount to be given after each stool, using a local measure. Show the mother how to mix ORS. Show her how to give ORS
- Give a teaspoonful every 1–2 minutes to a child under 2 years
- Give frequent sips from a cup to an older child
- If the child vomits, wait for 10 minutes. Then give the solution more slowly (for example, a spoonful every 2–3 minutes)
- If diarrhea continues after the ORS packets are used up, tell the mother to give other fluids as described above or return for more ORS

Abbreviations: ORS, oral rehydration salt; ORT, oral rehydration therapy

- Take the child to the health worker if the child does not get better in 3 days or develops any of the followings:
  - Many watery stools
  - Repeated vomiting
  - Marked thirst
  - Eating or drinking poorly
  - Fever
  - Blood in stool.

Explain three rules for treating diarrhea at home, which are as follows:

1. Give the child more fluid than usual to prevent dehydration
2. Give the child plenty of food to prevent under nutrition
3. Take the child to the health workers, if the child's condition does not improve in three days or develops any of the followings:
   - Many watery stools
   - Repeated vomiting
   - Marked thirst
   - Eating or drinking poorly.

Oral rehydration therapy in the management of acute diarrhea without dehydration is given in Table 3.

Fluid not containing salt but can be given as ORT and some unsuitable fluids are given in Table 4.

Show the mother how to mix ORS; show her how to give ORS:

If ORS is not available readily, it can be made at home from drink made from salt and molasses/sugar as shown in Figure 3.

- Give a teaspoonful every 1–2 minutes to a child under 2 years of age
- Give frequent sips from a cup to an older child

Table 4: Suitable non-salt containing fluid and unsuitable fluid

Fluids that do not contain salt	Unsuitable fluids
• Plain water • Water in which a cereal has been cooked (e.g. unsalted rice water) • Unsalted soup • Yoghurt drinks without salt • Green coconut (contains potassium) water • Weak tea (unsweetened) • Unsweetened fresh fruit juice	• A few fluids are potentially dangerous and should be avoided during diarrhea. Especially important are drinks sweetened with sugar, which can cause osmotic diarrhea and hyponatremia. For example: soft drinks, sweetened fruit drinks, sweetened tea • Other fluids to be avoided are those with stimulant, diuretic or purgative effects, e.g. coffee, medicinal teas

Fig. 3: Preparation of saline drink from salt and molasses/sugar. Mix three pinch finger table salt and one fist molasses/sugar in 0.5 L of drinking water

- If the child vomits, wait for 10 minutes, and then give the solution more slowly (for example, a spoonful every 2–3 minutes).

If diarrhea continues after the ORS packets are used up, tell the mother to give other fluids as described in the rule above or return for more ORS.

Treatment Plan B: Patients with Physical Signs of Dehydration

- All cases with obvious signs of dehydration need to be treated in a health center or hospital. However, oral fluid therapy must be commenced promptly and continued during transport. The fluid therapy for dehydration has three components:
  1. Correction of the existing water and electrolyte deficit as indicated by the presence of signs of dehydration *(rehydration therapy)*.
  2. Replacement of ongoing losses due to continuing diarrhea to prevent recurrence of dehydration *(maintenance therapy)*.
  3. Provision of normal daily fluid requirements.
- Oral zinc 10 mg/day for child below 6 months and 20 mg/day for 10 days should be given as an adjunct therapy
- Observe the child carefully and help the mother to give ORS solution (Plan B)
- Show her how much solution to give her child
- Show her how to give it—a teaspoonful every 1–2 minutes for a child under 2 years of age (Table 5 and Fig. 4) and frequent sips from a cup for an older child
- Check from time to time to see if there are problems
- If the child vomits, wait for 10 minutes and then continue giving ORS, but more slowly, for example, a spoonful every 2–3 minutes
- If the child's eyelids become puffy, stop ORS and give plain water or breast milk
- Give ORS according to Plan A when the puffiness is gone
- Show her how much ORS to give to finish the 4-hour treatment at home
- Give her enough ORS packets to complete rehydration, and for two more days as shown in Plan A
- Explain to her the following three rules in Plan A for treating her child at home:
  1. To give ORS or other fluids until diarrhea stops
  2. To feed the child
  3. To bring the child back to healthcare provider, if necessary.

Treatment Plan C

Children with severe dehydration (Fig. 5)

- Start IV fluids immediately. While the drip is being set up, give ORS solution if the child can drink
- The best IV fluid solution is Ringer's lactate solution. An ideal preparation should be Ringer's lactate with 5% added dextrose
- Give 100 mL/kg of chosen solution.

All children should be started on some ORS solution (about 5 mL/kg/hour) when they can drink without difficulty during the time they are getting IV fluids (usually within 3–4 hours for infants or 1–2 hours for elder children). If one is unable to give IV fluids (for reasons of access, logistic availability or during transport), immediately start rehydration with ORS using Nasogastric (NG) tube at 20 mL/kg/hour (total 120 mL/kg). Reassess the child every 1–2 hours; if there is repeated vomiting or abdominal distension, give the fluids more slowly. If there is no improvement in hydration status after 3 hours, try to start IV fluids as early as possible.

Oral zinc 10 mg/day for child below 6 months and 20 mg/day for 10 days should be given as an adjunct therapy when the child will be in a position to take it.

To treat severe dehydration quickly, follow the arrows. If answer is "YES", go across. If "NO", go down.

How to calculate rate of IV infusion to deliver a desired amount of fluid at a definite time period?

Rate (drop/minute) of infusion of IV fluid to be infused in 24 hours is equivalent to fluid volume to be infused in terms of mL in hundred. For example, if 500 mL (5 × 100) of fluid has to

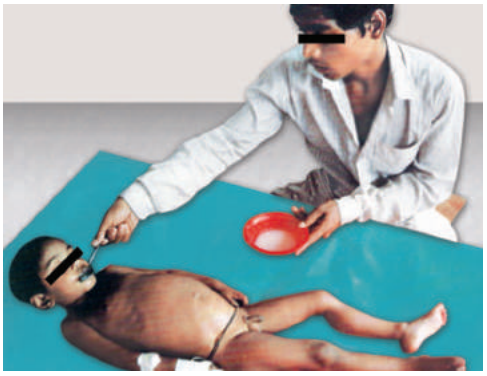


Fig. 4: A small child with diarrhea and some rehydration receiving frequent teaspoonful of ORS from feeding pot

Table 5: Guideline for treating patients with some (but not severe) dehydration

When body weight is not known (Plan B) Approximate amount of ORS solution to give in the first 4 hours						
Age	**< 4 months**	**4–11 months**	**12–23 months**	**2–4 years**	**5–14 years**	**15 years or older**
Approximate weight in Kg	< 5	5–8	8–11	11–16	16–20	> 30
ORS in mL	200–400	400–600	600–800	800–1,200	1,200–2,200	> 2,200
Local measure (glass)	1–2	2–3	3–4	4–6	6–11	12–20

- The approximate amount of ORS required (in mL) can also be calculated by multiplying the patient's weight (in kg) multiplied with 75
- For infants less than 6 months who are not breastfed, also give 100–200 mL clean water during this period
- Encourage breastfeeding

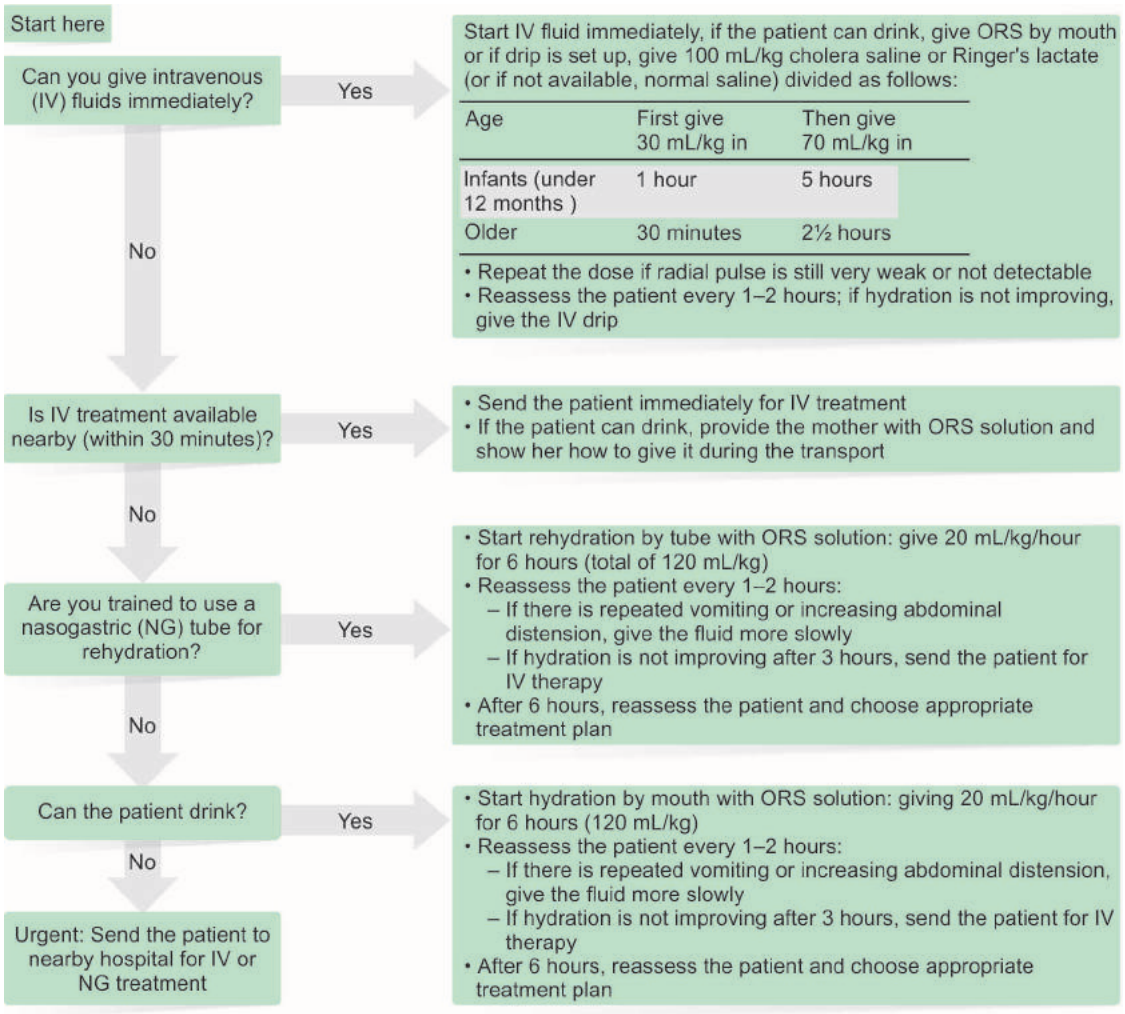


Fig. 5: Treatment plan C

be infused over 24 hours then the rate of infusion is 5 drops/minute. If microdrop is used via microburette, the rate will be 20 drops/minute in microburette (one drop in normal burette = four drops in microburette). Fifteen drops in normal burette or 60 drops in microburette are equivalent to 1 mL.

If fluid has to be given quickly as in correction of significant dehydration, the rate of infusion should be increased according to the magnitude of reduction of time from 24 hours fluid replacement.

As mentioned before, if 1,000 (10 × 100) mL of fluid is to be given in 24 hours then the rate of infusion will be 10 drops/minute. If 1,000 mL has to be given in 12 hours (half of 24 hours), the rate of infusion will be doubled that is 20 drops/minute. If it is given in 6 hours (four times less than 24 hours), the rate will be four times that of 24 hour duration infusion and therefore the rate will be 40 drops/minute for 6 hours and so on.

On the other hand, if 1,000 mL has to be given over 48 hours (e.g. in hypernatremic dehydration), the rate will be halved, i.e. 5 drops/minute for 48 hours. If the microdrop (microburette) is used, the rate should be increased by four times, i.e. 20 drops/minute in microburette.

PRACTICE

Correction of Severe Dehydration by IV Infusion

A 10-month-old baby with 10 kg weight presented with diarrhea associated with severe dehydration.

How will you correct dehydration and what type of fluid should be used?

Answer: In severe dehydration, the quantity of fluid to rehydrate is 100 mL/kg. For 10 kg child, 1,000 mL (100 × 10) therefore should be infused over 6 hour. Since the baby is below 1 year, 30 mL/kg to be given in 1 hour and remaining 70 mL/kg to be given over next 5 hours. Polyelectrolyte isotonic solution, like Ringer's lactate, Hartmann's or cholera saline, is preferably used; however, normal saline (isotonic) can also be used.

30 × 10 = 300 mL if infused in 24 hours, the rate will be 3 drops/minute.

However, 300 mL has to be infused over 1 hour in the index child and therefore the rate will be 24 times more than that of rate of 24-hour-duration infusion. Therefore, the rate at which

300 mL fluid infuses in 1 hour will be 3 × 24 = 72 drops/minute (in normal burette).

70 × 10 = 700 mL should be infused over next 5 hours at the rate of approx. 34 drops/minute in normal burette, calculated in the manner discussed above.

It is better to use in normal burette instead of microburette while correcting severe dehydration.

Rotavirus Gastroenteritis

Burden of Disease

Rotavirus is the principal cause of dehydrating diarrhea and leading recognized cause of diarrhea-related morbidity and mortality among infants and young children below 5 years of age, especially in Southeast Asia and Sub-Saharan Africa. Globally more than 114 million cases of gastroenteritis (GE) occur due to RV and 2.4 million inpatient visits are attributable to RV disease annually.

Rotavirus is ubiquitous—95% of children worldwide are infected by 3–5 years of age. Peak incidence of clinical cases is among children aged 6–24 months; the younger the child, the higher the risk of severe disease, hospitalization and death.

Rotavirus accounts for approximately one-third of cases of severe vomiting and diarrhea in infants requiring hospitalization.

Rotavirus belongs to Reoviridae family. It consists of two cuspids: (1) An inner cuspid (VP4) and (2) an outer cuspid which consist of VP7 (G serotypes) and VP4 (P serotype). VP7 and VP4 are critical to vaccine development, both proteins induce neutralizing antibodies and involve in protective immunity.

Four group A, RV serotype predominant globally G1 [P8], G2 [P8], G3 [P8] and G4 [P8].

Serotype G9 is emerging as the fifth globally important serotype.

Fecal oral route is the predominant mode of transmission. Other possible route of transmission are:

- Person to person spread via contaminated hands
- Respiratory transmission via droplets.

Transmission occurs regardless of public health and sanitary condition, as evidenced by similar incidence of the disease in both developing and developed countries.

Distribution of Diarrheal Pathogen

Characteristics of RV pathogens in developed and developing countries have been given in Table 6.

From the Table 6, it appears that the high incidence and disease burden of RV diarrhea is similar in both developed and developing countries. However, the mortality is much higher in developing countries due to inadequate access to medical care and malnutrition associated with diarrhea.

Rotavirus affects both undernourished and well-nourished children.

Incubation period: 1–4 days.

Symptoms last for: 4–8 days.

The first RV infection is usually most severe. Subsequent infection causes progressively milder symptoms.

Complications of Rotaviral Infections

Dehydration, electrolytes imbalance, hospitalization, concomitant bacterial infections and death.

Control of Rotavirus Gastroenteritis

Every year RV is associated with 600,000 deaths (2008) among children below 5 years of age, especially in Southeast Asia and Sub-Saharan Africa. Due to large disease burden of RV GE in children, prevention by vaccination has been advocated for both developing and developed countries.

A live attenuated human Rotavirus vaccine containing the R1X4414 strain of G1P [8] specificity has been developed from parent vaccine strain. Two doses are given below 6 months of age (2–6 months) with 1 month apart. Protection starts as early as first dose, lasts up to 2 years of age (*See* Chapter 14).

Management of Diarrhea in Dehydration in Severe Malnutrition

It is described in Chapter 6.

INVASIVE DIARRHEA

Dysentery or invasive diarrhea is usually defined as diarrhea associated with visible blood in stool. It is characterized by fever, abdominal cramping pain and loose stools, which may contain pus and blood. Visible blood in the stool generally indicates a more severe form of the disease. In some invasive diarrhea particularly in infants, it may not be visibly present. In such cases, stool microscopy may be helpful to detect RBC, pus cells and mucous as evidence of invasive diarrhea. Presence of frank blood or RBC in stool without pus cells or mucous points toward other causes of bleeding per rectum like anal fissures, rectal polyp, etc. It should be borne in mind that up to 20% of children suffering from invasive diarrhea may present initially with watery diarrhea.

Causative agents of invasive diarrhea:

- *Shigella* spp.
- *Salmonella* spp.

Table 6: Characteristics of rotavirus pathogens in developed and developing countries

	Developing countries	Developed countries
Incidence	Universal	Universal
Age of first clinically significant infection	Younger: <1 year	Older: 6 months to 2 years
Seasonality	Infection throughout the year with seasonal increase	Winter disease in temperate climate
Serotype	G1–G4 common strain producing disease. G9 emerging	G1–G4
Cost	Often not documented	High (US $ 1 billion) annually
Mortality	High in low and middle income countries. >600,000 deaths/year	Low in high income countries, <1,000 death/year
Medical care and access	Inadequate	Greater

- *Campylobacter* spp.
- Enteroinvasive *E. coli* and enterohemorrhagic *E. coli.*
- *Entamoeba histolytica.*

Shigella

It is the only organism causing dysentery that is frequently associated with clinically severe disease that may result in death. Evidence from recent multicenter study in Indonesia, China, Bangladesh, Vietnam, Thailand and Pakistan found that annual incidence rate of Shigella was 13.2 cases per 1,000 children under 5 years of age.

Shigella organisms are a group of Gram-negative, facultative intracellular organisms. They are grouped is four species: *Shigella dysenteriae, Shigella flexneri, Shigella boydii* and *Shigella sonnei*.

Geographical distribution and antimicrobial susceptibility varies with different species. *S. dysenteriae serotype* causes deadly epidemics; *S. Boydii* is restricted to Indian subcontinent. *S. flexneri* is most prevalent in Bangladesh. *S. Sonnei* is the most common Shigella in UK and other developed countries.

Pathophysiology

Shigella infection is a major public health problem in developing countries, where sanitation is poor. Human are the major reservoir.

Transmission: Oral-fecal route.

Other mode of transmission: Ingestion of contaminated food and water.

Vector: Housefly. Housefly can spread the disease by physically transporting infected feces.

Incubation period: Varies from 12 hours to 7 days but typically 2–4 days.

Pathology

The host response to primary infection is characterized by the induction of an acute inflammation, which is accompanied by polymorphonuclear (PMN) cell infiltration, resulting in massive destruction of colonic mucosa.

Gross pathology consists of mucosal edema, erythema, friability, superficial ulceration and mucosal hemorrhage involving the rectosigmoid junction primarily.

Microscopic pathology consists of epithelial cell necrosis, goblet cell depletion, PMN infiltrates and mononuclear infiltrate in lamina propria and crypt abscess formation.

Mortality and Morbidity

Although Shigellosis-related mortality is rare (<1%) in developed countries, mortality is substantial (up to 20–25%) in Far East and Middle East.

Age

According to recent CDC reports, Shigella infection accounts for 28% of all enteric infection. Children younger than 5 years have 7% of total reported case, a rate indicating a disproportionate disease burden in this population.

There is no racial or sex predilection.

Clinical Features

Symptoms

- Intestinal:
  - Abdominal pain
  - Tenderness
  - Fecal incontinence and small volume mucoid diarrhea with frank blood
  - Seizure may be an early manifestation
  - Sudden onset of severe abdominal cramping
  - High grade fever
  - Emesis
  - Anorexia
  - Large volume watery diarrhea.
- Extra-intestinal:
  - CNS symptoms: Headache, lethargy, meningism, delirium, convulsion (with *S. dysenteriae*, pathogenesis unknown)
  - Hemolytic uremic syndrome: Microangiopathic hemolytic anemia, thrombocytopenia and renal failure have been reported with *S. dysenteriae*
  - *Septicemia*: Rare, but can occur with malnourished children with *S. dysenteriae.* Septicemia is sometimes caused by other Gram-negative organisms and related to loss of mucosal integrity by Shigella infection. Shigella sepsis often complicated by disseminated intravascular coagulation (DIC)
  - *Rectal prolapse*: Rectal prolapsed and toxic mega colon may follow Shigellosis
  - Malnutrition may follow Shigellosis.

Hypoglycemia and profound dehydration can occur particularly with *S. dysenteriae* infection.

Diarrhea initially presents with watery diarrhea up to 20% of cases, followed by blood stained stool.

Signs

- Fever
- Toxic appearance
- *Dehydration*: Less common than acute watery diarrhea nevertheless can occur. Depending on degree of dehydration, signs of dehydration will be present
- *Abdominal tenderness:* Usually central lower abdomen
- If patient presents with febrile seizure, careful neurological evaluation is mandatory to exclude meningitis.

Treatment

Drugs: Antibiotics, zinc, rehydration and diet.

Antibiotics

Shigella, particularly *S. dysenteriae*, has been found resistant to many commonly used antibiotics. Antibiotics found effective in *Shigellosis* currently are:

- *Ciprofloxacin:* Orally 20–30 mg/kg in two divided doses. Between 10–20 mg/kg/day in two divided doses can be given IV if patient refuses to take orally, vomits or too sick to take oral suspension. Treatment duration is 5 days.

  It is mentioned worthy that minimum inhibitory concentration of ciprofloxacin has increased in recent past in some of the developing countries.

- *Mecillinam*: Between 50–60 mg/kg/day in four divided doses for 5 days.

  Not available in suspension form
- *Ceftriaxone*: Between 60–75 mg/kg/day IV/IM in single or two divided doses for 5 days. It has advantage of covering sepsis particularly if Gram-negative sepsis coexists.

Nalidixic acid may be tried above 3 months of age at 50–60 mg/kg/day in four divided doses. It may cause pseudotumor cerebri. It is better to avoid if other effective drugs are available.

Zinc as an Adjunct Treatment for Shigellosis

In 2004, WHO and UNICEF issued a joint statement recommending the use of zinc for treatment of all types of diarrhea including dysentery. After the recommendation, WHO updated current guidelines for the control of Shigellosis to include zinc as an adjunct therapy to currently recommended antibiotics.

Though incidence and fatality from Shigella has been declined, the need for effective treatment should not be underestimated. As the number of antibiotic resistant strains of Shigella continues to increase, nonantibiotic treatment, such as zinc, may play an increasingly important role in the treatment and control of Shigella especially during epidemics. Published studies showed zinc supplementation in children suffering from shigellosis has shorter duration of blood in stool and recovers earlier than nonsupplemented group.

Zinc supplementation in shigellosis also increases immune response with elevated Shigella antigen-specific IgG responses, lymphocytes proliferative response than nonsupplemented children.

Zinc effectively limits the growth of all four strains of Shigella, though *S. dysenteriae* and *S. flexneri* are more sensitive to zinc, with a sharper decline in growth as the zinc dose is increased, compared to decline in growth observed among *S. sonnei* and *S. boydii* isolates.

Diarrhea continues to be leading cause of all deaths among children under 5 years of age. If the Millennium Development Goal of reducing under-five mortality is to be met, the proper treatment of diarrhea, including all cases of dysentery with zinc and low osmolarity ORS must be a top priority.

Treatment of complications like sepsis, DIC, hypoglycemia, etc. should be done accordingly.

Rehydration

Although severe dehydration is not frequent as compared to acute watery (viral) diarrhea, nevertheless it can also occur, particularly with *S. dysenteriae*. Correction of dehydration should be done according to treatment plan outlined before.

Diet

Effective, safe and simple diet is an important part of management in all diarrheal diseases, including Shigellosis. Boiled green banana that is rich in amylase-resistant starch that stimulates colonic production of short chain fatty acid has been found useful diet in childhood Shigellosis. Green banana containing amylase-resistant starch remains undigested in small intestine. They are fermented by colonic bacteria in to short chain fatty acids mostly acetate, propionate and butyrate, which are major sources of metabolic energy for the colonocyte. The antidiarrheal effects of green banana are therefore related to its contents of resistant starch (inulin, oligofructose) and to an extent it is fermented to fatty acids by colonic microflora. Pectin, a fermentable source of resistant starch has also antidiarrheal effects, which is also observed when green banana is used in persistent diarrhea (PD).

ADVANCES IN MANAGING DIARRHEAL DISEASE

- Reduced osmolality ORS
- Rice-based ORS
- Use of zinc in diarrhea
- Rotavirus vaccine
- Use of probiotic in acute diarrhea.

New and improved ORS will save more lives.

For more than 25 years, WHO and UNICEF have recommended a single formulation of glucose-based ORS to prevent or treat diarrheal dehydration, no matter the cause or affected age group. The solution has played a major role in dramatically reducing global mortality due to diarrhea. During this time, researchers sought to develop an "improved" ORS formulation that was not only safe and effective as the original in preventing and treating diarrheal dehydration but also reduced stool output or offered additional clinical benefits, or both.

Research effort focused on reducing the osmolarity of ORS solution to avoid possible adverse effects of hypertonicity on net fluid absorption. Reducing the concentrations of glucose and salt (NaCl) in the solution accomplished this goal. Studies of this approach show that decreasing the sodium concentration of the ORS solution to 75 mEq/L, glucose concentration to 75 mmol/L, and total osmolarity to 245 mOsm/L, improved the efficacy of the ORS regimen for children with acute noncholera diarrhea.

The need for unscheduled supplemental intravenous therapy in children given the new ORS fell by 33%. An analysis of this and other recent studies of reduced osmolarity ORS solution (osmolarity 210–268 mOsm/L, sodium 50–75 mEq/L) found that stool output decreased by about 20% and vomiting by about 30%. The reduced osmolarity (245 mOsm/L) solution also appeared to be as safe and effective as standard ORS for use in children with cholera.

Recommended Formulation

Because of the improved effectiveness of reduced osmolarity ORS solution, especially for children with acute, noncholera diarrhea, WHO and UNICEF are recommending that countries manufacture and use reduced osmolarity formulation in place of the previously recommended ORS solution.

Composition and osmolality of reduced osmolality are given in Tables 7 and 8. Comparison of composition and osmolality of previous convention of WHO ORS containing high sodium with high osmolality is given in (Tables 9 and 10).

Table 7: Reduced osmolality (improved) oral rehydration salt composition

Ingredients	Grams/Liter
Sodium chloride	2.6
Glucose anhydrous	13.5
Potassium chloride	1.5
Trisodium citrate	2.9
Total weight	20.5

Table 8: Reduced osmolality (improved) oral rehydration salt osmolality

Component	mmol/Liter
Sodium	75
Chloride	65
Glucose anhydrous	75
Potassium	20
Citrate	10
Total osmolality	245

Table 9: Previous conventional WHO oral rehydration salt composition

Ingredients	Grams/Liter
Sodium chloride	3.5
Glucose anhydrous	20
Potassium chloride	1.5
Trisodium citrate	2.9
Total weight	27.9

Table 10: Previous conventional WHO oral rehydration salt osmolality

Ingredients	mmol/Liter
Sodium	90
Chloride	80
Glucose anhydrous	111
Potassium	20
Trisodium Citrate	10
Total osmolality	311

Role of Rice-based Oral Rehydration Salt in the Management of Acute Diarrhea

The effectiveness of ORT in reducing the diarrhea-related mortality has been established in clinical as well as community settings. ORT means suitable drinks other than WHO ORS used in the management of acute diarrhea. WHO launched a global diarrheal disease control program [control of diarrheal diseases (CDD)] in 1978 with close collaboration of UNICEF, UNDP and World Bank.

The short-term objective of WHO global CDD program involving a concentrate attack on diarrheal diseases was to endeavor to reduce childhood mortality due to diarrheal dehydration and malnutrition through the widespread implementation of ORT and improved feeding practice.

Oral rehydration fluid used in ORT should preferably have those that contain boiled starch such as rice. Ideally this drink contains starches or sugar as a source of glucose and energy, some sodium and preferably some potassium. Food-based fluid had been recommended for the purpose of ideal ORT and has the advantage of providing nutrients while replacing fluid lost during diarrhea.

In rice ORS, glucose is replaced by rice powder not just adding rice powder to ORS. Glucose has an osmolality of 111 mmol/L increasing the osmolality of ORS to 311 (Table 10), whereas rice has osmolality of 10–20 mmol/L which significantly lowers the total osmolality in oral saline (210 mmol/L) (Table 11) even lower than WHO reduced osmolality ORS (245 mmol/L). Therefore duration of diarrhea and stool output is significantly reduced due to increased absorption of intestinal fluid. Rice being complex carbohydrate (starch) is broken down slowly in to glucose as it travels through intestine which reduces sudden increase of osmotic load and thereby reduces gastrocolic reflex and increases total gut transit time which is associated with significantly early clinical recovery. Comparison of rice-based ORS is given in Table 11.

In comparison to glucose ORS, rice ORS has additional carriers apart from glucose for intestinal transport of fluid. Glycine and amino acid obtained from protein present in rice also act as carriers for intestinal absorption of glucose in addition to glucose obtained from digestion of starch present in rice.

- Due to decreased osmolality of rice ORS, it can be taken in high volume (up to 80 g rice powder) present in rice ORS against up to 20 g glucose present in WHO ORS without causing discomfort and osmotic diarrhea
- Apart from decreasing fluid loss from diarrhea and replacing lost electrolytes, rice-based rehydration preparations have the advantage of providing more calories while reducing the osmotic load in the intestine. Other cereal-based ORT, like maize-based ORT, has been found successful in Ghana where maize is their staple food.

Rice being staple food in developing countries and being easily available is also culturally acceptable.

Published studies have also demonstrated reduced vomiting associated with diarrhea and less requirement of medical supervision of diarrheal patient in comparison to management of diarrhea with glucose ORS.

Disadvantages

- It should be cooked before drinking. Once prepared, it cannot be kept for more than 6 hours in room temperature as it undergoes fermentation
- Costlier than glucose ORS.

WHO ORS has little impact on the nutritional consequences of diarrhea. Studies have shown that ORT combined with continued feeding greatly reduces diarrhea-related mortality among infants and children. Recognizing the role of feeding during diarrhea, food-based fluids, like rice ORS, have been advocated in the management of acute diarrhea to serve the dual purpose of providing nutrients while replacing lost fluids and electrolytes.

All ORS are available in health centers and also in shops. The effectiveness and importance of ORT in the management of acute diarrhea is universally acknowledged.

Oral Zinc in Treatment of Acute Diarrhea

Clinical Effect of Zinc in Treatment of Acute Diarrhea

- Short-term effects:
  - It reduces stool volume
  - It shortens duration of diarrhea

Table 11: Rice-based oral rehydration salt

Composition		Osmolality	
Ingredients	**g/L**	**Component**	**mmol/L**
Rice powder	50	Rice powder	10
Sodium chloride	3.5	Sodium	90
Potassium chloride	1.5	Trisodium citrate	10
Trisodium citrate	2.9	Chloride	80
Total weight	57.9	Potassium	20
		Total osmolality	210

  - It reduces the severity of diarrhea
  - Prevents growth faltering.
- Long-term effects:
  - Reduces the incidence and duration of next attack of diarrhea
  - Reduces hospital admission for diarrhea
  - Reduces number and duration of LRTI episodes
  - Reduces hospital admission for LRTI (pneumonia)
  - Net gain in length
  - Increases appetite.

WHO recommends oral zinc at a dose of 20 mg/day for children elder than 6 months of age and 10 mg/day for children younger than 6 months for 10 days, starting as early as possible after onset of diarrhea.

Occasionally zinc may cause vomiting in children; in that case, zinc should be postponed until vomiting stops. If the child vomits after giving zinc tablet, wait for an hour, when the child settles, give another dose.

Zinc is available as dispersible tablet and in liquid form for oral intake. It is preferred to give zinc in tablet form during diarrhea because of:

- Its low cost
- Easy to distribute and store
- Easy for the caretaker to count the dose
- Longer shelf life.

Zinc tablet should be dispersed in water where it dissolves readily. Zinc tablet should not be mixed with juice or any other liquid. However, a spoonful of ORS or breast milk can replace a spoonful of water. Other fluid is not recommended. In the recommended dose of zinc, there are no reported adverse effects; nonetheless if the child is vomiting, it is recommended to settle the child first.

Rotavirus Vaccine

Immunization with RV vaccine has made a breakthrough in the management of acute diarrhea. Due to large disease, burden of RV GE in children prevention by vaccination has been advocated for both developing and developed countries (for details *see* Chapter 14).

Use of Probiotic in Acute Infectious Diarrhea

Studies currently demonstrated that administration of probiotic *Lactobacillus rhamnosus* GG (LGG) significantly shortens the duration of acute RV diarrhea by a mean of 40 hours, but duration of diarrhea of any other etiology was not affected. Probiotic administration also shortens the time necessary for intravenous rehydration by a mean of 18 hours demonstrated in a study. Probiotics reduce the number of diarrheal stools and the duration of the diarrhea by approximately 1 day. No obvious adverse effects of the probiotics so far have been reported. In some countries, ORS are fortified with probiotics and zinc, called probiotic ORS containing *Lactobacillus reuteri* protectis and zinc. However, further trials and evidences for efficacy and safety in acute diarrhea are required for its wide use in acute infectious GE.

DYSELECTROLYTEMIA ASSOCIATED WITH DIARRHEA AND DEHYDRATION

Significant loss of electrolytes along with fluid loss may occur in diarrhea, which may complicate diarrhea. Depending on severity and nature of dehydration, electrolytes loss will vary. An example of water and electrolyte loss in severe (10%) dehydration is given in Table 12.

Hyponatremia (Serum Sodium Less than 130 mmol/L)

Sodium Depletion

Inappropriate or more loss of sodium in comparison to water in diarrhea.

Association

Hypovolemia and low urine Na (<10 mmol/L).

Causes

Inadequate Na intake, Na losses in excess of water loss in diarrhea particularly in cholera.

Consequences

When sodium losses exceed those of water, plasma Na falls and is associated with a shift of water from extracellular (EC) space to intracellular (IC) compartments. The increase in ICF leads to increase in brain volume (brain cell swelling) resulting sometimes in convulsion, whereas marked ECF depletion leads to a greater degree of shock per unit of water loss.

Treatment of Hyponatremia Associated with Diarrhea/ Dehydration (If Hyponatremia is not Severe or Symptomatic)

If the patient can drink and condition is not severe (asymptomatic), preferably offer standard WHO ORS, not hypo-osmolar ORS. This is more relevant in diarrhea associated with cholera.

If the patient cannot drink correct dehydration over 24–48 hours with 0.9% sodium chloride or cholera saline, calculate and replace deficit with formula below:

$$\text{Dose of Na (mmol)} = \text{Weight (kg)} \times 0.6 \times (140 - \text{current serum } Na^+)$$

Add potassium when urine output is established: Patients who are acutely symptomatic (convulsion, comatose) serum sodium is usually less than 125 mmol/L, sodium depletion should be corrected quickly as follows:

Use 3% NaCl saline (513 mmol/L or 0.5 mmol/mL or 1 mmol/2 mL). The exact sodium can be calculated (assuming volume of distribution of sodium of 60% of body weight) using the classical formula:

$$Na^+ \text{ deficit (in mmol)} = \text{Weight (kg)} \times 0.6 \times (125 - \text{plasma } Na^+)$$

Table 12: Water and electrolyte loses in 10% dehydration

Nature of dehydration	H_2O (mL/kg)	Na^+ mmol/kg	K^+ mmol/kg	Cl^- mmol/kg
Isotonic dehydration (Na 130–150 mmol/L)	100–120	8–12	8–10	8–10
Hyponatremic dehydration (Na<130 mmol/L)	100–120	10–12	8–10	10–12
Hypernatremic dehydration (Na>150 mmol/L)	100–120	2–4	0–4	2–6

For example, in a 10 kg weight child with plasma sodium of 120 mmol/L, the sodium deficit is:

Sodium deficit = 10 × 0.6 × 5 = 30 mmol

One mmol of sodium is present in 2 mL of 3% sodium chloride. 30 mmol of sodium is present in 60 mL of 3% sodium chloride. Therefore, if given quickly within 4 hours, give 3% sodium chloride at 15 mL/hour, so that in 4 hours, 60 mL 3% NaCl can be given.

If the patient is in hypovolemic shock associated with hyponatremia, correct by giving 0.9% NaCl 20 mL/kg quickly (within an hour or two). If the patient cannot drink after reviving from shock, correct dehydration over 24 hours with 0.9% NaCl or polyelectrolyte (cholera saline). Correction of sodium deficit in such case:

- Dose of Na^+ (mmol) = Weight in kg × 0.6 × (140 – observed current Na^+)
- Add potassium when urine output is established
- Stop at plasma sodium of 125 mmol/L, or if plasma sodium is increased to more than 0.5 mmol/hour. If hyponatremia is chronic (>48 hours) then take care not to correct plasma sodium quickly (aim of reaching plasma sodium of 125 mmol/L) as there is risk of central and extrapontine demyelination if corrected rapidly.

In chronic hyponatremia, the neurons adjust to the lower serum osmolality by lowering their own osmolality. Cerebral edema is less severe in such case, but it is the rapid treatment that can cause mortality or central pontine myelinolysis. In such condition, the sodium requirement is determined as follows:

- Sodium deficit (mEC) = (desired sodium – present sodium) × weight in kg × 0.6
- If desired sodium is 125 mmol/L and present sodium is 120 and child weight is 10 kg then sodium deficit is 5 × 10 × 0.6 = 30 mmol
- It should be corrected slowly over 48 hours.

Management of hyponatremia due to other causes and management of hyponatremia as a whole are discussed in fluid and electrolytes management (Chapter 3).

Hypernatremic (Na^+ >150 mmol/L) Dehydration Associated with Diarrhea

Results from either

- *Water deficiency:* More water loss in comparison to sodium loss in diarrhea
- Sodium excess (more than water loss) associated with previous conventional WHO ORS instead of hypo-osmolar ORS.

Management

- History of vomiting and diarrhea
- Thirst and polyuria, neurological symptoms (convulsion)
- Clinical signs of dehydration may be masked as ECF volume is protected by the high Na^+
- Investigations:
  - Serum electrolytes, glucose, urea, creatinine, urine electrolytes and osmolarity.
- Cautious replacement of dehydration with 0.9% or 0.45% NaCl saline over 48–72 hours. For example:
  For a 12 kg child with 5% dehydration, correction in 2 days or in 48 hours is done as follows:
  - Maintenance fluid = 1,100 mL/24 hours
  - Deficit: 5% of 12 kg = 600 mL
  - Replace deficit + maintenance (1,100 + 1,100 + 600 = 2,800 mL) over 48 hours at a rate of 58.3 mL/hour or 14 drops/minute.

Check serum electrolytes every 4 hours. Aim to reduce sodium by not more than 10 mmol/L on every 24 hours, as it may cause brain damage due to cerebral edema resulting from rapid shift of water from extracellular to intracellular brain tissue.

Hypokalemia associated with diarrhea (Ka^+ <3.5 mmol/L):

- Ensure that the sample is not contaminated
- If K^+ is less than 2.5 mmol/L, electrocardiography (ECG) changes as normally evident (ST depression + U waves and inverted U)
- Dysrhythmia
- *Neuromuscular*: Weakness, hypotonia, hyporeflexia, paresthesia, the child is not able to walk.
- *Gastrointestinal*: Ileus, constipation, abdominal distension with feeding difficulties, more associated with malnourished children
- If symptomatic or ECG changes give IV potassium 0.2 mL/kg (maximum 40 mmol/L). If more required, obtain central access and give 0.5 mL/kg with ECG monitoring. If symptomatic, give a slow bolus, otherwise infuse over 1 hour.
- Oral supplements 2 mmol/kg can be given.

PERSISTENT DIARRHEA

The diarrhea that follows an attack of acute episode and continues for more than 2 weeks is defined as persistent diarrhea (PD). The incidence varies from country to country. In Bangladesh, the incidence is about 7% (from last available published report), while in Ethiopia about 27%. Although PD follows acute diarrhea, which has infectious origin, intestinal pathogens are rarely isolated from stools of patients with PD. With the advancement of management and investigations, acute diarrhea is not considered to be dreadful to treat, when rehydration fluid and appropriate antibiotics are available. But considerable difficulties are encountered to manage a case of PD, because of multiple pathophysiological changes occurring in gastrointestinal system. Compared with acute diarrhea, dehydration management has little role.

Children presenting with PD have associated complication and overall management is not straight forward and remains problematic as actual cause of PD is unclear. Various anatomical and functional derangements have been demonstrated in cases of PD. Nevertheless, the majority of cause remains ill understood and case fatality rate may be as high as 45% or even 70%. Studies have been demonstrated that the incidence of PD is higher in malnourished children. Although the proportion of PD patients is much lower than acute diarrhea, death due to PD is more than half (52%) of total diarrheal deaths.

Compared with acute diarrhea, dehydration has a limited role and dietary manipulation remains the cornerstone of successful management of PD. In order to establish a proper dietary regimen for PD patients, it is essential to know the probable factors that determine the PD.

During PD, the malabsorption of nutrients attributeds to:

- Loss of brush border with brush border enzyme deficiency with disaccharidases including lactase deficiency resulting in lactose intolerance
- Small intestinal bacterial overgrowth
- Derangement of bile acid metabolism
- Mucosal injury associated with cow's milk protein (CMP) sensitivity enteropathy
- Severe protein energy malnutrition associated with PD causes reduction of brush border and pancreatic enzymes due to atrophy of intestinal mucosa and pancreatic enzyme reduction.

MANAGEMENT

Dietary management remains the principal therapy or the management of PD along with treatment of systemic infections. Lactose intolerance and CMP enteropathy can be managed with cereal-based diet. Nutrient absorption is substantially reduced in PD, and rice-based (complex carbohydrate instead of monosaccharide or disaccharide) has been effective in studies. Rice suji, a local and simple cereal-based lactose-free inexpensive diet has been found to be a successful therapeutic diet for management of PD. Difficult cases may need smashed green banana recipe, soya-based diet or hypoallergenic diet like comminuted chicken soup or semielemental diet like "pregestimil." Antibiotics may be needed in a few cases to treat abdominal bacterial overgrowth of infection. Table 13 shows some useful diet in PD. Composition of mineral mixed and vitamin mixed are given in Tables 14 and 15.

Due to complete and various changes in the digestive and absorptive capacity of the gastrointestinal tract during PD, a simplified algorithm of management approach is considered to be the most rational therapy (Flow chart 1). Choices of dietary ingredients, their availability, and simplicity of preparation, inexpensiveness and most importantly effectiveness remain critical elements of dietary therapy.

The stepwise management of persistent PD is as follows: Initially children are offered milk-based formula (milk suji). If it fails to improve within 3 days, then non-milk diets are given in the order *Rice suji → Green banana → Soya → Comminuted chicken soup (CCS) → and finally combined lactose* free, *CMP free, protein hydrolysate and medium chain triglyceride containing pre-elemental diet (pregestimil).* Majority improves with rice suji and boiled green banana diet or CCS and pregestimil.

Use of Zinc in Persistent Diarrhea

The role of zinc supplementation in acute childhood diarrhea is well-established. Nearly all children with PD globally are malnourished. Malnutrition which often includes deficiencies of micronutrients, such as zinc, may contribute to increased severity and duration of diarrhea as well as diarrhea-associated mortality. There are evidences to suggest that zinc supplementation improves PD and should be used as part of standard case management of childhood PD.

The mechanism involved in improvement of PD by zinc supplementation includes:

- Improved mucosal integrity as evidenced by improved increased mucosal permeability, particularly in malnourished children
- Improvement of immune function, especially cell-mediated immunity and increased production of secretory immunoglobulin A
- Early repair of damaged intestinal mucosa.

Zinc supplementation should be given as 20 mg of elemental zinc for a period of at least 2 weeks.

CHRONIC DIARRHEA

Although the terms persistent diarrhea, chronic diarrhea (CD) and malabsorption are used interchangeably and may overlap each other, strictly speaking they are different entities.

DEFINITION

Chronic diarrhea is defined as diarrhea lasting for more than 14 days without having acute onset. CD refers to primarily conditions associated with abnormal stool which continues or recurs to occur over several months. Dehydration is rare.

In contrast to PD, which has acute onset, CD is usually of noninfective origin.

Malabsorption is characterized by association of diarrhea, abdominal distension and failure to thrive due to suppressed intestinal absorption of dietary constituents with excessive fecal nutrient loss.

Although CD usually occurs as direct consequence of malabsorption, which in turn; may cause failure to thrive (FTT) and malnutrition, the CD may also occur without malabsorption like food intolerance, irritable bowel syndrome (IBS), toddler diarrhea, etc. without causing malnutrition.

Table 13: Easily digestible, protein and calorie rich non-milk diet from locally available food used in persistent diarrhea

Rice suji		Green banana recipe		Comminuted Chicken Soup (CCS)	
Ingredients	**Amount**	**Ingredients**	**Amount**	**Ingredients**	**Amount**
Rice powder	60 g	Green banana (medium size)	1 pc	Minced chicken	8 piece (90 g)
Egg white (albumin)	100 mL (4)	Puffed rice	1 tsf	Soybean oil	4 tsf (20 mL)
Soyabean oil	30 mL	Glucose	3 tsf	Glucose	6 tsf (30 g)
Glucose	35 g	Soybean oil	2½ tsf	Green papaya	1 pc (15 g)
Salt	1 g	Egg white	2 pc	Onion	1 pc (20 g)
Vitamin mix	140 mg	Salt	As required	Salt	½ tsf
Mineral mix	20 mL	Drinking water	2 glasses	Water	4 glasses (1 Liter)
Water	Up to 1,000 mL				
Cooked volume	1,000 mL				

Table 14: Composition of mineral mix solution	
Substances	**Amount**
Potassium chloride	89.5 g
Tripotassium citrate	32.4 g
Magnesium chloride	30.5 g
Zinc acetate	3.3 g
Copper sulfate	0.56 g
Potassium iodide	5 g
Calcium lactate	300 mg
Water	100 mL
Note: 20 mL of mineral mix is added to 1 liter of all form of liquid diet.	

Table 15: Composition of vitamin mix solution	
Vitamins	**Amount**
Thiamin (B1)	2.0 mg
Riboflavin (B2)	5.0 mg
Pyridoxine (B6)	3.0 mg
Folic acid	5.0 g
Ascorbic acid (Vit C)	125 g
Note: 140 mg of mineral mix is added to 1 liter of all form of liquid diet.	

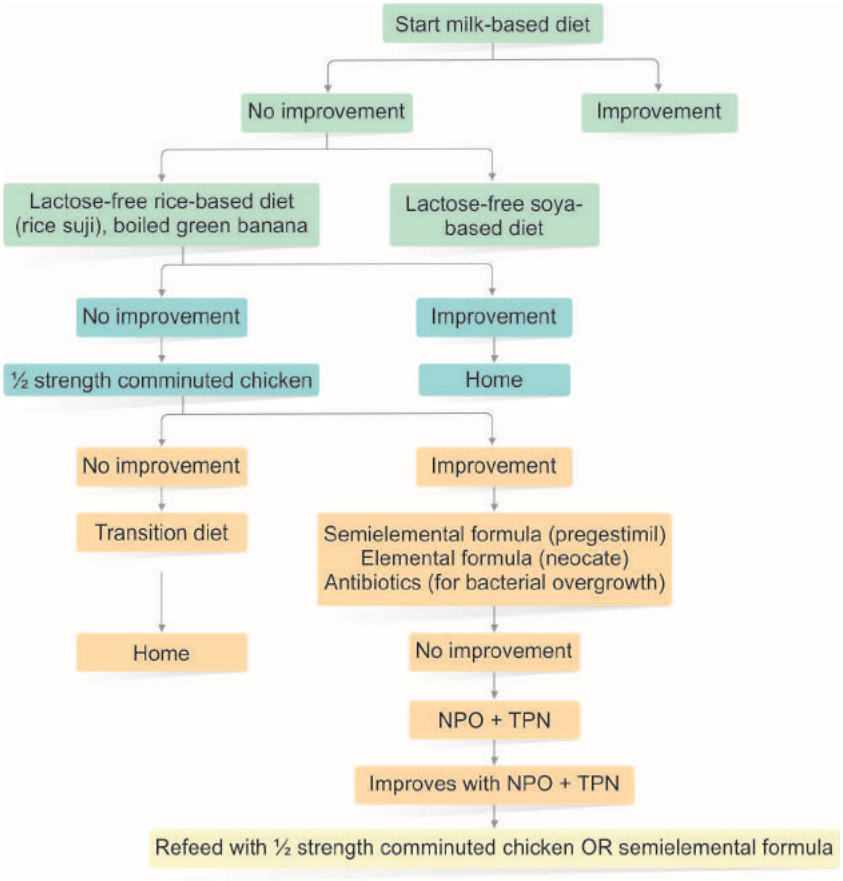
Pathophysiology of CD involves:

- Decreased gastrointestinal absorptive capacity, e.g. celiac disease
- Osmotic diarrhea, e.g. lactase deficiency
- Secretory diarrhea (rare), e.g. vasoactive intestinal peptide producing tumor.

CAUSES

- Age 0–24 months:
  - Malabsorption, e.g. postenteritis syndrome due to lactose intolerance, cystic fibrosis (CF), celiac disease.
  - Food hypersensitivity, e.g. CMP.
  - Toddler diarrhea
  - Excessive fluid intake
  - Protracted infectious GE
  - Immunodeficiency
  - Hirschsprung disease
  - Congenital mucosal transport defect
  - Autoimmune enteropathy
  - Tumors (secretory diarrhea)
  - Fabricated illness.
- Older children:
  - Inflammatory bowel disease (IBD)
  - Constipation (spurious diarrhea)
  - Malabsorption

Flow chart 1: Algorithm of dietary management in persistent diarrhea



Source: Modified from Akbar MS et al. J Trop Paediatr. 1993;39:332-9. *Abbreviations*: TPN, total parenteral nutrition; NPO, nil per os

- Irritable bowel syndrome
- Infections including bacterial overgrowth and pseudomembranous colitis
- Laxative abuse
- Excessive fluid intake
- Fabricated illness.

DIAGNOSIS

History

- Nature and frequency of stool
- Presence of undigested food
- Relationship to diet changes (e.g. weaning), travel
- Stool, blood or mucous.

Examination

Features of malnutrition or other illness, e.g. perianal disease, finger clubbing in CF.

Investigations

- Stool
  - *Inspection*: Microscopy for bacteria or parasites, leukocytes, fat globules (pancreatic disease), fatty acid crystals (diffuse mucosal defects).
  - *Culture*: pH (<5.5 = carbohydrate malabsorption).
  - *Reducing Substances*: (>0.5% = carbohydrate malabsorption)
    - Fecal occult blood (colitis)
    - Electrolytes (↑ Na^+ and K^+ = secretory diarrhea; ↑
    - Cl^- = congenital chloridorrhea).
- Blood: Full blood count (FBC) (↓ Hb = hematinic deficiency/blood loss; eosinophil = food hypersensitivity/parasites).
  - C-reactive protein (CRP)/erythrocyte sedimentation rate (ESR) (inflammatory)
  - Urea and electrolytes
  - Blood gas
  - Radioallergosorbent test (food allergy)
  - Hormone level (vanillylmandelic acid, catecholamine, vasoactive intestinal peptide) for secretory tumors
  - Celiac-specific antibody.
- *Radiology*:
  - Abdominal X-ray
  - Barium enema/meal, e.g. colitis
  - Ultrasonogram of abdomen.
- *Other*:
  - Breath hydrogen test (lactose malabsorption or *Helicobacter pylori* infection, bacterial overgrowth)
  - Gastrointestinal (GI) endoscopy/biopsy (e.g. upper for celiac disease, lower for IBD)
  - Sweat test/genetic testing for cystic fibrosis (CF)
  - Rectal biopsy (Hirschsprung's disease).

TREATMENT

Treat underlying cause. Nutritional intervention if deficiencies are present. Antibiotics are only useful if systemic illness or prolonged infection, e.g. Salmonella, Campylobacter, giardiasis or amebiasis. Rarely, other drug treatment (e.g. loperamide in toddler diarrhea or cholestyramine) may be useful.

MALABSORPTION

Malabsorption is defined as subnormal intestinal absorption of dietary constituents with excess fecal nutrient loss. The prognosis depends on the cause. Reduced adult height, teeth enamel defect and osteoporosis may result from long-term malabsorption.

Presentation

- Diarrhea
- Steatorrhea
- Flatulence
- Failure to thrive/weight loss
- Muscle wasting
- Abdominal distension
- Perianal excoriation
- Delayed puberty
- Features of underlying illness, e.g. abdominal pain in Crohn's disease
- Signs of nutritional deficiency states, e.g. ascites due to hypoalbuminemia.

Causes of Malabsorption

- Intraluminal digestive defects:
  - Carbohydrate intolerance (most common lactose intolerance)
  - Protein energy malnutrition
  - Cystic fibrosis
  - Shwachman-Diamond syndrome
  - Chronic pancreatitis
  - Cholestasis
  - Pernicious anemia
  - Specific digestive enzyme deficiency, e.g. lipase.
- Mucosal abnormality:
  - Celiac disease (subtotal villas atrophy)
  - Short bowel syndrome
  - Dietary protein intolerance, e.g. milk protein allergy
  - Intestinal infection/parasites, e.g. giardiasis
  - Inflammatory bowel disease
  - Abetalipoproteinemia (disorder of lipid metabolism: FTT, steatorrhea, progressive ataxia, retinitis pigmentosa, acanthocytes in blood film)
  - Protein energy malnutrition (subtotal villas atrophy)
  - Intestinal venous or lymphatic obstruction, e.g. congestive cardiac failure, intestinal lymphangiectasia.
- Miscellaneous:
  - Immunodeficiency syndrome, e.g. HIV
  - Drug reaction, e.g. postradiation
  - Bacterial overgrowth, e.g. pseudo-obstruction.

Investigations

- *Initial screening tests*: Full blood count, urine analysis, creatinine, albumin, total plasma protein, Ca^{2+}, PO_4, liver function tests, stool RE/ME, C and S, and pH (<5 indicates carbohydrate malabsorption).
  If diagnosis is unclear, consider:
  - 72-hours fecal fat measurement
  - Fecal α-1 antitrypsin
  - Sweat test

  - Breath hydrogen test (↑ hydrogen in carbohydrate malabsorption or bacterial overgrowth)
  - Serum iron, folate, vitamin B12 assay
  - Clotting screening
- Proximal small bowel biopsy via upper GI endoscopy or swallowed Crosby capsule; relevant to celiac disease
- Exocrine pancreas function tests

Treatment

- Treat underlying diseases, e.g. metronidazole for giardiasis
- Supplemental digestive enzymes, e.g. pancreatic enzymes if CF
- Nutritional supplementation to correct deficiencies
- Parenteral nutrition if malabsorption is severe or slow to recover.

TODDLER DIARRHEA

This occurs from 6 months to 5 years. It presents with colicky intestinal pain and increases flatus, abdominal distension, loose stools with undigested food ("peas and carrots" stools). Child is otherwise well. Normal examination and investigations.

Treatment

Reassurance

- *Dietary*: Increase fat intake, normalize fiber intake, decrease milk, fruit juice and sugary drink intake
- Loperamide may be helpful.

PROBIOTIC

DEFINITION

Probiotic: An oral supplement or a food product that contains a sufficient number or viable microorganisms to alter the microflora of the host and has the potential for beneficial health effects.

Prebiotic: A nondigestible food ingredient that benefits the host by selectively stimulating the favorable growth and/or activity of one or more indigenous probiotic bacteria.

Probiotics

These bacteria are fermentative, obligatory, or facultative anaerobic organisms and are typically nonmotile and produce lactic acid. These include members of the genera *Lactobacillus*, *Bifidobacterium* and *Streptococcus*.

Lactobacillus rhamnosus GG, *Bifidobacterium lactis*, *Saccharomyces boulardii* and *Streptococcus thermophilus* are the most studied probiotic bacteria.

Prebiotics

Prebiotics usually are naturally occurring indigestible oligosaccharides which may be added as dietary supplements to foods, beverages and infant formula. Examples of prebiotic oligosaccharides include fructooligosaccharides, galacto-oligosaccharides.

MECHANISM OF ACTION OF PROBIOTICS

Microflora benefits the host by increasing colonization resistance (preventing overgrowth of potentially pathogenic organisms).

Historically, ingested probiotic strains were believed to:

- Adhere to the gut wall
- Block pathogen adhesion and growth
- Give a nonspecific boost to immunity.

USE OF PROBIOTICS IN CURRENT CLINICAL PRACTICE

Acute Infectious Diarrhea

Probiotic in Prevention of Acute Rotavirus Gastroenteritis

Studies currently demonstrated that administration of LGG significantly shortens the duration of acute RV diarrhea by a mean of 40 hours, but duration of diarrhea of any other etiology was not affected. Probiotic administration also shortens the time necessary for intravenous rehydration by a mean of 18 hours. Probiotics reduce the number of diarrheal stools and the duration of the diarrhea by approximately 1 day. No obvious adverse effects of the probiotics have been reported so far. In some countries, ORS are fortified with probiotics and zinc called probiotic ORS containing Lactobacillus reuteri protectis and zinc. Clinical and statistical heterogeneity of the prophylactic interventions precluded drawing clear conclusions about the efficacy of probiotics in prevention of acute infectious GE.

Clostridium difficile

Recent studies have shown *Saccharomyces boulardii* at a dosage of 500–1,000 mg/day (depending on age) for 15 days led to a rapid regression of the symptoms in children, and clearance of toxin B and *C. difficile* in most of the children receiving probiotic.

Antibiotic-associated Diarrhea

The antibiotics with which antibiotic-associated diarrhea (AAD) is commonly associated are: Penicillin G and V (3%), Penicillin A and M, amoxyclav, cephalosporins, macrolides, trimethoprim-sulfamethoxazole and erythromycin.

Meta-analyses involving use of probiotic in AAD showed that the use of probiotic reduced the risk of AAD when compared with control.

The summary of the Cochrane review is as follows:

- Probiotics seem to have a positive effect on the incidence of diarrhea, i.e. their use prevented AAD
- However, once the AAD was set in the mean duration of diarrhea and stool frequency was no different with the use of probiotics versus controls
- The probiotic strains that were found to be most effective were Lactobacillus GG and *Saccharomyces boulardii*
- It was seen that the probiotic dose of more than 5 billion CFU/day had a significant impact in preventing the incidence of AAD as compared to the dose of less than 5 billion CPU/day.

Traveller's Diarrhea

The use of probiotics for this disease remains controversial.

ATOPIC DISEASES

Probiotics have been shown to reduce inflammatory cytokines and intestinal permeability in vitro. Such an effect would be

beneficial in allergic disorders, such as eczema, allergic rhinitis and food allergies. The results of these studies are promising, but a definitive role is yet to be confirmed. Beneficial effects found in study results are the followings:

- Lactobacillus GG given to pregnant mothers with atopic history (asthma, eczema allergic rhinitis) and their infants for 6 months after delivery significantly decreases atopic dermatitis in later childhood (2–4 years)
- Infants with cow's milk allergy (CMA) respond positively with probiotic.

Chronic Inflammatory Bowel Disease

In theory, probiotics may be beneficial in the treatment of IBD. It has been proposed that, in individuals with genetic susceptibility to IBD, chronic inflammation occurs in response to commensal digestive microflora because of various inherited defects of innate inflammatory-response pathways. Hence, modulating the commensal intestinal bacterial environment with probiotic supplements may reduce the inflammatory response in patients with IBD.

Chronic Ulcerative Colitis

Probiotic therapy, either alone or along with an adjuvant, may be an effective alternative for some UC patients. Pouchitis is the most frequent long-term complication following pouch surgery for ulcerative colitis. Increased gut bacterial concentration is one of the main risk factors.

VSL#3, a highly concentrated mixture of probiotics, has been shown to be effective in the prevention of pouchitis onset and relapses and may be helpful in patients with mildly active pouchitis.

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) may result from an absent intestinal microbial colonization. NEC in preterm neonates (gestation <33 weeks) with very low birth-weight (<1,500 g), starting probiotic within the first 10 days, with a duration of at least 7 days reduces risk of NEC significantly.

PROBIOTICS IN *H. PYLORI* INFECTION

A recent study indicates that the effectiveness of an eradication therapy regimen can be enhanced by using probiotics. A recent open, prospective trial undertaken in Italy showed that a mixture of nine probiotics and bovine-derived lactoferrin and inulin, as a prebiotic, increased the success rate of eradication of *H. pylori* infection when compared to those treated with triple therapy alone for 7 days.

PREBIOTICS AND PROBIOTICS IN INFANT FORMULA

Prebiotics

The European Commission's Scientific Committee on food concluded that they had no major concerns regarding the addition of oligosaccharides to infant formulas, including follow-up infant formulas (formulas modified especially for 6–12-month-old infants), up to a total concentration of 0.8 g/dL in ready-to-feed formula products.

Probiotics

The overall health benefit efficacy of adding probiotics to infant formula remains to be demonstrated in large randomized controlled trials.

SAFETY OF PROBIOTICS AND PREBIOTICS IN INFANTS AND CHILDREN

Most of the probiotics in the market are nonpathogenic assigned generally regarded as safe—US standards or qualified presumption of safety. Mild abdominal discomfort and flatulence are the only adverse effects reported regularly in most of the trials.

Infections

There are case reports of probiotics being assumed to have caused infection due to accidental contamination of lines with lyophilized powder opened in the ICU in immune incompetent patient or after tooth extraction.

Transfer of Antibiotic Resistance

The danger of transfer of antibiotic resistance from probiotics to pathogenic organism is the field of major concern.

Excessive Immune Stimulation

The cell wall components of the probiotics, especially bacterial species can induce cytokines and cause fever, arthritis and even induce autoimmunity.

GASTROESOPHAGEAL REFLUX AND GASTROESOPHAGEAL REFLUX DISEASE

DEFINITION

Gastroesophageal reflux (GER) is defined as the effortless regurgitation of gastric contents into the esophagus (Fig. 6). Gastroesophageal reflux disease (GERD) is defined as GER associated with sequel including faltering growth.

International consensus defines GERD as GER associated with troublesome symptoms or complications.

The prevalence in infants is between 20% and 40%, higher in children than adult. There is higher prevalence in infants due to transient immaturity of esophagus and stomach and features include:

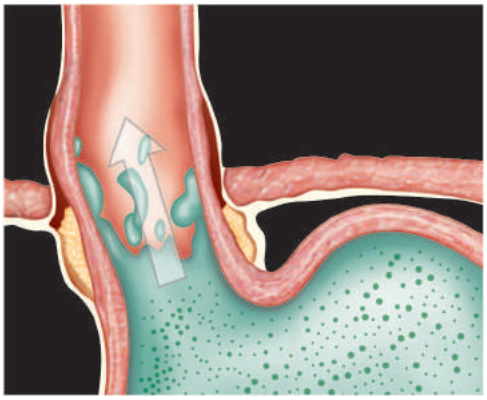


Fig. 6: Gastroesophageal reflux

- Short abdominal esophagus (<1 cm)
- Increased esophageal clearance
- Increased number of lower esophageal sphincter relaxation
- Prolonged gastric emptying.

Most refluxes are functional or physiological, occurring in otherwise healthy well-grown infants. Nevertheless, it carries a significant symptom burden and can cause considerable anxiety, with an estimated prevalence in infants less than 3 months old up to 50%. The natural history is of improvement, with 90–95% of infants being symptom-free by 12 months. Improvement with increasing age is due to:

- Growth in length of the esophagus
- Increased tone of lower esophageal sphincter
- A more upright posture
- A more solid diet
- Symptoms of gastroesophageal reflux disease are given in Tables 16 and 17.

DIAGNOSIS OF GER AND GERD

A diagnosis of functional reflux is usually based on the infant's symptom profile and its impact with further investigation reserved for infants with symptoms in whom diagnosis is not clear or for children with suspected GERD in whom investigations may impact on treatment.

INVESTIGATION FOR GER/GERD

In most cases of reflux disorder, diagnosis is based on clinical assessment without the need for investigations.
Indications are reserved for:

Table 16: Usual manifestation
i. Specific manifestation:
• Nausea
• Vomiting
• Regurgitation
ii. Symptoms related to GERD complications:
• Symptoms related to iron deficiency anemia
• Dysphagia (direct symptom of esophagitis or from stricture formation)
• Weight loss and/or failure to thrive
• Epigastric or retrosternal pain
• Noncardiac angina-like chest pain
• Belching, postprandial fullness
• General irritability
• Irritable esophagus
Abbreviation: GERD, gastroesophageal reflux disease

Table 17: Unusual manifestation and associations
• GERD related to chronic respiratory diseases (bronchitis, asthma, laryngitis, etc.)
• Sandifer-Sutcliffe syndrome
• Apnea, apparently life-threatening event and sudden infant death syndrome
• Congenital and/or central nervous system abnormalities
• Intracranial tumors, cerebral palsy, psychomotor retardation
Abbreviation: GERD, gastroesophageal reflux disease.

- Where there is doubt about diagnosis
- Empirical therapy is considered to be failed
- Extraintestinal manifestation, i.e. FTT, apnea, asthma, in which reflux is suspected to be a considerable factor.

The investigation of reflux is difficult but multiple investigative modalities are available. The clinical situation and the clinical question being asked determine the usefulness of each test, and may therefore affect the sensitivity and specificity of the test.

- The *24-hours pH study* is currently considered to be the gold standard investigation for assessing acid reflux
- *Barium meal* to exclude hiatus hernia or distal obstruction (e.g. malrotation)
- *Barium swallow*: A barium swallow can help to exclude surgical causes of vomiting (esophageal stricture or malrotation)
- *Scintography*: In some centers, it has a sensitivity of up to 59% and specificity up to 100% for GER and can be used to investigate aspiration of isotope into the lungs and assess gastric emptying.
- *Intraluminal impedance*: It measures the reflux from retrograde flow of liquid bolus as it passes through the esophagus toward the oropharynx.

pH Study

The pH probe is designed to measure acidity (acid reflux) in the lower esophagus. The pH probe is an electrode passed through the nose and down to the throat to sit above lower esophageal sphincter. An acid reflux episode is defined as an esophageal pH of less than 4 for a specified minimum duration of usually 15–30 seconds. A set period of usually 24 hours is recorded with note made of the numbers of episodes and the relationship of reflux to eating, position, sleeping or activity and specially symptoms. The most sensitive measure of acid reflux on pH study is the reflux index. This is defined as the percentage of time that esophageal pH is less than 4. Reflux index is normal up to 12% up to 12 years of age and up to 6% thereafter.

A pH study has a sensitivity of 93–96% in identifying acid reflux in patient with duodenitis with esophagitis on endoscope. In interpreting pH study, the most reliable marker of acid reflux is reflux index, which has reported sensitivity and specificity of more than 94% (Figs 7 and 8).

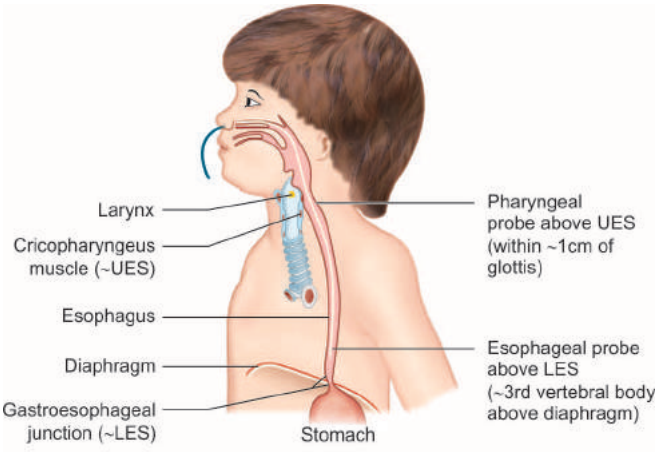


Fig. 7: Diagram showing correct placement of pH probe for 24-hour double-probe pH testing

Fig. 8: A child undergoing 24-hours pH study

Limitation of Test

- pH studies are unable to detect anatomical abnormalities, e.g. stricture, hiatus hernia, etc.
- Nonacid reflux will not be detected
- There is potential for technical difficulties
- pH provides no objective measures of inflammation.

MANAGEMENT OF GER/GERD

Although physiological GER has no adverse effects on health and self-limiting, nevertheless, it carries a significant symptom burden and can cause considerable anxiety to the parents.

In addition to vomiting, increasing cry, peak being at second month of life for 2–2.5 hour/day, decreasing thereafter ~1 hour/day in infant of 4–12 months is a distressing problem.

The practical management of functional reflux is an important issue for pediatricians, primary care physicians and allied healthcare professionals.

There is no evidence to support the pharmacological management of functional reflux as a first-line strategy. The principles of "*primum non nocere*" i.e. "first, do no harm" should apply in the management of functional reflux and conservative measures should be tried before H_2 antagonist, proton pump inhibitor or prokinetic agents are introduced.

TREATMENT OF GER OR MILD GERD

Normal steps in the management of mild conditions are usually nonpharmacological and may involve:

- *Reassurance* of parents/carers emphasizes its benign natural history.
- *Positioning*: Supine position at 40°, which is found to be more effective than other positions in multicenter trial.
- *Thickening of feeds*: The hydrolyzed formula in formula-fed infants and to breastfed infants. Cereal-based thickener can be used in infants under 1 year age to thicken feeds. For those infants being breastfed, the thickener can be given as a paste prior to feed.
- *Exclusion of cow's milk*: A period of cow's milk exclusion can be tried.
- *Antacids*: (Alginate formulation, for example, Gaviscon infant) Form a "raft" that floats on the surface of the stomach contents which should reduce reflux and afford some protection to the esophageal mucosa. That alginate preparation containing aluminum should be avoided in chronic use wherever possible, especially in neonates, infants and children with renal impairment, because of accumulation leading to an increased plasma-aluminum concentration.

MANAGEMENT OF MODERATE TO SEVERE GERD

Drug treatment in this group of patients usually combines a prokinetic agent with an appropriate acid suppressant. With the withdrawal of cisapride and the adverse effects associated with metoclopramide, the common prokinetic agents include domperidone and erythromycin.

Prokinetic Drugs

Domperidone: Domperidone is a peripheral D2 receptor antagonist that increases motility and gastric emptying and decreases the post-prandial reflux time. The immaturity of nervous system and blood brain barrier in premature babies, infants and children may make these patients more susceptible to neurological symptoms (extrapyramidal and oculogyric crisis). However, in clinical trials, no adverse events were documented.

Erythromycin: Erythromycin is a macrolide antibiotic which has demonstrated an increase in GI motility by acting directly up on motilin receptors in GI tract. Motilin is a hormone secreted in to the GI tract during times of fasting and has a function on smooth muscle contraction.

Effects of erythromycin which appear to be dose-dependent and side effects can be minimized without diminishing motility at dose of 1–3 mg/kg.

Adverse effects at these doses, although rare, can be severe. They include GI upset, hepatotoxicity, anaphylaxis, arrhythmias and infantile hypertrophic pyloric stenosis.

Metoclopramide

Metoclopramide is a dopamine antagonist which increases motility and accelerates gastric emptying by enhancing the GI tract's response to acetylcholine. It also increases the lower esophageal sphincter tone.

It is also associated with several serious adverse effects including drowziness, restlessness, galactorrhea as well as extrapyramidal reactions such as dystonia and tardive dyskinesia.

Withdrawal of Cisapride

Cisapride's potential side effects are prolonging QT interval which can lead to adverse events such as *torsades des pointes* or a clinical significant degree of heart block.

Gastric Acid Suppressants

Histamine-2-receptor Antagonists

Ranitidine*:* Ranitidine is the drug of choice in this group of drugs. It works by inhibiting the H_2 receptors of the gastric parietal cells. Side effects, although rare, can include fatigue, dizziness, diarrhea and other gastrointestinal disturbances.

Efficacy of ranitidine is greater in cases of mild esophageal gastritis than in severe ones where a proton pump inhibitor may be of more benefit.

Oral ranitidine given 2–3 times in a day provides symptomatic and endoscopic symptom improvement in erosive esophagitis. In infants, a three times regimen is often required as intragastric pH returns to its baseline level within 5 hours.

Tolerance of the antisecretory effects of histamine-2-receptor antagonists develops quickly, and the possible occurrence of rebound hypersecretion must be taken in to account up on discontinuation of the drug and a reduction in a stepwise manner is recommended.

Proton Pump Inhibitors

Lansoprazole, esomeprazole and omeprazole are Proton pump inhibitors (PPIs) that inactivate the H^+, K^+ ATPase pump in parietal cells inhibiting gastric acid secretion and increasing the intragastric pH.

Proton pump inhibitors are well-tolerated by patients with the commonest side effects including mild to moderate headaches, abdominal pain, vomiting and diarrhea. Occasional electrolyte disturbances and minor reversible elevation of transaminase levels have also been reported.

Prolonged periods of hypochlorhydria have been identified in neonates as well as adults, resulting in bacterial overgrowth.

Approximately 40% of children prescribed omeprazole will respond to a dosage of 0.73 mg/kg/day and a further 26% to an increase to 1.44 mg/kg/day while approximately 35% will fail at this dose.

Pharmacokinetic studies of omeprazole in children have shown a significant difference in the half-life of the drug in children under 7 years of age and those over 7 years of age. The younger cohort of patients appears to metabolize the drug quicker, and this higher metabolic rate suggests that these patients may benefit from a twice daily regime instead of a single morning dose.

Current treatment options involving PPIs can be limited due to lack of suitable "child friendly" formulation. There is no liquid PPI preparation available, and granule available in sachet has variable absorption and bioavailability.

An extemporaneous liquid formulation of omeprazole in sodium bicarbonate 8.4% can be made or granules in capsules can be mixed with a tea spoonful orange juice or pineapple juice for gastric acid protection before it can be offered to children.

The lansoprazole and esomeprazole FasTab is able to be administered down enteral feeding tubes if necessary, which makes it a viable choice for those infants requiring feed through NG tubes. Various drugs and their doses used in GERD are given in Table 18.

FUTURE TREATMENT OPTIONS

In order to achieve more rapid, potent and sustained degrees of remission, several other drugs have been tried.

Baclofen, a $GABA_B$ receptor agonist, has been used as an add-on therapy with PPIs particularly in cases where there are persisting reflux symptoms. It has been shown to inhibit transient lower esophageal sphincter pressure relaxation as well as possibly increasing the basal lower esophageal sphincter pressure. Further work is required to determine optimum doses required because of the variability in the volume of distribution of the drug due to evolving body composition.

SURGICAL MANAGEMENT

Surgery can play an important role in GERD. Surgical interventions, such as Nissen fundoplication, have usually been reserved for those patients who are resistant to drug therapy or who may require long-term medical management. However, recent advances in surgical techniques, such as endoscopic fundoplication which can be performed on a day case basis, may well allow a surgical intervention to be considered at a much earlier stage of the disease process.

CYCLICAL VOMITING SYNDROME

Although cyclical vomiting syndrome (CVS) was first described in 1983 by Samuel Gee, it was only regarded as a topic of research interest in the last decades. CVS is characterized

Table 18: Drugs used in management of gastroesophageal reflux disease

Drugs	Dose	Frequency
Domperidone	Neonate: 100–300 µg/kg 1 month to 12 years: 200–400 µg/kg 12–18 years: 10–20 mg	4–6 times daily before feeds 3–4 times daily before food 3–4 times daily before food
Erythromycin	3 mg/kg	4 times a day
Metoclopramide	Neonate: 100 µg/kg 1 month to 1 year: 100 µg/kg 1–3 years: 1 mg 3–5 years: 2 mg 5–9 years: 2.5 mg 9–18 years: 5 mg 15–18 years: 10 mg	Every 6–8 hours Twice daily 2–3 times daily 2–3 times daily 3 times daily 3 times daily 3 times daily
Ranitidine	Neonate: 2 mg/kg 1–6 months: 1 mg/kg 6 months to 12 years: 2–4 mg/kg 12–18 years: 150 mg	3 times daily 3 times daily Twice daily Twice daily
Lansoprazole and esomeprazole	Under 30 kg: 0.5–1 mg/kg Over 30 kg: 15–30 mg	Once daily at morning
Omeprazole	Neonate: 700 µg/kg 1 month to 2 years: 700 µg/kg up to 3 mg/kg	Once daily

by persistent or intense vomiting lasting hours to days with symptom-free interval of weeks to months, without identifiable organic cause.

There is significant burden of illness associated with CVS in terms of hospitalization and school absenteeism.

PRESENTATION

- Usual onset between ages 3 and 7 years
- A personal or family history of migraine
- May be an obvious trigger, e.g. infection, emotional stress, excitement
- May be a prodrome, i.e. abdominal pain
- Pallor, lethargy can arise ± fever and diarrhea.

INVESTIGATION

Exclude other causes of recurrent vomiting—especially gastrointestinal, renal and metabolic.

While a variety of treatment options exist which may be directed at one or more of the different phases of the syndrome, no definite treatment has been shown to be effective in most children. However, in acute symptomatic condition, following management should be done.

MANAGEMENT

If persistent vomiting and/or dehydration:

- Check serum electrolytes
- IV fluids: Rehydrate with 0.45% saline/5% dextrose
- Nasogastric suction often helps
- IV antiemetics after correction of fluid balance.

After recovery, discuss how to avoid triggers, prophylaxis with migraine medicine (e.g. pizotifen) and early administration of antiemetics during prodrome.

Outcome of CVS: Vomiting resolves in 60% children, often very quickly after diagnosis. Significant portion of those, whose symptoms resolve and those in whom symptoms persist, continue to suffer other somatic symptoms like migraine at follow-up.

A biopsychological approach of the management of CVS with the provision of information and explanation may greatly alleviate the burden of illness.

BULIMIA

Binge eating followed by vomiting, diarrhea, dieting and exercise. Most commonly found in adolescent girls with anxiety about body size and shape.

Features

- Vomiting may be induced by gagging, saline or other emetics
- Vague gastrointestinal symptoms are common
- Often dysfunctional family, substance abuse, sexual abuse
- Net loss of enamel on back of teeth and hypophosphatemia.

Refer to expert child psychiatry for assessment, psychotherapy and if required antidepressants.

Rumination

It is the frequent regurgitation of previously ingested food into the mouth. Food may be spat out but without nausea or forceful vomiting. It occurs in GER, mental retardation, bulimia, severe malnutrition, neglect including prolonged hospitalization.

- Assess and manage underlying and associated causes
- If neglect, increase attention especially during feeding
- Supportive measures, e.g. community nurses, social workers.

INTESTINAL PARASITES

Frequent intestinal and extraintestinal parasites, their transmission, tissue affected and disease produced are summarized in Table 19.

AT A GLANCE

Intestinal parasitic infection takes place usually via fecal-oral route. Pet and livestock can be host. Parasitic infection can mimic:

- Inflammatory bowel disease
- Hepatitis
- Sclerosing cholangitis
- Peptic ulcer disease
- Celiac disease

Presentation:

- Abdominal pain
- Diarrhea, dysentery, flatulence
- Failure to thrive and malabsorption
- Abdominal distension
- Intestinal obstruction
- Biliary obstruction; liver disease
- Pancreatitis
- Fever.

Investigations usually done for intestinal parasites:

- Stool:
  - Routine microscopic examination for ova, cyst parasites and leukocytes
  - Culture
- Specific stool staining for cryptosporidiosis
- Stool enzyme-linked immunosorbent assay (ELISA) for giardiasis and cryptosporidiosis
- Blood specific serology, e.g. *Entamoeba histolytica*.
- Duodenal fluid aspiration for microscopic examination and culture for Giardia
- Duodenal villous biopsy for Giardiasis, to exclude celiac disease.

AMEBIASIS

Entamoeba histolytica

Lesions produced by *E. histolytica*.

- Intestinal lesions:
  - Acute intestinal amebiasis
    - Multiple deep and extensive ulcers
  - Chronic intestinal amebiasis
- Extraintestinal lesions:
  - Liver: Amebic liver abscess
  - Lungs:
    - Primary
    - Secondary
- Brain: A small abscess in one of the cerebral hemisphere
- Spleen: Splenic abscess
- Skin: Granulomatous ulceration of the skin adjoining a visceral lesion (Fig. 9).

Table 19: Various parasites and their transmission and disease produced

Parasite	Infective stage	Transmission	Tissue affected	Main disease
		Protozoa		
Entamoeba histolytica	Cyst	Ingestion	Large intestine, liver, lungs, brains, skin	Amebic dysentery
Giardia lamblia	Cyst	Ingestion	Small intestine	Giardiasis
Trichomonas vaginalis	Flagellate	Sexual	Vagina, urethra	Vaginitis
Leishmania donovani	Promastigote	Bite of sand fly	Macrophage system (spleen, liver, bone marrow)	Visceral leishmaniasis
Plasmodium falciparum	Sporozoite	Bite of mosquito	RBCs, liver, spleen, placenta, brain, kidney, lungs, intestine	Falciparum malaria
Other species of plasmodium	Sporozoite	Bite of mosquito	RBCs, liver	Malaria
		Tapeworm		
Taenia solium	Cysticercus in pork	Ingestion	Adults in small intestine, larvae in muscle, brain	Teniasis (adult) Cysticercosis (larvae)
Taenia saginata	Cysticercus in beef	Ingestion	Small intestine	Teniasis
Echinococcus granulosus	Egg	Ingestion	Liver, lungs, brain, heart, spleen, kidney, bone	Hydatid cyst
		Nematodes		
Ascaris lumbricoides	Embryonated egg	Ingestion	Adults in small intestine, migratory larvae in liver, lungs, trachea	Ascariasis
Enterobius vermicularis	Embryonated egg	Ingestion	Adults in cecum, rectum Larvae in jejuna crypts	Enterobiasis
Trichuris trichiura	Embryonated egg	Ingestion		

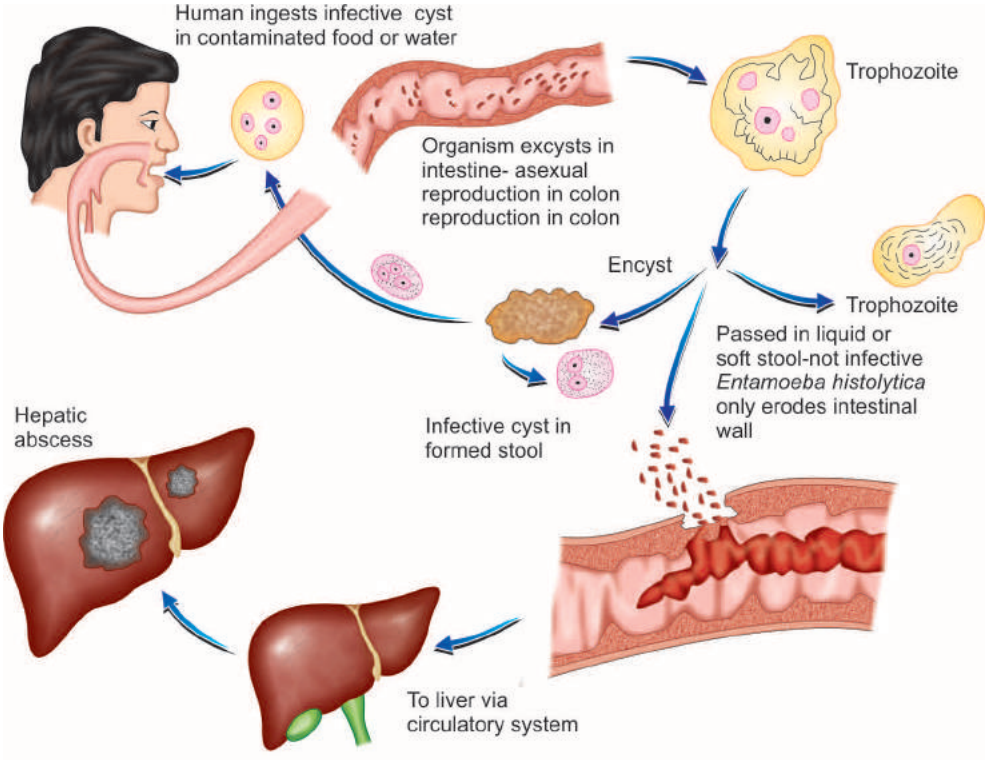


Fig. 9: Diagram showing pathogenesis of intestinal and extraintestinal (liver) amebiasis

Clinical Features

- Asymptomatic colonization
- Dysentery/amebic colitis:
  - Abdominal pain
  - Water, bloody or mucous diarrhea
  - Some may have only intermittent diarrhea alternating with constipation
  - Fulminant amebic colitis may present with profuse bloody diarrhea, fever, widespread abdominal pain, diffuse tenderness and pronounced leukocytosis

- Extraintestinal amebiasis:
  - Amebic liver abscess (occurs months to year after infection) presents with tender hepatomegaly usually without jaundice

Stool microscopic examination: For cyst and trophozoite form of *E. Histolytica.*

- *Serological diagnosis*: Serum antibody against *E. histolytica* more sensitive (>95%) in extraintestinal amebiasis.
- *Radiological imaging*: Hepatic abscess can be demonstrated by ultrasonogram or CT scanning.
- Aspiration under ultrasound guidance may yield "anchovy sauce" pus; rarely amebae are seen in necrotic abscess wall or adjacent parenchyma.

Diagnosis

Stool microscopy: Presence of cyst in stool microscopic examination. Trophozoites *of E. histolytica* may be seen in tissue biopsy of intestine or liver (Fig. 10).

Blood test: Blood-specific serology of *E. histolytica.*

Treatment of Amebiasis (Table 20)

Incidence declining with increased use of metronidazole in amebic and nonamebic dysentery. Antiamebic drugs are classified into two groups: (1) Tissue amebicides and (2) luminal amebicides.

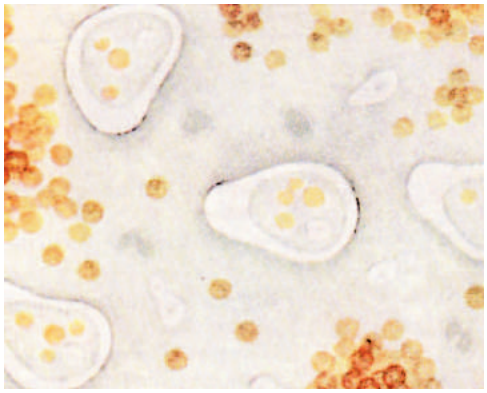


Fig. 10: Stool microscope showing clumped red blood cell and trophozoites of *E. histolytica* containing ingested RBC

- *Tissue amebicides*: This group comprises of 5-nitroimidazoles, chloroquine and dehydroemetine—they are effective in treatment of invasive amebiasis but less effective in luminal clearance. Nitroimidazole including metronidazole, secnidazole, tinidazole and ornidazole are the drugs of choice for treating invasive amebiasis. But nitroimidazole is ineffective against cysts.
- *Luminal amebicides*: Luminal amebicides include diloxanide furoate, diiodoquinol and paromomycin. Diloxanide furoate is the mainstay of treating asymptomatic carriers.

GIARDIASIS

Giardia Lamblia (also known as *G. intestinalis* or *G. duodenalis*)

Giardia is a major cause of diarrhea in children and travellers. It is a flagellated protozoan that infects the duodenum and small intestine of humans and causes varied clinical manifestations which may range from asymptomatic shedding of giardia cyst to symptomatic giardiasis, being responsible for abdominal cramps, nausea, acute or CD, with malabsorption and failure of children to thrive.

Clinical Features

Most infections in children and adult are asymptomatic. Symptomatic infections are more common in children than in adults. Those are as follows:

- Acute diarrhea with sudden onset of explosive, watery, foul smelling stools along with nausea and anorexia
- Abdominal distension
- Flatulence
- Pallor
- Epigastric cramps
- Mild fever
- There is no blood or mucus in stool
- May be seen in PD in up to 30% cases
- Variable degree of malabsorption may occur.

Laboratory Investigation

- Stool R/M/E:
  - Presence of giardial cyst
  - No blood or leukocytes in stool

Table 20: Treatment of amebiasis

		Colitis	Liver abscess
Invasive disease			
Tissue amebicides	Metronidazole Or	35–50 mg/kg/day (in three divided doses) for 7–10 days	35–50 mg/kg/day (in three divided doses) for 7–10 days
	Tinidazole	50 mg/kg/day (once daily) for 7 days	50 mg/kg/day (once daily) for 3–5 days
	Followed by		
Luminal amebicides	Paromomycin Or	25–35 mg/kg/day (in three divided doses) for 7–10 days	25–35 mg/kg/day (in three divided doses) for 7–10 days
	Diloxanide furoate Or	20 mg/kg/day (in three divided doses) for 7 days	20 mg/kg/day (in three divided doses) for 7 days
	Iodoquinol	30–40 mg/kg/day (in three divided doses) for 20 days	30–40 mg/kg/day (in three divided doses) for 20 days
Asymptomatic intestinal colonization			
	Paromomycin or diloxanide furoate or iodoquinone	As above dose	As above dose

- Enzyme immunoassay (EIA) and direct fluorescent antibody test for giardia antigen in stool
- *Duodenal aspirate*: Wet fresh mount is examined for trophozoite (when suspicion is high but stool test is negative for giardia).
- When duodenal aspirate is negative, intestinal biopsy may be considered in presence of any suggestive features like lactose malabsorption or abnormal radiographic findings (edema, segmentation in small intestine), or suggestive setting like absent secretory IgA or hypogammaglobulinemia.
- *Duodenal biopsy*: Subtotal villous atrophy may show giardia in trophozoite form (Fig. 11).

Treatment

All symptomatic cases—acute or PD, failure to thrive and malabsorption syndrome—require drug treatment. Asymptomatic cyst carriers are not treated except in specific situations like for outbreak control or for prevention control or for prevention of spread from toddlers to immunocompromised family members.

First line drugs are nitroimidazoles. Second line alternatives are albendazole, furazolidone, paromomycin and quinacrine.

Nitroimidazole

- *Metronidazole*: 15 mg/kg/day in three divided doses for 5–7 days (80–90% efficacy).
- *Tinidazole*: 50 mg/kg once (>90% efficacy).
- *Nitazoxanide*: Twice daily for 3 days.
  - 1–4 years: 100 mg
  - 4–12 years: 200 mg
  - More than 12 years: 500 mg.

TAPEWORMS (TENIASIS)

T. saginata (Beef tapeworm) and *T. solium* (Pork tapeworm) (Figs 12 and 13).

Host

Definitive host: Man.
Intermediate: Cattle (cow or buffalo).

Clinical Features

- Infection with *T. saginata* may produce:
  - Abdominal pain with intestinal disturbances
  - Loss of appetite
  - Appendicitis or cholangitis caused by migrating segments very occasionally.
- Infection with *T. solium* may produce:
  - Abdominal pain with intestinal disturbances
  - Loss of appetite.
- Infection with the larvae of *T. solium* can cause cystic nodule in subcutaneous tissues and muscles. When brain is affected, they may cause features of encephalitis: Epilepsy, personality change, staggering gait or signs of internal hydrocephalus.

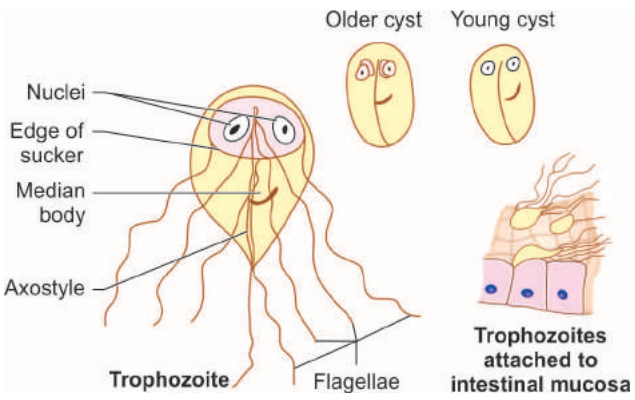


Fig. 11: Cyst (looks like kite) and trophozoite form of giardiasis

Laboratory Investigations

- Stool examination:
  - Naked eye examination for segments or scolex
  - Microscopic examination for eggs
- Perianal swab for demonstration of eggs occasionally
- Diagnosis of cysticercosis:
  - Radiological examination of calcified cysts in muscles
  - CT or MRI of brain
  - Histological examination of a subcutaneous nodule containing cysticerci
  - Serological tests:
    - Fluorescent antibody test
    - Enzyme-linked immunosorbent assay.

Treatment

- Treatment of intestinal teniasis:
  - Praziquantel (20 mg/kg as single dose) or
  - Niclosamide (1 g repeated after 2 hours).
- Treatment of cysticercosis:
  - Praziquantel (50 mg/kg thrice daily for 10 days)
  - Albendazole (15 mg/kg daily for minimum 8 days) is the drug of choice of neurocysticercosis
  - Prednisolone (10 mg 8 hourly for 14 days, starting 1 day before the albendazole or praziquantel).

Prevention

The transmission can be prevented simply by avoiding improperly cooked beef or pork.

DOG TAPEWORM

Echinococcus granulosus.

Host

Definitive host: Dogs, wolves and jackal. Dog is the optimum definitive host.

Intermediate host: Sheep is the optimum intermediate host. Human serves as accidental intermediate host (Fig. 14).

HYDATID DISEASE

Clinical Features

Hydatid cyst is the larval stage of *E. granulosus* found in human tissue. By handling a dog or drinking contaminated water, humans may ingest eggs of *E. granulosus.* Larvae released from the eggs penetrate the wall of the gut, enter the blood stream, and disseminated to deep organs, where they grow to form hydatid cyst.

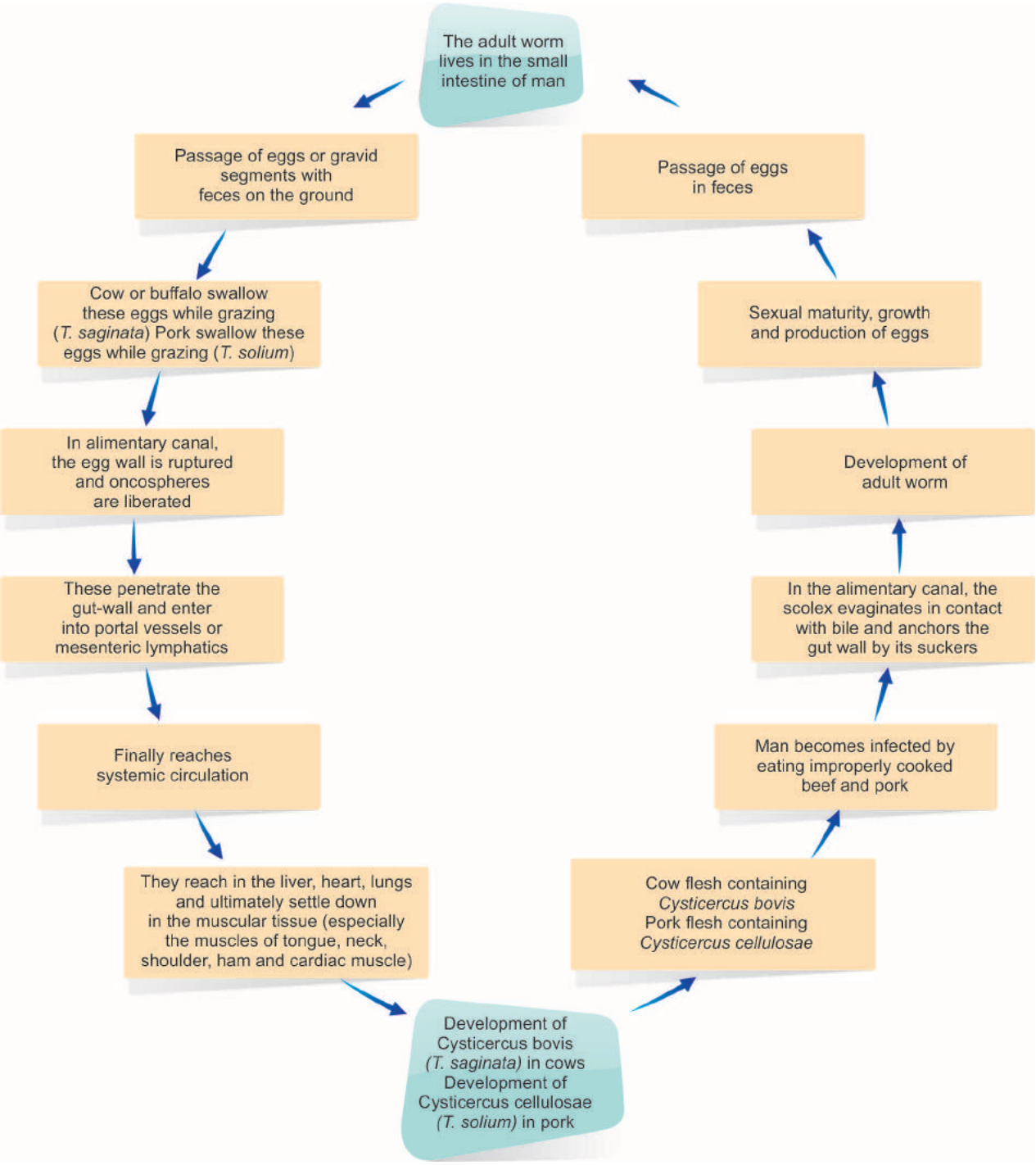


Fig. 12: Lifecycle of *T. saginata* and *T. solium*

Organs affected with hydatid cyst are:

- Liver (75%)
- Lungs (10%)
- Skeletal muscle
- Brain
- Heart
- Spleen
- Kidney
- Bone
- Female pelvic organs—urinary bladder, uterus, fallopian tube and ovary.

Laboratory Diagnosis

- Examination of cyst fluid for the presence of scolices, daughter cysts, brood capsule, or hydatid sand may be conducted on biopsy samples (Fig. 15)
- Serological tests: ELISA, indirect hemagglutination test
- Radiography
- Ultrasonography
- CT scan (Fig. 16)
- Blood examination: Generalized eosinophilia (20–25%)
- Casoni skin test.

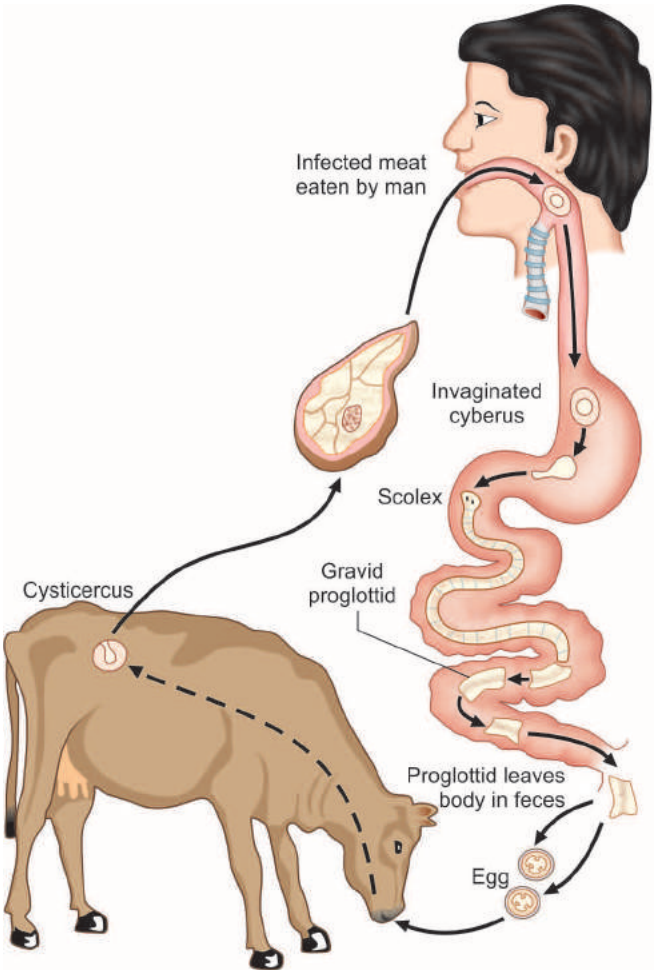


Fig. 13: Lifecycle of *Taenia saginata*

Treatment

- Surgical removal of the hydatid cysts wherever possible
- Cyst cavities are sterilized with 0.5% silver nitrate solution or 2.7% sodium chloride
- In inoperable cases and to reduce infectivity of cysts preoperatively—albendazole (400 mg 12 hourly for 3 months) is indicated
- Praziquantel (20 mg/kg 12 hourly for 14 days) kills protoscolices perioperatively.

Prevention

Careful handling of dogs, handwashing, proper cleaning of raw foods and vegetables with possible contamination of foods, fruits and vegetables, in particular, with dog feces.

HOOKWORM

Necator americanus (new world hookworm) and *Ancylostoma duodenale* (old world hookworm).

Host

Definitive host: Man is the only definitive host.

Intermediate host: No intermediate host.

Clinical Features

- Lesions in the skin:
  - Ground itch (ancylostoma dermatitis).
- Lesions in lungs:
  - Bronchitis
  - Bronchopneumonia (sore throat, bloody sputum, wheezing, cough, headache)
- Lesions caused by adult worm:
  - Microcytic hypochromic anemia
  - Dyspepsia.

Laboratory Diagnosis

Direct Methods

- Examination of stool:
  - Macroscopic examination may show yellowish-pink hookworm in fresh stool
  - Microscopic examination for hookworm eggs.

A direct saline preparation of feces usually shows hookworm eggs.

- Examination of duodenal contents obtained by Ryle's tube may reveal adult worm or egg.

Indirect Methods

- Blood examination for anemia or eosinophilia
- General examination of stool:
  - Occult blood test positive
  - Charcot-Leyden crystal often found.

Treatment

- Mebendazole (100 mg twice daily for 3 days) or
- Albendazole (200 mg twice daily for 2 days) or
- Pyrantel pamoate (10 mg/kg, not to exceed 1 g in a single dose).

Prevention

Proper maintenance of personal hygiene and sanitation and not to walk bare footed as larvae enters the human body by penetrating the skin of bare foot.

ROUNDWORM

Ascaris lumbricoides.

Host

Definitive host: Man is the only definitive host.

Intermediate host: No intermediate host.

Clinical Features

Infection with *A. lumbricoides* (AL) in man is called ascariasis. Two groups of lesions are produced by AL.

- Lesions produced by migrating larvae:
  - Larvae in lungs cause ascaris pneumonia (Loffler's syndrome) characterized by fever, cough, dyspnea
  - Larvae in general circulation may be filtered out to various organs where they may cause unusual clinical symptoms.
- Those produced by adult worm:
  - *Spoliative action*: Contribute to protein energy malnutrition and night blindness by utilizing host's nutrition and vitamin A
  - *Toxic action*: The body fluid of *Ascaris* when absorbed is toxic and may give rise to:

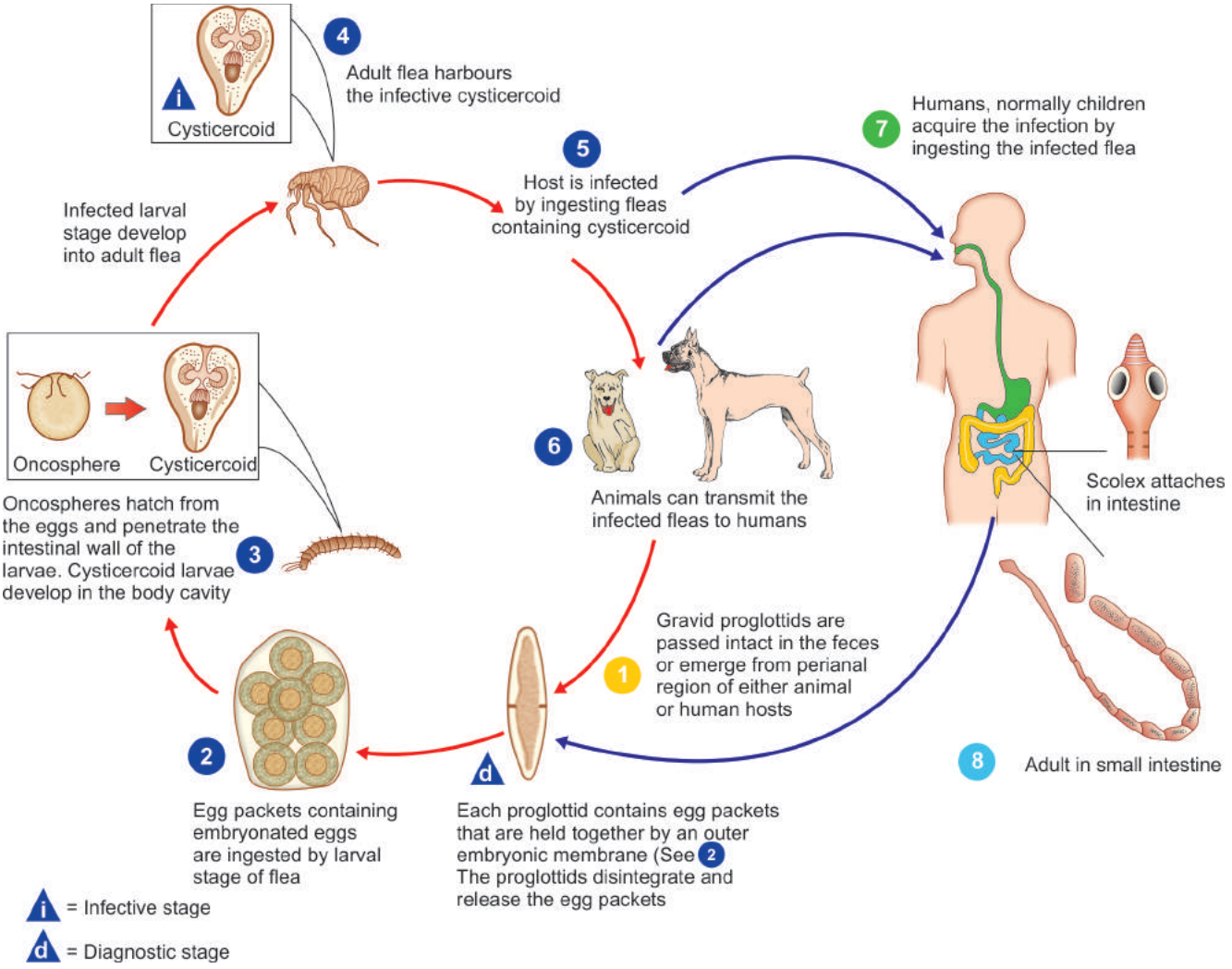


Fig. 14: Lifecycle of *Echinococcus granulosus*

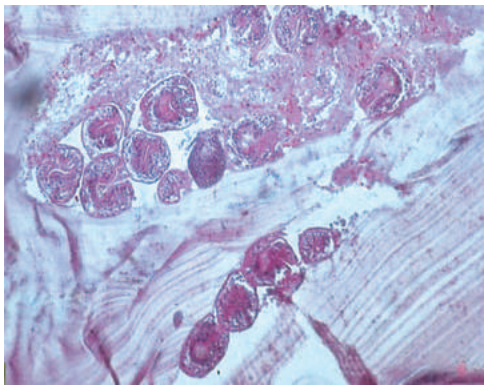


Fig. 15: Photograph of a resected hydatid cyst reveals numerous daughter cysts

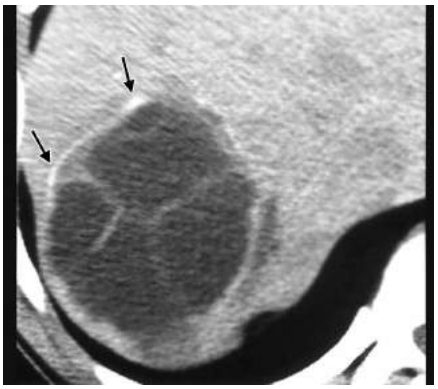


Fig. 16: Hydatid disease: unenhanced CT scan of the liver shows a large, cystic mass with multiple septa

- Typhoid-like fever
- Allergic manifestation (e.g. urticaria, edema of face, conjunctivitis, irritation of upper respiratory tract)

– *Mechanical effects*:
- Intestinal volvulus intussusceptions and obstruction
- Penetration through the ulcers of alimentary

– *Ectopic ascariasis*:
- Migrating adult worms may be regurgitated and vomited, escape through the external nares or rarely, may be inhaled into bronchus causing suffocation
- Wandering ascariasis may enter the lumen of appendix, causing appendicitis
- Invasion of bile ducts, gall bladder and liver may cause obstructive jaundice, ascending cholangitis and liver abscess

- They may occlude the ampulla of Vater and cause hemorrhagic pancreatitis
  - Worms may penetrate the intestinal wall, migrate into the peritoneal cavity and produce peritonitis.

Laboratory Investigation

Direct Evidence

- Stool R/M/E for eggs
- Adult worms may be expelled out through anus or mouth with stool or vomitus.

Indirect Evidence

- Blood examination for eosinophilia, which is present only at the early stage of invasion
- Dermal reaction, scratch test with ascaris antigen.

Treatment

Drugs

- Mebendazole: 100 mg twice daily for 3 days or
- Piperazine: 4 g as a single dose.

Surgery

It is needed in intestinal obstruction that fails to respond to NG suction and sedation.

PIN/THREADWORM

Enterobius vermicularis.

Host

Definitive host: Man is the definitive host (Fig. 17).

Intermediate host: No intermediate host.

Clinical Features

Infection with *E. vermicularis* is known as enterobiasis. Features of enterobiasis are as follows:

- Most common:
  - Intense itching
  - Inflammation of the anal and/or vaginal areas
  - Intestinal irritation
  - Mild nausea and vomiting
  - Irritability
  - Difficulty in sleeping
- Other complications:
  - Appendicitis
  - Urinary tract infection particularly in female child
- Very rare:
  - Multiple ulcers as well as mild intestinal inflammation
  - Abdominal pain.

Laboratory Investigations

- Demonstration of eggs microscopically in samples collected from perianal skin by cellophane tape technique. A perianal swab, moistened with normal saline, is an alternative method for demonstrating eggs
- Finding of adult worms in feces or during inspection of the anal region at the time of commencement of itching.

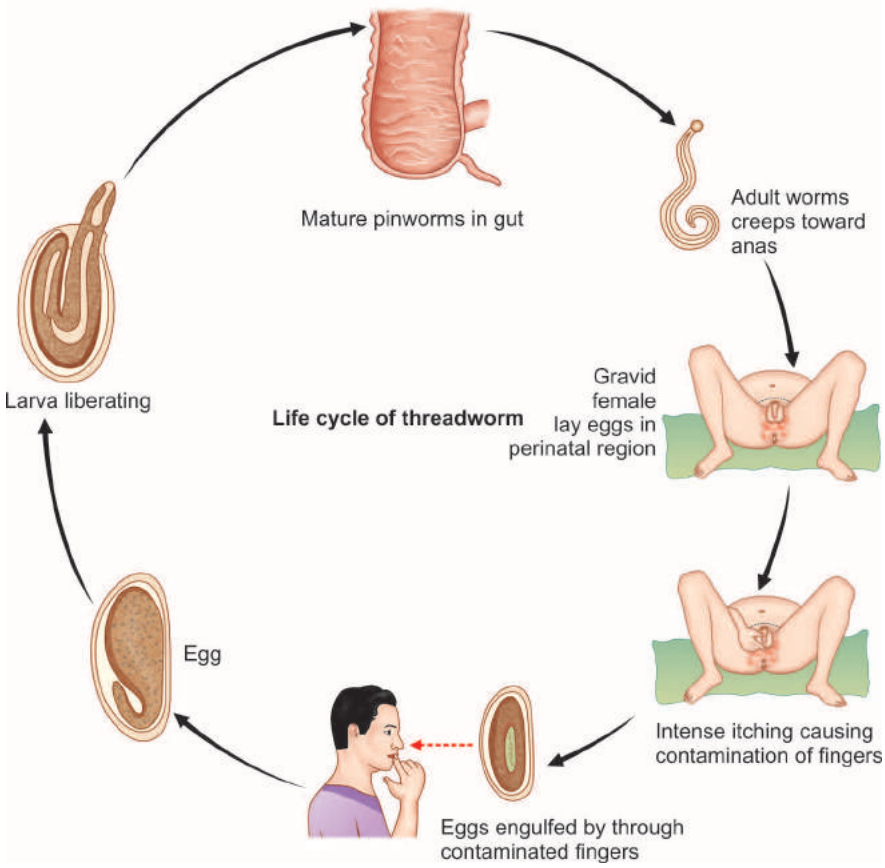


Fig. 17: Summary of lifecycle of *E. vermicularis*

Treatment

Drug Treatment

- *Mebendazole* (100 mg as a single dose, followed by a second dose 2 weeks later) or
- *Pyrantel pamoate* (10 mg base/kg as a single dose, followed by a second dose 2 weeks later) or
- *Piperazine* (4 g in a single dose, followed by a second dose 2 weeks later).

Prevention

Maintenance of personal hygiene (proper cleaning of genitalia) and proper cleaning of the food, bed linens and dresses including underwear and pants.

HELICOBACTER PYLORI INFECTION

- *H. pylori* is a Gram-negative organism. It is a very common infection worldwide. Infection is usually acquired in childhood, but prevalence rates are variable, being highest in developing countries. Most individuals infected with *H. pylori* do not experience symptoms or show signs
- Persistent infection causes an antral gastritis, the most common manifestation in childhood, which may be asymptomatic.

There is a strong relation between *H. pylori* infection and peptic ulceration in both adults and children (Fig. 18).

- *H. pylori* infection is highly prevalent in asymptomatic children and it varies between countries and often within a country as well. Initial infection probably occurs at an early age and prevalence increases with age.
- Ethnic and racial factors, socioeconomic status and living conditions affect the prevalence of infection. Long-term population-based studies are needed to identify the exact prevalence and clinical significance.
- There is a strong evidence for an association between in *H. pylori* infection and antral gastritis and duodenal ulcer diseases in children, but weak or no evidence for an association with recurrent abdominal pain (RAP). There is no correlation of antral gastritis with symptoms.
- Diagnostic tests for *H. pylori* are based either on direct demonstration of the organism or indirectly by detecting a by-product (of the urease reaction) or by demonstrating antibodies. Histopathological identification of *H. pylori* in antral biopsy specimen is by far the best method and is currently regarded as gold standard.

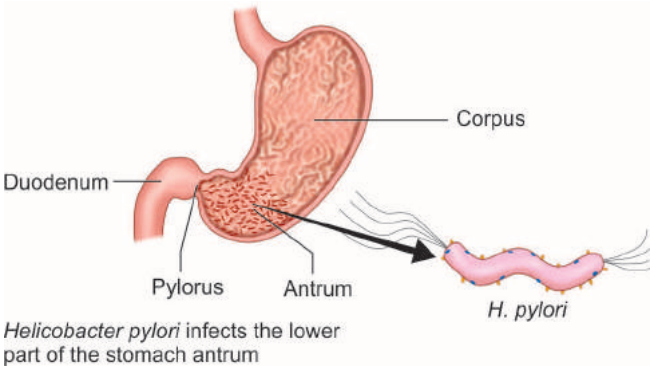


Fig. 18: The site of *H. pylori* invasion

- *Serology (IgG antibody)*: Less specific, with high false-positive rate; positive serology persists for 6–12 months after infection, negative test excludes *H. pylori* infection.
- Serological tests detecting IgG and IgA are possible tools for diagnosis but have many drawbacks. They may be useful for population surveys where invasive tests are infeasible.
- Urea breath test (C-13 breath test, urea level with carbon 13) is a highly sensitive noninvasive test for *H. pylori* infection and can be used even in a field setting. However, it needs to be validated against histopathology, especially in developing countries.
- *Stool antigen testing*: Under evaluation, highly sensitive and specific. Need to stop antibiotics, PPIs and H_2 antagonists before the test (local protocol).
- Endoscopy allows the detection of peptic ulcer disease, gastritis, and esophagitis with direct visualization of the mucosa and biopsy. Lymphoid nodular hyperplasia in the gastric antrum is commonly seen. Biopsies can be sent for culture (low yield), and PCR rapid urease testing can be done (e.g. Campylobacter-like organism test) on biopsies at the time of endoscopy.
- Routine testing for *H. pylori* is not indicated in children or adults. The decision to perform a diagnostic test has often to be linked with a therapeutic proposal.

Treatment

Treatment is indicated for *H. pylori* infection in the presence of ulceration, and although controversial, antral gastritis if *H. pylori* positive.

Treatment of children diagnosed through noninvasive testing is dependent on the clinical situation and factors such as the presence of the *H. pylori* infection in the local population and family history need to be taken into account when the decision is made.

There are several treatment regimens available, but it appears that at least three drugs including two antibiotics and a proton pump inhibitor are required for minimum 7 days for satisfactory eradication.

The most commonly used regiments include omeprazole, amoxicillin and metronidazole or clarithromycin.

Outcome after treatment is variable. Treatment failure usually indicates antibacterial resistance, reinfection within families or institutions or poor compliance.

In developing countries where the prevalence of infection is very high, case for treating or not treating remains unclear. Well planned double blind crossover studies are needed before any evidence-based answer can be provided.

WHIPWORM

Trichuris trichiura.

Host

Definitive host: Human is the definitive host.
Intermediate host: No intermediate host.

Clinical Features

- *Asymptomatic*: Light infection with whipworm often remains asymptomatic.
- *Trichuriasis*: Heavy infection with *T. trichiura* is known as trichuriasis (Fig. 19). Infected children present with:
  - Chronic dysentery

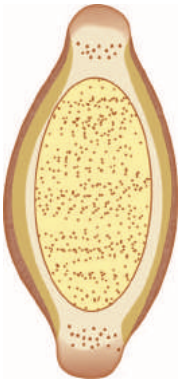


Fig. 19: Ova of *Trichuris trichiura*

- Severe anemia
- Growth retardation
- Prolapsed of rectum may occur in massive trichuriasis.

Laboratory Investigations

- Microscopic examination of a saline emulsion of the stool shows characteristic barrel-shaped eggs
- Sigmoidoscopy or proctoscopy may show adult worms attached to the mucous membrane of the intestinal tract and rectum
- Blood count usually shows eosinophilia.

Treatment

Mebendazole (100 mg twice daily for 3 days) is the treatment of choice.

Prevention

Maintenance of personal hygiene including hand washing after defecation and before feeding of the child and care giver and self-fed child.

ADVERSE REACTION TO FOOD

FOOD ALLERGY

Definition

Food allergy may be defined as abnormal immunological response to food (incidence of 6–8% in children <3 years):

- Immediate allergic reactions involve production of food-specific IgE antibodies
- Seventy percent have a family history of atopy
- Allergy becomes less common as age increases.

Presentation

- Diarrhea ± blood/mucus
- Vomiting
- Gastroesophageal reflux disease
- Abdominal pain
- Failure to thrive
- Eczema.
- Urticaria
- Erythematous rash, particularly periorbital
- Asthma symptoms or anaphylaxis.

Food Intolerance

Adverse reaction to food mediated by nonimmunological responses. More common than food allergy. Presentation is similar to above. May be due to:

- Enzyme deficiency, e.g. lactose intolerance, congenital fructose deficiency
- Pharmacological reactions to agents contained in food, e.g. caffeine, histamine, tyramine, acetylsalicylic acid
- Reactions to food toxins or microbes, e.g. hemagglutinins in soya or mycotoxin present in mould-contaminated cereals.

Management of Suspected Food Allergy or Intolerance

Approach to adverse food reaction
History including diet history and examination. Food diary may be helpful.

Investigations

These may include:

- Radioallergosorbent test or ELISA to detect specific food IgE antibodies
- Serum total IgE or eosinophil count
- Favorable response to dietary elimination of specific suspected food protein and recurrence after challenge
- Allergen skin testing
- *If diagnosis is still in doubt*, then double blind controlled food antigen challenge or small bowel endoscopy and biopsy (nonspecific inflammatory infiltrate) may be helpful
- Severe cases when allergen cannot be identified: Full elimination diet where only a few hypoallergic foods, e.g. lamb, rice, water, pears, are given for 1–2 weeks, followed by gradual reintroduction of increasingly allergenic foods until a food reaction is detected.

Treatment

- *Dietary treatment:* Exclusion of offending food(s) from diet, e.g. egg-free diet. Involve pediatric dietician in the diagnosis and management.
- *Drug treatment:* Regular therapy may have a role (e.g. oral sodium cromoglycate, corticosteroids, antihistamines) or IM adrenaline for emergency treatment of anaphylactic reactions by child himself or parents.

After at least 6–12 months of being symptom-free on exclusion diet, consider food challenge if food allergy. If previous reaction severe, this should only be done in hospital with full resuscitation facilities.

Prophylaxis

In newborns with a first degree relative with confirmed food allergy, exclusive breastfeeding to at least age 1 year decreases incidence. If this is not possible then a hydrolyzed milk formula should be used.

Prognosis of food allergy or intolerance: Depends upon cause. Majority of food allergic reactions resolve by 2 years.

Lactose Intolerance

- Usually due to postviral GE lactase deficiency
- Rarely due to congenital genetic lactase deficiency (primary) or acquired in late teens in certain populations, e.g. Southeast Asian, Afro-Caribbean.

Presentation

- Diarrhea
- Excessive flatus
- Colic
- Napkin rash
- Stool pH less than 5.

Treatment

- Lactose free cow's milk formula (soya milk formula and non-soya milk lactose free formula)
- Postviral GE lactose deficiency usually resolves after within 6 weeks.

COW'S MILK INTOLERANCE AND COW'S MILK PROTEIN ALLERGY

The use of cow's milk by human began 9,000 years ago. Ancient Greek and Roman used to make cheese from milk. Substitutes of human milk started long before modern age of infant formula, which were nutritionally inadequate and carried the risk of disease. As general sanitation improved during later part of 19th century and as the differences between human and mammal milk became better understood, humanized animal milk became common place. Despite many advances in the modification of cow's milk formula, human breast milk remains unchallenged as the gold standard of infant milk.

Hypersensitivity to cow's milk consists of:
- Allergy or immune-mediated
- Intolerance or nonimmune-mediated.

ADVERSE REACTION TO COW'S MILK

About 5–15% of infants show adverse reaction to cow's milk. Adverse reaction to CMP is called hypersensitivity reaction according to World Allergy Organization. Hypersensitivity to cow's milk consists of:
- Immune-mediated, also called cow's milk protein allergy (CMPA) which consists of:
  - Immediate allergy (IgE-mediated)
  - Delayed allergy (non-IgE mediated)
- Nonimmune-mediated, also called cow's milk intolerance.
  - *Nonimmune-mediated* hypersensitivity to cow's milk (cow's milk intolerance, lactose intolerance).

LACTOSE INTOLERANCE

Due to disaccharidase lactase deficiency which may be:
- Congenital, very rare
- *Primary lactose intolerance*: Common due to inadequate lactase (hypolactasia) in brush border of intestinal villi.
- *Secondary lactose intolerance*: Damage of intestinal villi, secondary to viral GE, giardiasis, celiac disease. These are reversible.

Osmotic effect of lactose and fermentation by intestinal flora, causes following symptoms:
- Flatulence
- Perianal excoriation
- Abdominal distension with spasm
- Recurrent abdominal pain.

DIAGNOSIS

- Elimination and rechallenge with cow's milk and observe symptoms
- Stool for reducing substances
- Hydrogen breath test (postlactose exposure).

TREATMENT

Dietary exclusion of cow's milk and other lactose containing food.
- *Immune-mediated:* Cow's milk protein allergy:
  - IgE mediated (immediate)
  - Non-IgE mediated (delayed).

IGE-MEDIATED ALLERGIC REACTION

IgE-mediated (immediate) food allergy affects between 3% and 6% of young children. Cow's milk contain both casein and whey protein. The major whey globular proteins include α-and β-lactoglobulin, which contribute 5% and 10% of total milk protein respectively.

The exact mechanism of sensitization to milk is not known; the impact of environmental factors remains unclear.

Cow's milk protein reaches to the fetus in extremely small amount and when introduction of breast milk is delayed or not possible in postpartum period, it is a common practice to offer a CMP-based formula to newborn infant. This early feed may represent the index of sensitizing event, with subsequent exposure to CMP, may act as booster sensitizing dose with allergic reactions like urticaria, anaphylaxis, etc.

When CMPA is established, other routes of CMP exposure such as skin contact, ingestion or even inhalation of CMP present in mother's milk derived by mother's intake of cow's milk, may cause allergic reaction to infant taking CMP containing mother's milk.

Clinical Features

- Urticaria
- Angioedema
- Severe form: Anaphylaxis (respiratory or cardiovascular arrest).

Risk factors: High IgE and associated asthma.

Diagnosis

Clinical history and investigation.
- *Age of onset:* Less than 3 years, uncommon in second decade of life for CMPA
- *Route*: Usually following oral intake. Rarely after skin contact or inhalation of CMP
- Also transmitted via breast milk (CMP present in mother)
- Allergic symptoms after milk exposure in a child aged less than 3 years (uncommon in children >10 years)
- *Postexposure timing of reaction:* Usually within 20 minutes and always within 2 hours.

Investigations

Positive allergy testing:
- Skin prick test (SPT)
- Specific serum IgE

If:
Positive allergy test + unequivocal history
Or, unequivocal allergy test + equivocal history.
Then supervised incremental oral milk challenge test:

- Usually unblind challenge
- Rarely double blind challenge.

The greater the SPT wheal diameter (>8 mm) or higher specific IgE (>15 KU/L), the greater the probability of allergy to cow's milk. However, severity does not correspond with test values.

Management

Avoidance of cow's milk and cow's milk product.

Allergic response to cow's milk is again of two types, depending upon processing of milk.

1. Heated cow's milk (baked) reactive children (HCRC).
2. Heated cow's milk tolerant children.

Heated cow's milk reactive children have significant larger SPT and higher IgE than heated milk tolerant children.

Treatment

Dietary exclusion and avoidance of cow's milk and cow's milk product.

Heated cow's milk tolerant children may tolerate cow's milk product (baked) better than an HCRC children.

PROGNOSIS

About 19% develop tolerance to CMPA by 4 years of age and 40% by 8 years of age and more than 79% by 16 years of age.

Tolerances usually develop earlier to extremely heated cow's milk, for example, baked food.

Heated cow's milk tolerant children group outgrow their allergy earlier than heated cow's milk reactive children.

Non-IgE mediated cow's milk protein allergy: Although non-IgE mediated but surprisingly more common in atopic children and symptoms improve by CMP exclusion. No validated diagnostic test, which is diagnostic problem.

Diagnosis is done by symptomatic improvement on an allergen exclusion diet followed by a return of symptoms on allergen reintroduction.

Cow's milk protein allergy associated with CMPA sensitive eczema commonly have related symptoms, which may improve with exclusion of cow's milk, and act as clue for role of CMPA in the underlying eczema.

Cow's Milk Protein-induced Proctocolitis

This is a disease of infancy, usually presenting by 2 months of age and represents the benign end of the spectrum of non-IgE-mediated allergy to CMP. Infants usually present with colic-like symptoms and visible fresh blood mixed with mucus in the stool, but otherwise thriving. It is surprisingly more common in, but not exclusive to, breastfed babies whose mothers are ingesting cow's milk or soy protein. Important differential include intestinal infection and anal fissures.

The diagnosis is usually made on the basis of a response to the exclusion of CMP either from the lactating mother's diet and/or by substitution by the extensively hydrolyzed formula (EHF) or amino acid formula (AAF).

Bleeding should resolve within 72 hours although persistent bleeding may only respond to an AAF.

Cow's Milk Protein-induced Enteropathy

Unlike patients with CMP-induced proctocolitis, infants with enteropathy usually have protracted diarrhea, sometimes vomiting. This may result in malabsorption and faltering growth; making a firm diagnosis is therefore very important. The natural history is similar to other forms of non-IgE-mediated milk allergy—that is, presenting in infancy and resolving by 1–2 years. Again, the underlying immune mechanism is unclear, with no association with raised cow's milk-specific IgE but nonetheless cow's milk-specific, involving T cell responses.

The diagnosis is usually made on a combination of clinical response to exclusion and, if necessary, endoscopic small-bowel biopsy.

Food Protein-induced Enterocolitis Syndrome

Food protein-induced enterocolitis syndrome (FPIES) is an acute, cell-mediated, GI food hypersensitivity characterized by severe protracted diarrhea and vomiting, pallor and hypotonia, most commonly following ingestion of cow's milk or soy-based formula (50% infants react to both), although solid food allergens, particularly prone, brief, hilsa fish, rice, have also been implicated. Unlike IgE-mediated reactions, symptoms usually appear between 1 hour and 3 hours after ingestion. Progression can occur to a state of dehydration; hypovolemic shock is described in 20% of cases. The combination of vomiting, lethargy and resulting acidosis in the infant may lead to a false diagnosis of sepsis; however, symptoms typically recur upon introduction of the food. Failure to recognize the link with a dietary allergen may lead to multiple admissions. There may be raised WBC count with predominantly neutrophil. The above findings in association with bloody diarrhea may also lead to a clinical suspicion of infective diarrhea, coagulation defects or intussusception. However, absence of fever, presence of eosinophilic debris in the stools and negative stool cultures can help differentiate these conditions.

The diagnosis is based on clinical criteria with a standardized oral challenge if doubt remains.

Confirmation of resolution requires supervised food challenge with facilities to manage the hypotension and shock that may arise. It is prudent to cannulate children before starting challenges.

Allergic Dysmotility

Cow's milk protein allergy may present with a range of GI motility abnormalities; including vomiting, GER and diarrhea. All GI motility disorders are common in infancy and early childhood.

Cow's milk protein may also trigger transient lower esophageal sphincter relaxations resulting GER episodes.

Cow's milk protein allergy has been suggested as the underlying cause in up to 40% of diagnosed GERD in infants and children. In these patients, a reflux symptom usually resolves within 2 weeks of commencement of a suitable hypoallergenic formula.

The differential diagnosis includes eosinophilic esophagitis, a diagnosis is made by the presence of more than 15 eosinophils in one high-power microscopy of esophageal biopsy.

Cow's milk allergy has also been implicated as a cause of constipation. The neural inflammatory response in the lower GI tract may cause insensitivity of the external anal sphincter so an infant may strain excessively but pass normal consistency stools.

Allergic Eosinophilic Gastroenteropathies

First described by Kaiser in 1937, this heterogeneous group of conditions is characterized by eosinophilic inflammation of the gut. These enteropathies are classified according to the site of the inflammation and it is the depth and severity of inflammation that influences the presenting symptoms.

Eosinophilic esophagitis is clearly associated with the atopic phenotype, the underlying mechanism remains uncertain.

Treatment consists of the supervised dietary exclusion, which may be guided by atopy patch testing, which has been shown to be effective in a subset of younger children.

Cow's Milk Protein "Sensitive" Eczema

Atopic eczema is a chronic inflammatory skin disorder associated with raised serum IgE, allergen sensitization and an atopic family history. A well-established and strong association exists between eczema and IgE-mediated food allergy. Published studies found that up to 64% of infants whose eczema commenced before 3 months of age had a high-risk for concomitant IgE-mediated food allergy to egg, cow's milk and/or peanuts. Most children with IgE-mediated food allergy will have a background of eczema and this possibly reflects a causal role of an impaired skin barrier increasing the likelihood of allergen sensitization by the cutaneous route.

A number of studies have used double blind placebo-controlled food challenges to demonstrate that food allergens, and in particular, CMPs are able to induce delayed eczematous reaction in children even in the absence of an immediate histamine-mediated, component. However, attempts to show that dietary exclusions can objectively influence the course of atopic eczema have remained unconvincing.

While SPT and specific IgE blood testing are extremely helpful in detecting IgE-mediated food allergy in children with eczema, their role in non-IgE-mediated reactions is less clear.

The gold standard test investigation for identifying the possible causative role of a food in the exacerbation of eczema remains an exclusion-reintroduction diet.

Historical points that influence the likelihood that food—for example, cow's milk exacerbating eczema—depends on following facts:

- How severe is the eczema and when did it start?
  Underlying food allergy is more likely in early-onset, more severe eczema, especially if it is resistant to conventional treatment.
- Is eczema being managed appropriately?
  Management regimens are often suboptimal. Consider cumulative number of tubes of steroid preparation used monthly, and potency of steroid.
- Is there a family or personal history of atopy?
  An atopic family history (particularly maternal) is common in food allergies children. Siblings of children with food allergy have an increased chance of having food allergies themselves.
- Are there associated symptoms?
  Consider food allergy in children with eczema and gastrointestinal symptoms such as gastroesophageal reflux, diarrhea/constipation, failure to thrive, irritability and sleep disturbance.
- Was infant breastfed?
  The course of the eczema in relation to the amount of cow's milk exposure in the diet (or via breast milk) can provide an important clue to its possible role. For example, it may be relevant that eczema first presented when cow's milk formula was introduced following a period of exclusive breastfeeding. Was an infant formula used in the nursery while breast feeding was established?

Management of IgE and Non-IgE-mediated Cow's Milk Protein Allergy

The mainstay of treatment for CMPA is the avoidance of all CMP (this includes CMP-derived infant formulas and other dairy products). The requirement for complete milk avoidance is very much dependent on the nature of the individual child's allergy.

While the majority of children with either IgE or non-IgE-mediated reactions should avoid CMP completely, a significant number may tolerate a small amount of extensively heated (baked) dairy. When this dietary intervention is adopted, it is important to consider the adequacy of the lactating mother's dietary intake, specifically her calcium and protein requirements. Avoidance diets therefore need to be individually tailored under the care of a pediatric dietician.

- *Choosing a hypoallergic formula for use in the CMPA infant*: In the absence of human milk, a hypoallergic infant formula will need to be selected. Formulae are also classified according to the degree of protein hydrolysis EHF and partially hydrolyzed formula
- *Use of soy formula*: The advantages of soy-based formula are favorable taste, absence of lactose and suitability for vegans. The prevalence of concomitant soy allergy in infants with CMPA differs between IgE and non-IgE-mediated disease. Infants with IgE-mediated CMPA have concomitant soy allergy, whereas associated soy allergy in non-IgE-mediated CMPA is much higher (up to 50%), in enterocolitis/enteropathy syndromes.
- *Use of other mammalian milk*: There is, however, a close homology between the allergenic proteins in goat's and cow's milk with an associated high potential to induce allergic reaction in CMPA infants. Anaphylaxis to goat's milk has also been described in CMA children.
- *Vitamins and minerals*: The intake of vitamins and minerals can be achieved by improving the weaning diet of the infant, a process that requires careful monitoring by a pediatric dietician. Breastfed infants above 6 months of age and CMPA infants consuming less than 500 mL of formula per day should be prescribed a multivitamin that contains vitamin D. Calcium intake should be reviewed, as both vitamin D and calcium-deficient rickets have been documented in food-allergic children.
- *Medical management of IgE-mediated reactions*: Patients and carers should be educated and empowered to recognize and respond to reactions when they occur. This process requires an individualized emergency plan, which includes an antihistamine and if needed, an epinephrine autoinjector. The successful treatment of CMP-induced

anaphylaxis relies on early administration of epinephrine, ideally via the IM route. The presence of asthma—especially when poorly controlled—has been shown to be major risk factor for the occurrence of more severe allergic reactions to cow's milk.

- *Follow-up and the development of tolerance*: The natural history of both IgE and non-IgE-mediated reactions is for the development of tolerance during childhood. The follow-up of cow's milk allergic patients is important to ensure a nutritionally complete diet, reinforce avoidance advice, to revise the management of allergic reactions, and to assess for the development of tolerance.

Adverse reactions to cow's milk encompass a diverse spectrum of conditions ranging from lactose intolerance to life-threatening IgE-mediated anaphylaxis.

CONSTIPATION

Constipation is defined as infrequent passage of stool associated with pain and difficulty, or delay in defecations.

Constipation is a common problem among children worldwide. Estimates to the prevalence rate of functional constipation in the pediatric population have varied from 4% to 37%.

This is a common problem in childhood. Critical periods occur around the time of infant weaning, toilet training and starting school. Constipation may follow a period of dehydration leading to hard stools that become painful to pass. The child therefore holds on to stool. Secondary soiling (overflow) is common and leads to anxiety at school that may lead to school refusals. It is important to review the past medical history for possible underlying reasons and causes of constipation.

- Ninety-five percent of infants pass more than or equal to 1 stool/day
- Ninety-five percent of school-going children pass more than or equal to 3 stool/day
- Approximately 5–10% of school-going children suffer from constipation
- Organic causes more likely if: Delayed passage of meconium beyond 24 hours, onset in infancy, FTT, abnormal physical signs.

Symptoms of constipation vary from mild and short-lived to severe and chronic and sometimes accompanied by fecal and urinary incontinence, urinary tract infections and abdominal pain.

Types of Constipation

Constipation is of two types:

- Organic
- Functional.

Constipation is again divided into:

- Constipation without fecal (soiling) and urinary incontinence
- Constipation with fecal incontinence (soiling) and ± urinary incontinence.

Definition of Functional Constipation

In functional disorders, there is no evidence of an inflammatory, anatomic, metabolic or neoplastic process.

- Functional constipation was defined in children more than 2 years of age by two or more of the following characteristics during the previous 8 weeks:
  - Less than three bowel movements per week
  - More than or equal to one episode(s) of fecal incontinence per week
  - Large stools in the rectum or felt on abdominal examination
  - Passing of stools so large that they obstruct the toilet
  - Retentive posturing (withholding behavior)
  - Painful defecation.
- For constipation occurring in children less than 2 years of age.

Passage of hard, scybalous or pebble-like stools with straining/withholding or painful defecation.

Acute constipation is defined if symptoms and treatment lasted less than 8 weeks. Functional fecal incontinence was defined as the involuntary loss of any amount of feces into the underwear once a week or more often at present or in the past in a child after the age of 4 years.

Urinary incontinence was defined as leakage of urine at least once per week after age of 5 years.

Functional fecal incontinence associated with constipation: It is the passage of formed, semisolid or liquid stool into the child's underwear. It can occur in the presence of functional constipation after the child has reached a developmental stage of 4 years. It is mostly associated with constipation. However, in a minority of children, it can occur without constipation which is called nonretentive fecal incontinence.

Urinary incontinence associated with constipation: It is the leakage of urine at once in a week after age of 5 years. It can be both daytime and night time incontinence.

Urinary and fecal incontinence associated with constipation with factors affecting delay in acquisition of continence and why constipation causes fecal incontinence and associated urinary incontinence are mentioned in Table 21.

Causes of Constipation

- Idiopathic
  Commonest due to a combination of:
  - Low fiber diet
  - Lack of exercise
  - Poor colonic motility (55% have positive family history).
- Gastrointestinal:
  - Hirschsprung's disease
  - Anal disease:
    - Stenosis
    - Ectopic
    - Fissure
  - Partial intestinal obstruction
  - Food hypersensitivity
- Nongastrointestinal:
  - Hypothyroidism
  - Hypercalcemia
  - Neurological disease, e.g. spinal disease
  - Sexual abuse
  - Chronic dehydration, e.g. diabetes insipidus
  - Drugs, e.g. opiates and anticholinergics

Presentation

- Straining and/or infrequent stool (Fig. 20)
- Anal pain on defecation
- Fresh rectal bleeding (anal fissure)

Table 21: Urinary and fecal incontinence associated with constipation

1. Importance of continence and knowing its epidemiology

The acquisition of continence is an essential element for children to be able to fully integrate with others and to access most public activities. Delays or disruptions in achieving continence will severely limit social life, and continence is an important marker of quality of life at any age beyond toddlerhood

2. Normal development of constipation

To achieve continence, the child must be able to perceive sensation arising from the bladder or rectum, assess the social consequences of passing urine and stool at that time, use appropriate voluntary muscles to delay micturition or defecation and make plans to find a lavatory depending upon the urgency of the sensation. This is not an innate ability but requires learning in a supportive environment. Sensation of the need to pass stool by rectal smooth muscle contraction and reflex partial inhibition of the smooth muscle internal anal sphincter allows stool to impinge on the sensory area of the mucosa of the upper anal canal

3. Factors affecting delay in acquisition of continence

- Painful conditions of anal region, e.g. anal fissure, dysuria
- Poor perception and poor toilet training due to child neglect and unskilled parental training
- Poor sensation of rectum and bladder, e.g. Neural tube defect, spinal dysraphism
- Fecal retention leads to acquire megacolon and megarectum and associate with urinary retention and UTI
- Fecal retention are often associated with anal canal inhibition resulting in falling out of pieces of dry stool or soft stool involuntarily without rectal or anal canal muscle contraction resulting in involuntary fecal soiling
- Fecal incontinence leads to low self-esteem, adverse peer relationship and adverse social pressure at home and at school resulting in to escape the child into dissociation
- Delayed acquisition of continence may also be due to inadequate and inappropriate training or unskilled parenting due to poor parental training or child neglect
- Pain related to excretion at this stage often leads to attempts to retain urine or stool (with associated strengthening of the pelvic floor muscles) which aggravates the tendency of urinary tract infection caused by incomplete bladder emptying, or withholding feces to the point of fecal impaction. The situation for the rectum is complicated by the degree of mega rectum
- However, during these brief periods of anal canal inhibition, soft stool or pieces of dry stool can fall out without the rectal contractions or upper anal canal compression evoking a perceivable sensation. This can be mimicked with anorectal manometry where it is frequently observed that no sensation of a need to defecate is reported until very high volumes of air are introduced into the distending rectal balloon despite brief (approximately 10 seconds) episodes of anal canal inhibition in association with provoked rectal contractions. A similar situation occurs with children who infrequently empty their bladders and appear to be unaware of bladder sensation until it reaches a critical stage and precipitate voiding does not allow them to reach the lavatory in time. Because wetting and fecal incontinence lead to peer and parental adverse pressure, the stress related to this may encourage the child to escape into dissociation and denial thus reducing their vigilance for sensations coming from these troubling areas

4. Why constipation causes fecal incontinence and associated urinary incontinence?

Loening-Baucke reports the association between constipation and urinary incontinence in her population and this has previously been reported. Often the bladder is indented, compressed or misplaced laterally, sometimes to the point where the upper part of the bladder is seen in the vicinity of the liver or spleen. Incomplete bladder emptying may be a learnt response of the fearful child attempting to withhold feces. The social consequences of overflow fecal incontinence may also disturb the child to the point where urinary incontinence occurs as a result of stress

- Abdominal pain
- Anorexia
- Flatulence
- Decrease growth
- Abdominal distension
- Palpable abdominal fecal masses
- Anal fissures
- Abnormal anal tone.

Diagnosis

Taking the History

Find out when problem first arose. In case of infants, ask parents about:

- Delay in passage of meconium
- Abdominal distension in early infancy
- Explosive stools.

These are possible indicators of underlying Hirschsprung's disease or short segment bowel.

Also ask about:

- Possible precipitants
- Current diet and fluid intake
- Psychological factors
- Coercive or chaotic toilet training:
  - Fear of toilet.
  - Parental neglect/discord/illness.
  - Environmental stressors.

Fig. 20: Anxious retentive position with folded hands pressing the tummy in a constipated child

Examination

- Look for facial dysmorphism:
  - Coarse facies for hypothyroid
  - Elfin facies for idiopathic hypercalcemia
- Inspect anus:
  - Fissures (Fig. 21)
  - Infection
  - Skin disease—excoriation/fistula
  - Dilatation.
- Palpate abdomen for impacted fecal mass
- General examination of child including growth, rarely presentation of hypothyroidism.
- CNS:
  - Neurological examination of lower limb
  - Abnormal deep reflexes in lower limb, e.g. paraplegia, spinal dysraphism.

Investigation

- X-ray abdomen (to demonstrate fecal loading) (Fig. 22)
- Blood:
  - Full blood count
  - Thyroid function test
- Others:
  - Serum calcium
  - Radioallergosorbent test
  - Rectal biopsy (Hirschsprung's disease)
  - Rectal manometry
  - Spinal imaging (neurological cause).

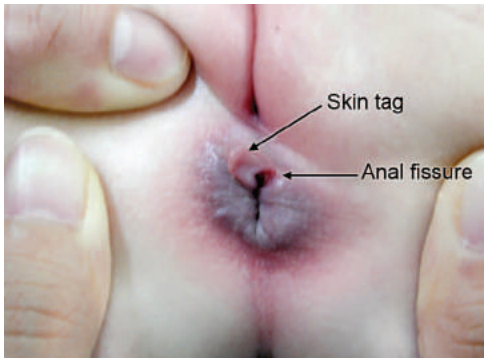


Fig. 21: Inspection of anus in a child with constipation showing anal fissure and anal tag of skin

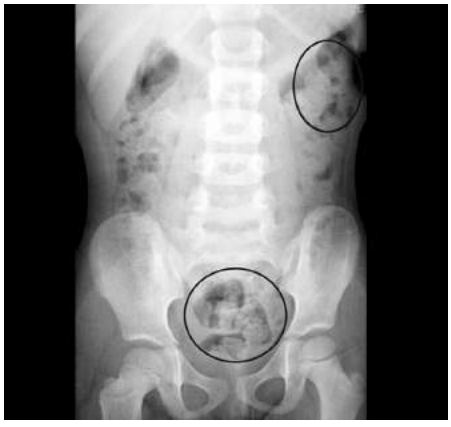


Fig. 22: Plain X-ray abdomen showing fecal impaction of colon

Management Strategies

Early simple treatment is likely to benefit the majority of children when young and so avoid the complex psychological and physiological vicious cycles that go on to damage later childhood.

The key to this is locally based provision of basic advice on adequate fluid intake, diet containing high fever (Fig. 23), sensible and developmental age appropriate pot training and rapid access to effective medical treatment for urinary tract infection, overactive bladder and constipation when these are found. Stepwise management of constipation is mentioned in Table 22.

Throughout this time parents and child will need considerable support from the nursing team (i.e. health visitor/school nurse/specialist nurse).

Fig. 23: High fiber diet for constipation

RECURRENT ABDOMINAL PAIN

Recurrent abdominal pain (RAP) is defined as at least three discrete episodes of abdominal pain over a period of 3 months, sufficiently to interfere with school/usual activities. It affects at least 10% of children over the age of 5 years. No organic cause was found in 90%. Historically John Apley, back in 1958 in his preface to the child with abdominal pain, wrote "I started with a bias toward organic causes but the accumulatory evidence gradually convinced me that in most cases an organic cause cannot be found." Since only 10% of RAP is attributable to organic cause, a conservative approach to investigation is

Table 22: Stepwise management of constipation

Treat in stepwise manner
• Treat any underlying cause
• Treat anal fissure with topical anesthetics (2% lignocaine ointment) to reduce pain and remove voluntary inhibition to defecate
• *Dietary*: ↑ oral fluid and fiber intake, natural laxatives, e.g. fruit juice (Fig. 23)
• *Behavioral measures*: toilet footrests; encourage parents to not show concern, star charts, regular 5 minute toilet time after meals
• Regular oral fecal softener, e.g. lactulose or sodium docusate
• Milk of magnesia
• Oral stimulant laxatives, e.g. senna, sodium picosulfate
• Macrogols
• Enemas: e.g. Micralax, or phosphate enemas, if no response to intensive treatment with above for at least 4 weeks. Fleet enema for children more than 2 years of age
• Hospital admission for either manual evacuation under sedation/GA if appropriate or oral polyethylene glycol

encouraged. On the other hand, there are evidences that children presenting with RAP, considered to be nonorganic, in fact have organic disorders including peptic ulceration and Crohn's disease which may subject to undue delay in diagnosis.

NONORGANIC

Functional and psychological.
Important features of nonorganic abdominal pain:
- Pain is real for child
- Psychological and physiological factors
- Lack of warning clinical signs
- Disrupted normal activities
- Environmental reinforcement common
- Irritable bowel syndrome subtype in older children and adolescence

Factors involved in nonorganic pain:
- Psychological: Stress, anxiety and depression
- Reinforcement of pain behavior
- Carbohydrate intolerance
- Small bowel dysmotility
- Copying family behavior, somatization

Important elements of psychogenic (nonorganic) pain:
- Pain is real for child.
- Overanxious child, timid, apprehensive, highly strung child
- Attention seeking child
- Eating time conflict often associated
- Environmental stress triggers pain
- School anxiety/school avoidance
- Personal physique associated (short stature/delayed puberty)
- Family reasons (single parent/parental conflict)
- Family psychopathology
- Sibling rivalry, school problems
- Children involved in role modeling
- Secondary gain pattern (avoids school, brings parents together who are separated, gets attention)

Stressful psychosocial stimuli:
- Recent change of home or school
- Altered peer relation (bullying at school)
- Separation—important family members
- Recent loss or absence of favorite pet/child caring maid
- Chronic illness in parents or sibling
- Family financial problems.

PATHOPHYSIOLOGY OF RECURRENT ABDOMINAL PAIN

Visceral hyperalgesic hypothesis of cause of pain:
- Altered sensation and motor reflex in response to physiologic stimuli
- Problem related to somatosensory cortex results in variability in pain experience and behavior
- Aberrant brain activation in IBS
- Distension in IBS.

Children with visceral hyperalgesia often have altered somatic pain threshold.

Studies using functional brain imaging techniques suggest that alteration in the brain gut axis in response to visceral stimuli may result in visceral hypersensitivity and an abnormal pattern of motility in the gastrointestinal tract. Interpretation of psychosocial factors can influence the brain gut axis thereby affecting symptoms experience. This current understanding has been utilized in treating functional abdominal pain in children by gut-directed hypnotherapy.

FUNCTIONAL ABDOMINAL PAIN

Functional abdominal pain consists of following subtypes:
- Irritable bowel syndrome
- Functional dyspepsia
- Abdominal migraine
- Aerophagia
- Functional abdominal pain syndrome.

Irritable Bowel Syndrome

Diagnostic Criteria

- History
- Pain lasting for at least 12 weeks
- Urgency for defecation after food
- Discomfort relieved with defecation
- Abnormal stooling pattern
- No structural or metabolic abnormality.

Types

Irritable bowel syndrome is of two distinctive types:
1. Constipation predominant.
2. Diarrhea predominant.

Functional Dyspepsia

Salient Features
- Epigastric discomfort after eating
- Nausea is associated
- With or without vomiting/regurgitation.

Diagnostic Criteria

- Symptoms for at least 12 weeks
- Upper abdominal pain
- No evidence of organic illness (no GERD)
- No relation with stool pattern.

Types

It is mainly of two types:
1. Ulcer type.
2. Dysmotility type.

Abdominal Migraine

Diagnostic Criteria

- Three or more episodes over 1 year
- No metabolic/structural/biochemical disease
- Any two of the following:
  - Headache during episode
  - Photophobia
  - Family history of migraine
  - Unilateral headache.

Aerophagia

Diagnostic Criteria

- Pain for more than 12 weeks

- With two or more of the following:
  - Air swallowing
  - Abdominal distension
  - Increased flatus
  - Belching.

Functional Abdominal Pain Syndrome

Diagnostic Criteria

- At least 12 weeks of nearly continuous pain in a school going child
- No relation of pain with physiological events like eating, defecation
- Some loss of daily functioning
- No resemblance to other functional gastrointestinal syndrome.

ORGANIC CAUSES

Some common causes are:

- Worm infestation, parasitic infection and other infections in children including *H. pylori*
- Tuberculosis of abdomen
- Gastroesophageal reflux
- Gastritis with or without *H. pylori* infection
- Duodenitis with or without *H. pylori* infection
- Carbohydrate malabsorption

Congenital malformation of GI tract:

- Malrotation, volvulus.

Renal causes:

- Pyelonephritis, renal calculus, obstructive uropathy
- Congestion of liver-cholelithiasis, lead poisoning, porphyria.

Pointers to Organic Pain

- Age less than 3 years
- Constant, consistent, well-localized pain
- Pain away from umbilicus (lateralized pain)
- Pain awakening the child from sleep
- Associated joint pain
- Tenderness on examination
- Weight loss, clubbing, perianal lesions
- Poor growth velocity, pubertal delay.

GASTRITIS, *HELICOBACTER PYLORI* AND RECURRENT ABDOMINAL PAIN

- There is association of *H. pylori* with gastritis
- Gastritis due to *H. pylori* improves with elimination of *H. pylori*
- *H. pylori* colonization is rare below 5 years of age
- *H. pylori* colonization increases with age, up to 50% by 60 years of age

However, *H. pylori* colonization is frequently asymptomatic and there is no significant association of *H. pylori* colonization and RAP.

- Strong relationship with gastritis and *H. pylori*. However, no significance with *H. pylori* colonization or even *H. pylori* gastritis with RAP
- No strong evidence of resolution of RAP with eradication of the organism.

Therefore, although *H. pylori* related gastritis improves with elimination of *H. pylori* by appropriate treatment, symptoms of RAP may persist even after adequate treatment of *H. pylori*.

Duodenitis

Duodenitis (*H. pylori can* cause duodenitis), as evidenced by small bowel permeability, is associated with RAP. Increased small bowel permeability tested by using radioactive chromium ethylenediaminetetraacetic acid (^{51}Cr EDTA) can occur in other GI abnormalities like celiac disease Crohn's disease. Subtle and abnormal duodenitis can also occur in asymptomatic children. Therefore association of duodenitis and RAP is inconsistent.

Gastroesophageal Reflux

Gastroesophageal reflux, as evidenced by 24 hours lower esophageal pH monitoring, is associated with RAP. Antireflux measures result in prolonged clinical improvement.

Carbohydrate Malabsorption

- Decline in brush border lactase, causing lactose malabsorption (as evidenced by breath hydrogen studies) and RAP
- Monosaccharide sorbitol present in certain "sugar free" products associated with RAP.

Simple dietary modification may prove beneficial in such cases.

Diagnosis of Recurrent Abdominal Pain

History

- Onset, frequency, duration and site
- Radiation, chronic (dull, colicky)
- Severity (not helpful)
- Exaggerating factors
- Relation to food, feeding and bowels
- Relieving factors
- Treatment received and effects
- Associated pains (legs, head, etc.).

The child

- Daily activities—eating, sleeping, playing, mixing and their effects on pain
- Change in activities or group activities
- Relation with siblings/friends/parents/fussy/conscientious, easily hurt
- Functioning at school
- School attendance, academic performance
- School teacher change.

The family

- Similar complaint in family
- Symptomatic pain or modeling
- Parents personality/illness
- Interparent relationship
- Low level family conflict
- Over attention/single child
- After life threatening illness
- Fear of parents regarding pain (Fig. 24)
- Recurrent abdominal pain history.

Fig. 24: Inter-relationship recurrent abdominal pain with personal, familiar and environmental conditions

Physical Examination

A thorough physical examination is a must even for reassurance:

- General physical examination:
  - Weight/height, anemia, lymphadenopathy, BP, urticaria, joint swelling, fever
- Abdominal examination:
  - Tenderness, organomegaly, mass
- Rectal examination:
  - For fecal impaction.

Laboratory Investigations

Since majority (>90%) of RAP is functional, a conservative approach should be taken for laboratory investigation.

If functional diseases are likely, very little (base level) investigation is needed:

- Complete blood count with peripheral blood film (PBF), ESR, CRP
- Urine R/M/E and C/S
- Stool R/M/E
- Plain X-ray abdomen

If organic diseases are likely, above investigations plus:

- Liver function test
- Serum creatinine
- Mantaux test
- Hydrogen breath test (lactose intolerance)
- ^{13}C breath test (*H. pylori*)
- Enzyme-linked immunosorbent assay test for *H. pylori*
- Stool R/M/E (for worm)
- Gastrointestinal endoscopy, colonoscopy
- Ultrasound scan of abdomen (cholelithiasis)
- Barium swallow of esophagus (for GER)
- Barium meal X-ray of stomach and duodenum and follow through (for searching site of lesion, flocculation of barium instead of feathery mucosa in malabsorption, ileocecal region in intestinal TB and Crohn's disease, etc.).

Management of Recurrent Abdominal Pain

Standard Medical Care and Reassurance

This is the cornerstone of effective medical management. Many cases will response to acknowledgment of the symptoms and reassurance regarding the lack of serious underlying organic disease.

Management of psychogenic and functional pain (nonorganic).

Exclude Organic Cause

Following points are important in nonorganic pain:

- Pain is real in children.
  Explain:
  Benign nature, commoness, growing pain (most grow out).
- Thorough history and physical examination: Helps win the child and parents confidence:
  - Attend the child, not pain
  - Watchful waiting
  - Reinforcement by parents, school and child physician
  - Specific attention at time of pain, e.g. rest
  - Medications given at the time of pain
  - Distraction, lying down, tactile stimuli
  - Minimize secondary gain from abdominal pain like school avoidance
  - Increase dietary fibers in IBS (constipation type) and complex carbohydrate
  - Healthy eating behavior, e.g. avoidance of junk food, refined sugar, polyalcohol sugar sorbitol containing food products, fizzy drinks
  - Dietary triggers should be avoided in abdominal migraine
  - *Healthy lifestyle*: Encourage physical activity (exercise) discourage physical inactivity (TV watching)
  - Promote school attendance if that is an issue
  - *Pain diary*: Maintained by parents and incorporating pain characteristics and aggravating and relieving factors are invaluable in evaluation and management of RAP.

Psychological Interventions

Aims to modify belief, thought and behavioral response to symptoms. It includes:

- Relaxation therapy
- Biofeedback
- Behavioral therapy:
  - Coping skill therapy
  - Cognitive therapy
  - Hypnosis
  - Family therapy.

Hypnotherapy

Currently gut directed hypnotherapy for refractory functional abdominal pain including IBS in children has been found effective. In hypnotherapy, a patient is induced into a hypnotic state and guided by a therapist to respond to suggestions for changes in subjective experience, alterations in perception, emotion, thought or behavior. This hypnotic state has several elements such as a feeling of ease or relaxation, an absence of judging and an absorbed attention on imageries. Guided imagery is a form of relaxed and focused concentration, in which children are encouraged by a therapist to imagine being in their favorite place or doing their favorite activity and image the sights, sounds and smell of that place/activity.

The mechanism by which hypnotherapy acts in improving abdominal symptoms in functional abdominal pain is still not well-understood. Hypnosis has been demonstrated to lead to be change in colonic motility. Hypnotherapy significantly reduces psychological factors such as somatization and psychological stress and this effect seems to persist overtime (Fig. 25).

Pharmacological Option

The evidence base of pharmacological intervention is poor, probably reflecting the wide spectrum of different etiologies and considerable differences in clinical phenotypes and triggering factors. This means that management tends to be

Fig. 25: Gut-directed hypnotherapy procedure in refractory functional abdominal pain in a child

Source: Reproduced from Rutten JMTM et al. Arch Dis Child. 2013;98: 252-7.

subjective and based largely upon the experience of individual working in the field.

Simple Analgesic and Antispasmodic

In functional dyspepsia, H_2 blockers and proton pump inhibitor or prokinetic like domperidone are given as treatment basis and continued only if effective.

Antidepressant in Low-dose

Imipramine and amitriptyline may be tried.

Abdominal Migraine

- *Dietary*: Avoid citrus food, chocolate, caffeine containing drinks, cheese.
- Laxatives in constipation and incomplete rectal evacuation.
- *Pharmacological*: Pizotifen or sumatriptan may be helpful.

Outcome of Nonorganic Recurrent Abdominal Pain

- Twenty-five percent of people with functional abdominal pain continue to have pain or headache in adulthood
- Recurrent abdominal pain may be antecedent of IBS in adults
- Incidence of psychiatric disorders particularly anxiety disorders in adults
- The acceptance of the biopsychosocial model by the patients and their families is an important factor in the response to therapy.

Management of Organic Cases of Recurrent Abdominal Pain

Treat underlying causes:

- *Treatment of H. pylori infection:*
  - Which children should be treated?
  - Children with RAP with evidence of *H. pylori* on endoscopy/histology/gastritis or peptic ulcer disease.
  - Drugs available:

  Antibiotics (amoxicillin/clarithromycin + metronidazole) + proton pump inhibitors (omeprazole/lansoprazole).
- Gastroesophageal reflux: Anti-reflux drugs:
  - *H_2 blockers*: Cimetidine
  - *Proton pump inhibitors*: Omeprazole, lansoprazole.
  - *Macrolides*: Erythromycin.
- Worm infestations:
  - *Antihelmintics*: Pyrantel pamoate, albendazole, mebendazole.
  - *Giardiasis and amebiasis:* Metronidazole.
- *Carbohydrate malabsorption*: Simple dietary exclusion of specific disaccharides and monosaccharides intolerant diet.
- Treatment of other organic diseases according to cause:
  - *Anti-TB:* In intestinal tuberculosis.
  - *Laparoscopic cholecystectomy*: In cholelithiasis.

The etiology of abdominal pain will likely remain obscure in many children for the foreseeable future. There is little doubt that emotional factors are of great importance in some cases, but in evaluating the child, it is of course necessary to consider that psychological disturbances and organic pathology may coexist. Rigid guideline cannot be outlined for the management of recurrent abdominal pain, and the physician is dependent on clinical judgment in deciding upon the proper course of action.

ACUTE ABDOMINAL PAIN IN CHILDREN

APPENDICITIS IN CHILDREN

- Acute appendicitis is the most important cause of acute organic abdominal pain in children
- It is the commonest cause that requires emergency surgery.

EPIDEMIOLOGY AND ETIOLOGY

Mean age of presentation is 6–10 years. Presenting below 2 years has serious complications like perforation. Males more commonly affected than females.

PATHOLOGY AND PATHOGENESIS

- Intraluminal obstruction of appendiceal lumen by fecalith, lymph node
- Intraluminal fluid accumulates due to venous and lymphatic obstruction
- Bacterial infection follows such obstruction
- Ischemia and necrosis developed in advanced cases
- Perforation and peritonitis if not timely managed.

CLINICAL PRESENTATION

Diagnosis is difficult in young children and may be atypical. Older children usually show typical clinical features which include:

- *Fever*: Most useful sign associated with abdominal pain. Absence of fever decreases the possibility of appendicitis
- Nausea, vomiting
- Pain in abdomen, leading to inability to walk, often presenting to doctor with limping
- Abdominal pain may be triggered by jumping, hoping or going over bump on the road
- *Migratory pain*: Periumbilical pain migrating to right iliac fossa
- Rebound tenderness and guarding of abdomen on percussion or palpation

Clinical Presentation in Young Children under 2 years of Age: Atypical nonspecific with:

- Vomiting
- Diarrhea

- Fever, irritability, grunting
- Abdominal pain
- Abdominal distension
- Right hip pain, limp

In such cases, diagnosis may be delayed which may increase the risk of perforation.

DIAGNOSIS

Mostly clinical investigations support the clinical diagnosis. A patient who presents with classical sign and symptoms and is assessed by an experienced surgeon does not require any radiological investigation.

CLINICAL FEATURES

Sensitivity and specificity of clinical features and investigations for diagnosis of acute appendicitis is less than that of adult appendicitis.

Important clinical features in favor of acute appendicitis include fever, migratory pain and presence of rebound tenderness.

LABORATORY INVESTIGATIONS

- Increased WBC count (>10,000/μL) with polymorph more than 7,500
- C-reactive protein more than 10 ms/dL
- Normal WBC and CRP however do not exclude diagnosis
- *Urine analysis*: Not helpful. Pyuria and bacteriuria may be present without UTI.

A pediatric appendicitis score (Samuel) may be adopted to increase the sensitivity of the diagnosis (Table 23).

A patient who has a score of less than 2 can be discharged home without any further investigation. A patient who has a score of more than 6 should be surgically intervened without delay and without further investigation. Patients scoring between 3 and 5 should have further imaging and to be kept under observation.

Ultrasound scanning in appendicitis children: Findings compatible with appendicitis are:

- Distended appendix (≥6 mm in diameter) with fluid filled
- Constant in shape and position
- No peristaltic activity.

Ultrasound is more specific but less sensitive.

Disadvantages

- Operator dependent
- Needs child cooperation
- Appendix is not seen in 10% cases.

Table 23: Pediatric appendicitis score

Feature	Score
Fever >38°C	1
Anorexia	1
Nausea, vomiting	1
Cough/percussion/hopping tenderness	2
Right lower quadrant tenderness	2
Migration of pain	1
Leukocytosis >10,000 (10^9/L)	1
Polymorphonuclear neutrophilia >7,500 (10^9/L)	1
Total	10

CT Scan of Appendix

It is more sensitive (>90%) than ultrasound in diagnosis of appendicitis. Better done in suspected cases (not conclusive diagnosis by clinical examination, FBC and ultrasound) to avoid unnecessary surgery.

CT Findings Suggested of Appendicitis

- Appendix more than 6 mm in maximum diameter
- Periappendiceal inflammation or abscess
- Presence of appendicolith.

Disadvantages

- More expensive investigation
- Risk of radiation.

Treatment

When suspected until surgery:

- Nothing orally
- IV maintenance fluid
- IV antibiotic (cephalosporin, metronidazole, aminoglycoside).

Surgery

Appendicectomy: Definitive treatment.

INTUSSUSCEPTION

DEFINITION

It is an invagination of proximal bowel into distal segment. Any part can be affected but in most cases is ileum which passes into cecum and colon through ileocecal valve (Fig. 26).

EPIDEMIOLOGY AND ETIOPATHOLOGY

- *Age specific*: 2–20 month (6–12 month peak)
- Enlarged Peyer's patch in the ileum acts as a lead point.
- May be triggered by viral infection
- In older children, polyp or Meckel's diverticulum acts as a pathological lead.

PRESENTATION

- Paroxysmal severe colicky pain, pallor and cry. Child draws up his legs with perioral pallor

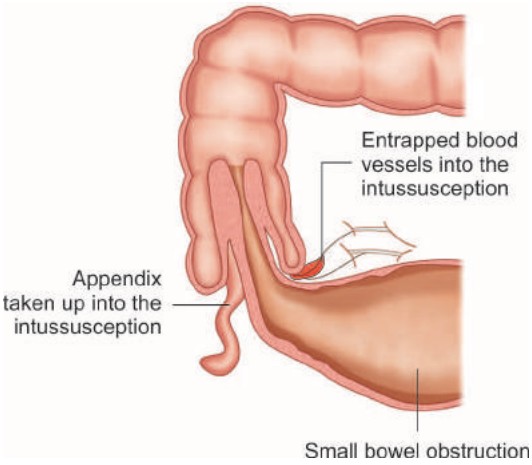


Fig. 26: An ileocolic intussusception

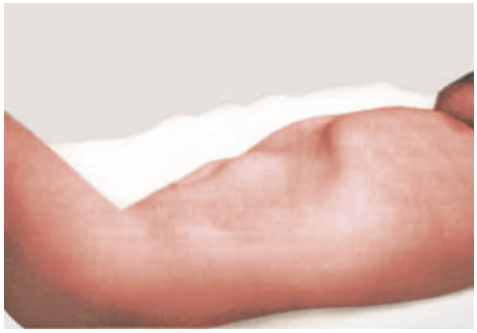


Fig. 27: A visible mass from an intussusception in a dehydrated child

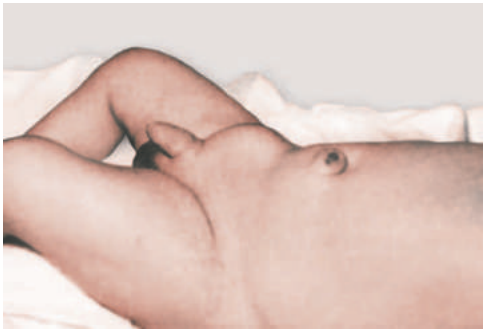


Fig. 28: Right-sided strangulated inguinal hernia in an infant

- Child may sleep in between attack
- A sausage-shaped mass often seen or palpable in upper abdomen (Fig. 27)
- Characteristic red currant jelly stool consisting of mucous and blood as a late sign, but can be seen early by rectal examination
- Shock occurs as complication and requires early intervention.

INVESTIGATION

- *Plain X-ray abdomen*: Distended bowel loop with absence of gas in distal colon or rectum
- Ultrasound confirms the diagnosis showing characteristic target signs.

MANAGEMENT

- *Resuscitation*: Large volume of IV fluid may be required to restore perfusion
- IV antibiotic
- Analgesic.
- *Nasogastric tube*: If the infant is vomiting.
- Rectal insufflation of air under fluoroscopic control by expert radiologist. It is the treatment of choice.
- *Laparotomy*: If pneumatic reduction fails or is contra-indicated because of concern about a gangrenous intussusception. The distal bowel is gently compressed to reduce the intussusception. If this is not successful then intussusception is resected.

INGUINAL HERNIA

Inguinal hernias below 2 years of age are almost invariably indirect. The majority presents as swellings, often more noticeable when the baby is crying. As inguinal hernias in infants less than a year old are very likely to strangulate (Fig. 28), they should be operated on the next routine operating list and not placed on a waiting list. When strangulated, inguinal hernias become tense and tender but even at this stage most can be reduced with gentle manipulation; should this prove difficult it can be repeated following sedation and elevation of the legs. If the hernia is successfully reduced, surgery can be performed 24–48 hours later, when the tissue edema has resolved. If unsuccessful, immediate operation will be necessary.

Neonatal acute surgical condition is discussed in Chapter 1.

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8 Hepatology

ACUTE VIRAL HEPATITIS

Acute viral hepatitis is a systemic infection affecting the liver predominantly. Almost all cases of viral hepatitis are caused by one of the five hepatotropic viral agents, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV) and hepatitis E virus (HEV). Other viruses which cause hepatitis are hepatitis G virus, non-A-E virus, Epstein-Barr virus (EBV), cytomegalovirus (CMV), dengue virus, herpes simplex virus (HSV), etc. Hepatitis A and E are self-limiting, but infection with hepatitis B and C may lead to chronic hepatitis.

All types of viral hepatitis produce clinically similar illness. These range from asymptomatic and inapparent to fulminant acute infection common to all types and from subclinical persistent infection to rapidly progressive chronic liver disease (CLD) with cirrhosis and even hepatocellular carcinoma, common to viral hepatitis caused by HBV, HCV and HDV on the other.

Clinical Features of Acute Viral Hepatitis (Table 1)

In children, acute viral hepatitis is less symptomatic than adults and up to 30–50% children do not develop jaundice. Majority of prodromal features and misery occur during preicteric phase. As jaundice appears or even deepens, patient usually feels better.

Clinical features include:

Preicteric phase

- Malaise
- Vomiting
- Headache
- Abdominal pain
- Lethargy
- Loss of appetite
- Polyarthralgia
- Popular rash (Gianotti-Crosti syndrome) associated with hepatitis B virus infection
- High-color urine usually appears before appearance of clinical jaundice.

Icteric phase

- Jaundice (yellow color of sclera and skin)
- Tender hepatomegaly
- Splenomegaly up to 30%
- Pruritus (associated with cholestasis and increased bile salts)
- Child may feel better during icteric phase, in uncomplicated acute hepatitis.

Clinical features of all acute viral hepatitis are almost similar and it is difficult to diagnose and differentiate different types of acute viral hepatitis clinically and from usual liver function test (serum bilirubin, ALT, AST). However, some serological markers of viral hepatitis are useful (Table 2) for diagnosis of various types of acute viral hepatitis.

HEPATITIS A

Hepatitis A virus is the most common cause of acute viral hepatitis worldwide. Globally, it is responsible for at least 1.4 million new infections each year. Although infection with HAV is often mild and asymptomatic in young children, the disease can be severe in adults. The distribution and prevalence of HAV infection is very closely related to local hygiene and sanitation conditions, and consequently may vary across countries depending on the socioeconomic status (SES) of the population.

The organism is transmitted almost exclusively by the fecal-oral route. The primary replication of the virus takes place in the small intestine where the virus penetrates into the liver through the portal vein.

The incubation period is about 15–50 days. Person to person spread of HAV is enhanced by poor personal hygiene, poor sanitation and overcrowding. Large outbreak as well as sporadic cases have been traced to contaminated food, water, milk, frozen foods and shell fishes. Interfamily and institutional spread is also common.

In developed countries, the incidence of type A hepatitis has been declining, presumably as a function of improved sanitation and public health.

Three epidemiological patterns of HAV endemicity are commonly observed worldwide. Each pattern is different with respect to seroprevalence in different age groups, transmission and disease burden. Most developing countries have high endemicity, in contrast to the generally low seroprevalence found in developed world. Furthermore, contrasting endemicity may exist in the same country or region or local difference in SES, water supply and hygiene. Although low seroprevalence is a good indicator of improved public health status of a country, people of low endemic zone are vulnerable to have more severe symptomatic hepatitis A. Subclinical or asymptomatic HAV infection during childhood in developing countries helps to protect such children to develop acute symptomatic HAV infection in later life.

Published study on seroprevalence shows a transition from high to intermediate HAV endemicity. Seroprevalences were found significantly low in children below 10 years of high SES groups of urban children and these children grow up on

Table 1: Clinical and epidemiological features of viral hepatitis

Features	HAV	HBV	HCV	HDV	HEV
Incubation (days)	15–45, mean 30	30–180, mean 60–90	15–160, mean 50	30–180, mean 60–90	14–60, mean 40
Onset	Acute	Insidious or acute	Insidious	Insidious or acute	acute
Age preference	Children, young adults	Young adults (sexual and percutaneous)	Any age, but more common in adults	Any age (similar to HBV)	Young adults (20–40 years)
Transmission					
Fecal-oral	+++	–	–	–	+++
Percutaneous	Unusual	+++	+++	+++	–
Perinatal	–	+++	±[a]		
Sexual	±	++	±[a]	+	–
Clinical					
Severity	Mild	Occasionally severe	Moderate	Occasionally severe	Mild
Fulminant	0.1%	0.1–1%	0.1%	5–20%[b]	1–2%[e]
Progression to chronicity	None	Occasional (1–10%)	Common (50–70% chronic hepatitis; 80–90% chronic infection)	common[d]	None
Carrier	None	0.1–30%[c]	1.5–3.2%	Variable[f]	None
Cancer	None	+ (neonatal infection)	+	±	None
Prognosis	Excellent	Worse with age debility	Moderate	Acute: good Chronic: poor	Good
Prophylaxis	Ig, inactivated vaccine	HBIg, recombinant vaccine	None	HBV vaccine (none for HBV carriers)	Unknown
Therapy	None	Interferon, lamivudine	Interferon + ribavirin	Interferon ±	None

Abbreviations: HAV, hepatitis A virus; HCV hepatits B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; Ig, immunoglobulin; HBIg, Hepatitis B immunoglobulin

a. Primarily with HIV coinfection and high-level viremia in index case; risk ~ 5%. b. Up to 5% in acute HBV/HDV coinfection; up to 20% in HDV superinfection of chronic HBV infection. c. Varies considerably throughout the world and in subpopulations within countries; see text. d. In acute HBV/HDV coinfection, the frequency of chronicity is the same as that for HBV; in HDV superinfection, chronicity is invariable. e. 10–20% in pregnant women. f. Common in Mediterranean countries, rare in North America and Western Europe

Table 2: Simplified diagnostic approach in patients presenting with acute hepatitis

Serologic tests of patient's serum				Diagnostic interpretation
HBsAg	IgM Anti-HAV	IgM Anti-HBc	Anti-HCV	
+	–	+	–	Acute hepatitis B
+	–	–	–	Chronic hepatitis B
+	+	–	–	Acute hepatitis A superimposed on chronic hepatitis B
+	+	+	–	Acute hepatitis A and B
–	+	–	–	Acute hepatitis A
–	+	+	–	Acute hepatitis A and B (HBsAg below detection threshold)
–	–	+	–	Acute hepatitis B (HBsAg below detection threshold)
–	–	–	+	Acute hepatitis C

environment where they are likely to have good access to clean water and sanitation. However, these groups of children are at risk of symptomatic illness during their adolescence and adult life. Preventive measures, with HAV vaccine need more consideration in those low seroprevalent groups of children.

The HAV is not cytopathic to hepatocytes and damage to liver cells is due to T cell-mediated immune response. HAV infection in children under the age of five years is asymptomatic in more than 90% cases whereas it is symptomatic in about 70–80% of adults. The recovery occurs usually within two to three weeks in most of the cases but the course may be delayed. On the other hand, relapse may occur in about 20% cases. Fulminant hepatic failure (FHF) may occur in 0.4% cases. However, the hepatitis A does not progress to chronic form.

Liver enzymes serum alanine aminotransferase (ALT), AST are sky high (>10 times normal value) and become high even before serum bilirubin is increased and before clinical jaundice appears. Frequently liver enzymes are disproportionately higher than serum bilirubin. However, increased liver transaminases do not correlate with the severity of the disease. It may be very high with mild jaundice. Serum bilirubin monitoring (once or twice weekly) is better index of disease activity than the liver enzymes. Prothrombin time (PT) is an index of liver damage. However, in majority of HAV, prothrombin time is within normal range.

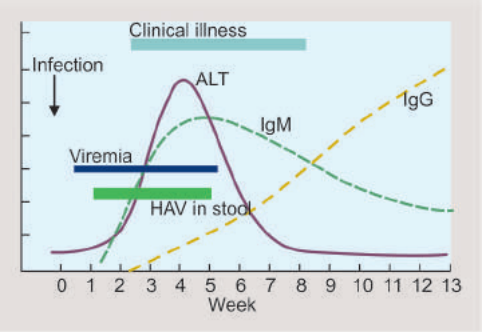


Fig. 1: Serology of acute hepatitis A

Abbreviations: ALT, alanine aminotransferase; HAV, hepatitis A virus

Serum biomarkers for diagnosis of hepatitis A are IgM anti-HAV. Figure 1 shows the various stages of acute hepatitis A in relation to serum biomarkers and viremia.

The therapy for hepatitis A is supportive. Majority can be treated at home and should take enough fluid orally. However, for children and adolescent in particular with intractable vomiting, loss of appetite and dehydration may require hospitalization for intravenous (IV) fluid replacement. Paracetamol should be avoided as antipyretic.

Prevention

Hepatitis A may largely be prevented by improvement of sanitation, supply of safe drinking water and hygienic handling of food. Effective vaccine is now available to prevent HAV. Passive immunization can be achieved by immunoglobulin which protects for a period of three months and more relevant to travelers traveling from developed countries to hepatitis A endemic developing countries.

Summary

- Hepatitis is the most common cause of acute viral hepatitis
- Children develop less symptomatic illness than adults
- HAV does not progress to chronic form
- Liver enzymes are very high in comparison to serum bilirubin and usually precedes development of clinical jaundice
- The serological markers for the diagnosis of hepatitis is IgM anti-HAV
- The prevalence is very low in developed countries due to improved sanitation and public health status
- The seroprevalence is high in developing countries
- Developing countries are going through transition from high endemic to intermediate HAV endemicity
- Children of high SES have very low anti-HAV seroprevalence and therefore, vulnerable for more symptomatic development of HAV in adolescent and adult life, which require more consideration of HAV vaccine of these group of children
- Treatment of HAV infection is supportive and can be managed at home. However, in rare case with severe symptomatic HAV infection with intractable vomiting may require hospitalization for intravenous fluid replacement.

HEPATITIS B

The HBV is a partially double-stranded DNA virus. The whole virus is known as Dane particle. The virus consists of outer surface coat containing HBsAg and inner core containing HBcAg, HBeAg, DNA and DNA polymerase.

The various definitions are frequently used in hepatitis B infection to indicate various stages and activity of HBV infection. These definitions are given in Table 3 for better understanding of the infection of HBV infection.

Serotype and Virologic Markers

After infection with HBV, the first virologic marker detectable in serum is HBsAg. Correlating HBsAg precedes elevation of serum aminotransferase activity and clinical symptoms and remains detectable during the entire icteric or symptomatic phase of acute hepatitis B and beyond. After HBsAg disappears antibody to HBsAg (anti-HBs) becomes detectable in serum and remains detectable indefinitely thereafter. Because HBcAg is sequestrated within an HBsAg coat, HBcAg is not detectable routinely in the serum of the patients with HBV infection. By contrast, anti-HBc is readily demonstrable in serum, beginning with the first 1–2 weeks after the appearance of HBsAg and

Table 3: Glossary of terms used in hepatitis B virus infection

Definitions
Chronic hepatitis B Chronic necroinflammatory disease of liver caused by persistent infection with hepatitis B virus (HBsAg positive for >6 months) Chronic hepatitis B can be subdivided into: • HBeAg positive chronic hepatitis • HBeAg negative chronic hepatitis
Inactive HBsAg carrier state Persistent HBV infection of the liver without significant, ongoing necroinflammatory disease
Resolved hepatitis B Previous HBV infection without further virological, biochemical or histological evidence of active virus infection or disease
Acute exacerbation or flare of hepatitis B Intermittent elevations of aminotransferases activity to more than 10 times upper limit of normal and more than twice than the baseline value
Reactivation of hepatitis B Reappearance of active necroinflammatory disease of the liver in a person known to have the inactive HBsAg carrier state or resolved hepatitis B
HBeAg clearance Loss of HBeAg in a person was previously HBeAg positive
HBeAg seroconversion Loss of HBeAg and detection of anti-HBe in a person who was previously HBeAg positive and anti-HBe negative
HBeAg reversion Reappearance of HBeAg in a person who was previously HBeAg negative, anti-HBe positive

preceding detectable level of anti-HBs by weeks or months. Because variability exists in to the true appearance of anti-HBs after HBV infection, occasionally a gap of several weeks or longer may separate the appearance of anti-HBs. *During this gap or "window" period (Fig. 2), anti-HBc (IgM anti-HBc in particular) may represent serological evidence of current or recent HBV infection.* Recent and remote HBV infection can be distinguished by determination of immunoglobulin class of anti-HBc. Anti-HBc of the IgM class (IgM anti-HBc) predominate during the first 6 months after acute infection, whereas IgG anti-HBc is the predominant class of anti-HBc beyond 6 months. Therefore, patients with current or recent acute hepatitis B, including those of the anti-HBc window, have IgM anti-HBc in the serum.

Anti-HBs is the protective antibody, which can be detected serologically. The other readily detectable serologic markers of HBV infection, HBeAg appear concurrently with or shortly after HBsAg. Its appearance coincides temporarily with high level of virus replication and reflects the presence of circulating intact virions and detectable HBV DNA. In self-limited HBV infection, HBeAg becomes undetectable shortly after peak elevation in aminotransferases activity, before the disappearance of HBsAg and anti-HBe then detectable, coinciding with a period of relatively lower infectivity. Because markers of HBV replication appear transiently during acute infection, testing for such marker is of little clinical utility in typical case of acute HBV infection. In contrast, markers of HBV replication provide valuable information in patients with protracted infection.

Typical Serologic Course of Hepatitis B Infection

- HBc, hepatitis B core antigen
- HBe, HBeAg, hepatitis B early antigen
- HBs, HBsAg, hepatitis B surface antigen
- IgM anti-HBc indicates acute or recent infection
- Anti-HBc indicates infection in the past
- Window period: (Blue square area between 24 weeks and 32 weeks) shown in Figure 2: Presence of IgM HBc in the absence of HBsAg and HBsAb, indicates only serological evidence of acute hepatitis in the recent past.

Departing from the patterns typical of acute HBV infection, in chronic HBV infection (Fig. 3), HBsAg remains detectable beyond 6 months, and anti-HBc is primarily of IgG class and anti-HBs is either undetectable or detectable at low levels. During *early chronic HBV infection*, HBV DNA can be detected in serum and in hepatocytic nuclei. *This replicative stage of HBV infection is the time of maximum infectivity and liver injury.* HBeAg is a qualitative marker and HBV DNA, a quantitative marker of this *replicative phase*, during which all three forms of HBV circulate, including intact virions. Over time, the replicative phase of chronic HBV infection gives way to a relatively *nonreplicative phase.* This occurs at a rate of approximately 10% per year and is accompanied by seroconversion from HBeAg-positive to anti-HBe-positive. In most cases, this seroconversion coincides with a transient acute hepatitis like elevation in aminotransferases activity, believed to reflect call-mediated clearance of virus-infected hepatocytes. In nonreplicative phase of chronic HBV infection, only spherical and tubular forms of HBV, *not intact virions,* circulate and liver injury tends to subside. Most such patients would be characterized as asymptomatic HBV carriers. In reality, the designations

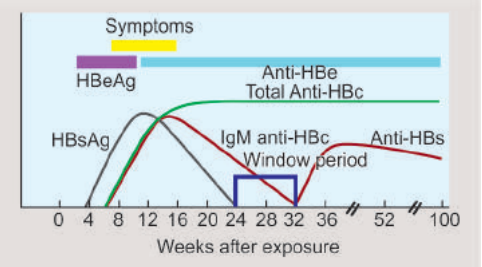


Fig. 2: Acute hepatitis B virus infection with recovery

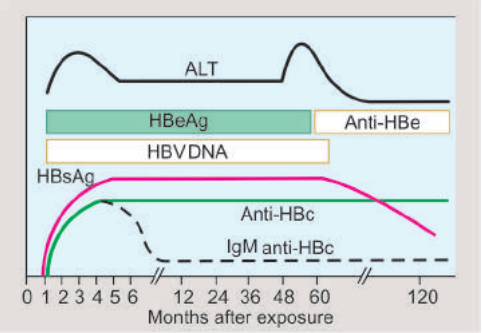


Fig. 3: Serologic course of hepatitis B, months after infection

replicative and *nonreplicative* are only relative, even in the so called nonreplicative phase, HBV replication can be detected with highly sensitive amplification probes such as the polymerase chain reaction. Occasionally, nonreplicative HBV infection converts back to replicative infection. Such spontaneous reactivations are accompanied by re-expression of HBeAg and HBV DNA, and sometimes of IgM anti-HBc, as well as by exacerbation of liver injury.

Route of Transmission

Hepatitis B virus is mainly transmitted:

- Particularly through contact with contaminated blood or body fluid by transfusion of blood and blood products
- Use of nonsterile syringe and other medical instruments and
- By sexual contact
- Substance abuse and sexual activity increase the risk of HIV/HBV coinfection in adolescents
- It is more importantly transmitted perinatally from infected mother to newborn. The child becomes infected through contact with contaminated maternal body fluid during birth. The perinatal transmission of HBV varies directly with the serological status of the mother. The rate of transmission is about 90% in children born to HBeAg positive mother. When the mother is only HBsAg positive, the rate of transmission is 22–67%. Acute HBV infection in the third trimester of pregnancy can infect the offspring whereas maternal infection occurring in the first and the second trimesters usually resolve without sequelae in the infant.

Disease Burden of Hepatitis B

Hepatitis B is a major cause of chronic liver disease and a significant public health issue. Between 350 million and 400 million people worldwide are chronically infected with HBV.

These include healthy adult population 4.4–9.7%, healthy children 3%, school girls 2.3%, a rural community 6.4% and slum communities 3.8%. Perinatal or vertical transmission of HBV is infrequent due to a low HBeAg positive rate among pregnant females with HBV infection.

Among the high-risk population HBV carrier rate varies widely such as professional blood donors 19.0–29.0%, family members of HBsAg carrier 20.6%, healthcare workers 8.7%, parenteral drug users 6.2–12%, truck drivers 5.9%, commercial sex workers 9.7%, and multiple units of blood recipients 13.8%. HBV is an important cause of liver disease and published studies showed that HBV is responsible for 19.0–35% of acute viral hepatitis, 35.7% of acute liver failure (ALF), 33.3–40.5% of chronic hepatitis and 46.8% of hepatocellular carcinoma (HCC).

Clinical Features

Most acute HBV infections in children are asymptomatic. Prodromal symptoms of lethargy, malaise, fatigue, nausea, and anorexia can occur. Jaundice and right upper quadrant pain can follow and, less commonly, hepatomegaly and splenomegaly. Gianotti-Crosti syndrome (papular acrodermatitis) (Fig. 4), urticaria, macular rash, or purpuric lesions may be seen in acute HBV infection. Extrahepatic manifestations associated with circulating immune complexes that have been reported in HBV-infected children include arthralgias, arthritis, polyarteritis nodosa, thrombocytopenia, and glomerulonephritis. Most children with chronic HBV infection are asymptomatic. However, rare cases of fulminant hepatic failure have occurred during childhood HBV infection. Most children with chronic HBV infection are asymptomatic. One quarter of infants and children with chronic HBV eventually will develop cirrhosis or HCC. However, these sequelae usually develop over 2–3 decades and rarely occur during childhood. Development of HCC correlates with HBV DNA levels and duration of HBV infection, with the highest risk in persons infected in early life. HIV/HBV-coinfected adults are at increased risk for cirrhosis, end-stage liver disease, and liver-related mortality.

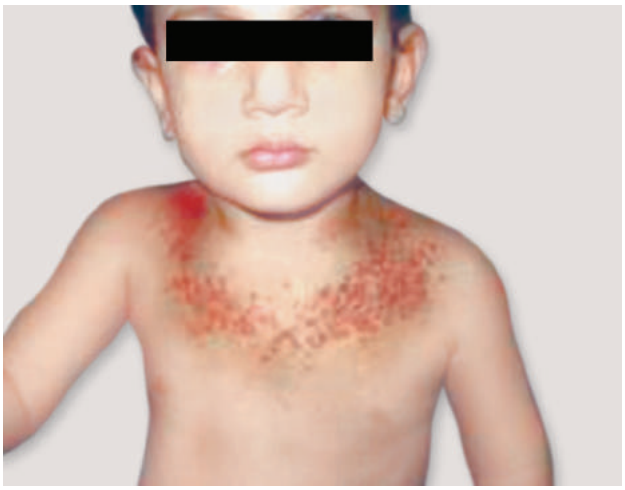


Fig. 4: Papular dermatitis of Gianotti-Crosti syndrome

Diagnosis

Diagnosis of HBV infection cannot be made on clinical ground alone; serological markers are the mainstay of diagnosis and various stages of infection. Investigations include serological markers, HBsAg, IgM HBc, IgG HBc, HBeAg, serum transaminases (ALT, AST), HBV DNA, PT. Significance of serological markers is given in Table 4.

Serological markers of different phases of acute and chronic hepatitis B infection and their interpretation are given in Table 5.

Diagnostic Criteria of Various Stages of Chronic Hepatitis B

- Chronic hepatitis B
  - HBsAg positive > 6 months
  - Serum HBV DNA >10^5 copies/mL
  - Persistent or intermittent elevation of ALT/AST levels
  - Liver biopsy showing chronic hepatitis (necro-inflammatory score ≥4)
- Inactive HBsAg carrier state
  - HBsAg positive >6 months
  - HBeAg negative, anti-HBe positive
  - Serum HBV DNA < 10^5 copies/mL
  - Persistently normal ALT/AST levels
  - Liver biopsy confirms absence of significant hepatitis (necroinflammatory score <4)
- Resolved hepatitis B
  - Previously known history of acute or chronic hepatitis B or the presence of anti-HBc ± anti-HBs
  - HBsAg negative
  - Undetectable serum HBV DNA
  - Normal ALT level.

Chronic Hepatitis B in Children

Chronic hepatitis B infection is defined as persistence of hepatitis B surface antigen (HBsAg) for more than 6 months. Like adults, children also can have acute and chronic hepatitis B. The incidence of chronic hepatitis B in children has declined in recent years due to implementation of universal hepatitis B vaccination of infants.

In children, perinatal transmission remains the most important cause of chronic infection. The likelihood of chronic HBV in children is inversely proportional to the child's age of acquisition. Chronic infection develops up to 90% of vertically infected newborn, but decrease to 25–50% in children infected

Table 4: Hepatitis B: Significance of serological markers

Markers	Significances
HBsAg	Acute or chronic hepatitis B carriage
IgM anti-HBc	Acute hepatitis B (high titer) Chronic hepatitis B (low titer)
Anti-HBc (total)	Past exposure to hepatitis B (with negative HBsAg) Chronic hepatitis B
Anti-HBs	Immune to hepatitis
HBeAg	Acute hepatitis B. Persistence means continued infectious state
Anti-HBe	Convalescence or continued infectious state
HBV DNA	Continued infectious state

Table 5: Serological markers of acute and chronic hepatitis B infection

HBsAg	HBeAg	IgM anti-HBc	IgG anti-HBc	Anti-HBs	Anti-HBe	HBV DNA	Interpretation
							Acute HBV infection
+	+	+	–	–	–	+++	Early phase
–	–	+	–	–	–	+	Window phase
–	–	–	+	+	+	±	Recovery phase
							Chronic HBV infection
+	+	–	+	–	–	+++	Replicative phase
+	–	–	+	–	+	±	Low, nonreplicative phase
+	±	+	+	–	–	–	Flare of chronic HBV
+	–	–	+	–	+	++	Precore/core promoter mutants (HBsAg negative)
–	–	–	–	+	–	–	Successful vaccination Rarely, after HBV infection

between the age of 1 year and 5 years and 6–10% in older children.

Most children with chronic HBV infection are asymptomatic that is hepatitis B infection without hepatitis B induced disease like cirrhosis etc. One quarter of infant and children with chronic HBV eventually develop cirrhosis or hepatocellular carcinoma (HCC). However, these sequelae develop over 2–3 decades and rarely occur during childhood.

The Natural History of Chronic Hepatitis B Virus Infection

The natural history of chronic HBV infection in children is variable, depending upon age, mode of acquisition and ethnicity. These differences are likely due to immune tolerance that develops when infection occurs at an early age. The exact mechanisms through which immune tolerance develops are unknown. Individuals with perinatally acquired chronic HBV infection typically enter an immune-tolerant phase, from which they eventually move on to an immune-active phase and thence to spontaneous clearance of the infection or to an inactive carrier state.

Three stages of chronic HBV infection were identified are as follows:

1. Immune tolerant phase.
2. Immune active phase.
3. The inactive hepatitis B due to spontaneous clearance of infection (inactive asymptomatic carrier stage).

Definitions of stages of chronic HBV infection are given in Table 6.

There is a little difference with this criteria with that of Asian-Pacific consensus statement on the management of chronic hepatitis B, 2005. According to this, the natural course of chronic hepatitis B infection was divided into three phases named:

1. Immune-tolerance phase with normal ALT followed by immune-active phase with increased ALT
2. Immune-clearance phase
3. Residual or inactive phase.

Figures 5 and 6 show status of HBV DNA, serum ALT, HBeAg and anti-HBe in various stages of chronic HBV infection.

- Hepatitis D may be coinfected in acute HBV infection and superinfected in chronic HBV carrier.

Three stages of chronic HBV infection are not only important to assess the stage and activity of chronic HBV

Table 6: Criteria for staging of chronic HBV infection

	Stages		
	Immune-tolerant phase	**Immune-active phase**	**Inactive hepatitis B**
HBeAg/ Anti-HBe	HBeAg	HBeAg or anti-HBe	anti-HBe
ALT	Normal	Elevated	Normal
HBV DNA (Copies/ mL)	>100,000	>100,000	<100,000
Liver histology	Normal or minimal inflammation	Chronic inflammation	Normal or minimal inflammation

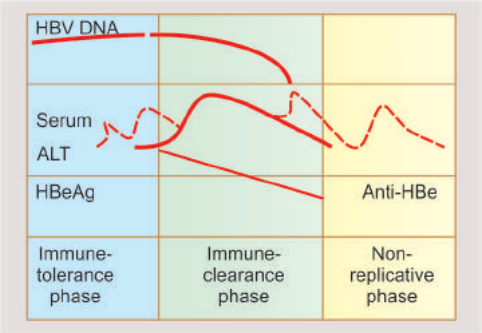


Fig. 5: Serum biomarkers, HBV DNA and liver enzymes in three stages of chronic HBV (nonreplicative) infection

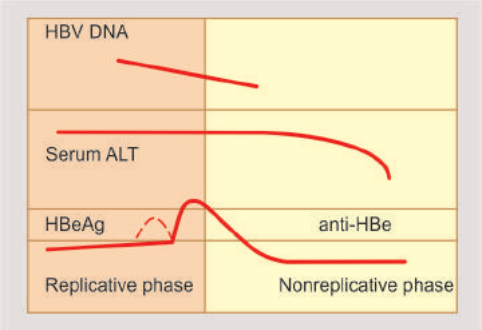


Fig. 6: Serum biomarkers, HBV DNA and liver enzymes in replicative (↑ HBeAg) and nonreplicative phase (anti-HBe) of chronic HBV infection

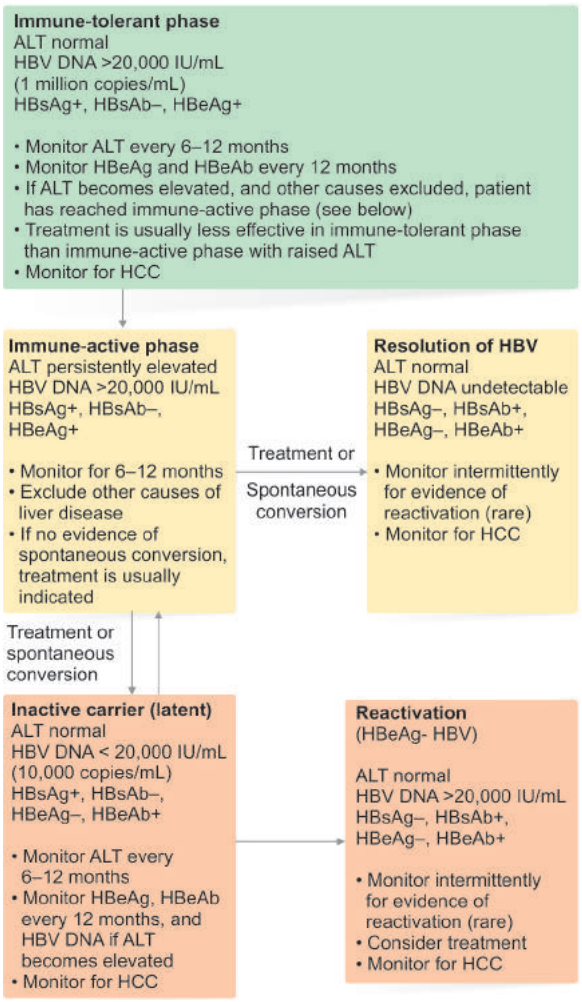


Fig. 7: Various stages of chronic hepatitis B virus infection and their respective management strategy

infection but also have significance in the management of strategy of treating the disease. Various stages of chronic HBV infection with their biomarkers and the treatment according to the stages are given in Figure 7.

Management of Chronic Hepatitis B in Children

Treatment for chronic HBV in children as a whole is unsatisfactory. Interferon (IFN) treatment for chronic HBV is successful in up to 50% cases infected horizontally and up to 30% children infected perinatally. Pegylated IFN is more effective in treating chronic HBV infection. Oral antiviral therapy with lamivudine is effective in up to 23% of cases, but limited by development of resistance.

Treatment Criteria

- Chronic infection that is HBsAg-positive in two samples taken 6 months apart or positive anti-HBc (total), not IgM.
- Raised ALT for 6 months associated with HbsAg positivity
- Raised HBV DNA
- Children older than 2 years. Liver biopsy is optional in children.

The two medications approved are monotherapy IFN-α and lamivudine, a nucleoside analog.

Treatment Recommendations

General Issues

Individualization of therapy is essential for any HBV-infected child and should be based on the child's age, age at acquisition of infection, HBV DNA levels, and serum transaminase levels. Antiviral therapy regimens for chronic hepatitis B are approved only for children aged more than 2 years who have compensated liver disease.

No clear recommendations exist for treating chronic childhood HBV infection. HBV-infected children often have milder disease than adults and may show spontaneous HBeAg seroconversion.

However, a 2004 consensus meeting of pediatric liver experts recommended that antiviral treatment be considered in children with chronic HBV infection and duration of necroinflammatory liver disease more than 6 months.

Interferon Alpha

Interferon-alpha treatment is administered for only 6 months but requires subcutaneous administration. It is better tolerated in children than adults, but response rates are low.

Dose: Interferon alpha given 3 million unit/m^2 body surface area subcutaneously three times weekly for1 week followed by a dose escalation 6 million unit/m^2 to complete 24-week course.

Pegylated interferon alpha, which results in more sustained plasma interferon concentration and can be administered by injection once a week for 48 weeks, has proven superior to standard interferon alpha. However, there is limited data of using pegylated interferon alpha in chronic HBV in children. Factors associated with higher likelihood of response with interferon (chronic hepatitis in children) are the following:

- Alanine aminotransferase two times the upper limit of normal or higher
- Female gender
- Low level of HBV DNA
- Younger age, with abnormal ALT
- Active inflammation on liver biopsy.

Disadvantages of interferon therapy:

- Subcutaneous injection
- Growth impairment
- Expensive.

Advantages of interferon therapy:

- No drug resistance
- Finite duration of treatment
- Durable treatment response
- Loss of HBsAg 5–8% cases.

Lamivudine

Lamivudine (3TC) is an oral nucleoside analog that inhibits HBV replication. It is approved for use in children aged 2–17 years who have compensated liver disease from chronic hepatitis B. In a placebo-controlled trial, in children who have chronic hepatitis B without HIV infection, lamivudine was well-tolerated, with virologic response (clearance of HBV DNA and HBeAg) in 23% of children receiving 52 weeks of lamivudine therapy, compared with 13% in placebo recipients.

Adefovir

Adefovir dipivoxil is an oral nucleotide analog active against HBV. Although active against HBV, adefovir has minimal anti-HIV activity, and HIV resistance has not been observed in patients receiving a 10 mg daily dose of adefovir for 48 weeks.

Safety and effectiveness of adefovir for treating chronic hepatitis B in children has not yet been established, but an ongoing randomized clinical trial is evaluating its use in HIV-uninfected children aged 2–17 years who have chronic hepatitis B.

Adefovir is now FDA-approved for adults who require treatment for chronic hepatitis B but do not yet require treatment for their HIV infection. Adefovir has been studied in HIV/HBV-coinfected adults with lamivudine-resistant HBV infection, and HBV suppression was demonstrated.

Other nucleotide analogs, like tenofovir, entecavir, telbivudine and emtricitabine are not recommended in children.

Advantages of Nucleoside Analog

- Oral delivery
- Negligible side effects
- Potent inhibition of virus replication
- Less expensive than IFN.

Disadvantages of Nucleoside Analog

- Drug resistance
- Long or indefinite treatment duration
- Low rate of HBsAg disappearance
- Moderately expensive when given for a long time.

Duration of Therapy

The optimal duration of therapy in HIV/HBV-coinfected children is not known. The duration of interferon-alpha treatment in HIV-uninfected children with chronic hepatitis B is 6 months. At least 1 year of lamivudine therapy is recommended for HIV-uninfected children who have chronic hepatitis B, with continuation of medication for more than or equal to 6 months after documented HBeAg seroconversion.

Monitoring of Treatment and Treatment Failure

The parameters of successful therapy for chronic hepatitis B are not well-defined, but markers of improvement include decreased hepatic necroinflammatory disease, normalization of serum transaminase levels, reduction of HBV DNA levels, and HBeAg seroconversion. In children starting treatment for chronic hepatitis B, serum transaminase levels should be measured every 3–6 months.

Monitoring of response to treatment for chronic hepatitis B is based on testing for HBV DNA and HBeAg and anti-HBe antibody on the same schedule as transaminase evaluations (every 3–6 months).

Among HBeAg-positive persons, treatment for chronic hepatitis B should be continued until HBeAg seroconversion has been achieved and more than or equal to 6 months of additional treatment have been completed after the appearance of anti-HBe. Close monitoring for relapse is needed after withdrawal of therapy.

Among persons who are HBeAg negative, treatment should be continued until HBsAg clearance has been achieved.

Management of Treatment Failure

Treatment failure is defined as ongoing HBV replication, persistent serum transaminase elevations, and the failure of HBeAg seroconversion in HBeAg-positive persons. Flares of liver disease with increasing HBV DNA levels can be seen with the development of *resistance to lamivudine or emtricitabine*. In some children who have received initial treatment for chronic hepatitis B with standard-dose interferon-alfa monotherapy, use of higher-dose interferon alfa for retreatment improves response. Lamivudine has also been used as secondary therapy for children without HIV infection who have not responded to standard interferon-alfa therapy in HIV-infected children, initiation of a lamivudine-based highly active antiretroviral therapy (HAART) regimen could be considered. For HIV/HBV-coinfected children developing lamivudine resistance during therapy, treatment options are more limited.

Treatment of HBV/HIV-coinfected Children

None of the clinical studies of treatment of chronic hepatitis B infection have specifically studied children with HIV/HBV coinfection. As in coinfected adults, choice of antiviral therapy for the HIV/HBV-coinfected child involves consideration of whether concurrent HIV treatment is warranted.

If treatment of chronic hepatitis B but not HIV infection is indicated, standard interferon alfa is the preferred agent. Adefovir also could be considered in older children able to receive adult dosing. Antiviral drugs with activity against HIV (e.g. lamivudine, emtricitabine, tenofovir, and possibly entecavir) should be avoided to prevent future development of drug-resistant HIV mutations.

- If treatment of HIV infection but not chronic hepatitis B is indicated, use of a HAART regimen that avoids drugs with activity against HBV (e.g. lamivudine, emtricitabine, or tenofovir) is recommended to prevent future development of HBV drug resistance. Alternatively, in older coinfected children who can receive tenofovir, use of a HAART regimen with a nucleoside analog backbone that contains two drugs effective against HBV (tenofovir plus lamivudine or emtricitabine) can be considered.
- If treatment for both HIV and chronic hepatitis B is indicated and the child is lamivudine-naïve, an antiretroviral regimen that includes lamivudine (or emtricitabine) is recommended. A regimen containing tenofovir and a nucleoside analog (either lamivudine or emtricitabine) is preferred for HIV/HBV-coinfected adults, and should be considered for use in older HIV-infected children or adolescents who can receive adult dosage. However, tenofovir is not approved for use in HIV-infected children less than 18 years, and no pediatric formulations are available. Although pediatric studies with an investigational pediatric formulation of tenofovir are under way, data are not yet available.
- If treatment for HIV and chronic hepatitis B is indicated and the child is receiving antiretroviral therapy including lamivudine or emtricitabine with HIV suppression but detectable plasma HBV DNA, HBV lamivudine resistance can be assumed. However, HBV drug-resistant isolates may have lower replicative capacity, and some experts recommend continued use of lamivudine or emtricitabine, although this recommendation is controversial.

Treatment options for such children who require HBV therapy include the addition of interferon therapy to the antiretroviral regimen, or tenofovir, or adefovir if the child can receive adult dosing. Data are insufficient on other anti-HBV drugs in children to make recommendations.

Prevention: Recommendations

Prevention of Exposure

All pregnant women should be tested for HBsAg during an early prenatal visit in each pregnancy. Testing should be repeated in late pregnancy for HBsAg-negative women at high risk for HBV infection (e.g. injection-drug users, women with intercurrent sexually transmitted infections, and women with multiple sex partners). Pregnancy is not a contraindication to hepatitis B vaccination for women who have not previously been vaccinated; current hepatitis B vaccines contain noninfectious HBsAg and should cause no risk to the fetus.

Preventing First Episode of Disease

- All infants born to HBV-infected women, including HIV coinfected women, should receive hepatitis B vaccine and hepatitis B immune globulin (HBIG) within 12 hours after birth, a second dose of hepatitis B vaccine at age of 6 weeks, and a third dose at age of 14 weeks.
- Currently, two well-recognized strategies are taken for primary hepatitis B vaccination. One preferable strategy is to give primary series vaccine at birth, followed by 6 weeks and third dose is given between 6 months and 18 months. Another strategy if not given at birth is to vaccinate at 6 weeks, 10 weeks and third dose is given between 6 months and 18 months. However, third dose can be given as early as 14 weeks which facilitates Hepatitis B vaccine to be given together with HepB containing combination vaccines like Penta or Hexa in same visit with one prick. The efficacy is found similar when third dose is given at more than or equal to 16 weeks after first dose. Similarly at 6 and 10 weeks, first and second dose can be given as combination vaccine with Penta and Hexa. In the same fashion, if first dose is given at birth, the subsequent vaccines can be given with primary Penta or Hexa series. In that case, one additional vaccine (1+3 primary vaccine) given will not be a problem.
- For preterm infants weighing less than 2,000 g, the initial vaccine dose given at birth should not be counted as part of the vaccine series because of the potentially reduced immunogenicity of hepatitis B vaccine in these infants; three further doses of vaccine (for a total of four doses) should be administered beginning when the infant reaches age 6 weeks followed by at 10, 14 weeks if hepatitis B containing combination vaccine is given or at 10 weeks and between 6 months and 18 months (final vaccine) if monovalent hepatitis B vaccine is used.
- A three-dose hepatitis B vaccine regimen is 95% effective in preventing HBV infection in HBV-exposed infants. Postvaccination testing for anti-HBs and HBsAg should be performed at age 9–18 months in infants born to HBsAg positive women. The level of anti-HBs that is considered protective is greater than 10 mIU/mL. Infants who are HBsAg negative and have anti-HBs levels less than 10 mIU/mL should be revaccinated with a second three-dose series of hepatitis B vaccine and retested 1–2 months after the final vaccine dose.
- The three-dose series of hepatitis B vaccine also is recommended for all children and adolescents aged less than 19 years who were not previously vaccinated. However, antibody responses to hepatitis B vaccination may be diminished in HIV-infected children, especially in older children or children with CD4 counts less than 200 cells/mm^3.
- In addition to hepatitis B vaccine, hepatitis A vaccine can prevent hepatitis infection and its potential devastating sequelae and thus all children should receive hepatitis A vaccination at age 12–23 months with the two doses in the series administered more than or equal to 6 months apart.

HEPATITIS C

The hepatitis C virus is a single positive-stranded RNA virus. Hepatitis C disease is uncommon in children.

Hepatitis C virus is transmitted through parenteral route, however, the role of inapparent parenteral or permucosal mode of transmission such as sexual activity, household contact and perinatal exposure is yet to be well-documented. *It is an important cause of post-transfusion hepatitis.*

There are three genotypes of HCV, namely genotype 1, 2 and 3. Prognosis and treatment strategy depends upon genotypic pattern.

Incubation period: Varies from 15–150 days.

Hepatitis C virus infection results in anicteric hepatitis in 75% cases. Fulminant hepatic failure is rare in acute hepatitis C. Chronicity is the hallmark of HCV infection irrespective of how the disease was initially contracted. Hepatitis C induced chronic liver disease occurs mostly in adults, although infection may be contacted in childhood. The serological course of HBC is given in Figure 8.

More than 50% of cases of acute hepatitis C develop chronic hepatitis; about 20% of these patients progress to cirrhosis and some of them eventually may develop hepatocellular carcinoma.

Diagnosis

It depends upon the detection of antibodies to HCV (anti-HCV). However, confirmation of viremia is done by the detection of HCV RNA by PCR. The average period for detection of anti-HCV is 12 weeks; however, it may take as long as 6 months.

Treatment (Algorithm of Management Protocol of Hepatitis C Virus Given in Figure 9)

- The treatment of hepatitis C is supportive. The alpha-interferon therapy should be considered for patients with well-compensated chronic hepatitis C with persistently raised serum transaminases. Antiviral treatment for hepatitis C has got better success than antiviral treatment of chronic hepatitis B as a whole. Up to 50% response to alpha-interferon, however relapses of 20–25%.
- Combination therapy with peginterferon and ribavirin for children 3 years and older with compensated HCV liver diseases.

Peginterferon Alpha-2b

60 μg/m^2 subcutaneously once per week.

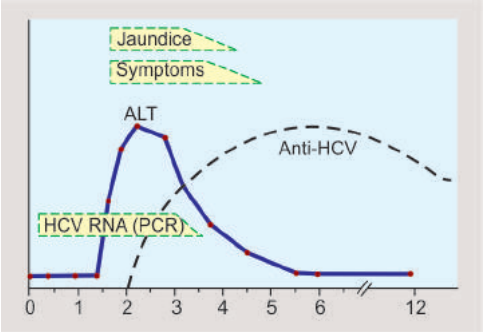


Fig. 8: The serologic course of acute hepatitis C
Abbreviations: HCV, hepatitis C virus; PCR, polymerase chain reaction

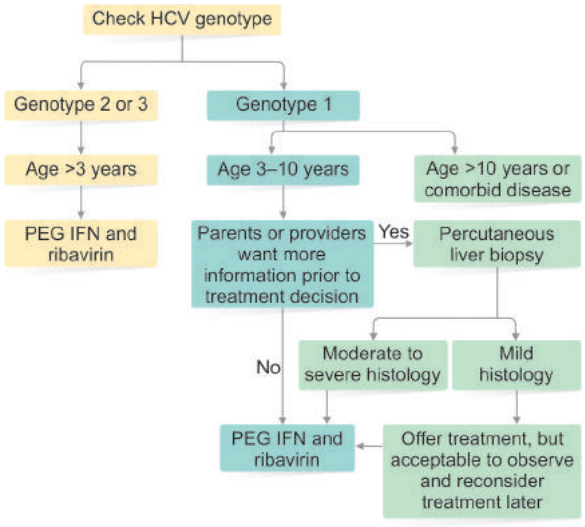


Fig. 9: Algorithm of management protocol of hepatitis C virus

Ribavirin

15 mg/kg/day orally with food divided into two doses.

Duration of Therapy

- For genotype 1: 48 weeks
- For genotype 2 and 3: 24 weeks.

Prevention

- Routine screening of blood donors for anti-HCV
- Use of disposable sterile syringes and hypodermic needles.

HEPATITIS D

Hepatitis D virus is also known as delta agent. It is the smallest animal virus known. It is a single-stranded RNA virus remaining within shell of HBsAg (Fig. 10). It cannot replicate on its own and it is infective only in presence of HBV. The maturation and completion of the course of HDV requires replication of HBV or at least expression of the genome coding for HBsAg (Fig. 11). Therefore, HDV can induce hepatitis in HBsAg positive host only.

Route of Transmission

Hepatitis D virus is transmitted mainly through parenteral route. Intravenous drug abusers are highly susceptible for HDV infection.

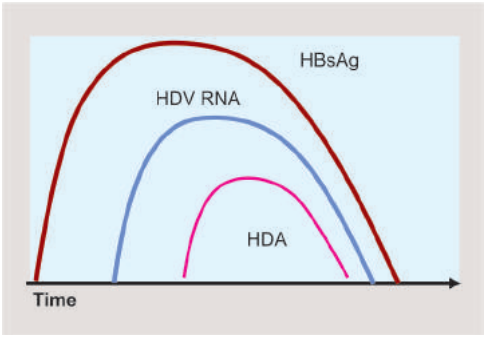


Fig. 10: Hepatitis D virus

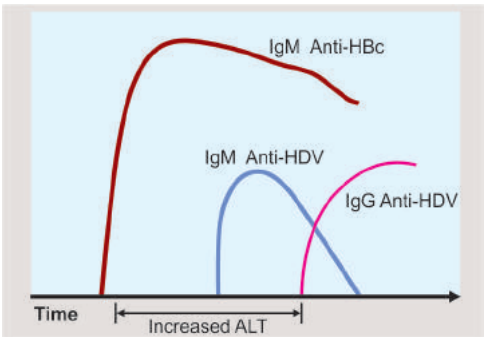


Fig. 11: Diagram of serological course of hepatitis D virus in presence of hepatitis B virus

Incubation Period

It ranges from 30 to 180 days.

Hepatitis D virus infection may occur simultaneously with HBV (coinfection) or it may infect a chronic HBV carrier (superinfection).

In coinfection, the hepatitis is of moderate form and the clinical picture is similar to that caused by HBV alone but there is increased risk of developing fulminant hepatitis. In coinfection, there is biphasic rise of aminotransferase. In superinfection, usually severe form of hepatitis develops which may be complicated by fulminant form. HDV superinfection should be suspected in a clinically stable HBV carrier who develops sudden flare-up hepatitis. The coinfection is diagnosed by detecting serum IgM anti-HDV in the presence of high-titer IgM anti-HBc. In superinfection, serum IgM anti-HDV is detected in the absence of IgM anti-HBc. However, IgM anti-HBc may be detected in low titers.

Considering its aggressive and progressive downhill course, alpha-interferon therapy should be attempted in all patients with chronic hepatitis D. The measures for the prevention of HDV provide prophylaxis of both HBV and HDV.

HEPATITIS E

Hepatitis E virus is a nonenveloped single-stranded RNA virus.

The HEV is transmitted enterically through fecally contaminated drinking water.

Incubation period: 2–9 weeks.

The HEV causes both sporadic and endemic acute hepatitis. Hepatitis E mainly occurs in young adults. About 20% patients develop cholestatic hepatitis. It may be complicated by fulminant hepatic and subhepatic failure. Hepatitis E in pregnancy, particularly in the third trimester, carries poor

prognosis with a mortality of about 20%. However, hepatitis E does not progress to chronic liver disease.

The acute hepatitis E is diagnosed by detecting serum IgM anti-HEV.

Therapy for hepatitis E is supportive. The preventive measures include improvement of sanitary and hygienic conditions, particularly water supply and sewerage.

LIVER FAILURE

Liver failure is a clinical syndrome rather than a specific disease entity. It represents the consequences of severe hepatocytic dysfunction and hepatocellular necrosis. Impairment of liver function is indicated by deranged synthesis of coagulation, detoxification and consequent encephalopathy. There are a multitude of causative factors, which differ between children and adults. Regardless of the antecedent cause, the clinical presentation is similar. The mortality is between 60% and 80% despite adequate care.

Definitions

Acute Liver Failure

This term is used for multisystem disorder in which severe impairment of liver function (INR ≥ 1.5 with encephalopathy or INR ≥2 with or without encephalopathy) occurs in association with hepatocellular necrosis in a patient with no recognized underlying chronic liver disease, within 8 weeks of the initial symptoms.

Fulminant Hepatic Failure

This term is used to describe patients without previous liver disease who develop a rapidly progressive liver failure within 4 weeks of onset of symptoms.

Hyperacute Liver Failure

If the features of ALF are evident within 1 week of onset of symptoms, it is termed as hyperacute liver failure.

Subacute Liver Failure

When the features of ALF are gradual occurring over 4 weeks to 6 months after onset of symptoms and associated with persistent icterus, ascites and/or encephalopathy.

Chronic Liver Failure

Appearance of signs of liver failure, such as hepatic encephalopathy and/or clinically detectable ascites at least 6 months after onset of hepatic illness.

Acute Liver Failure

Acute liver failure refers to the rapid development of severe acute liver injury with impaired synthetic function and encephalopathy in a person who previously had a normal liver or had well-compensated liver disease.

Epidemiology

The true incidence of ALF in children is not known. Approximately 0.2–1.0% of all acute hepatitis can progress to liver failure. Liver failure in children is different from adults; in children, especially in infancy, not only it is very difficult to identify signs of early encephalopathy but also encephalopathy can be a late presentation.

Etiology

Etiology of ALF not only provides indication of prognosis but also guides specific management option. In neonates, infections or inborn errors of metabolism are common, whereas viral hepatitis and metabolic causes are more likely in older children.

Hepatitis A is the most common form of hepatitis worldwide but it progresses to ALF only in 0.35% of cases. Patients with fulminant hepatitis A have a better prognosis with appropriate management than those with ALF due to any other cause; up to 70% of them may survive without resorting to transplantation.

Hepatitis B is the most common identifiable viral agent responsible for acute liver failure worldwide with fulminant hepatitis occurring in approximately 1% of cases.

Risk of acute liver failure increases by seven to eight times with coinfection or superinfection of HDV and HBV. Superinfection with HDV also carries greater risk of fulminant hepatitis than simultaneous infection (coinfection). Autoimmune liver disease may also present as acute liver failure. Intake of hepatotoxic drugs in a child with pre-existing liver disease of any etiology might enhance the probability of precipitating acute liver failure. Etiologies of acute liver failure are given in Table 7.

Pathophysiology

A thorough understanding of impaired hepatocyte synthetic functions and metabolic abnormalities associated with ALF is essential to quickly identify clinical features so that timely

Table 7: Etiology of acute liver failure

Viral hepatitis (isolated/mixed)
• Hepatitis A, B, C, D, E and others • Herpes simplex virus • Epstein-Barr virus • Parvovirus B19 • Varicella zoster • Cytomegalovirus • Adenovirus • Echovirus • Coxsackie virus
Drug-induced
• Acetaminophen (paracetamol) • Isoniazid • Halothane • Sodium valproate • Phenytoin
Metabolic cause
• Wilson's disease • Neonatal hemochromatosis • Tyrosinemia type 1 • Mitochondrial disorder • Hereditary fructose intolerance • Alpha-1 antitrypsin deficiency • Niemann-Pick disease • Indian childhood cirrhosis • Glycogen storage disease type IV • Urea cycle defect • Galactosemia
Autoimmune hepatitis
• Unknown causes

appropriate management of ALF can be done. Managing patients with ALF requires a thorough understanding of the many complications that can be present, including encephalopathy, cerebral edema, sepsis, renal failure, circulatory dysfunction, coagulopathy, gastrointestinal (GI) bleeding, and metabolic derangements, such as metabolic acidosis, hypoglycemia, and hypophosphatemia.

Important pathological and biochemical functions associated with liver failure are:

- *Coagulopathy*: Impaired synthesis of coagulation factors—important cause of GI bleeding
- *Encephalopathy*: Decreased hepatic ability to metabolize ammonia
- *Infection and sepsis*: Decreased synthesis of complement, albumin, decreased opsonization, altered WBC function, presence of central lines.
- *Hypoglycemia*: Depletion of hepatic glycogen store and impaired neoglucogenesis
- *Electrolyte imbalance*: Decreased Na^+, decreased K^+, decreased phosphate
- *Metabolic dysfunction*: Metabolic acidosis (due to tissue hypoperfusion → lactic acidosis)
- *Deepening of jaundice*: Hepatocytic dysfunction

Other pathologically ill understood but frequent SCr complications associated with ALF are:

- Cerebral edema
- Raised intracranial pressure (ICP)
- Acute renal failure
- Pulmonary dysfunction.

Clinical Features

Most patients with acute liver failure may have no elicitable history of any major medical problems or blood transfusion. Initially, the child has nonspecific prodromal symptoms such as malaise, nausea, fatigue, loss of appetite, followed by dark urine and jaundice.

Hepatic encephalopathy is one of the most important presentations of acute liver failure. Changes in sleep pattern and motor coordination are other early markers of hepatic encephalopathy.

The patients with acute liver failure are at high risk for metabolic (hypoglycemia) and electrolyte imbalance and infections. Presence of fever, leukocytosis, unexplained hypotension, severe acidosis and disseminated intravascular coagulation (DIC) indicates sepsis and warrants aggressive investigations for infection and appropriate management, while azotemia, oliguria, worsening encephalopathy indicates renal failure and appropriate management of renal failure. Cerebral edema is a major cause of mortality in patients with acute liver failure. A sustained rise of ICP to 30 mm of Hg or more is taken as an indication of raised ICP. Paroxysmal or sustained hypertension and increase in the tone of the muscles of the arms and/or legs is probably the earliest sign of raised ICP.

Hepatic encephalopathy:

Hepatic encephalopathy is a major complication of ALF. Although the precise mechanism remains unclear, the most widely accepted theory is related to increased production of ammonia from nitrogenous substances within the gut lumen and inability of failing liver to detoxicate increased ammonia produced from the gut lumen which affects brain resulting in encephalopathy and cerebral edema. Various stages of hepatic encephalopathy are given in Table 8 and Figure 12.

Cerebral edema:

Cerebral edema develops in 75–80% of patients with grade IV encephalopathy. Possible contributing factors include osmotic derangement in astrocytes, changes in cellular metabolism and alterations in cerebral blood flow.

Clinical manifestations*:*

The consequences of cerebral edema include elevated ICP and brainstem herniation, which are the most common causes of death in ALF. Cerebral edema also can lead to ischemia and hypoxic injury to the brain.

- The classic signs of elevated ICP include systemic hypertension, bradycardia, and irregular respirations (referred to as Cushing's triad).

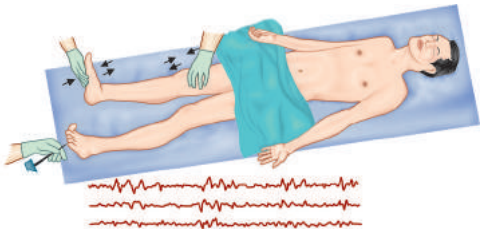


Fig. 12: Hepatic encephalopathy (stage III) with decreased level of consciousness (very sleepy) with positive Babinski sign with ankle and patellar clonus. Electroencephalogram showing slow waves suggestive of encephalopathy

Table 8: Staging of hepatic encephalopathy

Stage	Clinical manifestation	Asterixis	Electroencephalogram
Stage I	Slowness in mentation, disturbed sleep-wake cycle, incoordination	No	Minimal change
Stage II	Drowsiness, confusion, inappropriate behavior Disorientation, mood swing	Easily elicited	Usually generalized slowing of rhythm
Stage III	Very sleepy but arousable, unresponsive to verbal commands, markedly confused, delirious, hyperreflexia, positive Babinski sign	Present	Grossly abnormal slowing
Stage IV	Unconscious, decerebrate or decorticate response to pain in severe cases	Usually absent	Appearance of delta waves, decreased amplitudes

- Neurologic manifestations may include:
  - Increased muscle tone
  - Hyper-reflexia
  - Altered pupillary responses.

However, early in the course of ALF, these signs and symptoms may be absent or difficult to detect.

Sepsis:

Sepsis is evidenced by:

- Fever
- Leukocytosis
- Unexplained acidosis
- Hypotension
- DIC.

Management

Acute liver failure is a medical emergency associated with an unpredictable and an often fatal course; survival depends not only on the etiology, degree of hepatocyte damage, and capacity of liver to regenerate, but also on the intensive supportive medical care. The goals in the evaluation of any child with ALF are:

- To assess the severity of liver failure and the need for liver transplant
- To provide hepatic support till child recovers spontaneously or has liver transplantation
- To anticipate and prevent complications.

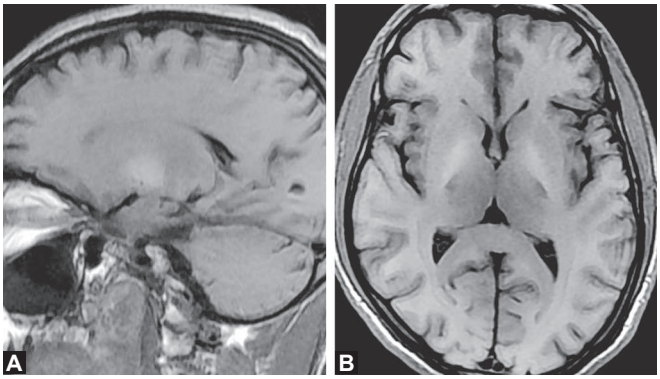
The child must be cared preferably in an ICU setting. This provides a calm and quiet environment, intensive monitoring facilities and quick access to life-supporting system.

Management consists of:

- Management of encephalopathy—depending upon the stage of encephalopathy
- Management of cerebral edema and raised intracranial pressure
- Management of infection or sepsis
- Management of coagulopathy
- Management of metabolic disturbances
- Management of hemodynamic disturbances
- Management of renal failure
- Nutritional management
- Management of pulmonary complications
- Supportive treatment for liver transplantation.

Following investigations should be done to assess ALF:

- Liver function test
  - Serum bilirubin, ALT, AST (AST >10,000 IU/L)
  - Serum albumin (hypoalbuminemia)
  - Prothrombin time (>40 sec)
- Full blood count
  - Increased WBC (sepsis)
  - Decreased platelet
- Plasma ammonia (>100 μmol/L)
- Blood glucose (decrease <3 mmol/L)
- Serum electrolytes ($\downarrow Na^+$, $\downarrow K^+$) and *blood gas analysis* (metabolic acidosis)
- Renal function test (BUN, serum creatinine)
- Septic screening
  - Blood culture
  - Urine culture
  - C-reactive protein (CRP)
  - Serum procalcitonin
  - X-ray chest.



Figs 13A and B: Sagittal and axial T1 images show bilateral symmetrical hyperintensity in the region of Globus pallidi in a patient with altered sensorium with liver failure suggestive of hepatic encephalopathy

- Electroencephalogram: To assess the severity of encephalopathy
- Computed tomography (CT) scan and MRI of brain (Fig. 13).

Investigation to know the underlying etiology may be deferred until the patient is stabilized hemodynamically and biochemical abnormalities are corrected.

The initial workup of the child should include identification of the stage of hepatic encephalopathy, assessment of metabolic derangement and also the presence of precipitating factors. Immediate outcome is determined by the degree of derangement in the hemodynamic parameters (circulating fluid volume, urine output) and biochemical abnormalities (blood sugar, urea, creatinine and electrolytes). After initial stabilization, further investigations are better if done simultaneously because stepwise investigation protocols cause unnecessary delays in arriving at a working diagnosis.

Guidelines for monitoring of patient with liver failure are given in Table 9.

Fluid and metabolic disturbances:

Appropriate management of fluid and metabolic abnormalities is important for improving outcomes.

Management guidelines for fluid and metabolic disturbances are given in Table 10.

Infections

- Patients with acute liver failure are at risk of infection but may not show fever and leukocytosis. Therapeutic antibiotic should cover both Gram-positive and Gram-negative bacteria and staphylococci. The empirical practice is to use a combination of third-generation cephalosporin and cloxacillin. Aminoglycosides are administered if renal function is normal. If there is no improvement within 72 hours, it is prudent to step up antibiotics to cover *Pseudomonas aeruginosa*, anaerobic organisms and/or fungi depending upon individual patient requirements.
- Consider antifungal agent like fluconazole if prolonged hospitalization, use of multiple antibiotics or steroid.

Hepatic encephalopathy:

- Bowel cleansing helps in decreasing the amount of ammonia in the gut by decreasing the colonic bacterial counts and changing the colonic milieu to acidic. To achieve adequate cleansing of the bowel, bowel washes need to be given 6–8 hourly with acidic fluid (like 0.5–2 mL/kg/dose of vinegar in half liter of water, maximum 30 mL/

Table 9: Monitoring of patient with acute liver failure

Clinical examination (4 hourly)
• Pulse rate • Respiratory rate • BP • Temperature • Fluid intake/output chart (6 hourly) • Neurological/coma grading (12 hourly)
Biochemical testing (12 hourly)
• Electrolytes • Sugar • Urea • pH • Bicarbonate
Parameters to be monitored (once daily)
• Weight • Liver span • Ascites • Evidence of bleeding or infection • Prothrombin time
Parameters to be monitored (twice weekly)
• LFT • Creatinine • Calcium • Phosphate
Parameters to be monitored (as required)
• Evidence of infection • Chest X-ray • Blood count • Blood and urine culture • ESR • C-reactive protein. • Urinary electrolytes, creatinine and osmolarity

Table 10: Fluid and metabolic disturbances

Fluid intake
• Normal maintenance requirement (10% Dextrose in N/5 saline)
Hypotension
• Resuscitate with normal saline, Ringer lactate, plasma or blood • If mean arterial pressure (diastolic pressure + 1/3 pulse pressure) is <60 mm Hg start dobutamine/dopamine
Metabolic acidosis
• Suspect fluid deficit; evaluate for sepsis
Hypokalemia
• Give KCl infusion/100 mL fluid according to serum K^+ level – 3 mEq (1.5 mL) if serum K^+ 3–3.50 mEq/L – 4 mEq (2.0 mL) if serum K^+ 2.50–3.0 mEq/L – 5 mEq (2.5 mL) if serum K^+ 2–2.5 mEq/L – 6 mEq (3.0 mL) if serum K^+ < 2 mEq/L
Hyponatremia (Na^+ <120 mEq/L)
• Restrict fluid to 66–75% maintenance • Restrict Na^+ infusion to less than 2 mEq/kg/day
Hypoglycemia (Blood glucose <3 mmol/L)
• Infuse 50% dextrose at 1 mL/kg • Increase dextrose concentration to maintain sugar between 100 mg/dL and 200 mg/dL.

dose) 6 hourly adjusted to produce two to four loose acidic stools per day. Syrup Lactulose 10–50 mL 2–4 hourly orally or in nasogastric tube can be given to produce two to four loose acidic stools per day.

- In patients with grade II encephalopathy, protein intake should be restricted. No sedative should be given as they interfere with the assessment of status of consciousness of the child. Anticonvulsants like phenytoin or phenobarbitone may be required if seizures are present. Prophylactic phenytoin can also be given for subclinical seizures or electrographic seizures.
- Patients should be ventilated in PICU electively if encephalopathy progresses to grade III or more.

Cerebral edema and raised intracranial pressure:

Cerebral edema is a serious complication found in up to 75–80% of patients with grade IV encephalopathy.

The goals to decrease cerebral edema can be accomplished using a combination of interventions:

- Patients should be placed in an environment with minimal sensory stimulation since stimulation can raise ICP. Placement of a nasogastric tube can cause gagging and thus their use should be minimized Similarly, endotracheal suction should be minimized
- Overhydration can elevate ICP. Thus, the fluid status of patients with ALF should be closely monitored
- The head of the patient's bed should be elevated to 30 degrees. However, bed elevation can also reduce cerebral perfusion. Thus, patients should remain supine if the cerebral perfusion pressure (CPP) falls below 50 mm Hg with bed elevation.

A standard approach has been suggested in patients who develop elevated ICP despite the above modalities.

- Patients with ICP above 20 mm Hg should be hyperventilated to keep the pCO_2 below 25 mm Hg (with intubation and ventilation)
- If no response or relapse is noted, mannitol (0.5–1 g/kg) should be administered as an IV bolus and then on an as-needed basis to maintain the plasma osmolality between 310 mOsmol/kg and 325 mOsmol/kg
- Dexamethasone: No role in cerebral edema due to hepatic failure.

Monitoring of intracranial pressure:

Four types of catheters have been used to measure ICP: epidural, subdural, parenchymal, and intraventricular.

An epidural ICP monitor should be placed in patients with grade IV encephalopathy or in patients in whom grade III encephalopathy is rapidly progressing. While CT scans do not provide a reliable assessment of intracranial pressure, they are useful to rule out other possible causes of rapidly altered mental status, such as intracranial hemorrhage which is a contraindication to insert ICP monitoring catheter.

Three parameters should be followed during intracranial pressure monitoring:

- Intracranial pressure
- Cerebral perfusion pressure
  Cerebral perfusion pressure is the difference between mean arterial pressure and intracranial pressure.
  The goals of therapy are to maintain the ICP below 20 mm Hg and the CPP above 50 mm Hg.
- Cerebral oxygen consumption.

Management of raised intracranial pressure:

The aim of management is to maintain ICP below 20–25 mm of Hg and cerebral perfusion pressure (mean arterial blood pressure—ICP) at >50 mm of Hg.

- Mannitol is the drug of choice and should be used as a rapid bolus of 0.5 g/kg as a 20% solution over a 15-minute

period. The dose can be repeated if the serum osmolarity is less than 320 mOsm/kg
- In cases of mannitol-resistant cerebral edema, sodium thiopental can be used at a bolus dose of 2–4 mg/kg over 15 minutes followed by a slow IV infusion between 1 and 2 mg/kg/hr (with intubation and ventilation in PICU)
- Dexamethasone has not proven to be effective in the treatment of cerebral edema caused by ALF and should not be administered
- Restrict fluid to 66–75% maintenance
- Patients are nursed with raised head end (30–45°) and head placed in a neutral position. There should be minimal handling of patients
- Hyperventilation and maintaining arterial pCO_2 level of 22–26 mm Hg has been shown to be effective in reducing the cerebral edema and increased ICP (with intubation and ventilation in PICU).

Induction of hypothermia
Hypothermia decreases cerebral edema core body temperature of 32–33°C is achieved using cooling blankets. It also reduces the use of inotropes. Risks of hypothermia are infection and cardiac arrhythmia.

Induction of hypernatremia
the induction of hypernatremia has the potential to decrease water influx into the brain and thereby reduce cerebral edema. Hypertonic saline infusion to maintain serum sodium levels of 145–155 mmol/L can sufficiently decrease elevated ICP.

Coagulopathy:
Coagulation defects require administration of fresh frozen plasma (FFP) or blood, preferably fresh. Platelets should be given in cases with thrombocytopenia.
- Prothrombin time >40 sec: Vitamin K at doses of 5–10 mg is administered intravenously or subcutaneously daily to increase the concentration of vitamin K dependent coagulation factors.
- Repeat IV vitamin K if PT is still prolonged after 3 hours.
- Fresh frozen plasma or blood transfusion (10 mL/kg)
- Gastrointestinal bleeds: Associated with coagulopathy
  - IV H_2 blockers (ranitidine: 3 mg/kg; omeprazole: 1–2 mg/kg).
- In extreme cases cryoprecipitate, coagulation factors like human recombinant rFVII can be effective.

Malnutrition:
Nutrition is a vital component in the treatment of ALF. In patients with grade I or II encephalopathy, oral or enteral feeding with a low protein diet is usually sufficient to meet metabolic requirements. Placement of a nasogastric tube can increase intracranial pressure (because of gagging) and thus should generally be performed only in patients who are intubated and sedated.

In patients with advanced encephalopathy, parenteral nutrition should be considered early to prevent catabolism of body stores of proteins.

Renal Failure and Hepatorenal Syndrome

Acute renal failure is noticed in 10–15% children with acute liver failure and can be prerenal or renal etiology.

The hepatorenal syndrome is indicated by:
- Decreasing urine output
- Rising blood urea and creatinine
- The urinary Na^+ is less than 10 mEq/L with urinary creatinine: Plasma creatinine ratio more than 30 and urinary osmolarity higher than plasma. There is no effective therapy, but salt and fluid restriction along with peritoneal dialysis/hemodialysis may be required.

Prevention of acute renal failure:
Ensure arterial perfusion by maintaining adequate systemic pressure, identifying and treating infection and avoid using nephrotoxic drugs.

Specific Treatment of Acute Liver Failure

Liver transplantation remains the backbone of treatment of ALF. However, depending upon etiology of ALF, specific therapy may be applied like administration of N-acetylcysteine (NAC) in acetaminophen (paracetamol) induced hepatic failure.

Encouraging results have also been reported with use of N-acetylcysteine (NAC) in children even with non-acetaminophen (non-paracetamol) induced liver failure if administered earlier because of its antioxidant anti-inflammatory property apart from its ability to increase glutathione in paracetamol poisoning.

Artificial Hepatic Assistant Devices

Extracorporeal assist devices currently under development use hepatocytes from human or nonhuman cell lines to provide synthetic capability.

Auxiliary Liver Transplantation

Auxiliary liver transplantation involves placement of a graft adjacent to the patient's native liver (auxiliary heterotopic liver transplantation) or in the hepatic bed after a portion of the native liver (auxiliary orthotopic liver transplantation) has been removed. A potential advantage is that this procedure may support the patient while the native liver regenerates, obviating the need for chronic immunosuppression. In addition, because only a relatively small portion of liver is required, the graft can be derived from a donor in whom the majority of the liver is used for a standard orthotopic liver or from a living-related donor, thereby increasing the number of available organs.

Bioartificial liver support systems have been developed which temporarily take over the functions of the liver without resorting to liver transplantation, thus giving the injured liver time to regenerate. These are of types, bioartificial and artificial. Bioartificial devices include the extracorporeal liver assist device (ELAD) and the bioartificial liver (BAL) which uses dialysis like cartridge, which house human hepatoblastoma cell line (ELAD) or porcine hepatocytes (BAL). The artificial device mostly used is the molecular adsorbent recycling system (MARS). Availability of these devices is limited in the country at present. The treatment of choice for these patients is liver transplantation. Overall survival rate for liver transplantation in children with acute liver failure is 60–70% as compared to 90% in children with chronic liver disease.

An algorithm of management steps in acute liver failure is shown in Figure 14.

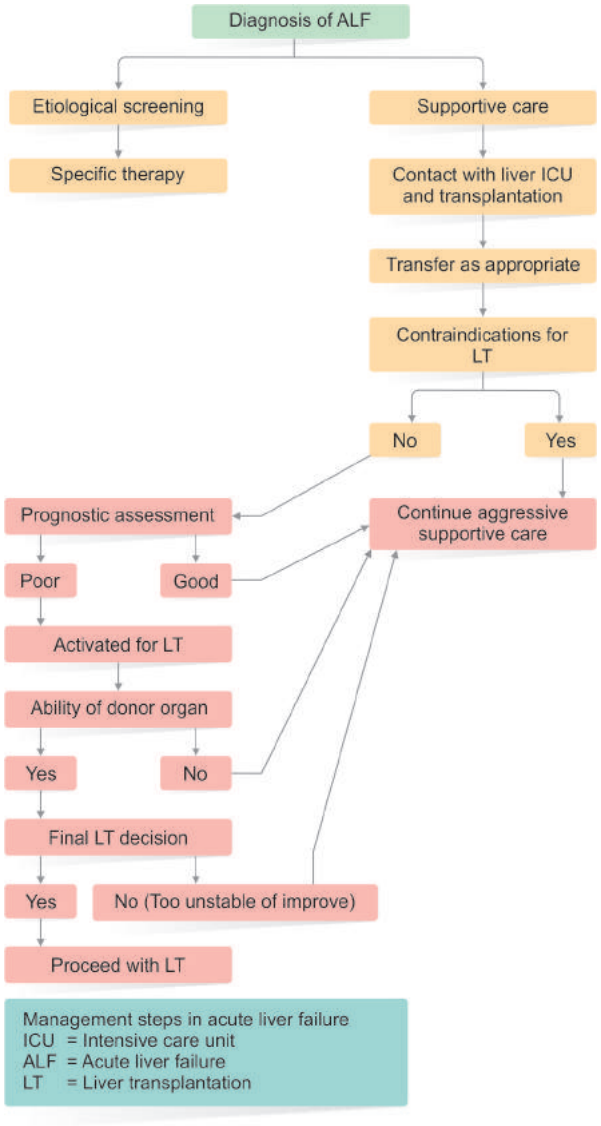


Fig. 14: Algorithm of management of ALF

Prognosis

Despite supportive care and nursing in intensive care units, 40–70% children with acute liver failure die.
Poor prognostic markers are:

- Grade III or more hepatic encephalopathy; prothrombin time more than 40 seconds
- Presence of sepsis or
- Chest infection.

Chronic Liver Failure

Chronic liver failure (CLF) is characterized by appearance of signs of liver failure such as hepatic encephalopathy and/or clinically detectable ascites at least 6 months after onset of hepatic illness.

Etiology

- Chronic hepatitis (positive hepatitis B or C)
- Biliary tree disease, e.g. biliary atresia
- Drug-induced, e.g. paracetamol
- α-1 antitrypsin deficiency
- Autoimmune hepatitis
- Wilson's disease (WD) (age >3 years)
- Cystic fibrosis
- Alagille syndrome
- Tyrosinemia
- Inflammatory bowel disease
- Budd-Chiari syndrome.

Presentation

- Jaundice (not always)
- Gastrointestinal hemorrhage (portal hypertension and variceal bleeding)
- Pruritus
- Failure to thrive
- Anemia
- Enlarged hard liver (though liver often small in cirrhosis)
- Nontender splenomegaly
- Hepatic stigmata, e.g. spider naevi
- Peripheral edema and/or ascites
- Nutritional disorders, e.g. rickets
- Developmental delay or deterioration in school performance
- Chronic encephalopathy.

Investigations

- Blood
  - Liver function test
    - Increased or ↔ bilirubin
    - Increased AST, ALT (2–10 times)
    - Albumin less than 35 g/L
  - Full blood count (↓ Hb if GI bleeding, decreased WBC count and platelet --- hypersplenism)
  - Coagulation profile (prothrombin time > 3 s if vitamin K deficiency)
  - Decreased blood glucose
  - Viral serology/PCR for hepatitis B and C
  - Increased IgG, decreased complement (C3, C4, autoimmune antibodies).
- Biochemical markers
  - Serum electrolytes (↓ Na^+ or ↓ Ca^{2+}, ↑ PO_4^{3-})
  - Increased alkaline phosphatase if biochemical rickets.
- Metabolic studies
  - Sweat test (cystic fibrosis); α-1 antitrypsin level and phenotype
  - Decreased serum copper and ceruloplasmin
  - Increased 24 houses urinary copper (Wilson's disease)
- Abdominal ultrasounds
  - Hepatomegaly
  - Echogenic liver
  - Splenomegaly
  - Ascites
- Upper GI endoscopy
  - Esophageal or gastric varices
  - Portal gastritis
- Electroencephalogram: To confirm chronic encephalopathy if suspected
- Liver biopsy (in specialized centers only): Histology, enzymes and electron microscopy.

Management

- Treat underlying cause and give nutritional support
- Lower protein, increased energy, increased carbohydrate diet

- Vitamin supplementation, particularly fat soluble vitamins A, D, E and K
- Involve dietician.
- Drug therapy
  - Prednisolone ± azathioprine for autoimmune hepatitis
  - Interferon-α ± ribavirin for chronic viral hepatitis
  - Penicillamine for Wilson's disease
  - Cholestyramin may be useful to control severe pruritus
  - Vitamin K and FFP (10 mL/kg) if significant coagulopathy and bleeding.
- Esophageal varices: Endoscopy, i.e. sclerotherapy or surgery
- Ascites
  - Fluid and Na^+ restriction (2/3rd of maintenance and sodium 1 mmol/kg/day respectively)
  - Spironolactone (1–2 mg/kg/12 hourly)
  - Consider IV 20% albumin if ascites resistant to above treatment
- Encephalopathy
- Decreased GI ammonia absorption by using oral lactulose or soluble fiber pectin
- Liver transplantation.

Prognosis

Up to 50% 5-year mortality without liver transplant. Poor prognostic factors are:

- Bilirubin >50 mol/L
- Albumin <30 g/L
- Prothrombin time >6 s
- Ascites
- Encephalopathy
- Malnutrition.

CHRONIC LIVER DISEASE

Chronic liver disease (CLD) may be defined as a continuing inflammatory lesion of the liver with the potential to either progress to more severe disease, to continue unchanged or to subside spontaneously or with treatment.

The possibility of CLD should be considered if clinical and biochemical abnormalities persist beyond the expected period of recovery from the acute liver disease.

The commonly used basis of using apparent duration of the disease (of greater than 6 months) is often misleading in children. Irreversible liver damage may have already taken place before any symptoms of liver disease are noticed and in the absence of clinical or laboratory features of chronic liver disease. Many disorders like autoimmune hepatitis and metabolic disorders should be considered as CLD at first contact, since left untreated, they have potential to progress to severe and incurable liver disease. However, the 6-month cutoff seems appropriate for chronic viral hepatitis due to B and C infection.

Grading and Staging of Chronic Liver Disease

Grading may be used to describe the severity of necroinflammatory activity in chronic hepatitis. The rationale of staging and grading is to record those features which indicate the severity and the progression of chronic hepatitis, and which might also be prognostic significance.

There are five criteria on which severity of chronic liver disease depend. These are serum bilirubin, prothrombin time, serum albumin, encephalopathy and the degree of ascites. Serum transaminases like serum AST, ALT do not correlate with the severity of CLD.

The severity of CLD is described in Table 11.

Severity of chronic liver diseases can be assessed by the Child-Turcotte-Pugh criteria (CTP).

Table 11: Child-Turcotte-Pugh scoring system

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
INR	<1.7	1.7–2.3	>2.3
Encephalopathy	None	Grade 1–2	Grade 3–4

Child A = Score 5–6, Child B = Score 7–9 and Child C = 10–15.
1-year patient survival for child A, B and C are— A: 100%, B: 80%, C: 45%.

Etiology

- Chronic viral hepatitis
  - Chronic hepatitis B
  - Chronic hepatitis C
- Autoimmune liver disease
  - Autoimmune hepatitis
  - Sclerosing cholangitis
  - Primary biliary cirrhosis
  - Overlap syndrome
- Metabolic liver disease
  - Wilson's disease
  - Hemochromatosis
  - Indian childhood cirrhosis
  - Hereditary fructose intolerance
  - Galactosemia
  - Gaucher's disease
  - Niemann-Pick disease
  - Wolman disease
  - Glycogen storage disease (GSD)
- Hepatic venous outflow tract obstruction
  - Budd-Chiari syndrome
  - Veno-occlusive disease.
- Congenital biliary malformations
  - Choledochal cyst
  - Congenital hepatic fibrosis
  - Caroli's disease.
- Cryptogenic.

Clinical Features (Fig. 15)

Insidious Onset

The patient may have clinical features of:

- Prolonged/repeated episodes of jaundice
- Features of portal hypertension
- Upper GI bleeding
- Abdominal distension
- Failure to thrive
- Shrunken or enlarged liver
- Presence of splenomegaly
- Ascites and cutaneous portosystemic shunts

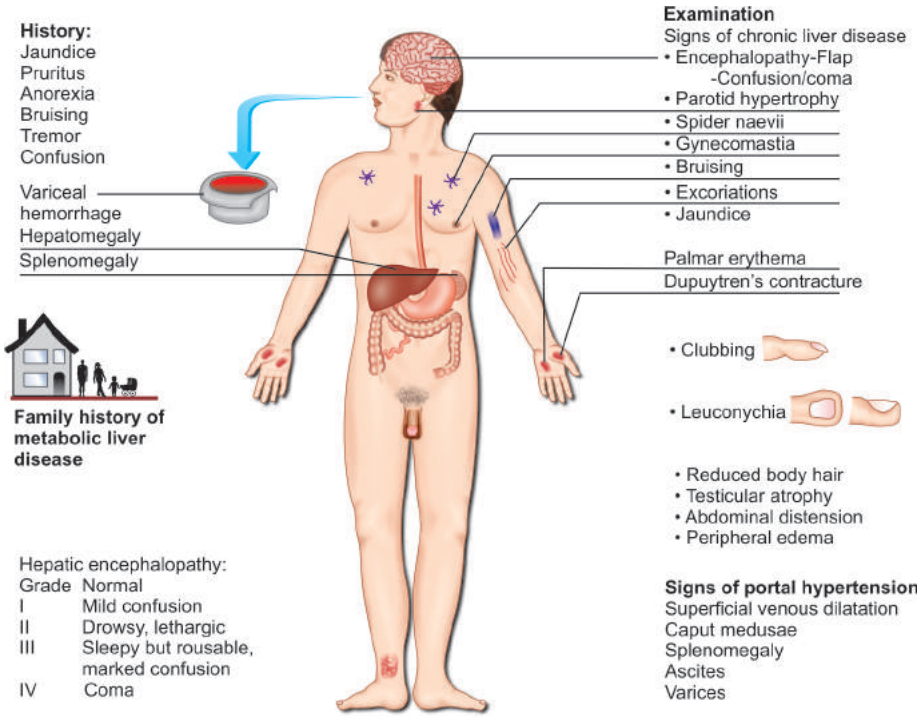


Fig. 15: Clinical features of chronic liver disease

- Encephalopathy
  - Flapping tremor, confusion/coma
- Jaundice
- Parotid hypertrophy
- Spider naevii, gynecomastia, testicular atrophy
- Bruising, reduced body hair
- Clubbing, leuconychia
- Excoriations
- Palmar erythema, Dupuytren's contracture
- Abdominal distension
- Peripheral edema.

Laboratory investigations may show:

- Increased transaminase
- Increased serum bilirubin
- With or without reversal of A:G ratio.

Acute Hepatitis

Metabolic and genetic disorders like Wilson's disease, α-1 antitrypsin deficiency and autoimmune hepatitis may present as acute viral hepatitis for the first time.

Asymptomatic Presentation

Occasionally, the condition is discovered in patients with no current or past history of jaundice. The only presenting feature might be hepatosplenomegaly with or without failure to thrive. Patients with any of the following features in the history should be suspected of having a CLD:

- History of conjugated hyperbilirubinemia in infancy
- Family history of CLD
- Inherited or autoimmune disorders
- Relapse of apparent acute hepatitis or persistence of clinical features of acute hepatitis for more than 3 months.

Clinical Examination Suggesting Chronic Liver Disease

- Jaundice (not always)
- Shrunken liver with enlarged left lobe
- Hard or nodular liver
- Ascites
- Edema
- Cutaneous portosystemic shunts
- Gastrointestinal bleeding
- Growth failure
- Muscle wasting
- Cutaneous features
  - Facial telangiectasia
  - Palmar erythema
  - Clubbing
  - Papular acrodermatitis
- Extrahepatic manifestation of autoimmune chronic hepatitis and presence of K-F (Kayser-Fleischer's) rings for Wilson's disease.

Diagnosis

The clinical features do not help differentiate between various etiologies. Investigations for diagnosis of CLD include estimation of blood levels of:

- Bilirubin
- Transaminase
- Alkaline phosphatase
- Serum proteins
- Prothrombin time
- Blood sugar
- Abdominal ultrasonography
- Upper GI endoscopy
- Liver biopsy to establish or rule out the disease (usually in marker negative acute hepatitis and children with suspected metabolic liver disease).

Specific Investigation

- Viral markers (HBsAg, HBeAg, anti-HCV)
- Autoantibodies (anti-SMA, ANA, anti-LKM-1, p-ANCA)

- Serum ceruloplasmin
- 24-hour urinary copper following penicillamine challenge
- Slit lamp examination for KF ring
- Liver biopsy
- Urinary reducing substances (clinitest) and urine glucose (clinistix) test (screening for galactosemia) urinary amino acid chromatography
- Enzyme assay (deficiency of galactose-1 phosphate uridyl transferase in galactosemia)
- Fructose tolerance test for hereditary fructose intolerance.

Other Investigations

- Hepatitis B virus DNA, HCV DNA
- Magnetic resonance cholangiopancreatography (MRCP)
- Endoscopic retrograde cholangiography (ERCP)
- Sigmoidoscopy
- Colonoscopy
- Bone marrow aspiration for abnormal storage materials (lipid storage disorders).

Complications of Chronic Liver Disease and Cirrhosis in Children

- Growth failure and malnutrition
- Hepatic encephalopathy
- Coagulopathy
- Hepatopulmonary syndrome
- Portal hypertension and variceal bleeding
- Ascites
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome
- Pruritus
- Hepatic osteodystrophy
- Endocrine dysfunction
- Hepatocellular carcinoma.

Management (Management of Specific Complications)

Ascites

Definition: Accumulation of fluid in the abdominal cavity in a child with liver disease usually indicates worsening portal hypertension and hepatic insufficiency.

It is a common major complication of decompensated cirrhosis. Onset may be insidious or precipitated by events such as GI bleeding, infections, or development of hepatoma.

Management:

- Nutritional support
- Dietary restriction of sodium should be considered
- Spironolactone at 2–3 mg/kg per day to 7 mg/kg per day
- If there is inadequate response, furosemide can be added; chlorothiazide is a preferred agent for long-term use
- If the ascites is still resistant, consider 20% human albumin infusion over 3–4 hours with furosemide cover
- Monitor weight, serum electrolytes, urea and creatinine closely
- If significant hyponatremia occurs, consider stopping diuretics and fluid restricts cautiously (50–75% of requirement)
- Therapeutic paracentesis should be considered in resistant ascites especially if compromising respiratory function. Concurrent infusion of albumin is recommended; replace 10% of the removed ascitic fluid volume with 20% albumin IV.
- Surgical invention apart from liver transplantation is rarely necessary but may include Le Veen shunt peritoneal to jugular) and transjugular intrahepatic portosystemic shunt (TIPS).

Spontaneous Bacterial Peritonitis

Definition: Bacterial infection of ascitic fluid in the absence of secondary cause such as bowel perforation or intra-abdominal abscess

Clinical features: These may be subtle, with fever and irritability.

Diagnosis:

- High index of suspicion in a child with ascites and non-specific deterioration is required
- Abdominal paracentesis and ascitic fluid microscopy and culture are essential. Presence of polymorphonuclear cell (PMN) >250/mm^3 is diagnostic and usually the infection is monomicrobial.

Treatment:

- Intravenous antibiotics, usually third-generation cephalosporins are the first choice but should be guided by the microbiologist and the culture yield. The duration of treatment is 5–7 days.
- Recurrent episodes of SBP should lead to consideration for liver transplantation.

Hepatorenal Syndrome

Definition: Functional renal failure in patients with severe liver disease.

Diagnosis:

- Exclusion of all other potential causes or renal impairment especially hypovolemia, shock, nephrotoxic drugs or kidney disease
- Hereditary tyrosinemia, Alagille syndrome and polycystic liver kidney disease are conditions where chronic liver disease occur concomitantly
- Urine sodium <10 mmol/L and urine: Plasma creatinine ratio <10 helps rule out ATN or glomerular disease
- Glomerular filtration rate (GFR) is markedly reduced.

Treatment:

- Hemofiltration may be used whilst awaiting transplant
- Terlipressin has been used with some success in adults
- Liver transplantation usually reverses the condition.

Pulmonary Complication

Hepatopulmonary syndrome:

Definition

- Triad of hypoxemia (SaO_2 <90%), intrapulmonary vascular dilatation and liver disease
- Arterial PaO_2 <70% room air with alveolar arterial gradient of >20 mm Hg.

Diagnosis

- High index of suspicion
- Cyanosis, digital clubbing with or without spider naevi is suggestive. Typically, there may be dyspnea on standing, improving on lying down (platypnea) with associated change in PaO_2 (orthodeoxia).

- Suggested diagnostic criteria are: (1) Presence of chronic liver disease; (2) Absence of intrinsic cardiopulmonary disease; (3) Pulmonary gas exchange abnormalities; (4) Evidence of intrapulmonary vascular shunting
- The intrapulmonary vascular shunting can be demonstrated by technetium 99m-labeled macroaggregated albumin study, or by contrast-enhanced echocardiography.

Management
Definitive treatment is by timely liver transplantation. Liver transplantation should be considered once the shunt on technetium 99m-labeled macroaggregated albumin scan is >5%.

Pruritus:

Definition: A complication of cholestatic liver disease; when intense, may affect sleep, feeding, and behavior.

Management
- Antihistamines are used as first line but are usually ineffective
- Phenobarbital and choleretics are helpful
- Ursodeoxycholic acid may help by improving bile flow
- Rifampicin may improve bile flow
- IV naloxone, plasmapheresis, acupuncture and photo-therapy may be used if itching is very intense
- Partial biliary diversion has been found to be helpful in children.

Endocrine dysfunction:

Definition
The regulation and function of multiple endocrine systems is affected in CLD. These are more frequent and more severe with progression of liver disease and development of portal hypertension.

Diagnosis
- In adolescent boys, the clinical features may include loss of muscle mass, testicular atrophy, palmar erythema and spider naevi. Adolescent girls may have amenorrhea or menstrual irregularities. The features of hypothyroidism may be nonspecific
- Total testosterone and free testosterone and estrogen levels along with LH and FSH levels may be helpful in older adolescent but are difficult to interpret in early puberty
- Low free T3 and high TSH suggest hypothyroidism; when there is uncertainty in diagnosis TRH stimulation test may be required.

Management
- Hypothyroidism is treated with levothyroxine; monitoring of treatment should be based on clinical response and free T_4 and TSH levels
- There is minimal data on treatment of feminization and hypogonadism in children and adolescent
- The long-term effects of liver transplant on recovery of endocrine dysfunction are not fully defined.

Dietary Management in Chronic Liver Disease

- Infants (0–1 years)
  - Energy and protein daily requirement
    - Energy: 100–150 kcal/kg depending upon degree of malabsorption, hypermetabolism, disease state
    - Protein 2–4 gm/kg
  - Feed
    - Aim for 150–180 mL/kg formula via oral or nasogastric (NG) tube
    - If cholestatic, use formula containing at least 50% of fat content as medium chain triglyceride (MCT)
    - Formulas with >75% MCT fat should be used with caution, as essential fatty acid deficiency has been reported when higher MCT are used.
    - If breastfed, give at least 100 mL/kg formula containing MCT in addition to breast milk.
  - Additional energy
    - If inadequate growth despite adequate intake of MCT-based formula:
      Supplement formula to provide 80–100 kcal, 2–2.6 g protein per 100 mL formula. This can be done by:
      - Concentrating the MCT-based formula to 15–17% w/v as tolerated
      - Addition of energy and protein supple ments to formula
      - High-energy formula if not cholestatic
- Preschool children
  - Energy and protein daily requirement
    - Energy: 120–150% elemental diet depending upon degree of malabsorption, hypermetabolism, disease state
    - Protein 3–6 gm/kg per day
  - Diet
    - High calorie-high protein diet; frequent meals/snacks
    - To ensure an energy-dense diet, fats should not be restricted although if symptomatic steatorrhea, adjust fat intake according to tolerance.
  - Nutritional supplements
    - Oral
    - High calorie-high protein nutritional supplement
    - It may be preferable to use one of the supplements containing MCT if there is cholestasis. An MCT emulsion can be given as additional energy supplement 10–30 mL per dose to tolerance
  - Nasogastric: If the child is unable to achieve growth with above measures, then supplementary nasogastric feeding is required which is ensured by continuous pump overnight feeding.

METABOLIC LIVER DISEASE

Liver has a central role in synthetic, degradative and regulatory pathways involving carbohydrates, proteins and lipids. Defects in the degradation of fructose, galactose, glycogen, amino acids, fatty acids and ketones lead to significant liver dysfunction by causing pathologic alteration of blood glucose, ammonia, lactate and ketone levels and pH. Metabolic diseases account for up to 15–20% patients of chronic liver disease.

Etiology

Etiology of Metabolic Liver Diseases in Children

- Wilson's disease
- Glycogen storage disease
- Hereditary fructose intolerance
- Lipid storage disorder

- Gaucher's disease
- Bile acid metabolic defects
- Tyrosinemia
- Hemochromatosis
- Organic acidemia
- Galactosemia
- Indian childhood cirrhosis
- Byler's disease
- Niemann-Pick disease
- Unknown.

Clinical Features

Metabolic liver diseases can broadly be classified under four main headings on the basis of their dominant clinical presentation, cholestasis, hepatocellular necrosis (acute/subacute), cirrhosis and hepatomegaly. Clinical signs and symptoms of most metabolic liver diseases are similar and indistinguishable from those seen in acquired hepatic disorders such as infection, intoxication and immunologic diseases. Most of the metabolic diseases affecting liver presents with hepatomegaly documented incidentally with or without splenomegaly. Most of them are asymptomatic and anicteric. It may be associated with failure to thrive, diarrhea, fever, etc.

Features of Metabolic Liver Diseases

- Hypoglycemia, lactic acidema, hyperammonemia
- Recurrent vomiting, failure to thrive, dysmorphic facies
- Rickets, unusual odors in urine or sweat, cataracts, cardiac dysfunction
- Developmental delay, hypotonia, neuromuscular deterioration, seizures.

Clinical Approach for Diagnosis of Metabolic Liver Disease

History

- Seizures due to hypoglycemia
- Failure to thrive
- Vomiting
- Visual impairment
- Developmental delay.

Examination

- Look for nutritional status
  - Look for evidence for wasting, stunting—GSD
  - Evidence of rickets (tyrosinemia, pseudo-Hurler syndrome)
- Eye sign
  - Look for cataract—galactosemia
  - KF ring—Wilson's disease
  - Cherry red spot on fundoscopy—Niemann-Pick, Tay-Sachs
- Eye movement disorder: Gaucher's disease
- Perabdominal examination
  - Hepatomegaly
- CNS
  - Muscle tone and reflex: Dystonia, spasticity: In Tai-Sachs, Gaucher's type III
  - Hypotonia: GSD.

Confirmation of the diagnosis of specific metabolic disease has important implications not only clinically and therapeutically, but also for family screening.

A very high index of suspicion is required for timely diagnosis of metabolic liver diseases.

History of consanguinity, ethnicity and neonatal death in family should alert the treating physician to strongly consider metabolic cause.

Diagnostic laboratory evaluation of liver diseases must be broad and should include workup of most common metabolic causes, especially so in neonates. Diagnosis of metabolic liver disease requires availability of specific tests.

The pointers towards metabolic liver diseases are:

- Younger age (<2 years)
- Hepatomegaly with no jaundice
- Associated hypoglycemia, metabolic acidosis, vacuolated cytoplasm or intracellular deposits on liver biopsy.

It is important to establish the exact etiology as management is etiology-specific.

Specific Investigations

This includes:

Serum/plasma

- Galactose-1-phosphate uridyl transferase (GALT) assay: quantitative and qualitative
- Aminoacidogram
- Ammonia
- pH and bicarbonate
- Lactate
- Ceruloplasmin
- Serum copper (for Wilson's disease)
- Lysosomal enzyme study (specific enzyme deficiencies: Gaucher's, GM1, GM2 gangliosidosis, Niemann-Pick)
- Pyruvate
- 3-hydroxybutyrate
- Acetoacetate
- Transferrin saturation
- Ferritin
- Alpha-fetoprotein
- Very long chain fatty acids
- Urine succinylacetone
- Ketones
- Organic acids: Esporotic acid and bile acids
- Sweat chloride.

Urine

- Clinitest for reducing substances
- Clinitix test for glucose to exclude galactosemia
- Urine aminoacid chromatography
- Urine sugar chromatography
- Urine ketones.

Bone marrow biopsy

- Lipid engorged Gaucher's cells
- Sea blue histiocytes: In Niemann-Pick.

Management

Management is two pronged:

1. Specific treatment of the underlying disease
2. Supportive therapy for arrest and reversal of liver damage.

Specific Therapy

Whenever specific therapy is available and affordable, it must be offered, e.g.:

- Chelation therapy for Wilson's disease d-penicillamine

- 2-nitro, 4-trifluoromethylbenzoyl-1, 3-cyclohexanedione (NTBC) for tyrosinemia
- Galactose-free milk (galactomin) in galactosemia.

Supportive Therapy

Supportive therapy with:

- Hepatoprotective agents
- Antioxidants
- Nutritional support
- Vaccines (hepatitis A and B) if specific therapy is not available.

Liver transplantation has emerged as the definite treatment modality of most of the metabolic diseases and outcomes are encouraging.

NONALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease (NAFLD) describes a spectrum of liver disease in persons who have not consumed alcohol in significant amounts so as to cause liver damage, and in whom no other known etiology for fatty liver is present. The pathological spectrum ranges from simple hepatic steatosis to infiltration by inflammatory cells and mild to moderate fibrosis (nonalcoholic steatohepatitis—NASH) leading to cirrhosis.

Although exact prevalence of NASH/NAFLD is not known, the prevalence of NAFLD in obese children is reported to range from 20% to 77%.

Pathogenesis (Fig. 16)

Pathogenesis of nonalcoholic fatty liver disease is shown in Figure 16.

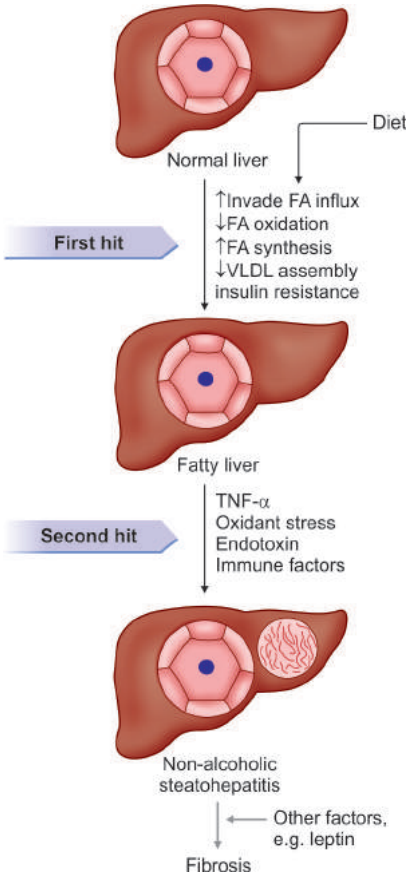


Fig. 16: Pathogenesis of nonalcoholic fatty liver disease

Etiology

The causes of fatty liver in children include:

Hepatic cause
• Overweight and obesity-related
• Metabolic liver diseases (Wilson's disease, galactosemia, hereditary fructose intolerance, glycogen storage disorders, etc.)
• Syndromes (Schwachman-Diamond syndrome, Berdet-Biedel syndrome, lipodystrophy syndromes, Turner's syndrome, Prader-Willi syndrome)
• Chronic viral hepatitis C
• Autoimmune hepatitis, sclerosing cholangitis

Nonhepatic cause
• Nutritional: Prolonged protein calorie malnutrition, total parenteral nutrition, starvation
• Infections: HIV
• Drugs: Glucocorticoides, hypervitaminosis A, methotrexate, L-asparaginase, zidovudine • Toxins: *Amanita phalloides*
• Diabetes mellitus
• Inflammatory bowel disease, cystic fibrosis, celiac disease, nephrotic syndrome

Diagnosis

These children are mostly asymptomatic and detected to have incidental hepatomegaly or raised transaminases while evaluating for abdominal pain or some other cause.

- Alanine aminotransferase and AST levels may be elevated to up to five times the upper limit of normal
- Ultrasonography
- CT and MRI scanning are reliable for detecting moderate to severe fatty changes in the liver but no imaging method is able to distinguish between simple steatosis and NASH and/or indicate the stage of fibrosis.
- Liver biopsy changes include:
  - Microvesicular steatosis
  - Perisinusoidal or pericellular fibrosis
  - Foci of lobular inflammation
  - Lipid granuloma
  - Mallory hyaline and megamitochondria.

Diagnosis is made after clinicopathologic correlation and exclusion of other causes.

Management

- The key principles of NASH management are weight reduction and hepatocyte protection. Normalization of serum aminotransferases and steatosis occurs with weight reduction
- Dietary modification, changes in lifestyle with increasing physical activity is the key for this effort
- Ursodeoxycholic acid and vitamin E have been used in NASH with promising effects.

WILSON'S DISEASE

Wilson's disease is an inborn error of metabolism characterized by toxic accumulation of copper in liver, brain, cornea and other tissues. The hallmarks of the disease are:

- Presence of liver disease
- Neurological symptoms
- Kayser-Fleischer's corneal ring (Fig. 17).

Clinical Features

Clinical features are given in Table 12.

Algorithmic Approach of Diagnostic Tests for Wilson's Disease

Algorithmic approach of diagnostic tests for Wilson's disease is given in Figure 18.

Treatment

Drugs approved for the treatment of Wilson disease include trientine, d-penicillamine, and zinc. Trientine and penicillamine promote the urinary excretion of copper; zinc blocks copper absorption and promote fecal excretion.

Acute liver necrosis and chronic hepatitis may respond to anti-copper therapy quite dramatically.

Liver transplantation is indicated for patients with Wilson disease and fulminant hepatic failure or decompensation of chronic liver disease despite medical therapy.

GLYCOGEN STORAGE DISEASES

The glycogen storage diseases are a group of genetic disorders involving the pathways for storage of carbohydrate as glycogen and for its utilization to maintain blood sugar and to provide energy. The disorders therefore are associated with increase in glycogen content in tissues like liver, muscle, etc. causing visceromegaly. The glycogen storage diseases have been clinically recognized since 1929. In 1962, Coris demonstrated a deficiency of glucose-6-phosphate in Von-Gierkes (liver involvement). Enzyme studies since then have been the bases for the delineation of numerous other genetically determined abnormalities of glycogen metabolism. Glycogen storage disease is a rare disease. One of the most common liver

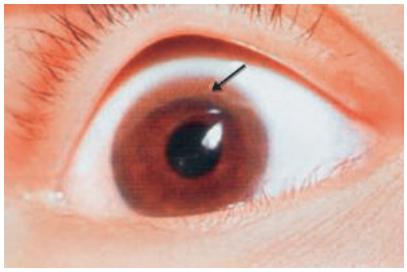


Fig. 17: Kayser-Fleischer rings at the junction of the cornea and sclera (arrow) in a patient with Wilson's disease

Table 12: Clinical features in patients with Wilson's disease

Hepatic	• Asymptomatic hepatomegaly • Isolated splenomegaly • Persisted elevated liver enzyme (ALT, AST) • Acute liver failure	• Fatty liver • Acute hepatitis • Resembling autoimmune hepatitis • Cirrhosis
Neurological	• Movement disorder (tremor, involuntary movements) • Drooling • Dysarthria • Rigid dystonia • Pseudobulbar palsy	• Dysautonomia • Migraine headache • Insomnia • Seizures
Psychiatric	• Depression • Neurotic behavior	• Personality change • Psychosis
Other system	• Ocular: K-F (Kayser-Fleischer) rings • Sunflower cataract	• Cardiomyopathy, dysrhythmias • Pancreatitis • Hypoparathyroidism • Rickets, osteomalacia and arthritis • Cholelithiasis

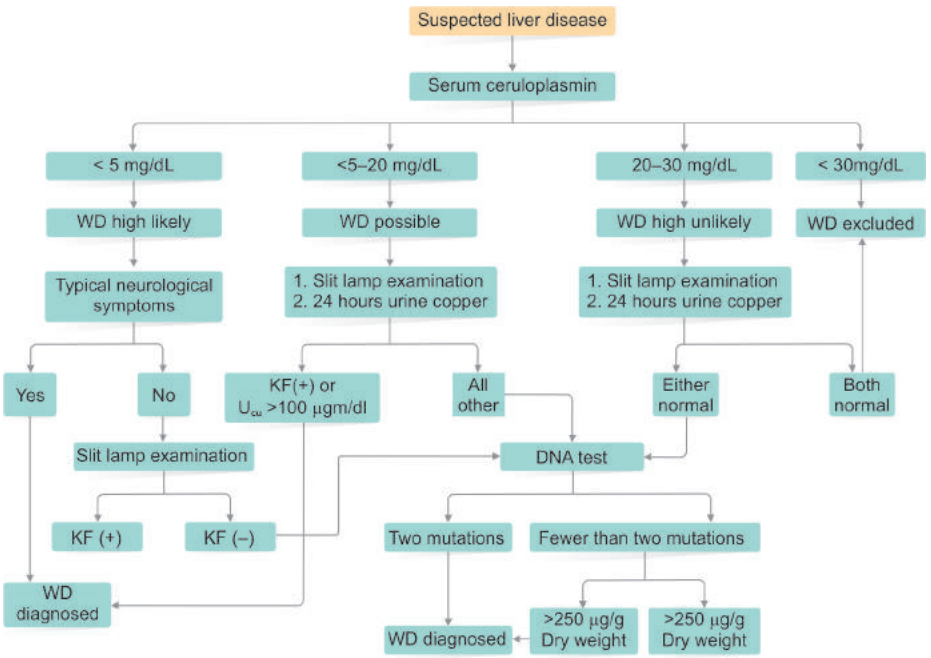


Fig. 18: Diagnostic approach of diagnostic tests for Wilson's disease
Abbreviations: WD, Wilson's disease; KF, Kayser Feischer ring; DNA Deoxyribonucleic acid

Table 13: Types of glycogen storage disease

Type	Enzyme defect	Onset	Liver	Muscle	Features
Type I von Gierke	Glucose-6-phosphatase	Infant	+++	–	• Enlarged liver and kidneys • Growth failure. Hypoglycemia • Good prognosis
Type II Pompe	Lysosomal α-glucosidase	Infant	++	+++	• Hypotonia and cardiomegaly at several months. Death from heart failure
Type III Cori (Type IIIa)	Amylo-1,6-glucosidase	Infant	++	+	• Milder features of type I, but muscles may be affected • Good prognosis
Type V McArdle	Phosphorylase	Child	–	++	• Temporary weakness and cramps muscles after exercise • Myoglobinuria in later life

Table 14: Distinguishing clinical and biochemical features of three most common hepatic glycogenesis

	Type I GSD	Type III GSD	Type VI GSD
Symptoms	Symptomatic Hypoglycemic convulsion Fit, apnea	Usually asymptomatic	Usually asymptomatic
Serum lipid and uric acid	↑↑	↑	↑
Glucagon tolerance test (post prandial)	No rise of glucose	↑ Glucose	↑ Glucose
Glucose tolerance (fasting)	No rise of glucose	No rise of glucose	↑ Glucose
Serum lactate	↑ on fasting	↑ on fasting	↑ on galactose ingestion

glycogenesis, type-I glycogen storage disease has an incidence of 1 in 100,000–400,000.

Glycogen storage disease is an autosomal recessive condition, with close association with consanguineous marriage with multiple affected sibs, both male and female, with normal parents. Diagnosis of hepatic GSD can be made in patient with hepatomegaly and tendency to hypoglycemia, who have normal liver function tests, with exception of serum transaminases, which are often mildly elevated in GSD patients. Of the hepatic GSDs, type I (von Gierkes disease), type II (Pompe), type III (Debrancher) and type VI (hepatic phosphorylase - hers disease) are most frequently diagnosed. Having made a tentative diagnosis of GSD, the three enzyme deficiencies can be distinguished clinically and biochemically.

Of all hepatic glycogenesis, type I GSD due to enzyme deficiency glucose-6-phosphatase is the most severe, with the tendency of hypoglycemia is most outstanding and can be life-threatening. The other two conditions are milder, and with the exception of hepatomegaly, clinical symptoms including symptomatic hypoglycemia seldom occur. Moreover, hyperlipidemia and hyperuricemia are more commonly found in type-I GSD. However, the disease can be confirmed by assay of enzymes from liver tissue or leukocytes. Types of GSD and their characteristic features are given in Table 13.

A screening procedure can be made for differentiation of the three most frequent enzyme deficiencies, by glucose, glucagon and galactose tolerance test as follows (Table 14):

1. In glucose-6-phosphatase deficiency, fasting lactate is abnormally high and decreases steadily after glucose ingestion, where in debranching enzyme deficiency, fasting lactate is normal and increases markedly with glucose ingestion.
2. In phosphorylase deficiency, there is equivocal rise of lactate with glucose but increased with galactose, glucagon (test for glycogenolysis) tolerance will show no rise of glucose, by glucagon ingestion in type I GSD.

The two other types can be differentiated by glucagon test in fasting state only. If a normal glucose curve is observed, type VI (phosphorylase deficiency) is more probable. A postprandial glucagon test in patient with debranching enzyme deficiency will however give a normal result with glucose rise. Distinguishing clinical and biochemical features of these three common GSDs are given in Table 14.

Biochemical Pathways of Glucose-6-phosphatase Deficiency Resulting in (Type I GSD) Hyperlipidemia and Hyperuricemia (Fig. 19)

The disorder usually manifests during the first 12 months of life by symptomatic hypoglycemia or by recognition of hepatomegaly. Occasional patients experience hypoglycemia in the immediate neonatal period with apnea or refractive convulsion, and there are rare patients who will never have hypoglycemia. Convulsion accompanying severe degree hypoglycemia may occur during the first year of life while in others, profound hypoglycemia is seen without clinical symptoms.

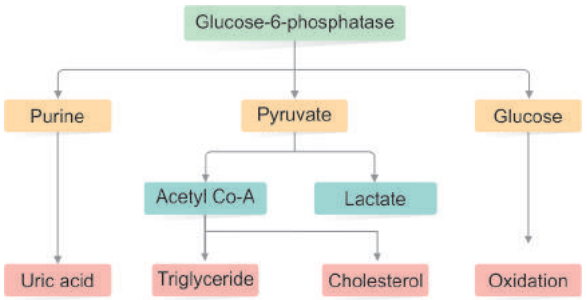


Fig. 19: Biochemical pathway of glucose-6-phosphatase

Clinical Features (Fig. 20)

- A dull cheek rounded face
- A protuberance abdomen due to marked hepatomegaly without splenomegaly and thin extremities
- Growth is usually normal for the first few months of life. Growth retardation then supervenes
- Short stature without disproportion of head, limbs and trunk length
- The musculature is poorly developed and flabby.
- Hyperlipidemia: Without glucose-6-phosphatase activity glucose-6-phosphate is converted to purine than to uric acid and pyruvate, which is converted to lactate and acetyl-Co-A, the substrate for triglyceride and cholesterol synthesis
- Paramacular lesion in the fundi seems to be quite specific for this disorder
- Hyperuricemia
  In type I GSD by two mechanisms:
  - Increased uric acid synthesis
  - Decreased renal urate clearance
- Defective platelet aggregation and adhesion
- Steatorrhea occurs in some patients.

Characteristic biochemical features are following:

- Hypoglycemia
  - Abnormal glucose tolerance test with sharp rise and delayed fall
  - Galactose tolerance test is also abnormal due to inability of these patients to convert galactose into glucose
  - Decreased response to blood sugar to epinephrine and glucagon
- In spite of huge hepatomegaly, liver function tests are usually normal, except liver enzymes which may be mildly elevated.

Linear growth and motor development are usually retarded but intelligence needs not to be retarded unless severe hypoglycemia has been a problem.

With increasing age, fasting hypoglycemia becomes less severe. The disease is compatible with a reasonably long life. During adult life, uric acid nephropathy may develop.

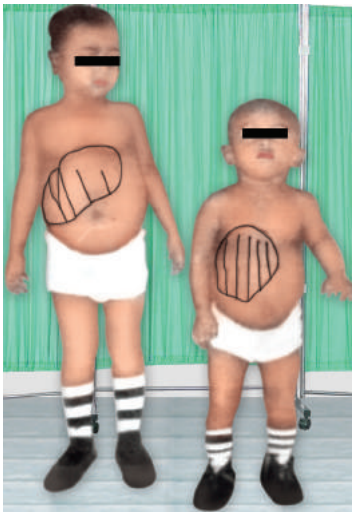


Fig. 20: Picture of two siblings showing rounded face, protruberance of abdomen, huge hepatomegaly (marked area) suffering from GSD type I

Source: Shakur MS, Hossain AT. Hepatic glycogen storage disease: Case reports in two sibling of a family. DS (child) HJ. 1992;1-2:66-71.

Prenatal diagnosis is difficult. It can be made by enzymes study from fetal tissue (liver) biopsy and from fetal blood sampling by cordocentesis.

Management

- The mainstay of management is frequent feeding. The most widely used approach in children has been the combination of frequent daytime feeding by mouth and continuous night-time feeding by nasogastric tube
- Raw cornstarch feeding provides a convenient, economical and palatable source of slowly digested glucose polymer and cornstarch therapy may become the primary dietary treatment for this disease
- Diazoxide has been used to increase blood sugar
- Portocaval shunt was found to reduce liver glycogen by over 50% in USA and was found, most promising surgical procedure.

PORTAL HYPERTENSION

Portal hypertension (PH) is one of the commonest causes of GI bleeding in children. PH is defined as clinical syndrome in which the pressure in the portal vein rises above 10–12 mm of Hg (normal value being 7 mm of Hg).

Pathophysiology (Fig. 21)

The portal vein carries nutrient rich blood to the liver from the GI tract and spleen. At the hilum of liver, it divides into the major right and left portal veins. Within the liver, these veins undergo further divisions to supply each segment, and terminate in small branches, which pierce the limiting plate of the portal tract and enter the hepatic sinusoids through small channels.

Portal pressure depends upon portal blood flow and vascular resistance. A rise in portal pressure leads to the development of collaterals to carry blood from the portal system to the systemic circulation. These portosystemic collaterals occur in specific sites: The distal esophagus (esophageal varices), the anal canal (anorectal varices) the falciform (umbilical varices) and the abdominal wall and retroperitoneum. Dilated cutaneous collateral veins are a sign of established portal hypertension and carry blood from the umbilicus towards tributaries of the vena cava. Portal hypertension also causes splenomegaly, the development of ascites, and may cause small intestine mucosal edema leading to malabsorption and consequent failure to thrive.

Causes (Table 15)

Portal hypertension can be caused by obstruction to the portal blood flow anywhere along its course. According to the anatomical site of obstruction, causes of PH can be classified into (1) prehepatic; (2) hepatic; (3) posthepatic causes, though there are many overlaps. Studies reveal that extrahepatic portal venous obstruction (EHPVO) is the predominant cause of PH in children in Indian subcontinent compared to hepatic causes in developed countries.

Extrahepatic portal venous obstruction indicates obstruction in the portal vein outside liver and may be at any part in the course of the portal vein. Portal venous thrombosis can occur in cases with infections and inflammation of umbilical infection with or without catheterization, acute

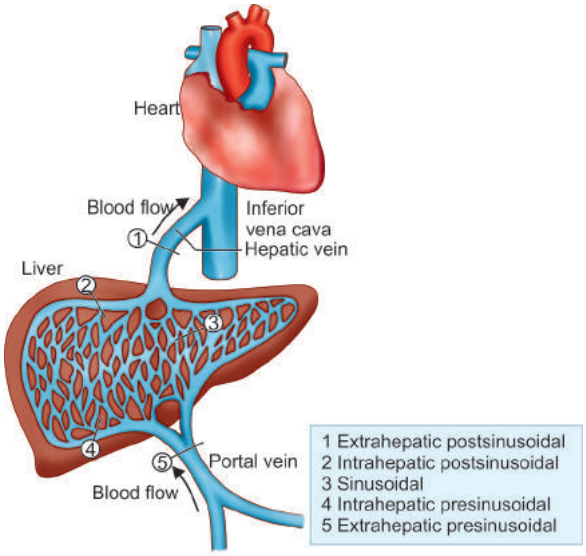


Fig. 21: Pathophysiology of portal hypertension

Table 15: Causes of portal hypertension

Presinusoidal or prehepatic	
Extrahepatic	Portal vein or splenic vein thrombosis, Splenic AV fistula Massive splenomegaly
Intrahepatic	Congenital hepatic fibrosis Idiopathic portal fibrosis Intrahepatic biliary atresia Sarcoidosis Schistosomiasis Myeloproliferative disorders Nodular regenerative hyperplasia
Sinusoidal	
	Cirrhosis due to any cause Chronic infectious hepatitis Autoimmune hepatitis Extrahepatic biliary atresia Choledochal cyst Alagille syndrome Progressive familial intrahepatic cholestasis Drugs Genetic and metabolic defects such as cystic fibrosis, α-1 antitrypsin deficiency and Wilson's disease
Postsinusoidal or posthepatic	
	Budd-Chiari syndrome Right heart failure Constrictive pericarditis Web in inferior vena cava

appendicitis, primary peritonitis, pancreatitis, portal pyemia, hypercoagulable states (acute dehydration, polycythemia) and inherited and acquired deficiencies of anticoagulant proteins like protein C, protein S and antithrombin III, trauma to portal vein and invasion or compression by tumor or pancreatic mass.

Hepatic venous outflow obstruction (Budd-Chiari syndrome) may be congenital or acquired and the obstruction can be anywhere between the hepatic veins and right atrium.

Clinical Presentation

Portal hypertension leads to many clinical complications like portosystemic vascular shunting and related problems and ascites. Portosystemic vascular shunting is an attempt of the body to decompress the portal hypertension by forming shunts between collaterals from portal vascular channel and systemic caval venous channels. These shunts are formed at various sites of the body. The most serious consequence of PH is GI bleeding usually from the varices around the proximal stomach and distal esophagus (gastroesophageal varices). The mortality after hematemesis in variceal bleeding is 30% and after recurrent variceal bleeding is as high as 70% and depends on the degree of hepatic function.

- Patients with EHPVO usually presents about 5–6 years of age with hematemesis with or without melena has generally good prognosis with satisfactory hepatic function
- Splenomegaly is almost universal in patients with EHPVO and size of spleen is usually dependent on the duration of blockage
- Liver is usually normal in size
- Ascites is usually rare in these patients
- Children with EHPVO also have variable extent of growth retardation.

Investigations

- Hematology
  - Complete blood count (CBC): Anemia, leukopenia, thrombocytopenia in hypersplenism
  - Prothrombin time/INR: Prolonged in intrinsic liver disease
  - Thrombophilia screening (sometimes to include bone marrow aspirate) must be performed to investigate underlying causes of portal vein occlusion or Budd-Chiari syndrome
- Biochemistry
  - Biochemical liver functions (LFT) may be deranged in intrinsic liver disease, with:
    - Raised bilirubin, transaminase and low albumin
    - Sodium may be low in ascites and renal function may become deranged in severe disease.
- Radiology
  - Invasive
  - Splenoportovenography, arterioportography, percutaneous transhepatic portography and inferior venocavography, for detailed delineation of the vasculature
  - Noninvasive
    - Abdominal ultrasound scan: Splenomegaly, collateral veins, reduced portal vein flow, raised hepatic artery resistance index may be seen in portal hypertension and heterogenous hepatic echotexture with underlying intrinsic liver disease
    - MRI: To evaluate focal liver lesions
    - MR angiography: To delineate vasculature of the portomesenteric system. Useful before shunt surgery, or to examine portal vein before liver transplantation
- Gastrointestinal endoscopy
  To evaluate varices and mucosal features of portal hypertension as well as gives opportunity to therapeutic procedures (ligation or sclerotherapy)
- Liver biopsy
  May be diagnostic of underlying liver disease, used to assess liver architecture, fibrosis, or cirrhosis

Management

Emergency Management of Variceal Bleeding

- Resuscitation
  - Airway: secure
  - Breathing: O_2 if shocked
  - Circulation: Two large-bore cannulae, IV fluids
- Investigations
  - Complete blood count, clotting , urinalysis, blood culture, cross-match (at least 2 units)
  - Monitoring and maintaining blood glucose
  - Monitoring and stabilizing fluid balance and cardiorespiratory status
  - Watch for encephalopathy
- Treatment
  - Nil by mouth
  - Ranitidine 1 mg/kg. IV TDS and sucralfate PO
  - Antibiotics IV if evidence of sepsis
  - Vitamin K 1–5 mg IV
  - Fresh frozen plasma and/or platelets if coagulopathy
  - Octreotide infusion 25 µg/hour (continue until after bleeding ceases for 24 hours and wean slowly) (Octreotide is a somatostatin analog; somatostatin reduces splanchnic blood flow and therefore portal pressure)
  - Blood transfusion to attain Hb to 10 gm/dL (avoid over transfusion)
  - Upper GI endoscopy to confirm source of bleeding and treat varices
  - Balloon tamponade with a Sengstaken tube is rarely required and should only be used by an experienced clinician.

Endoscopic Treatment of Esophageal Varices

- Variceal banding is an endoscopic ligation technique whereby the varix is aspirated into a plastic tube placed on the distal end of the endoscope. An elastic band is then released from the plastic tube to around the varix, thus strangulating the varix which then thromboses and sloughs off
- Injection sclerotherapy involves injecting a sclerosant via the endoscope into the variceal column.

Other Varices

Gastric varices are usually contiguous with esophageal varices and are therefore eradicated by treating esophageal varices. Ectopic varices are much less likely to bleed, but rarely may require evaluation by endoscopy or angiography and occasionally resection. If bleeding is persistent or recurrent, liver transplantation or portosystemic shunting may be required.

Surgery

Surgical portosystemic shunting is indicated in children with portal vein occlusion or those with chronic liver disease and reasonable liver function if:

- Uncontrolled variceal bleeding unresponsive to banding/sclerotherapy
- Severe hypersplenism.

Many types of shunt are possible, but mesocaval and splenorectal are the most commonly used. Shunt thrombosis is a major complication and may be manifested by recurrent variceal bleeding.

- Rex shunt: (mesenterico-left portal) is the insertion of a vein graft to bypass portal vein occlusion and restore hepatic portal blood flow
- Transjugular intrahepatic portosystemic stent shunt (TIPSS): Used in refractory variceal bleeding as a bridge to transplantation. In this technique, a wire is passed into a hepatic vein and a needle advanced into a portal vein. Balloon catheter dilatation of this tract is followed by stent insertion.

  Encephalopathy is a complication of shunting in those with cirrhotic liver disease.

Liver Transplantation

The treatment of choice in portal hypertension and variceal bleeding complicating end-stage liver disease.

Primary Prophylaxis

Beta-blockers reduce portal pressure by causing splanchnic vasoconstriction and reducing cardiac output. They are effectively used in adults, but in children the benefits must be weighed against the side effects.

Prophylactic sclerotherapy and/or banding are being investigated in controlled trials.

INDICATIONS FOR LIVER TRANSPLANTATION

Liver transplant is standard treatment for:

- Acute liver failure
- Chronic liver failure
- Selected metabolic disorders
- Selected hepatic malignancy.

Other indications are as follows:

Complications of end-stage liver disease of any etiology:

- Refractory ascites
- Hepatorenal syndrome
- Encephalopathy
- Gastrointestinal bleeding due to portal hypertension
- Portopulmonary hypertension
- Hepatopulmonary syndrome
- Hepatocellular carcinoma
- Cholangiocarcinoma.

Fulminant Hepatic Failure

Listing Criteria for Transplantation

Onset within 8 weeks of initial symptoms and one of the following:

- Stage 2 encephalopathy
- Bilirubin >15 mg/dL
- INR >2.5
- Hypoglycemia (glucose level <50 mg/dL)

Chronic Liver Failure

Patients with CLF and Child Pugh score ≥10 in the critical care unit, with a life expectancy without a liver transplant within 7 days with one of the following criteria:

- Unresponsive active variceal bleeding with failure or contraindication of surgical or transjugular intrahepatic shunt
- Hepatorenal syndrome

- Refractory ascites/hepatorenal syndrome (hydrothorax)
- Stage 3 encephalopathy unresponsive to therapy.

Metabolic or Genetic Diseases

- Hyperoxaluria
- Familial amyloidosis
- Polycystic liver disease
- Caroli disease
- Glycogen storage disease I, IV
- Hemophilia A, B
- Byler disease
- Crigler-Najjar syndrome
- Alagille syndrome.

Miscellaneous Diseases

- Budd-Chiari syndrome
- Sinusoidal obstruction syndrome (veno-occlusive disease)
- Graft-versus-host disease
- Nodular regenerative hyperplasia
- Hepatic tumors (adenoma, carcinoid, pancreatic islet cell tumors, epithelioid hemangioendothelioma, fibrolamellar carcinoma, hepatoblastoma)
- Hepatic trauma.

Contraindications to Liver Transplantation

Absolute

- Active extrahepatic malignancy (except superficial skin cancer)
- Hepatocellular cancer beyond accepted transplantation criteria
- Active substance abuse (alcohol, street drugs)
- Severe cardiopulmonary disease
- Advanced HIV or AIDS
- Medical noncompliance
- Brain death.

Relative

- Advanced age
- Severe obesity
- HIV (center-dependent)
- Previous nonhepatic malignancy within 2–5 years
- Active psychiatric illness
- Poor social support.

Pretransplant Assessment

Before transplantation, patients require rigorous assessment to identify pre-existing comorbidities that may preclude transplantation or may impact on management after transplantation.

- Cardiac
  - 12 lead ECG, echocardiography
- Pulmonary
  - Pulse oximetry
  - Chest radiograph
  - Pulmonary function test in case of cystic fibrosis
- Renal
  - Ethylenediaminetetraacetic acid (EDTA) GFR to assess for pre-existing renal dysfunction
- Nutritional
  - Height, weight, skin fold thickness, mid-arm circumference (aggressive nutritional support is required before transplantation)
- Vascular
  - Pretransplant assessment by Doppler ultrasound scan to detect anomalous vascular anatomy
- Viral immune status (IgG)
  - Hepatitis A, B, C, adenovirus, parvo virus, B19, CMV, measles, varicella zoster, herpes simplex, Epstein-Barr virus
- Immunization
  - All routine vaccines are given; in addition, varicella, hepatitis A and B
  - Live vaccines are usually not given after transplantation
- Dental
  - Patient on long-term immunosuppression need excellent dental hygiene
- Social
  - It is important that issues that may impact on the ability of the family to comply with the care of a transplanted child are identified and resolved before transplantation.
- Education
  - The care of a child with a liver transplant requires a high level of understanding from family. This is important for compliance with medication and follow-up, recognition of complications.

Types of Liver Transplantation

Whole Graft Transplantation

The diseased liver is removed and is replaced by a donor liver. The hepatic artery, portal vein and hepatic veins are then anastomosed to their corresponding structures. Bile duct is usually anastomosed to a Roux-en-Y loop created from small bowel.

Reduced Liver Transplantation

Reduced liver transplantations are necessary for patients who are disadvantaged in organ allocation because of the relative rarity of size-matched organ donors. For this reason, surgical techniques have been developed to reduce the size of an adult liver to fit within the morphological restriction of a pediatric recipient.

Split Graft

The donor liver is divided and shared between two recipients. The smaller left lobe goes to a pediatric patient.

Living-related

The mortality of patients on waiting lists has led to the expansion of the donor pool to include family members of a patient.

Auxiliary

In this operation, a recipient partial hepatectomy is performed and a reduced donor graft is transplanted into the resulting space. The recipient then has:

- A residual portion of their own liver
- A donor graft.

Two indications for this are:
1. Acute fulminant hepatic failure.
2. Metabolic liver disease.

Hepatocyte Transplantation

Hepatocyte transplantation occurs by the vascular injection of hepatocytes derived from cadaveric liver into the spleen or liver.

Choice of an Appropriate Graft

ABO blood group compatibility is the principal requirement for matching donor to recipient. HLA typing has not been shown to have role in liver transplantation.

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GLOSSARY AND ABBREVIATIONS

ALT	Alanine Amino Transferase
AST	Aspartate Amino Transferase
bDNA	Branched Chain Complementary DNA
ELU	Enzyme-linked Immunoassay Unit
EMC	Essential Mixed Cryoglobulinemia
HAV	Hepatitis A Virus
HBcAg	Hepatitis B Core Antigen
HBeAg	Hepatitis B e Antigen
HBIG	Hepatitis B Immunoglobulin
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HBxAg	Hepatitis B x Antigen
HCV	Hepatitis C Virus
HDV	Hepatitis D Virus
HEV	Hepatitis E Virus
IG	Immunoglobulin
LKM	Liver-Kidney Microsome
NS	Non-structural
PCR	Polymerase Chain Reaction
PT	Prothrombin Time
RIBA	Recombinant Immuno Assay
SES	Socio-Economic Statu

9 Structure of the Respiratory Tree (Applied Anatomy)

FETAL LUNG DEVELOPMENT

INTRODUCTION

Fetal lung development is divided into four stages:

Embryonic (0–7 weeks)	Trachea, left and right main stem bronchi
Pseudoglandular (6–17 weeks)	All conducting (preacinar) airways
Canalicular (16–27 weeks)	Respiratory bronchioli
Saccular-alveolar (27 weeks-term)	Saccules and alveoli

- Pulmonary blood vessel formation accompanies but lags airway development
- Gas exchange is not possible until the late canalicular—early saccular—alveolar stage of lung development
- Surfactant production begins at about 32 weeks but is not maximal until much nearer term. This is the basis for the development of respiratory distress syndrome (RDS) in preterm babies
- During early infancy pulmonary arteries decrease in muscularity accounting, at least in part, for the normal drop in pulmonary vascular resistance that follows birth. This is relevant to appearance of clinical feature (audible heart murmur) in congenital heart disease with left to right shunt [ventricular septal defect (VSD)].

During early childhood, alveoli and small blood vessels multiply and lung structures increase in size.

UPPER AIRWAY

The upper airway anatomy of babies is different from that of older children and adults.

The following are the characteristics of the upper airway anatomy in children:

Anatomical features	Clinical significance
Large tongue/high anterior larynx	Difficult to visualize during intubation
Floppy, U-shaped epiglottis	Obstructs view, greater area for swelling
Narrowest part of airway at cricoid cartilage	Site for stenosis; limits ET size
Small tracheal radius	Increasing airway resistance
Small tracheal length	Risk of ETT displacement
Floppy tracheal wall	Risk of airway collapse
Abbreviations: ET, endotracheal; ETT, endotracheal tube.	

Some infants are obligate nose breathers, and become apneic if the nose is obstructed with mucus or a nasogastric (NG) tube.

In older children, tonsillar hypertrophy may lead to significant airways obstruction (Fig. 1).

LOWER AIRWAY

Infants and young children have a softer, less efficient respiratory engine. Airways collapse occurs more easily:

Characteristic anatomical features	Clinical significance
Compliant rib cage	Less efficient ventilations and increased work of breathing (responsible for FTT in VSD, PDA)
Poorly developed intercostal muscles	Fatigue easily (lead to type II respiratory failure)
Horizontally aligned ribs	Less increase in AP diameter in inspiration
Protuberant abdomen	Less efficient diaphragmatic contraction
Low lung compliance/ high airways resistance	Short lung time constant
High closing volume	Early airways closure
High metabolic rate	Increasing oxygen demands
Abbreviations: FTT, failure to thrive; VSD, ventricular septal defect; PDA, patient ducts arteriosus; AP, anteroposterior	

PULMONARY GAS EXCHANGE

Disorders in gas exchange manifested as hypoxemia and/or hypercapnia are best evaluated by measuring:

- Arterial oxygen partial pressure (PaO_2)
- Arterial carbon dioxide partial pressure ($PaCO_2$)
- Oxygen saturation (SaO_2)
- Alveolar-arterial gradient [$P(A\text{-}a)O_2$]:
  - When PaO_2 falls, it is vital to know the difference between alveolar and arterial PaO_2, i.e. A-a gradient
  - A-a gradient is affected by age and position and is a sensitive marker of gas exchange impairment in respiratory disease
  - In air, a value of $P(A\text{-}a)O_2$ of >3 kPa indicates significant pulmonary dysfunction
  - PaO_2/Fraction of inspired oxygen (FiO_2) ratio: A normal PaO_2/FiO_2 ratio is 300–500 mm Hg with values of less than 300 mm Hg indicating abnormal gas exchange. Values of less than 200 mm Hg indicate severe hypoxia.

PULMONARY MECHANICS

Disorders of pulmonary mechanics result in:

- *Compliance*: Volume/Pressure, i.e. change in lung volume per unit change in pressure. It is the volume change per

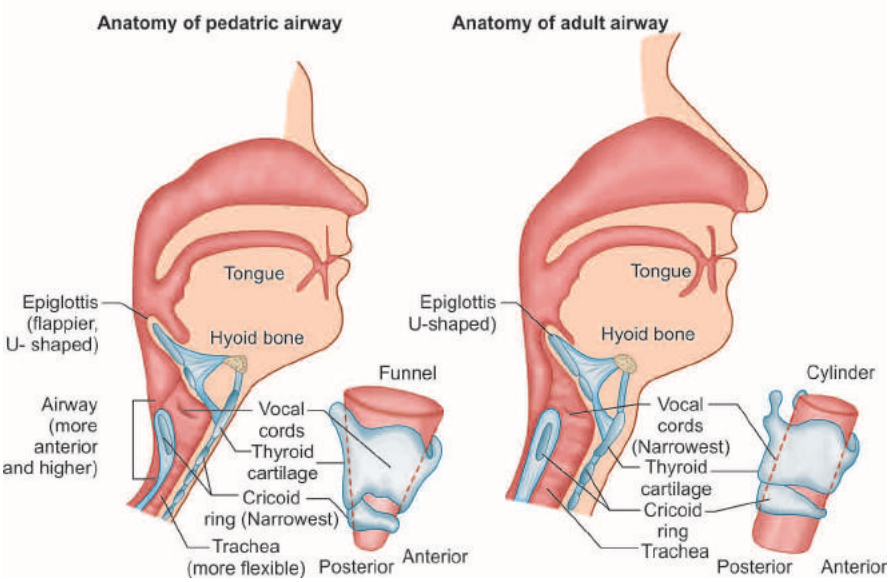


Fig. 1: Differences between the pediatric and adult upper airway

unit of pressure change. Measured as change in mL for change of pressure per cm of H_2O, e.g. mL/cm H_2O. Relevant to RDS in preterm baby, where lung complaint is less due to lack of surfactant formation, as surfactant is required for lung compliance in newborn. Preterm babies have therefore poor lung compliance, causing atelectasis.

- *Lung compliance in adult*: 200 mL/cm H_2O.
- *Term newborn:* 6 mL/cm H_2O.
- *Preterm newborn:* 0.5–3 mL/cm H_2O.
- *Alveolar ventilation:* 100–150 mL/kg/minute (adult 60 mL/kg/minute).
- *Resistance (Pressure/Flow):* Varies with airway radius, airway length, flow rate, density and viscosity of gas.
- *Time constant (Resistance × Compliance):* The time taken for alveolar pressure to reach 63% of the change in airway pressure.

Lungs with decreasing compliance (e.g. in RDS) have shorter time constants. Very short inspiratory times on a ventilator may lead lo incomplete delivery of tidal volume. Short expiratory time may lead to inadvertent positive end-expiratory pressure (PEEP) and air trapping.

CONTROL OF BREATHING

Central Control

The respiratory center is in the lower part of the brain stem (the medulla oblongata) and controls normal, rhythmic, cyclic pattern of breathing. Breathing is controlled by:

- *Central chemoreceptors:*
  - An increase in $PaCO_2$ results in increasing CO_2 and $[H]^+$ in the cerebrospinal fluid (CSF) resulting in an increase in ventilation, thereby lowering $PaCO_2$
  - A low $PaCO_2$ level inhibits the respiratory center.
- *Peripheral chemoreceptors:*
  - Carotid and aortic bodies respond to changes in PaO_2 and $PaCO_2$ by inputting into the central respiratory center
  - In the presence of hypoxia and hypercapnia, there is an immediate increase in breathing.
- *Brain:*
  - Breathing can be influenced by consciousness and this can happen before exercise or be triggered by emotion.
- *Lung*:
  - Receptors in the wall of the bronchi respond to irritant stimuli producing cough, sneezing, and breath hold
  - Stretch receptors prevent overdistention and equally low lung volume cause further inspiration
  - Stretch receptors in the blood vessels in the lung in the presence of heart failure produce hyperventilation.

Respiratory Drive

The efferent nerves pass from the respiratory center to the diaphragm, intercostal muscles, and accessory muscles of inspiration in the neck.

During normal breathing, inspiration is an active muscular process but expiration is passive reliant on natural elasticity of the tissues.

Any damage to the efferent pathways from the respiratory center to C3, C4 and C5 and then the phrenic nerve to the diaphragm, may cause severe difficulty in breathing; trauma to the cervical cord, above C3, is normally fatal.

Measurement of Oxygen Delivery and Consumption (Oxygen Flux)

All cells require a constant supply of oxygen to maintain metabolic demands and cellular function. Situations such as shock, as defined by oxygen demand exceeding supply, can result in organ dysfunction and failure. Early detection and correction of tissue hypoxia is fundamental in the management of critically ill patients.

Oxygen delivery (DO_2) from atmosphere to body cells requires the following:

- Inspired O_2 diffuses across the alveolar membrane into the blood
- O_2 combines reversibly with hemoglobin in red blood cells
- Bound O_2 is delivered by cardiac output to the tissues

- At the target tissue, O_2 dissociates from the hemoglobin, diffuses into the cells and ultimately reaches the mitochondria where it is utilized to supply energy.

ASSESSMENT OF PULMONARY FUNCTION

The various causes of hypoxemia and hypercapnia can be distinguished by a thorough understanding of the underlying pathophysiology. For sake of simplicity and interpretation, pulmonary function can be divided into two major components:

1. Pulmonary gas exchange
2. Respiratory mechanics.

Pulmonary Gas Exchange

Arterial gases are the most commonly performed of all intensive care unit (ICU) tests. Adequacy of gas exchange depends on the balance between pulmonary ventilation and capillary blood flow. Derangements in gas exchange lead to both hypoxia and hypercapnia.

The primary derangements are:

- Hypoventilation, i.e. not breathing adequately
- Diffusion impairment
- Shunt, i.e. blood supply without ventilation
- Ventilation perfusion inequalities (V/Q mismatch)
- DO_2/VO_2 (oxygen extraction rate in %) imbalance (DO_2: Oxygen delivery, VO_2: Oxygen consumption/minute).

In reality, most disease processes cause hypoxemia and hypercapnia through a combination of these processes. The intensivist makes therapeutic interventions with this in mind.

Hypoventilation and the Alveolar Gas Equation

Hypoventilation or reduced alveolar ventilation causes a rise in $PaCO_2$. One can see from the alveolar gas equation that a rise in $PaCO_2$ will result in a fall in P_AO_2 and consequently a fall in PaO_2.

Shunt

- Most hypoxemia is caused by low V/Q match, of which "true" shunt is an extreme form, V/Q = 0
- In contrast to hypoxemia from hypoventilation, true shunt is unaffected by increases in inspired oxygen
- Shunt fraction (low V/Q) increases when:
  - The small airways are occluded (bronchiolitis, asthma)
  - Alveoli are fluid-filled (pneumonia, pulmonary edema)
  - Alveoli are collapsed (pneumonia, atelectasis)
- Hypoxemia from the above (low V/Q) should be corrected via alveolar recruitment maneuvers [continuous positive airway pressure (CPAP), PEEP, high frequency oscillatory ventilation (HFOV)] rather than just increasing inspired O_2 (which can be toxic)
- $PaCO_2$ is unaffected by shunt but may fall as the patient hyperventilates (initially) or rise as the patient tires and hypoventilation ensues (further aggravating hypoxemia).

Ventilation/Perfusion Mismatch (Fig. 2)

- Low V/Q match is the most common cause of hypoxemia
- V/Q mismatch covers, a range of V:Q ratios in the lung that tend from areas of shunt (low V/Q) through to areas that equate with physiological dead space (high V/Q), i.e. ventilated but not perfused areas

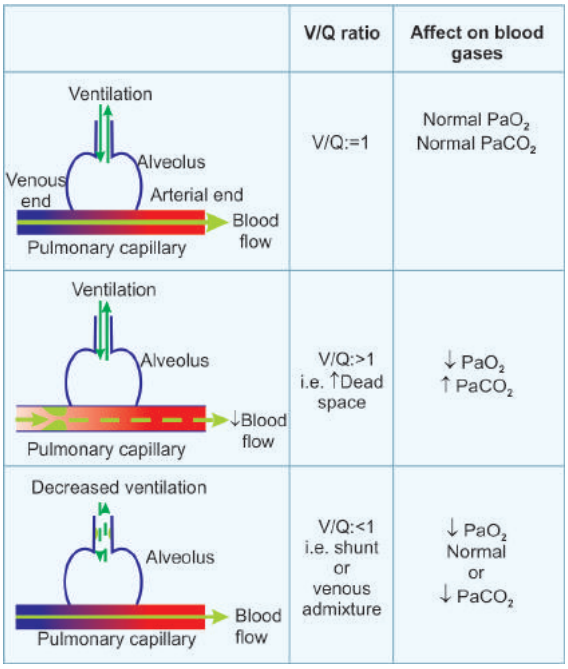


Fig. 2: Ventilation perfusion (V/Q) abnormalities and their effect on blood gases. Shunt occurs when blood flows across nonventilated alveoli

Abbreviations: PaO_2, arterial oxygen partial pressure; $PaCO_2$, arterial carbon dioxide partial pressure.

- V/Q varies with posture and causes a small physiological alveolar arterial difference (A-a difference):
  - Upper areas of the lung often have high V/Q ratios (good ventilation, less perfusion) V/Q >1.
  - Dependent areas have increasing shunt fraction, i.e. low V/Q (poor ventilation better perfusion) V/Q <1
- Pulmonary venous blood from areas of low V/Q (V/Q <1) has similar composition to mixed venous blood. Blood draining from high V/Q areas (V/Q >1) has similar composition to inspired gas. This blood then mixes in the pulmonary vein to give normal arterial blood gas (ABG) composition
- Ventilating the lung with large breaths can compress pulmonary vessels leading to rises in pulmonary vascular resistance and thus, abnormal V/Q
- It is worth noting that nonselective pulmonary vasodilators such as milrinone and prostacyclin can aggravate V/Q mismatch in areas of low V/Q but may improve V/Q match in areas of high V/Q.

Oxygen Delivery and Oxygen Consumption Imbalance (DO_2/VO_2)

This usually occurs in situations of low cardiac output. Thus:

- DO_2 is reduced (oxygen delivery)
- In response oxygen extraction increases with increased oxygen extraction ratio (OER)
- Mixed venous SvO_2 falls to less than 70%.

EVALUATING HYPOXEMIA AND HYPERCAPNIA

Hypoxemia

When a patient has a blood gas with significant reduction in PO_2, there are three principle disorders to consider:

- Hypoventilation: Normal A-a DO_2 (difference between oxygen delivery in artery and alveoli)

- Pulmonary disorder: Increasing A-a DO_2
- Reduced DO_2 and increased OER.

Evaluation of Hypoxemia

- The first step is to calculate A-a DO_2:
  - Normal A-a DO_2 indicates hypoventilation as the primary cause, e.g. neuromuscular conditions, central hypoventilation
  - Increasing A-a DO_2 indicates V/Q abnormality, e.g. increasing shunt fraction (low V/Q).

Hypercapnia

- Hypercapnia is commonly due to decreasing alveolar ventilation, e.g. when a patient gets tired from increasing work of breathing (asthma, bronchiolitis, pneumonia)
- Lung disease can also cause increased physiological dead space from V/Q mismatch (V/Q >1) which contributes to hypercapnia (Fig. 2)
- Hypercapnia with normal A-a DO_2 is due to neuromuscular weakness or central hypoventilation (e.g. drugs, rare brain disorders)
- Expired PCO_2 can be estimated from end-tidal carbon dioxide concentration in the expired air ($EtCO_2$).

Assessment of Oxygen Delivery

- It is imperative that both pulmonary and cardiac functions are assessed in the context of global oxygen delivery and consumption
- Oxygen delivery is determined from the product of cardiac output and the oxygen content (by SaO_2 rather than PaO_2) and the means by which oxygen is transported to the cell (hemoglobin level and cardiac output); the intensivist can assess the patient in terms of global oxygen delivery
- Oxygen delivery is influenced by the behavior of the oxyhemoglobin dissociation curve.

Oxygen Transport and the Hemoglobin Dissociation Curve (Fig. 3)

The affinity for oxygen by hemoglobin increases with increased arterial saturation (SaO2). As a result, the oxygen hemoglobin curve has a sigmoid shape.

Certain conditions can displace the oxygen dissociation curve. These will affect SaO_2 and therefore oxygen delivery (DO_2).

- Factors which shift curve to right and help offload O_2 to tissues include:
  - Increasing 2,3-diglycerophosphate
  - Acidosis
  - Hyperthermia, e.g. fever.
- Factors which shift curve to left and therefore reduce DO_2 (i.e. increase hemoglobin saturation) include:
  - Decreasing 2,3-diglycerophosphate
  - Alkalosis
  - Hypothermia.
- Abnormal hemoglobins such as carboxyhemoglobin not only shift the curve to the left but also have increasing oxygen binding capacity. As a result, severe tissue hypoxia can result.
- Cardiac output and hence oxygen delivery varies inversely with blood viscosity. Normally hematocrit dictates blood viscosity—a high hematocrit is associated with falling DO_2. The optimal hematocrit for maximum DO_2 is unknown but there is good evidence that a lower limit of hemoglobin of 7 g/dL is adequate for most children.
- Global estimates of total body oxygen delivery allow for bedside interpretation:
  - Metabolic acidosis
  - Lactate production
  - Central venous oxygen saturation from a central line ($ScvO_2$).

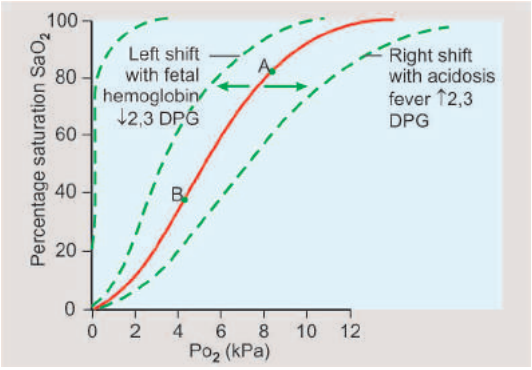


Fig. 3: Diagram of the oxyhemoglobin dissociation curve. Point A represents a serious hypoxia and B the level at which consciousness is lost. A is important in the fact that from here small drop in oxygen tension may cause profound desaturation of oxygen of hemoglobin

Abbreviation: 2,3 DPG, 2,3-diphosphoglycerate.

CONCLUSION

An appreciation of basic physiology of both pulmonary and cardiac systems allows the intensivist to make in-depth bedside evaluations of their patients based on underlying pathophysiology.

ACID-BASE BALANCE INVOLVING RESPIRATORY SYSTEM

(*See* Chapter on Acid-base Disorder).

RESPIRATORY FAILURE (TABLES 1 AND 2)

Definition

It is the inability of the lungs to perform gas exchange.

- PaO_2 <8 kPa (60 mm Hg) and/or with
- $PaCO_2$ >6.5 kPa (50 mm Hg).

Caveats

- A low PaO_2 is found in children with cyanotic heart disease and does not in itself imply respiratory failure
- A raised $PaCO_2$ may sometimes occur as a compensatory mechanism in metabolic alkalosis (e.g. persistent vomiting). Here, "central" sensitivity to $PaCO_2$ is not impaired but the threshold is shifted upward.

Types

Respiratory failure has traditionally been classified as:

- Oxygenation/type 1 failure (PaO_2 <60 mm Hg) occurs in the absence of hypercapnia, whereas ventilatory/type 2 failure occurs when hypercapnia and hypoxemia coexist.

Table 1: Causes of respiratory failure

	Extrathoracic airway	Intrathoracic airway/lung	Respiratory pump
Congenital	• Laryngomalacia • Subglottic stenosis, web or cyst • Tracheomalacia • Vascular ring	• Congenital lung disorders, e.g. congenital diaphragmatic hernia (CDH), congenital lobar emphysema • Congenital cystic adenomatoid malformation (CCAM) • Surfactant protein B and C deficiency syndromes	• Spinal muscular atrophy • Eventration of diaphragm • Duchenne muscular dystrophy
Acquired	• Infection, e.g. croup, retropharyngeal abscess • Trauma, e.g. foreign body aspiration, burns • "Other", e.g. hypertrophic tonsils and adenoids	• Bacterial/viral pneumonia • *Streptococcus pneumoniae* • *Mycoplasma pneumoniae* • *Staphylococcus aureus*, B. perfusion RSV, influenza, adenovirus, bronchiolitis • Asthma	• CNS infection • Drug overdose • Guillain-Barré syndrome • Spinal cord trauma, myasthenia gravis, kyphoscoliosis, flail chest

Abbreviations: CNS, central nervous system; RSV, respiratory syncytial virus.

Table 2: Investigating respiratory failure

Routine	Indicated by clinical scenario
Blood gases CXR Blood cultures Nonbronchoscopic BAL: Viruses bacteria, TB culture, and rapid antigen tests IgM for *Mycoplasma*	Pernasal swab and PCR for Bordetella Bronchoscopic BAL Echo CT chest CT brain MRI spine Lumbar puncture (Guillain-Barré) Genetics for surfactant protein B T-cell and B-cell function studies Lung biopsy Bone marrow aspirate and trephine

Note: Consider immunological disorders (chronic granulomatous disease, severe combined immunodeficiency disease and immunodeficiency virus) in case of suspected or proven opportunistic infection [cytomegalovirus (CMV), fungal].
Abbreviations: CXR, chest X-ray; BAL, bronchoalveolar lavage; PCR, polymerase chain reaction; CT, computed tomography; MRI, magnetic resonance imaging; Echo, echocardiogram; IgM, immunoglobulin M.

For management purposes, respiratory failure is better classified as either:

- *Acute:* Rapid respiratory decompensation
- *Chronic:* Long-standing inability to perform gas exchange leading to compensatory "adaptations." Signs of adaptation include: Absence of dyspnea at rest (altered central chemoreceptor sensitivity); compensated respiratory acidosis (↑HCO_3 normal blood pH); high hemoglobin/hematocrit (untreated hypoxemia)
- *Acute on chronic respiratory failure:* Acute respiratory decompensation in a child with compensated respiratory failure. Commonly present with profound hypercapnia >12 kPa and worsening hypoxemia.

Presenting Features

- Dyspnea subcostal, intercostal, sternal recession and grunting.
- *Stridor:* Upper airway obstruction.
- *Tachypnea:* Not a sensitive sign in young infants.
- *Apnea:* Prominent feature in young infants with respiratory syncytial virus (RSV) bronchiolitis.
- *Cyanosis:* Sign of impending decompensation.

Important is not to confuse dyspnea due to respiratory diseases with Kussmaul-type breathing in children with diabetic ketoacidosis (DKA) and other syndrome, associated with metabolic acidosis.

Other Features

- Poor feeding
- Floppiness
- Inability to talk—acute severe asthma.

Management

- Follow ABC (Airway, Breathing and Circulation). Assess airway. Inspect for obstruction, e.g. foreign body and remove. Head tilt, chin lift or jaw thrust. For breathing assess efficacy—look, listen feel, if breathing is ineffective give 5 rescue breaths. For circulation, assess for signs of life. Check pulse, if heart rate below 60 and poor perfusion start chest compression.
- Treat cause
- The mainstay of management is to ensure adequate oxygen. Normal blood pressure (BP), normal hemoglobin and SaO_2 >90% should ensure adequate oxygen delivery
- Accept a relatively high $PaCO_2$ (8–10 kPa) so long as systemic pH is between 7.2 and 7.3 (permissive hypercapnia)
- Many clinicians use a relatively high PEEP (5–10 cm H_2O) and limit peak inflation pressures (30 cm H_2O) as lung-protective strategy in ventilated patients with poor lung compliance
- Start enteral feeding early but watch for overhydrating and overfeeding if ventilated and sedated/paralyzed
- Tracheostomy should be considered for children with structural airway abnormalities not immediately amenable to surgery and children needing chronic ventilator support
- Extracorporeal membrane oxygenation (ECMO) support has been shown to be life-saving in neonates and adults with respiratory failure. Early consideration should be given to this treatment option as outcomes for patients referred late (>10 days of ventilation) are no better than using non-ECMO modalities of respiratory support.

Treatment

The treatment for the respiratory failure has been described in Table 3.

Table 3: Treating respiratory failure

Antibiotic therapy	• Suspected bacterial infection. Antibiotic guided by: – Age, child <3 months consider "perinatal" organisms – Immunization status – Community-acquired or nosocomial – Suspected opportunistic infection or TB – Blood and lung fluid culture results
Antiviral therapy	Only in cases where HSV or CMV is proven or strongly suspected
Pulmonary vasodilators	• Severe hypoxemic respiratory failure with high pulmonary vascular resistances • Thoracic surgery (including tracheostomy)
Immunoglobulins	• Guillain-Barré syndrome • Primary or secondary immunoglobulin deficiency
Plasmapheresis	Guillain-Barré syndrome
Corticosteroids	Lymphoproliferative disorders, asthma
Chemotherapy	Lymphoproliferative disorders

Abbreviations: TB, tuberculosis; HSV, herpes simplex virus; CMV, cytomegalovirus.

CLINICAL ASSESSMENT OF RESPIRATORY SYSTEM

VITAL SIGNS

- *Temperature:* There are various ways in which the body temperature can be measured. Different units use different methods:
  - An electronic thermometer in the axilla; or
  - A chemical dot thermometer in the axilla; or
  - An infrared tympanic thermometer.

  A sick child could have a high, or abnormally low, temperature.
- *Pulse rate*: The pulse rate should be assessed from the radial pulse. (In the younger child, you may find it easier to use brachial pulse). Assess the rate, character and rhythm at the radial pulse.
- *Respiratory rate*: In the older child, you can observe the chest and count the number of breaths per minute. Breaks or pauses in breathing that last longer than 15 seconds are abnormal. In the infant, count abdominal movements over 1 minute, if you find that it is easier to see diaphragmatic rather than chest wall movement (Table 4).
- *Blood pressure*: Measurement is now commonly performed using an automated method where the blood pressure is displayed on screen. It is important that the size and width of the cuff is appropriate for the size of the limb in which pressure is being measured. Use a cuff that covers 50–75% of the upper arm or thigh. A single measurement is required in most instances, but if you suspect heart disease then four-limb measurements are needed. If you are considering hypertension then a standard technique is required and plot the observations on BP centile charts (Table 5).

Table 4: Normal values of respiratory rate and heart rate at different ages

Age	Respiratory rate (breaths/min)	Heart rate (beats/min)
0–6 months	30–50	120–140
6–12 months	20–40	95–120
1–5 years	20–30	90–110
6–10 years	18–25	80–100
>10 years	12–25	60–100

Table 5: Normal values of blood pressure (BP) at different ages

Age	BP, mean (mm Hg)	BP range (mm Hg)
0–6 years	95/65	80/50–115/80
10 years	110/70	90/55–130/85
15 years	120/75	110/60–145/90

Respiratory System

- *Lips and buccal mucosa*: What is the color of the mucous membranes and lips? Is the tongue in good condition? What is its color?
- Are there any plaques, white patches, or spots?
- *Oropharynx*: What is the color and size of the tonsils? Is there an exudate? What is the shape of the palate, uvula, and posterior pharynx?
- *Chest*: What is the shape of the chest? Are there any scars or deformity? What is the position of the trachea? What is the chest-like on percussion—hyperresonant or dull? Where?
- *Breathing*: Are there any signs of respiratory distress: is there nasal flaring, intercostals, subcostal, and sternal recession, use of accessory muscles, forced expiration, grunting, or tracheal tug? Is there an audible noise during inspiration or expiration?
- *Auscultation of the lungs*: Listen for breath sounds in all regions of the chest. Evaluate inspiration and expiration. In the crying child you will still be able to listen during inspiration. Are there any fine crackles, rhonchi, or wheezes? Is there a pleural friction rub?
- *Ears*: The child will need to be positioned correctly for this part of the examination. It is often easier to have the child sitting on the mother's lap; one of her arms should be held around the upper body, and with the other arm she should place her hand against the side of the child's head so that it is firm against her. Is there an evidence of otitis externa? Is there a rash in the postauricular area (a feature of dermatitis, measles, and rubella)? On otoscopy check the state of the tympanic membrane. What is its color and degree of lucency? Is it perforated, or is there a myringotomy tube present?
- *Nose*: Is there discharge? Can the child breathe through each nostril?

Practice Point

One should also consider the following as additional features essential to the respiratory examination:

- Sputum pot contents
- Peak flow rate measurement and assessment in relation to height

- Inhaler technique in those using such devices
- Evidence of previous tracheostomy or use of current one.

One should be able to recognize the following patterns of abnormal signs:

- Consolidation
- Collapse
- Pleural effusion
- Pneumothorax
- Airflow obstruction
- Bronchiectasis.

COMMON CLINICAL PRESENTATION OF RESPIRATORY DISORDERS

It includes cough, breathlessness, snoring, wheeze and stridor.

Cough

Cough is a protective response for removing secretions and particulate matter from the airway. Its main feature is a sudden expulsion of air out of the lungs.

Differential Diagnosis of Acute Cough

Upper airway disease:

- Common cold, e.g. viral influenza and parainfluenza, rhinovirus
- Allergy
- Vocal cord dysfunction
- Infections other than common cold, e.g. sinusitis, tonsillitis, laryngitis, croup.

Lower airway disease:

- Bronchial asthma
- Infection, e.g. RSV bronchiolitis, bronchitis due to influenza, parainfluenza and adenovirus
- Lung parenchymal disease:
  - Bacterial and viral pneumonia
  - Atypical pneumonia.

Clinical Diagnosis of Respiratory Disorder Depending on Quality and Timing of Cough History (Table 6)

Quality:

- Paroxysms with or without vomiting/whoop/apnea/cyanosis—whooping cough
- Barking—croup
- Loud, "honking"—psychogenic
- Cough coming from deep inside chest—pneumonia
- Short, sharp "staccato"—*Mycoplasma, Chlamydia*.

Timing:

- Night-time, more frequent:
  - Asthma—late night or early morning
  - Postnasal drip—early part of night before going to sleep
  - Sinusitis
  - Croup
  - Cardiac failure
  - Gastroesophageal reflux (GER).
- Early morning:
  - Asthma—also midnight or late night feature
  - Lower respiratory tract infection (LRTI)
  - Cystic fibrosis
  - Bronchiectasis.
- Exercise/cold-induced:
  - Asthma
  - Cardiac failure.
- Only when awake–school days, when observed:
  - Psychogenic.

Table 6: Differential diagnosis of cough based on age and anatomy

	Location		
Age	**Upper airway**	**Lower airway**	**Nonrespiratory**
Infancy	URTI	Bronchiolitis	Impaired gag/cough reflex
	GER	LRTI	
	Croup		
	Foreign body		
	Whooping cough	TOF	
	Laryngeal edema	Tracheal compression	
	Aspiration	Pulmonary edema	
Preschool	URTI	Asthma	
	Croup	LRTI	
	Foreign body	Cystic fibrosis	
	Laryngeal edema	Acute bronchitis	Heart failure
		Aspiration	Phrenic or vagal nerve irritation
		Noxious fume inhalation	
School age	URTI	Asthma	
	Sinusitis	LRTI	
	Postnasal drip	Noxious fume inhalation	
	Smoking		
			Psychogenic

Abbreviations: LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection; GER, gastroesophageal reflux; TOF, tracheoesophageal fistula.

Examination:
- Listen to cough
- Associated symptoms such as tender sinuses, pharyngitis, snoring, stridor, bovine cough—all suggest upper airway
- Wheeze, crackles, reduced-air entry, suggest LRTI (pneumonia), asthma
- Big liver, gallop rhythm suggest cardiac failure.

Investigation:
- Depending on the clinical condition which includes pulse oxymetry in all
- Consider chest X-ray.

Treatment:
Depending on the clinical conditions (discussed in individual disease).

Differential Diagnosis of Chronic Cough
A chronic cough is one that has persisted for at least a few weeks. In developing countries, the three important causes of chronic cough are:
1. Pulmonary tuberculosis (TB)
2. Pertussis
3. Hyperreactive Airway Disease (HRAD).

Other Causes
Upper airway disease:
- Infection, e.g. chronic sinusitis and tonsillitis
- GER.

Lower airway disease:
- Asthma (one of the HRAD)
- Infection, e.g. post-bronchiolitis symptoms, atypical infections
- Foreign body
- Bronchiectasis, e.g. damage to the airway from chronic infection and TB or immunodeficiency
- Cystic fibrosis
- Congenital abnormalities, e.g. tracheoesophageal fistula, cleft larynx, pulmonary artery sling.

Lung parenchymal disease:
- Infection, e.g. pneumonia (recurrent and persistent pneumonia) and empyema.

Central Causes
- Psychogenic cough
- Tourette disease with a tic involving throat clearing or cough.

Treatment

Treatment depends on underlying cause.

Common Presentation: Breathlessness

Being short of breath can be due to heart or lung disease. In lung disease, this sensation arises because of lack of oxygen, difficulty in breathing due to airway obstruction, or abnormal lung mechanics (Table 7).

Common Presentation: Wheeze

Wheeze is a breath sound that is heard during expiration. It is often associated with prolongation of the expiratory phase of the breathing cycle. Wheeze indicates obstruction of airflow in lower respiratory tract. Although predominantly expiratory, but may be biphasic. Wheeze may be audible from outside if loud or only can be heard by auscultation by stethoscope. Do not presume that all the wheezes are asthma.

Table 7: Causes of respiratory distress

Respiratory	Nonrespiratory
Upper respiratory tract infection	Cardiac failure
Lower respiratory tract infection	Muscle weakness, e.g. Duchenne muscular dystrophy, diaphragmmatic paralysis
Foreign body	Restrictive lung disease, e.g. chest wall (obesity), chest deformity, kyphoscoliosis
Asthma	
Pneumothorax	

Causes may be acute:
- Viral-induced wheeze
- Bronchiolitis
- Foreign body
- Aspiration
- Anaphylaxis
- Air pollutants—sulfur dioxide.

However, causes may also be acute exacerbations of a chronic problem:
- Asthma
- Postviral airway sensitivity
- Airway malformation—intrinsic or extrinsic
- Chronic lung disease (bronchopulmonary dysplasia)
- Cystic fibrosis.

Common Presentation: Stridor

Stridor is a noise heard during the inspiratory phase of breathing. It is a high-pitched, harsh noise secondary to turbulent flow through a partially obstructed airway. Stridor is a course inspiratory noise through a narrowed nasopharynx. Usually inspiratory, but may be biphasic and variable.
- *Inspiratory:* Usually extrathoracic lesion, at or above glottis. During inspiration, extrathoracic intraluminal airway pressure is negative, relative to atmospheric pressure, leading to collapse of supraglottal structures.
- *Biphasic:* Glottic, subglottic and tracheal. A fixed obstruction resulting in a fixed caliber airway.

Typically arises in children aged 6 months to 5 years. Stridor in children under 6 months is suggestive of congenital defects, e.g. laryngomalacia vascular ring, and warrants investigation. Older children suffering stridor tend to have airway sensitivity, e.g. hay fever, asthma, and have recurrent episodes.

Most common causes are:
- Croup
- Epiglottitis
- Foreign body
- Anaphylaxis
- Laryngomalacia.

PNEUMONIA

Pneumonia remains a major killer of children under 5 years of age. It accounts for nearly one-fifth of childhood deaths worldwide, with approximately 2 million children under 5 years of age dying each year and the majority of deaths occur in Africa and Southeast Asia.

Most of the deaths from acute respiratory infection (ARI) are due to pneumonia. The annual global incidence of pneumonia is estimated at 151 million, of which 11–20 million (7–13%) are severe enough to require hospitalization. It is also important to know that in contrast to diarrheal death where mortality rate has reduced dramatically, despite the introduction of a global program for the control of ARI almost 18 years ago, there has been insignificant change in overall burden of morbidity and mortality from pneumonia.

The bulk of death from childhood pneumonia affects the poor children of developing countries who have higher exposure rate of risk factors for developing ARI, such as overcrowding, poor environmental conditions, malnutrition and also limited access to curative health services.

Recognition of pneumonia as an important public health problem in developing countries is recent. Around 600,000 children's lives could be saved yearly through universal treatment of pneumonia with appropriate low-cost antibiotic alone.

Inadequate or delayed medical care results in child death from ARI and for cases of severe acute lower respiratory infections (ALRIs), such as pneumonia, quick and appropriate treatment is essential for survival.

Severely malnourished children have three times more chance of death from ALRI than children with normal or mild malnutrition associated with ALRI. Among various clinical problems associated with severe acute malnutrition (SAM), pneumonia is found in up to 80% among SAM.

In severely malnourished children with pneumonia, fast breathing and chest indrawing may not be as evident as in other well-nourished children and a severely malnourished child may have an impaired or absent response to hypoxia and a weak or absent cough reflex. Therefore careful management is needed because case fatality rates are higher in such children. Pneumonia is a leading and frequent cause of case fatality in children suffering from severe malnutrition, and case management is rewarding if managed early and properly.

Classification

Community-aquired Pneumonia: Pneumonia Aquired from Outside Hospital

Bacteria involved are *Streptococcus pneumoniae, Haemophilus influenzae* and *Staphylococcus aureus*. Viruses are RSV, adenovirus, measles virus, etc. Other organisms involved are *Chlamydia*, *Mycoplasma pneumoniae,* Rickettsiae (*Coxiella burnetii*).

Hospital-acquired or Nosocomial-induced Pneumonia

Pneumonia occurring at least 2 days after hospital admission. Common organisms involved are *Pseudomonas, Klebsiella pneumoniae, Escherichia coli, S. aureus,* etc.

Pneumonia in the immunocompromised patient: *Pneumocystis carinii*, Cytomegalovirus (CMV), Herpes virus, *Mycobacterium tuberculosis*.

Pneumonia in damaged lung: Aspiration pneumonia, cystic fibrosis, etc.

Anatomic Classification of Pneumonia

- Lobar or lobular pneumonia
- Bronchopneumonia
- Interstitial pneumonia.

Etiological Classification of Pneumonia

- Viral:
  - RSV
  - Influenza
  - Parainfluenza
  - Adenovirus.
- Bacterial:
  - First 2 months of life:
    - *Klebseilla spp.*
    - *E. coli.*
    - *Staphylococci.*
  - 3 months to 3 years:
    - *S. pneumoniae.*
    - *H. influenzae.*
    - *Staphylococci.*
  - After 3 years:
    - *S. pneumoniae.*
    - Staphylococci.
    - β-hemolytic streptococcus.
- Atypical organisms:
  - Community-acquired pneumonia.
    - *Chlamydia spp.*
    - Mycoplasma.
  - In immunocompromised children:
    - *Pneumocystis carinii.*

Clinical Features

Onset of pneumonia may be insidious starting with upper respiratory tract infection (URTI) or may be acute with high fever, dyspnea and grunting respiration. Respiratory rate is usually increased.

Rarely, pneumonia may present with symptoms of acute abdominal emergency. This attributes to referred pain from the pleura. Apical pneumonia may sometimes be associated with meningismus and convulsion. In these patients, the CSF is always clear.

On examination, following features can be found:

- Flaring of alae nasi
- Retraction of the lower chest and intercostal spaces (Fig. 4)
- Signs of consolidation are observed in lobar pneumonia.

Pneumonia due to *Streptococcus pneumoniae*

Route of Transmission

Droplet infection. More common in winter.

Pathogenesis and Pathology

Overcrowding and diminished host resistance predisposes children to infection with pneumococci. Bacteria multiply in the alveoli and inflammatory exudate is formed. Scattered areas of consolidation occur, which coalesce around the bronchi and later become lobular or lobar in distribution. There is no tissue necrosis. Pathological process passes from the stage of congestion to red and gray hepatization before the final stage of resolution.

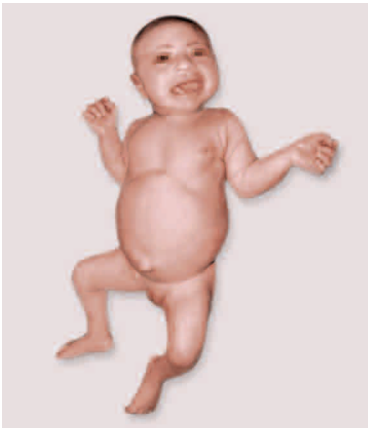


Fig. 4: A child with pneumonia showing lower chest indrawing

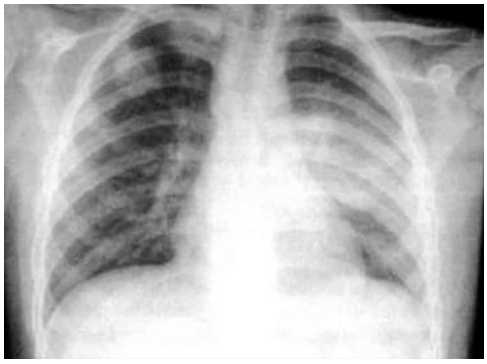


Fig. 5: Chest X-ray showing lobar pneumonia in left lower lobe

Chest X-ray: Lobar consolidation (Fig. 5).

Incubation Period

1–3 days.

Clinical Features

The onset is abrupt. Presents with:

- Headache
- Chills
- High fever
- Cough—initially dry but may be associated with rusty sputum (uncommon in children)
- Increased respiratory rate (tachypnea) more than age specific value
- In severe cases:
  - Grunting
  - Chest indrawing (Fig. 5)
  - Difficulty in feeding
  - Cyanosis.

Examination reveals:

- Percussion note is impaired
- Air entry diminished
- Crepitation and bronchial breath sound may be heard over areas of consolidation
- Bronchophony and whispering pectoriloquy may be observed
- Meningismus may be present in apical pneumonia.

Diagnosis

The diagnosis is based on history, physical examination, X-ray finding of lobar consolidation and leukocytosis.

Bacteriological confirmation is difficult but sputum may be examined by Gram staining and culture. Blood culture may be positive in 5–15% of cases.

Demonstration of polysaccharide antigen in urine and blood may be done.

Treatment

- Penicillin G 50,000 Units/kg/day IV/IM in divided doses for 5–7 days
- Procaine penicillin 600,000 Units/day IM
- Orally penicillin V, amoxicillin or ampicillin
- In patients allergic to penicillin or in severe case, injection ceftriaxone/cefotaxime are the alternatives
- Oxygen should be given if cyanosis and respiratory distress are present
- Vancomycin is recommended in penicillin resistant pneumococcus (PRP).

Pneumonia due to *Staphylococcal pneumoniae*

The pulmonary lesion may be primary infection of the parenchyma; or may be secondary to generalized staphylococcal septicemia. It may be a complication of measles, influenza and cystic fibrosis of the lungs or may follow minor staphylococcal pyoderma.

Predisposing Factors

Debilitating conditions including malnutrition, diabetes mellitus and macrophage dysfunction.

Pathology

In infants, the pneumonic process is diffuse initially, but soon the lesions suppurate, resulting in bronchoalveolar destruction. Multiple microabscesses are formed, which erode the bronchial wall and discharge their contents in the bronchi. Several pneumatocele may form and they may fluctuate in size over the time, ultimately resolving and disappearing within a period of few weeks to months. Staphylococcal abscess in the lung may erode into the pericardium causing purulent pericarditis. Empyema in a child below 2 years of age is nearly always staphylococcal in origin.

Clinical Features

The illness usually follows upper respiratory tract infection, pyoderma or other associated purulent disease.

- Grunting respiration
- Fever
- Anorexia
- Listlessness and irritability
- Abdominal distension (due to septicemia and ileus)
- Cyanosis may be present.

Sometimes pulmonary infection may be complicated by disseminated disease, i.e. involvement of more than two anatomical sites. This may manifest as metastatic abscesses into joints, bones, muscles, pericardium, liver, mastoid or brain.

Diagnosis

A newborn or an infant with respiratory infection who has evidence of staphylococcal infection elsewhere in the body is suspicious of staphylococcal pneumonia and pyopneumothorax and pericarditis are highly suggestive of complications of staphylococcal pneumonia.

Chest X-ray: Pneumatocele in the lung field (Fig. 6).

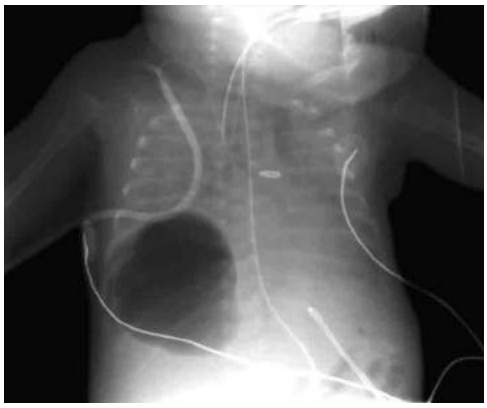


Fig. 6: Pneumatocele in a right lower lobe in newborn due to Staphylococcal pneumonia

Management

The child should be hospitalized immediately for isolation and prevention of spreading.

- Supportive:
  - Antipyretics to control fever
  - Intravenous infusion for hydration
  - Oxygen administration to relieve dyspnea and cyanosis.
- Specific:
  - Empyema is aspirated and pus is sent for culture and sensitivity
  - Vigorous antibiotic therapy:
    - Penicillin G, erythromycin, cloxacillin, cephalosporin
    - Vancomycin or ticoplanin—if the child does not respond quickly to penicillin and cephalosporins.

Duration of Treatment

Treatment should be continued till all the evidences of the disease disappear both clinically and radiologically, which usually requires 6 weeks or longer.

Complications

- Empyema thoracis
- Pyopneumothorax
- Large pneumatocele may cause respiratory distress
- Metastatic abscess
- Pleural thickening.

Hemophilus Pneumonia

Age Group

Usually occurs between 3 months and 3 years. As the infants have transplacentally transferred antibodies during the first 3–4 months of life, infection with *H. influenzae* is relatively less frequent during this period.

Pathology

Pathology is similar to that of infection with pneumococci. There is extensive destruction of bronchial epithelium and hemorrhagic edema extending in to interstitial area.

Clinical Features

The onset of illness is gradual with nasopharyngeal infection. Certain viral infections as those due to influenza virus probably act synergistically with *H. influenzae*. Presentation may mimic acute bronchiolitis. The course is subacute and prolonged.

The child presents with:

- Moderate fever
- Dyspnea
- Grunting respiration
- Retraction of the lower intercostal spaces.

Treatment

Antibiotics for 7–10 days with one of the following drugs:

- Ampicillin: 100–150 mg/kg/day
- Chloramphenicol: 50 mg/kg/day in four divided doses
- Cefotaxime: 100 mg/kg/day
- Ceftriaxone: 50–75 mg/kg/day.

Complications

- Bacteremia
- Pericarditis
- Empyema
- Meningitis
- Polyarthritis.

Group A Beta-hemolytic Streptococci

Streptococcal infection of the lungs by group A beta- hemolytic streptococci is usually secondary to measles, chicken pox, influenza or whooping cough.

Clinical Features

- Fever
- Chills
- Dyspnea
- Rapid respiration
- Blood streaked sputum
- Cough
- Extreme prostration
- Signs of bronchopneumonia are less pronounced as the pathology is interstitial.

Diagnosis

- Chest radiograph shows:
  - Interstitial pneumonia
  - Segmental involvement
  - Diffuse peribronchial densities
  - Effusion
- Blood count show increased neutrophil.

Treatment

- Penicillin G: 50,000–100,000 Units/kg/day in divided doses for 5–7 days
- Closed drainage of empyema with indwelling intercostal tube.

Complications

- Serosanguinous or purulent empyema
- Bacteremia (10%).

Prevention of Pneumonia

A community strategy to reduce the burden of pneumonia and to prevent death from pneumonia is essential,

particularly for developing countries. These include preventive strategies:

- Control of environmental factors (indoor air pollution in particular)
- Dealing with malnutrition
- Addressing prevalent micronutrient deficiency such as zinc and vitamin A deficiencies
- Promotion of household behaviors such as exclusive breastfeeding and handwashing
- Avoidance of overcrowding
- Satisfactory housing condition with good ventilation and adequate light
- Many of these preventive strategies have additional health benefits that far exceed mere reduction in respiratory infections such as reduction in diarrhea and improvement in nutrition indices.

Prevention of Death from Pneumonia

- Early diagnosis of pneumonia at community level by simple clinical observation of fast breathing and chest indrawing
- Use of timely appropriate antibiotic
- Referral to appropriate medical center of very sick children suffering from pneumonia.

Prevention by Vaccine

There has been considerable progress in vaccination strategies for prevention in childhood pneumonia. Vaccines involved in prevention of pneumonia are measles vaccine—Measles, Mumps, and Rubella (MMR) vaccine and pertussis vaccine given in combination with other vaccines. They will prevent measles and pertussis-induced pneumonia respectively.

Pneumococcal Conjugate Vaccine

Ten valent pneumococcal conjugate vaccine PHiD-CV (polysaccharide and nontypeable *H. influenzae* protein D conjugate vaccine) and 13 valent pneumococcal conjugate vaccine (PCV-13) vaccine now available in some South Asian countries. Three primary series vaccines are given starting at 1½ month age along with other primary vaccines followed by two vaccines at 1–2 month intervals. A booster dose is given after 1 year age.

Haemophilus influenzae B Conjugate Vaccine

Hib vaccine helps to prevent *Haemophilus influenzae* B induced pneumonia in children. This is given as a single dose or as a combination vaccine [Penta by Expanded Programme on Immunization (EPI) and Pentaxim®, Hexa). Three primary vaccines are given at 6 weeks, 10 weeks and 14 weeks. Booster dose may be given at 15–18 month.

COMMUNITY MANAGEMENT OF ACUTE RESPIRATORY INFECTIONS

(Also discussed in Chapter on IMCI)

The World Health Organization (WHO) estimates that, in 1990s, ARIs were the main cause of death in young children. Over 4 million children under 5 years of age die from ARI globally every year, over that period and 90% of them were from developing countries.

Guidelines for Acute Respiratory Infection Control Program in Children under 5 Years of Age

Objectives

- To reduce the mortality of ARI
- To improve case management
- Early case detection and prompt institution
- Health education to mothers

Standard case management of upper and lower respiratory tract infection will be prompted at every level which includes:

- Government health workers
- NGO's health worker
- Parents.

Since the etiology of clinical manifestations in very young infants of less than 2 months of age differs from those in older children, guidelines will introduce special instructions, treatment and referral of pneumonia in young infant.

ACUTE RESPIRATORY INFECTIONS

Acute respiratory infections (ARI) are caused by a wide number of organisms including viruses (RSV, rhinovirus, adenovirus, measles virus, influenza and parainfluenza viruses), bacteria (*Diplococcus pneumoniae, Staphylococcus aureus, Staphylococcus pyogenes, Corynebacterium diphtheriae, Mycoplasma* and *Chlamydia*).

Different Types ARI and Role of Case Management (Table 8)

Table 8: Different types of acute respiratory infection (ARI) and role of case management

Otitis media	Common, treatable, but rarely fatal
Sinusitis	Probably uncommon in children, treatable, not fatal
URTI: tonsillitis, pharyngitis	Common, treatable, not fatal
Diphtheria	Treatable, often fatal, main emphasis should be on its prevention
Viral croup	Uncommon, not treatable by CHW, may be fatal
Bronchitis	Common, treatable (bacterial, viral), nonfatal
Pertussis	Common, main emphasis should be on its prevention. Treatable, fatal element is often pneumonia
Bronchiolitis	Common, treatable, fatal element is often pneumonia (bronchodilators usually ineffective under 12 months of age)
Pneumonia	Common, often fatal, treatment cheap and effective
Measles	Common, main emphasis should be given on prevention; treatable, fatal element is often pneumonia

Abbreviations: URTI, upper respiratory tract infection; CHW, community health worker

Causative Organisms and Antimicrobial Agents (Table 9)

Acute respiratory infection is, in a way, an unfortunate term. It has reduced the emphasis on pneumonia which is, by far, the most common and treatable cause of death from ARI. To be clinically useful, the management of ARI must be discussed according to the mode of presentation rather than the anatomical region involved. Most children with pneumonia will present with cough.

Table 9: Causative organisms of acute respiratory infection (ARI) and antimicrobial agents

Organisms	Choice of drugs
Streptococcus pneumoniae	Benzyl penicillin, ampicillin
Haemophilus influenzae	Chloramphenicol, ampicillin, cotrimoxazole
Streptococcus pyogenes	Benzyl penicillin + cloxacilin; gentamicin, cefuroxime, sodium fusidate
Klebsiella pneumoniae	Chloramphenicol, cefotaxime
Proteus mirabilis	Ampicillin, cotrimoxazole
Pseudomonas aeruginosa	Carbenicilin, ceftazidime
Mycoplasma pneumoniae	Oxytetracycline, erythromycin
Coxiella burnetii	Oxytetracycline, erythromycin
Chlamydia psittaci	Oxytetracycline, erythromycin
Legionella pneumophila	Erythromycin, rifampicin
Anaerobes	Benzyl penicillin, metronidazole

Etiological Diagnosis of Pneumonia

- Leukocyte count
- Spectrum
- X-ray
- Blood culture
- Culture of nasolaryngotracheal aspirate
- Culture of lung puncture aspirate (reliable but invasive).

Management

- Plan of management by doctor (as per WHO guidelines)
- Plan of case management by community health workers [WHO and Integrated Management of Childhood Illness (IMCI)].

It is mentioned worthy that, in the management of ARI for the doctors, the ARI is divided into no pneumonia, pneumonia, severe pneumonia, and very severe pneumonia, depending upon severity in children aged 2 months to 5 years; whereas for health workers, ARI is classified into no pneumonia, pneumonia, severe pneumonia, and very severe disease as per IMCI. The term very severe pneumonia is not used for health worker in the management of ARI in children above 2 months to 5 years.

Plan of Management by Doctor (as per WHO Guidelines)

1. Management for the young infant aged less than 2 months (Table 10).
   Management of the young infant with cough or difficult breathing at the small hospital.
2. Management for the child aged 2 months up to 5 years (as per WHO guidelines) (Table 11).

Plan of Case Management by Community Health Workers (As Per WHO guidelines/IMCI) (Tables 12 to 16)

1. Management for the young infant aged less than 2 months.
2. Management for the child age 2 months up to 5 years (also see IMCI guidelines).

Table 10: Management of acute respiratory infection for the young infant aged less than 2 months

Clinical signs	Classify as	Summary of treatment
• Stopped feeding well • Convulsions • Abnormally sleepy or difficult to wake • Stridor in calm child • Wheezing • Fever (≥38°F) or low body temperature (<35.5°F) • Fast breathing[a] • Severe chest indrawing • Central cyanosis • Grunting • Apneic episodes or • Distended and tense abdomen	Severe pneumonia or very severe disease	Admit Give O_2[b] if: • Central cyanosis • Not able to drink
• No fast breathing • No sign of pneumonia or very severe disease	No pneumonia Cough or cold	Advise mother to give following home care: • Keep young infant warm • Frequent breastfeed • Clear nose if it interferes with feeding • Return quickly if: – Breathing becomes difficult – Breathing becomes fast – Feeding becomes a problem – The infant becomes sicker

[a]Fast breathing is 60 breaths/minute if the young infant age is less than 2 months.
[b]If O_2 supply is ample, also give oxygen to a young infant with:
Restlessness (if O_2 improves the condition)
Severe chest indrawing, or
Grunting.

Table 11: Management of acute respiratory infection for the young infant aged 2 months up to 5 years

Clinical signs	Classify as[a]	Summary of treatment
Central cyanosis or Not able to drink	Very Severe pneumonia	Admit[b] Give O_2[c] Give an antibiotic (Chloramphenicol) Treat fever, if present Treat wheeze, if present Give supportive care Reassess twice daily
Chest indrawing, No central cyanosis and Able to drink	Severe pneumonia	Admit[b] if signs of meningitis or severe malnutrition: Give an antibiotic (Chloramphenicol) Treat fever, if present Treat wheeze, if present Give supportive care Reassess daily
No chest indrawing and Fast breathing[d]	Pneumonia	Advise mother to give home care Give an antibiotic (at home): cotrimoxazole, amoxicillin, ampicillin, procaine penicillin Treat fever, if present Treat wheeze, if present Advise the mother to return in 2 days for reassessment, or earlier if the child is getting worse
No chest indrawing and No fast breathing[d]	No pneumonia: Cough and cold	If coughing more than 30 days, assess for causes of chronic cough Assess and treat ear problem or sore throat, if present Assess and treat other problems Advise mother to give home care Treat fever, if present Treat wheeze, if present

[a]These classifications include some children with bronchiolitis and asthma.
[b]If the child has stridor, treat accordingly. If the child has severe undernutrition, admit for nutritional rehabilitation and medical therapy. If the child has signs of meningitis, admit and treat with chloramphenicol.
[c]If O_2 supply is ample, also give O_2 to a child with:
Restlessness (if O_2 improve the condition)
Severe chest indrawing, or
Breathing rate of 70 breaths/minute or more.
[d]Fast breathing is:
60 breaths/minute for a child less than 2 months of age
50 breaths/minute or more in a child age 2–12 months
40 breaths/minute or more in a child age 12 months up to 5 years.

Table 12: Management for the young infant aged less than 2 months with very severe disease

Signs	Stopped feeding well
	Convulsions
	Abnormally sleep or difficult to wake
	Stridor in calm child
	Wheezing
	Fever (≥37.5°C) or low body temperature (<35.5°C) with/without: fast breathing (60 breath/min) or more
	Severe chest indrawing
Classify as	Very severe disease
Treatment	Refer urgently to hospital
	Keep young infant warm
	Give first dose of an intramuscular antibiotic
	Give IM phenobarbitone, if convulsing
	Treat the young infant to prevent low blood sugar

Table 13: Management for the young infant aged less than 2 months with severe pneumonia

Signs	• Severe chest indrawing or • Fast breathing (60/minutes or more)	• No severe chest indrawing • No fast breathing (<60/minute)
Classify as	Severe pneumonia	No pneumonia: Cough or cold
Treatment	"Refer urgently" to hospital or nearby health center	Advise mother to give the following home care: • Keep the young infant warm • Breastfeed frequently • Clear nose if it interferes with feeding Return quickly if: • Breathing becomes difficult • Breathing becomes fast • Feeding becomes a problem • The infant becomes sicker

Table 14: Management for the young infant aged 2 months up to 5 years with very severe disease

Signs	• Not able to drink • Convulsions • Abnormally sleep or difficult to wake • Stridor in calm child • Severe under nutrition
Classify as	Very severe disease
Treatment	• Refer urgently to hospital • Give first dose of an antibiotic • Treat the child to prevent low blood sugar • Treat fever, if present • Treat wheeze, if present • If cerebral malaria is possible, give an antimicrobial

Table 15: Management for the young infant aged 2 months to 5 years with severe pneumonia, pneumonia or no pneumonia (also see IMCI guidelines)

Signs	Chest indrawing (if also recurrent wheeze, go directly to treat wheeze)	• No chest indrawing and • Fast breathing (50 breaths/min if aged 2 months up to 12 months, 40 breaths/min if age >5 years)	• No chest indrawing and • No fast breathing (<50 breaths/min if aged 2–12 months, <40 breaths/min if age >5 years)
Classify as	Severe pneumonia	Pneumonia	No pneumonia: Cough or cold
Treatment	• Refer urgently to hospital • Give first dose of an antibiotic • Treat fever, if present • Treat wheeze, if present (if referral is not feasible, treat with an antibiotic and follow closely)	• Advise mother to give home care • Give an appropriate antibiotic for 5 days • Treat fever, if present • Treat wheezing, if present • Advise mother to return with child in 2 days for reassessment, or earlier if the child is going worse	• If coughing continues more than 30 days, refer for assessment • Assess and treat ear problem and sore throat, if present • Assess and treat other problems • Advise mother to give home care • Treat fever, if present • Treat wheeze, if present

Table 16: Reassess in 2 days a child who is taking an antibiotic for pneumonia

Signs	• Worse • Not able to drink • Has chest indrawing • Has other danger signs	The Same	• Improving • Breathing slower • Less fever • Eating better
Treatment	Refer urgently to hospital	Change antibiotic or refer	Finish 5 days of antibiotic

Reassess for Pneumonia

Drugs and doses of drugs used in acute respiratory infection (ARI) (as per WHO guidelines):

Drugs	Dose, Route and Frequency
Chloramphenicol	25 mg/kg/dose PO, IV, IM 6 hourly
Gentamicin	2 mg/kg/dose IM or IV 8 hourly
Benzyl penicillin	25,000–40,000 U/kg/dose IV or IM 6 hourly
Procaine penicillin	50,000 U/kg IM once daily for 5 days
Ampicillin, amoxicillin, cephalexin or cotrimoxazole can be used as the drug of first choice.	

Note:

- IM penicillin has the advantage of reliable administration to an ill child who may vomit oral medication; and is often less costly
- Growing drug resistance reported with cotrimoxazole
- Chloramphenicol is clearly the drug of choice for children over 2 months of age with severe pneumonia; it is very effective against both *S. pneumoniae* and *H. influenzae*, resistance is rare. It is effective also against *S. aureus*, though cloxacillin is preferred.

Chloramphenicol is also effective against meningitis which is common in child with severe pneumonia. Large randomized prospective trials in Papua New Guinea children have shown that chloramphenicol alone is as effective as combined therapy with chloramphenicol plus penicillin. The drug is absorbed quickly after IM administration.

Neonatal pneumonia should be treated with penicillin plus gentamicin since chloramphenicol is toxic to neonates and bacteriostatic against coliforms.

Supportive Therapy

- An infant with pneumonia should be nursed lightly clothed in a warm room. Overheating is just as dangerous as cooling
- Gently clean the nose
- If possible, oxygen should be administered to any child who is cyanosed by an intranasal catheter at the rate of 0.5 L/minute (in infants). The catheter should be inserted one-half of the distance between the tip of the nose and the tip of the ear
- Drugs, such as expectorants, cough suppressants; mucolytics, decongestants and antihistamine are expensive and ineffective or even harmful in pneumonia
- Paracetamol to be given when temperature is more than or equal to 101°F; patients should be sponged with tepid water.
- Breastfeeding and/or small frequent meals should be continued. Fluid should be given if the child is thirsty, but excess fluid administration should be avoided.

Preventive Measures

Specific

Immunization against diphtheria, pertussis, measles and TB should be done. It has been reported that pneumococcal vaccine could reduce mortality due to ARI by 50%. *Haemophilus influenzae* B (Hib) vaccine provided by EPI in combination vaccine (Penta) can effectively prevent Hib pneumonia, a major bacterial cause of pneumonia in developing countries. Currently pneumococcal conjugate vaccines are also available to prevent pneumococcal invasive disease including pneumonia.

Nonspecific Measures of Prevention

- Increasing birthweight
- Breastfeeding
- Proper nutrition
- Protection against chills and reduction of parenteral smoking and other indoor air pollution
- Supplementation of high potency vitamin A capsule
- Zinc supplementation and zinc fortified food.

RECURRENT AND PERSISTENT PNEUMONIA

While acute lower respiratory tract infections remain the most important cause of mortality and morbidity in under fives in the developing countries, persistent pneumonia is uncommon.

DEFINITION

There is no consensus on the definition of either recurrent or persistent pneumonia.

Recurrent pneumonia (RP) has been defined as two episodes of pneumonia in 1 year or three episodes in any time frame.

Persistent pneumonia (PP) implies a chronic, nonresolving pneumonia. It is defined as persistence of symptoms and radiographic abnormalities for more than 1 month. However, some authors prefer to use the cutoff of 3 months.

The speed of radiographic resolution depends on the etiologic agent; this may vary from 2 weeks with RSV or parainfluenza virus infection to as long as 12 months with adenovirus infection.

The causes of recurrent and persistent pneumonias overlap considerably; hence, are discussed together.

RP and PP usually result from decrease in local pulmonary or systemic host defense or from underlying disorder that modify lung defense. The underlying disorders associated with the infections can be broadly classified into the following categories:

- Congenital malformations of the upper or the lower respiratory tract, and cardiovascular system
- Recurrent aspirations
- Defects in the clearance of airway secretions, especially cystic fibrosis, ciliary abnormalities
- Disorders of systemic/local immunity.

ETIOLOGIC FACTORS

- Congenital malformations:
  - Airways:
    - Cleft palate
    - Pierre Robin syndrome
    - Tracheoesophageal fistula (TOF)
    - Tracheomalacia
    - Laryngomalacia.
  - Lungs:
    - Pulmonary hypoplasia
    - Pulmonary sequestration
    - Congenital adenomatoid malformation of the lung
    - Bronchogenic cyst.
  - Cardiovascular:
    - Congenital heart disease especially left to right shunts
    - Vascular ring.
- Aspirations:
  - GER
  - Swallowing abnormalities
  - Foreign body
  - Anomalies of the upper airways.
- Defects in the clearance of airways secretion:
  - Cystic fibrosis
  - Abnormalities of the ciliary structure of function
  - Abnormal clearance secondary to infections, repair of congenital defects
  - Airway compression (intrinsic/extrinsic), e.g. mediastinal tubercular lymphadenopathy.
- Post-infectious disorders:
  - Post-tubercular bronchiectasis
  - Post-pertussis bronchiectasis
  - Post-measles bronchiectasis.
- Noninfectious disorders:
  - Bronchial asthma
  - Hypersensitivity pneumonia
  - Pulmonary hemosiderosis.
- Disorders of local/systemic immunity:
  - Primary immunodeficiency
  - Acquired immunodeficiencies:
    - Human immunodeficiency virus (HIV) infection
    - Immunosuppressive therapy
    - Malnutrition
    - Micronutrient deficiency, especially zinc deficiency.

While TB is likely to be the most important cause of persistent pneumonia in developing countries, it is likely that causes of recurrent/tubercular persistent pneumonia are similar to those in the developed countries. The common organisms responsible for recurrent pneumonia in children are *H. influenzae, S. pneumoniae*, Staphylococci, etc. In a child who is immunocompromised, may be infected with CMV, *Chlamydia, P. carinii*, fungi, *Legionella*, etc.

Although underlying hyper-responsive airway disorders, like bronchial asthma is an important cause of RP/PP, they are frequently found together. Uncomplicated asthma may be wrongly diagnosed as bronchopneumonia and because of repeated episodes, the child may erroneously be suspected to workup for recurrent pneumonia. The problem may be sorted out by a careful assessment of the history and physical examination.

It is interesting to note that while underlying asthma is an important cause of recurrent and persistent pneumonia; on the other hand, recurrent pneumonia in infancy and early childhood are more likely to develop bronchial asthma in later childhood, surprisingly in nonatopic children rather than in atopic children.

History Relevant to Persistent and Recurrent Pneumonia

- Onset of symptoms:
  - Symptoms appearing soon after birth increase the possibility of presence of hereditary/congenital disorder. Congenital malformations such as TOF, cystic adenomatoid malformation and congenital lobar emphysema present early in life. Disorders of humoral immunity usually present in later infancy.
- Perinatal history to be taken:
  - Prolonged neonatal intensive care unit (NICU) Care with ventilator support is relevant to broncho-pulmonary dysplasia (BPD) or chronic lung disease (CLD)
  - Delayed passage of meconium relevant to cystic fibrosis
  - Vomiting, cough and choking attack associated with feeding are suggestive of GER.
- Relevant family history:
  - History of contact with adults suffering from TB
  - Family history of atopy (bronchial asthma).
- Past history/associated complaints:
  - Occurrence of repeated infections at other sites should be asked for; a positive history may suggest systemic immunodeficiency.
- Bowel habit:
  - Bulky loose motion (steatorrhea), associated with recurrent chest infection suggestive of cystic fibrosis. Although uncommon in Indian subcontinent, but it is under diagnosed and under reported.
- Environmental factors:
  - Risk factors for sources of exposure to respiratory infection should be evaluated. Exposure to inhaled pollutants, irritants and passive tobacco smoking should be carefully assessed.

PHYSICAL EXAMINATION

The aim of the physical examination is to document presence of respiratory disease, localize the site of infection, and to detect any underlying etiologic factor.

- General physical examination:
  - Assess growth and development [for failure to thrive (FTT)]
  - Look for clubbing of fingers and toes (bronchiectasis, cystic fibrosis)
  - Throat examination (absence of tonsils may suggest hypogammaglobinemia)
  - Cervical lymphadenopathy (TB, HIV, histiocytosis)
  - Nose (nasal polyp in cystic fibrosis)
  - Paranasal sinuses, ear (recurrent middle ear infection suggestive of immune-deficiency).
- Respiratory system examination:
  - Respiratory rate
  - Evidence of distress
  - Thoracic deformities
  - Wheezing
  - Stridor
  - The dimensions of the chest
  - Careful auscultation of the chest to localize the infection.
- Cardiovascular system examination:
  - Heart sounds and murmurs for heart disease with left to right shunt.

When aspiration is suspected as underlying cause, observation of child during feeding is essential for coughing/choking attack.

The severity of disorder is assessed from:

- Failure to thrive
- Limitation of activity
- Persistent fever
- Persistent tachypnea and respiratory distress
- Persistent hyperinflation
- Persistent hypoxemia
- Persistent radiological findings/abnormal pulmonary function test (PFT).

Presence of clubbing, growth retardation, and increased Anteroposterior (AP) diameter of the chest indicate chronicity of the disease/infection.

INVESTIGATIONS

Investigations should be planned only after careful evaluation of history and examination findings and should be done judiciously. It is absolutely necessary to rule out TB and underlying cardiovascular disease before proceeding to the further investigations.

Investigations include:

- Mantaux test (MT)
- Chest X-ray for:
  - Pulmonary TB
  - Foreign body obstruction
  - Hilar haziness, pulmonary plethora and with cardiomegaly suggestive of congenital heart disease with left to right shunt
- PFT
- Sweat chloride estimation to exclude cystic fibrosis
- Barium swallow esophagus and esophageal manometry—to exclude GER
- Bronchoscopic examination—may be done for abnormality of bronchial anatomy or foreign body aspiration
- Bronchoalveolar lavage (BAL) can be performed in attempt to identify the etiologic agent. The BAL fluid should be subjected to microbiological evaluation and cytopathology. Isolation of mucoid *Pseudomonas aeruginosa* is a strong pointer to the diagnosis of cystic fibrosis. Demonstration of *P. carinii* suggests underlying immunodeficiency
- Computed Tomography (CT) scan of chest—helpful to diagnose bronchiectasis, enlarged lymph node, congenital anomalies (lobar emphysema, cysts, sequestration)
- Radionucleotide study for GER
- Immunological workup to exclude immunodeficiency.

The presence of other features of the recognized specific immunodeficiency syndrome provides supportive evidence for disorders of systemic immunity.

The initial investigations include complete and differential blood counts, quantitative serum immunoglobulin, and skin tests (MT) of delayed hypersensitivity.

Further investigations may include T and B cell subset quantification. If phagocytic defects are suspected, screening

tests including neutrophil count and nitroblue tetrazolium test should be done.

TREATMENT

Treatment of RP/PP includes therapy for current infection and definitive therapy for underlying disease, which may not always be possible.

Micronutrient and Macronutrient Deficiency

It is well-recognized that malnourished children are more vulnerable to RP and PP. Mortality increases significantly when pneumonia is associated with malnutrition. One of the important causes of recurrent pneumonia in malnourished children is due to impaired cell-mediated immunity (CMI), and zinc deficiency in malnourished children is mostly responsible for impaired CMI. Published studies have found that malnourished children are zinc deficient with increased association of pneumonia and recurrent pneumonia. Published studies have also found that zinc supplement during acute watery diarrhea in developing countries also significantly lowers future pneumonia in comparison to nonsupplemented children.

SUMMARY

The important causes of RP are congenital malformation, structural abnormalities, underlying TB in developing countries, hyper-responsive airways (bronchial asthma), diseases like cystic fibrosis in Caucasian children and aspiration syndrome. History and physical examination have an important role in guiding for investigation plan. Chest radiograph, MT test, sweat test, bronchoscopy, CT scan of chest are the most helpful investigations. Immunological workup should be performed if the child's clinical features suggestive of common cause of recurrent or persistent pneumonia have been excluded. The treatment remains causes specific.

ASPIRATION PNEUMONIA

Aspiration pneumonia can be caused by either inhalation into the lungs of gastric or oropharyngeal contents. These contents produce intense inflammation in the lower airways producing aspiration pneumonia.

In practice, aspiration events are either:

- Acute and large leading to aspiration pneumonia, or
- Subacute and minor.

In subacute aspiration, there may be no immediate symptoms due to individual aspiration events, but repeated lung inflammation leads to tissue damage and symptoms develop over time. The most common etiology is GER disease.

Disorders of upper gastrointestinal (GI) tract and airways that may increase the risk of aspiration are mentioned in Table 17.

Other disorders that may increase the risk of aspiration in children due to GER are:

- Head injury and trauma
- Urgent surgery with rapid sequence anesthesia
- Neuromuscular and neurological disorders associated with laryngeal dysfunction

Table 17: Disorders of upper gastrointestinal tract and airways

Abnormality	Conditions
Nasal and oral	Cleft lip, craniofacial syndromes, choanal atresia
Larynx, trachea and esophagus	Laryngomalacia, laryngeal cleft, tracheoesophageal fistula
Major vessels	Double aortic arch: other vascular abnormalities
Infection	Tonsilitis, retropharyngeal abscess, epiglottitis, esophagitis
Neuromuscular	Hypotonia syndrome, neuromuscular junction disease, muscular disease
Autoimmune disorder	Scleroderma

- Cerebral palsy
- Nasogastric (NG) tube
- Tracheostomy
- History of seizures
- Obesity
- Hiatus hernia
- Extreme preterm with chronic lung disease.

COMMUNITY-ACQUIRED ASPIRATION PNEUMONIA

Aspiration pneumonitis and pneumonia are prevalent in community-acquired aspiration pneumonia (CAP) from causes outlined in the previous sections. Presenting features may be variable and include:

- Fever
- Sudden onset dyspnea
- Hypoxia and cyanosis
- "Infiltrations" on chest X-ray (CXR) and widespread crepitations.

MANAGEMENT OF ASPIRATION PNEUMONIA

- Airway suctioning especially in infant
- If still cyanosed and not maintaining blood gases with oxygen administered via a rebreathing bag, intubate and ventilate
- Continue cardiovascular monitoring and transfer to Pediatric ICU (PICU)
- Commence antibiotics: Penicillins and metronidazole or coamoxiclav
- Steroids not recommended.

PREVENTION OF ASPIRATION PNEUMONIA IN HOSPITALIZED PATIENT

- Semirecumbent position especially obese persons
- The use of promotility agents
- Avoiding excessive sedation
- Avoiding large volume enteral feeding via NG tube.

FOREIGN BODY ASPIRATION

Foreign body aspiration is an important cause of pediatric morbidity and mortality, particularly in children between the age of 6 months and 5 years. It is potentially life-threatening event and may also cause chronic lung injury, if not properly managed.

The symptoms and signs can be confused with those of asthma, and the roentgenographic findings with those of pneumonia. Foreign bodies may cause chronic pulmonary infections, bronchiectasis and lung abscess. An early diagnosis and management of the patient with an inhaled foreign body offers a diagnostic challenge to the physician.

Common Foreign Bodies

Peanut is the most common foreign body causing aspiration followed by pulses, seeds and almond.

Site of Impaction

- Right main bronchus (most common)
- Left main bronchus
- Carina
- Trachea
- Subglottis
- Cricopharynx
- Pyriform fossa.

CLINICAL FEATURES

It is important for the clinician to have a high index of suspicion, especially in patients with sudden appearance of a wheeze without a previous history of asthma, especially if unilateral.

- Choking (most of the children present with choking with a definite history of foreign body aspiration)
- Paroxysmal cough
- Stridor
- Decreased air entry
- Wheezing
- Fever
- Cyanotic episodes
- Syncope.

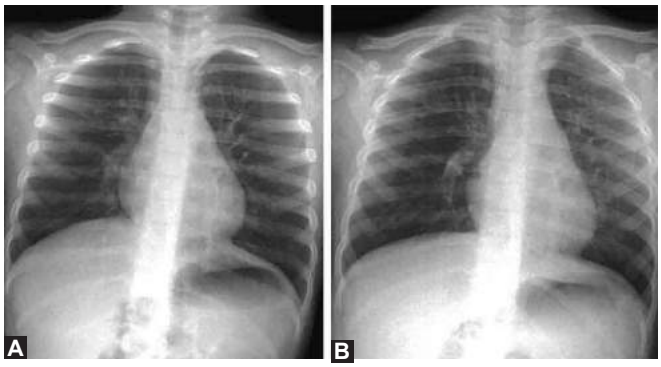
Factors Which may Delay the Diagnosis

- Parental negligence and wrong diagnosis by the doctor
- Lack of symptoms, particularly after the acute initial phase of dyspnea
- Diverse clinical features due to inhalation of foreign body.

INVESTIGATION (FIGS 7A AND B)

- *Chest X-ray:* Since the most common aspirated objects are vegetative and thus radiolucent, their presence is usually established by the indirect signs of atelectasis or air trapping due to partial obstruction.

  The presence of X-ray findings is related to size, type, shape and location of foreign body and pattern and length of bronchial obstruction.
  - It may be normal or
  - There may be emphysema or hyperinflation.
- *Bronchoscopy:* It may show:
  - Impacted foreign body usually in the right main bronchus
  - Tracheobronchial edema
  - Granulation tissue
  - Inflammation
  - Purulent secretions.



Figs 7A and B: Four-year-old boy who aspirated a peanut. (A) Inspiratory chest X-ray (CXR); (B) Expiratory chest X-ray show air-trapping in the right lung. On bronchoscopy, the peanut was found in the right main bronchus

INDICATIONS FOR BRONCHOSCOPY

- History of definite or suspected foreign body aspiration
- Features of foreign body aspiration, e.g. choking, wheezing, stridor and paroxysmal cough
- Recurrent chest infections with no apparent cause, when bronchial asthma has been excluded
- Chest radiograph suggestive of foreign body aspiration.

MANAGEMENT

Rigid bronchoscopy under general anesthesia is the standard management for such patients.

PREVENTION

Foreign body aspiration is a dramatic event with potentially lethal sequelae. Education is the best preventive measure for decreasing the incidence of this problem.

BRONCHIOLITIS

Bronchiolitis is the most common LRTI requiring admission to hospital and the most frequent cause of respiratory failure requiring PICU admission.

Respiratory syncytial virus infections responsible for bronchiolitis affect almost everyone by the age of 2 years. RSV invades nasopharyngeal epithelium and spread to the lower airway where it causes increased mucous production, desquamation and then bronchiolar obstruction. The net effect is pulmonary hyperinflation and atelectasis. The other causes of bronchiolitis include infection with parainfluenza, influenza, adenovirus, rhinovirus, *Chlamydia*, etc.

There is an increased risk of severe infection with congenital heart diseases, CLD of prematurity, immunodeficiency and other lung diseases.

CLINICAL FEATURES

Bronchiolitis is a clinical diagnosis. The following are the usual clinical features:

- Coryza
- Antecedent URTI in an infant, less than 2 years, followed by signs of respiratory distress
- Dry/harsh cough
- Tachypnea
- Poor feeding
- Suprasternal and intercostal recession

- Wheeze and crackles
- Prolonged expiration
- Cyanosis and pallor
- Hyperinflated chest (AP diameter of chest increasing with liver pushed down due to air trapping)
- Apnea especially of preterm infants
- 50% is afebrile.

RISK FACTORS

- Chronological age less than 3 months
- Ex-preterm (gestational age <34 weeks)
- Apnea currently or during neonatal period
- Congenital heart diseases with pulmonary hypertension
- Cystic fibrosis
- Smoking at home
- Low socioeconomic class
- Nonbreastfed
- Male sex
- Neurodevelopmental delay
- Immunodeficiency
- Upper airway obstruction.

INDICATORS OF SEVERITY

- Ill, toxic looking, irritable exhausted infant
- Hypoxemia (SPO_2 <90%) is the single best predictor of severity
- Respiratory rate more than 70/minute
- Underlying lung diseases (cystic fibrosis), congenital heart diseases
- Streaky atelectasis on chest roentgenogram
- Apneic spell.

Wheeze and Disease Severity

It is mention worthy, although wheeze is characteristic feature of bronchiolitis, the degree of wheeze do not correlate with degree of severity. A child with audible significant wheeze may be active, playful having nonsevere bronchiolitis. On the other hand, a drowsy hypoxemic child with bronchiolitis without wheeze is a serious condition.

KEY INVESTIGATIONS

- Pulse oxymetry to assess oxygenation
- Chest X-ray to assess hyperinflation, atelectasis, excludes consolidation (Figs 8 and 9)
- Nasopharyngeal swab by immunofluoroscent antibody for detecting RSV.

TREATMENT OF BRONCHIOLITIS

Treatment of bronchiolitis is mainly supportive and includes the following:

- Nonsevere case:
  - Clear mucous from nostrils
  - Continue breastfeeding
  - Maintaining enough hydration; offer age appropriate drink for child: Tea, soup, lemon drink, etc.
  - Offer nutritious feed to maintain nutrition
  - Oral antipyretic, if febrile.

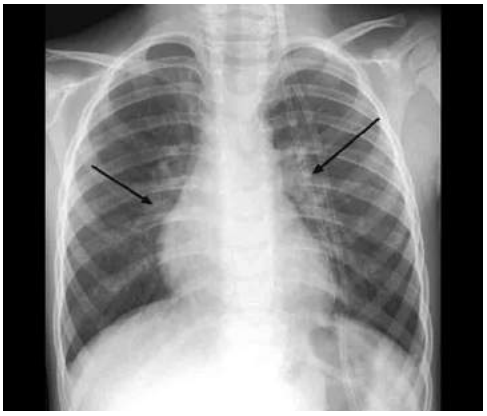


Fig. 8: Showing perihilar fullness in acute bronchiolitis

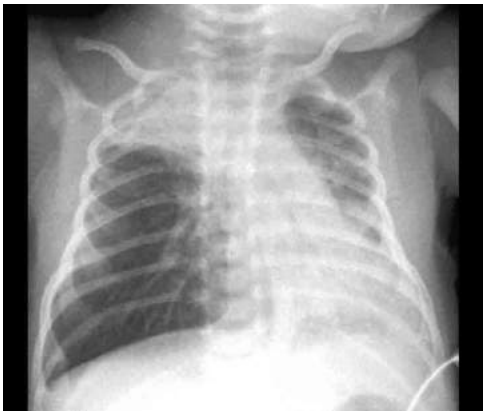


Fig. 9: Showing flattening of diaphragm and right upper atelectasis

- Hospital care for acute severe bronchiolitis: Mostly supportive and includes the following:
  - Maintenance of adequate oxygen saturation, respiratory rate and heart rate
  - Administer oxygen either via nasal cannula or head box to maintain saturation over 92%
  - Restrict fluid at two-thirds maintenance fluid, check electrolytes daily as risk of syndrome of inappropriate antidiuretic hormone secretion (SIADH)
  - IV fluid may be required if the infant is dehydrated or too sick to take enteral food
  - If tachypnea or significant feeding difficulty, use an NG tube.

Pharmacological Treatment of Wheeze

Nebulized salbutamol, terbutaline and ipratropium have all been tried in studies. There is no compelling evidence to suggest that they produce clinical benefit. Selective β_2-agonist has vasoactive property and may worsen hypoxemia due to V/Q imbalance. However, a trial of oxygen-driven nebulized bronchodilator can be given, particularly in older children when distinction between asthma may be difficult. Discontinue if no clinical benefit or in clinical deterioration.

Nebulized steroid (nebulized budesonide) may bring symptomatic relief in children with history of atopy including food allergy, eczema or hyperactive airway disease.

Nebulized hypertonic saline (3% NaCl) has also been currently found in published studies to be effective in decreasing the symptoms and the reduction of duration of hospital stay.

Nebulized adrenaline may improve oxygenation and clinical signs, but does not improve outcome. Epinephrine (adrenaline) is a nonselective β-agonist with a short half-life and rapid onset of action. Its lack of selectivity may be of use in the treatment of viral bronchiolitis. While the Cochrane review demonstrated that bronchodilators are relatively ineffective in the treatment of acute bronchiolitis, but the same is not true of epinephrine. Epinephrine has an additional theoretical benefit because it contains α-adrenergic properties in addition to the β-adrenergic effects. It has been proposed that this additional α-adrenergic effect may reduce mucosal edema and therefore improve clinical status during bronchiolitis.

Systemic steroids and antibiotics are not useful.

Antiviral therapy with ribavirin should be reserved for immunodeficient patients and those with underlying heart diseases.

If there is increasing oxygen requirement and signs of fatigue and CO_2 retention, ventilation will be required.

Infants with increasing respiratory distress or apnea should be managed in PICU. A capillary or arterial blood gas should be measured. Progressive rise in CO_2 is an indicator for early ventilator support.

Respiratory Support

About 2% of infants with bronchiolitis require respiratory support for either apnea or respiratory failure.

Noninvasive Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) delivered noninvasively via nasal prongs (usually between 5 cm H_2O and 8 cm H_2O), may avoid the need for intubation in many infants.

Mechanical Ventilation

- High inspiratory pressure may be required to help oxygenation
- PEEP of 5–10 cm H_2O
- Low rates and increased inspiratory pressure
- In refractory hypoxia, high frequency oscillatory ventilation (HFOV) may be required
- If pneumonia is present, the ventilator requirement is prolonged.

DRUG PROPHYLAXIS

Palivizumab is a monoclonal antibody to RSV and can be used as prophylaxis for vulnerable babies—the ex-preterm babies, cystic fibrosis, congenital heart diseases, etc. Monthly 1 mg injection of palivizumab reduces the risk of hospitalization and needs for mechanical ventilation.

In developing countries under IMCI, health workers do not have enough knowledge, skill to diagnose bronchiolitis, as under WHO definition, both pneumonia and bronchiolitis have similar definition. Health workers should be trained to auscultate chest to detect wheeze by stethoscope and wheeze of bronchiolitis should be differentiated from wheeze of pneumonia, or recurrent wheeze of bronchial asthma.

OUTCOME

The rate of wheezing following bronchiolitis is between 30% and 50% (post-bronchiolitis wheeze). Majority of them neither have asthma nor suffering from recurrent bronchiolitis and can be managed in outpatient departments.

An association with subsequent airway reactivity particularly in association with RSV bronchiolitis has been recorded.

SUMMARY

- Bronchiolitis is the most common LRTI requiring admission to hospital and the most frequent cause of respiratory failure requiring PICU admission
- Hypoxemia is the single most indictor of severe bronchiolitis which has no relationship with severity of wheeze in bronchiolitis
- Supportive care with oxygen (SpO_2 <92%) and NG feeding (if fluid intake is inadequate) are the mainstay of treatment of nonsevere bronchiolitis
- There are limited or no evidence of benefit for most other pharmacological treatment (β_2-agonist, corticosteroids and antibiotics).

CROUP SYNDROMES

The term croup is used for a variety of conditions in which a peculiar brassy cough is the main presenting feature. Inspiratory stridor, hoarseness or respiratory distress may not always be associated with croup.

The diseases include:
- Acute epiglottitis
- Laryngitis
- Laryngotracheobronchitis
- Spasmodic laryngitis.

ACUTE EPIGLOTTITIS

Supraglottitis includes both epiglottic and inflammatory edema of the hypopharynx.

Agents

Haemophilus influenzae type B is the most common organism.

Others include:
- *Pneumococcus.*
- Beta-hemolytic streptococcus.
- Staphylococcus.

Clinical Features

- High fever, toxic look and toxic appearance
- Mouth breathing and drooling (Fig. 10)
- Difficulty in swallowing
- Noisy breathing (softer in laryngotracheobronchitis)
- Marked suprasternal and subcostal retraction of chest
- As the child becomes fatigue, stridor diminishes.

Diagnosis

X-ray Neck Lateral View

Thumb-shaped swelling of epiglottis can be seen (Fig. 11).

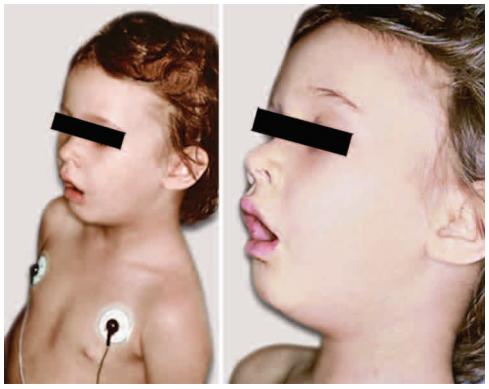


Fig. 10: A toxic looking child with mouth breathing and chest retraction in acute epiglottitis

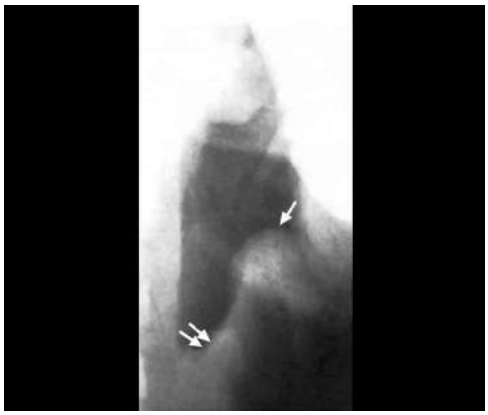


Fig. 11: Lateral neck radiograph in acute epiglottitis showing the characteristic features. The epiglottis is swollen and thumb-shaped (single arrow), the aryepiglottic folds are widened distended (double arrow)

Direct Laryngoscopy

Epiglottis appears to be angry red and swollen.

Injudicious attempt to examine throat may at times cause death by sudden reflex spasm of the larynx. It is therefore prudent not to force a child to lie down for throat examination. Child can be sent to radiology department for an urgent X-ray film if the clinical diagnosis is otherwise obvious. In case laryngoscopy is considered essential, the equipment and personnel for respiratory resuscitation should always be readily available.

Treatment

- Immediately call most senior anesthetist and ear, nose, and throat (ENT) surgeon available
- Arrange for careful transfer to area where gaseous induction of anesthesia is possible, and where emergency tracheostomy can be performed, if intubation is impossible
- Start IV cefotaxime 50 mg/kg/dose or IV ceftriaxone 75 mg/kg stat before transfer to PICU.

LARYNGITIS AND LARYNGOTRACHEOBRONCHITIS

Agents

Always viral usually with parainfluenza type I.

Table 18: Assessment of severity of croup

	Mild	Moderate	Severe
Stridor	±	+	++
Sternal tug	-	+	++
Recession	-	+	++
Accessory muscle	-	+	++
Nasal flare	-	+	++
Cyanosis	-	-	+
Drooling	-	-	+
Air entry	Normal	Reduced	Poor
Hydration	Normal	Normal/↓	↓
Saturation	Normal	Normal/↓	↓
Heart rate	Normal	↑	↑(bradycardia is a preterminal event)

Other viruses:

- RSV
- Parainfluenza types 2 and 3
- Influenza virus
- Adenovirus
- Rhinovirus.

Clinical Features

- In infectious croup, the onset of the illness is more gradual. Usually there is a mild cold for a few days before the child develops a brassy cough and mild inspiratory stridor
- As obstruction increases, the stridor becomes more marked and the suprasternal and sternal recession become evident
- Restlessness and anxious with fast breathing due to increasing hypoxemia
- Cyanosis
- As the condition worsens, breath sound may become inaudible and stridor may apparently decrease.

Assessment of severity of croup is shown in Table 18.

Investigation

- Pulse oximetry.

Treatment

- Oxygen, if saturation is less than 92%
- Steroids:
  - Dexamethasone 0.15 mg/kg PO/IV, one or two doses
  - Budesonide (Bud) nebulized is an effective alternative.

How to differentiate between croup (laryngotracheobronchitis) and potentially catastrophic epiglottitis (Table 19)?

Table 19: Distinguishing croup and epiglottitis

	Croup	Epiglottitis
Time, course	Days	Hours
Cough	Barking	Weak
Fever	None or mild	>38°F
General appearance	Well	Ill, with drooling
Timing	Worse at night	No diurnal variation
Cyanosis	Rare	Common
Treatment	Supportive, steroid	Intubation and antibiotics

SPASMODIC CROUP

It occurs in children between the age of 1 year and 3 years. There may not be preceding coryza. The child wakes up suddenly in the early hours of the morning with brassy cough and noisy breathing. The symptoms improve within a few hours. The illness may recur on subsequent days. The course is benign and patients recover completely. Etiology is unknown.

STRIDOR IN CHILDREN

Stridor is high-pitched, harsh noise, secondary to turbulent flow through a partially obstructed airway. Stridor is a coarse inspiratory noise through a narrowed nose/pharynx (Darth-Vader like).

Usually inspiratory, but may be biphasic and variable.

Inspiratory

Usually extrathoracic lesion is at or above glottis. During inspiration, extrathoracic, intraluminal airway pressure is negative, relative to atmospheric pressure, leading to collapse of supraglottic structures.

Biphasic

Glottis, subglottic, tracheal. A fixed obstruction resulting in fixed caliber airway.

Differential diagnosis of stridor according to frequency is mentioned in Table 20.

Stridor typically arises in children aged 6 months to 5 years.

- Stridor in children below 6 months of age is suggestive of congenital defects, e.g. laryngomalacia, vascular ring and warrants investigation.
- Older children suffering from stridor tend to have airway sensitivity, e.g. hay fever, asthma and have recurrent episodes. Stridor may be severe in ex-premature infants and those with low muscle tone, e.g. Down's syndrome, myotonia.

Immediate Management of Stridor

Make certain that you are dealing with croup. Assess severity, from the end of the cot, without disturbing the child (Table 18).

- If severe, emergency treatment with O_2 and nebulize adrenaline, otherwise, take history and examine.
- Do not disturb child—leave on carer's lap, in the position of comfort.

History

- Is it definitely stridor, not wheeze? Has the child's cry/voice changed?
- When was the onset? Has the severity changed?
- Any precipitants, e.g. URTI, contact with peanuts, playing with small toys?
- Any effect on activity, talking?
- Any cough, vomiting or diarrhea? Any rash noticed?
- Any drooling?
- Any possibility of foreign body? NB choking episode in past months.
- Any previous episode of stridor?
- Ask about neonatal events, particularly if ventilation was required and its duration. NB ventilation may be ongoing but noninvasive.
- Is the child fully immunized?
- Any congenital abnormalities?
- Is the child thriving?

Examination

General

- Level of consciousness—less responsive, if hypoxic
- Drooling

Table 20: Differential diagnosis of stridor

Common	Uncommon	Rare	Very rare
Supralaryngeal			
Hypertrophic adenoids	Macroglossia, e.g. Down's, syndrome, Beckwith-Wiedemann syndrome	Choanal atresia	Vallecular cyst
		Thyroglossal cyst	Tongue dermoid
			Tongue teratoma
Laryngeal			
Viral croup	Spasmodic croup	Epiglottitis	Laryngeal cleft
Laryngomalacia	Foreign body	Retropharyngeal abscess	Bilateral vocal cord palsy
Hypertrophic tonsils	Anaphylaxis—angioneurotic edema	Subglottic stenosis	Laryngeal web
		Peritonsillar abscess	Cyst/hygroma
		Hysterical	Hemangioma
		Hypocalcemic laryngospasm	Papillomata
Tracheal			
	Foreign body	Double aortic arch	Deep strawberry nevus
Tracheomalacia	Bacterial tracheitis	Aberrant innominate artery	Bronchogenic cyst
	Tracheal stenosis	Aberrant subclavian vein	
		Pulmonary artery sling	

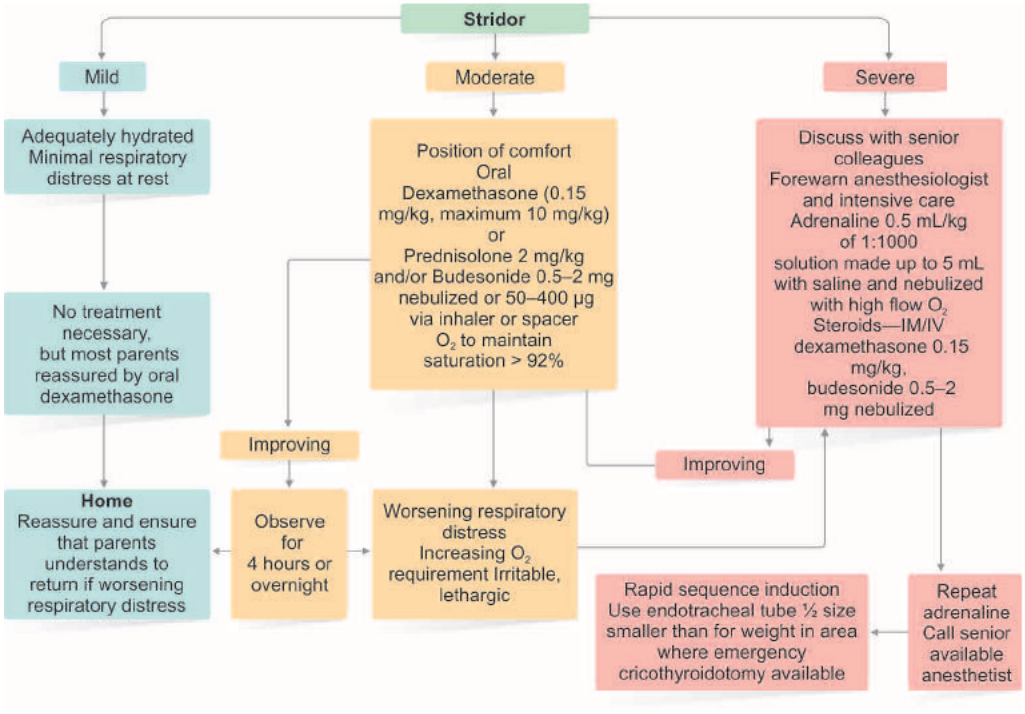


Fig. 12: Algorithm of management of stridor

- Fever
- Dysmorphic features (Down's syndrome, craniofacial), cutaneous nevi (capillary hemangioma may be deep and involve underlying structures).

Specific

- Any respiratory distress; tachypnea, tracheal tug, recession, air entry
- Barking cough, hoarse cry
- Tachycardia, murmur.

Stridor

- At rest or intermittent; worse with crying or anxiety?
- Timing.
- Loudness not indicative of severity.

Investigation

- Usually none is necessary before treatment
- Otherwise only saturations, if probe tolerated
- Neck X-rays are usually not indicated

Other tests may be indicated for rarer causes (*See* Individual Disease).

Treatment

See the algorithm for management (Fig. 12). *Also refer* to specific disease management.

PLEURAL EFFUSION AND EMPYEMA (POSTPNEUMONIC)

As long ago as 300 BC, hippocrates commented that a person "with empyemata ... shall die on the 14th day, unless something favorable supervene."

However, modern management of empyema thoracis has positively changed the outcome of empyema thoracis.

SOME ESSENTIALS OF PLEURAL EFFUSION AND EMPYEMA

- Parapneumonic effusions are accumulations of fluid and inflammatory cells due to an underlying LRTI
- The small amount of fluid normally present in the pleural cavity (~0.3 mL/kg) contains a few cells and is constantly being generated and absorbed
- The presence or association with pneumonia of a small effusion that does not cause any respiratory distress can be managed conservatively without the need for aspirating a sample
- An empyema is a collection of viscous fluid and cells (pus). The fluid and pus is often loculated separated by fibrin septae into one or more pockets

The etiology and management of empyema thoracis depend on geographical variation.

PREDISPOSING FACTORS

Half of the patients with empyema develop it as a complication of pneumonia particularly not treated timely and appropriately. Other predisposing factors include:

- Neglected foreign body can cause bronchiectasis and predispose to empyema
- Abscess: Lung abscess, retropharyngeal abscess, abscessed mediastinal lymph nodes
- Cerebral palsy
- Congenital heart disease
- Aspiration pneumonia.

MICROORGANISMS RESPONSIBLE FOR EMPYEMA THORACIS (TABLE 21)

Anaerobes are more common after 6 years of age. In developing countries like Indian subcontinent, *S. aureus* is the most common organism. In developed countries, majority of the cases are due to pneumococcal infections and most of them are due to infection with organism of serotype I.

STAGES OF EMPYEMA

There are three stages of empyema formation:

1. *Exudative stage (1–3 days):* During this time, fibrinous material forms on both pleural surfaces.
2. *Fibrinopurulent stage (4–14 days):* As more fibrin is deposited, the pleural surface may be joined by fibrinous septae which cause the fluid to become loculated.
3. *Organizing stage (after 14 days):* This is the final stage and is characterized by proliferation of fibroblast on the pleural surfaces which form an inelastic covering preventing adequate lung expansion (fibroarthrosis).

Early intervention prevents the third stage from developing.

CLINICAL FEATURES

In postpneumonic (more common cause) empyema, there is a symptom-free period, when bacteria multiply in pleural fluid. Common symptoms raising high index of suspicion of empyema are: Fever, chill and rigor, night sweat, malaise and productive cough.

On Physical Examination

- Diminished breath sound
- Dullness on percussion
- Pleural friction rub
- Bronchophony above pleural effusion and mediastinal shifting.

Clinical difference of pleural effusion/empyema thoracis, consolidation and pneumothorax is given in Table 22.

INVESTIGATIONS

- Chest X-ray:
  - Normal size heart
  - Normal mediastinum may be shifted to opposite side
  - Body of fluid on one side of chest
  - Obliteration of the costophrenic angle only—a small effusion
  - A thick rim of fluid ascending the lateral chest wall—moderate sized effusion
  - A dense opacification of involving one or other lower zones—large effusion
  - A generalized, unilateral hazy opacification of a lung field may be seen in a young child—difficult to estimate amount of fluid (Fig. 13).
- Ultrasonographic assessment:
  - An ultrasonographic examination will show the size, position and presence of the fluid and may determine whether it is loculated

Table 21: Common organisms causing empyema thoracis

Aerobes	Anaerobes
Staphylococcus aureus	Bacteroides species
Streptococcus pneumoniae	Fusobacterium species
Haemophilus influenzae	Clostridium perfringens
Pseudomonas aeruginosa	Microaerophilic streptococci
Escherichia coli	Peptococcus
Klebsiella aerogenes	Peptostreptococcus
Staphylococcus epidermidis	Catalase negative nonspore-forming Gram-positive bacilli
Streptococcus viridans	*Veillonella parvula*
Serratia marcescens	Propionibacterium acne
Enterobacter species	
Streptococcus milleri	
Legionella pneumophila	
Mycobacterium tuberculosis	

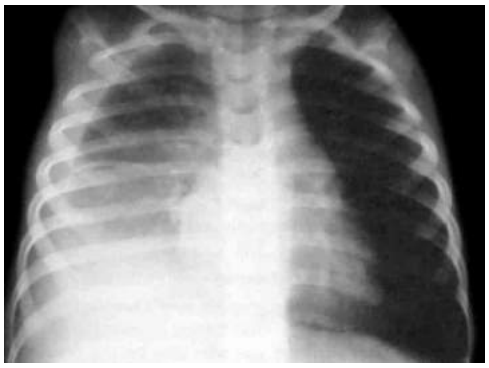


Fig. 13: Chest X-ray showing empyema in right hemithorax

Table 22: Physical findings in different pulmonary condition

		Consolidation	Pleural effusion/empyema	Pneumothorax
Inspection	Movement of chest	Restricted on the affected side	Restricted on the affected side	Restricted on the affected side
Palpation	Position of trachea	Central	Shifted to the opposite side	Shifted to the opposite side
	Position of apex beat	In normal position	Shifted to the opposite side	Shifted to the opposite side
	Vocal fremitus	Increased	Decreased/absent	Decreased
Percussion	Percussion note	Woody dull	Stony dull	Hyper-resonant
Auscultation	Breath sound	Bronchial	Absent	Absent
	Vocal resonance	Increased	Decreased/absent	Decreased
	Added sounds	Coarse crepitation	Absent, but crepitation may be present above the level of effusion	Absent

- A child with a moderate to large pleural effusion on ultrasonogram should be managed in a specialist unit with access to cardiothoracic surgeons. Conservative treatment with antibiotics alone will result in a prolonged illness and hospital stay. There is no place for repeated thoracocentesis in this situation.

Fluid Sample

A fluid sample collection is needed if there is:

- A large effusion
- No clear diagnosis
- Respiratory distress
- Persistent fever despite antibiotic treatment
- Long history (>14 days).

After ultrasound of the chest and checking blood clotting studies, a small chest drain (or pigtail drain) should be inserted into the pleural fluid. Samples should be sent for the following:

- *Microbiology:* Bacterial culture and sensitivity, acid fast bacilli.
- *Cytology:* Presence of pus cells and microscopic assessment of aberrant cell types. Cytology for lymphoma may give false negative result in up to 10% of cases.
- *Biochemistry:* Glucose, protein, lactate dehydrogenase (LDH) and pH.

Laboratory Diagnosis of Empyema

The diagnosis of empyema can be based on presence of:

- *Fluid:* pH <7.2, glucose <3.3 mmol/L, protein >3 g/L, pus cells.
- *Ultrasound scan:* Loculation or fibrin strands seen.

MANAGEMENT OF EMPYEMA

Medical Management

- High-dose antibiotics IV for 3 weeks:
  - Injection cloxacillin along with injection cefotaxime or injection ceftriaxone can be used for initial therapy
  - In methicillin resistant *S. aureus* IV vancomycin 60 mg/kg/day in four divided dosages is the drug of choice
  - Penicillin G 100,000–400,000 units/kg divided in 4–6 doses—pneumococci and streptococci
  - Clindamycin 24–40 mg/kg in 3–4 doses—for anaerobic bacteria
  - In tubercular empyema—antituberculosis drugs initially four drugs to start (HRZE) for 2 weeks followed by three drugs (HRE) for 5–6 months.
- Fibrinolysis:
  - Insert small percutaneous chest drain
  - Urokinase
  - Clamp drain and encourage mobility 4 hour after urokinase
  - Alteplase is an alternative
  - Do not forget analgesia, e.g. bupivacaine 0.25% 0.5 mL/kg into drain and nonsteroidal anti-inflammatory drug (NSAID).

Fluid Drainage

Empyema drainage is a major component of empyema treatment. Small bore percutaneous catheter can be useful if the fluid is thin. A chest tube with an underwater seal should be placed. Use of small pigtail catheters is associated with shorter hospital stay than using large bore tubes.

Urokinase (Thrombolytic Therapy) for Empyema

- *Dose:* 40,000 U in 40 mL (10,000 U in 10 mL if < 10 kg) given 12 hourly into the drain for 3 days.
- *Method:* Instil via the chest drain and then clamp the drain and encourage the patient to move and roll around over the next 4–8 hours. *Suction:* Use a low pressure suction device to maintain suction pressure of approximately 20 cm H_2O between doses.
- *Local anesthetics:* Bupivacaine around drain site may control pain.

Surgical Management

Napoleon's surgeon, Dupuytren, developed an empyema in 1835; he was heard to comment that "he would rather die at the hands of God than of surgeons." He lived 12 days. Over one and half century later, role of surgeon has made revolutionary change in the management of empyema thoracis. A major problem in the management of empyema is the formation of fibrinous adhesions resulting in loculation of the pleural fluid and entrapment of lung. This renders it difficult to drain the pleural space and re-expand the lungs by using antibiotics and thoracocentesis alone. Simple aspiration is unsatisfactory as this leads to very high rate of subsequent reintervention.

Surgical managements are video-assisted thoracoscopic surgery (VATS) and open surgical decortications.

The surgical procedures although appear dangerous and appear to be associated with increased morbidity, they have gained popularity due to evidence-based facts that they cause marked reduction in hospital stay and the need for further investigation. These are also found to be quite safer procedures, particularly for children, compared to adult.

Video-assisted Thoracoscopic Surgery

Video-assisted thoracoscopic surgery is performed under general anesthesia with either one or both lungs ventilated, depending on the size of the child. Two or three ports are made in the chest with the child in the lateral decubitus position (Fig. 14). One port is utilized for the camera and the

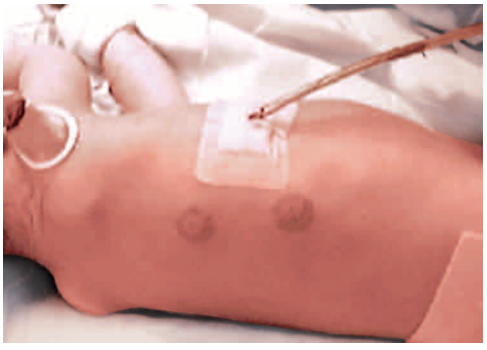


Fig. 14: Video-assisted thoracoscopic surgery (VATS)

others for grasping instruments, which can be rotated round the ports, if required.

Video-assisted thoracoscopic surgery has the advantage over open surgery of limiting the morbidity to skin, muscles, nerves and supporting structures which occurs following a large surgical incision. Complications of large surgical incision include: Pain, both acute and long-term; infection; limitation of movement; and cosmetic scarring. Scoliosis can occur in children following open thoracotomy with a reported incidence of up to 15%. In addition to damaging the superficial structures, exposing the internal organs in small children may cause drying of tissues and impair healing.

Video-assisted thoracoscopic surgery offers significant benefits over chest drain insertion alone because of the marked reduction in hospital stay and the need for further interventions.

It is arguable whether this technique is significantly less invasive, as three intercostal incisions are usually required for insertion of instruments and drains.

Open Surgical Decortication

Early thoracotomy and decortication has proved to be very safe and does produce impressive results with rapid resolution of fever, discharge after a total median stay of only 4 days, and complete radiological and clinical resolution.

The installation of fibrinolytics into the intercostal space via a chest drain has been successfully used to avoid formal thoracotomy in adults; this approach has now been adapted to the management of this problem in children.

The vast majority of children presenting with empyema are previously well in comparison to adults who usually suffer prior chronic disease and disability. Therefore chronic morbidity after treatment is unusual, and death is extremely rare in children associated with surgical management of empyema thoracis.

Although study reports indicate addition of urokinase result in a reduced hospital stay compared to placebo, but this is still longer than that achieved in the uncontrolled retrospective studies of early decortication. There are evidences to suggest that fibrinolytic therapy fails in 10% of patients, necessitating formal decortication.

The recent increase in incidence of empyema thoracis has highlighted the need to optimize management with the recognized primary short-term goals of minimizing time to defervescence and length of hospital stay. In addition to antibiotics, therapeutic options include aspiration, thoracocentesis with or without instillation of fibrinolytics, thoracotomy with decortication, and VATS.

SLEEP APNEA AND SLEEP ASSOCIATED BREATHING DIFFICULTY

Apnea is defined as lack of breathing. Obstructive apnea refers to a lack of airflow in the face of respiratory effort. It is most often associated with sleep. The obstructive sleep apnea syndrome (OSAS) may be due to tonsillar/adenoidal hypertrophy, macroglossia, or micrognathia.

DIAGNOSIS

History

- Snoring and sleep disturbance
- Only about 15% of snoring children have significant airway obstruction.

Examination

A thorough history and examination is needed:

- Symptoms of upper airway obstruction and OSAS are more likely to be due to adenoidal hypertrophy rather than just tonsillar hypertrophy
- Middle ear infection and chronic effusion are features associated with adenoidal hypertrophy
- Mouth breathing leading to dry mouth and cracked lips.

Investigations

A thorough history and examination should identify children who need further treatment. However, there is a place for the following as part of an assessment:

- Sleep study: This could include just overnight pulse oximetry, but more extensive polysomnography may be needed in special instances.
- CXR, X-ray nasopharynx (Figs 15 and 16).
- Electrocardiogram (ECG): To examine for secondary right heart cardiac consequences of airway obstruction.

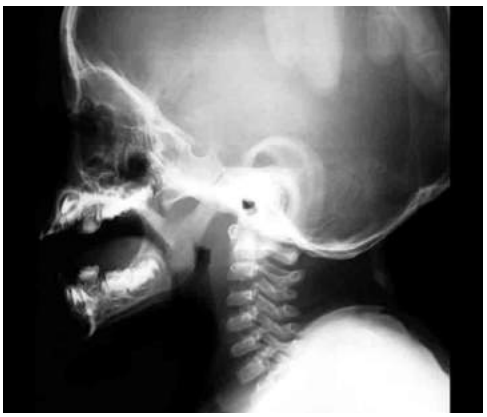


Fig. 15: Enlarged and inflamed adenoid almost completely obstructing airway

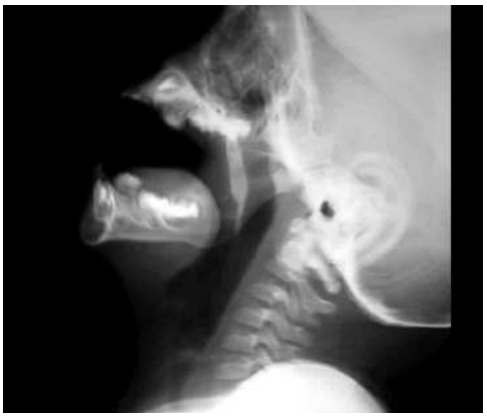


Fig. 16: Same child with small adenoid with patent upper airway after medical treatment only

TREATMENT

Surgery is indicated when the following criteria are met.

Tonsillectomy

In case of any of the following:
- Airway obstruction (usually performed with adenoidectomy)
- History of recurrent tonsillitis (>7 episodes in 1 year, or >10 episodes in 2 years)
- History of two episodes of peritonsillar abscess.

Adenoidectomy

In case of any of the following:
- Airway obstruction
- Recurrent or chronic middle ear infection
- Recurrent or chronic nasopharyngitis
- Chronic mouth breathing.

CPAP may be helpful in sleep apnea.

ALLERGIC RHINITIS

Up to 20% of the population has symptoms of allergic, rhinitis, which include nasal congestion, itching, sneezing and discharge.

Diagnosis

History

- Identify seasonality of the symptoms and history of atopy
- Take a history of environmental exposure such as parental smoking, pets, dust mite, stuffed toys, carpet, bedding, etc.

Examination

Check for:
- Mouth breathing
- Postnasal drip
- Cough
- Nose rubbing
- Suborbital venous congestion
- Watery-red eyes.

Investigations

- Skin test for specific antigen
- Specific serum IgE measurement.

Treatment

Allergen Avoidance

- Dust covers on bedding
- Avoid stuffed toys.

Symptom Relief

- Antihistamines
- Intranasal steroids.

CYSTIC FIBROSIS

Cystic fibrosis (CF) is an autosomal recessive genetic disorder leading to a defect in the CF transmembrane receptor (CFTR)

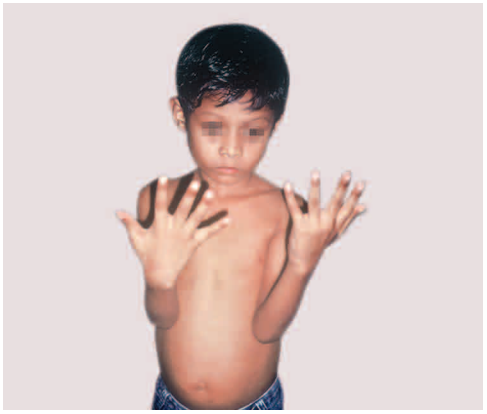


Fig. 17: Cystic fibrosis, showing clubbing of fingers and wasting. The child suffered from recurrent chest infection with *P. aeruginosa* and malabsorption (*Source:* Reproduced from Shakur MS. Cystic fibrosis: A case report. Bang J Child Health. 1995;19(1):23-8.)

protein, which results in defective transport in exocrine glands. In the lung, abnormal sodium and chloride ion transport causes thickening of respiratory mucus. The lung is therefore prone to inadequate mucociliary clearance, chronic bacterial colonization and lung injury. Among colonization of lung by various bacteria, infection with *P. aeruginosa* is associated with disease progression. There are also similar effects—although not with super added infection—in other organs that lead to pancreatic insufficiency, liver disease, and in male, infertility. There are over 1,000 mutations in the CFTR gene; the most common is the ΔF508 deletion. CF is the most common genetic disease in Caucasians (1/2580). CF is rare in Indian subcontinent but it is under reported (Fig. 17).

Diagnosis

Screening

Cystic fibrosis can be identified by newborn screening for abnormally raised immunoreactive trypsinogen (IRT) and CFTR ΔF508 deletion from blood-spot analysis (Guthrie card).

History

Give particular attention to:
- Cough and wheeze
- Shortness of breath
- Sputum production
- Hemoptysis
- Weight loss.

About 10–20% of CF patients present in the neonatal period with meconium ileus. However, most children with CF present with:
- Malabsorption
- Failure to thrive
- Recurrent chest infection.

Examination

- General examination: Look for finger clubbing, nasal polyp and rectal prolapse
- Full assessment of respiratory system
- Liver and GI system
- Growth and development.

Table 23: Information needed for the annual multisystem review of CF patients

Blood tests	
Hematology	FBC, clotting (APTT, PTT)
Biochemistry	Creatinine, urea, Na, K, Cl, HCO_3^- (Mg, Ca if on Colistin)
Liver functions	ALP, ALT, bilirubin, albumin, protein
Glucose control	RBS, HbA1C, OGTT
Immunology	IgE, IgG, RAST to *Aspergillus*, *Pseudomonas* precipitin
Radiology	
X-ray	Chest
Ultrasound	Liver and bowel
DEXA scan of bone	Consider in children >10 years, or those on increasing doses of steroids, or those who have increasing fractures
Lung function	
Measurement	FEV1, FVC, PEFR, RV, TLC
Oximetry	Resting SpO_2
Bacteriology	
Sputum/cough swab	Culture including *Pseudomonas aeruginosa*, Burkholderia cepacia, acid fast bacilli
Morbidity	
Hospital	Number of admissions and days in hospital
Reviews	
Medications	Requirements (dose)
Physiotherapy	Technique, education, equipment
Nutrition	Education, enzymes, supplements
Social	Family support, genetics, housing, school, statement of special needs
Psychology	Is an assessment needed?

Abbreviations: FBC, full blood count; APTT, activated partial thromboplastin time; PTT, partial thromboplastin time; ALT, alanine transaminase; ALP, alkaline phosphatase; RBS, random blood sugar; HbA1C, glycated hemoglobin; OGTT, oral glucose tolerance test; RAST, radioallergosorbent test; PEFR, peak expiratory flow rate; FVC, forced vital capacity; FEV1, timed forced expiratory volumes; TLC, total lung capacity; RV, residual volume; DEXA, dual-energy X-ray absorptiometry

Investigations

- Sweat test showing increased chloride level (>60 mmol/L)
- CXR, hyperinflation, increased AP diameter, bronchial dilatation, cysts, linear shadows and infiltrates
- *Lung infection:* Obstructive pattern with decreased forced vital capacity (FVC) and increased lung volume.

All patients with CF should have a thorough annual multisystem review. Relevant investigations for CF are given in Table 23.

Problems Associated with Cystic Fibrosis

Infancy

- Meconium ileus
- Neonatal jaundice.

Childhood

- Bronchiectasis
- Rectal prolapse
- Nasal polyp
- Sinusitis.

Adolescence

- Diabetes mellitus
- Cirrhosis and portal hypertension
- Pneumothorax
- Hemoptysis
- Aspergillosis
- Male sterility
- Psychological problems.

Management of Cystic Fibrosis

The management of the child with CF requires close cooperation between local hospitals and regional center. Patients and their families gain much from expert clinics and from other patients and their families. Effective management requires a multidisciplinary team approach, which should include:

- Pediatric pulmonologist
- Physiotherapist
- Dietician
- Nurse liason or practitioner in CF
- Primary care team
- Teacher
- Psychologist.

Pulmonary Care

- *Physiotherapy:* All children with CF should have physiotherapy at least twice a day. Parents and older children are taught how to do:
  - Chest percussion
  - Postural drainage
  - Self-percussion
  - Deep breathing exercise.
- *Antimicrobial therapy:* Most experts recommend antibiotic therapy:
  - Oral: During periods when well, against *Staphylococcus aureus* and *Haemophilus influenzae*.
  - Antipseudomonas: Oral ciprofloxacin or IV ceftazidime.
  - IV for acute exacerbations: Initially courses of antibiotics can be administered via an indwelling long-line that should last a number of weeks if needed. However, as infections become more frequent, a permanent form of IV access (such as indwelling Port-a-cath) will help
  - Nebulize for those colonized with *P. aeruginosa*. Nebulized inhaled hypertonic saline is useful in respiratory difficulty.
- Other therapies:
  - Annual influenza immunization and pneumovaccine
  - Bronchodilators for those with reversible airway obstruction
  - *Mucolytics:* Nebulized acetylcysteine (8 mL/day of 10% solution used before physiotherapy) or recombinant deoxyribonuclease (DNAase) 2 hours before physiotherapy.

Gastrointestinal Management

- Distal intestinal obstruction (meconium ileus equivalent):
  - Lactulose: 1 mL/kg/day
  - Oral acetylcysteine solution: Prophylaxis 15 mL of 10% per day in less than 7 years old and 30 mL in more than 7 years old. Treatment doses are doubled to three times this amount
  - Gastrografin®: Oral dose can be used as a single treatment dose (50 mL for children 15–25 kg and 100 mL for those >25 kg). Fluid intake should be encouraged for 3 hours after administering the Gastrografin®.
- Nutrition:
  - Pancreatic insufficiency
  - Treated with oral enteric coated pancreatic supplements taken with all meals and snacks. Ranitidine may be useful if the response to enzymes is unsatisfactory
  - High-calorie diet
  - Children with CF require 150% of normal energy intake
  - Salt supplements
  - Salt depletion is a risk in CF patients during the first year of life, and in the summer months in older patients. In exceptionally hot weather, supplements include 500 mg/day during the first year, 1 gm/day in less than 7 years old, and 2–4 gm/day in more than 7 years old.
- Fat-soluble vitamin supplements:
  - Multivitamin: Multivitamin drop 1 mL/day.
  - Vitamin E:
    - 50 mg/day if less than 1 year old
    - 100 mg/day for age 1–16 years
  - Vitamin K: 300 mg/kg if there is evidence of liver diseases (hepatosplenomegaly or abnormal clotting).

BRONCHIAL ASTHMA

Asthma is a chronic airway inflammatory disorder associated with bronchial hyper-responsiveness and reversible airway obstruction presenting with wheeze, breathlessness, and coughing and chest tightness. It is the most common chronic respiratory disorder in children. Despite revolutionary improvement of the management of bronchial asthma with bronchodilators and steroids and new technique of drug administration by spacer devices and nebulizers, there are raising trends of asthma prevalence. Although asthma related mortality has started to fall more recently in both industrialized and developing countries, the burden of asthma remains high worldwide irrespective of developed and developing countries. It is an important cause of school absenteeism, restricted activity and anxiety for the child and the family. Acute asthma remains one of the most common reasons for emergency admission to hospital. The prevalence as reported in a study in 2004 was high in UK (>15%), New Zealand (15.1%), Australia (14.1%), Canada (14.1%) and USA (10.9%).

"Why asthma incidence is increasing worldwide particularly in industrialized countries where atmospheric pollution level is low which is popularly thought as an important cause of bronchial asthma?"

No strong evidence-based cause for growing incidence for asthma has been found. However, in industrialized countries, "the hygiene hypothesis" has been proposed to explain the reason of allergic disease including asthma." Improved hygiene and reduced family size resulting in reduced microbiological exposure has been considered to influence the development of immune system. The natural development of immune system is thought to be partly dependent on environmental microbiological factors particularly low virulent bacteria which may influence the relation between thymocyte 1 (Th1) and thymocyte 2 (Th2) by switching toward noninflammatory Th1 response with subsequent reduced risk of allergy. It is increasingly accepted that product of lymphocyte of the Th2 subtype including interleukin-5 (IL-5) and IL-3 regulate the inflammatory activity of eosinophil and mast cell within the asthmatic lung. These cells can generate activity of mediators, toxic enzymes and oxygen radical which account for airflow obstruction and epithelial damage and airway hyper-responsiveness of asthma. T-cell (Th2) induced cytokines and mast cells also help to direct eosinophil growth and maturation and to promote the isotype switching from isotype IgM to IgE that provides a rational explanation of inflammatory response of asthma. Cytokines also stimulate lipooxygenase pathway to produce strong inflammatory mediators, leukotrienes. The presence of nonvirulent or less-pathogenic bacteria in respiratory system helps Th1 and Th2 system to switch toward Th1 response and disturbs differentiation of Th1 to Th2 with reduced risk of allergy as it is Th2 response which provokes above mentioned inflammatory responses. Lipopolysaccharide capsid antigens from bacteria interfere with cytokine expression of T-cell and are suggested to disturb the Th1 differentiation process (Fig. 18). Exposure

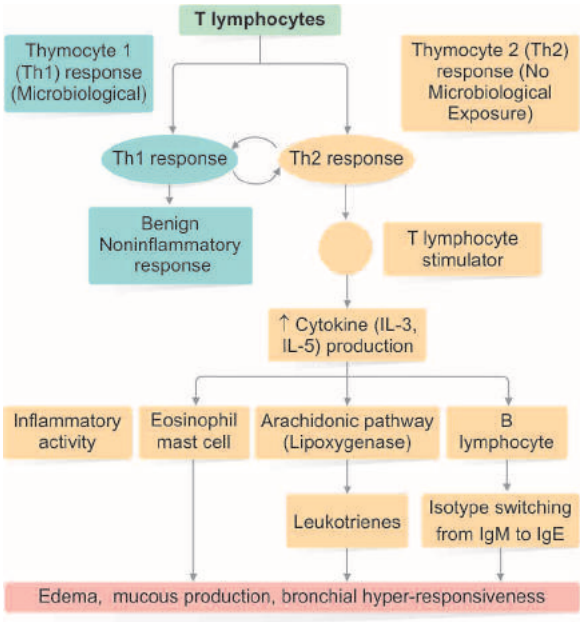


Fig. 18: Algorithm showing thymocyte 1 (Th1) and thymocyte 2 (Th2) system explaining "hygiene hypothesis" for prevalence of Bronchial asthma. Th2 response for inflammatory response can be diverted to benign Th1 system by microbiological exposure. In its absence, Th2 system continues to produce allergic and inflammatory response. Antibiotic administration also helps to generate uninhibited Th2 response (by destroying microbes) to produce allergic and inflammatory response

of endotoxin and bacterial component has been proposed to protect against development of allergy in children raised in farmers' house compared to schoolmates from nonfarming house.

The virtual absence of such less pathogenic bacteria in hygienic western world environment and in respiratory tract in children of an industrialized country due to improved hygienic conditions helps to tilt Th1 toward Th2 system and thereby increasing the incidence of allergic disorder including asthma.

In developing countries, Th1 and Th2 systems are also involved or contribute to increase asthma incidence but in probably different way. This is due to the fact that the injudicious use of antibiotic particularly broad-spectrum antibiotic used in recurrent respiratory tract infections occurring in developing countries irrespective of bacterial or nonbacterial (mostly viral) etiology eliminate respiratory microbe responsible for prevention of Th1 maturation to Th2 response. This is also the reason why antibiotics should not be used in asthma exacerbation (unless complicated by bacterial pneumonia) and if used at all, it is better to use narrow spectrum antibiotics, like macrolides (azithromycin, erythromycin, etc.), which have less possibility to eliminate microbes involved in Th1 response.

ETHNICITY

Ethnic origin may also play a role in the prevalence of asthma. This was confirmed by a study conducted in German children of whom 7% were Turkish nationality. The prevalence of asthma, atopy and bronchial hyper-responsiveness are lower in Turkish origin German children than in native German children.

In developing countries, higher level of atmospheric pollution and increased viral infection contribute to rising incidence of bronchial asthma.

Viral respiratory infections are important trigger factor for asthma exacerbation. Infection with rhinovirus, RSV, parainfluenza virus or corona virus causes 50–60% of exacerbation among asthmatic patient. Higher viral titer strongly correlates with a more severe exacerbation of asthma.

The relation between childhood asthma and respiratory infection also has impacts on the risk of hospital admission. During winter and autumn months, the incidence of URTI increases in parallel with increased incidence of asthma exacerbation requiring hospital admission.

Interestingly nonatopic children with recurrent chest infection in first 3 years of life are significantly more likely to develop asthma, while atopic children with recurrent chest infection or febrile illness in first 3 years of life have significantly reduced risk of developing atopy or asthma in later life. Other factors are irritants (e.g. house dust mite, grass pollen, moulds), smoking (active or passive), cold air, exercise, emotional upset or excitement, chemical irritants (e.g. paint, domestic aerosol).

Taking a New Look at Asthma

Although asthma prevalence, particularly in children, is increasing worldwide, it is under diagnosed and undertreated but fortunately:

- New methods are available for recognizing, diagnosing, treating and controlling asthma
- Personal, social and economic burdens of asthma can be minimized
- Patient education increases the likelihood of lifelong success
- One can make difference.

PATHOPHYSIOLOGY

An outline of the pathophysiology of asthma is shown in Figure 19. Asthma results in chronic inflammation of the airways involving eosinophils, lymphocytes, mast cells and neutrophils. The airflow obstruction is often reversible, either spontaneously or with treatment, and is associated with an increase in airway responsiveness to a variety of stimuli such as exercise, cold air or allergen exposure.

Pathophysiology and Its Clinical Implications

Asthma was once regarded as a primary disease of airway smooth muscles leading to treatment with oral and inhaled bronchodilators. Investigations over last decades have shown asthma to be chronic inflammatory disease complicated by periodic acute exacerbated inflammatory changes. Indeed it is now clear that even patients with asymptomatic asthma have obvious inflammatory changes in their airways characterized by infiltration of the mucosa and epithelium with activated T-cell, mast cells and eosinophil. With increased awareness of importance of inflammation in the pathogenesis of asthma, the use of anti-inflammatory drugs early in the course of disease might be an opportunity to minimize lung damage. The consequences of inflammation include increased microvascular permeability, stimulation of local and neural reflexes, epithelial disruption and stimulation of mucus secreting gland, smooth muscle hypertrophy and airway obstruction. Therefore inhaled corticosteroids (ICSs) have become the cornerstone of management of asthma particularly in persistent asthma and in frequent episodic asthma, with inhaled β_2-agonist being used as needed basis.

Chronic low-grade airway inflammatory changes occur in children due to genetic predisposition (atopic) or environmental factors. These low-grade inflammations are also associated with bronchial hyper-responsiveness to various stimuli and trigger factors, like URTI, allergens (house dust mite, grass pollen, mould, animal dander,

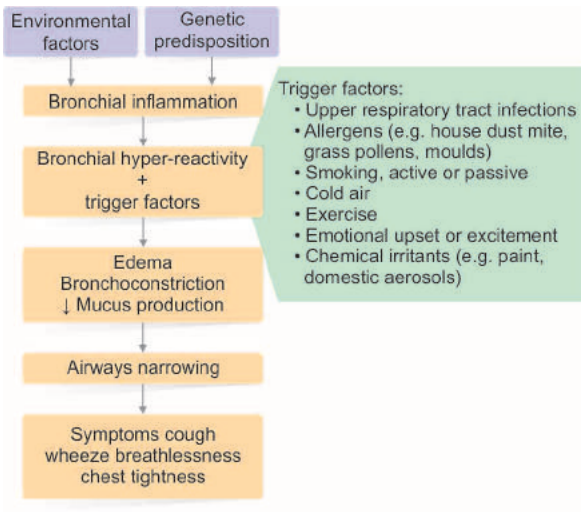


Fig. 19: Pathophysiology of bronchial asthma

etc.), smoke, cold air, exercise, exaggerate the already hyper-responsive bronchial mucosa causing increased mucous production, mucosal edema, bronchoconstriction and subsequent airway narrowing. The consequence of exacerbated inflammation results in presentation of clinical symptoms characterized by cough, wheeze, breathlessness and chest tightness.

It is increasingly accepted that the products of activated Th2, cytokines of subtype IL5 and IL3 regulate the inflammatory activity of eosinophil and mast cell within the asthmatic lung. These cells can generate activity of mediators, toxic enzymes and O_2 radicals which account for airflow obstruction, epithelial damage and airway hyper-responsiveness of asthma.

The cytokines also switch the B lymphocyte from IgM to IgE and stimulate lipooxygenase pathway of arachidonic acid which produces inflammatory mediators leukotrienes including strong inflammatory mediators LTD4.

All these factors which include the increasing IgE production, eosinophilic and basophilic stimulation contribute to airway inflammation and narrowing, thus producing asthma symptoms.

ATOPY, ALLERGY AND ASTHMA

Asthma is a heterogeneous condition of different clinical phenotypes, with wheezing being the major clinical expression. Two wheezing phenotypes have been identified in children with asthma:

1. IgE-mediated wheezing (atopic asthma)
2. Nonatopic wheezing in the preschool and school going child.

Another wheezing phenotype is a transient wheeze or happy wheezer which is not a genuine asthma although wheeze occurs due to recurrent viral infection in infants with congenital narrow airway caliber.

Nonatopic Wheezing

Nonatopic wheezers have normal lung function early in life, but a lower respiratory illness due to a viral infection (usually RSV) leads to increased wheezing during the first 10 years of life. This phenotype seems to cause less severe persistent wheezing, and symptoms improve during adolescence.

IgE-mediated Wheezing (Atopic Asthma)

Atopic wheezing is the usual perception of asthma. Lung function is normal at birth, but recurrent wheeze develops with allergic sensitization, with increased blood IgE and positive skin prick tests to common allergens. Atopic wheezers have persistence of symptoms and have decreased lung function later in childhood. Risk factors for the development of atopic wheeze (asthma) are family history of asthma or allergy and a history of eczema.

Atopy and Allergy

Atopy is an inherited predisposition to sensitization to allergens, and is present in up to 40% of children, most of whom are asymptomatic. Atopic children are at increased risk of allergic disease. The presence of one allergic condition within a child increases the risk of another; for example, half of children with allergic asthma will have eczema at some stage during their lives.

Allergic disorders are:

- Asthma
- Eczema
- Allergic rhinitis
- Allergic conjunctivitis
- Urticaria and angioedema
- Food and drug allergies.

Differential Diagnosis of Childhood Asthma Causing Recurrent Wheeze in Infancy

- Bronchiolitis
- Happy wheezers
- Postbronchiolitis wheeze
- Viral croup
- Gastroesophageal reflux disease (GERD)
- Cystic fibrosis
- Pulmonary TB
- Laryngotracheomalacia
- Bronchiectasis
- Postnasal drip syndrome
- Recurrent pneumonia
- Inhaled foreign body
- Recurrent aspiration of food.

Triggers of Asthma

- URTI—viral infection, common cold
- Changes in season, weather and temperature
- Indoor allergens:
  - House dust mite (Fig. 20)
  - Dander or flakes—from the skin, hairs or feathers of warm blooded pets (dogs, cats, birds, rodents, etc.)
  - Molds—harbored in vacuum cleaner, air conditioners, humidifier
  - Insects—cockroach
- Outdoor allergens:
  - Pollens—from grass, flowers, trees
  - Molds of some fungi
- Stress: Emotion, surgery, pregnancy
- Irritants (more generalized):
  - Tobacco smoke
  - Wood smoke
  - Strong odors, perfumes and spray, cosmetics, paints, cooking especially with spices
- Certain drugs—β-blockers, aspirin, NSAIDS
- Food allergens—rarely cause an asthmatic attack.Beef, prawn, hilsa, duck egg, nuts, some vegetables, etc.

Fig. 20: Schematic diagram of house dust mite

DIAGNOSIS OF ASTHMA

The diagnosis of asthma is clinical. The diagnosis of asthma in children should be suspected in any child with wheezing on more than one occasion, ideally heard on auscultation by a health professional, and distinguished from transmitted upper respiratory noises. Wheezing is a whistling noise heard from the chest, and parents' perception of wheezing often varies from health professionals. In practice, the diagnosis is usually made on a history of recurrent wheeze, with exacerbations usually precipitated by viral respiratory infections.

History and Clinical Features

- Cough, worse particularly at night disturbing sleep or chronic unproductive cough without apparent cause
- Recurrent wheeze
- Recurrent breathing difficulty
- Recurrent chest tightness
- Family history of allergy or atopy (asthma, eczema, hay fever)
- Personal history of other allergic conditions (dry skin, itchy skin with scratch marks, allergic eye signs, eczema, allergic rhinitis, enlarged adenoids in the same child currently or in the past) (Figs 21 to 23)
- Limitation of physical activities and exercise
- Chest hyperinflation
- Evidence of chest deformity:
  - Pectus carinatum
  - Harrison sulcus
  - Bowing of chest, etc. (Fig. 24)

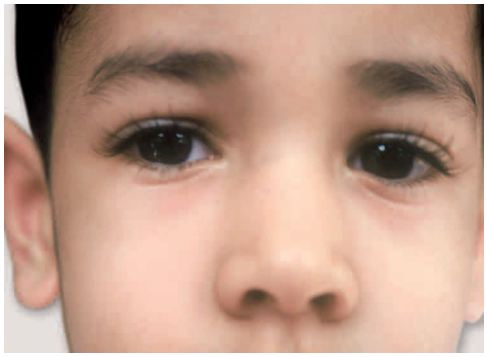


Fig. 21: Allergic pleats in both eyes (allergic shines) showing folds of periorbital skin with creases (Morgagni fold of skin)

Fig. 22: Evidence of allergic rhinitis with red inflamed nasal mucosa and perinasal skin

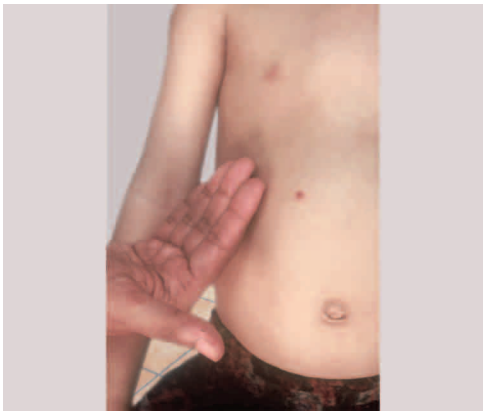


Fig. 23: Dry skin felt by dorsum of hand. Notice the red scratch mark from itching

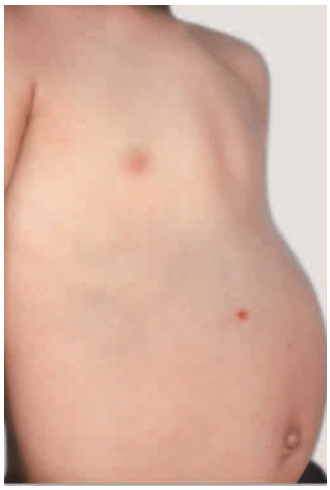


Fig. 24: Child with persistent asthma showing chest deformity (chest bowing) with Harrison sulcus

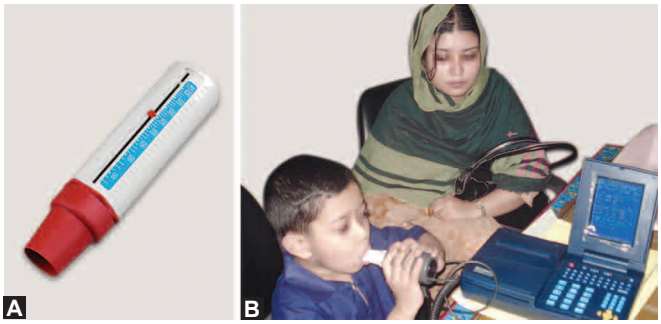
- Symptom aggravates with triggers reversible at least partially by drugs (bronchodilators)

The pattern of asthma should be assessed by asking following questions:

- How frequent are the symptoms?
- How much school has been missed due to asthma?
- Are sport and general activities affected by the asthma?
- How often is sleep disturbed by asthma?
- How severe are the interval symptoms between exacerbations?

On Auscultation

- Poor air entry with prolonged expiration, rhonchi
- Reversible and variable airflow limitation:
  - As measured by peak expiratory flow (PEF) meter in any of the following way:
    - PEF increases more than 15%, 15–20 minutes after short acting β_2-agonist
    - PEF varies more than 20% from morning measurement upon arising to measurements 12 hours later
    - PEF decreases more than 15% after 6 minutes of running or exercise—exercise-induced asthma.



Figs 25A and B: (A) Peak flow meter, (B) Performing a spirometry with pediatric mouth piece

Investigations

- Blood for:
  - Full blood count, total eosinophil count
  - Total eosinophil count
- Serum IgE—(↑), Serum IgA—(↓)
- Skin allergy test: House dust mite, pollen animal dander, fever, mold.
- Spirometry:
  - Peak expiratory flow rate (PEFR) by portable peak flow meter (Fig. 25A)
  - Less than 80% PEFR of predicted for height
  - FEV_1/FVC less than 80% predicted lung function by pediatric spirometry (Fig. 25B)
  - Bronchodilator response to β-agonist (i.e. 15% increase PEFR or FEV_1).
- Chest X-ray:
  - Not needed if there has been recent imaging, should be done in acute exacerbation not responding to standard management to exclude other comorbidity like pneumonia, pneumothorax. CXR may show:
    - Hyperinflation
    - Flattened hemidiaphragm
    - Peribronchial cuffling
    - Atelectasis.

Skin prick testing for common allergens is often considered both as an aid to the diagnosis of atopy and to identify allergens which may be acting as triggers. A CXR is usually normal but may help to rule out other conditions.

In doubtful cases, methacholine or histamine challenge test can be done to demonstrate bronchial hyper-responsiveness. It should be performed under specialist supervision with adequate preparation to manage possible complications. More than 20% fall in PEFR, with histamine challenge suggestive of asthma.

Check reversibility with nebulized β_2-agonist.

Subsets of Wheezy Infants and Toddlers

(See Table 24).

Transient Early Wheezing

Transient early wheezing is thought to result from small airways being more likely to obstruct due to inflammation secondary to viral infections. Transient early wheezers have decreased lung function from birth, reflecting small airway caliber. It usually resolves by 5 years of age, presumably from the increase in airway caliber.

Table 24: Subsets of wheezy infants and toddlers

	Happy wheezers	Persistent wheeze (later develops to childhood asthma)
Caliber of airway	Congenital narrowing Decreasing Vmax FRC*	Normal airway caliber Normal Vmax FRC
Chest hyperinflation	No appreciable change	Appreciable change
Family history of atopy	Absent	May be present
Serum IgE	Normal	Increased
Sensitivity to airway allergen (skin test)	Decreased	Increased
Family H/O asthma in parents	No significant association	Four times in asthmatic children
Family H/O eczema	No significant association	Twice common in parent
Sex	No sex difference	Two times more in male
Prognosis	Better	More likely to develop bronchial asthma
Management	Less intervention	More intervention and drug prophylaxis

*V_{max} FRC, maximum volume functional residual capacity
Abbreviation: H/O, history of.

Postbronchiolitis Wheeze

Postbronchiolitis wheeze (mostly occur in preschool children) due to combinations of early airway obstruction due to viral infection and hyper-responsiveness to aeroallergens. Small airway obstruction due to clinical viral infection is independent of atopy. If it is associated with wheeze between viral infections, or other than viral infections (house dust, pollen animal dander, etc.) or associated with personal history of atopy (eczema, allergy in the same child currently or in the past) then later development of asthma should be considered.

CLASSIFICATION OF ASTHMA

Depending upon frequency of symptoms:

- Intermittent asthma:
  - Frequent episodic
  - Infrequent episodic.
- Persistent asthma:
  - Mild persistent asthma
  - Moderate persistent asthma
  - Severe persistent asthma.

Intermittent Asthma

Characteristics

- Symptoms less than four episodes per year (infrequent episode) to less than or equal to one episode per week (frequent episode)
- Night time symptoms less than two times a month
- PEFR more than 80% predicted and variability less than 20% in between attacks
- Symptom-free between acute episodes.

Management Strategies

- Treat acute attack with β_2 bronchodilator
- Use nebulized bronchodilator and short course of prednisolone in more severe episodes (prednisolone 5 days: Given once daily in the morning after breakfast and no need to tapper treatment)
- Low-dose regular ICS may be considered in frequent episodic intermittent asthma.

Persistent Asthma

Characteristics

- Less than 10% of asthmatic
- Depending upon frequency, it can be classified into (Table 25):
  - Mild persistent asthma
  - Moderate persistent asthma
  - Severe persistent asthma.

Table 25: Classification of severity of persistent asthma

	Symptoms	Night time symptoms	PEF
Mild persistent	1 time a week but <1 time a day	>2 times a month	³80% predicted variability 20–30%
Moderate persistent	Daily	>1 time a week	>60%–< 80% predicted variability >30%
Severe persistent	Continuous Limited physical activity	Frequent	≤60% predicted Variability >30%

Mild Persistent Asthma

Characteristics

Symptoms:
- Asthma symptoms occurring more than one time in a week but less than one time in a day
- Night symptom more than two times in a month
- PEFR more than 80% predicted and variability less than 20–30%.

Management Strategies

- Low-dose ICS
- Oral leukotriene inhibitor may enable reduction in steroid use (steroid sparing role).

Moderate Persistent Asthma (Persistent Poor Control)

Characteristics

Symptoms:
- Daily symptoms
- Night time symptoms more than one time in a week
- PEFR more than 60% to less than 80% predicted, variability more than 30%.

Management Strategies (Add on Therapy)

- Low-dose ICS + inhaled long acting β_2-agonist (LABA) like salmeterol
- Leukotriene inhibitor may be added
- If inadequate control—use high-dose ICS.

Severe Persistent Asthma or Chronic Severe Asthma

Characteristics

Symptoms:
- Continuous, limited physical activity
- Frequent night time symptom
- PEFR less than 60% and variability more than 30%.

Management Strategies

- Daily oral steroid in low-dose for adequate control
- Referred to specialist care:
  - May require anti-IgE (omalizumab) therapy
  - Immunosuppressive therapy and psychological input.

Classification of Asthma Depending upon Severity of Symptoms (Asthma Exacerbation)

Depending on severity of symptoms, it can be divided into mild, moderate and severe and life-threatening asthma. The features are mentioned in the Table 26.

Both intermittent and persistent asthma may show asthma exacerbation of different magnitude. For example, intermittent asthma if becomes severe, it is called "acute severe exacerbation" of intermittent asthma. Similarly, if mild persistent asthma has moderate exacerbation, it is called acute moderate exacerbation of mild persistent bronchial asthma (Fig. 26).

It is worthwhile to mention that asthma status can change over time. For example, an intermittent bronchial asthma may deteriorate to persistent asthma. On the other hand, severe or moderate persistent asthma may improve over time to mild persistent or intermittent bronchial asthma. Management strategy therefore varies according to asthma status and asthma severity.

Special Variants of Asthma

- Cough variant asthma
- Exercise-induced asthma
- Seasonal asthma
- Drug-induced asthma
- Occupational asthma.

Cough Variant Asthma

Chronic cough, which particularly occurs at night (late night cough) or early morning cough is an important and predominant feature or only symptom in children, where wheeze is conspicuous by its absence. When other causes of chronic cough like pulmonary TB, whooping cough are excluded, cough variant asthma is the most likely clinical diagnosis. This group of children is currently called cough dominant asthma. They respond less promptly by antiasthma drug in comparison to wheeze dominant asthma.

Exercise-induced Asthma

A group of otherwise normal children develop wheeze or disturbing cough or both after exercise like running, or after

Table 26: Severity of asthma attacks

Parameters	Mild	Moderate	Severe	Life-threatening
Breathlessness	Walking can be done	Talking shorter	At rest infant stops feeding, vomiting Hunched forward	
Talks in	Sentence	Phrase	Words	
Alertness	May be agitated	Agitated	Agitated	Drowzy confused
Respiratory rate	Increased	Increased	Increased	
Wheeze	No audible wheeze, often only end expiratory	Loud	Loud	Absent
Pulse/minute	<120	>160	>160	Bradycardia
PEF	>80%	60–80%	<60%	<33%
SaO_2	>95%	91–95%	<90%	
$PaCO_2$ (mm Hg)	<45	<45	>45	

Abbreviation: PEF, peak expiratory flow.

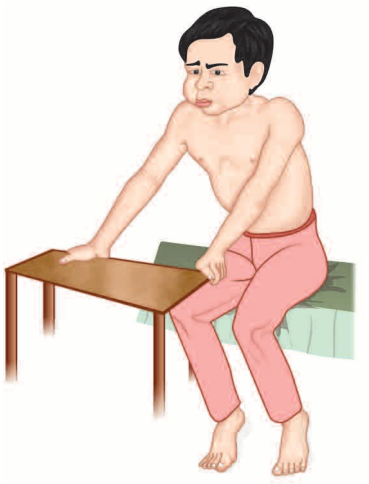


Fig. 26: A child with acute severe asthma with hunched forward posture, hyperinflated chest and agitated face

performing outdoor sports. This group of children is called exercise-induced asthma. Usually they are asymptomatic other times. This can be diagnosed clinically at the outpatient in the following way:

- Record basal PEF of the child
- Ask the patient to run to and fro in the outpatient room or to perform treadmill exercise for 5 minutes
- Look and listen for audible wheeze or cough or both after exercise
- Take also PEF immediately after running or treadmill.

If PEF decreases to more than 15% of baseline after running or treadmill is suggestive of exercise-induced asthma.

Check reversibility with inhaled β_2-agonists.

Seasonal Asthma

A group of asthmatic children develop asthma symptoms during specific seasons (seasonality) like in winter when season is dry, cold when lots of allergens and respiratory viruses are present in the atmosphere. Similarly some children develop asthma attack in rainy season when humidity is high. However, significant numbers of asthmatic children do not show any significant asthma symptoms in association with change of season (nonseasonality).

Table 27: Drugs used in asthma

Type of drug	Drugs
Bronchodilators (quick relievers)	
β_2-agonists	Salbutamol Terbutaline
Anticholinergic bronchodilator	Ipratropium bromide
Preventive/prophylactic treatment	
Inhaled steroids	Budesonide Beclomethasone Fluticasone
Long-acting β2 bronchodilator	Salmeterol Formoterol
Methylxanthines	Theophylline
Leukotriene inhibitors	Montelukast
Oral steroid	Prednisolone

Drug-induced Asthma

Some children are more vulnerable to develop asthma in response to drugs like aspirin, prostaglandin inhibitors, beta-blockers which inhibit cyclooxygenase pathway of arachidonic acid products. Product of cyclooxygenase produces prostaglandins which are associated with bronchodilation and negate the activity of inflammatory products of lipooxygenase pathways, leukotrienes (Table 27). Children already diagnosed as bronchial asthma show exacerbation with drugs which inhibit cyclooxygenase pathway like aspirin, indomethacin. However, otherwise normal children, without current or previous history of asthma can produce asthma symptoms only after taking such group of drugs.

Occupational Asthma

This is not common in children. People working in polluted environment like in textile, jute mills, cotton mills, etc. may develop asthma due to fibers, molds of raw materials. Children living near such factories may develop asthma due to atmospheric pollution.

DRUG USED IN PERSISTENT (CHRONIC) AND FREQUENT EPISODIC INTERMITTENT ASTHMA

Asthma represents a number of different phenotype defined by age, triggers, and other host and environmental factors. Response to asthma medication demonstrates significant interindividual variability, suggesting that future guidelines that recognize these phenotypes must provide more successful symptom control.

Inhaled Corticosteroid

Inhaled corticosteroids are the cornerstones of treatment of chronic asthma, and their use has significantly decreased mortality. They modulate the inflammatory response in the lungs by acting intracellularly, binding to the glucocorticoids receptors. Bound to the receptor, they enter the nucleus where they act to suppress the expression of proinflammatory genes, through the deacetylation of histone, and upregulate genes that encode anti-inflammatory proteins. The inhaled steroids currently in common use in children are Beclomethasone Dipropionate (BDP), Bud and Fluticasone Propionate (FP). The BDP and Bud are approximately equipotent and FP is about twice as potent.

Significant benefit in terms of symptoms and lung function improvement is seen by low to moderate doses of the drugs (BDP and Bud up to 400 μg/day; FP up to 200 μg/day). Increasing the dose further provides a much smaller degree of benefit, although some children with more severe asthma may respond to higher doses.

Budesonide

In addition to its role as preventer drug in chronic asthma, Bud if used along with LABA like formoterol has reliever property. Bud with formoterol can be used both as maintenance and as needed reliever reducing asthma exacerbation. Nebulized Bud has more predictable efficacy in treating acute asthma exacerbation in children below 1 year of age when β_2-agonist role is unpredictable at that age.

Side effects of ICS are rare in lower doses, even with long-term use. Low to medium dose of ICS use shows a small effect on growth velocity. Adrenal suppression is a concern and appears to be more common than previously recognized. However, this evidence was collected with much higher dose of ICS than are used in clinical practice.

Ways to Minimize the Risk of Side Effects

- Use the minimum dose that controls symptoms
- Re-evaluate regularly:
  - Can dose be reduced?
  - Are child and family adherent?
  - Is inhaler technique good?
- Use a spacer device
- Advise teeth brushing and mouth rinsing after ICS administration
- Monitor growth

β_2-AGONIST IN PERSISTENT ASTHMA

Short-acting β_2-agonist

Regular use of salbutamol, a short acting β_2-agonist (SABA), as a maintenance therapy was once used widely for a while and a short crossover study in adult demonstrated reduced "wheezing attacks" in patients using salbutamol as regular therapy.

Subsequent evidences have demonstrated no benefit in adults or children using salbutamol as maintenance therapy of asthma. However, β_2-agonist can be used in persistent asthma with acute exacerbation along with preventers. It can also be used as preventer in exercise- induced asthma to abort exercise-induced asthma.

Long-acting β_2-agonist

Two inhaled Long-acting β_2-agonists (LABAs) are currently in common use, formoterol and salmeterol, both with durations of action of approximately 12 hours. Salmeterol is very lipophilic and rapidly penetrates into the cell membranes following administration, through which it gradually diffuses until it reaches the bronchial smooth muscle to effect its action, resulting in a much slower onset of action of about 30 minute to maximum effect. Tachyphylaxis to both the bronchoprotective and bronchodilator activity of LABAs has been documented in adults, which can be attenuated by concomitant corticosteroid therapy. Use of LABA should be restricted to add-on therapy with ICS when indicated. Addition of salmeterol resulted in significantly better asthma control and lung function compared with doubling the dose of FP.

The combination of formoterol (a LABA) and Bud in an inhaler to be used as needed has shown better efficacy over standard preventer and reliever therapy in reducing asthma exacerbations.

Sodium Cromoglycate

The mode of action of sodium cromoglycate is not fully understood. Although it appears to stabilize mast cells and thus inhibits the release of inflammatory cytokines. Although a popular treatment for asthma in the 1980s, a Cochrane review published in 2006 found that ICS were significantly superior to sodium cromoglycate in terms of improvement of lung function and asthma control.

LT Receptor Antagonists

The cysteinyl-leukotrienes, LTC4, LTD4 and LTE4, are end products of the arachidonic acid pathway, and are potent mediators of antigen-induced contract ions of airway smooth muscle.

Montelukast acts by antagonizing these compounds at their receptor, thus protecting against bronchoconstriction. It is the only LT receptor antagonists (LTRA) currently licensed for use in children with asthma. There is well-accepted evidence that oral Montelukast is an effective initial preventer therapy for children with mild asthma, down to the age of 1 year and possibly even younger.

In addition, it seems to confer additional benefit as an add-on therapy to ICS. Montelukast is generally safe and well-tolerated; headache and GI symptoms are the most commonly reported side effects.

Theophylline

Theophylline is a xanthine derivative which, in the context of asthma, acts to relax bronchial smooth muscle and has

some anti-inflammatory properties. The mechanism of this action is not fully elucidated; theophylline acts mainly as an adenosine receptor antagonist, but a putative role in phosphodiesterase inhibition has also been proposed.

A systematic reviews of the use of theophylline in children with asthma confirmed its ability to alleviate symptoms and reduce the use of reliever medication in mild-moderate asthma.

At present, theophylline tends to be restricted to use in severe asthma, unresponsive to other agents. It has a narrow therapeutic index with a higher incidence of side effects than other maintenance therapies even when plasma levels are within the therapeutic range. These commonly include headache and sleep disturbance, and GI problems, particularly anorexia and nausea. As a result, its utility is reduced and it should probably be reserved for use by respiratory pediatric specialists.

NEWER THERAPIES

Anti-IgE Therapy

The humanized recombinant monoclonal antibody omalizumab inhibits the binding of IgE to its high affinity receptor on the surface of mast cells and basophils, thus preventing their release of inflammatory mediators.

Most studies have been carried out in adults and adolescents, but one double-blind placebo-controlled trial involved aged 6–12 years whose asthma was well controlled with ICS. In this trial, the omalizumab-treated group suffered fewer exacerbations of asthma and were more successful in reducing their ICS dose than the placebo group.

The cost of treatment, however, remains prohibitive, and, as a result, the use of omalizumab is restricted to children with severe asthma who have failed other therapies.

Sublingual Immunotherapy

The role of allergens in childhood asthma remains incompletely elucidated.

However, the role of sublingual immunotherapy remains uncertain in children. A recent meta-analysis identified significant benefit for children with mild-moderate asthma monosensitized to house-dust mite. For those who are polysensitized or who have more severe asthma, the evidence is less conclusive or lacking.

Inhaler Devices and Choosing the Correct Inhaler (Figs 27 and 28)

Inhaler Devices

Inhaled drugs may be administered via a variety of devices, chosen according to the child's age and preference:

- Metered dose inhaler (MDI)
- Breath-actuated metered dose inhaler, e.g. Autohaler, accuhaler (salmeterol + fluticasone)
- Dry powder devices, e.g. Rotahaler (salmeterol + fluticasone), Turbohaler (terbutaline sulfate).

A significant proportion of drugs are used to control chronic asthma in children, administered by aerosol inhalation. In this way, the drugs are delivered directly to their site of action in the lungs in higher concentrations, and with less systemic

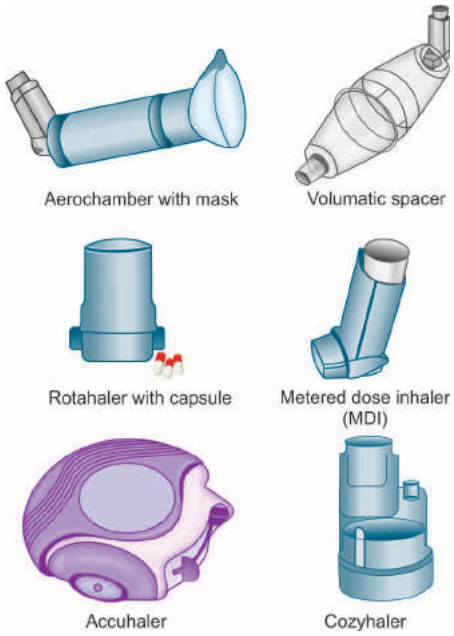


Fig. 27: Various devices suitable for asthma patients of various age

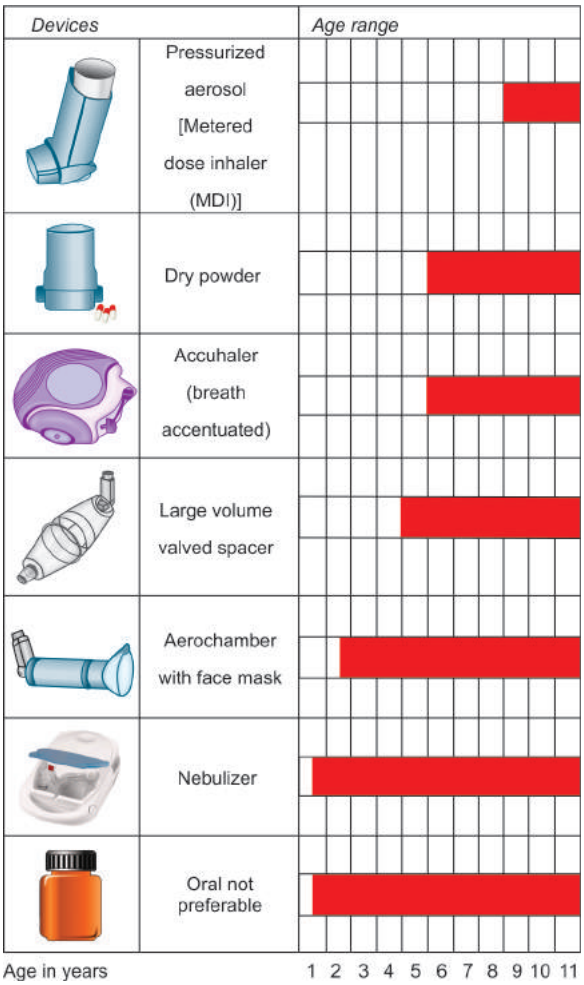


Fig. 28: Selection of devices by age: Drugs in oral and nebulized form can be given as less than or equal to 6 months of age. Drugs inhaled from inhaler can be given by low volume device with face mask from 1 year to 1½ year of age. Appropriate average age to use large volume valved spacer is from 4 year. Inhaled drugs from rotahaler and accuhaler can be used by children from age of 5 years. By 8 years trained children can coordinate breathing with meter dose inhaler (MDI). Ages are very approximate as there is marked variation from child to child

Fig. 29: Child receiving nebulized antiasthma drug from nebulizer by face mask

Fig. 30: Ultrasonic (soundless) portable nebulizer: suitable for children who are apprehended from sound of nebulizer. Soundless nebulizer machine held by parents provides better cooperation from small child

exposure leading to fewer side effects. Several different inhaler devices are available, most commonly variants of pressurized metered dose inhalers (pMDI) and dry powder inhalers (accuhaler or rotahalers) (Fig. 29). All inhaled medication for children under 5 years of age should be delivered by spacer devices. Selection of devices by age is shown in Figure 30.

A spacer device or holding chamber reduces the need to coordinate inhalation of actuation of a pMDI, as well as diminishing the degree to which the inhaled drugs impacts in the oropharynx and is absorbed via the GI route. There are a large number of commercially available spacer devices, each with their own characteristics and some are inhaler specific. The larger volume spacer device with valve (uptake spacer) which can be used in older children appears to deliver large amount of drug to the lungs per actuation than those small holding chambers which are suitable for infants and toddlers. However, low volume spacer devices may provide significant benefit to compliance by virtue of portability.

Other device dependent factors also affect drug delivery and therefore lung deposition. Face mask fit is convenient for children but delivers less drugs to lungs as compared to inhaled by mouthpiece by older children. This is because a significant proportion of inhaled drug is obstructed in hairy nasal mucosa and nasopharynx.

Ideally inhaled steroids should always be given by MDI and spacer, and spacers should be used in young children and for delivering beta agonists during acute asthma attacks. Spacers are very effective at delivering bronchodilators and inhaled steroids to the preschool child.

Both breath-actuated devices (accuhaler) and dry-powder inhalers (rotahaler, turbohaler) require less coordination than MDIs and can be used for delivering beta agonists and inhaled steroids or both together in school-age children.

Nebulized treatment ideally should be given for severe life-threatening asthma, or rarely for children who need inhaled therapy but are unable to use any of these devices or require high doses. There are good evidences to support the view that pMDI in combination with large volume spacers are at least as effective as nebulizers for bronchodilator inhalation to treat moderate or more severe asthma. However, infants and toddlers frequently cannot use spacer devices and drugs for asthma are better delivered by nebulizers (Figs 30 and 31). Preventers like Bud which has also reliever property can also be given on short-term or long-term basis in nebulized form in infants and toddlers who cannot use spacers appropriately. Many children fail to gain benefit of their treatment because they cannot use the inhaler they have been given. The correct way to use an inhaler must be demonstrated and the child's ability to use should be checked (Figs 31 to 33).

Fig. 31: A bigger child taking nebulized antiasthma drug from nebulizer machine by mouthpiece

Fig. 32: Demonstration of use of low volume spacer with face mask.The child is keenly following the procedure

Fig. 33: Technique of using inhaler (high volume valved spacer)

MANAGEMENT OF ASTHMA

Drug treatment is not the only treatment of asthma. A holistic approach is required for optimal management of asthma and consists of:

- Drug treatment
- Allergen avoidance
- Family education
- Awareness of psychological factors.

The aims of treatment in the control of asthma are:

- Minimally (ideally no) chronic symptoms, including nocturnal symptoms
- Minimal (infrequent) episodes of exacerbation
- No emergency visit
- Minimal need for β_2-agonist
- No limitation of activities including exercise
- PEF variability less than 20%
- Near normal PEF
- Minimal or no adverse effects from medicine.

Management of Persistent (Chronic) and Frequent Episodic Intermittent Asthma

Assess the child for evidence of persistent asthma (evidence of chest deformity, other personal evidence of atopy like eczema, allergic rhinitis, etc.) and its effect of growth development, school performance, etc. Figure 34 shows the assessment various parameter of assessment child with persistent asthma.

Escalating Therapy

Having reviewed the history and categorized the patient in terms of clinical pattern and severity, caregiver should then use a logical, stepwise approach to escalating therapy. The following steps provide such an approach.

Stepwise Approach to Drugs (Fig. 35)

Before altering a treatment it should be ensured that the treatment is being taken in an effective manner.

Step 1: Occasional use of relief bronchodilators (intermittent and infrequent episodic asthma and exercise-induced asthma). Short acting β_2-bronchodilator (SABA) for relief of symptoms.

Step 2: Regular inhaled preventive therapy (frequent episodic and mild persistent asthma):

- Short acting β_2-bronchodilator as required + regular low-dose inhaled steroids (200–400 µg/day of BPD and Bud or 100–200 µg/day of FP) + antileukotriene can be considered.

Step 3: Add on therapy (Poorly controlled on conventional dose of ICS):

- Inhaled long acting β_2-bronchodilator + low-dose inhaled steroids, or
- If no benefit with LABA® → stop LABA and increase ICS to upper limit of standard dose range
- Consider to add leukotriene receptor antagonist (LTRA) or slow release theophylline.

Step 4: Persistent poor control:

- High-dose of inhaled steroids (up to 800 µg/day of BPD or Bud or 400 µg/day of FP) + continue long acting bronchodilator + SABA as required (during exacerbation)
- Consider to add LTRA or slow release theophylline.

Step 5: Continuous or frequent use of oral steroid:

- Use daily steroid tablet in low dose
- Maintain high dose inhaled steroid at 800 µg/day of Bud or BPD 400 µg/day of FP
- Refer to respiratory specialist.

Other Management

- Avoidance of allergen
- Family education
- Awareness of psychological factors.

Avoidance of Allergen

In some children, it is possible to identify allergens which precipitate asthma (e.g. house dust mite, molds are the most common). It may be appropriate to test asthmatic children

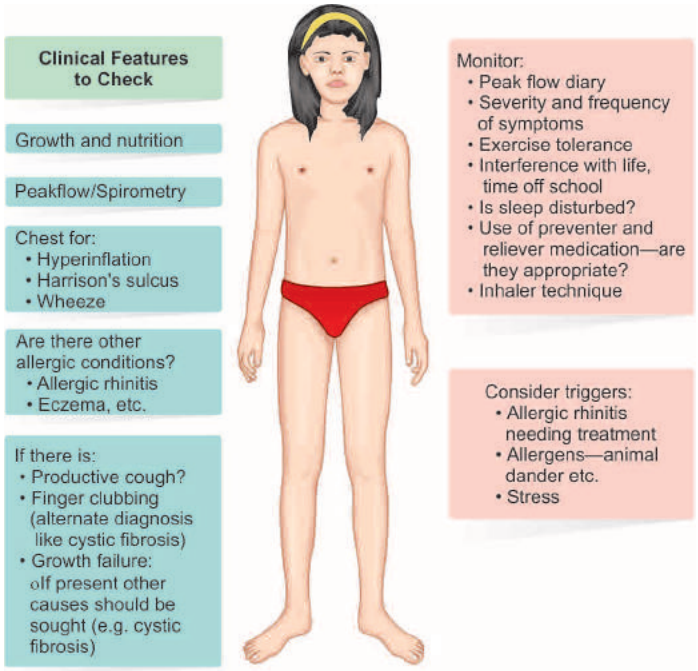
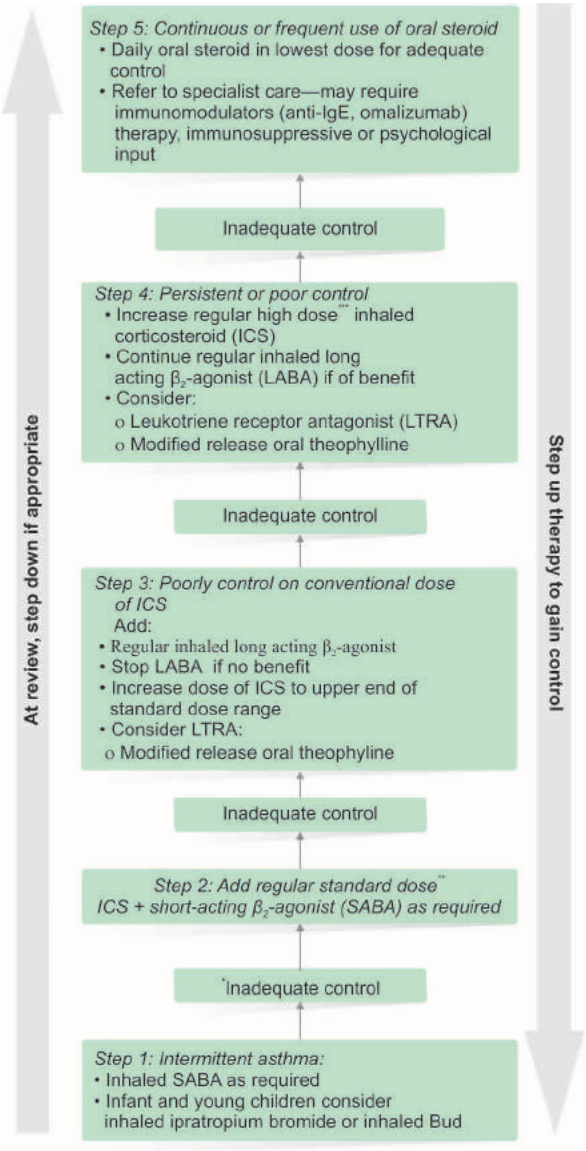


Fig. 34: Assessment of a child with persistent asthma



Note:

* Use of short-acting β2-agonist more than twice a week, night time symptoms more than once a week.

** Standard dose ICS: 100–400 µg twice daily beclomethasone or 50–200 µg twice daily fluticasone propionate (age dependent).

*** 200–1000 µg (1 mg), twice daily beclomethasone, 100–500 µg twice daily fluticasone (age dependent).

Fig. 35: Stepwise care management of asthma

for skin test and blood for total and specific IgE level likely to be allergic triggers. Once diagnosed allergen avoidance is often difficult to achieve. However, following measures can be taken to avoid allergen (Table 28).

Family Education

Education of the child and family helps compliance and enable them to feel in control of the treatment. They should be taught how to use various spacer devices appropriately. It is important that they recognize the symptoms of asthma and know how and when to seek help. Many children are given dairy card to help them recognize symptoms and also have asthma card which gives them an individual treatment plan for acute attacks.

Education of the patients and parents involve following steps:

- Take medications correctly
- Correct technique to use nebulizers and spacers
- Understand the difference between quick relief and long-term medication
- Avoid triggers
- Monitor status by PEF induction
- Recognize signs that asthma is worsening and take action
- Seek medical help as appropriate.

Awareness of Psychological Factors

Asthma has a psychosomatic component which may be prominent in some patients. The most severe asthmatic has major family problems and psychosocial problems are associated with high risk of asthma-related death. Treatment for children affected by parental separation, child abuse is very difficult and a combined medical and psychiatric approach to treatment may be necessary.

ACUTE ASTHMA

Acute asthma remains most common reason for admission to hospital. The vast majority of children respond well to treatment with oral steroids and inhaled bronchodilators with deaths from childhood asthma is now declining. However, identifiable causes of death from asthma include suboptimal routine and emergency care in a third or to half of all children.

Table 28: Identify and avoid triggers for allergen

Allergens	Measures
Domestic house dust mite	Wash bed linens and blanket once a week in hot water and dry in hot dryer or the sun. Remove carpets. Use vacuum cleaner with filter
Tobacco smoke	Stay away from tobacco smoke. Parents should not smoke
Allergens from animal with fur	Remove animals from home. Also remove fur containing toys like teddy bear, cover blanket with cotton covering
Cockroach allergen	Clean the home thoroughly or often use pesticide spray
Outdoor pollen and molds	Close windows and doors and remain indoor when pollen and mold contains are highest
Air pollutants	Face mask, close automobiles, windows having air conditioner (AC)
Change in temperature and humidity	Use adequate winter clothes, low cool AC may be helpful in hot humid condition
Physical activities	Do not avoid physical activity. Use inhaled β_2-agonist or sodium cromoglycate before strenuous exercise
Drugs	Do not take aspirin or β-blocker

Drug Therapy and Drug Delivery in Acute Asthma

Drug delivery: Large volume spacer versus nebulizers

There is good evidence to support the view that pMDI in combination with large volume spacers are at least as effective as nebulizers for bronchodilator inhalation to treat moderate or more severe asthma. In mild attacks 2–4 puffs of salbutamol (200–400 μg) may be sufficient, but in moderate or severe attacks 10 puffs of salbutamol may be required. Allowing up to 30 seconds for salbutamol to be inhaled by tidal breathing means that it takes 5–6 minutes to deliver 10 puffs of salbutamol. During this time, it is difficult to administer supplemental oxygen and significant hypoxia may practically preclude the use of spacers in the first instance. For children who do not initially require supplemental oxygen, β_2-agonists given via a pMDI with spacer are less likely to provoke hypoxia or tachycardia than when the same drug is given by a non-oxygen driven nebulizer.

Intermittent versus Continuous Nebulizers

Salbutamol is a partial agonist. It therefore reaches its maximal bronchodilating effects at relatively low doses. Increasing the dosage does not increase the absolute bronchodilatation but does prolong the bronchodilator effect. It is therefore not surprising that bronchodilators nebulized every 20 minutes are more effective than bronchodilators nebulized hourly. Continuous nebulization in low dosages (0.15 mg/kg in 5 mL) is the most effective as it provides sustained stimulation of the pulmonary β_2 receptors and prevents the rebound bronchoconstriction that may occur with intermittent therapy.

Standard nebulizer driven with 8 L/minute of oxygen takes approximately 10 minutes to complete. In children it is appropriate to nebulize 0.15 mg/kg of salbutamol up to a maximum of 5 mg made up to 5 mL with normal saline.

Other Drugs Used in Acute Asthma

Combined Inhaled Anticholinergic and β_2-Agonist

There are evidences to support that the use of nebulized ipratropium bromide (125–250 μg/dose) in addition to β_2-agonists for the first 2 hours is more efficacious in the treatment of a severe asthma attack in children.

Steroids in Acute Asthma

Children with an acute exacerbation of asthma should receive steroid treatment as early as possible. This has been shown to reduce the risk of admission to hospital and prevent a relapse in symptoms after initial presentation. The limited available data suggest that IV steroids are no more effective than oral steroids in moderate to severe asthma and both begin to work after 3–4 hours. Intravenous hydrocortisone (4 mg/kg) should therefore be reserved for children who are unable to tolerate oral fluids. Despite their widespread use, very few studies have addressed the optimal dose of oral steroid required for the treatment of acute childhood asthma. A dose of 1–2 mg/kg/day for 5 days without tapering is currently recommended for children with acute severe asthma.

Although ICSs form the cornerstone of chronic asthma treatment, they have been poorly studied in the management of the acute phase. However, inhaled Bud together with inhaled LABA has reliever property in acute asthma along with its use in maintenance therapy in persistent asthma.

Intravenous Aminophylline or Intravenous Salbutamol

When first line of treatment of acute asthma fails to improve clinical condition then IV salbutamol or IV aminophylline should be used. Both the drug should better be used keeping the child in PICU or high dependency unit (HDU).

Intravenous Aminophylline

Although IV aminophylline has established role in the management of acute severe asthma, it is not used as the first line of treatment of acute severe asthma. Majority of children with acute severe asthma can be improved by oxygen inhalation, inhaled β_2-agonists and short course of oral or IV steroids.

There are limited data to suggest an improvement in lung function indices at 6 hours following IV aminophylline, there is no apparent reduction in symptoms, in the number of nebulizers treatment required or in the length of hospital stay. It is also associated with side effects like vomiting, seizures, and tachyarrhythmia.

However, in case of no improvement with inhaled or nebulized salbutamol, ipratropium and IV/oral steroids, injectable aminophylline bolus (5 mg/kg) followed infusion of aminophylline (0.9 mg/kg/hour) can be given (caution if already receiving theophylline).

Intravenous Salbutamol

It can also be used as second line of treatment instead of IV aminophylline. The exact role of IV treatment for the management of acute severe asthma in childhood remains controversial. Most authors state the need for an initial loading dose of salbutamol (15 μg/kg over 5 minutes) as without this it takes 10–20 hours for a plateau concentration to be reached. It should be then followed by a continuous infusion (1–5 μg/kg/min). The plasma half-life of salbutamol in adults is 2–3 hours.

Hypokalemia is a common consequence of salbutamol administration and serum potassium should be monitored in children with severe asthma receiving salbutamol regardless of route of administration.

Magnesium

Intravenous magnesium sulfate is a safe and established treatment for acute asthma in adults. There is mounting evidence that IV magnesium can provide additional bronchodilation when given in conjunction with standard bronchodilating agents and corticosteroids. Fifty percent magnesium sulfate is given initially at 0.5 mL/kg IV infusion in 20 minutes followed by 0.06 mL/kg/hour until acute condition improves. Doses of up to 75 mg/kg/day have been used for asthma in the emergency department. Whilst magnesium sulfate can also be nebulized, there are only limited data regarding its efficacy.

Epinephrine

There are several studies which have examined the benefit of nebulized epinephrine in adults and children with acute asthma, but meta-analysis shows no statistically significant advantage of nebulized epinephrine when compared to salbutamol or terbutaline.

Acute asthma is usually treated with salbutamol. This is a racemic mixture of (R)-salbutamol and (S)-salbutamol, but the bronchodilator effects of salbutamol are mediated predominantly by the (R)-salbutamol isomer, levalbuterol. Observational studies in adults have suggested that levalbuterol may be effective in reducing hospital admissions. A randomized controlled trial in children, however, comparing levalbuterol to combined treatment with racemic mixture salbutamol and ipratropium bromide showed no benefit in terms of hospital admissions or respiratory distress.

Criteria for Hospital Admission

Children require hospital admission if, after high-dose inhaled bronchodilator therapy, they:

- Have not responded adequately clinically—persisting breathlessness, tachypnea
- Are exhausted
- Still have a marked reduction in their predicted (or usual) peak flow rate
- Have a reduced oxygen saturation (<92% in air).

Investigations (Table 29)

The most important investigation in children with difficulty in breathing is measurement of oxygen saturation. Oxygenated and deoxygenated hemoglobin differ in their ability to absorb particular wavelength of red light. Oxygen saturation monitors measure this difference and estimate the proportion of blood that is saturated with oxygen. Because they are noninvasive, they are much more practical than measuring blood gases. The chest X-ray is mainly useful in excluding alternate diagnosis, e.g. pneumonia, pneumothorax and on first presentation, excluding an unexpected anomaly. It is not required subsequent asthma attack. It should be done only in subsequent asthma attack in patients who do not respond satisfactorily to first line of acute asthma drugs. In asthma, it may show hyperinflation, bronchial thickening or small areas of collapse (atelectasis) due to mucus plugging but is quite often normal. Known asthmatic patients do not necessarily need an X-ray every time they have an attack.

Table 29: Questions to be asked to determine disease severity

Question	Comments
Can he speak in sentences? (for infants, does he struggle to breathe when feeding)	Gives an idea of the degree of respiratory distress and tachypnea
How much can he move about?	Is he in bed all the time? Can he get up to go to the toilet; can he climb stairs; can he manage to get to school? These gives information on the child's functional disability
Has he been blue?	Acute cyanosis is a sign of serious respiratory embarrassment
How much bronchodilator (reliever) has he taken?	For known asthmatics

Management of Acute Asthma

Acute breathlessness associated with asthma is frightening for both the child and the parents. Calm and skillful management is the key to their reassurance.

Clinical features associated with acute exacerbation of asthma are:

- Wheeze and tachypnea (respiratory rate >50 breaths/min in children 2–5 years, >30 breaths/min in children 5 or over)—but poor guide to severity
- Increasing tachycardia (>130 beats/min in children aged 2–5 years, >120 beats/min in children 5 or over)—better guide to severity
- The use of accessory muscles and chest recession—also better guide to severity
- The presence of marked pulsus paradoxus (the difference between systolic pressure on inspiration and expiration) indicates moderate to severe asthma in children but is difficult to measure accurately and is therefore unreliable
- If breathlessness interferes with talking, the attack is severe
- Cyanosis, fatigue and drowsiness are late signs, indicating life-threatening asthma; this may be accompanied by a silent chest on auscultation as little air is being exchanged.

However, the severity of an acute asthma may be underestimated by clinical examination alone. Therefore:

- Measurement of the PEF rate should be routine in school-age children
- Arterial oxygen saturation should be measured with a pulse oximeter in all children presenting to hospital with acute asthma. Oxygen saturations less than 92% in air imply severe or life-threatening asthma
- The features of a severe and life-threatening acute attack are shown in Figure 36.

Drug Treatment

High-dose of inhaled bronchodilators, steroids and oxygen form the foundation of therapy of severe acute asthma.

As soon as the diagnosis has been made, the child should be given a β_2-bronchodilator.

- For severe exacerbations, high-dose therapy should be given and repeated every 20–30 minutes
- For moderate to severe asthma, 10 puffs of β_2-bronchodilator should be given via MDI and large volume spacer. Nebulized bronchodilator can be given if the child cannot use spacers
- For severe to life-threatening asthma, a β_2-bronchodilator should be given via nebulizer.

The addition of nebulized ipratropium to the initial therapy in severe asthma is beneficial.

Oxygen is given when there is evidence of arterial oxygen desaturation. Oxygen should be given at high flow (10–15 L/minute) via a mask with reservoir. It is better to deliver oxygen driven (from central oxygen line or from oxygen cylinder) nebulized salbutamol or ipratropium (Fig. 37) rather than air driven nebulized salbutamol from portable nebulizer machine which are used in home management.

A short course (5 days) of oral Prednisolone (1–2 mg/kg/day) expedites the recovery from moderate or severe acute asthma and should be given at the initiation of treatment. IV therapy has a role in the minority of children. IV hydrocortisone 4 mg/kg 6 hourly can be given who cannot

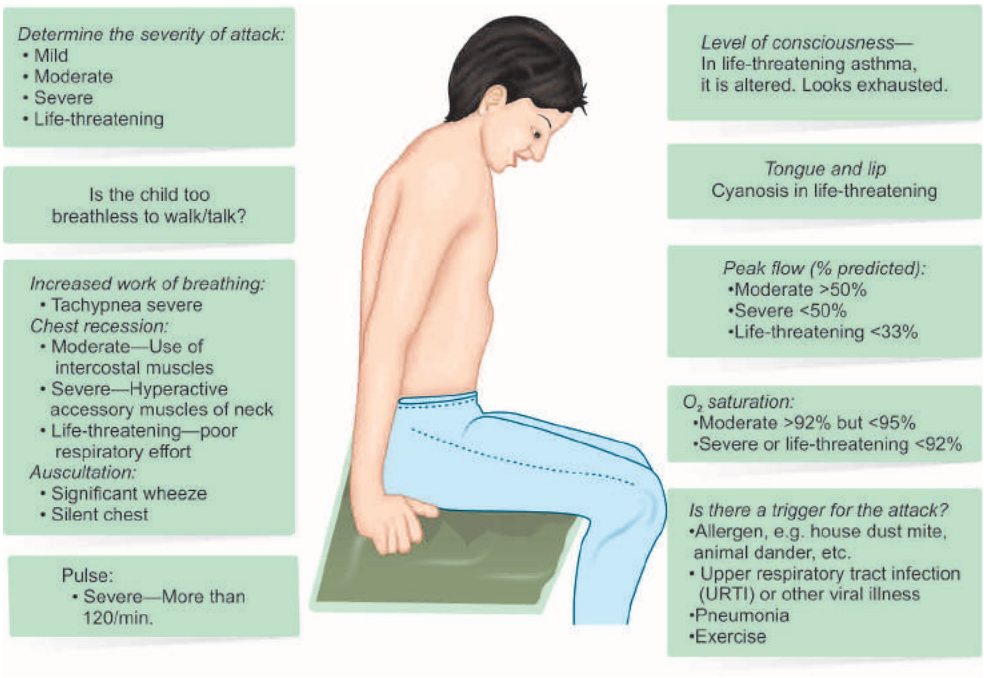


Fig. 36: Assessment of a child with acute asthma

Fig. 37: A hospitalized child receiving oxygen driven nebulized salbutamol. Oxygen is delivered under pressure from central oxygen line

take oral Prednisolone due to intolerance or due to severity of the disease.

The treatment should be given to the child in sitting posture to minimize ventilation perfusion mismatch.

Children not responding to initial management (inhaled bronchodilator, oxygen inhalation and systemic steroids) should be managed in PICU, HDU and either IV aminophylline or IV salbutamol should be given. In addition IV magnesium sulfate is also useful in the management of acute asthma. For IV aminophylline, a loading dose (5 mg/kg) is given over 20 minutes, followed by continuous infusion (0.9 mg/kg/hour). If the child is already on oral theophylline, the loading dose of aminophylline should be omitted. Seizures, severe vomiting and fatal cardiac arrhythmias may follow a rapid infusion. With both aminophylline and salbutamol, the ECG should be monitored and blood electrolytes checked (Fig. 38).

If IV salbutamol is used, a loading dose of 15 µg/kg over 5 minutes followed by continuous infusion (1–5 µg/kg/minute) can be given as a second line of acute asthma treatment. Hypokalemia is almost invariably occurs and children should be monitored clinically as well as biochemically.

There is increasing evidence that IV magnesium is helpful in life-threatening asthma in addition to IV salbutamol or aminophylline. Dose up to 75 mg/kg/day can be used. Fifty percent magnesium sulfate is given initially at 0.5 mL/kg IV infusion in 20 minutes followed by 0.06 mL/kg/hour until acute condition improves.

Antibiotics should only be given if there are clinical features of bacterial infection.

A narrow spectrum antibiotic, like erythromycin, clarithromycin and azithromycin, is preferred unless otherwise indicated as it is less likely to disturb Th1, Th2 system in comparison to broad spectrum antibiotics.

Rarely, these measures are insufficient, and artificial ventilation is required.

The child should be given a written individualized asthma action plan. Follow-up arrangements should be made to monitor progress by the general practitioner or, for the more problematic patients, by a pediatrician.

Summary of Initial Medical Treatment of Acute Severe Asthma

- Providing high O_2 concentration (10–15 L/minute) via reservoir bag via mask with reservoir bag
- Continuous bronchodilator (salbutamol aerosol) therapy with oxygen
- Early steroid either orally if tolerated or intravenously
- Sitting the child up to minimize ventilation perfusion mismatch
- Failure to improve treatment with initial treatment necessitates admission to PICU or HDU.

Therapy Not Recommended in Acute Asthma

- Sedative
- Mucolytics drugs
- Chest physical therapy
- Hydration with large volume of fluids (may be necessary for young children and infants).

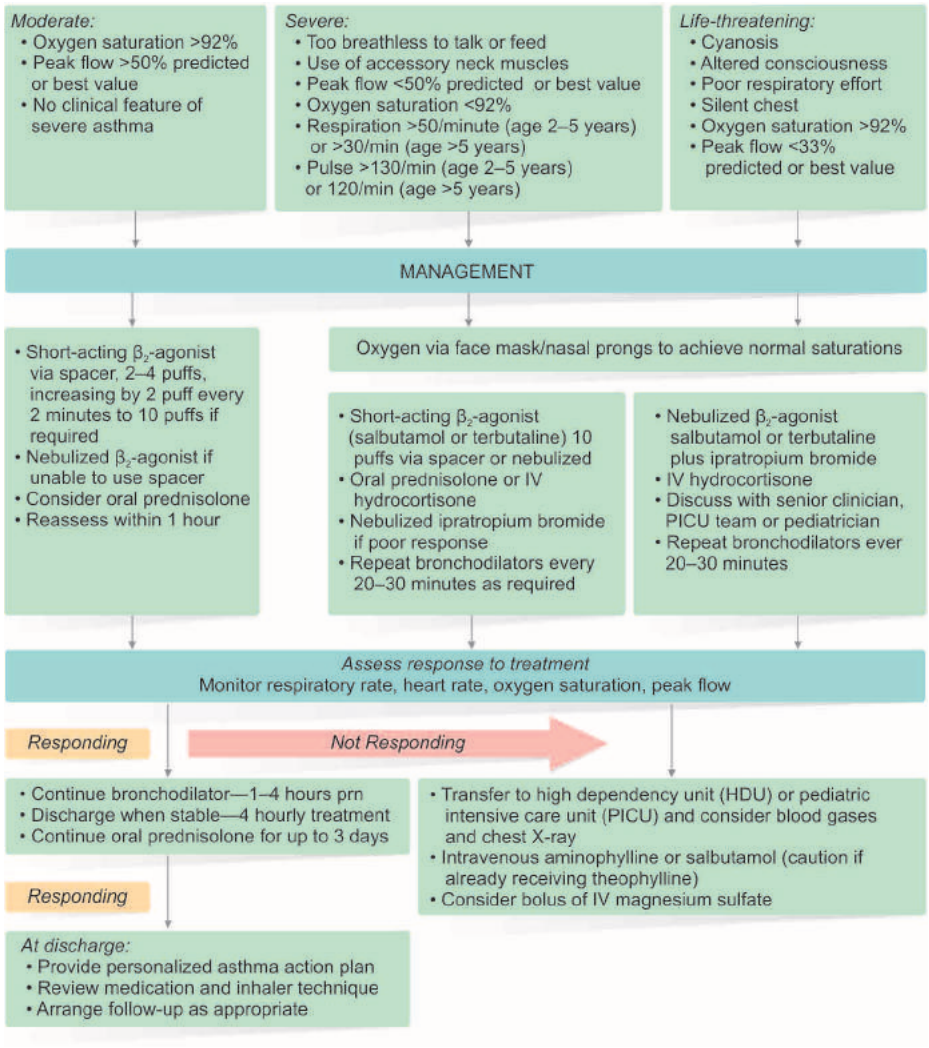


Fig. 38: Algorithm of assessment and management of acute exacerbation of asthma

Patient with High-risk of Asthma-related Death

- Current use of or recent withdrawal of oral steroids.
- Hospitalization or emergency visit for asthma within the past years, or prior intubation for asthma
- History of psychological problems
- Denial of asthma or its severity
- History of noncompliance with asthma medication plan.

Parent should immediately seek medical care if:

- The attack is severe
- The response to the initial bronchodilator treatment is not prompt and sustained for at least 3 hours
- There is no improvement 2–6 hours after systemic corticosteroids treatment is started.
- There is further deterioration.

Management Strategies for Exercise-induced Asthma

Mild to Moderate Exercise-induced Asthma

- Use β_2-bronchodilator before exercise, strenuous exercise or outdoor games
- In this fashion β_2-agonist which is a reliever drug, also acts as preventer.

Severe Exercise-induced Asthma

Low-dose inhaled steroid can be used in addition to β_2-agonist.

Admission to Pediatric Intensive Care Unit and High Dependency Unit

Not all patients admitted to PICU and HDU require intubation and mechanical ventilation. Indications for admission to PICU or HDU include patients requiring ventilator support and those with severe acute or life-threatening asthma who are failing to respond to therapy.

Evidences of poor response to therapy are as follows:

- Decreasing PEFR
- Persistent or hypoxia
- Hypercapnia ($PaCO_2$ >8 kPa)
- ABG analysis showing fall in pH
  - Exhaustion, feeble respiration, drowsiness, confusion, coma or respiratory arrest.

Management in Pediatric Intensive Care Unit/ High Dependency Unit

- Continuous nebulized salbutamol
- IV hydrocortisone 4 mg/kg 6 hourly

- IV aminophylline or IV salbutamol, if not given previously.
- IV aminophylline has a narrow therapeutic range.

Intravenous Bronchodilator Therapy

Intravenous salbutamol (if available) should be given if no response to initial management of asthma. Salbutamol infusion 5 µg/kg for 1 hour, then 1 µg/kg/hour (continue nebulization), watch for hypokalemia.

If no response to IV salbutamol or if IV salbutamol is not available consider IV aminophylline. Initial bolus dose of 5 mg/kg over 20 minutes (if theophylline is not given previously) followed by continuous infusion (0.9 mg/kg/hour).

Intravenous magnesium sulfate should be administered upon arrival to the PICU, 50 mg/kg/hour (0.1 mL/kg 50% $MgSO_4$) over 20 minutes, followed by infusion if desired at 30 mg/kg/hour (0.06 mL/kg of 50% $MgSO_4$), aim for serum magnesium up to 2.5 mmol/L.

Noninvasive ventilator (NIV) like mask CPAP may help while waiting for medical therapy to work in children. However, NIV requires a cooperative child. Intubation and ventilation is rarely required, ideally performed with assistance from anesthetist.

Blood Gas Status and Arterial Blood Gas for Acute Severe Asthma

Blood gas analysis is rarely required as it may disturb the child. It should be done in children with severe acute asthma not responding to initial management with O_2, β_2-agonist and steroid therapy and requiring PICU care particularly who are under consideration for ventilator support.

In young children, the severity of physiological disturbance as shown by blood gas estimation (Table 30) may easily be underestimated from clinical criteria. Hypoxia occurs easily but $PaCO_2$ is initially low because of hyperventilation. In fact, respiratory alkalosis is the most frequent blood gas abnormality associated with acute severe asthma. Only in severe cases, $PaCO_2$ is raised due to hypoventilation associated with exhaustion and bronchoconstriction. This causes respiratory acidosis. However, metabolic acidosis also occurs secondary to hypoxia, poor peripheral perfusion and dehydration causing lactic acidosis from anaerobic glycolysis.

Although some of the children will be too dyspneic to be able to perform a peak flow meter, it can be used subsequently to assess their progress provided that they are old enough to use a flow meter.

Table 30: The severity of respiratory status

Assessing for the severity of respiratory distress (RD) by blood gases			
Degree of RD	**PaO_2**	**$PaCO_2$**	**Acid base dysfunction**
++	↓	↓	Respiratory alkalosis
+++	↓↓	Normal or ↓	Normal
++++	↓↓↓	↑↑↑	Metabolic acidosis with respiratory acidosis

Abbreviation: RD, respiratory distress

Criteria for Intubation

- Respiratory arrest
- Hypoxia and rising hypercapnia despite maximum oxygen and medical treatment and NIV
- Exhaustion and unable to vocalize
- Altered mental status.

DIFFICULT/POORLY CONTROLLED AND STEROID- RESISTANT ASTHMA IN CHILDREN

A child can be defined to have developed difficult/poorly controlled asthma if he/she has following characteristics:

- Bronchodilator requirement, more than 3 times a week
- ICS (Bud or equivalent) requirement of more than 800 µg/day
- School absence, more than 5 days in a term
- Attack with wheeze, more than or equal to 1 time/month
- Acute medical OPD visit, more than or equal to 1 time/month
- Hospital admission, more than 1 time/6 months.

Asthmatic children needing more than 500 µg FP per day is unusual. Ninety percent of benefit is achieved with 100–200 µg/day of FP.

Height velocity is affected with inhaled beclomethasone more than 400 µg/day. Adrenal suppression can occur on more than 400 µg/day of beclomethasone. Side-effects of high-dose inhaled corticosteroids (ICS) are more associated with mild asthma than in those in whom the asthma is severe as absorption seems to be greater in mild asthma.

It is therefore recommended that those who need higher doses of ICS to control their asthma should be referred to respiratory specialist for a thorough review of the diagnosis which includes evaluation of child environments, psychological factors in both child and family that could affect symptom reporting and adherence to treatment. If after a full evaluation of these issues, the child's asthma remains poorly controlled the detailed evaluation of airway function and pathology including bronchoscopy and bronchial biopsy is justified.

Before diagnosing a child as difficult or poorly controlled or steroid resistant asthma, it is desirable to diagnose whether the child has got asthma at all or not.

RE-EVALUATION OF DIAGNOSIS OF ASTHMA: CONSIDER ALTERNATE DIAGNOSIS

In children who are suspected to have developed difficult, poorly controlled asthma or steroid resistant asthma, the first task is to ensure whether the child has asthma and to exclude other wheezing disorders. Some children treated with large doses of ICS do not have asthma at all, but have other symptoms such as functional breathing problem. Many children have deep sighing respiration from physical or mental fatigue or due to psychological problem which are misdiagnosed as asthma. Evaluating respiratory sounds is not easy for the nonspecialist. Infant with prolonged wheezing following bronchiolitis is misdiagnosed as asthma and difficult to manage. A few of these children will turn out to have asthma but ICS do not prevent post-bronchiolitis wheeze unless they have an atopic family history. Chronic stridor

(laryngomalacia), particularly biphasic, may be considered as wheeze of bronchial asthma. Persistent isolated cough previously considered as cough variant asthma is now regarded as a different disorder and respond poorly to high dose ICS.

Once alternate diagnosis has been excluded, even then the questions arise:

- Is the treatment satisfactory?
- Is the treatment adherence satisfactory?

One of the most common reasons for the escalation for children prescribed ICS doses is that children do not adhere to and parents do not supervise treatment and consequently they report poor control. Many parents, however, deny nonadherence to treatment schedule. Noncompliance to treatment schedule can be checked by admitting the child and supervising the treatment schedule and monitoring the response. An approach that may differentiate rare case of true steroid resistant asthma from persistent wheezing due to nonadherence is the short-term use of depot injection of triamcinolone or depot-prednisolone. A marked response would suggest nonadherence is the problem.

Another important cause of difficult or steroid resistant or poorly controlled asthma is the failure to use drug properly, particularly with spacer devices. Whether the drugs are delivered properly with spacer devices with appropriate technique should be checked in presence of caregivers. Any faulty technique discovered should be corrected by giving demonstration of drug delivery by caregiver followed by rechecking with the asthmatic child.

Environmental Factors

An adverse environment may be responsible for poorly controlled asthma which may necessitate an asthmatic child to take high dose of ICS. Passive smoking can make asthmatic child steroid resistant. Similarly, children staying at allergic environment like staying in industrial area may find their asthma status difficult to control.

Psychological Factors

Psychological factors both in the child and in the family make asthma status difficult to control. Family dysfunction like parental separation, single parent family, depression and anxiety in the child or in the parents can make asthma in children difficult to control.

In summary, a child who has been diagnosed to have developed difficult asthma or poorly controlled asthma may have one or more of the following features:

- First of all a previously diagnosed asthmatic child whose symptoms are difficult to control may not have genuine asthma and other clinical conditions which simulate asthma clinically may be misdiagnosed as asthma
- Secondly, even if the child has genuine asthma, his/her symptoms may be difficult to control (difficult asthma):
  - If adherence is poor
  - Faulty drug delivery including faulty technique of use of inhaler devices
- Adverse environment like passive smoking
- Psychological factors.

Finally, the child may have difficult asthma due to steroid unresponsive (resistant) bronchial mucosa, when all the above probable factors which contribute to poor control of asthma have been carefully excluded. However, genuine steroid resistant bronchial asthma is very rare.

Genuine Steroid Resistant Asthma (Phenotypic Treatment)

Symptoms of genuine asthma if persists in spite of high dose of ICS with additional long acting beta-agonist and LTRA may reflect a heterogeneous group of condition. The concept of phenotype specific treatment needs developing. Determining the relative contribution of inflammation and bronchial activity might be beneficial in guiding treatment. Not all inflammation is eosinophilic and neutrophilic inflammation should be considered. If there is no functional improvement with prednisolone 40 mg/day for 2 weeks with adherence checked by serum prednisolone and cortisol levels, a fiberoptic bronchoscopic examination with bronchoalveolar lavage and large airway biopsy is justified. Bronchial biopsy is safe in experienced hands (Fig. 39).

Corticosteroid resistant defined by low number of poor function of corticosteroid receptor is quite rare. True congenital corticosteroid resistance is characterized by very low number of normally functioning steroid receptors. Much more common is secondary steroid resistance in which the receptor numbers are normal or increased, but binding affinity reduced.

There are children with steroid resistance who has marked bronchoconstriction but no evidence of inflammation on biopsy material. A subcutaneous beta agonist infusion will show satisfactory response in such children. In eosinophilic inflammation identified on biopsy material in a child (eosinophilic phenotype) who has not responded to prednisolone therapy an alternative anti-inflammatory treatment such as cyclosporine therapy should be considered. Neutropohilic phenotypes might be treated with macrolide antibiotic to down regulate IL-8 production and 5-lipooxygenase inhibitor like LTB4, anti-IgE or newer cytokine specific treatment. The number of truly difficult asthmatic children is small, so multicenter study of intervention would be essential and should take place in centers where full assessments, including biopsies, could be undertaken.

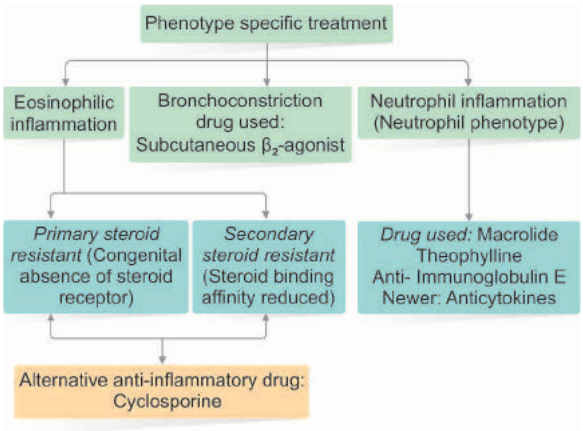


Fig. 39: Algorithm of management of steroid resistant asthma

TUBERCULOSIS IN CHILDREN

Tuberculosis continues to be a significant cause of morbidity and mortality for children throughout the world. After a steady decline in the number of cases for decades, there was a resurgence of pediatric TB in the developed and industrialized countries. Tuberculous infection and disease in children are much more prevalent in developing countries, where resources for TB control are scarce. Since most children with tuberculous infection and disease acquire the organism from adults in their environment, the epidemiology of childhood TB follows that in adult. The most important reasons for the recent resurgence of pediatric TB include:
Increased population migration.

- The HIV epidemic
- The emergence of drug resistance
- Continued poverty and poor access to medical care
- Inadequate public health infrastructure required to prevent TB in children.

Worldwide an estimated 8.8 million new cases of TB were diagnosed in 2010 (WHO Report 2011), of which 40% from India and China. In 1994, it was estimated that there were a total of 7,500,000 TB cases, of which 650,000 (9%) occurred in children. According to worldwide estimates in 2000, each year about 1 million cases (11%) occur in children under 15 years of age, with the 22 high-burden countries accounting for majority (75%) of these.

TRANSMISSION OF TUBERCULOSIS

Transmission of TB is from person to person, usually by droplet of mucus that become airborne when individual coughs, sneezes, laughs or sings. When young children do cough, they rarely produce sputum, and they lack tussive force of adults. When transmission of *M. tuberculosis* has been documented in a children's hospital, it almost invariably has come from an adult staff member, parents or visitor with undiagnosed pulmonary TB.

Human Immunodeficiency Virus Related Tuberculosis in Children

The HIV epidemic can increase the incidence of TB in children by two major mechanisms:

- HIV infected adults with TB may transmit *M. tuberculosis* to children, a portion of whom will develop tuberculous disease
- Children with HIV infection may be at increased risk of developing TB after infection has occurred.

Generally children acquire TB from adults with active, usually smear-positive, pulmonary disease. Pulmonary involvement is common among HIV-seropositive adults with TB, especially when the TB precedes other opportunistic infection. Children who acquire HIV infection by vertical transmission may have a rapid progression of TB from infection to disease.

The most efficient methods of finding children with *M. tuberculosis* is through contact investigations of adults with infectious pulmonary TB.

PATHOGENESIS

Primary Tuberculosis in Children

The primary complex of TB consists of a local disease at the portal of entry and the regional lymph nodes that drain the area of primary focus. In more than 90% of cases, the portal of entry is the lung. The incubation period in children between the time the tubercle bacilli enter the body and the development of cutaneous hypersensitivity is usually 2–12 weeks, most often 4–8 weeks. The onset of hypersensitivity may be accompanied by a febrile reaction that lasts from 1 week to 3 weeks. During this phase of intensified tissue reaction, the primary complex may become visible in chest radiograph. The primary focus grows larger and but does not yet become encapsulated. As hypersensitivity develops, the inflammatory response becomes more intense and the regional lymph nodes often enlarge. The parenchymal portion of the primary complex often heals completely by fibrosis or calcification after undergoing caseous necrosis and encapsulation. If caseation is intense, the center of the lesion liquefies, empties into the associated bronchus, and leaves a residual primary tuberculous cavity.

During the development of the parenchymal lesion, tubercle bacilli from the primary complex spread via the bloodstream and lymphatics to many parts of the body. The areas most commonly involved are the apices of the lungs, liver, spleen, meninges, peritoneum, lymph nodes and bones.

Viable *M. tuberculosis* may persist for decades after calcification of the node. Because of their location, hilar and paratracheal lymph nodes that become enlarged by the host inflammatory reaction may encroach upon the regional bronchus. More often, inflamed caseous nodes attach to the bronchial wall and erode through it, leading to endobronchial TB or a fistulous tract. The extrusion of infected caseous material into the bronchus can transmit infection to the lung parenchyma and cause bronchial obstruction and atelectasis. The resultant lesion is a combination of pneumonia and atelectasis. The radiographic findings of this process have been called *epituberculosis, collapse-consolidation,* and *segmental tuberculosis*.

Timetable of Childhood Tuberculosis

There is fairly predictable timetable of events related to the primary TB infection and its complications.

- When symptomatic lymphohematogenous spread occurs, it does so no later than 3–6 months after the initial infection leading to military disease and tuberculous meningitis
- Endobronchial TB, often accompanied by segmental pulmonary changes, usually develops between 4 months and 9 months after infection
- Clinically significant lesions of bones and joints do not appear until at least 1 year after infection
- Renal lesions develop 5–25 years later.

Pregnancy and Newborn

True congenital TB is very rare. Hageman and others have redefined congenital TB, identifying two major routes of true congenital infection.

Prenatal

1. Transplacental passage of *M. tuberculosis* via the umbilical vein from a mother with lymphohematogenous spread during pregnancy (e.g. tubercular pleural effusion, meningitis or military TB).
2. Through aspiration or ingestion of infected amniotic fluid in utero. Amniotic fluid can be infected from tubercular endometritis or the presence of ruptured caseous lesions in the placenta. Inhalation of amniotic fluid is the most likely cause of congenital TB if multiple primary foci are present in the lung or gut and middle ear.

Postnatal

Postnatal acquisition of TB by inhalation of tubercle bacilli from the mother is the most common route of infection for the neonate. It is often impossible to differentiate postnatal infection from true congenital TB on clinical ground.

CLINICAL FORMS OF TUBERCULOSIS

Intrathoracic Disease

Pulmonary Disease

A primary pulmonary complex includes the parenchymal focus and regional lymphadenitis.

Seventy percent of primary foci are subpleural, and localized pleurisy is a common part of the primary complex. All lobar segments are at equal risk of being seeded, and in 25% of cases, there are multiple primary lung foci. The initial parenchymal inflammation usually is not visible on chest radiograph, but a localized, nonspecific infiltrate may be seen.

The hallmark of primary TB in the lung is the relatively large size and importance of the hilar, mediastinal (better seen in lateral CXR) or subcarinal adenitis compared with the relatively small size of the initial parenchymal foci (Fig. 40).

In most children, the parenchymal infiltrate and adenitis resolve early. In some children, especially infants, the lymph nodes continue to enlarge.

The common radiographic sequence is hilar adenopathy, followed by localized hyperaeration and, eventually atelectasis. These findings are similar to those caused by aspiration of a foreign body; in TB, the lymph node acts as the foreign body. The common radiographic sequence is hilar adenopathy, followed by localized hyperaeration and, eventually atelectasis. These findings are similar to those caused by aspiration of a foreign body. In TB, the lymph node acts as the foreign body. In Ghon complex (Fig. 41), infected mediastinal lymph node may calcify with associated hilar adenopathy. The third component of the ghon complex is regional lymphatic vessels. Various types of lungs involvement may occur in tuberculosis such as atelectasis, collapse, consolidation, calcification, etc. (Figs 42 to 44). In small child, lungs may be involved intensively giving impression of snow storm appearance on chest X-ray called military tuberculosis (Fig. 45). In older children, pleural effusion may occur like adult (Fig. 46). Tuberculus lesion tends to calcify which can be seen by diagnostic imaging (Figs 42 and 47).

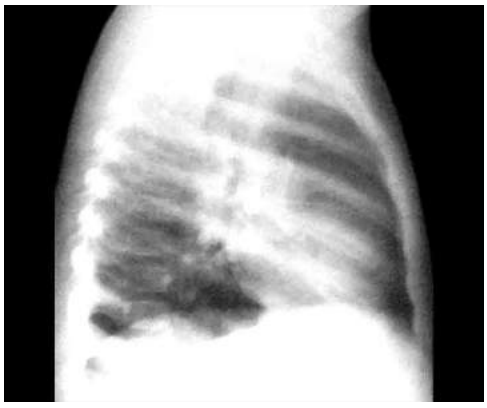


Fig. 40: X-ray chest showing enlarged tuberculous mediastinal lymph glands better seen in lateral view

Physical signs and symptoms caused by hilar lymphadenopathy and segmental lesions are surprisingly uncommon but are more frequently seen in infants (Table 31).

As the primary complex progresses, nonspecific symptoms, such as fever, cough, night sweat and weight loss occur. Pulmonary signs are usually absent. Some children have localized wheezing or diminished breath sounds, which are rarely accompanied by tachypnea or respiratory distress.

Occasionally, the primary complex may progress rapidly to chronic pulmonary TB while the hilar lymph node involvement characteristic of primary TB is still present.

A primary tuberculous infection in infancy rarely leads to chronic TB in adolescence. A primary infection acquired between ages 7 and 10 years is more likely to result in reactivation during adolescence.

Neonatal Disease

The clinical manifestations of TB in fetus and newborn vary according to the site and size of the caseous lesions. Clinical symptoms usually become apparent in the second or 3rd week of life, in the form of:

- Respiratory distress syndrome
- Fever
- Hepatic or Splenic enlargement
- Poor feeding
- Lethargy or irritability
- Lymphadenopathy
- Abdominal distension
- Ear discharge
- Skin lesion.

The clinical presentation can be similar to that caused by bacterial sepsis and other congenital infections such as syphilis and CMV.

- Diagnosis is often difficult
- The tuberculin test is essentially always negative
- The chest radiograph may be normal initially and become abnormal as the disease progresses, but most neonates have an abnormal chest radiograph, 50% with a miliary pattern. Less than 50% of infected newborns develop meningitis (Figs 41 to 45).

The diagnosis is usually established by finding acid-fast bacilli in gastric aspirate, urine, middle ear fluid, bone marrow aspirate or liver biopsy.

Infants born to a mother with TB can be prevented from postnatal infection by giving isoniazid to the newborn or isolating the infant from infectious adult while initiating treatment on the adult and administering bacillus Calmette-Guérin (BCG) vaccine to the newborn.

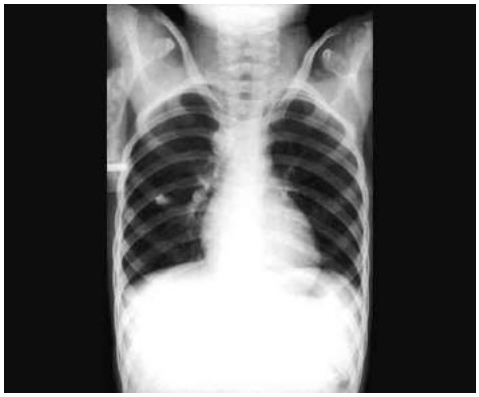


Fig. 41: Ghon complex: A right-sided calcified lymph node with associated right hilar adenopathy. The third component of the Ghon complex—regional lymphatic vessels—is not visible on radiography

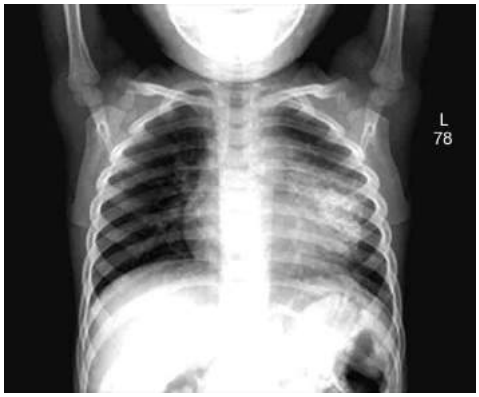


Fig. 42: Left-sided calcification in 3-years-old child with pulmonary disease and accompanying tuberculoma

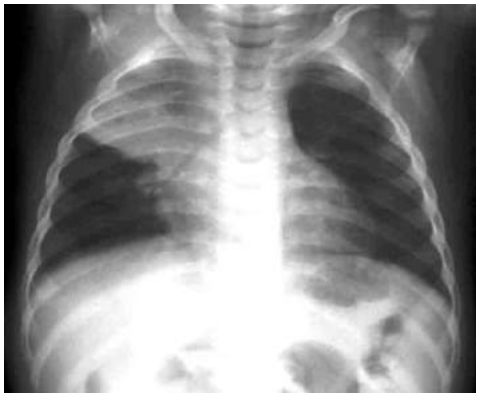


Fig. 43: Right upper lobe consolidation with cavitations and air bronchogram

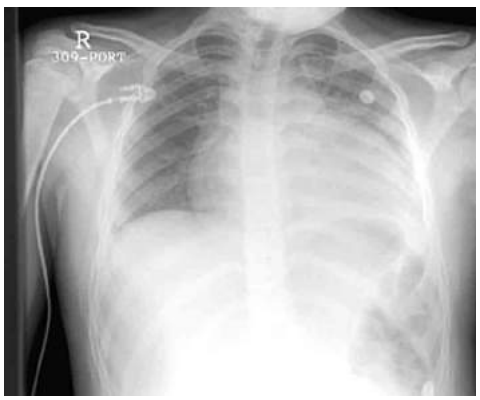


Fig. 44: Tuberculous pericarditis, showing cardiomegaly

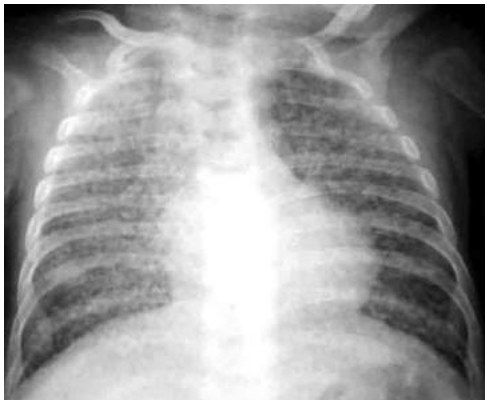


Fig. 45: Chest X-ray in a 3-month-old boy shows a typical bilateral miliary pattern, with widespread tiny nodules in both lungs

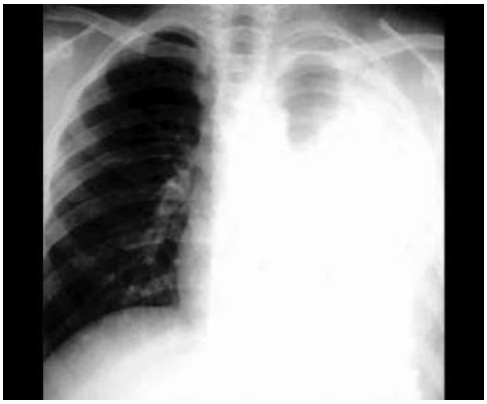


Fig. 46: A 14-year-old girl. Chest X-ray depicts unilateral pleural effusion. Pleural fluid culture yielded *Mycobacterium tuberculosis*

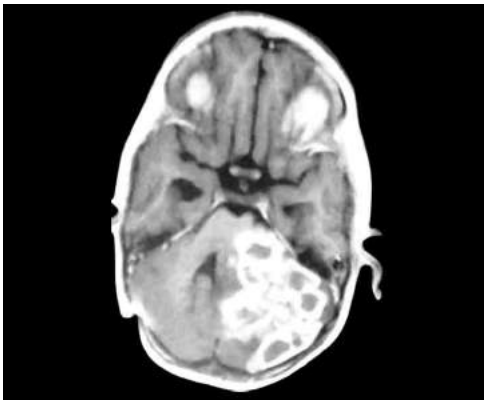


Fig. 47: Contrast MRI of brain showing tuberculoma

Diagnosis of Tuberculosis in Children

The diagnosis of TB in children relies on careful and thorough assessment of all the evidence derived from a careful history, clinical examination and relevant investigations, e.g. Tuberculin skin test (TST), CXR and sputum smear (if possible) microscopy. Most children with TB have pulmonary TB.

A trial of treatment with antituberculosis medications is not recommended as a method to diagnose TB in children. The decision to treat a child should be carefully considered and once such a decision is made, the child should be treated with a full course of therapy.

Adult with smear positive TB infects children with TB. The likelihood of development of disease is high shortly after infection. Infants and children under 5 years are at risk of

Table 31: Symptoms and signs of pediatric pulmonary tuberculosis

		Occurrence in		
		Infants	**Children**	**Adolescents**
Symptoms	Fever	Common	Uncommon	Common
	Night sweat	Rare	Rare	Uncommon
	Cough	Common	Common	Common
	Productive cough	Rare	Rare	Common
	Hemoptysis	Never	Rare	Rare
	Dyspnea	Common	rare	Rare
Signs	Rales	Common	Uncommon	Rare
	Wheezing	Common	Uncommon	Uncommon
	Dullness on percussion	Rare	Rare	Uncommon
	Diminished breath sounds	Common	Rare	Uncommon

developing disease. Immunosuppressive illness including measles, malnutrition, whooping cough and HIV infection facilitate progression of TB infection to disease. Children can be infected with TB at any age, but the most common age is between 1 year and 4 years.

The proposed approach to diagnose TB in children is based on limited published evidence and rests heavily on expert opinion.

Diagnosis of TB in children less than 10 years old is difficult as they cannot produce sputum for microscopic examination, and the tuberculin or Mantoux test is often negative in children with malnutrition. Symptoms of TB are not typical in children. Clinical suspicion of TB in a child is based on one or more of the following features:

- Cough for more than 3 weeks
- Chronic low-grade fever
- Persistent loss of appetite
- Weight loss or failure to thrive
- Matted cervical lymph nodes
- Pneumonia not responding to conventional therapy with broad-spectrum antibiotics
- Abnormal finding on CXR not compatible with clinical condition and therapy
- Poor rate of weight gain (i.e. <5 g/kg/day) during nutritional rehabilitation of a severely malnourished child
- History of TB in a family member.

Recommended Approach to Diagnose Tuberculosis in Children

- Careful history (including history of TB contact and symptoms consistent with TB)
- Clinical examination (including growth assessment)
- Tuberculin skin testing
- Fundoscopic test (for choroid tubercle)
- Bacteriological confirmation whenever possible [acid-fast bacilli (AFB) from sputum or from gastric aspirated and culture]
- Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB
- HIV testing (in high HIV prevalence areas).

Key Risk Factors for Tuberculosis

- Household contact with a newly diagnosed smear-positive case
- Age less than 5 years
- HIV infection
- Severe malnutrition.

Key Features Suggestive of Tuberculosis

The presence of three or more of the following should strongly suggest a diagnosis of TB:

- Chronic symptoms (cough, fever) suggestive of TB
- Physical signs highly suggestive of TB
- A positive TST
- CXR suggestive of TB.

Existing diagnostic tests for TB in children have shortcomings, and the full range of tests (including bacteriological culture and TST) is often not available or possible in settings where the vast majority of TB cases are diagnosed.

Recommended Approach to Diagnose Tuberculosis in Children

Careful History (Including History of Tuberculosis Contact and Symptoms Consistent with Tuberculosis)

Contact: Close contact is defined as living in the same household as or in frequent contact with a source case (e.g. the child's caregiver) with sputum smear-positive pulmonary TB. However, presence of TB in family past or present as reported by family member/s is considered infectious but to lesser degree (scores 1 as national TB guideline) (Table 32).

If a child presents with infectious TB, child contacts must be sought and screened, as for any smear-positive source case. Children should be regarded as infectious if they have sputum smear-positive pulmonary TB or cavitary TB on CXR.

Symptoms: The most common are: Chronic symptoms, chronic cough and fever.

- Chronic cough: An unremitting cough that is not improving and has been present for more than 21 days. Although not chronic according to national TB treatment guideline TB score of 1 is given for cough more than 2 weeks. However, score 3 is given for cough more than 4 weeks (Table 32)
- Fever: Body temperature of more than 38°C for 14 days, after common causes such as malaria, typhoid or pneumonia have been excluded. Fever duration of more than 4 weeks carries more point in favor of TB
- Weight loss or failure to thrive: In addition to asking about weight loss or failure to thrive, it is necessary to look at the child's growth chart.

Clinical Examination (Including Growth Assessment)

There are no specific features on clinical examination that can confirm that the presenting illness is due to pulmonary TB. Some signs, although uncommon, are highly suggestive of extrapulmonary TB (i.e. TB of organs other than the lungs).

Table 32: Interpretation of tuberculin skin test (TST)

Size of induration	**Interpretation**
<5	Negative, no active disease
5–10	Borderline/doubtful but positive in immunocompromised host including HIV, malnutrition and contact with adult patient with sputum smear AFB positive tuberculosis
>10	Positive irrespective of BCG vaccination and suggestive of tubercular disease in presence of clinical features

Abbreviations: HIV, human immunodeficiency virus; BCG, bacillus Calmette-Guérin; AFB, acid-fast bacilli

Important physical signs are:

- Physical signs highly suggestive of extrapulmonary TB:
  - Gibbus (Fig. 48), especially of recent onset (resulting from vertebral TB)
  - Nonpainful enlarged cervical lymphadenopathy with fistula formation
- Physical signs requiring investigation to exclude extrapulmonary TB:
  - Meningitis not responding to antibiotic treatment, with a subacute onset or raised intracranial pressure
  - Pleural effusion
  - Pericardial effusion
  - Distended abdomen with ascites
  - Nonpainful enlarged lymph nodes without fistula formation (Fig. 49)
  - Nonpainful enlarged joint
  - Fundoscopic examination for choroid tubercles, pathognomonic of TB (Fig. 50)
  - Signs of tuberculin hypersensitivity like phlyctenular conjunctivitis (Fig. 51), erythema nodosum, etc.

Tuberculin Skin Test

A positive TST occurs when a person is infected with *M. tuberculosis*, but does not necessarily indicate disease. However, the TST can also be used as an adjunct in diagnosing TB in children with signs and symptoms of TB.

Using the test: The TST should be standardized for each country using either 5 TU of purified protein derivatives (PPDs) or 2 TU Tuberculin PPD gives similar reaction in TB infected children.

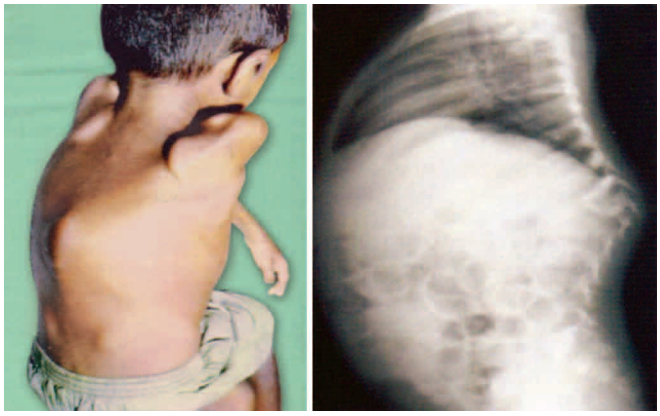


Fig. 48: Spinal deformity (gibbus) damage of vertebra by tuberculosis

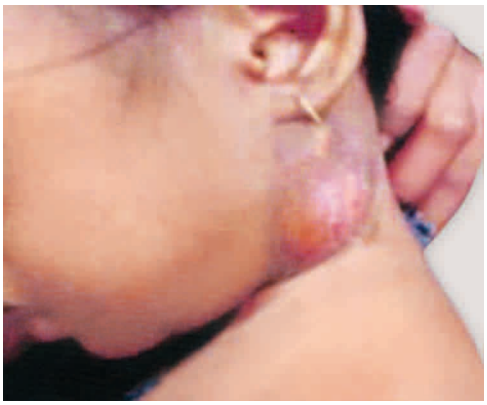


Fig. 49: Tuberculous cervical lymph gland with abscess formation (cold abscess)

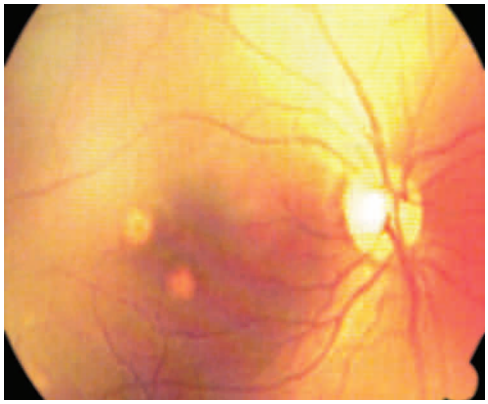


Fig. 50: Fundus-Choroid tubercles, pathognomonic of tuberculosis

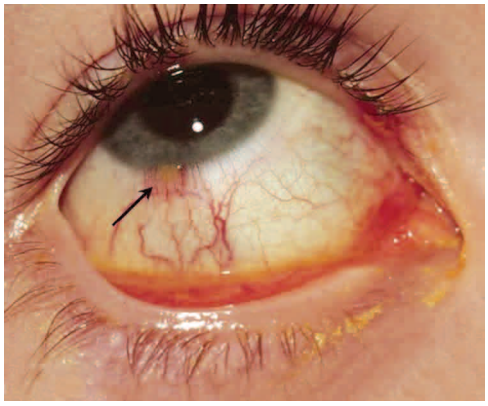


Fig. 51: Phlyctenular conjunctivitis (arrow)

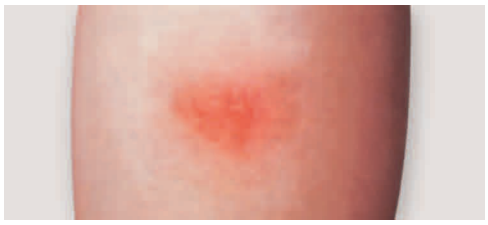


Fig. 52: Positive tuberculin skin test showing significant area of red induration

Healthcare workers must be trained in performing and reading a TST.

Tuberculin skin test (Mantoux test) is performed by injection 0.1 mL of tuberculin PPD into the anterior aspect of forearm using a disposable tuberculin syringe 10 mm long 25 Gauze needle. The volume is injected intradermally slowly to produce a pale wheal (Fig. 52).

A health worker who has experience in administration takes the reading after 72 hours. The reading is limited to measurement of the "induration" at the test site.

The TST is useful in HIV-infected children to identify those with dual TB/HIV infection and as an aid in the diagnosis of TB, although fewer HIV-infected children will have a positive TST, as a normal immune response is required to produce a positive test and many HIV-infected children have immune suppression.

Reading

The results should be read between 48 hours and 72 hours after administration. A patient who does not return within 72 hours will probably need to be rescheduled for another TST.

- Inspect site: Visually inspect injection site under good light, and measure induration (thickening of the skin), not erythema (reddening of the skin)

- Palpate induration: Use fingertips to find margins of induration
- Mark induration: Use fingertips as a guide for marking widest edges of induration across the forearm
- Measure diameter of induration using a clear flexible ruler: Place "0" of ruler line on the inside-left edge of the induration. Read ruler line on the inside-right edge of the induration (use lower measurement if between two gradations on millimeter scale).
- Record diameter of induration: Do not record as "positive" or "negative". Only record measurement in millimeters. If no induration, record as 0 mm.

There can be false positive as well as false negative TST. Possible causes for these results are given below.

Causes of False Positive and False Negative Mantoux Test (Box 1)

Box 1: False positive results and false negative Mantoux test
• Infections due to atypical mycobacteria
• BCG vaccination
• Infection at the site of test
• False negative results
Infections: • Viral (measles, mumps, chicken pox, HIV) • Bacterial (typhoid fever, brucellosis, typhus, leprosy, pertussis, overwhelming TB) • Live virus vaccination (measles, mumps, rubella, varicella)
Metabolic derangement: • Chronic renal failure • Liver failure • Severe malnutrition
Disease affecting lymphoid organs: • Hodgkin's disease • Lymphoma • Chronic leukemia • Sarcoidosis
Drugs: • Corticosteroids and other immunosuppressive agents
Age: • Newborns, elderly patients
Stress: • Surgery • Burns • Mental illness • Graft-versus-host reactions
Factors related to tuberculin used: • Improper storage (exposure to light and heat) • Improper dilutions • Chemical denaturation • Contamination • Adsorption (partially controlled by adding Tween® 80)
Factors related to the method of administration: • Injection of too little antigen • Subcutaneous injection • Delayed administration after drawing into syringe • Injection to close to other skin test
Factors related to reading the test and recording results: • Inexperienced reader • Conscious or unconscious bias • Error in recording

Abbreviations: HIV, human immunodeficiency virus; BCG, bacillus Calmette-Guérin; TB, tuberculosis

Sometimes it is useful to repeat the TST in children once their nutritional status has improved or their severe illness (including TB) has resolved, as they may be initially TST negative (false negative), but positive after 2–3 months on treatment. A negative TST never rules out a diagnosis of TB in a child.

Diagnosis of Tuberculosis in Children in Resource-poor Setting

In resource-poor settings in developing countries, there are two scoring chart namely (1) Modified Kenneth Jones criteria, and (2) TB score chart is used. Both of the scores are mentioned in Tables 33 and 34.

Interpretation of the Tuberculosis Score Chart

A score of 7 or more indicates high likelihood of TB, starting treatment is justified.

Interpretation of Modified Kenneth Jones Criteria

According to this scoring system:

- Points ≥ 7: Unquestionable TB.
- Points 5–6: Probable TB.
- Points 3–4: Further investigations are requirew

Bacteriological Confirmation Whenever Possible

It is always advisable to confirm diagnosis of TB in a child using whatever specimens and laboratory facilities are available. Appropriate clinical samples include sputum, gastric aspirates and certain other material (e.g. lymph node biopsy or any other material that is biopsied).

Fine-needle aspiration of enlarged lymph glands—for both staining of AFB and histology—has been shown to be a useful investigation, with a high bacteriological yield.

Bacteriological confirmation is especially important for children who have:

- Suspected drug-resistant TB.
- HIV infection.
- Complicated or severe cases of disease.
- An uncertain diagnosis.

Common ways of obtaining samples for smear microscopy include the following:

- Expectoration: Sputum should always be obtained in adults and older children (10 years of age or older) who are pulmonary TB suspects. As with adult TB suspects, three sputum specimens should be obtained: an on-the-spot specimen (at first evaluation), an early morning specimen and a second on-the-spot specimen (at a follow-up visit).
- Gastric aspiration: Gastric aspiration using an NG feeding tube can be performed in young children who are unable or unwilling to expectorate sputum. Gastric aspirates should be sent for smear microscopy and mycobacterial culture. A gastric aspirate should be obtained on each of three consecutive mornings.

LABORATORY TEST

Investigations Relevant for Suspected Pulmonary Tuberculosis and Suspected Extrapulmonary Tuberculosis

The diagnostic tests for pulmonary TB can be divided into two categories: (1) Demonstration or isolation of *M. tuberculosis*

Table 33: Tuberculosis (TB) score chart

Features	0	1	2	3	4	Score
General						
Duration of illness (cough and fever) (weeks)	<2	2–4		>4		
Nutritional status (% weight-for-age)	>80	60–80		<60 and/or presence of bilateral pedal edema		
Family TB (past or present)	Nil	Reported by family		Proved sputum positive		
Mantoux test				Positive		
Malnutrition				Not improving after 4 weeks of management		
Unexplained fever and night sweat				No response to malaria treatment		
Local						
				Enlarged, painless lymph nodes, sinus in neck, axilla, groin		
				Joint or bone swelling		
				Abdominal mass or ascites		
				CNS signs (change in temperament, lethargy, fits, coma) and usually abnormal CSF findings	Angle deformity of spine	
					Total score	

(*Source*: Harries A, Maher D, Uplekar M, et al. TB: a clinical manual for South East Asia. Geneva, Switzerland: World Health Organization; 1997.)
Abbreviations: TB, tuberculosis; CNS, central nervous system; CSF, cerebrospinal fluid.

Table 34: Diagnosis of tuberculosis (TB): The modified Kenneth Jones criteria

Score +3	Score +2	Score +1	Score –1
Recovery from AFB from sputum, gastric lavage, laryngeal swab, etc.	X-ray chest suggestive of lymphadenitis with or without parenchymal lesion	Nonspecific changes on X-ray	BCG vaccination in last 2 years
TB granuloma, granulomatous lesions in lymph node biopsy or choroids tubercle on fundoscopy	Suggestive physical findings: Pleurisy, skin lesions, osteomyelitis, Pott's spine, etc.	Compatible physical features: Erythema nodosum, phlyctenular conjunctivitis, meningitis, cervical lymphadenitis, arthritis, hemoptysis	
Positive MT	Recent MT conversion from negative to positive	History of contact with a patient suffering from TB	
	Contact with sputum positive patients	Nonspecific granuloma	
		Age <2 years	
		No response to antibiotic therapy	
		3rd degree malnutrition	

Abbreviations: TB, tuberculosis; MT, Mantoux test; BCG, bacillus Calmette-Guérin.

or one of its components and (2) Demonstration of host's response to exposure to *M. tuberculosis*.

M. tuberculosis can be demonstrated by:

- Ziehl-Neelsen (ZN) staining
- Special stain
- Culture
- Polymerase chain reaction
- Other methods
- The above methods can be used on sputum, gastric lavage, bronchoscopic lavage fluid, or pleural fluid.

The best specimen for demonstration of *M. tuberculosis* in children is the early morning gastric aspirate obtained by using an NG tube before child arises. The yield of *M. tuberculosis* on ZN stain is less than 20% and depends on extent of pulmonary disease and number of specimen tested. For better results, three consecutive specimen of gastric aspiration are recommended. If a delay in the processing of specimen is expected, the gastric acid should be neutralized with sodium bicarbonate for higher yield.

Culture

Lowenstein-Jensen (LJ) medium is the most widely used medium for determination of characteristics features of colonial morphology, growth rate and pigment production. Though the culture technique is simple, 7–10 weeks of incubation may be necessary for detection of organisms.

Serodiagnosis

In absence of good diagnostic method for childhood TB, a lot of interest has been generated in serodiagnosis. Enzyme-linked immunosorbent assay (ELISA) has been used in

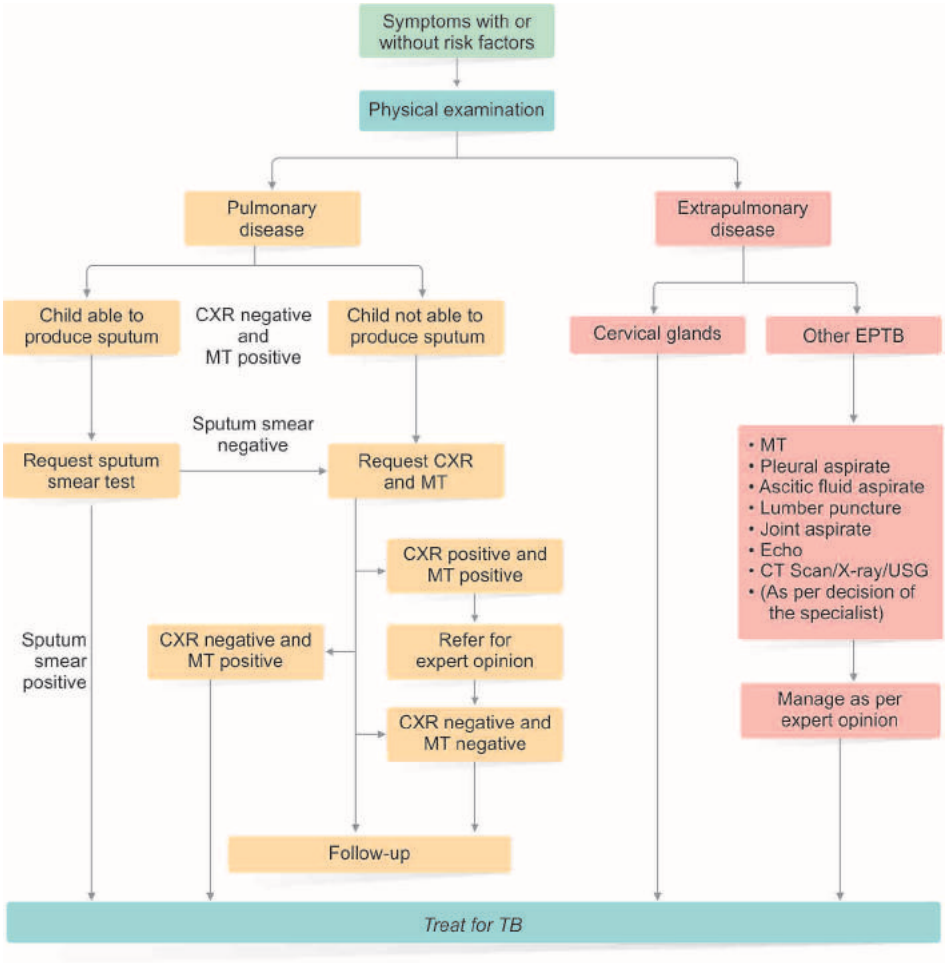


Fig. 53: Algorithm showing general approach to diagnosis of tuberculosis (TB) in children

Abbreviations: CXR, chest X-ray; MT, Mantoux test; EPTB, extrapulmonary tuberculosis; CT, computerized tomography; USG, ultrasonograpy

children to detect antibodies to various purified or complex antigens of *M. tuberculosis*. Despite a large number of studies published, serology has found little place in the routine diagnosis of TB in children.

OTHER INVESTIGATIONS FOR DIAGNOSIS OF TUBERCULOSIS (FIG. 53)

Radiology

Chest X-ray has an important role in diagnosis of childhood TB especially in pulmonary TB. In presence of extrapulmonary TB, lesion in CXR supports diagnosis of TB.

Chest radiography is useful in the diagnosis of TB in children. In large number of cases, children with pulmonary TB have CXR changes suggestive of TB. The most common picture is that of persistent opacification in the lung together with enlarged hilar or subcarinal lymph glands. A lateral CXR is more useful than posteroanterior view. A miliary pattern of opacification in HIV-uninfected children is highly suggestive of TB. Patients with persistent opacification which does not improve after a course of antibiotics should be investigated for TB. Adolescent patients with TB have CXR changes similar to adult patients with large pleural effusions and apical infiltrates with cavity formation being the most common forms of presentation. Adolescents may also develop primary disease with hilar adenopathy and collapse lesions visible on CXR. Good-quality CXRs are essential for proper evaluation. CXRs should preferably be read by a radiologist or a healthcare worker trained in their reading.

Drawback of X-ray chest: Only up to 50% of the bacteriological or histological proven pulmonary TB case has suggestive X-ray findings in children.

BCG Test

An accelerated response after injection of the vaccine in individual suffering from TB. An induration more than 5–6 mm after 3 days after inoculation is considered a positive reaction.

Histology

Lymph node, liver and other tissue for histological evidence of TB by fine-needle aspiration.

Suspected Extrapulmonary Tuberculosis

Table 35 shows the investigations usually used to diagnose the common forms of extrapulmonary TB. In most of these cases,

TB will be suspected from the clinical picture and confirmed by histology or other special investigations.

Table 35: Common forms of extrapulmonary tuberculosis (TB) and their diagnostic methods

Sites	Practical approach to diagnosis
Peripheral lymph nodes (especially cervical)	Lymph node biopsy or fine needle aspiration
Miliary TB (e.g. disseminated)	Chest X-ray and lumbar puncture (to test for meningitis)
TB meningitis	Lumbar puncture (and computerized tomography where available)
Pleural effusion (older children and adolescents)	Chest X-ray, pleural tap for biochemical analysis (protein and glucose concentrations), cell count and culture
Abdominal TB (e.g. peritoneal)	Abdominal ultrasound and ascitic tap
Osteoarticular	X-ray, joint tap or synovial biopsy
Pericardial TB	Ultrasound and pericardial tap

HIV Testing

In areas with a high prevalence of HIV infection in the general population, where TB and HIV infection are likely to coexist, HIV counseling and testing is indicated for all TB patients as part of their routine management. In areas with lower HIV prevalence, HIV counseling and testing are indicated for TB patients with symptoms and/or signs of HIV-related conditions, and in TB patients having a history suggestive of high risk of HIV exposure.

DIAGNOSTIC ADVANCES IN TUBERCULOSIS

Less than 20% of children with proven TB have sputum or gastric aspirate positive on ZN staining, compared to 75% adults. On the other hand, only 50% of the bacteriological/histopathological proven pulmonary TB have suggestive X-ray finding.

In view of the above limitations, newer diagnostic tools have developed that have assumed greater significance.

QuantiFERON-TB Test (In Vitro Interferon γ Assay)

Methods of In Vitro Diagnosis of M. tuberculosis

It involves interferon γ release assay (IGRA) principle. This is an in vitro diagnostic aid that measures a component of cell-mediated immune activity to *M. tuberculosis*, and is based on the quantification of interferon-gamma (IFN-γ) released from sensitized lymphocytes in whole blood incubated overnight with PPD from *M. tuberculosis* and control antigens. The principles involved in IGRA as shown in Figure 54.

This provides same information as tuberculin test but uses antigen which do not crossreact with BCG and therefore, more specific and sensitive.

The T-SPOT TB

Also involves IGRA principle. This TB test ideally requires 5 mL of venous blood, which is collected in a single tube designed for the preparation of peripheral blood mononuclear cells in the laboratory. Blood should reach the laboratory as soon as possible to be separated by skilled personnel. These cells are collected following centrifugation steps and washed, counted and then plated out in precoated special tissue culture plates containing no antigen (negative control), *M. tuberculosis*-specific antigens or phytohemaglutinin (positive control). The plates are incubated overnight at 37°C, washed and the assay then developed with additional reagents to finally visualize the number of antigen-specific T-cells producing the key cytokine (interferon γ). These are then enumerated in comparison with the negative and positive controls using an ELISPOT reader instrument. The results are reported as negative, positive or uninterpretable, which can happen due to technical problems, such as high background in the ELISPOT. Such assays ought to be repeated.

Advantages

It is more sensitive than ZN staining, LJ culture and even PCR (IS 6110). Although it measures a components of cell-mediated immunity (CMI) to *M. tuberculosis*, it is in vitro test (test done from patient blood) and does not require to bring patient after 72 hours like MT test, to get test result, which patient sometime cannot comply. Interpersonal error of measuring induration to MT test is also avoided.

Disadvantages

- Although highly sensitive, but less specific (up to 48%)
- Unable to differentiate between latent and active disease and cannot distinguish between infected, disease and treated cases.

Other Similar Test

ELISPOT-TB also can diagnose latent infection.

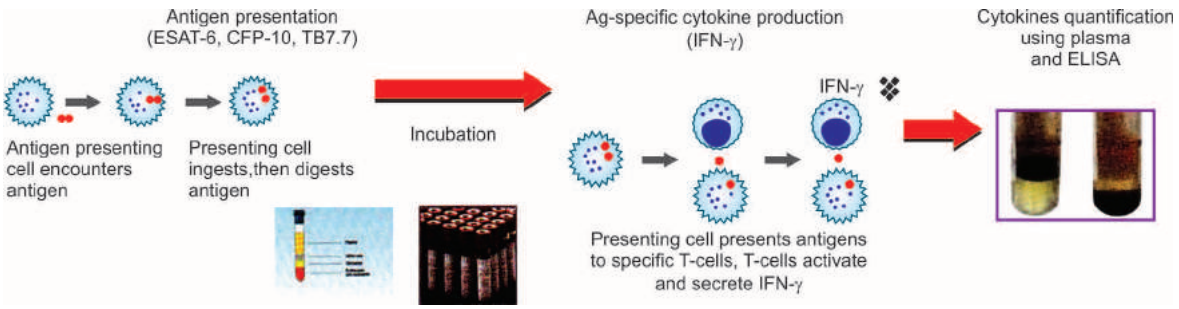


Fig. 54: Immunological principles of commercially available interferon γ release assays

Advanced Serological Test Based on Cell Culture and ELISA Technique

Antilymphocytic Secretion for Tuberculosis (ALS for TB)

This is also in vitro quantitative test for *M. tuberculosis* and helps to complement diagnosis of TB when standard tests are not conclusive or difficult to perform. The method uses cell culture and ELISA technique to quantify antibody to *M. tuberculosis* antigen. Results are interpreted as positive, suggestive and negative.

Culture

Traditionally culture on LG media takes 4–6 weeks. Liquid culture system (BACTEC™ and MGIT™, BD diagnostic, Sperk Maryland, USA) offers a more sensitive and rapid alternative to conventional solid culture and may detect growth in 1–3 weeks. MGIT technology can yield results in less than 8 days.

Polymerase Chain Reaction

Polymerase chain reaction is the most commonly used technique of nucleic acid amplification, for diagnosis of TB. The PCR may be used to:

- Diagnose TB rapidly by identifying DNA from *M. tuberculosis* in clinical samples that are negative by microscopic examination
- Determine rapidly whether acid-fast organisms identified by examination of clinical specimen are *M. tuberculosis* or atypical mycobacteria
- Identify the presence of genetic modifications known to be associated with resistance of some antimicrobial agents.

The genomics of *M. tuberculosis* has been fully sequenced with the rrn operon situated at 1,500 KV from putative *oriC a* probable reason for a slow growth of *M. tuberculosis*.

The newer WHO approved screening test for diagnosis of TB, and drug resistance utilizes the automated nucleated acid amplification technology which probes for specific gene conferring drug resistance (e.g. *rpoB* gene for rifampicin resistance and *inhA* gene for isoniazid resistance).

These screening methods give results in less than 2 hours.

Various Polymerase Chain Reaction Technology Used for Diagnosis of Tuberculosis

PCR-IS 6110: This is the most common target of PCR.

Other Better Diagnostic Polymerase Chain Reaction

Real time PCR (RT-PCR): Detect presence of amplified nucleated acid target.

GeneXpert MTB/RIF (Closed RT-PCR)

This test not only identifies *M. tuberculosis*, but also simultaneously identifies rifampicin resistance using a region of the *rpoB* gene of *M. tuberculosis*. It requires minimal manipulation of sample and operator training.

Sensitivity and Specificity of Polymerase Chain Reaction

Commonly used PCR (PCR IS-6110) has sensitivity ranging from 40% to 50% in adults and 20% to 40% in children. Newer PCR like geneXpert MTB/RIF has higher sensitivity. Current preliminary studies reflected sensitivity of 71% in smear negative but culture positive cases and 100% sensitivity in smear positive cases. Specificity of PCR is almost 100%.

Polymerase chain reaction gives rapid results and has a greater sensitivity compared with traditional microbiological methods. This makes PCR a suitable technique in childhood TB, especially when diagnosis is difficult or needed urgently.

It is particularly useful in developing countries where the burden of the disease is very high and early diagnosis is required to prevent morbidity and mortality.

Drug-resistant Tuberculosis

Children are as susceptible to drug-resistant as to drug-sensitive TB. There are two types drug resistance:

1. Acquired resistance: It is defined as resistance to one or more anti-TB drugs, which arises during the course of treatment, usually due to nonadherent to the recommended regimen or due to incorrect drug prescription and intake.
2. Primary resistance: It is defined as the presence of resistant strains of *M. tuberculosis* in patients, who have been infected with resistant bacilli by another patient and subsequently develop the disease (it should be ascertained that the patient did not receive previous treatment with anti-TB drugs).

Drug-resistant TB is a laboratory diagnosis. However, drug-resistant TB should be suspected if any of the features below are present:

- Features in the source case suggestive of drug-resistant TB:
  - Contact with a known case of drug-resistant TB (primary resistance)
  - Remains sputum smear-positive after 3 months of treatment
  - History of previously treated TB
  - History of treatment interruption (acquired resistance)
- Features of a child suspected of having drug-resistant TB:
  - Contact with a known case of drug-resistant TB
  - Not responding to the anti-TB treatment regimen
  - Recurrence of TB after adherence to treatment.

The diagnosis and treatment of drug-resistant TB in children is complex and should be carried out at referral centers.

Miliary Tuberculosis in Children

There are no specific clinical features. Features commonly associated with miliary TB include fever, wasting, cough, lymphadenopathy and splenomegaly. The MT may be false negative, and the diagnosis is based on typical X-ray finding of miliary mottling (Fig. 55).

Tubercular Meningitis in Children

Tubercular meningitis is a disease with insidious onset and is fatal if left untreated. The course of illness is divided into three stages:

1. Stage of invasion or prodromal stage: Symptoms are nonspecific and include apathy, irritability, headache, vomiting and mild fever.
2. Stage of meningitis: There are manifestations of meningismus, i.e. headache, vomiting, fever, convulsions, bulged fontanelle in infants, altered mental status. Neck rigidity appears, Kernig sign may be positive with a

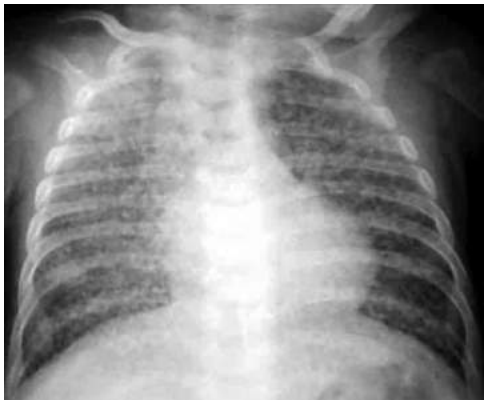


Fig. 55: Chest X-ray of a 3-month-old boy shows a typical bilateral miliary pattern, with widespread tiny nodules in both lungs

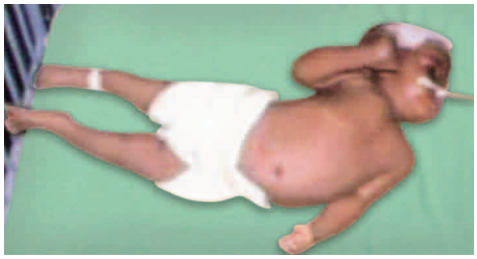


Fig. 56: TB meningitis with head retraction and rigidity

plantar extensor response. Ocular paralysis, strabismus and nystigmus may occur. Papilledema may be present. Choroid tubercle if seen on fundoscope is pathognomonic of tubercles (Fig. 51).

3. Stage of coma or terminal stage: Case fatality is high in this stage. The incidence of hydrocephalus, blindness, deafness and mental retardation is high among survivors. At this stage, the child is comatose, may have convulsions, head retraction or decerebrate or decorticate rigidity (Fig. 56).

Classically, the CSF studies show lymphocytosis with high protein and low sugar levels. It forms a clot-like cobweb if left in a test tube placed in a refrigerator.

TREATMENT OF CHILDHOOD TUBERCULOSIS

The main objectives of anti-TB treatment are to:

- Cure the patient of TB (by rapidly eliminating most of the bacilli).
- Prevent death from active TB or its late effects
- Prevent relapse of TB (by eliminating the dormant bacilli)
- Prevent the development of drug resistance (by using a combination of drugs)
- Decrease TB transmission to others.

Children usually have paucibacillary pulmonary disease (low organism numbers), as cavitating disease is relatively rare (about 6% of cases or fewer) in those under 13 years of age (the majority of the organisms in adult-type disease are found in the cavities). In contrast, children develop extrapulmonary TB more often than adults do. Severe and disseminated TB (e.g. TB meningitis and miliary TB) occur especially in young children (<3 years old). Both the bacillary load and the type of disease may influence the effectiveness of treatment regimens. Treatment outcomes in children are generally good, even in young and immunocompromised children who are at higher risk of disease progression and disseminated disease, provided that treatment starts promptly (Figs 57 and 58). There is a low risk of adverse events associated with use of the recommended treatment regimens. The treatment recommendations presented here are based on the best available evidence.

RECOMMENDED TREATMENT REGIMENS

Anti-TB treatment is divided into two phases: (1) An intensive phase and (2) A continuation phase. The purpose of the intensive phase is to rapidly eliminate the majority of organisms and to prevent the emergence of drug resistance. This phase uses a greater number of drugs than the continuation phase. The purpose of the continuation phase is to eradicate the dormant organisms. Fewer drugs are generally used in this phase because the risk of acquiring drug resistance is low, as most of the organisms have already been eliminated. In either phase, treatment can be given daily or three times weekly. Table 36 shows the first-line (or essential) anti-TB drugs and their recommended doses.

The recommended treatment regimens for each TB diagnostic category (Table 37) are generally the same for children as for adults. New cases fall under category I with new smear-positive pulmonary TB; new smear-negative pulmonary TB with different forms of extrapulmonary TB; severe concomitant HIV disease also fall under category I according to newly formulated National Guidelines for treatment of TB in children. Previously smear negative pulmonary TB with only extensive parenchymal lesion was included in category I. Children with TB meningitis also fall under category I, but deserve special consideration with different treatment regimen. Previously treated cases (relapse, treatment interruption, treatment failure) fall under category

Table 36: Recommended doses of first-line anti-TB drugs for children

Drugs	Recommended doses			
	Daily		Three times weekly	
	Dose and range (mg/kg body weight)	Maximum (mg)	Dose and range (mg/kg body weight)	Daily maximum (mg)
Isoniazid (H)	5 (4–6)	300	10 (8–12)	-
Rifampicin (R)	10 (8–12)	600	10 (8–12)	600
Pyrazinamide (Z)	25 (20–30)		35 (30–40)	
Ethambutol (E)	20 (15–25)		30 (25–35)	
Streptomycin (S)	15 (12–18)		15 (12–18)	

Abbreviations: E, ethambutol; H, isoniazid; R, rifampicin; S, streptomycin; Z, pyrazinamide

Table 37: Recommended treatment regimens for children in each tuberculosis (TB) diagnostic category

TB diagnostic category	TB cases	Regimen[a]	
		Intensive phase	Continuation phase
I	New smear positive pulmonary TB (PTB)	2 HRZE	4 HR
	New smear negative PTB with different forms of extrapulmonary TB (other than TB meningitis) Severe concomitant HIV disease TB meningitis	2 HRZS[b]	4 RH
II	Previously treated smear-positive PTB: • Relapse • Treatment after interruption • Treatment failure	2 HRZES + 1 HRZE	5 HRE
*	Chronic and MDR-TB	Specially designed standardized or individualized regimens	

Note: The numerical values denote number of months for which the drug is to be given, e.g. 4 HR means giving 4 months of INH and rifampicin.
Abbreviations: PTB, pulmonary TB; MDR-TB, multidrug-resistant tuberculosis; E, ethambutol; H, is oniazid; R, rifampicin; S, streptomycin; Z, pyrazinamide
[a]Direct observation of drug administration is recommended during the initial phase of treatment and whenever the continuation phase contains rifampicin.
[b]In comparison with the treatment regimen for patients in diagnostic category I, streptomycin replaces ethambutol in the treatment of TB meningitis.

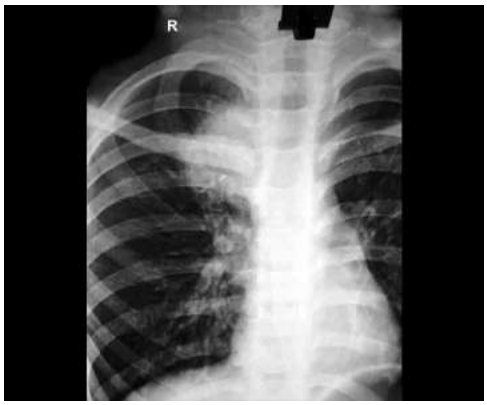


Fig. 57: X-ray chest showing mass of paratracheal gland caused by TB

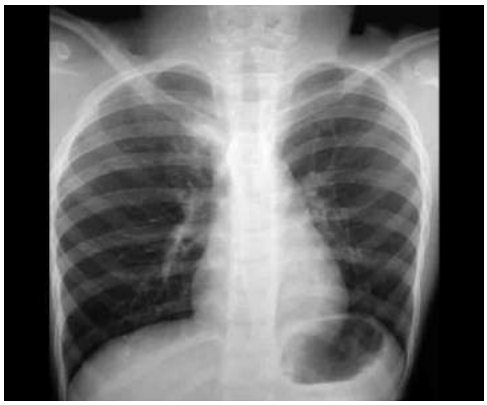


Fig. 58: X-ray of same child 2 months after anti-TB treatment showing disappearance of the mass

II. Response to treatment may take few weeks to months. Figs 57 and 58 showing a chest X-ray of enlarged tuberculus paratracheal gland before and two months after treatment with anti-TB drugs.

Chronic and multidrug-resistant tuberculosis (MDR-TB) are not categorized currently, and treatment regimen is specially designed with standardized regimen.

Corticosteroids

Corticosteroids may be used for the management of some complicated forms of TB, e.g. TB meningitis, complications of airway obstruction by TB lymph glands, and pericardial TB. In cases of advanced TB meningitis, corticosteroids have been shown to improve survival and decrease morbidity, and thus are recommended in all cases of TB meningitis. In order to reduce inflammation and prevent blockage of CSF flow, Prednisolone is given, 1–2 mg/kg per day for 1–3 months and then gradually tapered.

Dispersible, fixed-dose combination (FDC) tablets are now available with the National TB Control Program. During the initial phase of 2 months, treatment is with three FDC tablets each containing rifampicin 60 mg, isoniazid 30 mg, and pyrazinamide 150 mg. In addition ethambutol should be given according to body weight. During the continuation phase of 4 months, two FDC tablets each containing rifampicin 60 mg and isoniazid 30 mg are given. This is written as 2(HRZ)E/4HR. The Table 38 below shows the drugs and age-specific dosage for the initial phase and continuation phase of treatment.

Table 38: Dispersible fixed dose combination (FDC) treatment of tuberculosis according to body weight

Body weight (kg)	Initial phase	Continuation phase
	No. of 3 FDC (R/H/Z: 60/30/150 mg) + E (400 mg) Daily during first 2 months	No. of 2 FDC (RH: 60/30 mg) Daily during next 4 months
2–3	0.5	0.5
4–7	1	1
8–14	2	2
15–19	3	3
20–29	4	4

Abbreviations: H, isoniazid; R, rifampicin; Z, pyrazinamide

Management of Tuberculosis Meningitis and Miliary Tuberculosis

Tuberculosis meningitis and miliary TB are more common in young children and are associated with high rates of death and disability, particularly if the diagnosis is delayed. It is therefore

important to consider these diagnoses in young children as early as possible, especially in children who have a history of contact with an adult with infectious TB.

Diagnosis

Miliary or hematogenously disseminated TB has a high risk (60–70%) of meningeal involvement and should therefore be managed similarly to TB meningitis. For this reason, many experts recommend that all children with miliary TB (or suspected of having miliary TB) should undergo a lumbar puncture to test for the presence of meningitis (Table 39).

Table 39: Selected regimen for treatment of TB meningitis in children

Intensive phase	Continuation phase
2 HRZS	4 HR (commonly used regimen)
2 HRZ (S or Eth)	7–10 months HR
6 HRZEth	None (regimen for 6 months in total)

Abbreviations: H, isoniazid; R, rifampicin; S, streptomycin; Z, pyrazinamide; Eth, ethionamide.

Treatment

Children with tuberculous meningitis should be hospitalized and given streptomycin, 15 mg/kg per day, during the initial phase in addition to HRZ. Pyrazinamide is concentrated in the CSF and is, therefore, particularly useful in tuberculous meningitis. In order to reduce inflammation and prevent blockage of CSF flow, corticosteroids are given as mentioned earlier.

Corticosteroids (usually prednisone) are recommended for all children with TB meningitis in a dosage of 2 mg/kg daily for 4 weeks. The dose should then be gradually reduced (tapered) over 1–2 weeks before stopping. The dosage of prednisone can be increased to 4 mg/kg/day (maximum 60 mg/day) in the case of seriously ill children because rifampicin will decrease corticosteroid concentrations, but higher doses carry a risk of greater immune suppression (Table 39).

All children with suspected or confirmed TB meningitis or miliary TB should be hospitalized initially until their clinical status has stabilized. Children with TB meningitis are at high risk of long-term disability and therefore benefit from specialist care, where this is available.

Chemoprophylaxis for Children

Children aged less than 1 year, whose house hold contacts are under treatment for TB should be given chemoprophylaxis with isoniazid 5 mg/kg per day for 6 months irrespective of BCG status and the child is free of active TB. Follow-up should be carried out at least every 2 months until completion of treatment. An infant born to a mother with infectious pulmonary TB can be safely breastfed if given isoniazid prophylaxis. If a child receiving isoniazid develops symptoms, assessment for TB should be done. If the child has not been BCG vaccinated, BCG should be given after completion of isoniazid treatment.

BCG Vaccination (Fig. 59)

BCG vaccine is recommended as soon as possible after birth. The vaccine is known to prevent the more severe types of TB such as TB meningitis and miliary TB. However, the efficacy of the vaccine in general ranges from 0% to 80%.

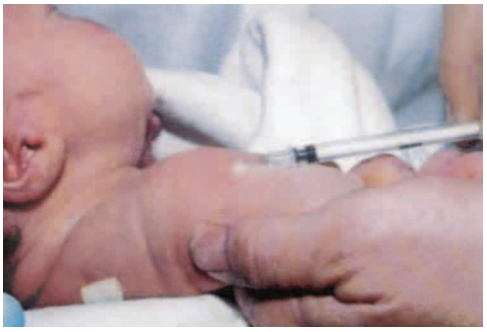


Fig. 59: BCG vaccincation showing typical intradermal wheal

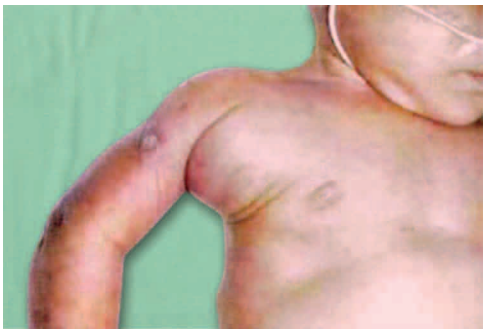


Fig. 60: BCG adenitis

The reasons for this variability are: Different types of BCG used in different countries, differences in the strains of *M. tuberculosis* prevailing in different regions, different levels of exposure, etc. Revaccination offers no added protection, and is therefore not recommended.

A small number of children (1–2%) develop complications following BCG vaccination.

These include local abscesses, secondary bacterial infections, suppurative adenitis (Fig. 60), and local keloid formation. Most reactions resolve over a few months. Children who develop disseminated BCG disease should be treated for TB and investigated for immunodeficiencies.

The assessment should include inquiry about symptoms, treatment adherence, adverse events, and weight measurement. Dosage of anti-TB medicines should be adjusted to account for any weight gain. Follow-up chest X-rays are not routinely required as many children will have a slow radiological improvement.

BCG acceleration is not recommended.

DIRECTLY OBSERVED TREATMENT IN COMMUNITY-BASED MANAGEMENT OF TUBERCULOSIS UNDER NATIONAL TUBERCULOSIS CONTROL PROGRAM

Directly observed treatment (DOT) is a very important component in the internationally recommended policy package for TB control (DOTS strategy).

Patient compliance is a key factor to treatment success. A proportion of patients stop treatment before completion, for various reasons so strict adherence to treatment should be ensured to cure the patients and prevent the development of drug-resistant TB.

Directly observed treatment means that an observer watches the patient swallowing their drugs, which is essential for completion of treatment and recovery from TB. This ensures

that the patient takes the right anti-TB drugs, in the right doses, at the right intervals and for the right period. All patients in community-based management of tuberculosis under national TB control program (NTP) irrespective treatment category should receive all anti-TB drugs under DOT.

The first dose of the drug should be given in respective health facility where after the patient is referred to DOT provider. At the time of start of treatment, all drugs for the whole course of treatment (intensive and continuation phase) of the respective patient should be ensured.

To ensure adherence to treatment, DOT should be provided as conveniently as possible to the patient. This often means as close to the patient's home or workplace as possible. Patients may wish to attend any of the NTP recognized DOT centers according to patients convenience. The DOT provider may be a facility-based or community-based health worker or a trained and supervised community member. These DOT providers include health assistants (HAs), assistant health inspectors (AHIs), community health workers (CHWs), shasthya shebikas, village doctors, community leaders, cured patients, etc. All nonmedical personnel who deliver DOT should be supervised at least monthly.

Health workers/DOT providers can monitor side effects of drugs by teaching patients how to recognize symptoms of common side effects and to report if they develop such symptoms, and by asking about symptoms when the patients report to collect drugs.

Management of Side Effects or Adverse Reactions Related to the Use of Antituberculosis Drugs

Most TB patients complete their treatment without any significant adverse effects of drugs. However, a few patients do experience adverse effects (Table 40). Patients sometime discontinue the treatment due to major or even minor adverse effects. It is therefore important that patients be clinically monitored during treatment so that adverse effects can be detected promptly and managed properly. Routine laboratory monitoring is not necessary.

Low Tuberculosis Prevalence Countries

Low TB prevalence countries are those in which there is an:

- Average annual notification rate of smear-positive pulmonary TB for the past 3 years less than 5 per 100,000 population
- Average annual notification rate of TB meningitis in children aged under 5 years for the past 7 years less than 1 case per 1,000,000 population
- Average annual risk of TB infection 0.1% or less.

Multidrug-resistant Tuberculosis

MDR-TB is defined as TB resistant to at least isoniazid and rifampicin, the two most potent anti-TB drugs.
Although its causes are microbial, clinical and programmatic, MDR-TB is essentially a man-made phenomenon. From a microbiological perspective, resistance is caused by a genetic mutation that makes a drug ineffective. An inadequate or poorly administered treatment regimen allows drug-resistant mutants to become the dominant strain in a patient infected with TB.

Treatment of MDR-TB with Category 1 or 2 may create even more resistance to the drugs used. This has been termed the "amplifier effect" of the short-course chemotherapy. Ongoing transmission of established MDR-TB strains in a population may also contribute to new drug-resistant cases.

Types of Drug Resistance

Depending on the number of resistant drugs, we distinguish the following categories of resistance:

- Monoresistance: Resistance to one type of drugs (e.g. isoniazid)
- Polyresistance: Resistance to more than one type of drug (e.g. streptomycin, isoniazid and ethambutol)

Table 40: Possible side-effects of anti-TB drugs

Side-effects	Drug(s) probably responsible	Management
Minor	**Continue anti-TB drugs, check drug doses**	
Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin	Give drugs with after meals
Joint pain	Pyrazinamide	Give nonsteroidal anti-inflammatory drug (NSAID)
Burning sensation in the feet	Isoniazid	Give pyridoxine 100 mg daily
Orange/red urine	Rifampicin	Reassurance; the patient should be informed at the beginning of the treatment that it happens commonly and is normal
Itching with minor skin rash	All drugs	Exclude skin diseases Give antihistamines
Major		
Itching with skin rash	All drugs	Stop anti-TB drugs. Identify the offending drug (need expert opinion)
Deafness (no wax on auroscopy)	Streptomycin	Stop streptomycin and never use again
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin and never use again
Jaundice (other causes excluded), hepatitis	Most anti-TB drugs (especially isoniazid, pyrazinamide and rifampicin)	Stop all anti-TB drugs until jaundice resolves (need expert opinion)
Vomiting and confusion (suspect drug induced acute liver failure if jaundice present)	Most anti-TB drugs	Stop all anti-TB drugs until jaundice resolves; urgent liver function test and prothombin time test (need expert opinion)
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol and never use again
Shock syndrome, purpura, acute renal failure, acute hemolytic anemia	Rifampicin	Stop rifampicin and never use again

- MDR-TB: This is a subcategory of polyresistance. TB resistant to at least isoniazid and rifampin
- Extremely drug-resistant tuberculosis (XDR-TB): This is a subcategory of MDR-TB. XDR-TB is defined as MDR-TB plus resistance to a quinolone and an injectable second-line drug (kanamycin, capreomycin, etc.).

Tuberculosis that is sensitive to all drugs is called *pan-susceptible TB*.

Depending on the way resistance is required, two types are distinguished:

1. Acquired or secondary resistance: This is defined as resistance to one or more anti-TB drugs, which arises during the course of treatment, usually due to non-adherence to the recommended regimen or due to incorrect drug prescription and intake.
2. Primary resistance: This is defined as the presence of resistant strains of *M. tuberculosis* in patients, who have been infected with resistant bacilli by another patient and subsequently develop the disease.

Magnitude of MDR-TB

In 1992, the Third World Congress on tuberculosis concluded that there was little recent information on the global magnitude of multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid and rifampicin. Through the WHO/IUATLD Global Project on Drug-Resistance Surveillance launched in 1994, a large number of reliable and accurate data have allowed us to understand the magnitude of the problem of MDR-TB. MDR-TB is limited to local epidemics but the evidence is not yet irrefutable, as many countries have only provided short-term data.

TUBERCULOSIS AND HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Throughout the industrialized and developing world, TB and HIV disease are closely linked in mutually disadvantageous synergy: HIV infection promotes tuberculous infection to disease and vice versa. Tuberculosis is the most common cause of death in persons with HIV infection throughout the world.

INFLUENCE OF HIV INFECTION ON THE PATHOGENESIS OF TUBERCULOSIS

Tuberculosis develops by either direct progression from recently acquired infection or reactivation of latent infection. It is generally thought that most cases arise from latent infections. HIV impairs host response to both new and latent infections. However, the risk of rapid progression of new infection is much greater among persons with HIV infection.

Cell-mediated immunity is the predominant mechanism by which a contained TB infection is kept quiescent. Because of the effect HIV infection has on CMI, the likelihood of reactivation of latent tuberculous infection leading to clinical TB is greatly increased. For this reason, persons with latent tuberculous infection are greatly increased risk of developing TB after being infected with HIV.

In healthy host, once the cell-mediated immune response to infection with *M. tuberculosis* develops; there is a low likelihood that new exogenous infection will be acquired.

Because of the immune defect induced by the HIV, someone who has been previously infected with *M. tuberculosis* may still be vulnerable to new infection. Reinfection with drug resistant organisms has been demonstrated by restriction fragment length polymorphism (RFLP) analyzing among HIV-infected persons being treated for drug susceptible tuberculosis.

In situations where groups of HIV infected persons are exposed to a patient with infectious TB, explosive outbreaks of TB may occur.

Population-based application of DNA fingerprinting over a 5-year-period in San Francisco has demonstrated that, although clustering (more than one case caused by the same strain of *M. tuberculosis*) occurs in both HIV-infected and uninfected persons, large clusters are more likely to involve persons with HIV infection.

Tuberculosis can occur later in the course of HIV infection, however, and the clinical manifestations tend to vary with the level of HIV-induced immunosuppression. Patients with lower CD4 counts tend to have more dissemination of their disease, including mycobacteria.

DIAGNOSIS OF HIV INFECTION AND TUBERCULOSIS

The approach to diagnosis of tuberculous infection in the setting of HIV infection is essentially the same as is used in persons without HIV infection.

Tuberculin Skin Testing and Anergy Testing

The TST may show little or no reaction in persons with advanced HIV infection. The prevalence of positive (≥5 mm indurations) TSTs decreased progressively as the CD4 cell count decreased.

Because of the frequency of blunted skin test responses or anergy, it is recommended by American Thoracic Society and the CD that a reaction of more than or equal to 5 mm induration of 5 tuberculin units of purified protein derivative be regarded as indicative of tuberculous infection in HIV infected persons.

Clinical Features of Tuberculosis

The clinical manifestation of TB in patients with HIV infection depends at least in part on the severity of immunosuppression. As noted previously, presumably because of the virulence of *M. tuberculosis*, TB may occur relatively early in the course of HIV infection.

In a study, it had been observed that the median CD4 lymphocyte count within 6 months before the diagnosis of tuberculosis was 144/μL, with a range from 2/μL to 543/μL.

Clinical reports have emphasized that TB in advanced HIV infection is frequently disseminated, has unusual radiographic manifestations, and produces nonreactive TSTs. The investigators reported a clear association between low CD4 cell counts and an increased frequency of extrapulmonary TB, positive blood cultures for *M. tuberculosis* and intrathoracic adenopathy on chest radiograms.

A variety of unusual manifestations of TB have been noted in HIV infected persons, these are:

- Brain abscess, tuberculoma, meningitis
- Bone (including vertebral) disease

- Pericarditis
- Gastric TB
- Tubercular peritonitis
- Scrotal tuberculosis.

In addition, *M. tuberculosis* has been cultured from the blood as well as bone marrow. However, despite the increased frequency of unusual forms of tuberculosis in persons with HIV infection, standard pulmonary disease tends to predominate in most series.

Radiographic Findings

Lower lung zone or diffuse infiltrations have been commonly observed rather than the usual upper lobe involvement. Cavitation is less frequent and intrathoracic adenopathy is relatively frequent.

Bacteriological Examinations

The proportion of positive smears and cultures in patients with pulmonary TB is approximately the same in HIV-infected and noninfected persons. The general lack of cavitations in patients with HIV-related TB probably accounts for a lower number of bacilli in expectorated sputum. Because of the high frequency of extrapulmonary involvement, specimens from any site of abnormality in patients with or suspected of having HIV infection should be examined for mycobacteria by smear and culture. Potential high yield sources include lymph nodes, bone marrow, urine and blood. The value of nucleic acid amplification assays for diagnosis HIV-related TB is no greater than other patient population.

TREATMENT

The treatment regimens that include isoniazid and rifampin for 6 months supplemented by pyrazinamide and ethamabutol (or streptomycin) are effective in treating HIV-infected patients with TB.

PREVENTION OF TUBERCULOSIS IN HIV-INFECTED PERSONS

- All HIV-infected individuals should have a baseline TST
- Annual testing should be considered in those patients at risk of exposure to infectious TB
- Anergy testing is of no value and should not be included as part of TB screening
- A positive TST is defined as more than or equal to 5 mm induration
- Preventive therapy should be given to the following patients:
  - Tuberculin positive (≥ 5 mm)
  - History of tuberculin positivity without prior prophylaxis
  - Exposure to infectious TB, regardless of tuberculin test results
- Preventive therapy regimen:
  - Isoniazid 300 mg daily for 12 months
  - Isoniazid 15 mg/kg twice weekly for 12 months
  - Rifampicin 600 mg/pyrazinamide 20 mg/kg/day for 2 months
  - Rifampicin/pyrzinamide 20 mg/kg twice weekly for 2 months
  - Isoniazid 300 mg/rifampicin 600 mg daily for 3 months.

INFLUENCE OF TUBERCULOSIS ON THE COURSE OF HIV INFECTION

There is substantial evidence that tuberculosis accelerates the course of HIV disease. The mechanism by which TB accelerates the course of HIV disease is thought to be via immune activation by *M. tuberculosis* leading to increased viral replication. Tuberculosis leads to activation of mononuclear cells, resulting increased levels of cytokines.

MULTIDRUG-RESISTANT TUBERCULOSIS AND ITS MANAGEMENT

DRUG-RESISTANT TUBERCULOSIS

Children are as susceptible to drug-resistant as to drug-sensitive TB. Drug-resistant TB is a laboratory diagnosis. However, drug-resistant TB should be suspected if any of the features below are present.

- Features in the source case suggestive of drug-resistant TB:
  - Contact with a known case of drug-resistant TB
  - Remains sputum smear-positive after 3 months of treatment
  - History of previously treated TB
  - History of treatment interruption
- Features of a child suspected of having drug-resistant TB:
  - Contact with a known case of drug-resistant TB
  - Not responding to the anti-TB treatment regimen
  - Recurrence of TB after adherence to treatment.

The diagnosis and treatment of drug-resistant TB in children is complex and should be carried out at referral centers.

Child Contacts of Infectious Multidrug-resistant Tuberculosis Cases

The only chemoprophylaxis regimens to have been studied are based on isoniazid and, to a lesser extent, on rifampicin. Since by definition MDR-TB is resistant to both of these drugs, it is unlikely that use of these drugs to treat latent infection caused by an MDR—*M. tuberculosis* strain will prevent the development of active TB disease. Close contacts of MDR-TB patients should receive careful clinical follow-up for a period of at least 2 years. If active disease develops, prompt initiation of treatment with a regimen designed to treat MDR-TB is recommended. On the basis of the currently available evidence, WHO does not recommend second-line drugs for chemoprophylaxis in MDR-TB contacts.

MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS IN CHILDREN

Monoresistance and Polyresistance

Resistance to isoniazid and/or rifampicin is the most important, as these two drugs form the mainstay of current

chemotherapy. In the case where monoresistance to isoniazid is known or suspected when treatment is initiated, the addition of ethambutol to isoniazid, rifampicin and pyrazinamide in the intensive phase is recommended. Some authorities would also recommend the addition of ethambutol in the continuation phase lasting 6–9 months. For patients with more extensive disease, consideration should be given to the addition of a fluoroquinolone and to prolonging treatment to a minimum of 9 months. Monoresistance to rifampicin should be treated with isoniazid, ethambutol and a fluoroquinolone for at least 12–18 months, with the addition of pyrazinamide for at least the first 2 months.

Multidrug-resistant Tuberculosis

MDR-TB is resistant to both isoniazid and rifampicin, with or without resistance to other anti-TB drugs.

MDR-TB in children is mainly the result of transmission of a strain of *M. tuberculosis* that is MDR from an adult source case, and therefore often not suspected unless a history of contact with an adult pulmonary MDR-TB case is known. Treatment is difficult—specialist referral is advised. Some basic principles of treatment are as follows:

- Do not add a drug to a failing regimen
- Treat the child according to the drug susceptibility pattern (and using the treatment history) of the source case's *M. tuberculosis* strain if an isolate from the child is not available
- Use at least four drugs certain to be effective
- Use daily treatment only; directly observed therapy is essential
- Counsel the child's caregiver at every visit, to provide support, advice about adverse events and the importance of compliance and completion of treatment
- Follow-up is essential: Clinical, radiological and bacteriological (mycobacterial culture for any child who had bacteriologically confirmed disease at diagnosis)
- Treatment duration depends on the extent of the disease, but in most cases will be 12 months or more (or at least 12 months after the last positive culture)
- With correct dosing, few long-term adverse events are seen with any of the more toxic second-line drugs in children, including ethionamide and the .

Children with MDR-TB should be treated with the first-line drugs to which their *M. tuberculosis* strain (or that of their source case) is susceptible, including streptomycin, ethambutol and pyrazinamide. Ethambutol is bactericidal at higher doses, so daily doses up to 25 mg/kg should be used in children being treated for MDR-TB. Table 41 summarizes second-line (or reserve) anti-TB drugs for treatment of MDR-TB in children.

Choosing a Chemotherapy Regimen for a Patient with Apparent Multidrug-resistant Tuberculosis

All patients with apparent drug resistant tuberculosis will have bacilli resistant to isoniazid.

Patients with additional resistance, or suspected resistance to streptomycin and/or thioacetazone (but not to rifampicin) should respond well to the WHO standard retreatment regimen in the initial phase. Resistance at least to isoniazid and rifampicin, patients considered to have failed on the WHO standard treatment regimen.

Such patients will often require the use of at least some second-line drugs. These drugs and less effective and have more side-effects than the present standard essential drugs.

The patient must try to tolerate any unpleasant side effects in order to achieve survival. He/she must agree to remain under direct observation, with each dose supervised, at least until the sputum or gastric aspirate is negative. The patient must receive clear and complete explanations before treatment, and permanent psychological support and attention.

In designing a regimen, do not aim to keep drugs in reserve. In the first place prescribe drugs which the patient has not had previously. The initial regimen should consist of at least three drugs, preferably four or five, to which the bacilli

Table 41: Second-line anti-TB drugs for treatment of multidrug-resistant tuberculosis (MDR-TB) in children

Drug	Mode of action	Common side effects	Recommended daily dose	
			Range mg/kg/body weight	Maximum dose (mg)
Ethionamide or prothionamide	Bactericidal	Vomiting, gastrointestinal upset	15–20	1,000
Fluoroquinolones		**Arthropathy, arthritis**		
Ofloxacin	Bactericidal		15–20	800
Levofloxacin	Bactericidal		7.5–10	
Moxifloxacin	Bactericidal		7.5–10	
Gatifloxacin	Bactericidal		7.5–10	
Ciprofloxacin	Bactericidal		20–30	1,500
Aminoglycosides		**Ototoxicity, hepatotoxicity**		
Kanamycin	Bactericidal		15–30	1,000
Amikacin	Bactericidal		15–22.5	1,000
Capreomycin	Bactericidal		15–30	1,000
Cycloserine terizidone	Bacteriostatic	Psychiatric, neurological	10–20	1,000
Para-aminosalicylic acid	Bacteriostatic	Vomiting, gastrointestinal upset	150	12,000

Table 42: Acceptable "third-line" regimen before (or without) susceptibility results

Initial phase		Continuation phase	
Drugs	**Minimum duration (months)**	**Drugs**	**Minimum duration (months)**
Aminoglycoside*	3	Ethionamide	18
Ethionamide	3	Ofloxacin	18
Pyrazinamide	3		
Ofloxacin$^{\varphi}$	3		

*Kanamycin or amikacin, capreomycin
$^{\varphi}$The daily dose of 800 mg can be reduced to 400 mg if poorly tolerated, if ofloxacin is not available use cycloserine

Table 43: Acceptable "third-line" regimens if there is resistance to INH but susceptibility to rifampicin

Resistance to	Initial phase		Continuation phase	
	Drugs	**Minimum duration (in months)**	**Drugs**	**Minimum duration (in months)**
Isoniazid (streptomycin, thioacetazone)	Rifampicin Aminoglycoside* Pyrazinamide Ethambutol	2–3 2–3 2–3 2–3	Rifampicin Ethambutol	6 6
Isoniazid and ethambutol (streptomycin)	Rifampicin Aminoglycoside* Pyrazinamide Ethionamide	3 3 3 3	Rifampicin Ethionamide$^{\varphi}$	6 6

*Streptomycin, if still active, if resistance to Streptomycin, use kanamycin or capreomycin
$^{\varphi}$If ethionamide is not available or poorly tolerated (even at a dose of 500 mg/day), use ofloxacin

Table 44: Acceptable "third-line" regimen for the treatment of multidrug-resistant tuberculosis (MDR-TB)

Resistance to	Initial phase		Continuation phase	
	Drugs	**Minimum duration (in months)**	**Drugs**	**Minimum duration (in months)**
Isoniazid, rifampicin and streptomycin	Aminoglycoside* Ethionamide Pyrazinamide Ofloxacin Ethambutol	3 3 3 3	Ethionamide Ofloxacin$^{\varphi}$ Ethambutol	18 18 18
Isoniazid, rifampicin, streptomycin and ethambutol	Aminoglycoside* Ethionamide Pyrazinamide Ofloxacin$^{\varphi}$ Cycloserine$^{\pi}$	3 3 3 3	Ethionamide Ofloxacin Cycloserine$^{\pi}$	18 18 18

*Kanamycin or amikacin or capreomycin
$^{\varphi}$The daily dose of 800 mg can be reduced to 400 mg if poorly tolerated
$^{\pi}$Para-aminosalicylic acid (PAS) if cycloserine is not available or too toxic

are likely to be fully sensitive, i.e. drugs not previously used for that patient.

Among these drugs, it is desirable to use in combination and injectable aminoglycoside and pyrazinamide. The treatment with these weaker regimens should be continued for at least 18 months after sputum conversion to prevent relapse. In any regimen chosen, especially when weaker drugs are used, the treatment should be given daily and should be directly observed. It is also mandatory to monitor bacteriological results (smear and culture) monthly from the second month until the 6th month, and then quarterly until the end of treatment.

Situation A: Susceptibility test results are not available before starting the new treatment (Table 42)

Situation B: Susceptibility test results are available (Table 43) Resistant to at Least Isoniazid and Rifampicin (Table 44)

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10 Integrated Management of Childhood Illness

INTRODUCTION

Integrated management of childhood illness (IMCI) is a systemic approach to children's health which focuses on the whole child. This means not only focusing on curative care but also on prevention of disease. The approach was developed by United Nation Children's Fund (UNICEF) and The World Health Organization (WHO) in 1992. It identifies and categorizes the major illness responsible for death of children under age of 5 years and what action to be taken.

RATIONALITY FOR EVIDENCE-BASED SYNDROMIC APPROACH TO CASE MANAGEMENT

Many simple low-cost and low-technology clinical interventions have saved millions of children worldwide. For example, widespread use of oral rehydration salt (ORS) in diarrhea, early detection of pneumonia by simple clinical signs and prompt use of low-cost appropriate antibiotic, prompt treatment of malaria, childhood vaccination, modest improvement of breastfeeding practices, etc. have reduced childhood death significantly. However, child health programs need to move beyond single disease in order to address overall health and wellbeing of the child. Many children have overlapping signs and symptoms of diseases, and the single diagnosis can be difficult and may not be feasible. This is especially true for the first-level health facilities where examinations involve few instruments, detail or no laboratory test and no X-ray.

Consequently, during mid-1990, WHO and UNICEF developed evidence-based syndromic approach to address child health and child disease in an integrated way. Although the major reason for developing the IMCI strategy stemmed from the needs of curative care, the strategy also addresses aspects of nutrition, immunization and other public health problems.

OBJECTIVES OF IMCI

- To reduce under-five years mortality
- To reduce severity and frequency of illness and disability
- To promote improved growth and development.

COMPONENTS OF IMCI

The strategy includes three main components:

1. Imploring case management skills of healthcare staff
2. Imploring overall health system
3. Imploring family and community health practice.

STEPS OF IMCI CASE MANAGEMENT

- Management of sick children using IMCI strategy is executed at outdoor of health center and in referral hospitals called facility-based IMCI.
- In the community as community-based IMCI.

Management strategy according to IMCI is executed under following headings:

1. Assess and classify the sick child aged 2 months up to 5 years:
   - Assessment of danger sign
   - Assessment of cough, breathing difficulty and wheeze in order to classify various types of pneumonia and severe disease
   - Assessment of diarrhea and dehydration in order to classify type of diarrhea and severity of dehydration
   - Assessment of febrile illness in order to classify severity of illness and probable cause of fever like malaria, measles
   - Assessment of ear problem in order to classify type of ear infection and mastoiditis
   - Assessment of nutritional status in order to classify various diseases of malnutrition
   - Assessment of pallor in order to identify degree of anemia.

   It also includes assessment of immunization status as whole, deworming status and detects necessary measures.
2. Assess, classify and treat the sick young infant aged 1 day up to 2 months:
   - Which include clinical assessment to assess for severe disease and local bacterial infection and to manage accordingly
   - To check for jaundice and to assess if severity and advise accordingly
   - Assessment of diarrhea and dehydration in order to classify severity of dehydration and manage accordingly
   - Assessment of feeding problem associated with very severe disease or very low weight and give management accordingly
   - To check the young infants' immunization status and take measures accordingly.
3. It also includes counseling of the mother about feed, feeding recommendation during sickness and health and advising mother when to return to health worker.
4. Counsel the mother about feeding problems.
5. Teach the mother to treat local infections at home.

The managements in tabulated forms are given in Appendices I to IV.

Appendix I: Assess and Classify the Sick Child Aged 2 Months up to 5 Years (Management of Acute Respiratory Infections)

Assess	Classify	Identify Treatment

Greet the mother/caregiver ask what the child's problems are
Determine if this is an initial or follow-up visit for this problem.

- If follow-up visit, use the follow-up instructions on "treat the child" chart
- If initial visit, assess the child as follows:

Check for general danger signs

Ask:	Look:
• Is the child able to drink or breastfeed? • Does the child vomit everything? • Has the child had convulsions?	• See if the child is lethargic or unconscious • Is the child convulsing now?

A child with any general danger sign needs "urgent" attention; complete the assessment and any pre-referral treatment immediately so referral is not delayed

Use all boxes that match the child's symptoms and problems to classify the illness

Then ask about main symptoms:
Does the child have cough or difficult breathing?

If yes, ask:
• For how long?

Look and listen:
• Count the breaths in 1 minute
• Look for chest indrawing
• Look and listen for stridor
• Look and listen for wheezing.

Child must be calm

***If wheezing and either fast breathing or chest indrawing:** Give a trial of rapid-acting inhaled bronchodilator for up to three times 20 minutes apart. Count the breaths and look for chest indrawing again, and then classify.

Classify Cough or Difficult Breathing

If the child is: / **Fast breathing is:**
2 months up to 12 months — 50 breaths per minute or more,
12 months up to 5 years — 40 breaths per minute or more

Fig. 1: Child with chest indrawing

Signs	Classify as	Identify treatment (urgent pre-referral treatments are in bold print)
• Any general danger sign or • Chest indrawing (Fig. 1) or • Stridor in calm child	Severe pneumonia or very severe disease	• Give first dose of an appropriate antibiotic • Treat the child to prevent low blood sugar • Refer "urgently" to hospital
• Fast breathing	Pneumonia	• **Give an appropriate antibiotic for 5 days** • If wheezing (even if it disappeared after rapidly-acting bronchodilator) give an inhaled bronchodilator for 5 days¨ • Soothe the throat and relieve the cough with a safe remedy • If coughing >3 weeks or if having recurrent wheezing, refer for assessment for tuberculosis (TB) or asthma • Advise mother when to return immediately • Follow-up in 2 days
• No signs of pneumonia or very severe disease	No pneumonia cough or cold	• If wheezing (even if it disappeared after rapidly acting bronchodilator) give an inhaled bronchodilator for 5 days** • Soothe the throat and relieve the cough with a safe remedy • If coughing >3 weeks or if having recurrent wheezing, refer for assessment for TB or asthma • Advise mother when to return immediately • Follow-up in 5 days if not improving

¨In setting where inhaled bronchodilator is not available, oral salbutamol may be the second choice.

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Appendix I: Continued Management of Diarrhea

Does the child have diarrhea?

If yes, ask:

- For how long?
- Is there blood in the stool?

Look and Feel:

- Look at the child's general condition: Is the child:
  - Lethargic or unconscious?
  - Restless and irritable?
- Look for sunken eyes
- Offer the child fluid. Is the child:
  - Not able to drink or drinking poorly?
  - Drinking eagerly, thirsty?
- Pinch the skin of the abdomen Does it go back:
  - Very slowly (longer than 2 seconds)?
  - Slowly?

Fig. 2: Skin pinch going back slowly in a severely dehydrated child

For dehydration	Two of the following signs: • Lethargic or unconscious • Sunken eyes • Not able to drink or drinking poorly • Skin pinch goes back very slowly (Fig. 2)	Severe dehydration	• If child has no other severe classification: o Give fluid for severe dehydration (Plan C) or • If child also has another severe classification: o Refer "urgently" to hospital with mother giving frequent sips of ORS on the way. Advise the mother to continue breastfeeding • If child is 2 years or older and there is cholera in patient's area, give antibiotic for cholera
Classify diarrhea	Two of the following signs: • Restless, irritable • Sunken eyes • Drinks eagerly, thirsty • Skin pinch goes back slowly	Some dehydration	• Give fluid, zinc supplementation, and food for some dehydration (Plan B) • If child also has a severe classification: o Refer urgently to hospital with mother giving frequent sips of ORS on the way. Advise the mother to continue breastfeeding • Advise mother when to return immediately • Follow-up in 5 days if not improving
	Not enough signs to classify as some or severe dehydration	No dehydration	• Give fluid, zinc supplementation, and food to treat diarrhea at home (Plan A) • Advise mother when to return immediately • Follow-up in 5 days if not improving
And if diarrhea for 14 days or more	• Dehydration present	Severe persistent diarrhea	• Treat dehydration before referral unless the child has another severe classification • Refer to hospital
	No dehydration	Persistent diarrhea	• Advise the mother on feeding a child who has "persistent diarrhea" • Give vitamin A, multivitamins and minerals (including zinc) for 10 days • Follow-up in 5 days
And if blood in stool	• Blood in stool	Dysentery	• Treat for 5 days with an oral antibiotic recommended for Shigella (Ciprofloxacin or Pivmecillinam) • Follow-up in 2 days

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Appendix I: Continued (Management of Febrile Illness including Measles and Malaria)

Does the child have fever?
[by history or feels hot or temperature 99.5°F (37.5°C) or above]

If yes: Decide malaria risk: high or low If "low" risk:, ask: • Have you traveled outside the area? • If yes, have you been in a high malaria risk area in the last 30 days? **Then ask:** • For how long? • If >7 days, has fever been present every day? • Has child had measles within the last 3 months?	• **Look and feel** • Look or feel for stiff neck • Look for runny nose Look for signs of measles • Generalized rash and • One of these: cough, runny nose, or red eyes	**High malaria risk** **Classify fever**
If the child has measles now or within the last 3 months:	• Look for mouth ulcers • Are they deep and extensive? • Look for pus draining from the eye • Look for clouding of the **cornea**	**Low malaria risk**

If measles now or within last 3 months, classify

• Any general danger sign or • Clouding of cornea or • Deep or extensive mouth ulcers	Severe complicated measles***	• Give vitamin A • Give first dose of an appropriate antibiotic • If clouding of the cornea or pus draining from the eye, apply tetracycline eye ointment • Refer "urgently" to hospital
• Pus draining from the eye or • Mouth ulcers	Measles with eye or mouth complications***	• Give vitamin A • If pus draining from the eye, treat eye infection with tetracycline eye ointment • If mouth ulcers, treat with gentian violet • Follow-up in 2 days
• Measles now or within	Measles	• Give vitamin A

High Malaria Risk

• Any general danger sign or • Stiff neck	Very severe febrile disease	• Give quinine for severe malaria (first dose) after an RDT/BSE • Give first dose of an appropriate antibiotic • Treat the child to prevent low blood sugar • Give one dose of paracetamol in clinic for high fever (38.5°C/101.5°F or above) • Refer urgently to hospital
• Fever (by history or feels hot or temperature 99.5°F or above)	**Malaria**	• **Give oral antimalarial (ACT or other recommended antimalarial after an RDT/BSE)** • **Give one dose of paracetamol in clinic for high fever (38.5°C/101.5°F or above)** • Advise mother when to return immediately • Follow-up in 2 days if fever persists • If fever is present every day for >7 days, refer for assessment

Low Malaria Risk

• Any general danger sign or • Stiff neck	Very severe febrile disease	• Give quinine for severe malaria (first dose) after an RDT/BSE • Give first dose of an appropriate antibiotic • Treat the child to prevent low blood sugar • Give one dose of paracetamol in clinic for high fever (38.5°C/101.5°F or above) • Refer "urgently" to hospital
• No runny nose and • No measles and • No other cause of fever**	**Malaria**	• **Give oral antimalarial (Chloroquine) and make a smear for BSE** • **Give one dose of paracetamol in clinic for high fever (38.5°C/101.5°F or above)** • Advise mother when to return immediately • Follow-up in 2 days if fever persists • If fever is present every day for >7 days, refer for assessment
• Runny nose present or • Measles present or • Other cause of fever present	**Fever-malaria unlikely**	• **Give one dose of paracetamol in clinic for high fever (38.5°C/101.5°F or above)** • Advise mother when to return immediately • Follow-up in 2 days if fever persists • If fever is present every day for >7 days, refer for assessment

*These temperatures are based on axillary temperature.
**Other causes of fever: Diarrhea, dysentery, respiratory infections, ear infection, abscess, cellulitis, etc.
***Other important complications of measles: pneumonia, stridor, diarrhea, ear infection and malnutrition are classified in other tables.

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Appendix I: Continued (Management of Ear Problem)

Does the child have an ear problem?

If yes, ask:	Look and feel	Classify ear problem
• Is there ear pain? • Is there ear discharge? • If yes, for how long?	• Look for pus draining from the ear • Feel for tender swelling behind the ear	

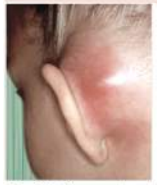


Fig. 3: Inflammed postauricular swelling in mastoiditis

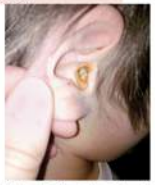


Fig. 4: Purulent discharge in ear infection

• Tender swelling behind the ear	**Mastoiditis (Fig. 3)**	**• Give first dose of an appropriate antibiotic • Give first dose of paracetamol for pain • Refer urgently to hospital**
• Ear pain or • Pus is seen draining from the ear and discharge is reported for less than 14 days	Acute ear infection (Fig. 4)	• Give an antibiotic for 5 days • Give paracetamol for pain • Dry the ear by wicking • Follow-up in 5 days
• Pus is seen draining from the ear and discharge is reported for 14 days or more	Chronic ear infection	• Dry the ear by wicking. • Treat with topical quinolone ear drops for 14 days • Follow-up in 5 days
• No ear pain and • No pus seen draining from the ear	No ear infection	• Assure the mother/caregiver, no additional treatment

Then Check for Malnutrition and Anemia

Check for malnutrition

Look and feel:	Classify
• Look for visible severe wasting • Look for edema of both feet • Determine weight for age	**Nutritional status**

Fig. 5: Pedal edema

Fig. 6: Very low weight for age with wasting

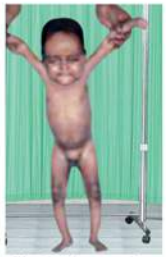
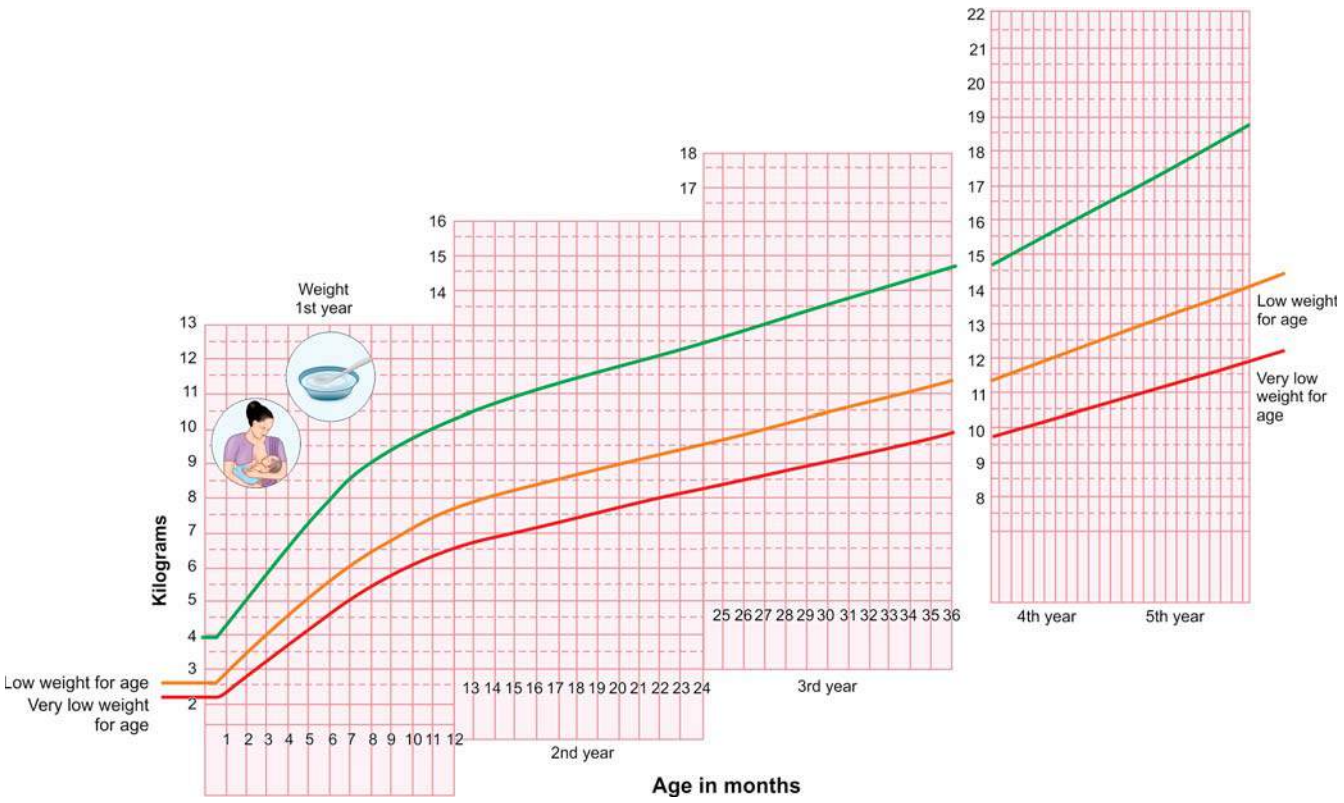


Fig. 7: Not very low weight for age

• Visible severe wasting or • Edema of both feet (Fig. 5)	Severe malnutrition	• Give first dose of an appropriate antibiotic • Give vitamin A • Treat the child to prevent low blood sugar • Keep the child warm • Refer "urgently" to hospital
• Very low weight for age (Fig. 6)	Very Low weight (see weight for age chart)	• Assess the child's feeding, and counsel the mother on feeding according to the feeding recommendations. ° If feeding problem, follow-up in 5 days • Advise mother when to return immediately • If very low weight for age, follow-up in 30 days
• Not very low weight for age and no sign of severe acute malnutrition. (Fig. 7)	Not very low weight	• If child is <2 years old, assess the child's feeding and counsel the mother on feeding according to the feeding recommendations • If feeding problem, follow-up in 5 days • Advise mother when to return immediately

Weight-for-age Chart to Identify Low Weight and Very Low Weight Children



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Check for Anemia

Look:
- Look for palmar pallor. Is it:
  - Severe palmar pallor?
  - Some palmar pallor?

Classify anemia

Fig. 8: Showing some pallor with control

Fig. 9: Showing severe pallor

• Severe palmar pallor (Fig. 9)	Severe anemia	• Refer "urgently" to hospital
• Some palmar pallor (Fig. 8)	Anemia	• Give iron or multiple micronutrient Give albendazole if child is 1 year or older and has not had a dose in the previous 6 months • Advise mother when to return immediately • Follow-up in 14 days
• No palmar pallor	No anemia	• Counsel the mother about feeding

Then Check the Child's Immunization, Vitamin A Supplementation and Deworming Status and Take Necessary Measures

Immunization schedule: Follow national guidelines

Age	Vaccine
Birth	BCG
6 weeks	Penta 1 + OPV-1
10 weeks	Penta 2 + OPV-2
14 weeks	Penta 3 + OPV-3
9 months	Measles + Vitamin A capsule (100,000 IU) + OPV-4

Vitamin A supplementation
Give every child a dose of vitamin A every 6 months from the age of 9 months. Record the dose on the child's card

Deworming
Give every child albendazole every 6 months from the age of 1 year. Record the dose on the child's card

Prophylactic MMN/MNP (Multivitamin micronutrient/iron/folic acid)
Give 1 sachet of MMN or 20 mg elemental iron + 100 µg folic acid (one tablet of Pediatric IFA or 5 mL of IFA syrup or 1 mL of IFA drops) for a total of 100 days in a year after the child has recovered from acute illness if:
- The child is of 6 months of age or older, and
- Has not received pediatric IFA tablet/syrup/drops for 100 days in last year

Assess Other Problems and Refer If Needed

Make sure child with any general danger sign is referred after first dose of an appropriate antibiotic and other urgent treatments. Exception: Rehydration of the child according to Plan C may resolve danger signs so that referral is no longer needed.

Appendix II: Assess, Classify and Treat the Sick Young Infant Aged 1 day upto 2 Months		
Assess	**Classify**	**Identify Treatment**
• Greet the mother/caregiver • Ask the mother what the young infant's problems are – Determine if this is an initial or follow-up visit for this problem: – If follow-up visit, use the follow-up instructions on the bottom of this chart – If initial visit, assess the young infant as follows:	**Use all boxes that match infant's symptoms and problems to classify the illness.**	

Check for Very Severe Disease and Local Bacterial Infection

Ask:
Is the infant having difficulty in feeding?

Has the infant had convulsions?

Look, listen, feel:
Convulsion now
- Count the breaths in 1 minute
- Repeat the count if elevated
- Look for severe chest indrawing
- Look and listen for grunting
- Measure temperature (or feel for fever or low body temperature)

Young infant must be calm

- Look at the umbilicus. Is it red or draining pus?
- Look for skin pustules
- Look at the young infant's movements. If infant is sleeping, ask the mother to wake him/her
  - Does the infant move on his/her own? If the infant is not moving, gently stimulate him/her
  - Does the infant move only when stimulated but then stops?
  - Does the infant not move at all?

Classify all young infants

Fig. 10: Neonatal seizure

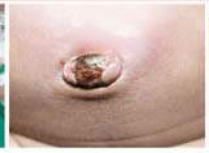

Fig. 11: Umbilical nedness due to umbilical sepsis

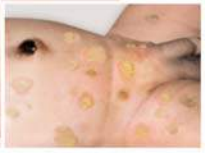

Fig. 12: Showing skin pustules

Signs	Classify as	Identify treatment (Urgent pre-referral treatments are in bold print)
• Fever (37.5°C* or above or feels hot) or low body temperature (<35.5°C* or feels cold) or • Convulsions or (Fig. 10) • Bulging fontanel or pus draining from ear or • Umbilical redness extending to the skin (Fig. 11) or • Many or severe skin pustules (Fig. 12) or • Not feeding well or • Fast breathing (60 breaths per minute or more) or • Severe chest indrawing or • Grunting or • Movement only when stimulated or no movement at all	Possible serious bacterial infection or Very severe disease	• Give first dose of intramuscular antibiotics • Give IM phenobarbitone, if convulsing • Treat the young infant to prevent low blood sugar • Advise mother how to keep the infant warm on the way to the hospital • Refer "urgently" to hospital**
• Umbilicus red or draining pus or • Skin pustules	Local umbilical/ skin infection	• Give an appropriate oral antibiotic • Teach mother to treat local skin infection at home • Follow-up in 2 days
• None of the signs of very severe disease or local infection in a sick child	Severe disease or no local infection	• Advise mother to give home care look for jaundice, diarrhea or other illness and manage accordingly

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Then Check for Jaundice

If jaundice ask:	Look:	Classify jaundice		
• When did jaundice first appear?	• Look for jaundice (yellow eyes or skin) • Look at the young infant's palms and soles. Are they yellow?	• Any jaundice if age less than 24 hours (Fig. 13) or • Yellow palms and soles at any age	Severe jaundice	• Treat the young infant to prevent low blood sugar • Advise mother how to keep the infant warm on the way to the hospital • Refer urgently to hospital
		• Jaundice appearing after 24 hours of age or • Palms and soles not yellow	Jaundice	• Advise the mother to give home care for the young infant • Advise mother lo return immediately if palms and soles appear yellow • If the young infant is older than 3 weeks, refer to a hospital for assessment • Follow-up in 2 days
		• No jaundice	No jaundice	• Advise the mother to give home care for the young infant

Fig. 13: Infant with jaundice

Then Ask:
Does the young infant have diarrhea?*

If yes, look and feel:	Classify diarrhea	For dehydration		
• Look at the young infant's general condition: – Infant's movements: - Does the infant move on his/her own? - Does the infant move only when stimulated but then stops? - Does the infant not move at all? - Is the infant restless and irritable? • Look for sunken eyes • Pinch the skin of the abdomen: – Does it go back: Very slowly (longer than 2 seconds)? – Or slowly?		Two of the following signs: • Movement only when stimulated or no movement at all • Sunken eyes • Skin pinch goes back very slowly.	Severe dehydration	• If infant does not have "very severe disease": → Give fluid for severe dehydration (Plan C) or • If infant also has very severe disease: Refer urgently to hospital with mother giving frequent sips of ORS on the way and advise mother how to keep the infant warm on the way to the hospital • Advise mother to continue breastfeeding
		Two of the following signs: • Restless, irritable • Sunken eyes • Skin pinch goes back slowly	Some dehydration	• Give fluid for some dehydration (Plan B) • If infant also has very severe disease: refer urgently to hospital with mother giving frequent sips of ORS on the way and advise mother how to keep the infant warm on the way to the hospital • Advise mother to continue breastfeeding • Follow-up in 2 days if not improving
		• No enough signs to classify as some or severe dehydration	No dehydration	• Give fluids to treat diarrhea at home (Plan A)
		• Diarrhea lasting 14 days or more	Severe persistent diarrhea	• If the young infant is dehydrated, treat dehydration before referral unless the infant has also possible serious bacterial infection • Refer to hospital
		• Blood in the stool	Dysentery	• Treat for 5 days with an oral antibiotic recommended for Shigella in your area • Follow-up in 2 days

***What is diarrhea in a young infant?**
A young infant has diarrhea if the stools have changed from usual pattern and are many and watery (more water than fecal matter).
The normally frequent or semi-solid stools of a breastfed baby are not diarrhea.

**If infant also has very severe disease, refer urgently to hospital with mother giving frequent sips of ORS on the way and advise mother how to keep the infant warm on the way to the hospital.

***If diarrhea with or without dehydration is associated with convulsion, unconsciousness, fever, grunting, fast breathing or severe chest indrawing, it will be considered as very severe disease and managed accordingly.

Contd...

Contd...

Then Check for Feeding Problem or Low Weight

Ask:
- Is the infant breastfed? If yes, how many times in 24 hours?
- Does the infant usually receive any other food or drink? If yes, how often?
- What do you use to feed the infant?

Look and feel:
- Determine weight for age
- Thrush (ulcers or white patches in mouth)

If an infant:
- Has any difficulty in feeding
- Is breastfeeding <8 times in 24 hours
- Is taking any other foods or drinks
- Is low weight for age
- Has no indications to refer urgently to hospital

Assess breastfeeding:
- Has the infant breastfed in the previous hour?
  - If the infant has not fed in the previous hour, ask the mother to put her infant to the breast. Observe the breastfeed for 4 minutes
  - If the infant was fed during the last hour, ask the mother if she can wait and tell you when the infant is willing to feed again

1. Is the infant well-positioned?

To check positioning, look for:
- Straight head and body. Yes__ No__
- Body close to the mother. Yes__ No__
- The whole body fully supported. Yes__ No__
- Facing breast, nose opposite to nipple. Yes__ No__

2. Is the infant able to attach?

No attachment at all | Not well attached | Good attachment

To check attachment, look for:
- Chin touching breast Yes__ No__
- Mouth wide open Yes__ No__
- Lower lip turned outward Yes__ No__
- More areola above than below the mouth Yes__ No__

(All of these signs should be present if the attachment is good)

3. Is the infant sucking effectively?

Slow deep sucks, sometimes pausing

Not suckling at all | Not suckling effectively | Suckling effectively

Clear a blocked nose if it interferes with breastfeeding

1. Look for ulcers or white patches in the mouth (thrush)
2. Does the mother have pain while breastfeeding? If yes, look and feel for:
   - Flat or inverted nipples, or sore nipples
   - Engorged breasts or breast abscess

Classify feeding

• Not able to feed • No attachment at all • Not sucking at all	Very severe disease or very low weight	• Give first dose of intramuscular antibiotics • Treat the young infant to prevent low blood sugar • Advise the mother how to keep the young infant warm on the way to the hospital • Refer urgently to hospital
• Not well-positioned or attached to breast (Fig. 14) or • Not suckling effectively or • <8 breastfeeds in 24 hours or • Receives other foods or drinks or • Feeding bottle is used or • Low weight for age or • Breast or nipple problems (breast involvement, flat nipple, crack nipple) or • Thrush (ulcers or white patches in mouth) (Fig. 17)	Feeding problem or low weight	• If not well-attached or not suckling effectively, teach correct positioning and attachment (Fig. 15) • If not able to attach well immediately, teach the mother to express breast milk and feed by a cup • If breastfeeding <8 times in 24 hours, advise to increase frequency of feeding. Advise her to breastfeed as often and for as long as the infant wants, day and night • If receiving other foods or drinks, counsel mother about breastfeeding more, reducing other foods or drinks, and using a cup: If not breastfeeding at all: ° Refer for breastfeeding counseling and possible relactation ° Advise about correctly preparing breast milk substitutes and using a cup • If low weight for age, advise the mother how to feed and keep the low weight infant warm at home • If thrush, teach the mother to treat thrush at home • If breast problem like breast involvement or nipple problem, teach the mother to treat breast or nipple problems accordingly (Fig. 16) • Advise mother to give home care for the young infant • Follow-up any feeding problem or thrush in 2 days. Follow-up low weight for age in 14 days
• Not low weight for age and no other signs of inadequate feeding	No feeding problem	• Advise mother to give home care for the young infant • Praise the mother for feeding the infant well

Contd...

Well-positioned	Not Well-positioned	Breast abscess			
		Correct	Incorrect		

Fig. 14: Positioning during breastfeeding

Fig. 15: Attachment during breastfeeding

Fig. 17: Oral thrush. White flaky plaques on the tongue and oral mucosa

Fig. 16: Process of hand expression of expressing milk in breast engorgement

Then check the young infant's immunization status			
Immunization schedule	**Age**	**Vaccine**	
	Birth	BCG	OPV-0
	6 weeks	Penta 1 (DPT-1+Hep B1+HIB1)	OPV-1
• Check the mother's tetanus toxoid (TT) status and giver her TT, if needed • Check the mother's vitamin A status and give her vitamin A, if needed			
Assess other problems			

Appendix III: Counsel the Mother

Feeding the Child

- Assess the child's feeding: Assess feeding in every child below 2 years of age and in children with very low weight or anemia
  Ask questions about the child's usual feeding and feeding during this illness. Compare the mother's answers to the feeding recommendations for the child's age in the box below.
- **Ask:**
  - Do you breastfeed your child?
    - How many times during the day?
    - Do you also breastfeed during the night?
  - Does the child take any other food or fluids?
    - What food or fluids?
    - How many times per day?
    - What do you use to feed the child?
    - If very low weight for age: How large are servings? Does the child receive his own serving? Who feeds the child and how?
  - During this illness, has the child's feeding changed? If yes, how?
  - How do you play with your child?
  - How do you communicate with your child?

Feeding recommendations during sickness

First 6 months of age	*After 6 months up to 12 months*	*12 months up to 2 years*	*2 years and older*
• Breastfeed as often as the child wants, day and night, at least 8 times in 24 hours (Fig. 18) • Do not give other foods or fluids. Not even water	• Breastfeed as often as the child wants • After breastfeeding, give adequate servings of rice with dal, halwa, khichuri, egg, fish, green leafy vegetables, and yellow fruits such as papaya, mango, banana and jackfruit* • Three times per day if breastfed • Five times per day if not breastfed	• Breastfeed as often as the child wants • Before breastfeeding, give adequate servings of rice with dal, halwa, khichuri, egg, fish, green leafy vegetables, and yellow fruits such as papaya, mango, banana and jackfruit; or give family foods five times per day	Give family foods at least three meals each day. Also, twice daily, give nutritious food between meals, such as puffed rice with oil, roti, biscuit, ripe papaya, ripe banana, ripe mango, jackfruit

Fig. 18: Breastfeeding the child

Fig. 19: Foods recommended during sickness of child

*A good quality food should be adequate in quantity and include an energy-rich food (for example, thick cereal with added oil); meat, fish, eggs or pulses; and fruits and vegetables (Fig. 19)

Feeding recommendations for a child who has persistent diarrhea

- If still breastfeeding, give more frequent, longer breastfeeds, day and night
- If taking other milk:
  - Replace with increased breastfeeding or
  - Replace half the milk with nutrient-rich semisolid food
- For other foods, follow feeding recommendations for the child's age

Advise the mother to increase fluid during illness

For any sick child:

- If child is breastfed, breastfeed more frequently and for longer at each feed. If child is taking breast milk substitutes, increase the amount of milk given
- Increase other fluid. For example, give rice water, chira pani, dub water, yogurt drink or clean water

For child with diarrhea:

- Giving extra fluid can be lifesaving. Give fluid according to Plan A or Plan B on "treat the child" chart (Appendices V and VI)

Contd...

When to Return

Advise the mother when to return to health worker (Fig. 20)

Follow-up Visit
Advise the mother to come for follow-up at the earliest time listed for the child's problems.

If the child has:	Return for follow-up in
Pneumonia Dysentery Malaria, if fever persists Fever-malaria unlikely, if fever persists Measles, if measles now	2 days
Persistent diarrhea Acute ear infection Chronic ear infection Feeding problem Any other illness, if not improving	5 days
Anemia	14 days
Very low weight for age	30 days

Well-child visit
Advise mother when to return for next immunization according to immunization schedule.

Fig. 20: Showing a mother taking her sick child to community clinic

When to return immediately	
Advise mother to retun immediately if the child has any of these signs	
Any sick child	Not able to drink or breastfeed Becomes sicker Develops fever
If child has no pneumonia: cough or cold, also return if:	Fast breathing Difficult breathing
If child has diarrhea, also return if:	Blood in stool Drinking poorly

Counsel the mother about feeding problems
If the child is not being fed as described in the above recommendations, counsel the mother accordingly. In addition:

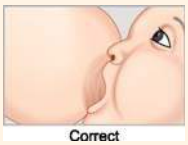


Fig. 21: Child taking food from cup

Fig. 22: Child taking food from bowl

- If the mother reports difficulty with breastfeeding, assess breastfeeding (see young infant chart)
  As needed, show the mother correct positioning and attachment for breastfeeding (Fig. 15)
- If the child is <6 months old and is taking other milk or foods:
  - Build mother's confidence that she can produce all the breast milk that the child needs
  - Suggest giving more frequent, longer breastfeeds day or night, and gradually reducing other milk or foods
- If other milk needs to be continued, counsel the mother to:
  - Breastfeed as much as possible, including at night
  - Make sure that other milk is a locally appropriate breast milk substitute
  - Make sure other milk is correctly and hygienically prepared and given in adequate amounts
  - Finish prepared milk within an hour
- If the mother is using a bottle to feed the child:
  - Recommend substituting a cup for bottle
  - Show the mother how to feed the child with a cup (Fig. 21)
- If the child is not being fed actively, counsel the mother to:
  - Sit with the child and encourage eating
  - Give the child an adequate serving in a separate plate or bowl (Fig. 22)

- If the child is not feeding well during illness, counsel the mother to:
  - Breastfeed more frequently and for longer if possible
  - Use soft, varied, appetizing, favorite foods to encourage the child to eat as much as possible, and offer frequent small feeds
  - Clear a blocked nose if it interferes with feeding
  - Expect that appetite will improve as child gets better
- If the child has poor appetite:
  - Plan small, frequent meals
  - Clear a blocked nose
  - Check regularly
- If the child has sore mouth or ulcers: Give soft foods that will not burn the mouth, such as, eggs, mashed potatoes, banana, papaya, mango, etc.
- Follow-up if any feeding problem in 5 days

Counsel the mother about her own health

- If the mother is sick, provide care for her, or refer her for help
- If she has a breast problem (such as engorgement, sore nipples, breast infection), provide care for her or refer her for help
- Advise her to eat well to keep up her own strength and health
- Check the mother's immunization status and give her tetanus toxoid, if needed
- Check the mother's vitamin A status and give her vitamin A, if needed
- Make sure she has access to:
  - Family planning
  - Counseling on STD and AIDS prevention

Abbreviations: STD, sexually transmitted diseases; AIDS, acquired immunodeficiency syndrome.

Appendix IV: Teach the mother to treat local infections at home

- Explain to the other what the treatment is and why it should be given
- Describe the treatment steps listed in the appropriate box
- Watch the mother as she does the first treatment in the clinic (except remedy for cough or sore throat)
- Tell her how often to do the treatment at home
- If needed for treatment at home, give mother the tube of tetracycline ointment or a small bottle of gentian violet
- Check the mother's understanding before she leaves the clinic

Dry the ear by wicking

- Dry the ear at least three times daily:
  - Roll clean absorbent cloth into a wick
  - Place the wick in the child's ear
  - Remove the wick when wet
  - Replace the wick with a clean one and repeat these steps until the ear is dry

Treat eye infection with tetracycline eye ointment

- Clean both eyes three times daily:
- Wash hands
- Ask child to close the eye
- Use clean cloth and water to gently wipe away pus
- Then apply tetracycline eye treatment in both eyes three times daily:
- Ask the child to look up
- Squirt a small amount of ointment on the inside of the lower lid
- Wash hands again
- Treat until redress is gone
- Do not use other eye ointments or drops, or put anything else in the eye

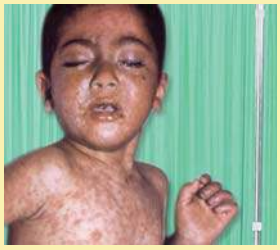
Treat mouth ulcers with gentian violet

- Treat the mouth ulcers twice daily:
  - Wash hands
  - Wash the child's mouth with wet clean soft cloth wrapped around the finger
  - Paint the mouth with half-strength gentian violet
  - Wash hands again

Soothe the throat, relieve the cough with a safe remedy

- Safe remedies to recommend:
  - Breast milk for exclusively breastfed infant
  - Warm water
  - Tulsi *(Ocimum tenuiflorum)* leaf juice
  - Lemon juice
- Harmful remakes to discourage:
  - Medicines containing codeine, antihistaminics, and alcohol

Appendix V: Summary of Urgent Pre-referral Treatments for the Sick Child from Age 2 months up to 5 years

Classification	Treatment
Manage treatable danger sign	For all children before referral: Prevent low blood sugar by giving breast milk or sugar water. Keep the baby warm
Convulsion	If the child is convulsing (Fig. 23), give diazepam (10 mg/2 mL solution) in dose 0.1 mL/kg rectally; if convulsions continue after 10 minutes, give a second dose of diazepam rectally  **Fig. 23:** Convulsing child
Severe pneumonia or very severe disease	Give first dose of an appropriate antibiotic. Recommended choices are cotrimoxazole (5 mg of trimethoprim/kg)* or amoxicillin (50 mg/kg). If the child cannot take an oral antibiotic (children in shock or those who vomit everything or are unconscious), give the first dose of intramuscular ampicillin (100 mg/kg). Other options for an intramuscular antibiotic for pre-referral use include amoxicillin (50 mg/kg) or Inj. ceftriaxone (50 mg/kg). Inj. chloramphenicol
Very severe febrile disease	Give one dose of paracetamol (15 mg/kg) for high fever (101.3°F or above) Give first dose of intramuscular quinine (20 mg/kg) for severe malaria (high malaria risk) Give first dose of an appropriate antibiotic
Severe complicated measles (Fig. 24)	Give vitamin A (for children from 9 months to12 months 1 lac unit and >1 year 2 lac unit If there is clouding of the cornea or pus draining from the eye, apply tetracycline eye ointment and pad bandage Give first dose of appropriate antibiotic  **Fig. 24:** Complicated measles
Severe dehydration	WHO treatment Plan C If there is no other severe classification, IV fluids should be given in the outpatient clinic according to WHO treatment Plan C Give 100 mL/kg IV fluids, cholera saline/Ringer's lactate solution is preferred. Normal saline can also be given in absence of above infusion If IV infusion is not possible, urgent referral to the hospital for IV treatment is recommended When referral takes >30 minutes, fluids should be given by nasogastric tube. If none of these are possible and the child can drink, ORS solution must be given by mouth Note: In areas where cholera cannot be excluded for patients >2 years old with severe dehydration, antibiotics are recommended. Two recommended choices are tetracycline and erythromycin Full strength ORS containing high NaCl (previous conventional ORS) Rather current hypoosmolar ORS is preferable as inappropriately more sodium and chloride are lost in diarrheal stool of cholera
Severe persistent diarrhea (persistent diarrhea with dehydration)	If there is no other severe classification, treat dehydration before referral using WHO treatment Plan B for some dehydration and Plan C for severe dehydration. Then refer to hospital
Mastoiditis	Give first dose of an appropriate antibiotic. Two recommended choices are co-trimoxazole* and amoxicillin. If the child cannot take an oral antibiotic (children in shock or those who vomit everything or who are unconscious), give the first dose of intramuscular ampicillin (100 mg/kg). Another option for an intramuscular antibiotic for pre-referral use include benzyl-penicillin or ceftriaxone Give first dose of paracetamol for pain
Severe malnutrition	Give first dose of vitamin A, as mentioned above. Manage the child in CMAM if SAM is without complication. If with complication or infant <6 months give first dose of antibiotic and refer to facility-based management for inpatient care of SAM

*Cotrimoxazole containing trimethoprim has shown growing resistance to common bacterial pathogens.
Abbreviations: CMAM, community management of acute malnutrition; SAM, severe malnutrition.

Appendix VI: Treatment of a Sick Child Aged 2 Months up to 5 Years in the Outpatient Health Facility

<table>
<tr><th>Classification</th><th>Treatment</th></tr>
<tr><td>Pneumonia</td><td>
• Give an appropriate antibiotic for 5 days
• The choice of antibiotic is based on the fact that most childhood pneumonia of bacterial origin is due to Streptococcus pneumoniae or Haemophilus influenzae. Non-severe cases of pneumonia can be treated with either oral amoxicillin or cotrimoxazole* for 5 days. These two oral antibiotics are usually effective against these two bacteria, both are relatively inexpensive, widely available, and are on the essential drug list of most countries. Other antibiotics like cephalosporins (cephalexin, cefixime), etc. Macrolides (erythromycin, azithromycin, clarithromycin) are also effective. However, they are expensive and probability of drug resistance in the community is high. Therefore not advised by WHO in the community management of pneumonia in developing countries
• If wheezing, give inhaled/nebulized bronchodilator for 5 days. If inhaled bronchodilator is not available, oral salbutamol may be given
• Soothe the throat and relieve the cough with a safe remedy (raw lemon tea, soup, lemon juice, honey, etc.)
• If coughing >3 weeks or if having recurrent wheeze refer for assessment for TB or asthma
• Advise mother when to return immediately
• Follow-up in 2 days
</td></tr>
<tr><td>No pneumonia cough or cold</td><td>
• Soothe the throat and relieve the cough with a safe remedy (raw lemon tea, soup, lemon juice, honey, etc.)
• If wheezing, give inhaled/nebulized bronchodilator for 5 days. If inhaled bronchodilator is not available, oral salbutamol may be given
• Advise mother when to return immediately
• If coughing >3 weeks or if having recurrent wheeze refer for assessment for TB or asthma
• Follow-up in 5 day if not improving
</td></tr>
<tr><td>Severe dehydration

Some dehydration</td><td>
WHO Treatment Plan C
Start IV fluid immediately. If the child can drink, give ORS by mouth till the drip is ready. Give 100 mL/kg of cholera saline or Ringer's lactate solution (or, if not available, normal saline), divided as follows:
<table>
<tr><th>Age</th><th>First give 30 mL/kg in:</th><th>Then give 70 mL/kg in:</th></tr>
<tr><td>Infants (under 12 months)</td><td>1 hour</td><td>5 hours</td></tr>
<tr><td>Children (12 months up to 5 years)</td><td>30 minutes</td><td>2½ hours</td></tr>
</table>
• Repeat once if radial pulse is still very weak or not detectable
• Reassess the child every 1–2 hours. If hydration status is not improving, give the IV drip more rapidly
• Also give ORS (about 5 mL/kg/hour) as soon as the child can drink
• Usually after 3–4 hours (infant) or 1–2 hours (children)
• Reassess an infant after 6 hours and a child after 3 hours. Classify dehydration. Then choose the appropriate plan (A, B or C) to continue treatment
Note: If possible, observe the child at least 6 hours after rehydration to be sure the mother can maintain hydration giving the child ORS solution by mouth
WHO Treatment Plan B
Give initial treatment with ORS over a period of 4 hours. The approximate amount of ORS required is 75 mL/kg; during these 4 hours, the mother slowly gives the recommended amount of ORS by spoonful or sips.
Note:
• Advise the mother to continue breastfeeding, if breastfeed
• If the child vomits, wait for 10 minutes and then give more slowly
• If the child wants more, give more ORS solution
• After 4 hours, the child is reassessed and reclassified for dehydration and feeding should begin. When there are no signs of dehydration, the child is put on Plan A. If there is still some dehydration, Plan B should be repeated. If the child now has severe dehydration, the child should be put on Plan C
• Advise mother when to return immediately
• Follow-up in 5 days if not improving
</td></tr>
<tr><td>No dehydration
 
Fig. 25: Homemade oral rehydration salt (ORS)</td><td>
WHO Treatment Plan A
Plan A focuses on the four rules of home treatment: Give extra fluids, continue feeding, and advise the caregiver when to return (if there is blood in the stool, the child drinks poorly, becomes sicker or is not getting better in 2 days)
Fluids should be given as soon as diarrhea starts; the child should take fluids as much as he/she wants. Correct home therapy can prevent dehydration in many cases. ORS may be used at home to prevent dehydration (Fig. 25). Teach mother how to prepare homemade ORS. Teach to prepare saline drink from salt and molasses/sugar at 3 pinch finger table salt and 1 fist molasses/sugar in ½ L of drinking water
Oral fluids which can be given during diarrhea are:
• Plain water
• Water in which a cereal has been cooked (e.g. unsalted rice water) including cooked rice water (Bhater Mar)
• Unsalted soup
• Yogurt drinks without salt
• Green coconut (contains potassium) water
• Weak tea (unsweetened)
• Unsweetened fresh fruit juice
• Chira-pani
However, they do not contain salt. A two finger pinch salt may be added in this fluid if the child likes. Other fluids that are commonly available in the home which are less costly, more convenient and effective can be offered when given with food. Oral fluids not suitable for drinks in diarrhea are:
• A few fluids are potentially dangerous and should be avoided during diarrhea. Especially important are drinks sweetened with sugar, which can cause osmotic diarrhea and hyponatremia, e.g. soft drinks, sweetened fruit drinks, sweetened tea
</td></tr>
</table>

Contd...

Classification	Treatment
	• Other fluids to be avoided are those with stimulant, diuretic or purgative effects, e.g. coffee, medicinal tea • Feeding: Encourage mother to continue breastfeeding and family food according to age
Persistent diarrhea	• Encourage the mother to continue breastfeeding, if they are breastfeed. If they are given artificial milk, it is better to avoid and to offer non-milk easily digestible diet. Dietary management remains the principal therapy on the management of persistent diarrhea (PD) along with treatment of systemic infections. Lactose intolerance and cow's milk protein enteropathy can be managed with cereal-based diet. Nutrient absorption is substantially reduced in PD and rice-based (complex carbohydrate instead of monosaccharide or disaccharide) has been effective in studies. Rice suji (prepared from rice powder, egg albumin, soya oil, glucose, salt and mineral mixed), a local and simple cereal-based lactose-free inexpensive diet has been found to be a successful therapeutic diet for management of PD. Difficult cases may need smashed green banana recipe, soya-based diet or hypoallergic diet like comminuted chicken soup or semi-elemental diet like "pregestimil" • All children with persistent diarrhea should receive supplementary multivitamins and minerals (iron, magnesium, zinc) each day for 2 weeks • (Dose for zinc: 2 mg elemental zinc/kg/day) • Diarrhea with dehydration in PD called severe persistent diarrhea is managed with current hypo-osmolar ORS instead of previous conventional ORS containing high salt and high osmolality. This is because most persistent diarrhea are associated with severe malnutrition with salt retention and low potassium
Dysentery	The four key elements of dysentery treatment are: 1. Antibiotics 2. Fluids 3. Feeding 4. Zinc In feeding boiled green banana has been found very effective feeding regimen in the management of Shigella dysentery. Oral zinc used in acute watery diarrhea is also found useful in acute bloody diarrhea (dysentery) Selection of an antibiotic is based on sensitivity patterns of strains of Shigella isolated in the area. Ciprofloxacin found effective in the treatment of Shigella diarrhea currently showing resistant to Shigella dysentery or showing sensitivity only at higher minimum inhibitory concentration (MIC) value. In that case, pivmecillinam can be more confidently used in Shigella dysentery Recommended duration of treatment is 3–5 days
Measles with eye or mouth complications	Give first dose of vitamin A. If clouding of cornea or pus draining from the eye is present, apply tetracycline eye ointment and pad bandage. Also give first dose of vitamin A if there is a history of last 3 months. Offer, energy and calorie rich diet to prevent malnutrition. Give proper antibiotic if there is evidence of bacterial infection (pneumonia)
Anemia or very low weight	Assess the child's feeding practice and counsel the mother accordingly on feeding If pallor is present: Give oral iron supplement, advise to offer the child easily available cheap iron fortified diet like green leafy vegetables, green banana, egg yolk, small fish, boiled chicken or goat liver (if affordable). Give oral antimalarial if high malaria risk Give albendazole/mebendazole if the child is 2 years or older, pyrantel pamoate in a child <2 years (under registered medical practitioners supervision) and has not had a dose in the previous 6 months
No anemia and not very low weight	If the child is <2 years old, assess the child's feeding and counsel the mother accordingly on feeding
Acute ear infection	Give appropriate antibiotic (amoxicillin, ampicillin, cefixime, cotrimoxazole) for 5 days Give one dose of paracetamol for pain and advise mother to give paracetamol at home for pain Dry the ear by wicking
Chronic ear infection	• Dry the ear by wicking • Treat with topical quinolone ear drops for 14 days • Insertion of grommet, depending on available facility and affordability
Malaria	• Give an oral antimalarial drug • Give one dose of paracetamol for high fever (101°F or above) • And advise mother to give paracetamol at home for fever
Fever	• Give one dose of paracetamol for high fever (101°F or above) • Treat other obvious causes of fever

*Cotrimoxazole containing trimethoprim has shown growing resistance to common bacterial pathogens.

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11 Cardiac Disorders

APPLIED CARDIOVASCULAR ANATOMY

Cardiac Anatomy

Left Heart

- Oxygenated blood from the lungs returns to the left atrium (LA) through the right- and left-sided pulmonary veins
- During diastole, blood enters the left ventricle (LV) through the mitral valve (MV), which is a bicuspid valve (posterior/mural leaflet and anterior leaflet)
- Each leaflet is secured at the base to the mitral annulus and the free end is linked to the papillary muscles via thin tendinous structures (chordae tendineae)
- During systole, the papillary muscles contract to increase tension on the chordal apparatus and thus maintain valvar competency
- The aortic valve is in fibrous continuity with the MV and is a trileaflet structure
- Two of its cusps (left and right) support the origin of the appropriate coronary arteries, the third leaflet being termed noncoronary
- The left ventricular wall is three times thicker than the right ventricle (RV)
- Its fibers are oriented in three layers; the inner (subendocardial) layer is the most important in children and young adults
- The outermost oblique layer, along with the subendocardial layer, has their fibers running longitudinally from the apex to the base, while the middle layer is made up of a radial arrangement of fibers
- Systole involves ventricular contraction which shortens, thickens and twists toward the apex.
- The aorta ascends as a central structure from the heart and usually arches to the left curving over the heart to descend posteriorly to the left of the spine.

Right Heart

- Deoxygenated blood from the systemic circulation returns to the right atrium (RA) through the superior and inferior caval veins [superior vena cava (SVC) and inferior vena cava (IVC)]
- Cardiac venous blood enters the heart through the coronary sinus and directly through the Thebesian veins
- During diastole, blood flows from the RA to the RV through the tricuspid valve; this valve has three leaflets (anterosuperior, septal and inferior leaflets)
- The RV is triangular shaped and much thinner than the LV. It is heavily trabeculated and it has a muscular sleeve (infundibulum) separating the tricuspid valve from the pulmonary valve
- The main pulmonary trunk arises to the left and anterior relative to the aorta
- It courses posteriorly before branching into the left and right pulmonary arteries.

Sequential Segmental Analysis

To evaluate patients with suspected congenital heart disease (CHD), it is imperative to analyze the heart in a segmental pattern based on:

- Position of the heart and other organs (thoracic and abdominal).
  - Visceral sidedness (situs solitus or inversus)
  - Cardiac position (location and orientation)
- Connections between the different regions (veins, atria, ventricles and arteries)
- Description of a cardiac region based on its morphological characteristics rather than its position, or relation to other structures.

It is also important to understand that:

- Connections is an anatomic term showing a direct link between two structures; drainage a hemodynamic one, referring to flow of blood.
- Single refers to an absence of a corresponding contralateral structure (single valve in tricuspid atresia); common refers to bilateral components with an absent division [e.g. common atrioventricular (AV) valve].

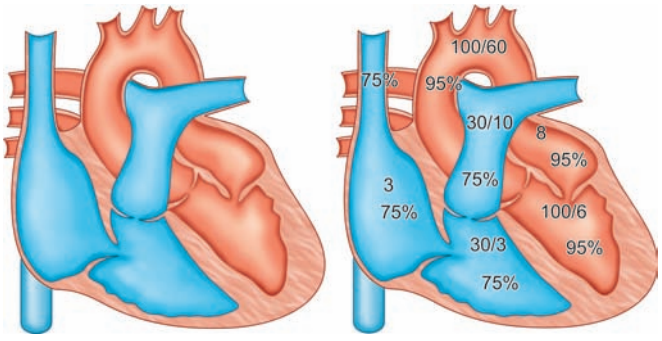
The endocardium is the inner layer of the heart, which is metabolically active in contributing to cardiovascular function.

The pericardium, a fibroserous sac consisting of visceral and parietal layers, is a dynamic and adaptive structure which:

- Protects the heart by acting as a barrier.
- Reduces friction due to cardiac motion.

Conduction System

Contraction is triggered by electrical impulses which are generated and conducted through a system of specialized cells, the conduction system. The sinoatrial node generates the electrical impulse which spreads through the atrial chambers.



Figs 1A and B: (A) Normal heart structures; (B) Normal O_2 saturation and pressure measurements

- Sinoatrial node is situated at the SVC/RA junction

There is a single point of electrical connectivity between the atria and the ventricles; the AV node

- AV node is situated in the triangle of Koch (near the coronary sinus).

The conduction system then proceeds as the bundle of His before dividing into the left and right bundles and then into various fascicles.

APPLIED CARDIOVASCULAR PHYSIOLOGY

The Cardiac Cycle (Fig. 2)

- Phase of contraction (systole): Consists of phase of isovolemic contraction and rapid ejection when the arterial valve opens
- Phase of relaxation (diastole): Consists of isovolemic relaxation and opening of the AV valve following by filling. Atrial systole contributes to end-diastolic filling.

Blood Pressure

Blood pressure (BP) = Cardiac output × Systemic vascular resistance (SVR)

- Low BP may be due to low cardiac output, low SVR or both
- BP is often normal (or slightly low) in situation of low cardiac output because the SVR rises. This is compensatory response mediated via the symptomatic nervous system (the cold, clammy patient). Beyond maximal compensation BP will fall. This is seen in both hypovolemic and cardiogenic shock
- In septic shock (warm shock), the SVR is low due to vasodilation.

Ventricular Function

Ventricular performance is determined by both systolic and diastolic function—abnormalities of either can cause cardiac failure.

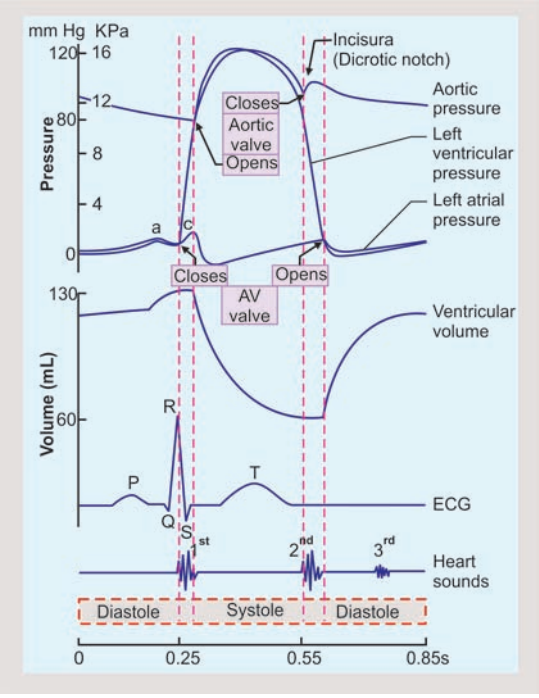


Fig. 2: Cardiac cycle during diastole and systole

Cardiac Output

Cardiac output = Stroke volume (SV) × Heart rate (HR)
Stroke volume falls in situations of both hypovolemia and myocardial dysfunction and leads to fall in cardiac output.

Stroke Volume

Systolic function determines SV which is in turn dependent on four factors. Low cardiac output may be caused by any combination of these factors:

1. Heart rate
2. Preload
3. Inotropy or contractility
4. Afterload.

Heart Rate

- Tachycardia may compensate for a falling SV (again a sympathetic response) to a degree but, if excessive, may reduce ventricular filling time to a degree that worsens SV and hence cardiac output
- Severe bradycardia and tachyarrhythmias generally cause fall in cardiac output.

The Otto Frank and Ernest Starling law of the heart states "the energy of contraction is a function of the length of the muscle fiber," therefore as ventricular filling (preload) increase, SV (and therefore, cardiac output) increases. Due to its dependency on preload and afterload it follows that cardiac output is a crude index of ventricular performance.

Preload

- Preload is the passive force that stretches resting muscle fibers
- It represents end diastolic volume and is inferred from end diastolic pressure
- Preload depends upon:
  - Circulating blood volume (filling)
  - Venous tone
- Clinical purposes: Central venous pressure (CVP) and left atrial pressure (LAP) provide an estimate of right ventricular and left ventricular preload
- Generally a low CVP equates to low preload and underfilling in this instance volume loading will raise preload, hence cardiac output and thus BP.

Afterload

- Afterload is the force opposing ventricular ejection, i.e. the force opposing muscle fiber shortening
- An increase in afterload will increase myocardial work and reduce cardiac output
- Minimizing afterload can reduce ventricular stroke work (stroke work = SV × BP) and myocardial oxygen consumption. This can be an effective treatment for the failing myocardium. Reductions in SVR must be balanced against maintaining perfusion pressure (to other vital organs) and diastolic pressure (coronary perfusion).

The SVR index (SVRi) and the pulmonary vascular resistance index (PVRi) are measures of the afterload of the systemic and pulmonary circulations, respectively (indexed for weight).

SVRi = (MAP – CVP)/cardiac index
PVRi = (Mean PAP – LAP)/cardiac index

MAP: Mean arterial pressure
PAP: Pulmonary arterial pressure

Pediatric versus Adult Heart Failure

In adults, myocardial dysfunction secondary to ischemic heart disease is the usual cause of heart failure (HF) and pulmonary edema. In children, the usual cause of pulmonary edema is high pulmonary blood flow (PBF) and ventricular volume overload due to left-to-right shunt. It seems rather illogical to describe a child's heart in this state as failing as it is often working very hard. In some cases of cardiac failure, the heart is consuming so much energy, there is little left for growth, leading to failure to thrive (FTT).

When myocardial dysfunction is severe, reductions in both preload and afterload can be achieved by positive pressure ventilation as well as by veno- and vasodilation.

Inotropy/Contractility (Fig. 3)

- Increase in inotropy provides increased SV and hence cardiac output for the same preload and afterload conditions
- The net effect is an upward and leftward shift of the Frank-Starling curve
- Inotropes increase myocardial oxygen consumption and are often best combined with vasodilators to reduce preload and afterload to minimize this effect.

Ventricular Performance and Dysfunction

Pressure-volume (PV) Relationship

- By plotting ventricular pressure against ventricular volume throughout the cardiac cycle, a PV loop can be constructed which can be used to provide objective information about the compliance of the ventricle and ventricular contractility and arterial elastance
- The normal LV and RV-PV relationships during a single cardiac cycle. The area within the PV loop is the stroke work while the width of the loop is the SV (Fig. 4)
- By constructing a series of PV loops under different conditions of preload and afterload, a series of loops can be obtained, from which a number of parameters can be derived
  - The slope of the end-diastolic PV curve gives information about the compliance of the ventricle
  - The slope of the end-systolic PV curve is a measure of ventricular contractility.

Diastolic Dysfunction

Diastolic dysfunction is an increasingly recognized phenomenon both in children and adults. In cases of poor ventricular compliance, higher filling pressures will be required for a given end-diastolic volume. In classic cases of diastolic dysfunction, such as tetralogy of Fallot (TOF), higher filling pressure (CVP) may be required to ensure adequate ventricular filling. Additionally, positive pressure ventilation and tachycardia are less well-tolerated as they reduce venous return and ventricular filling.

Cardiovascular Function and Age

Newborn hearts slow functional immaturity. As infancy and childhood occur, the myocardium develops.

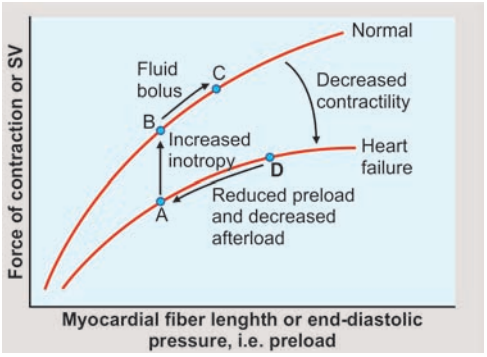


Fig. 3: Frank-Starting curves effect of filling and increased inotropes Y-axis: force of contraction can be represented by cardiac output, SV, or stroke work. X-axis: myocardial fiber length can be represented by end-diastolic volume or end-diastolic pressure. (A to B represents increased contractility from inotropic therapy. B to C represents a fluid bolus. D to A represents preload or afterload reduction by vasodilators and/or diuretics

Abbreviations: SV, stroke volume

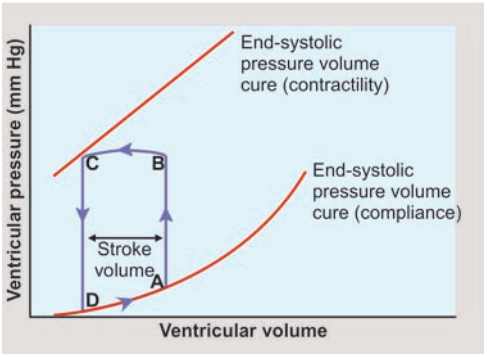


Fig. 4: Normal pressure-volume relationship. During diastole the ventricle fills and pressure increases from D to A. Pressure then rises sharply from A to B during isovolumic contraction and from B to C during ventricular ejection. From C to D, the aortic valve closes and pressure fails (isovolumic relaxation)

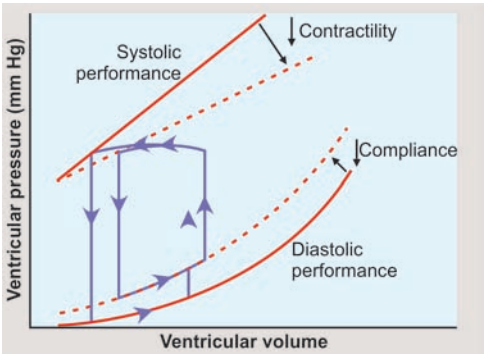


Fig. 5: Pressure-volume curve with reduced contractility (systolic performance) and reduced compliance (diastolic performance)

- Neonates have limited inotropic reserve and stiff noncompliant ventricles. Their cardiac output and BP are dependent on circulating volume and they do not tolerate hypovolemia well
- Sympathetic innervation of the neonatal heart is relatively undeveloped and relatively resistant to β-adrenergic catecholamines, e.g. adrenaline
- Both bradycardia and tachycardia decrease cardiac output in neonates
- The neonatal LV is nonconcentric and is dependent on right ventricular and septal function.

ALTERNATIONS IN RESPIRATORY PHYSIOLOGY DUE TO CONGENITAL HEART DISEASE

Physiology of Interstitial and Pulmonary Edema

The rate of filtration of fluid across a capillary bed depends on a balance of forces, sometimes called Starling forces. A hydrostatic pressure gradient (pressure within the capillary minus the pressure within the interstitial fluid) encourages fluid filtration into the interstitium while an osmotic pressure gradient across the capillary wall discourages it.

Any lesion that results in increased intracapillary pressure may lead to interstitial edema or even alveolar edema, if severe. Lesions associated with elevated pulmonary artery (PA) pressure, but low, normal, capillary pressure will not result in pulmonary edema.

Pulmonary Congestion

May result from:

- Increase in PBF due to a left-to-right shunt
- Pulmonary venous obstruction as in total anomalous pulmonary venous drainage (TAPVD)
- Pulmonary venous hypertension secondary to elevated LAP
  - Mitral stenosis
  - Left ventricular failure (LVF).

Effects can be:

- Ventilation-perfusion (V/Q) mismatch
- Increase in shunt and hypoxia
- Increase in lung weight
- Airway obstruction with gas trapping
- Increase in airway pressures (if ventilated).

These alternations can cause hypoxia, reduced lung compliance. Supporting these patients acutely should include oxygen therapy, diuresis, inotropic and vasodilator therapy. Some children may need positive pressure ventilation.

Decreased Pulmonary Blood Flow

Due to right-to-left shunts (e.g. TOF), and/or decrease in PBF (pulmonary atresia). Alterations in respiratory mechanics may be due to:

- V/Q mismatch (↑ physiological dead space)
- Decrease in lung weight
- May develop airway hypoplasia to more or less increase in airway resistance.

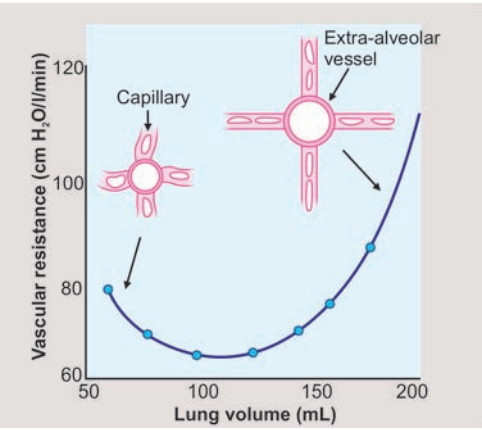


Fig. 6: The relationship between lung volume and pulmonary vascular resistance

Alterations in Cardiovascular Physiology during Mechanical Ventilation

- The RV is more sensitive to respiratory changes than the left. This is more apparent in children
- Increase in positive pressure leads to a reduction in venous return and thus reduction in RV preload
- RV afterload can be manipulated by judicious use of ventilation; under or overexpansion of the lung → increased PVR → increased RV afterload
- Ventilatory effects on both RV contractility and myocardial perfusion are more pronounced in cardiac disease and postoperative states
- In the setting of severe restrictive right ventricular physiology following TOF repair, positive pressure ventilation is poorly tolerated
  - Aim to wean ventilation relatively quickly, if possible
  - Negative pressure ventilation has been used successfully
- Continuous positive airway pressure (CPAP) and positive pressure ventilation both reduce left ventricular afterload. In children with LV dysfunction, one should aim to optimize oxygenation, reduce mean airway pressure (to augment preload) and maintain positive pressure ventilation to reduce LV afterload.

THE NORMAL ELECTROCARDIOGRAM

The approach to the analysis of an electrocardiogram should be systematic and start with consideration of the P wave and progress to the RR interval, QRS complex, ST segment and T wave. Electrocardiogram of adult and children are not same and interpretation should be given accordingly. The electrocardiogram of the infant or growing child undergoes dynamic processes, reflecting changes due to the anatomical growth of the heart and alterations in cardiac hemodynamics. In the first 6 months of life, right ventricular dominance is normally present and regression may take 2–3 years though normally the LV is dominant by the age of 6 months. With increasing age, the R wave in V1 and the S wave in V6 become less, and the S wave in V1 and R wave in V6 become more are prominent.

The P wave is a result of electrical activity which originates from sinus node then spreads across atria. Since the impulse spreads from right to left, the P wave is upright in leads I, II and aVF and inverted in aVR.

QRS interval represents depolarization of the ventricular muscle. The duration of the QRS complex is 0.06–0.08 seconds and should not exceed 0.10 seconds. The Q wave is due to depolarization of intraventricular septum from the left side of the heart to the right. By definition, the Q wave is the negative deflection preceding the R wave and is usually not greater than 0.3 mV and if more than 0.4 mV is abnormal.

The R wave is any positive deflection in ECG. If there are two R waves, the second is denoted R'. A small voltage R is denoted as small (r). The size of the R and S waves in different leads is determined by the thickness of the ventricle walls and thus reflects right and left ventricular hypertrophy. T wave result from depolarization of the ventricle. T wave is normally upright in the right precordial leads (V_4R and V1) in normal newborn up to 72 hours and if persistently upright after 7 days then it is abnormal.

The QT interval is measured from the beginning of the Q wave and the end of the T wave and its duration varies with (HR).

QRS axis of the heart is the direction of the maximum electrical force during depolarization.

Electrocardiography Leads

Instead of conventional 12 leads, in pediatric practice 13 leads, including either V_3R or V_4R, are placed on the surface of the body to record the electrical potential. These leads are divided into two groups: "limb leads and chest leads", 6 and 7 in numbers, respectively.

The six-limb leads are further subdivided into bipolar and unipolar leads. There are three bipolar leads, I, II and III, each of which records the difference in potential between two electrodes at two extremities:

1. Lead I = Left arm-right arm
2. Lead II = Left leg-right arm, and
3. Lead III = Left leg-left arm.

The three unipolar leads, (1) aVR, (2) aVL ,and (3) aVF, each of which measure voltage (V) at one site relative to an electrode (called the central terminal) that has approximately zero potential. Thus,

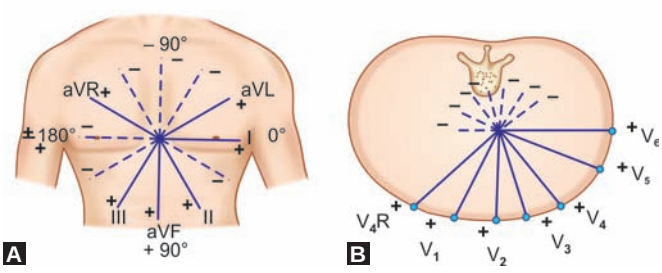
1. aVR = right (R) arm
2. aVL= left (L) arm, and
3. aVF = left leg (F, foot).

The chest leads are unipolar recordings obtained by electrodes in the following positions:

- V_1, fourth intercostal space at right sternal border
- V_2, fourth intercostal space at left sternal border
- V_3, midway between V_2 and V_4
- V_4, left fifth intercostal space at midclavicular line
- V_5, at left anterior axillary line, same level as V_4
- V_6, at left midaxilary line, same level is V_4 and V_5
- V_3R, same as V_3 but on the right side
- V_4R, same as V_4 but on the right side.

Heart rate in electrocardiography (ECG) can be measured in the following way: Count the number of large divisions (0.02 seconds) between two R waves and divide that into 300 numbers of small divisions (0.04 seconds) by 1,500. The HR may be calculated more accurately dividing 60 by the R-R interval (measured in seconds). For example, if the R-R interval is 0.4 seconds (10 small divisions), the HR is 60 ÷ 0.4 = 150 beats/minute.

The following is a guide to the interpretation of the ECG in children. It is useful in the diagnosis of CHD when considered in conjunction with the findings on clinical examination, the chest radiograph and blood gas results. A serious or lethal cardiac malformation may exist with a normal ECG. In children the ECG must include V_4R.



Figs 7A and B: (A) The six frontal plane and (B) seven horizontal plane leads provide a three dimensional representation of cardiac electrical activity. The frontal plane (extremity or limb) leads are represented on a hexaxial diagram. Each ECG lead has a specific spatial orientation and polarity. The positive pole each lead axis (solid line) and negative (hatched line) are designated by their angular position relative orientation. Positive pole of lead I (0°). The mean electrical axis of the QRS complex is measured with respect to this display

ELECTROCARDIOGRAPHY ANALYSIS

Rate and Rhythm

Infants have a fast HR, and the normal values at different ages are shown in Table 1.

Atrial Hypertrophy

Atrial hypertrophy is present if the P wave in lead II is greater than 0.28 mV at any age.

Abnormalities of Conduction

The normal P-R interval is:

- 0.07–0.12 seconds, if less than 1 year
- 0.09–0.16 seconds, if more than1 year.

Mean Frontal QRS Axis

Method

1. Consider leads I and aVF (Fig. 8).
2. Count the number of squares of the QRS forces above the line as positive and below as negative.
3. Take the sum of the R (positive) and S (negative) wave in I and aVF, i.e. height of R wave-height of S wave.
4. Plot an appropriate axis.
5. Extend two perpendicular lines and draw a line through the point of intersection to obtain the mean frontal QRS axis.
6. Normal values for the mean frontal QRS axis are shown in this Table 2.

Table 1: Heart rate at different ages

Age	Heart rate	
	Mean	Range
0–24 hours	145	80–200
1–7 days	133	100–175
8–30 days	163	115–190
1–3 months	154	115–205
3–6 months	140	115–205
6–12 months	140	115–175
1–3 years	126	100–190
3–5 years	98	55–145
5–8 years	96	70–145

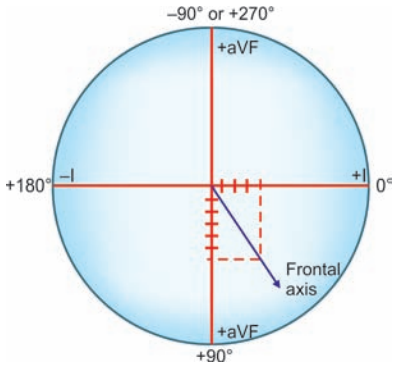


Fig. 8: Orientation of leads I and aVF in the frontal plane, showing an example of how the mean frontal QRS axis is calculated

Table 2: Normal frontal QRS axis

	Mean	Range
0–24 hours	135	60–180
1–7 days	125	60–180
8–30 days	110	0–180
1–3 months	80	20–120
3–6 months	65	40–100
6–12 months	65	20–120
1–3 years	55	0–120
3–5 years	60	0–80
5–8 years	65	–20–100

The mean frontal QRS axis is best stated in degrees. The term "superior axis deviation" is preferable to "left axis deviation" and it is present if the QRS forces in aVF are dominantly negative. Its presence is strongly suggestive of CHD, especially endocardial cushion defect. In a cyanosed infant, it may indicate a univentricular heart with or without an absent right AV connection (tricuspid atresia).

It should be remembered that in pediatric CHD superior axis deviation (left axis deviation) occurs only in two conditions: (1) Tricuspid atresia, (2) Endocardial cushion defect (common AV canal defect) occurring mostly in down children. These two can be differentiated by ECG by the fact that in tricuspid atresia there will be superior axis deviation with left ventricular hypertrophy, whereas in AV canal defect, there will be superior axis deviation with RVH.

Criteria for Ventricular Hypertrophy

Hypertrophy is assessed from the R and S voltages and T wave patterns on the chest leads.

Right Ventricular Hypertrophy

Tall R in V_4R, V_1	>20 mV under 1 week
	>15 mV 1 week to 3 months
	>10 mV over 1 year
Deep S in V_6	>15 mV under 1 week
	>10 mV 1 week to 3 months
	>5 mV over 1 year

Upright T in V_4R, V_1 after 1 week of age.

Left Ventricular Hypertrophy

Tall R in V_6	>1.2 mV under 1 week
	>20 mV 1 week to 3 months
	>25 mV over 1 year
Deep S in V_4 and V_4R	>20 mV under 1 week
	>10 mV 1 week to 1 month
	>20 mV over 1 month

Inverted T in V_5 V_6

Right ventricular hypertrophy (RVH) or left ventricular hypertrophy (LVH) should be diagnosed only if both V_4R and V_6 are abnormal.

Biventricular Hypertrophy

- R+S waves in V_3 and V_4 exceed 70 mV
- Criteria for right ventricular hypertrophy (RVH) and LVH satisfied
- RVH plus inverted T in V_6
- Left ventricular hypertrophy plus wide or bifid R wave in V_4R or V_1 over 0.8 mV.

Ultrasound Investigation (Echocardiogram)

The combination of imaging ultrasound with spectral and color Doppler provides a very accurate assessment of cardiac anatomy, hemodynamics and function.

Cardiac Catheterization

Although cardiac catheterization is a safe procedure, death can occur, most commonly in those with severe PH. Complications of catheterization include femoral artery occlusion, dysrrhythmias, intramyocardial injection with pericardial effusion, cerebral embolus or thrombosis.

Interventional catheterization is now an important part of the management of heart disease in pediatrics. Balloon valvuloplasty is now the accepted treatment for pulmonary valve stenosis. It is relatively straightforward and safe, and with the exception of the dysplastic valve, effective in virtually all cases. Many centers also perform aortic valvoplasty but there is not universal agreement that this is appropriate; it may be that open surgical valvotomy is a more precise procedure with less resulting aortic regurgitation. Similarly, the risk of aneurysm formation following dilatation of coarctation of the aorta has to be balanced against the relatively safe and effective surgical repair. Controlled comparative studies have not been reported with evidence suggests that balloon dilation may be equally effective. Closure of an arterial duct with an "umbrella" or "coil" device is now well-accepted. Catheter closure of atrial or ventricular septal defects (VSDs) can be effective. Interventional cardiology can be of value in patients with distal pulmonary narrowing. Where surgical intervention is difficult, stent placement may allow the narrowed area to be opened up. This is usually undertaken percutaneously but in some smaller subjects can be done as an intraoperative procedure.

COMMON PRESENTATIONS OF CARDIOVASCULAR DISEASE

The majority of children with cardiovascular disease will present with one or more of the following three clinical problems:

1. Cyanosis.
2. Heart failure.
3. Heart murmur.

THE CARDIOVASCULAR EXAMINATION AND ASSESSMENT IN CHILDREN

Many congenital heart anomalies are identified antenatally. However, the clinician should be aware of cardiac conditions presenting with collapsed neonate whose duct has just closed, the evolving cyanosis of Fallot's tetralogy or the discovery of a murmur not previously heard.

History

Symptoms may be nondescriptive, e.g. feeding difficulties, with FTT, recurrent chest infections, or else resemble other conditions, e.g. myocarditis having features of bronchiolitis or asthma. History suggestive of HF (breathlessness, tachypnea, cough, etc.), cyanotic heart disease like squatting, hypoxic and cyanotic spells.

If a child is known to have a cardiac condition, remember that medication can influence a child's clinical status, e.g. β-blockers mask hypoglycemia; digoxin and amiodarone interact with other commonly used drugs.

Examination

The key features to determine are whether the child is:

- Acyanotic or cyanotic (pink or blue)
- In cardiac failure
- Adequately perfused.

Other clinical signs such as growth failure, murmurs or organomegaly not only are suggestive of cardiac disease, but also should alert the clinician to potential complications, e.g. susceptibility to fluid overload, risk of endocarditis.

The following should be checked and recorded:

- Skin color: Pale or pink or blue—oxygen saturations 85–95% are acceptable for cyanotic heart disease: Ask the parents what are the usual saturations for their child
- Pulse rate: Too fast or slow, regular versus irregular
- Respiratory rate: Tachypnea
- Weight gain: Too little; or too rapid [fluid retention due to congestive cardiac failure (CCF)]
- Perfusion: Distal and central
- Pulse especially femoral: Character, e.g. bounding, weak
- Finger clubbing
- Blood pressure: Cuff must cover two-thirds of the upper arm. Blood pressure is age-dependent and a lower BP than expected for age should be re-evaluated as hypotension is an alarming sign
- Any precordial scars, thrills, murmurs
- The position of the apex beat, edge of the liver.

N.B. High temperature ± rash: Consider acute rheumatic fever endocarditis, Kawasaki's.

How to Examine and Present a Child with Heart Disease Before Examiner and in Clinical Setting?

Examine the child systematically, do not jump to look for or describe heart murmurs.

First look for peripheral pulse. All pulse including femoral pulse. Pulse: Rate, rhythm, volume (high or low volume), character if any (water hammer), symmetry in both hands (aberrant arteries), delay (radiofemoral delay in coarctation of aorta).

Blood pressure must be recorded; if not recorded, the reason for not recording should be mentioned.

Examination of Precordium

Inspection: Look for thoracotomy scare for cardiac surgery. Any chest deformity, look for dynamic precordium, with visible apex beat or left parasternal impulse (RVH). Inspect quickly the faces and eyes for facial dysmorphism, cleft palate, cataract, etc. for association of autosomal trisomies (Down's syndrome with AV canal defect), congenital infection [patent ductus arteriosus (PDA) in congenital rubella], monosomies (coarctation of aorta in Turner's syndrome), etc. with CHD.

Look for Finger Clubbing [usually Associated with Cyanotic Heart Disease and Infective Endocarditis (IE)]

Palpation of precordium: Look for palpable murmur or thrill, at apex (mitral incompetence), suprasternal notch (AS, coarctation of aorta), left parasternal border (VSD), look for left parasternal heave (RVH) and palpable P_2, (PH) at left second parasternal area.

Also palpate abdomen for hepatomegaly in suspected CCF.

Percussion: Not much important.

Auscultation

Auscultate all important parts of precordium which includes apex, lower left parasternal area, second left intercostal (pulmonary area) and second right intercostal area (aortic area). Auscultate with both diaphragm and bell of stethoscope. Do not forget to listen back of child. Do not concentrate or try to speak about audible murmur initially. First listen and describe about heart sounds.

Heart sound:

Audible, not audible, not clearly audible.

If audible describe about rate, rhythm, character of the heart sounds and whether there is any pulse deficit.

- First heart sound: Normal, muffled, inaudible or loud (mitral stenosis).
- Second heart sound: Normally audible, splitting, normal splitting, wide splitting, wide fixed splitting [atrial septal defect (ASD)]
- Second heart sound whether single (TOF)
- Second heart sound soft or inaudible (buried by pansystolic murmur of VSD)
- Second heart sound loud pulmonary hypertension (PH).

Added sound (Murmurs):

The following should be looked for while discovering and listening a murmur.

- Systolic, diastolic murmur or continuous (PDA). If systolic, whether holosystolic or ejection systolic.
- Quality of murmur, i.e. soft, vibratory (innocent), harsh (VSD)
- Grading of murmur (I-V/VI)
- Where murmur is best audible
- Is there any radiation of murmur and if present in which direction?
- Is there any diastolic flow murmur and if present in which area of precordium (mitral area in large VSD and PDA), is the murmur changes with change of position (venous hum)?

  Also listen lung bases for crepitations (CCF).

Case-based Discussion

You are asked to auscultate precordium of a suspected VSD in a short case of your clinical examination. How will you approach?

Auscultate all important areas of precordium as mentioned earlier. Do not forget to listen over back. Use both bell and diaphragm. Although asked to auscultate you can palpate to feel possible thrill for grading of murmur (thrill indicates at least grade IV murmur) and for hepatomegaly for HF relevant to CVS.

How to Express Findings before Examiner/Senior Pediatrician?

Begin with heart sounds in the following way, e.g. first heart sound is normally audible. Second heart sound is audible but muffled by murmur. HR: 120/minute, regular, no splitting.

There is pansystolic murmur grade 4/6 (thrill felt) heard all over precordium but best audible at lower left parasternal area. It is harsh in quality with no definite radiation. There is also diastolic murmur (flow murmur due to significant left-to-right shunt) at apex. Crepitations heard at lung bases. On palpation liver is palpable 4 cm below right costal margin (RCM) in Midclavicular line (MCL).

What is the Most Likely Clinical Diagnosis?

The most likely clinical diagnosis is VSD with significant left-to-right shunt (diastolic flow murmur) with HF as evidenced by basal crepitations and hepatomegaly.

Tips about murmur:

Usually almost all the audible murmurs of CHD are systolic in nature. Therefore, if there is any doubt of clinical evaluation of murmur (whether diastolic or systolic) the best guess of murmur will be systolic. The thrill can also guide the grade of murmur. A murmur associated with thrill has minimum grade IV/VI murmur.

The Innocent Murmur

The innocent murmur is a frequent finding in normal children which can be heard at some time in almost 30% of children. This occurs due to turbulent flow in the outflow tracts or great vessels on either side of the heart. It does not signify the presence of any underlying cardiac abnormality or any other pathology. It is obviously important to be able to distinguish an innocent murmur from a pathological one. There are mainly two types of innocent murmur:

1. Ejection murmur.
2. Venous hum.

Characteristics of Innocent Heart Murmur

- Systolic murmur—always. Never diastolic
- Short duration/low-intensity sound
- Intensities increase with increased cardiac output (e.g. exercise or fever)
- Usually audible along left sternal border
- May change in intensity with change in posture and head position
- No associated cardiac thrill or heave
- No radiation
- Asymptomatic patient.

The features of innocent murmur can be remembered as five S:

- S = Systolic
- S = Short
- S = Soft
- S = Symptomless
- S = Sternal border (left).

Innocent Ejection Murmur

Generated in the ventricle outflow tract or vessels on either side of the heart by turbulent blood flow. It is not associated with any structural abnormality.

It usually has vibratory, buzzing, musical, groaning or twanging quality sound localized to the lower left sternal age. Although experience suggest its nature, it is not always possible to distinguish it from small VSD.

Another ejection type of midsystolic murmurs can be often be heard at the upper left sternal edge, originating from flow through the pulmonary valve, and may raise the possibility of mild valve stenosis. It usually appears in the first few months of life in premature infants and disappears before 1 year of age.

Venous Hum

Venous hum from turbulent blood flow in the head and neck veins. It is a continuous low-pitched rumble heard beneath either clavicle. It may increase on inspiration and will be louder after exercise. It may be mistaken for a PDA, but can be distinguished by its disappearance on lying flat or with compression of the jugular veins on the same side.

During a febrile illness or anemia, innocent murmurs are often heard because of increased cardiac output.

Differentiating between innocent and pathological murmurs can be difficult. For the practical purpose, a pediatrician has to decide whether the child requires referral to a pediatric cardiologist and if not, whether there is need for antibiotic prophylaxis against infective endocarditis (IE). When a child is seen in infancy, it is worthwhile reassessing the situation at about 1 year of age. Thereafter, if the child is well, acyanotic with no other physical signs, growing satisfactorily and the electrocardiogram shows no abnormality, it is unlikely that referral is necessary at that stage. If there is uncertainty about whether it is innocent, the child should be seen by an experienced pediatrician to decide about referral to a pediatric cardiologist for echocardiography. A chest X-ray and ECG may help with the diagnosis beyond the neonatal period.

When the murmur is innocent, firm reassurance of the parents is necessary. It may be more reassuring to use the term "normal" rather than "innocent murmur".

CLASSIFICATION OF CONGENITAL HEART DISEASE

Congenital heart diseases are classified under two broad headings:

1. Congenital cyanotic heart disease.
2. Congenital acyanotic heart disease.

Congenital cyanotic heart diseases are the followings:

- Five Ts (D-TGA, TOF, truncus arteriosus, tricuspid atresia, TOPVR)
- DO (double outlet RV)
- ESP (Ebstein's anomaly, single ventricle, pulmonary atresia/critical stenosis).

Mild or no Cyanosis with Systemic Hypoperfusion and Congestive Heart Failure

Hypoplastic left heart syndrome, AS, coarctation of the aorta, aortic arch interruption, cardiomyopathy, others.

Congenital Acyanotic Heart Disease with Mild or No Respiratory Distress

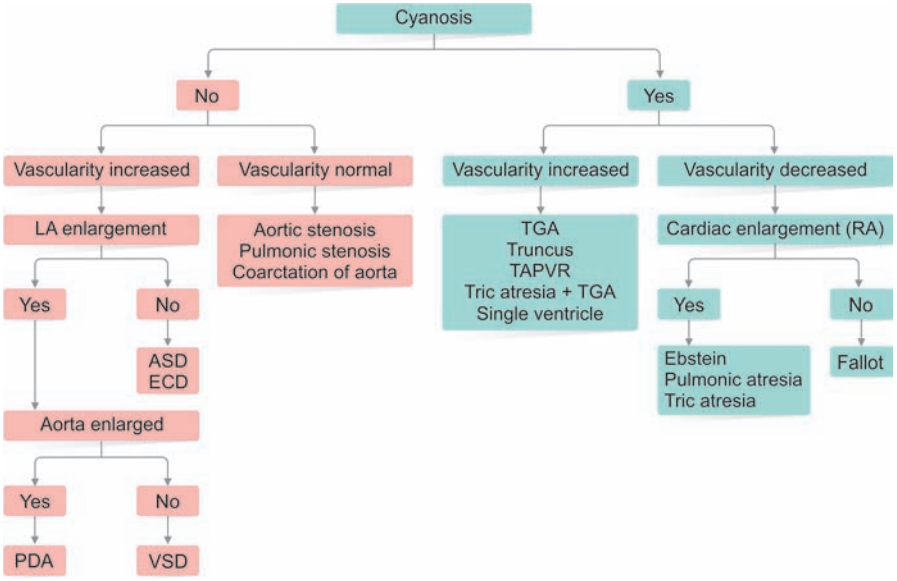
Ventricular septal defect (VSD), ASD, endocardial cushion defect (partial), PDA, aortopulmonary window.

HEART FAILURE IN INFANTS AND CHILDREN

DEFINITION

Heart failure is defined as inability of the heart to keep up with the demands on it and, specifically, failure of the heart to pump blood with normal efficiency. Heart failure results when cardiac output is insufficient to meet the metabolic demands

Flow chart 1: Diagram of coronary heart disease (CHD)



Abbreviations: ASD, atrial septal defect; ECD, endocardial cushion defect; VSD, ventricular septal defect; PDA, patent ductal arteriosus; TAPVR, total anomalous pulmonary venous return; TGA, transposition of great arteries; Tric atresia, tricuspid atresia;

of the body. The largest HF burden comes from children born with congenital malformations. It has been estimated that 15–25% of children who have structural heart disease develop HF. Although cardiomyopathy is relatively rare, approximately 40% of patients who experience cardiomyopathy develop HF of such severity that it leads to transplantation or death.

PATHOPHYSIOLOGY

Unmet tissue demands for cardiac output result in activation of the renin-aldosterone-angiotensin system, the sympathetic nervous system, cytokine-induced inflammation and recently appreciated "signaling" cascades that trigger cachexia.

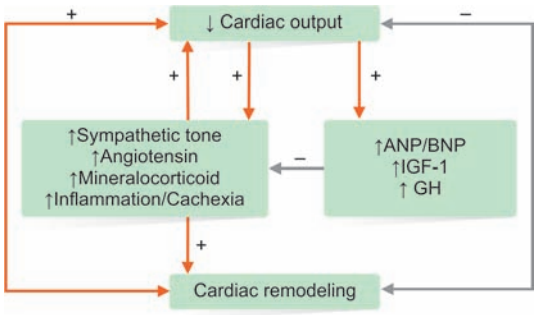
Cardiac remodeling is a structural transformation in which the normally elliptical heart increases in mass and becomes more spherical. This increase in cardiac mass (maladaptive cardiac hypertrophy) involves an expansion of the myofibrillar components of individual myocytes (new cells rarely form), an increase in the myocyte/capillary ratio, and activation and proliferation of abundant nonmyocyte cardiac cells, some of which produce cardiac scarring.

CLINICAL MANIFESTATIONS

Because HF has multiple causes, it has a variety of age-dependent clinical presentations. In neonates, the earliest clinical manifestations may be subtle. Most commonly, infants have feeding difficulties due to dyspnea, increased fatigability, and secretion of anorexic hormones that limit the volume of feedings. Ultimately, affected babies fail to thrive. Physical findings in infants who have HF include mild-to-severe retractions, tachypnea or dyspnea with grunting (a form of positive end-expiratory pressure), tachycardia, a gallop rhythm (S3, S4) and hepatomegaly.

Older children manifest exercise intolerance, somnolence, anorexia or more "adult-like" symptoms such as cough, wheezing or crackles (rales). As with younger children, the physical examination may reveal a gallop rhythm and hepatomegaly as well as peripheral edema and jugular venous distention.

Flow chart 2: Heart failure results from an interaction of beneficial and deleterious pathways that ultimately modulate cardiac output and remodeling



Abbreviations: ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; GH, growth hormone; IGF-1, insulin-like growth factor 1

COMMON CAUSES OF HEART FAILURE

Heart failure can result from cardiac and noncardiac causes. Cardiac causes include those associated with congenital structural malformations and those involving no structural anomalies.

Cardiac Malformations Leading to Heart Failure

Shunt Lesions

- Ventricular septal defect
- Patent ductus arteriosus
- Aortopulmonary window
- Atrioventricular septal defect
- Single ventricle without pulmonary stenosis
- Atrial septal defect (rare).

Total/Partial Anomalous Pulmonary Venous Drainage

Valvular Regurgitation

- Mitral regurgitation
- Aortic regurgitation.

Inflow Obstruction

- Cor triatriatum
- Pulmonary vein stenosis
- Mitral stenosis.

Outflow Obstruction

- Aortic valve stenosis/subaortic stenosis/supravalvular
- Aortic stenosis
- Aortic coarctation.

SOURCES OF HEART FAILURE WITH A STRUCTURALLY NORMAL HEART

Primary Cardiac

- Cardiomyopathy
- Myocarditis
- Myocardial infarction
- Acquired valve disorders
- Hypertension
- Kawasaki syndrome
- Arrhythmia (bradycardia or tachycardia).

Noncardiac

- Anemia
- Sepsis
- Hypoglycemia
- Diabetic ketoacidosis
- Hypothyroidism
- Other endocrinopathies
- Arteriovenous fistula
- Renal failure
- Muscular dystrophies.

Laboratory Studies

- Pulse oximetry is helpful in identifying cyanosis in infants who have HF caused by increased PBF (left-to-right shunts), in addition to cyanotic heart disease
- The 12-lead electrocardiogram is essential to assess arrhythmia-induced HF
- The chest radiograph may demonstrate cardiac enlargement, increased PBF, venous congestion, or pulmonary edema
- Echocardiography is essential for identifying causes of HF such as structural heart disease, ventricular dysfunction (both systolic and diastolic), chamber dimensions, and effusions (both pericardial and pleural).

Heart Failure Biomarkers

Recently, a number of HF biomarkers have been identified that aid in assessing the severity of HF and predicting the course of the disease. Brain natriuretic peptide (BNP), pro-BNP measurement is a readily available test that can distinguish between primary respiratory disease and cardiac-induced tachypnea. C-reactive protein (CRP), high-sensitivity CRP (HS-CRP) and tumor necrosis factor alpha are both sensitive markers of systemic inflammation that correlate positively with a worse HF outcome in adult studies.

Management

The first goal of HF care is to treat the specific cause. Prompt treatment of noncardiac causes of HF such as anemia or endocrinopathies as well as timely referral for surgical corrections of structural cardiac anomalies can prevent or ameliorate HF.

Medical management aims to maximize cardiac output and tissue perfusion while minimizing stresses that increase oxygen consumed by an organ per unit time [mixed venous oxygen saturation (MVO_2)]. These goals are accomplished by reducing the amount of force the heart needs to generate to eject blood (reducing afterload stress) and by reducing overfilling of the heart (preload). Thus, treatments that "rest" the heart, such as vasodilators, are preferred to inotropic agents that increase MVO_2. Some patients who experience acute and severe unresponsive HF are treated with extracorporeal membrane oxygenation or left ventricular assist devices. These measures serve largely as bridges to transplantation. The ultimate therapy for HF that is unresponsive to treatment is cardiac transplantation.

PRINCIPLES OF MANAGING HEART FAILURE

Recognition and Treatment of Underlying Systemic Disease

Timely Surgical Repair of Structural Anomalies

General measures:

- Optimize nutrition, hemoglobin (Hb)
- Optimize respiratory function
- Oxygen
- Respiratory support: CPAP, ventilation.

Afterload reduction:

- Angiotensin-converting enzyme inhibitors (captopril, enalepril)
- Angiotensin receptor blockers (losartan)
- Phosphodiesterase inhibitor in refractory HF—milrinone
- Nitrates
- Brain natriuretic peptide—not well-practiced.

Preload reduction:

Diuretics, loop diuretics (furosemide), aldosterone inhibitor (spironolactone).

Inotropy:

- Digoxin
- Dopamine.

Sympathetic inhibition:

- β-blockers (metopropalol, carvedelol)
- BNP (not well-practiced)
- Digoxin.

Cardiac remodeling prevention:

- Mineralocorticoid inhibitors
- Drug doses are given in drug therapy section.

CONGENITAL ACYANOTIC HEART DISEASE

VENTRICULAR SEPTAL DEFECTS

It is a defect in the ventricular septum which separates the two ventricles and can occur in any part of ventricular septum. Roger H provided the first clinical description of VSD in 1879.

Prevalence

Isolated VSD accounts for approximately 20% of all congenital heart defects with reported prevalence of 0.3–3.3 per 1,000 live births. VSD is more common among preterm infants and stillborns as compared to term infants. VSDs are slightly more common in females accounting for approximately 56% female

and 44% male among affected children with VSD. The prevalence of VSD is lower in adults due to spontaneous closure of many defects. VSDs are most common congenital cardiac lesion found in association with various chromosomal syndromes including trisomy 13, trisomy 18, trisomy 21 and others.

Embryology

Ventricular septal defect results from a delay in closure of the interventricular septum beyond the first 7 weeks of intrauterine life. The reason for this delayed or incomplete closure is still unknown. The normal development of interventricular septum depends upon the endocardial cushions, conotruncal ridges, and growth of tissues at the crest of interventricular septum and muscular septum. VSD occurs as a result of maldevelopment of one or more of these structures.

Ventricular Septal Defect Classification

Ventricular septal defects are classified according to their anatomical location:

- Perimembranous VSD (Figs 9A and B): Most common type of VSDs and account for approximately 80% of the VSDs. They involve the membranous part of ventricular septum
- Inlet VSD: These VSD account for 5–8% of all the VSDs
- Subarterial VSD or doubly committed VSD or subpulmonary VSD: These VSD account for 5–7% of all the VSDs. They are located just beneath the pulmonary valve
- Muscular VSD: These VSD account for 5–20% of all the VSDs and are further subclassified depending on their location in the muscular septum.
  - Central
  - Apical
  - Swiss cheese.

Physiology and Pathophysiology

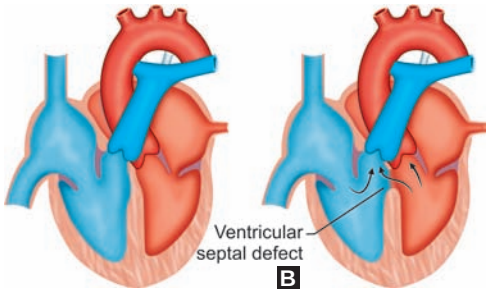
In small or medium-sized VSD, the size of the defect limits the left-to-right shunt; however, in large defects, there is essentially no resistance to flow across the VSD and the relative resistance of the systemic and pulmonary circulations regulate flow across the defect.

In moderate to large VSD, there will be left-to-right shunts with volume overload of the LA and LV with LVH. Right ventricular systolic work and muscle mass are usually only mildly increased. Two types of pulmonary hypertension (PH) can occur in moderate to large VSD. PH is measure of PBF and PVR and if one is increased there will be PH, i.e. PH = PBF × PVR. Pulmonary hypertension, due to increased flow (↑PBF), due to left to right shunt, cause volume overload and right HF or CCF (Fig. 11A). This feature usually occurs in early childhood with significantly large VSD. However if not corrected, increased PBF may be associated with pulmonary vessels injury with thickened adventitia, medial hypertrophy and intimal injury resulting in PVR and increase PH will be due to increase PVR which will cause reverse shunt (Fig. 11B) clinically manifested by cyanosis and clubbing.

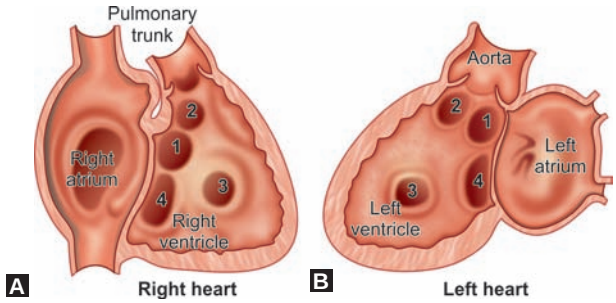
Clinical Manifestations

Infant with Small VSDs, a Murmur Usually is Detected at 1–6 Weeks of Age

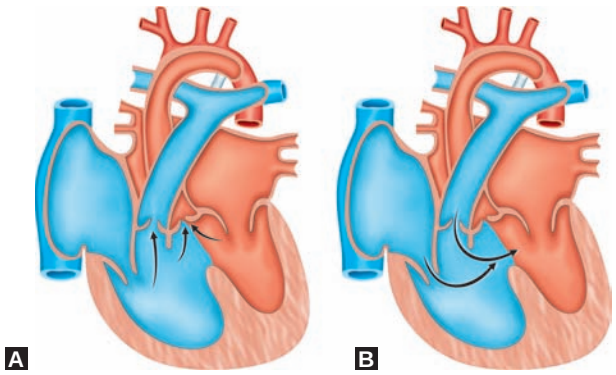
- Normal patterns of feeding, growth and development. The only risk is endocarditis, which is rare before the age of 2 years



Figs 9A and B: (A) Normal heart; (B) Isolated defect in the membranous portion of the interventricular septum. Blood from the left ventricle flows to the right through the interventricular foramen



Figs 10A and B: Anatomic position of defects



Figs 11A and B: Diagrammatic presentation of: (A) Pulmonary hypertension due to pulmonary blood flow; (B) Pulmonary hypertension due to pulmonary vascular resistance with reverse shunt (resulting in Eisenmenger's syndrome)

- Precordial activity is normal. Thrill palpable along lower left sternal border (LLSB) associated with a grade IV/VI holosystolic murmur, start with S_1 extend A_2 or slightly past it. It can radiate cephalad along the LPS, (ejection across the outflow tract of the RV). In outlet defect, the murmur and thrill maximal at the second left intercostal space or suprasternal notch.

Infants with Moderate or Large VSDs

- Develop symptoms as early as 2 weeks of age. The initial symptoms consist of tachypnea with increased respiratory effort, excessive sweating owing to increased sympathetic tone, and fatigue when feeding
- The infant progressively tires with feeding; this symptom begins during the first month and increases in severity as PVR decreases. Symptoms occur earlier in the premature than in the full-term infant, respiratory symptoms probably is pulmonary edema of mild-to-moderate degree with elevated pulmonary venous pressure and decreased lung compliance

- Infants' normal length and decreased weight
- Hyperdynamic precordium with large shunts by 4–6 months, the left anterior thorax bulges outward
- Moderate-sized defects are associated with a thrill and S_1 is coincident and holosystolic and harsh along LLSB, a prominent third sound with a short early mid-diastolic (flow murmur) rumble at the apex
- S_1 coincident murmur from a large VSD is maximal along the LSB, usually is decrescendo and disappears during the latter third of systole before closure of the aortic valve, P_2 loud.

Complications

- Feeding difficulty
- Delayed growth and development (FTT) in infancy
- Congestive cardiac failure
- Infective endocarditis on right ventricular side
- Aortic insufficiency
- Complete heart block
- Damage to electrical conduction system during surgery (causing arrythmias)
- Pulmonary stenosis behaving like TOF
- Pulmonary hypertension, initially due to increased flow from left-to-right and later due to increased PVR resulting in Eisenmenger's syndrome (Fig. 12).

Radiologic Features

Radiologic features in VSD with PH due to increased flow (PBF) show increase cardiac size, pulmonary plethora, dilatation of LA and pulmonary trunk (Fig. 13). If Eisenmenger develops due to increased PVR, pulmonary oligemia occurs (Fig. 14).

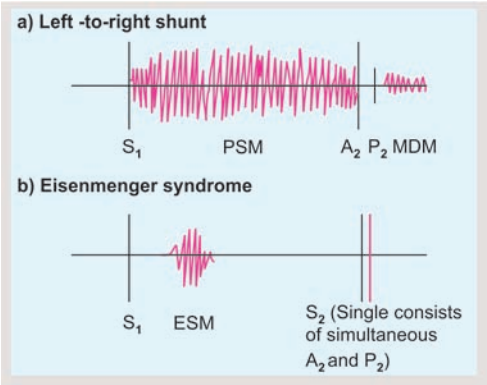


Fig. 12: Physical findings

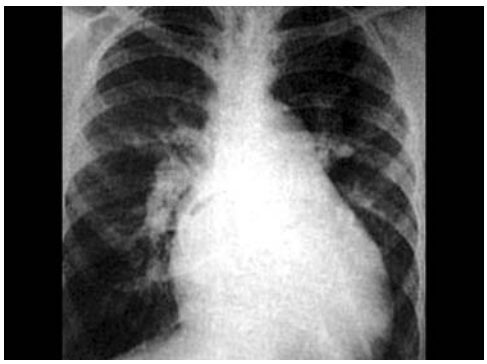


Fig. 13: Chest X-ray showing increased cardiac size with dilatation of the left atrium, pulmonary trunk and pulmonary plethora in a ventricular septal defect with pulmonary hypertension

Electrocardiography

Left ventricular hypertrophy (Fig. 15) initially occurs with PH due to increased PBF. Later biventricular hypertrophy and finally RVH with right axis deviation (RAD) occurs if Eisenmenger develops (Fig. 16).

Echocardiography

Transthoracic two-dimensional color Doppler echocardiography is the modality of choice to evaluate the size, number and anatomical location of most VSDs apart from

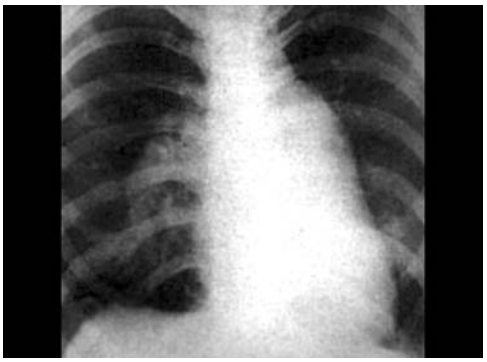


Fig. 14: Chest X-ray is Eisenmenger ventricular septal defect showing slight enlargement of the heart and gross enlargement of the central pulmonary vessels with peripheral pulmonary oligemia

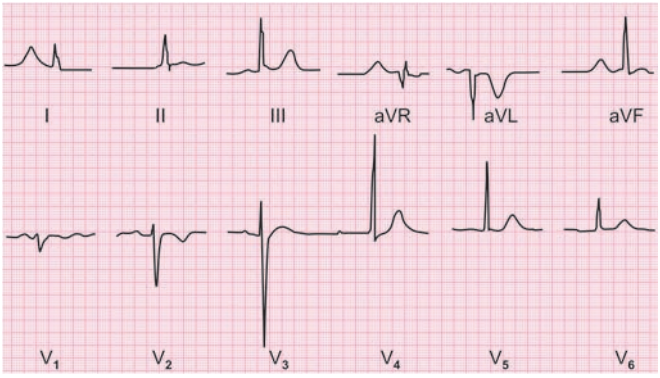


Fig. 15: Electrocardiogram of a 10-year-old patient with ventricular septal defect. The pulmonary flow ratio was 2:1 and the pulmonary vascular resistance was normal. There is evidence of slight left ventricular hypertrophy as shown by the increased voltage of R wave in the left precordial leads

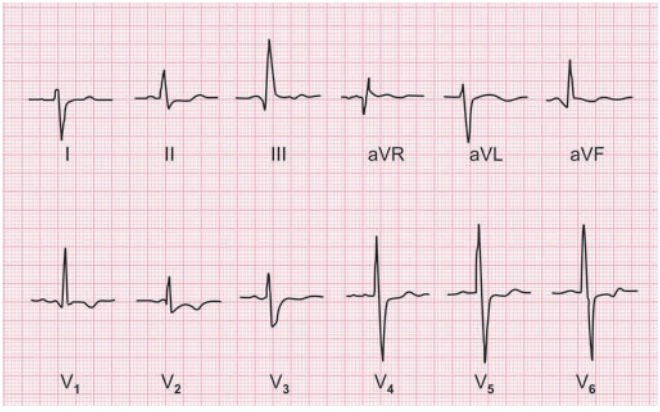


Fig. 16: Electrocardiogram of a patient aged 21 with Eisenmenger ventricular septal defect showing right axis deviation with dominant R wave inverted T wave in right chest leads, and deep S-wave in V_5 and V_6. *Note:* 1 mV = 0.5 cm

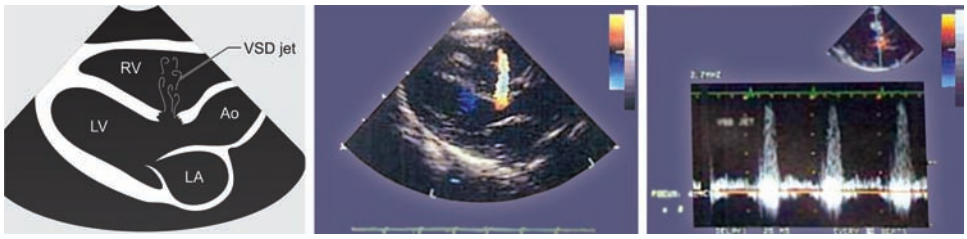


Fig. 17: Diagrammatic and anthracic echocardiograph for diagnosis of ventricular septal defect (VSD)

measurement of atrial and ventricular dimensions and estimation of PA pressure, associated defect (Fig. 17).

Cardiac Catheterization and Angiography

In the past, cardiac catheterization and angiography was a standard diagnostic modality but in the last two decades noninvasive modalities (especially transthoracic and transesophageal echocardiography) provide excellent information and therefore, this modality is reserved for children with ill-defined anatomy, associated lesions or those with pulmonary arterial hypertension (PAH) of unknown reactivity.

Natural History

Small defects are asymptomatic and rarely need treatment. The spontaneous closure is reported in approximately 40% cases being much more common with small muscular defects (approximately 80%). Majority of small VSDs close in the first 2 years of life. The spontaneous closure rate in moderate defects is approximately 8–10%. Pulmonary vascular obstructive disease has been reported in large defects as early as second year of life. VSD associated with Down's syndrome may develop PVR earlier even below one year of age. Aortic regurgitation (AR) secondary to prolapse of aortic valve is well-reported and tends to be progressive especially in association with doubly committed VSDs. Patients with moderate and large-sized VSDs occasionally develop significant infundibular pulmonary stenosis which can progress in severity and require surgical intervention (Fig. 18). Children developing PVR develops clubbing and cyanosis and although respiratory symptoms decreases, the condition is irreversible and VSD becomes surgically uncorrectable.

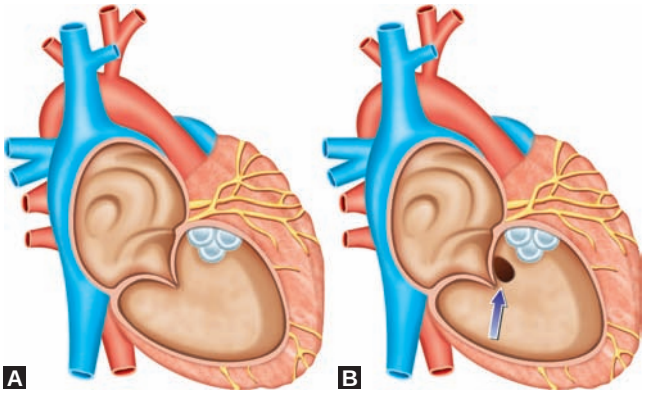
MEDICAL MANAGEMENT

Children with small VSD are asymptomatic and have excellent long-term prognosis and hence should just receive bacterial endocardial prophylaxis. Children with moderate to large-sized VSDs develop symptoms due to congestive heart failure (CHF) and in such patients a trial of medical therapy is indicated. The goal of medical therapy in such patients is to:

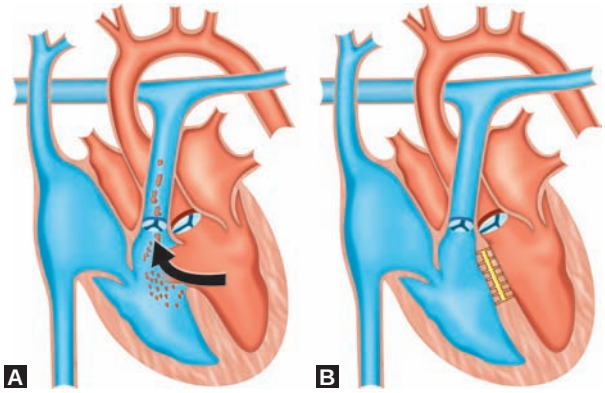
- Relieve symptoms of congestive HF
- Reduction in risk of respiratory tract infections and
- Ascertain adequate weight gain. The treatment of CHF in such patients includes fluid restriction, diuretic therapy, digoxin, angiotensin-converting enzyme inhibitors and caloric supplementation.

SURGICAL MANAGEMENT

Surgical closure of VSDs is the preferred modality. With improving cardiopulmonary bypass techniques, infants with weight as low as 3 kg can undergo successful repair (Fig. 19).



Figs 18A and B: (A) Normal heart; (B) Ventricular septal defect



Figs 19A and B: Surgical closure of ventricular septal defect (VSD)

Indications of VSD Closure

- Moderate to large VSD with uncontrolled CHF, recurrent lower respiratory tract infections or growth failure (early infancy)
- Older children with left-to-right shunt greater than 2:1
- Small perimembranous or doubly committed VSDs with associated aortic insufficiency require early repair to prevent progression of aortic insufficiency
- Small VSD with history of IE
- Contraindication to surgery: Significant PVR.

Transcatheter Therapy

In the recent years, muscular VSD and lately perimembranous VSD have been closed with transcatheter approach. This can be done in children greater than over 8–10 kg in weight. The procedure is accomplished via femoral approach and in some cases jugular venous approach.

Prophylaxis for Infective Endocarditis

- To prevent bacteremia prior to high-risk procedures

- Dental, oral, respiratory tract or esophageal procedures need to be covered
- Oral amoxicillin: 50 mg/kg orally 1 hour before procedure or injection. Ampicillin 50 mg/kg IV 30 minutes before procedure.

Timing of Surgical Correction of VSD

- Large VSD: Surgical closure by 6 months of age
- VSD with prolapse AV and AR—early surgery
- VSD with PAH—surgical closure before 1 year of age
- Moderate VSD without PAH—surgery at 2–3 years of age.

ATRIAL SEPTAL DEFECTS

Any opening in the atrial septum, other than a competent foramen ovale, is an ASD.

CLASSIFICATION OF ASD (FIG. 20)

- Interatrial communications in the region of the fossa ovalis may represent either a true secundum ASD or a valvular incompetent patent foramen ovale
- Defects anterior to the fossa ovalis (primum defects) often are associated with a cleft in the anterior leaflet of the MV (Fig. 21). Also called partial atrioventricular septal defect
- Those posterior and superior to the fossa ovalis, the sinus venosus defects, usually occur in conjunction with anomalous connection of the right pulmonary veins.

There are two main types of ASD:

1. Secundum ASD which constitute 80% of ASD (Fig. 22).
2. Primum ASD also called partial atrioventricular septal defect (PAVSD) (Fig. 23).

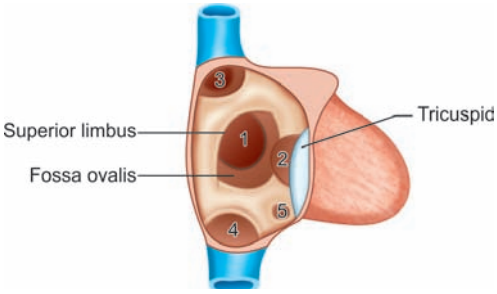


Fig. 20: Types of atrial septal defect: (1) Ostium secundum; (2) Ostium primum; (3) Superior sinus venosus; (4) Inferior sinus venosus; (5) Coronary sinus

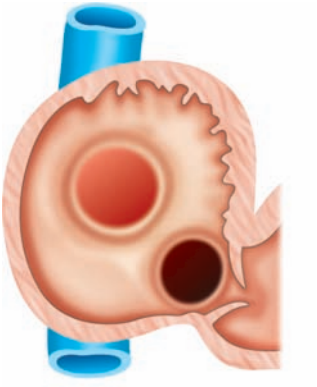


Fig. 21: Ostium primum defect caused by incomplete fusion of the endocardial cushion

Both presents initially with similar symptoms and signs but their anatomies are quite different. The secundum ASD is a defect in the center of the atrial septum involving the foramen ovale. PAVSD is defect of the atrioventricular septum and is characterized by:

- An interatrial communication between the bottom end of the atrial septum and AV valves (primum ASD)
- Abnormal AV valve with left AV valve which has three leaflets and tends to leak.

Secundum ASDs represent 6–10% of all cardiac anomalies and are more frequent in females than males by about 2:1. Recurrence risk is 3–10% children with affected parents. Defects at the level of the fossa ovalis presumably result from deficiency, perforation or absence of the septum primum (the valve of the fossa ovalis). Because the ostium secundum appears enlarged or unguarded, these defects are labeled as secundum type.

SECONDARY EFFECTS ON THE HEART

In the setting of a large interatrial communication, a chronic left-to-right shunt imposes a volume overload on the right-sided cardiac structures and results in dilation of the RA and RV. Dilation of the central PAs also may occur. Dilation of the LA usually is mild.

SECONDARY EFFECTS ON THE LUNGS

The chronic volume overload causes dilation of the entire pulmonary vascular bed. Microscopically, the arteries, capillaries, and veins are engorged. Medial hypertrophy is evident in the muscular PAs and the pulmonary veins. Muscularization of arterioles may also occur.

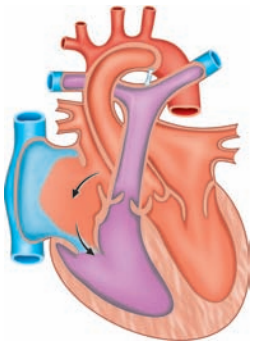


Fig. 22: Atrial septal defect. Blood flows across the atrial septum (arrow) from left to right

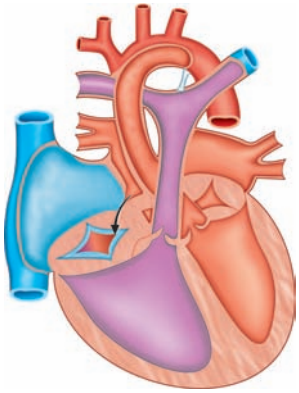


Fig. 23: Partial atrioventricular septal defect (PAVSD) (arrow)

In a few patients with a secundum ASD, severe and irreversible hypertensive pulmonary vascular disease develops, and there is a striking female preponderance for this association.

PHYSIOLOGY

The direction in which blood flows through the defect primarily is related to the relative compliances of the ventricles. Generally, the RV is more compliant than the left, resulting in less resistance to filling from the right atrium. In most situations, shunting is left to right.

In infancy, the RV is thick, stiff and not very compliant. Therefore, there is a minimal amount of left-to-right shunting. In the first few weeks of life, the PVR decreases, the RV becomes more compliant, and the amount of left-to-right shunting increases. Generally, there is increased PBF; often three to four times normal. However, the PA pressure is only slightly increased, and in most patients, pulmonary resistance remains in the normal range.

CLINICAL FEATURES

- Most infants with ASDs are asymptomatic and the condition goes undetected.
- Older children with a moderate left-to-right shunt often are asymptomatic. Children with large left-to-right shunts are likely to complain of some fatigue and dyspnea. Growth failure is very uncommon
- They may present at 6–8 weeks of age with a soft systolic ejection murmur and possibly a fixed and widely split S_2
- Inspection of the chest may reveal a precordial bulge and a hyperdynamic cardiac impulse, especially in the older child and when the left-to-right shunt is large. Palpation of the precordium reveals a prominent systolic impulse
- There are three important auscultatory features:
  1. A typical wide and fixed splitting of the second heart sound.
  2. A soft systolic ejection murmur at the second left intercostal space, and
  3. An early to mid-diastolic murmur at the lower left sternal border.
- When significant PH develops, the above characteristic findings change because of a smaller or absent left-to-right shunt. The widely split S_2 can disappear, P_2 becomes louder, the systolic murmur becomes shorter, and the diastolic murmur disappears
- With a partial AVSD (ostium primum) and apical pansystolic murmur from AV valve regurgitation is heard.

RADIOLOGIC FEATURES

The heart is usually enlarged, with a cardiothoracic ratio greater than 0.5. Pulmonary vascular markings are increased because of engorged PAs, and this finding becomes more prominent with age and the larger left-to-right shunt. If pulmonary vascular obstructive disease develops, the main PA becomes quite large and the peripheral lung fields become clear or oligemic.

ELECTROCARDIOGRAPHY

- It has strong diagnostic clue and can differentiate between ostium secundum and ostium primum (AVSD) type ASD
- In about half of the cases, tall P wave reflect right atrial enlargement. There is usually some variant of the rsR pattern (incomplete right bundle branch block pattern) in lead V_1, consistent with right ventricular volume overload (Fig. 24).
- Usually, normal sinus rhythm is present; however, in a few patients, usually older, junctional rhythm or supraventricular tachyarrhythmia, such as atrial flutter, can occur.
- Partial AVSD (ostium primum): Left axis deviation (superior axis) is characteristic (Fig. 25).

ECHOCARDIOGRAPHIC/DOPPLER FEATURES

Echocardiography shows increased right atrial and right ventricular dimensions and the defect in the atrial septum. The secundum ASD is characterized by dropout of the midatrial septum; the primum ASD by a defect in the lower atrial septum; the sinus venosus ASD by a deficiency in the posterosuperior atrial septum.

CARDIAC CATHETERIZATION

Cardiac catheterization is unnecessary for the diagnosis of secundum ASD. Occasionally, questions about pulmonary vascular obstructive disease or associated cardiac defects arise that require catheterization. However, for most patients clinical assessment in conjunction with noninvasive testing provides the correct diagnosis.

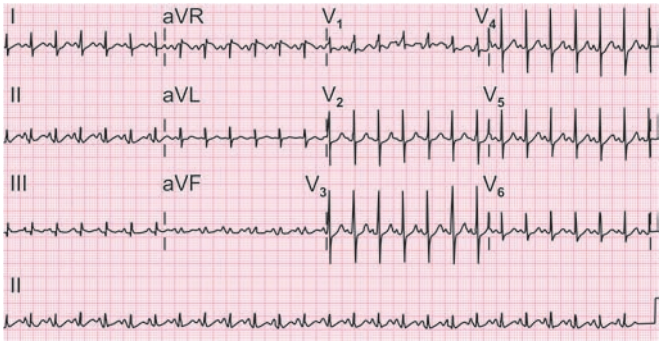


Fig. 24: Electrocardiography (ECG) of ostium secundum atrial septal defect (ASD) showing right atrial hypertrophy and rsR' pattern in V_1, V_2, V_3

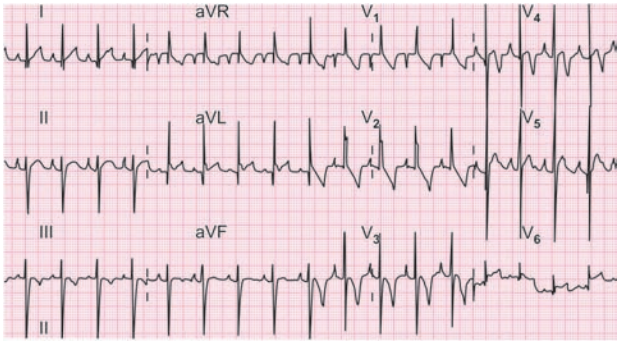


Fig. 25: Electrocardiography (ECG) of ostium primum atrial septal defect (ASD) showing left axis deviation (negative QRS in AVF and positive QRS in Lead 1) and rsR' pattern in V_2

NATURAL HISTORY

The natural course of ASDs is relatively benign except for the largest openings and those associated with other cardiac defects. Typically, patients with ASDs remain active and asymptomatic through early childhood, and many patients have lived into their fourth, fifth, sixth and even seventh decades with ASDs of moderate size before symptoms developed.

Secundum ASDs can close spontaneously, remain open or enlarge. It appears that spontaneous closure, or a decrease in size, is most likely to occur in ASDs less than 7–8 mm and with younger age at diagnosis.

Congestive heart failure is rarely found in the first decade of life, but it can become common once the patient is older than 40 years of age. The onset of atrial fibrillation or, less commonly, atrial flutter can be a hallmark in the course of patients with ASDs. The incidence of atrial arrhythmias increases with advancing age to as high as 13% in patients older than 40 years of age and 52% in those older than 60 years of age.

Pulmonary vascular disease can occur in 5–10% of patients with untreated ASDs, predominantly in females. Usually it occurs after 20 years of age.

TREATMENT

Surgery

Prior to the advent of interventional catheter procedures for major ASDs (Qp–Qs ratio >1.5:1) in children and young adults, surgical repair was the treatment of choice. Since most ASDs are well-tolerated in infancy and may spontaneously close, elective repair frequently has been deferred until the child is at least 4 years of age. Early operation has been recommended for those infants and young children who have unremitting HF or associated PH.

Percutaneous Transcatheter Closure (Ostium Secundum)

In recent times, secundum ASD have been closed by using a variety of catheter-implanted occlusion devices rather than by direct surgical closure with cardiopulmonary bypass. These devices are placed through a femoral venous approach and are deployed like an umbrella to seal the septal defect (Fig. 26). These devices work best for centrally located secundum defects.

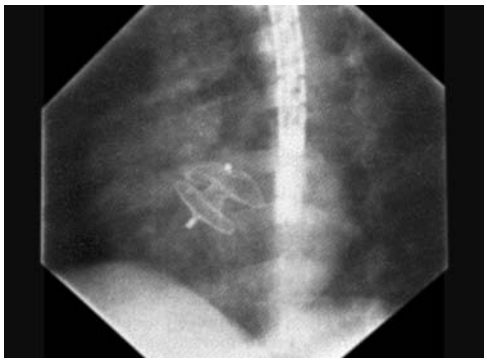


Fig. 26: Amplatzer™ device: Closure of atrial septal defect (secundum type)

Ostium Primum ASD (Partial Atrioventricular Septal Defect)

Device closure is not possible and surgical correction is required.

Time of Definitive Treatment

It is usually required at 3–5 years of age in order to prevent right HF and arrhythmia in later life.

PATENT DUCTUS ARTERIOSUS

The PDA is a vascular structure that connects the proximal descending aorta to the roof of the main PA near the origin of the left branch PA.

EMBRYOLOGY

The proximal portions of the sixth pair of embryonic aortic arches persist as the proximal branch PAs, and the distal portion of the left sixth arch persists as the ductus arteriosus, connecting the left PA with the left dorsal aorta.

Schematic diagram of embryonic aortic arch system is given in Figure 27. The six pairs of embryonic aortic arches are demonstrated (left-sided arches are numbered). The portions that normally involute are indicated by broken lines. The distal left sixth embryonic arch normally persists and becomes the PDA, connecting the left PA to the proximal descending aorta. The right distal sixth arch normally involutes, as does the eighth segment of the right dorsal aorta, which results in a leftward aortic arch.

HISTOLOGY AND MECHANISMS OF NORMAL CLOSURE

Mediae of surrounding aorta and PA are composed mainly of circumferentially arranged layers of elastic fibers, the media of the ductus arteriosus is composed of longitudinally and spirally arranged layers of smooth muscle fibers within loose, concentric layers of elastic tissue. The intima of the ductus arteriosus is thickened and irregular, with abundant mucoid material, sometimes referred to as intimal cushions (Fig. 28).

Functional complete closure usually occurs within 24–48 hours of birth in term neonates. Within the next 2–3 weeks, infolding of the endothelium along with subintimal disruption and proliferation result in fibrosis and a permanent seal.

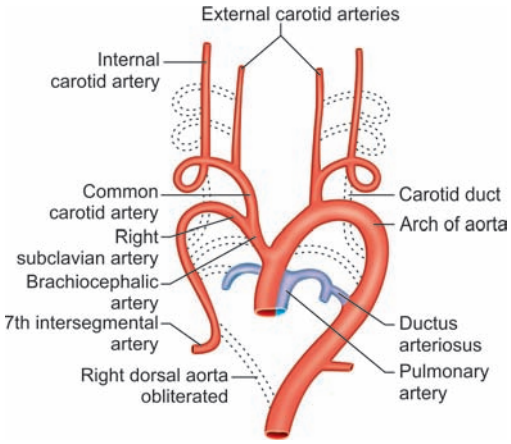


Fig. 27: Embryology of patent ductus arteriosus (PDA). Changes from original aortic arch system

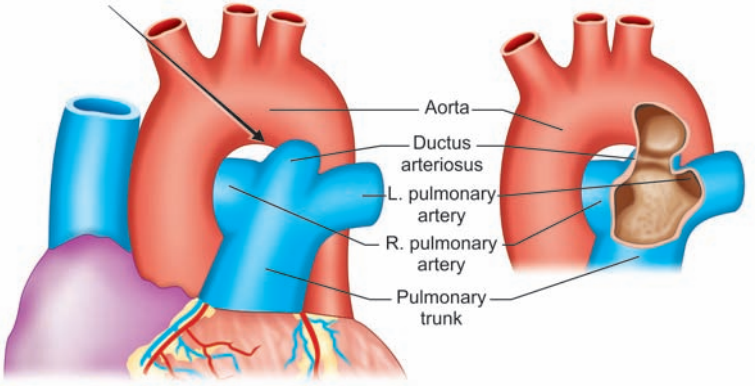


Fig. 28: Anatomy of normal closure of patent ductus arteriosus (PDA)

INCIDENCE

In children who were born at term, the incidence of PDA has been reported to be 1 in 2,000 births. This accounts for 5–10% of all CHD. However, if we include children with "silent" patent ductus (those discovered incidentally by echocardiography performed for another purpose), the incidence has been estimated to be as high as 1 in 500. The female to male ratio is 2:1 in most reports.

GENETIC FACTORS

Patent ductus arteriosus occurs with increased frequency in several genetic syndromes, including those with defined chromosomal aberrations (such as trisomy 21 and 4p-syndrome), single-gene mutations (such as Carpenter's syndrome and Holt-Oram syndrome), and X-linked mutations (such as incontinentia pigmenti). In a family having one sibling with a PDA, there is a 3% chance of a PDA in a subsequent offspring.

INFECTION AND ENVIRONMENTAL FACTORS

Rubella infection during the first trimester of pregnancy, particularly in the first 4 weeks, is associated with a high incidence of PDA. PDA has been reported to be associated with other environmental factors, such as in fetal valproate syndrome, although the mechanism has not been determined.

PHYSIOLOGY

Unlike the ductus arteriosus in premature infants, in whom failure of closure is due to physiologic developmental retardation, the ductus arteriosus in full-term infants is abnormal, and failure to constrict is probably related to a significant structural abnormality.

The magnitude of left-to-right shunting depends upon the diameter of the ductus and ratio of pulmonary to SVR.

CLINICAL FEATURES

Small PDA—no symptoms and is usually detected a murmur on a routine examination.

MODERATE TO LARGE DUCTUS

- Easy fatigability
- Symptoms associated with congestive HF
- Respiratory symptoms suggestive of lung collapse (very large ductus in small babies).

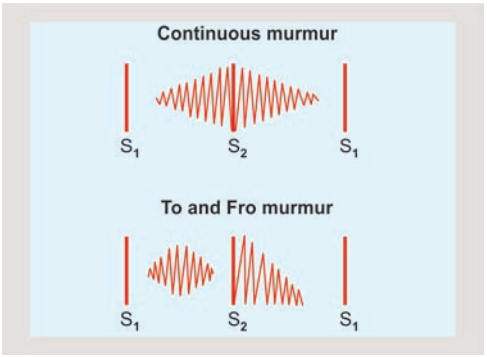


Fig. 29: Diagrammatic presentation of murmur of PDA

EXAMINATION

Arterial pulse is bounding in all but patients with very small ductus.

- Left ventricle impulse hyperdynamic with large shunts
- A thrill may be felt upper left sternal border (ULSB) in the suprasternal notch
- S_1 normal and S_2 buried within the murmur.
- Continuous murmur best audible along ULSB. The murmur begins in systole (Fig. 29) and continues through S_2 into the diastole. The systolic component crescendos up to S_2 while the diastolic part decrescendos to a varying distance (time) into the diastole, grade I to V/VI in intensity. Diastolic component of the murmur is heard better in a supine than in an upright position
- Mid-diastolic murmur heard at the apex (increased flow across the MV)
- It is possible that murmur may not be clearly audible or only systolic murmur is heard in early neonatal period or in large PDA in older age due to PVR (↑PVR). To and fro murmur or continuous murmur becomes obvious when PVR falls and left-to-right shunt of PDA is established.

RADIOLOGIC FEATURES

Chest X-ray in persistent ductus arteriosus with a large left-to-right shunt showing a large heart and pulmonary trunk, prominent aortic kunckle and obvious pulmonary plethora (Fig. 30).

ELECTROCARDIOGRAPHY

Electrocardiogram in persistent ductus arteriosus showing (LVH) tall R-wave in left ventricular leads and deep S wave in opposing leads—the pattern of diastolic overload (Fig. 31).

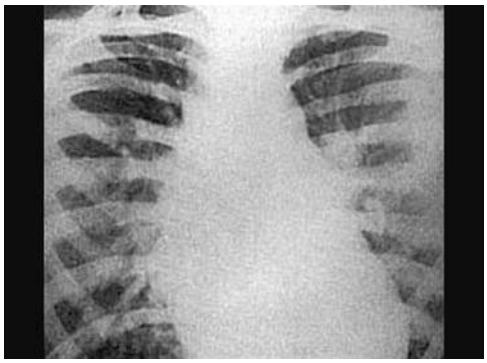


Fig. 30: X-ray of PDA showing enlarged heart and pulmonary plethora

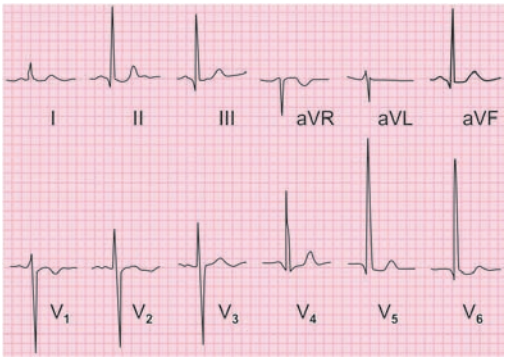


Fig. 31: Electrocardiography (ECG) of patent ductus arteriosus (PDA) showing tall are in V_5, V_6 and deep-S in V_1, V_2 LVH

ECHOCARDIOGRAM

The echocardiogram is the procedure of choice to confirm the diagnosis and to characterize a PDA. In conjunction with the clinical information, the echocardiogram is often useful in classifying the PDA as silent, small, moderate or large. In addition to evaluating the ductus arteriosus, the echocardiogram is used to identify and evaluate other associated cardiac defects (Figs 32A to C).

CARDIAC CATHETERIZATION

Therapeutic catheterization is currently the treatment of choice at most centers for most children and adults with patent ductus. Complete diagnostic assessment of hemodynamics including PVR and degree of shunting before intervention is particularly important. Angiography defines the anatomy of the ductus arteriosus. Detailed assessment of the ductal anatomy is essential before transcatheter closure so that the proper device and device size can be chosen for the intervention.

NATURAL HISTORY AND COMPLICATIONS

The natural history of PDA depends largely on the size and magnitude of the shunt and the status of the pulmonary vasculature. Many patients with small ductus arteriosus never have signs of significant hemodynamic impairment and, other than the risk of endarteritis, have a normal prognosis. Those patients with significant left heart volume overload, however, are at risk of CHF or irreversible pulmonary vascular disease, even if asymptomatic or minimally symptomatic during childhood.

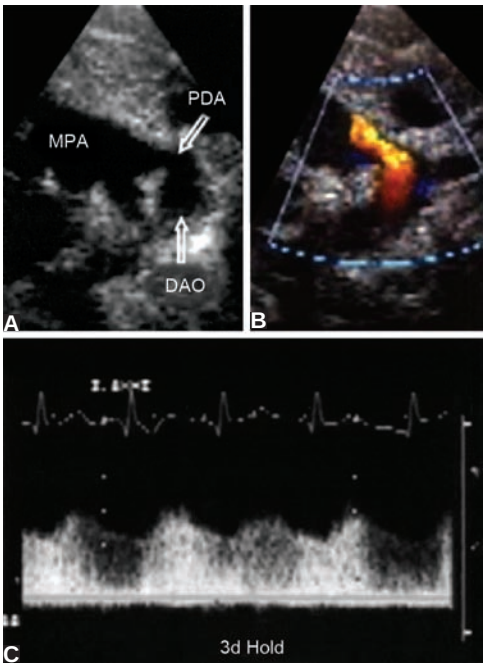
Medical Management

Symptomatic patients with PDA usually improve with a medical regimen of diuretics, digoxin and angiotensin-converting enzyme inhibitor. Observance of IE prophylaxis precautions are recommended for all patients with PDA, including those with silent PDA, until 6 months after closure.

DEFINITIVE THERAPY: CLOSURE OF PDA

Indications for Closure of PDA

Ductus closure is clearly indicated for any child or adult who is symptomatic from significant left-to-right shunting through the PDA. In asymptomatic patients with significant left-to right shunting that result in left heart enlargement, closure is indicated to minimize the risk of complications in the future.



Figs 32A to C: Echocardiogram study demonstrating PDA. (A) Two-dimensional image of a PDA as seen in a high parasternal shortaxis view; (B) Color Doppler image in a similar view shows left-to-right shunting through the ductus; (C) Spectral Doppler profile of continuous left-to-right ductal flow

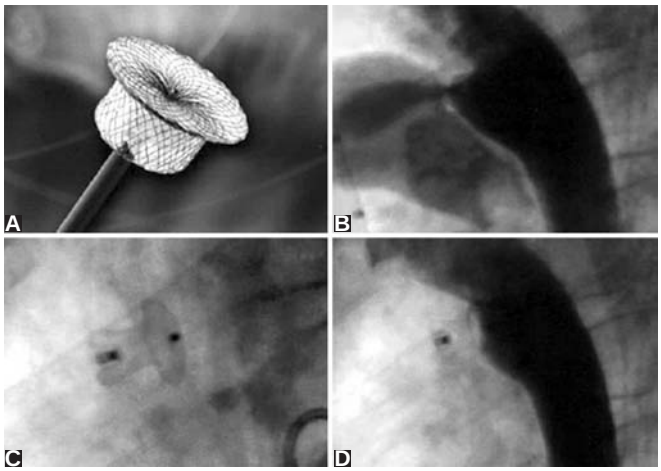
Abbreviations: PDA, patent ductus arteriosus; DAO, descending aorta; MPA, main pulmonary artery

Transcatheter Closure

Transcatheter occlusion has become the treatment of choice for most patent ductus in children and adults (Fig. 33). Results of transcatheter occlusion of PDA have been excellent. Complete closure rates at follow-up generally exceed 90–95% in most studies. The most common complication is device embolization. Other potentially important complications are flow disturbance in the proximal left PA or descending aorta from a protruding device, hemolysis from high-velocity residual shunting, femoral artery or vein thrombosis related to vascular access and infection.

Surgical Therapy

Complete closure rates of surgical ligation (often accompanied by division of the ductus) in published reports range from 94%



Figs 33A to D: Example of patent ductal articular (PDA) occlusion with an Amplatzer™ duct occluder device. (A) Image of an Amplatzer™ duct occluder device; (B to D) Lateral angiograms demonstrating closure of a PDA with an Amplatzer™ duct occluder device

to 100%, with 0–2% mortality. Important complications include bleeding, pneumothorax and infection.

Patent Ductal Articular in Preterm Neonates (also discussed in Neurology Chapter)

Patent ductal articular in neonates particularly in preterm neonates have special significance. PDA is a major morbidity encountered in preterm neonates, especially in babies less than 28 weeks' gestation or 1,000 g weight. Natural duct closure is inversely proportional to age of gestation. Hemodynamically significant ductus arteriosus (HSDA) PDA is more associated with preterm low birthweight (LBW) babies.

Physiologic Effects of PDA

The presence of PDA has significant effect on myocardial functions as well as systemic and PBF. Preterm newborn adapt by increasing left ventricular contractibility and thereby maintaining effective systemic blood flow. This is mainly accomplished by an increase in SV rather than HR. Despite the increased left ventricular output, there is significant redistribution of blood to major organ systems, with the presence of "ductal steal" in PDA due to left-to-right shunt. Usually, there is shunting from systemic to pulmonary circulation called ductal steal the maximum of which occurs at the beginning of cardiac systole, when the pressure gradient is maximum. This steal phenomenon may lead to selective hypoperfusion, despite increased cardiac output. Hence HSDA, PDA has negative effect on cerebral circulation and oxygenation, which may lead to injury to the immature brain.

Clinical Significance

Clinically and hemodynamically significant PDA in newborn babies may cause a major systemic to pulmonary shunt that can lead to considerable postnatal morbidities in extremely low birthweight babies (ELBW), either from pulmonary over-circulation causing chronic lung disease (CLD) and or systemic hypoperfusion (necrotizing enterocolitis), intraventricular hemorrhage (IVH), acute renal impairment. IVH of most severity (Grade III and IV) and mortality associated with IVH is more associated with HSDA, PDA. In preterm, LBW babies it can be associated with prolonged RDS with CLD, necrotizing enterocolitis, pulmonary hemorrhage, IVH with increased incidence of mortality and morbidity.

Echocardiogram

A transductal diameter of greater than 1.5 mm is considered to be significant. The magnitude of transductal shunt not only depends on duct diameter, but also influenced by pulmonary and SVR. It also depends on cardiac volume overload (i.e. ratio of LA to aortic root size).

Biomarkers

An increasing numbers of biological substances, which are markers of cardiac stress, dysfunction or myocardial injury, collectively called biomarkers are emerging as diagnostic and prognostic markers. Echocardiography alone cannot identify the high risk of PDA group. Addition of biochemical markers can delineate infants with severe PDA. Evidence suggests biomarker can predict severe IVH and its catastrophic consequences associated with PDA. Important biomarkers, predicting HSDA, PDA are B-type natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP), serum cardiac troponin T (cTnT), a marker of cardiac injury also found useful in predicting severity. ProBNP (NT-proBNP) is same as BNP, but has longer plasma half-life.

TREATMENT

Management: Medical and Surgical

- In newborn: No treatment, medical and rarely surgical
- In term, normal birthweight babies with hemodynamically normal and clinically stable baby, no active treatment is required in neonatal period
- In preterm, LBW babies, spontaneous ductal closure is less likely. Management strategies consist of no active treatment, medical or surgical. In hemodynamically significant PDA which is associated with significant morbidity and mortality due to major left-to-right shunt and systemic hypoperfusion (steal effect), active treatment is associated with at least short-term benefit. Medical treatment consist of:
  - Fluid restriction
  - Diuretic (furosemide)
  - Low dose of dopamine.

Pharmacological

- Active pharmacological treatment closure of duct by nonselective cyclooxygenase (COX) inhibitors
- Indometacin is the most widely used COX inhibitor for pharmacological closure of PDA. The most commonly used dose regimen is three intravenous doses at 12-hour interval, with starting dose of 0.2 mg/kg, followed by 0.1 mg/kg
- Adverse effect of indometacin:
  - Transient alteration of cerebral perfusion
  - Reversible renal impairment.

Ibuprofen

Ibuprofen can also be used as pharmacological treatment of PDA. Considering the fact that intravenous indomethacin or

ibuprofen if not easily available, oral ibuprofen is a promising alternative. It has advantage over indomethacin in the fact that it is available in oral solution form and has less side effects than indomethacin.

Surgical Intervention

- Rarely required in neonatal period. However large duct, nonresponding to pharmacological treatment or not undergoing spontaneous closure will require surgery
- Large ductus: Early closure in first year of life
- Small ductus: Transcatheter closure at 2–5 years of age.

Complications of Ligation

Reversible pneumothorax infection, hemorrhage, irreversible complication like chylothorax and local cord paralysis. Post-ligation cardiac syndrome consists of oxygen failure due to pulmonary edema, systolic hypotension and need for cardiotropic support.

To Treat or Not to Treat PDA in Neonate

Short-term benefits of treatment have to be balanced against adverse effect such as temporary renal impairment, cerebral hypoperfusion. There is no compelling evidence to suggest that treatment of PDA results in long-term benefit including neurodevelopmental outcome.

An individualistic and rational approach in which informations obtained from echocardiographic assessment is analyzed in conjunction with clinical parameters to make more focused clinical discussion to treat PDA in newborn and early infancy.

PULMONIC STENOSIS

Anatomically pulmonic stenosis is located at the valvar or subvalvar level. The subvalvar pulmonic stenosis is called infundibular pulmonic stenosis. Uncommonly, pulmonic stenosis may be in the PA above the valve or in the main right or left branches or the peripheral branches. There are called supravalvar, right and left main branch stenosis and peripheral pulmonic stenosis respectively; however, peripheral pulmonic stenosis gives a wrong impression in the sense that like coarctation, it results in the proximal area being hypertensive.

HEMODYNAMICS

Flow across the narrow pulmonary valve results in a pulmonary ejection systolic murmur. To keep the flow normal, the RV increases its systolic pressure and develops concentric RVH. The PA beyond the obstruction shows post-stenotic dilatation visible on the thoracic roentgenogram as a dilated pulmonary arterial segment. Because of the obstruction, the right ventricular systole is prolonged resulting in delayed closure of the pulmonic component (P_2) of the second sound. The delay in the P_2 results in a widely split second sound. The split is variable becoming wider in inspiration.

In valvar pulmonic stenosis, a pulmonary ejection click is audible during expiration but disappears or becomes softer during inspiration. It precedes the start of the murmur (Fig. 34).

The concentric hypertrophy results in maintaining a normal heart size and at the same time reduces the RV distensibility. In severe pulmonic stenosis with marked RVH, the right ventricular diastolic pressure also increases. The right atrial pressure increases to be able to fill the RV and results in a right atrial fourth sound (S_4) as well as prominent "a" waves in the jugular venous pulse.

CLINICAL FEATURES

Most are asymptomatic. It is diagnosed clinically. A small number of neonates with critical pulmonary stenosis have a duct-dependent pulmonary circulation and present in the first few days of life.

Physical Signs

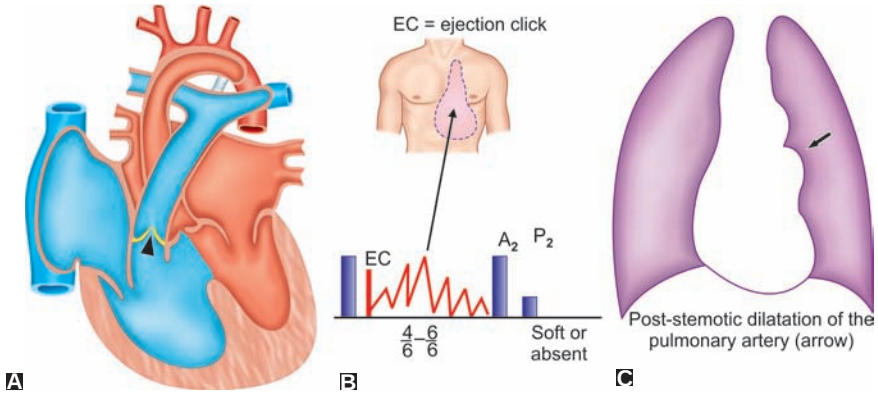
- An ejection systolic murmur best heard at the upper left sternal edge; thrill may be present
- An ejection click best heard at the upper left sternal edge
- Wide splitting second sound
- When severe lesion-prominent right ventricular impulse, with delayed pulmonary valve closure on auscultation.

ELECTROCARDIOGRAPHY

- Normal when the RV systolic pressure is below 60 mm Hg
- As the lesion severity worsens, evidence of RA enlargement, RAD and RV hypertrophy may occur
- The systolic overloading pattern in the electrocardiogram is suggested by a pure "R" or a "qR" type of complex in V_4R and V_1 leads. This is not very specific and rsR type of complex can be present. P pulmonale suggests severe pulmonic stenosis.

CHEST X-RAY (FIG. 35)

- The heart size on chest X-ray is normal unless there is RV failure or an associated cardiac lesion



Figs 34A to C: (A) Pulmonary valve stenosis; (B) Murmur; (C) Chest X-ray (diagrammatic)

- Vascular fullness in the left lung base greater than the right (Chen's sign) is due to the preferential flow
- In severe PS, vasculature markings may be diminished
- Dilatation of the main PA is common in doming but not in dysplastic PS or in subpulmonic stenosis
- Calcification may be seen in older patients
- The RA and RV may be enlarged if there is RV decompensation.

CARDIAC CATHETERIZATION

- Rarely necessary for diagnosis
- Gradients above, at and below the PV should be obtained
- A peak RV systolic value of below 35 mm Hg and a systolic PV gradient of below 10 mm Hg are the upper limits of normal
- Right ventricle function can be assessed, and shunting through any patent foramen ovale can be defined
- Right ventricle angiography helps to define contractile function, the presence of infundibular obstruction, and the mobility of the PV
- Pulmonary angiography assesses the degree of PI and any stenotic lesions in the main, branch or peripheral PAs.

NATURAL HISTORY

- There is little progression in PS severity when the peak Doppler gradient is below 30 mm Hg
- Patients should be followed up every 2–3 years
- Those with more significant stenosis should be followed up yearly
- Survival into adulthood is usual
- Usually there is no progression in patients with peak gradients below 25 mm Hg
- There is a 20% chance of an intervention if the gradient is between 25 mm Hg and 49 mm Hg, and intervention is generally required with gradients above 50 mm Hg.

Assessment of Severity

The severity of pulmonic stenosis can be assessed by the following:

- Symptomatic patients have severe pulmonic stenosis
- Cyanosis and cardiac enlargement indicate severe pulmonic stenosis
- The closer the pulmonary ejection click to S_1, the more severe the stenosis
- The wider the splitting of S_2, the more severe the stenosis
- The longer the murmur the more severe the stenosis
- A pure R in V_1, of 20 mm and appearance of S wave in left precordial leads suggests severe stenosis
- Cardiomegaly and decreased pulmonary flow indicate severe pulmonic stenosis
- Doppler echo can quantitate the gradient accurately (Fig. 36).

MANAGEMENT

American Heart Association committee report recommends:

- No restriction of activity with mild PS
- No restriction of nonstrenuous exercise with moderate PS
- Restricts only those with severe PS
- For the competitive athlete, the Special Task Force report recommends that PS patients with gradients below 50 mm Hg may participate in all competitive sports
- Those with severe PS should only participate in low-intensity sports.

Balloon Pulmonary Valvoplasty (Fig. 38)

- Treatment of choice for patients with classic domed PS

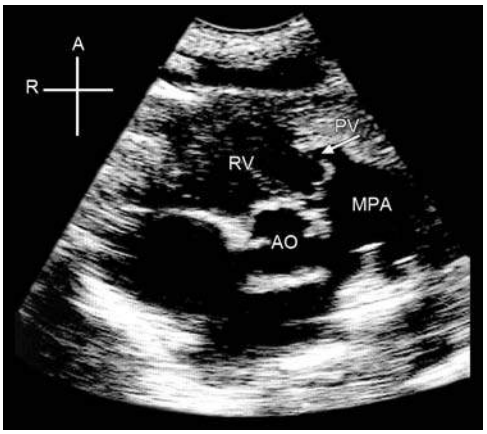


Fig. 36: Echocardiogram can identify the site of pulmonary stenosis and using Doppler can assess severity by quantitating the gradient accurately

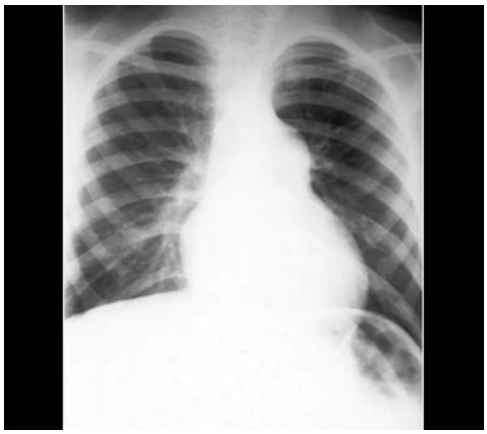


Fig. 35: X-ray showing pulmonary stenosis with poststenotic dilatation of pulmonary artery along left heart border

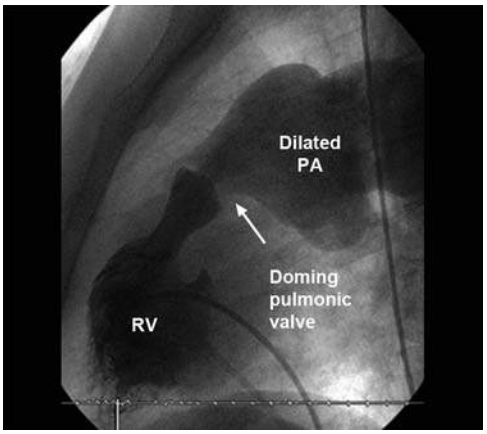


Fig. 37: Pulmonary angiography showing doming pulmonic valve and dilated PA
Abbreviations: PA, pulmonary artery; RV, right ventricle

- A successful procedure is defined by final peak gradient of below 30 mm Hg and is obtained in above 90%
- Ten-year follow-up data are now available with excellent outcomes
- Restenosis rate is low, generally occurring only if there is a residual gradient immediately after the procedure
- Surgical treatment is indicated if balloon valvotomy is unsuccessful, as in dysplastic valves or if the pulmonary valve annulus is small. The operation is done under cardiopulmonary bypass with a low risk. Infundibular stenosis requires surgical resection either through atrial or right ventriculotomy.
- However, several studies have compared balloon valvuloplasty with matched surgical controls and have found similar long-term results, although there appears to be more pulmonary incompetence and ventricular ectopy in the surgical groups.

CONGENITAL AORTIC VALVE STENOSIS

- Three to six percent of CHDs.
- Gender.
  - M:F is 4:1
- Associated anomalies (20%)
  - Patent ductus arteriosus
  - Bicuspid aortic valve
  - Ventricular septal defect
  - Coarctation

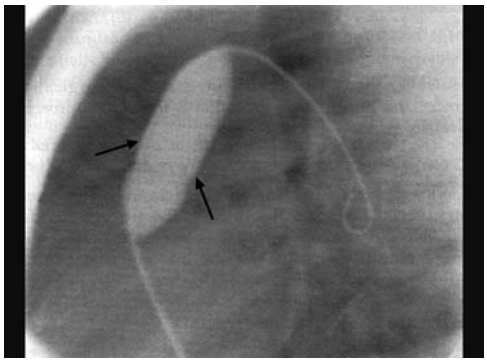


Fig. 38: Figure showing balloon valvoplasty of valvar pulmonic stenosis. Balloon is inflated at the level of pulmonary valve (shown by arrow). Catheter was passed from inferior venacava to right atrium, right ventricle and pulmonary artery

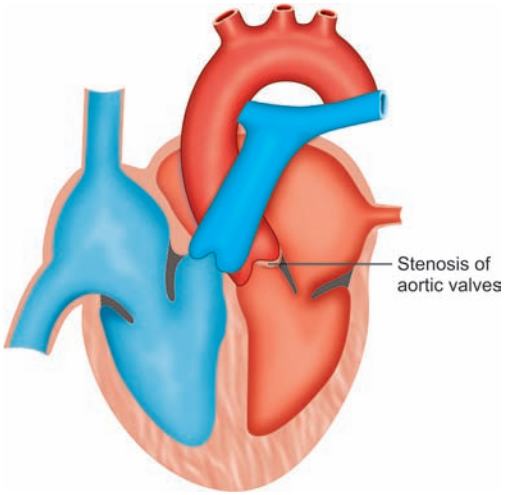


Fig. 39: Aortic valvular stenosis

- Caused by cusp deformities
  - Either with or without narrowing at ventriculoaortic, or annulus
- Figures 39 and 40 show the aortic value stenosis and anatomical site.

MORPHOLOGY: CONGENITAL AORTIC VALVE STENOSIS (COMMON)

- Tricuspid valve
  - Cusps may be:
    - Incompletely developed strands of fibrous tissue with rolled valve edges
    - Well-developed with thickened edges
  - Varying degree of commissural fusion
- Annulus—normal/narrowed
  - Severe → underdeveloped annulus
    - Hypoplastic left heart syndrome
    - Aortic atresia
    - Hypoplasia complexes.

Supravalvular Aortic Stenosis

- Least common type
- Two anatomic variants:
  - Discrete—33–45%, associated left ventricular outflow tract obstruction (LVOTO)
    - Hour-glass (stricture)—discrete marked thickening of aortic media and fibrous intimal proliferation above the sinuses of Valsalva
    - Membranous types → fibrous or fibromuscular semidiaphragm with small central opening
  - Diffuse types—15–7%, severe associated anomaly
    - Hypoplasia of entire ascending aorta and bracheocephalic branches.

Subvalvular Aortic Stenosis

- Rare congenital cardiac abnormality
- Occurs: Isolation or associated structural defects
- Gender; M:F ratio is 2:1
- Postnatal development: "Acquired" defect—initiated abnormal flow characteristics
- Infrequently in the neonatal period.
- Appears after first year of life and causes LVOTO of rapid hemodynamic progression
  - Idiopathic

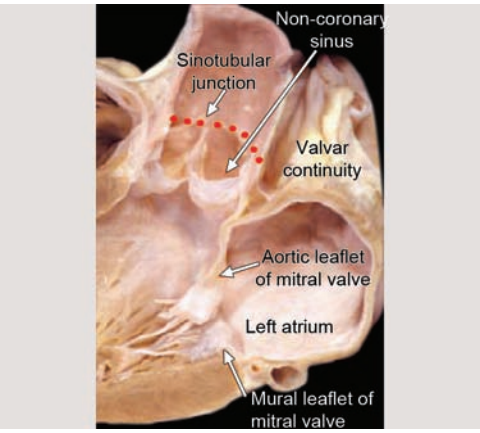


Fig. 40: Anatomical site of aortic stenosis

- Distorted anatomy (abnormal aortoseptal angle)—increased stress → stimulate growth factors and cellular proliferation

- The four basic anatomic variants are:
  1. Thin discrete membrane—endocardial fold and fibrous tissue.
  2. Fibromuscular ridge—thickened membrane with a muscular base at the crest of the IVS.
  3. Fibromuscular ring or collar circumferentially attached to the left ventricular outflow tract (LVOT) and to the base of the anterior mitral leaflet.
  4. Diffuse fibromuscular tunnel-like narrowing of the LVOT.
- Others:
  - Focal muscular
  - Hypoplastic LVOT
  - Complex subaortic stenosis

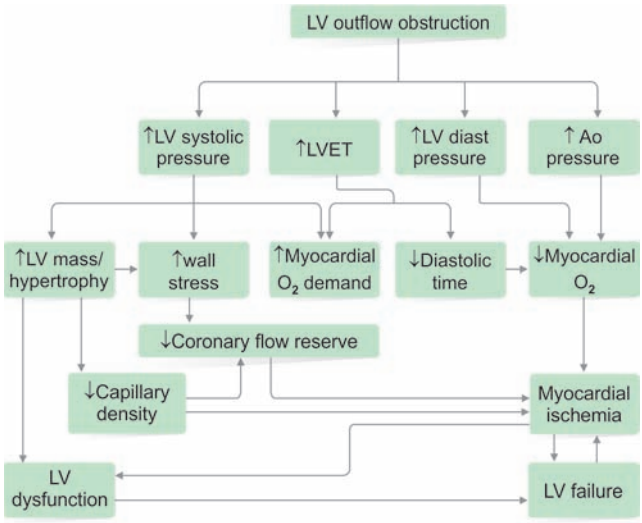
Other causes of subvalvular AS:

- Mitral valve anomalies:
  - Hypoplastic, accessory tissue, leaflet malposition-AV canal defects, anomalous papillary muscle or muscular band, muscularization of anterior leaflet or myxoma
- Abnormal infundibular development and malalignment
  - VSD, coarctation single ventricle or interruption.
- Shone's complex
  - Bicuspid aortic valve, parachute MV, CoA, supravalvular mitral ring or fibromuscular subaortic stenosis
- Accessory endocardial cushion tissue in LVOT
- Hypertrophic obstructive cardiomyopathy
- Glycogen storage disease—Pompe disease
- Postoperatively:
  - After pulmonary banding ← conal septal or crista superventricular hypertrophy)
  - After mitral ring annuloplasty due to the systolic anterior motion of the ventricular septum
  - Postoperative SAS (biventricular repair of DORV, Fontan).

PATHOPHYSIOLOGY (FLOW CHART 3)

- Neonates
  - Role of PFO and PDA
  - Increased LA pressure → left-to-right shunting across stretched PFO → increased RV volume → increased flow across PDA
    PFO: Patent foramen ovale
    LA: Left atrium
    RV: Right ventricle
- Utero-fetus
  - Mild-to-moderate AS → tolerated
  - Moderate-to-severe
    - Chronically reduced flow → LV hypoplasia (HLHS) → duct-dependent systemic circulation
    - But LV may → impaired by fibroelastosis → LV dysfunction → CCF → non-immune hydrops fetalis
- After birth, symptoms depends on:
  - Degree of LVOTO
  - Degree of prenatal injury to the LV
  - Completeness of transition from fetal circulation to neonatal (in-series) circulation
- Neonates- closure of PDA → symptoms – critically ill
  - Normal flow through left side → increased LV load → left ventricular failure (LVF) → increased pulmonary venous pressure and decreased CO → CHF

Flow chart 3: Pathophysiology of aortic stenosis



Abbreviations: LV, left ventricle; LVET, left ventricular ejection time

  - If normal LV function → murmur
- Infancy and beyond
  - Asymptomatic murmur
  - Symptoms – HF (1–2 months, <2) years

NATURAL HISTORY

- Asymptomatic
  - Latency for many years
- Progression
  - Moderate AS > increased jet velocity by 0.3 m/s
  - Increased mean pressure gradient by 7 mm Hg/year
- Predictors of progression
  - Velocity increased by more than 0.3 m/s in 1 year symptoms:
    - Increase in pressure gradient during exercise
    - Low ejection fraction (EF).

CLINICAL FEATURES

In Neonates

Depend on degree of LVOT and closure of PDA (*see* also hypoplastic left heart syndrome)

- Critically ill
- Heart murmur
- Decreased cardiac output
- Shock
- Congestive cardiac failure.

Infancy and Beyond

- Family history—evidence of supravalvular AS
- Antenatal history
  - Ingestion of vitamin D
  - Rubella illness
- Asymptomatic in childhood
- Symptoms
  - Effort intolerance
  - Fatigue + dyspnea, HF—(1–2 months, <2) years
  - Syncope, presyncope–rest/effort
  - Sudden death
  - Inappropriate diaphoresis—recurrent, especially in neonates with HF

- Growth and developmental delay associated with
  - Williams syndrome
  - Congenital rubella
- Physical signs
  - Pulse: Small volume, slow rising pulse
  - Thrill: Systolic thrill can be felt at right second intercostal space and suprasternal notch
  - Ejection systolic murmur at upper right sternal border radiating to neck
  - Delayed and soft aortic second sound
  - Apical ejection click.

ASSOCIATED COMPLICATIONS

- Infective endocarditis
- Bleeding tendencies
  - von-Willebrand disease
  - Heyde's syndrome (angiodysplasia in adult, mainly along ascending aorta)
- Sudden death
- Arrhythmia
  - Ventricular tachycardia
  - Conduction system disease
  - Atrial fibrillation
- Calcific emboli—rare (adults).

PHYSICAL FINDINGS

- Appearance: Growth and development
- Facial dysmorphism characteristics of (if associated):
  - William's syndrome with elfin facies, hypertelorism (Fig. 41)
  - Turner's syndrome, 45,XO biscuspid aortic valve (BAV) (Fig. 42)
  - Noonan's syndrome (tunnel type).

ELECTROCARDIOGRAPHY (FIG. 43)

- Vary according to severity, associated lesions
- QRS axis—normal (>95%)
- Normal to LVH
  - Tall R wave (II, aVf), deep S wave (V_1), tall R (V_{5-6})
- More or less repolarization changes, "strain pattern"
  - ST-T segment depression (V_{4-6}, 2 mm)
  - Reciprocal elevated ST-T segment (V_{1-3})
  - Asymmetrical T-wave inversion
- Wide QRS-T angle
- Reflect major normality in complex lesions.

CHEST X-RAY (FIG. 44)

- Depends on age/severity of disease
- CTR—normal → cardiomegaly
- LVH → rounding of the cardiac apex
- LA—enlarged
- Aorta
  - Ascending aorta → post-stenotic dilatation
  - Aortic root
    - Undersized → Sub- and supravalvular AS
    - Less conspicuous → some supravalvular AS.
- Pulmonary trunk—normal except in pulmonary venous hypertension
- RA and RV—cases of 20 PH
- Valvular calcification.

ECHOCARDIOGRAPHY

- Echocardiography is the principle method of diagnosis of AS. It can identify:
  - Valve anatomy
  - Severity of stenosis
  - Left ventricular response to the pressure overload
- Other
  - Valvular or nonvalvular conditions
  - Concomitant defects: Coarctation or dissection of aorta
- Subaortic stenosis (Fig. 45)
- Supra-aortic membrane (Fig. 46)

CARDIAC CATHETERIZATION

- Not diagnostic
- Pressure gradients: Pull-through gradient method
- Ventriculography (Figs 47 and 48)
  - Wall thickness, LV size, aortic root/ascending aorta
  - Stenotic area—jet of contrast (central/eccentric)

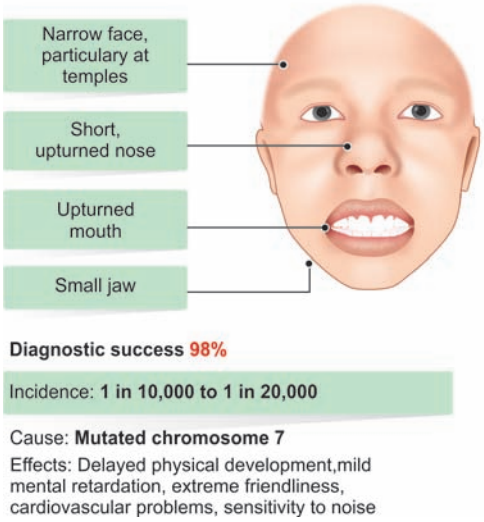


Fig. 41: Features of Williams syndrome

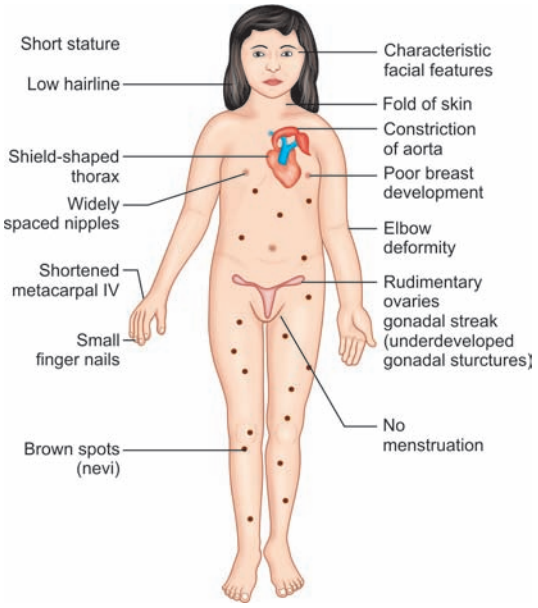
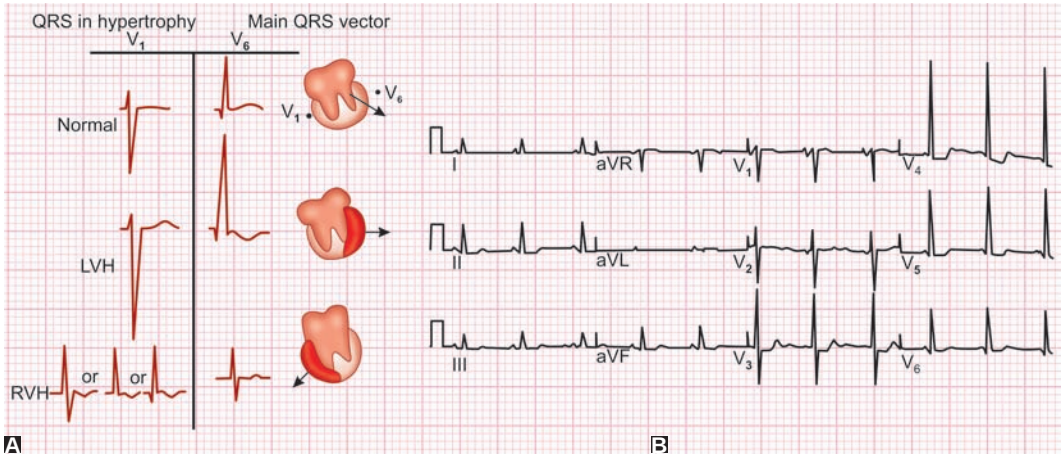


Fig. 42: Features of Turner's syndrome



Figs 43A and B: Electrocardiography of changes of aortic stenosis

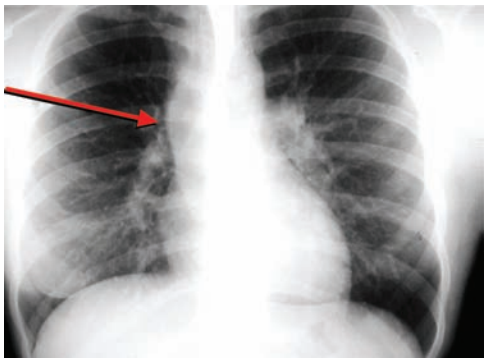


Fig. 44: Chest X-ray showing poststenotic dilatation of ascending aorta (arrow)

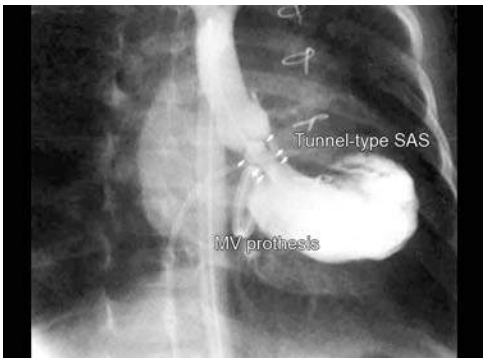


Fig. 47: Ventriculography showing subvalvular aortic stenosis (SAS)

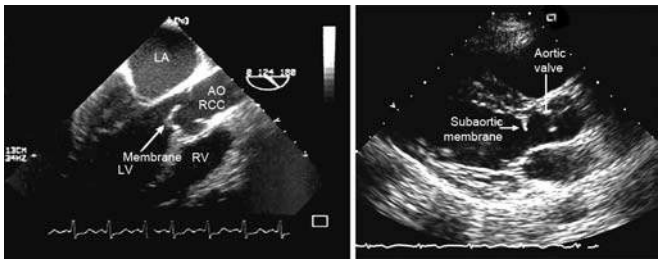


Fig. 45: A linear structure in the LVOT. Early, mid-systolic closure with fluttering of the aortic cusps
Abbreviation: LVOT, left ventricular outflow tract obstruction

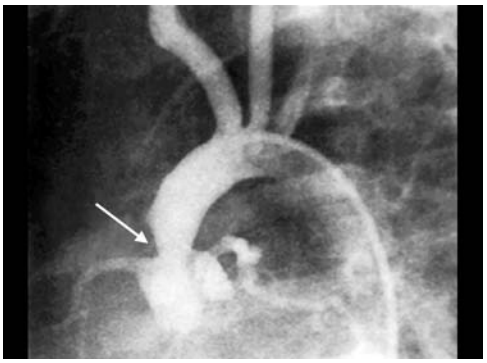


Fig. 48: Ventriculography showing supravalvular aortic stenosis (arrow)

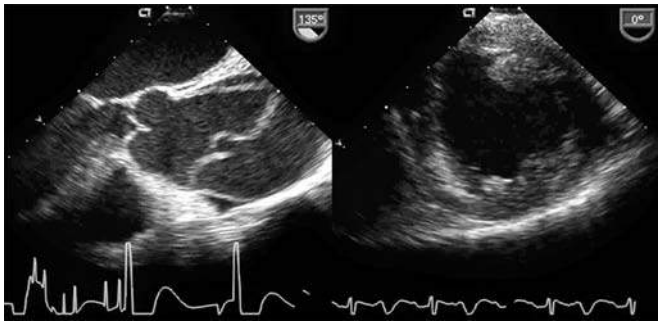


Fig. 46: Echocardiogram showing supra-aortic membrane

- Valve morphology
  - Aortic regurgitation, patency of MV, thickness, movement, calcification (rare in children)
  - Poststenotic dilatation
- Aortic root injection
  - Number of cusps
  - Assess for AR and poststenotic dilatation.
- Subvalvular:
  - Presents with a high Doppler velocity on LVOT with normal AV on echocardiography
  - Frequent AR due to aortic valve jet.

INDICATIONS FOR SURGERY

- Symptomatic
- Mean pressure gradient (PG): Above 40 mm Hg, no lower ejection fraction (EF) limit
  - NB: Valve area or PG are not primary determinants of AVR
- Severe AS
  - Peak gradient: Above 60 mm Hg
- Asymptomatic
  - Severe AS and LV dysfunction

- Abnormal exercise test
- Velocity increases to more than 0.3 m/second/year
- Marked LVH + strain pattern
- Low gradient AS (<40 mm Hg) + low EF with contractile reserve.

MANAGEMENT OF AORTIC VALVULAR STENOSIS

- Neonates, if severe stenosis with shock:
  - Ionotropic support
  - Mechanical ventilation
  - Prostaglandins
  - Emergency balloon valvuloplasty
  - Surgery—determined by size of LV and aortic root
    - Effective—multistage Norwood approach
      Systemic → pulmonary arterial Blalock-Taussig shunt (BTS)
      Systemic venous → PA (Fontan)
    - Heart transplant
      LV structures are too small to support life
- Operative strategy
  - Valvotomy
    - Preferred in neonate, infant and child
    - Neonates and infants—salvage operation with high operative risk
    - Older children—palliative operation of choice
  - Aortic valve replacement
    - Mechanical aortic valve/aortic autograft/homograft
    - Ross procedure
- Outcome of surgery in neonates and infants
  - Results dependent upon associated left-sided pathology (e.g. LV size, MV and AV cross-sectional area
  - Severely hypoplastic left-sided structures—management as a single ventricle
- Valvotomy operative risk
  - Neonate/Infant: 12.5% (range 25–79%)
  - Less than 1 year: Less than 4%
- Reoperation after valvotomy
  - In 10 years, 2–5%
  - In 20 years, 35–50%
  - Neonate: 5.5 times higher rate of reoperation than if valvotomy performed after age of 1 year.

COARCTATION OF AORTA

Coarctation derived from Latin term *coartatio*, which means a drawing together. It refers to an area of narrowing of the thoracic aorta in the region of the insertion of arterial duct, with or without additional abnormalities of the aortic arch (Fig. 49).

PREVALENCE AND ETIOLOGY

- In 5–8% of all congenital cardiac defects
- More commonly in males than in females
- Long been recognized in the Turner's XO syndrome (35% of patients are affected)
- Isolated defect or in association with various other lesions, most commonly bicuspid aortic valve and VSD
- Latin term coarctatus, means contracted, tightened and pressed together
- Narrowing of the lumen of a vessel producing an obstruction to flow
- A localized segment of narrowing is called a coarctation, whereas a diffuse segment of narrowing is known as tubular hypoplasia (Long segment coarctation).

LOCATION

- Located near the aortic attachment of ligamentum arteriosum or PDA
- Preductal or postductal type depending on location with PDA (Figs 50A and B)
- An obtuse indentation in the posterolateral wall of the aorta corresponds to the location of internal ridge that eccenterically narrows the aortic lumen
- The ridge consists of smooth muscle, fibrous tissue and elastic tissue.

EMBRYOLOGY

- Coarctation is due to an abnormality in development of the embryologic left fourth and sixth aortic arches that can be explained by two theories
- The ductus tissue theory
- The hemodynamic theory.

Ductus Tissue Theory

- Coarctation develops as the result of migration of ductus smooth muscle cells into the periductal aorta, with subsequent constriction and narrowing of the aortic lumen
- Commonly, coarctation becomes clinically evident with closure of the ductus arteriosus.

Hemodynamic Theory

- Coarctation results from reduced volume of blood flow through the fetal aortic arch and isthmus
- In a normal fetus, the aortic isthmus receives a relatively low volume of blood flow

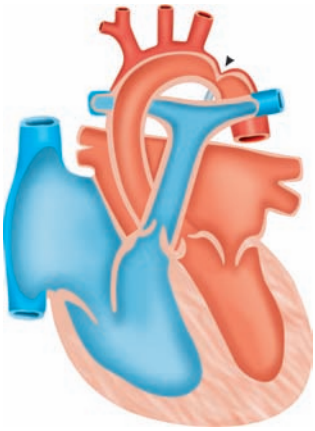
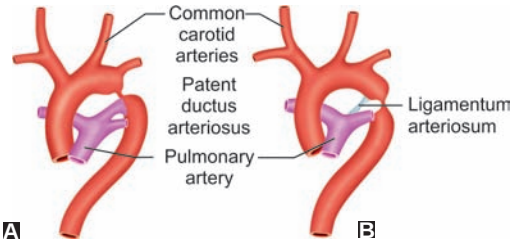


Fig. 49: Coarctation of the aorta



Figs 50A and B: Coarctation of the aorta (A) Preductal type; (B) Postductal type

- Most of the flow to the descending aorta is derived from the RV through the ductus arteriosus
- The LV supplies blood to the ascending aorta and brachiocephalic arteries, and a small portion goes to the aortic isthmus
- The aortic isthmus diameter is 70–80% of the diameter of the neonatal ascending aorta.

CLASSIFICATION DEPENDING ON ASSOCIATION WITH OTHER CARDIAC LESIONS

- Group I: Isolated coarctation
- Group II: Coarctation and VSD
- Group III: Coarctation and complex CHD
- Other coarctations:
  - Pseudocoarctation: Tortuous aorta but normal blood flow surgery for compression or aneurysm only
  - Abdominal coarctation: 2% of all coarctations.

CLASSIFICATION DEPENDING ON HISTO-PATHOLOGICAL DEFECT OF THE AORTA

- Primary coarctation
- Coarctation with isthmus hypoplasia (portion of the aorta between the left subclavian artery and the patent ductus or ligamentum arteriosum)
- Coarctation with tubular hypoplasia (involving the isthmus and segment between the left carotid and left subclavian arteries).

ASSOCIATIONS OF COARCTATION

- Eighty-two percent isolated lesion
- Eleven percent VSDs
- Eight percent other cardiac abnormalities
- 50–65%: distal aortic arch narrowing
- 27–46% bicuspid aortic valve.

PATHOPHYSIOLOGY

- Coarctation imposes significant afterload on the LV, resulting in increased wall stress and compensatory ventricular hypertrophy
- The afterload may be imposed acutely, as occurs following closure of the ductus arteriosus in neonates with severe coarctation rapidly developing CHF and shock
- As the ductus (aortic end) constricts, the left ventricular afterload rapidly increases, increasing left ventricular pressure (systolic and diastolic). Elevation of the LAP, opens the foramen ovale, causing left-to-right shunt and dilatation of the RA and RV
- If the foramen ovale does not open, pulmonary venous pressure and PA pressure increase, and right ventricular dilatation develops.

MECHANISM FOR DEVELOPMENT OF HYPERTENSION

- Mechanical obstruction theory: Higher BP is required to maintain flow through the coarcted segment and collateral vessels. The SV, ejected into the limited aortic receptacle, produces a higher pressure proximal to coarctation
- The humoral theory postulates activation of the renin-angiotensin system secondary to reduction of renal blood flow. In addition, activation of central sympathetic nervous system may also be responsible for hypertension of aortic coarctation
- Neural theory: Reduced distensibility of precoarctation aorta resets carotid sinus baroreceptors to operate at a higher pressure.

CLINICAL FEATURES IN NEONATES

May have storming clinical features during neonatal period with:

- Heart failure after a variable time of being well
- Tachypnea, feeding difficulties, progress to acidosis
- BP mismatch with decreased or absent femoral pulse
- Systolic murmur left sternal border with extension posteriorly
- Clinical features related to PDA closure
- Clinical features depend on degree to which collaterals develop
- Clinical feature also depends on presence of major noncardiac anomalies.

Clinical Presentations after Neonatal Period

- Infancy: Variable clinical manifestations
  - Hypertension, but seldom severe
  - Cardiomegaly on chest X-ray, RVH on ECG
- Childhood (1–14 years): Mostly asymptomatic unless associated lesions are present
  - Hypertension 90%, cardiomegaly 33%
  - Rib notching: 15% (>3 years)
  - Left ventricular hypertrophy on ECG, or normal ECG in 40%
- Adolescence/Adult: Many asymptomatic
  - Hypertension common and more severe
  - Murmur, decreased pulse, rib notching.

CLINICAL FEATURES AND PHYSICAL EXAMINATION FINDINGS

- May be asymptomatic
- Differential cyanosis (pink upper extremities with cyanotic lower extremities) may occur when right-to-left shunt across a PDA provides flow to the lower body
- However, in the presence of lesions with large left-to-right shunt (e.g. VSD), PA saturations may approximate aortic saturations with less obvious differential oximetric findings
- Reversed differential cyanosis (upper body cyanosis with normal lower-body saturation) may occur with transposition of the great arteries, PDA and PH, resulting in right-to-left ductal shunting
- Pulse: Radio-femoral delay—This is due to blood bypassing the obstruction via collateral vessels in the chest wall and hence the pulse in the legs is delayed.
- Systemic hypertension in the right arm
- Systemic thrill may be felt in suprasternal notch
- Arterial pulsation may be seen in the suprasternal and carotid vessels
- First heart sound is accentuated and followed by loud ejection click

- Second heart sound is normally split with loud aortic component
- Ejection systolic murmur at upper sternal edge. May be heard over the back in the interscapular area
- Collaterals at the back (Fig. 51).

IMAGING STUDIES

- Radiograph:
  - Early in life, cardiac enlargement and pulmonary venous congestion
  - In older children, shows a prominent aortic knob, and the stenotic region may be observed as an indentation of the proximal thoracic descending aorta in the shape of a number 3 (Fig. 52)
  - Rib notching is observed as irregularities and scalloping on the undersurface of the posterior ribs (Fig. 53).
- Barium esophagram shows the classic "E sign" representing compression from the dilated left subclavian artery and poststenotic dilatation of the descending aorta.

Echocardiography

Two-dimensional echocardiography and Doppler studies provide an accurate, noninvasive assessment of coarctation anatomy and physiology in most patients. Color flow Doppler assists in localizing the site of obstruction and is particularly helpful in cases where two-dimensional imaging is difficult or inconclusive (Figs 54 and 55).

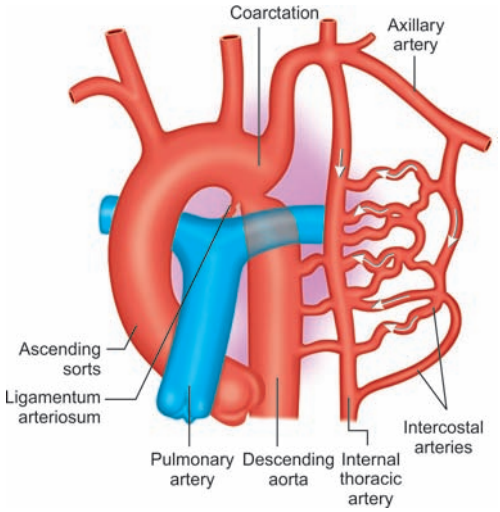


Fig. 51: Colateral vessels in coarctation of the aorta

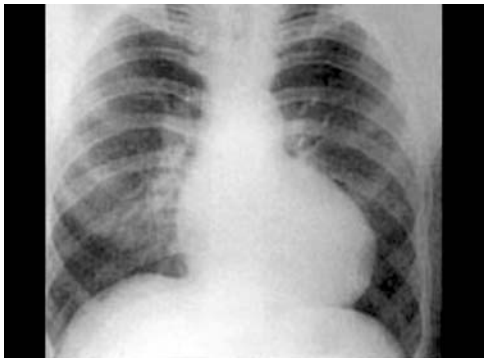


Fig. 52: Chest X-ray in coarctation. The "3" sign is present. The upper bulge in the position of a rather high aortic knuckle is formed by a large left subclavian artery, coming off the aortic arch before the coarctation. The lower bulge is formed by post-stenotic dilatation of the descending aorta below the coarctation

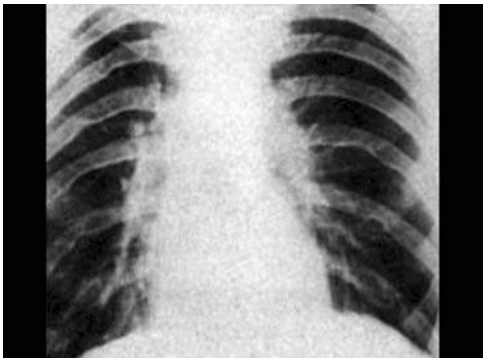


Fig. 53: Chest X-ray in coarctation showing marked rib notching

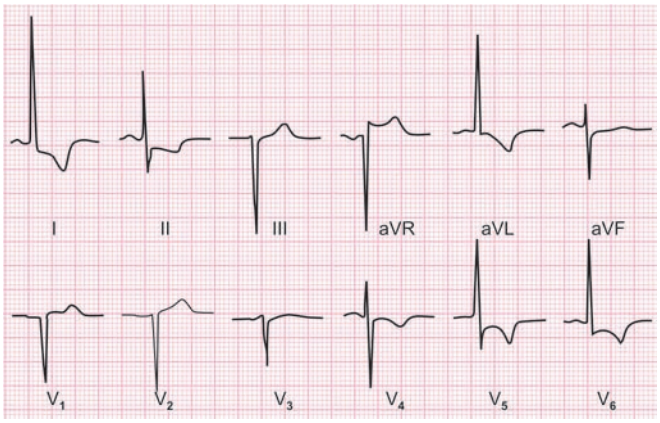


Fig. 54: Electrocardiogram of a patient with coarctation of the aorta. Note high voltage QRS complexes and ST-T changes in leads I, II, aVL and V_4-V_6 indicating hypertrophy, for V_1 to V_6, 1 mV = 0.5 cm

CARDIAC CATHETERIZATION (FIG. 56)

Cardiac catheterization provides following information:

- The type of aortic coarctation [diffuse, long segment, aortic kinking (pseudocoarctation)]
- Extent of collateral circulation
- Size of ductus arteriosus if patent
- Presence and degree of hypoplasia of transverse aortic arch and aortic isthmus, especially in neonates.
- If thoracic coarctation is not demonstrated despite clinical features of coarctation abdominal aortography may be needed to demonstrate (or exclude) abdominal coarctation.

MANAGEMENT

- Critically-ill neonates
  - Prostaglandin E1 (PGE1): 0.01–0.1 mg/kg/minute
  - Emergency repair either surgery/balloon dilatation
- Coarctoplasty to be done when diagnosed to avoid residual hypertension

Surgical repair: Primary coarctations less than 6 months of age

- Balloon dilatation
  - Native coarctations more than 6 months
  - Recoarcts/coarctations with CHF
  - Long-term follow-up is essential
  - Pseudoaneurysms, recoarcts, persistent hypertension.

Guidelines for Various Procedural and Surgical Management

- Children older than 1 year and adults with discrete native coarctation are candidates for balloon dilatation
- Long-segment coarctations or those associated with significant isthmic hypoplasia may be candidates for stent placement
- Recurrent coarctation following previous balloon angioplasty may be treated with repeat balloon angioplasty. If the recoarcted segment is long, surgical treatment necessitates
- Balloon angioplasty is the treatment of choice in extremely ill neonates and infants with severe coarctation
- Balloon angioplasty is the treatment of choice for postsurgical recoarctations.

Balloon Angioplasty

The size of the balloon chosen for angioplasty is two or more times the size of the coarcted segment, but no larger than the size of the descending aorta at the level of the diaphragm.

Results

- A reduction of PG across the coarctation and an increase in the size of the coarcted segment have been observed
- The collateral vessels diminish promptly
- The femoral pulse, which had been either absent or markedly reduced and delayed (when compared with brachial pulse) become palpable with increased pulse volume after balloon angioplasty.

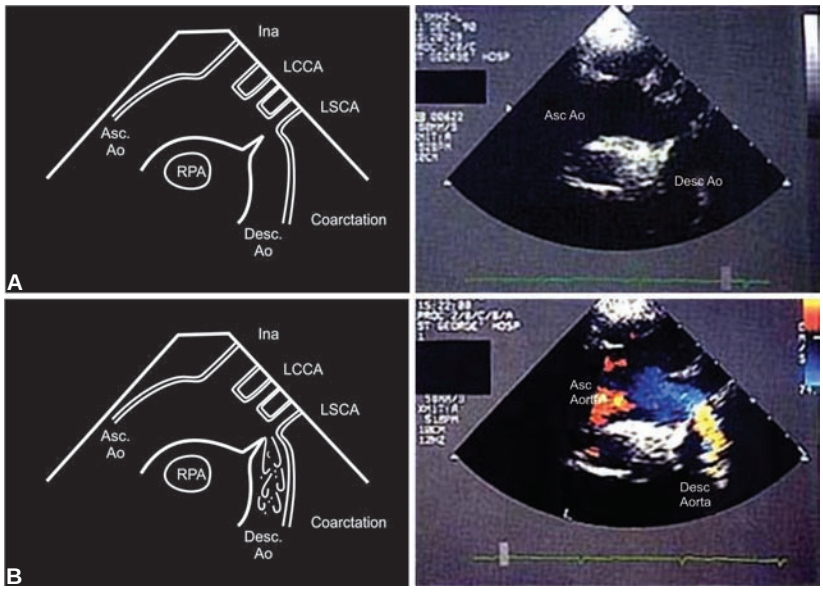
Aortic Stents (Fig. 57)

The aortic stents are placed for following benefits:

- The ability to expand tubular long-segment coarctation, hypoplastic isthmus, and the distal transverse aortic arch
- To increase the coarcted segment diameter independently of the intimal tear
- To decrease the probability of restenosis
- To prevent dissection of the torn intimal flap by facilitating apposition of the intima against the media
- To prevent aneurysms because of the support of the weakened aortic wall with the stent and neointima.

Surgical interventions are done in following conditions:

- Coarctations that involve the long segment of the aorta
- Coarctations that are completely or almost completely occluded so that no catheter or guidewire can be passed across the coarcted segment
- Coarctations that is associated with a large PDA and VSD.



Figs 55A and B: Echocardiogram of coarctation aorta. (A) Two-dimensional suprasternal view showing the aortic arch and upper-body vessels. There is a bright "wedge" of tissue restricting the aortic lumen just distal to the left subclavian artery; (B) Color Doppler shows an increase in velocity and turbulence at this point

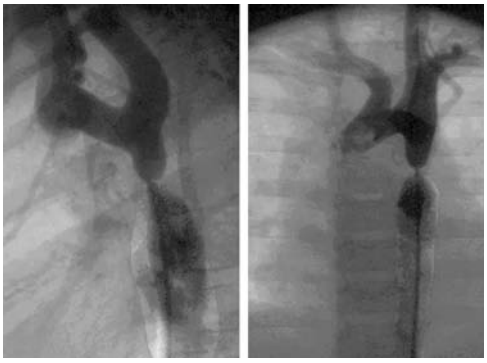
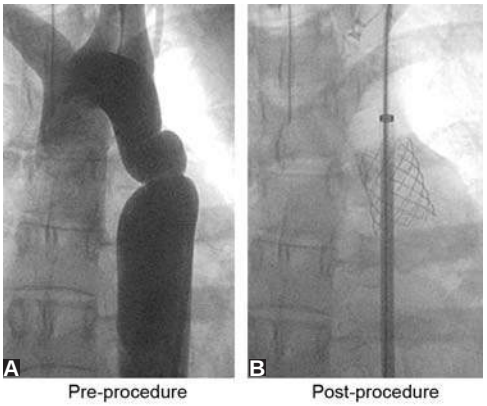


Fig. 56: Coarctation of aorta as seen in the cardiac catheterization



Figs 57A and B: Aortic stents (A) Preprocedure; (B) Postprocedure

OPERATIVE REPAIR

- Resection and end-to-end anastomosis (ETE)
- Subclavian flap aortoplasty (SFA)
- Resection and extended ETE
- Combined ETE and SFA (Fig. 58).

POSTCOARCTECTOMY SYNDROME

- Restoring pulsatile blood flow to the mesenteric arteries may result in mesenteric arteritis. Reflex arteriolar vasoconstriction occurs as part of autoregulation of blood flow leading to ischemia
- This syndrome may be related to early return to feeding after coarctation repair. Thus, feedings are usually delayed for 48 hours after surgery, slowly advanced as tolerated
- Patients with severe postcoarctectomy syndrome may require exploratory laparotomy for treatment of bowel necrosis or perforation.

CONGENITAL HEART DISEASE WITH MILD OR NO CYANOSIS WITH SYSTEMIC HYPOPERFUSION

Hypoplastic Left Heart Syndrome

Second most common CHD presenting with cyanosis in the first week of life (Fig. 59).

Pathophysiology

- Severe stenosis or atresia of aortic or MV
- Hypoplastic LV
- Aortic arch hypoplasia
- Aortic coarctation often associated
- In utero, RV can provide adequate blood flow, growth of fetus usually normal
- Neonate requires PDA and left-to-right atrial flow

Common associations are:

- Right aortic arch or aortic atresia
- Anomalies of pulmonary venous return
- Absent corpus callosum.

Clinical Presentation

- Timing and severity depends on:
  - Presence or absence of PDA
  - Adequacy of left-to-right atrial flow
  - Relative PVR versus SVR (high PVR leads to increased PA blood flow into systemic circulation)
- Immediately after birth:
  - Few symptoms (may be mild tachypnea and cyanosis)
- With closure of PDA and decreased PVR, systemic circulation:
  - Drops with resultant poor perfusion to vital organs
  - Can lead to multiple organ dysfunction syndrome (MODS) and shock
  - CHF also develops secondary to increased LA pressure and all PBF going to lungs
- In utero diagnosis has changed the presentation because of (now) early and aggressive management strategies
- Single S_2; one-third have a gallop
- No murmur; or may have tricuspid regurgitation murmur or "flow murmur" from increased PBF
- Pulse initially may be normal (if PDA present), but after closure, pulse may be absent with accompanying poor perfusion
- Significant pulmonary edema/CHF especially if ASD/PFO is restrictive
- Chest X-ray (Fig. 60): Shows cardiomegaly and pulmonary plethora.

Management

- PGE1
- Norwood three-stage repair
- Transplant.

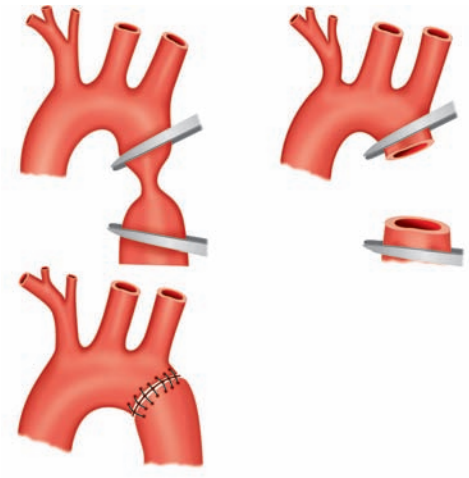


Fig. 58: Surgical repair of coarctation aorta

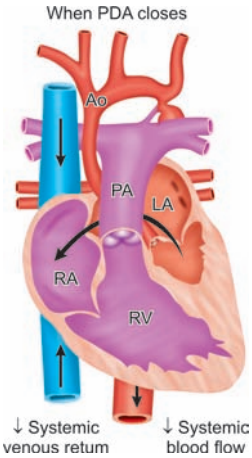


Fig. 59: Diagrammatic anatomy of hypoplastic left heart syndrome

Abbreviations: Ao, aorta; LA, left auricle; PA, pulmonary artery; RA, right auricle; RV, right ventricle

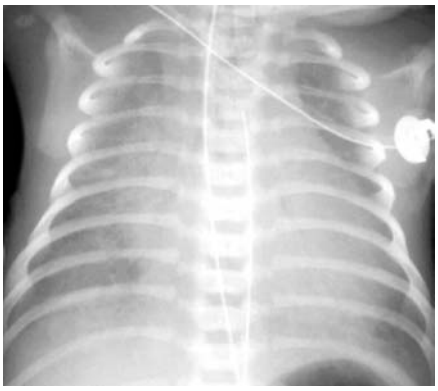


Fig. 60: Cardiomegaly and increased pulmonary vascular markings

Aortic Stenosis (Neonatal and Early Infancy)

- Five percent of all CHD; males greater than 4:1.

Pathophysiology

- Supravalvular (associated with Williams syndrome)
- Valvular (sometimes associated with bicuspid aortic valve)
- Subvalvular (IHSS-like).

Clinical Features

- In utero, may develop ventricular hypertrophy and even dilation if obstruction is significant and may lead to poor LV function.
- No cyanosis, but may have CHF
- If severe, cardiogenic shock (and death) with ductal closure
- But, commonly, especially if mild valvular, not detected until several years of age; but may present in early infancy too
- Systolic ejection murmur at upper right sternal border (URSB) which radiates to neck (not back, as in pulmonary stenosis)
- Narrow pulse pressure (decreased systolic).

Chest X-ray

Critical AS with CHF (note pleural effusion) shown in Figure 61.

Management

- If seemingly critical AS, treat with PGE1
- Treat CHF
- Valvuloplasty (unfortunately, restenosis is common)
- Valvotomy
- May even require Norwood procedures if left ventricular not functioning well or severe obstruction present
- Even if only mild valvular with bicuspid valve, will require bacterial endocarditis prophylaxis.

CYANOTIC CONGENITAL HEART DISEASE

MANAGEMENT OF A CYANOSED NEONATE

- Stabilize the child
- Check pulse, BP, SPO_2 in all four limbs.

Hyperoxia Test

- Place infant on 100% oxyhood for 10 minutes
  - PaO_2 above 100 mm Hg parenchymal lung disease
  - PaO_2 equal to 50–100 mm Hg parenchymal lung disease or cardiovascular disease
  - PaO_2 below 50 mm Hg fixed right-to-left shunt cyanotic CHD or persistent pulmonary hypertension (PPHN)

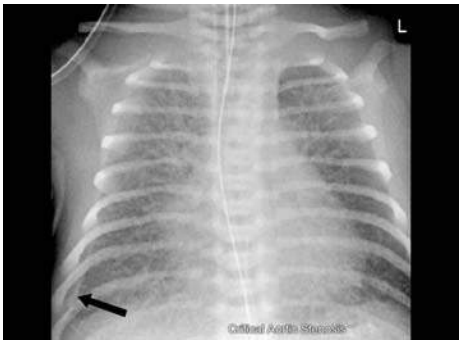


Fig. 61: X-ray chest of critical aortic stenosis in neonate with pulmonary plethora and pleural effusion (arrow)

- If fixed right-to-left shunt
  - Need to get a preductal and postductal arterial blood gases (ABGs) with infant on 100% O_2
    - Preductal—radial or temporal artery
    - Postductal—umbilical artery
  - If difference in PaO_2 is above15 mm Hg, then ductal shunting
  - If difference in PaO_2 is below 15 mm Hg, then no ductal shunting.

Hyperoxia-hyperventilation Test

- Hyperinflate baby with manual resuscitator and 100% O_2 until $PaCO_2$ reaches 20–25 mm Hg
  - PaO_2 equal to 100 mm Hg with hyperinflation
    - Persistant Pulmonary hypertension (PPHN)
  - PaO_2 less than 100 mm Hg with hyperinflation
    - Abnormal echo shows CHD
    - Normal echo suggestive of PPHN.

Chest X-Ray

Chest X-ray will help to differentiate between cyanotic heart diseases with decreased lung vascularity (tetralogy of Fallot, tricuspid atresia, etc.) and with increased lung vascularity (TGA, truncus arteriosus).

Echocardiography

Echocardiography will help to diagnose most of the cyanotic congenital heart diseases.

Prostaglandin Infusion

When to give?

- In a cyanotic infant in whom cardiac disease is suspected a low threshold for starting PGE is needed
- Even in a stable infant, the risk of withholding PG is usually greater than the risks associated with PG due to the risk of rapid clinical deterioration when the duct closes, especially in a transport environment.

If the diagnosis is uncertain a trial of PGE for 30–60 minutes with repeat ABG may be warranted and will usually outweigh the risks of delaying treatment.

What dose?

- When the duct is still open
  - Priority is to prevent further loss of patency
  - Starting dose of 10 µmg/kg/minute infusion
  - If no improvement in SaO_2 then increase dose by 10 ng/kg/minute increments up to 50 ng/kg/ minute until SaO_2 improves
- When the duct is closed:
  - Higher starting dose of 100 µg/kg/minute will be required to reopen the duct
  - When saturations improve then dose can be decreased to a dose to maintain ductal patency.

Side-effects

- Fever: 12%
- Apnea: 12%
- Flushing: 10%
- Hypotension.

- Will rarely occur at 10 ng/kg/minute
- It is not an indication to decrease the dose if the infant is responding clinically, rather respiratory support is warranted
- The likelihood of apnea is very high at a dose of 100 µg/kg/minute and most infants on this dose should have ventilatory support.

TETRALOGY OF FALLOT

Background

La maladie bleue, as described by Louis Arthur Etienne Fallot in 1888, is the clinical description of the physiology created by a combination of anatomic malformations now referred to as TOF. The cardinal features consist of an interventricular communication, or VSD, biventricular connection of the aortic root, which overrides the muscular ventricular septum, obstruction of the right ventricular outflow tract, and RVH.

Epidemiology

Tetralogy of Fallot occurs in three of every 10,000 live births. It is the most common cause of cyanotic cardiac disease in patients beyond the neonatal age, and accounts for up to one-tenth of all congenital cardiac lesions.

Anatomy

The combination of the deviated outlet septum and the hypertrophied septoparietal trabeculations produce the characteristic right ventricular outflow tract obstruction of TOF. The deviation of the muscular outlet septum is also responsible for creating the malalignment type VSD, and results in the aortic override. The associated hypertrophy of the right ventricular myocardium is the hemodynamic consequence of the anatomical lesions created by the deviated outlet septum (Figs 62A and B).

Clinical Manifestations and Diagnostic Workup

The initial presentation of TOF varies depending on the severity of the obstruction of blood flow to the lungs. The cyanosis may be present at birth or shortly thereafter, generally appearing within the first 6 months of life. Hypoxemic episodes, also called hypercyanotic spells or tetralogy spells, are characterized by severe cyanosis, hyperpnea. These "tet spells" may be initiated by crying or by exercise, or they may be brought on without obvious stimulation (Fig. 63B). The hypoxemic episodes are mediated by dynamic changes in the degree of subpulmonic obstruction, decrease in SVR. Such cyanotic episodes can lead to seizure activity and death. Patients with the tetralogy commonly exhibit squatting behavior following exercise. This practice helps to improve arterial oxygen saturation by increasing arterial BP, cardiac output, peripheral resistance and venous return to the heart. Growth of the affected child will generally proceed normally unless extreme cyanosis or other predisposing conditions are present. Pink TOF patients may develop symptoms of mild pulmonary overcirculation. Significant symptoms of CHF, however, are rarely seen unless there is a large PDA or aortopulmonary collateral arteries. In the cyanotic patient, clubbing of the fingers is a common finding, often appearing after 6 months of age. TOF has been associated with significantly increased susceptibility to cerebral abscesses. Patients with symptoms of unexplained headache, lethargy, fever, and later, persistent emesis must be carefully evaluated and promptly treated. Another complication frequently encountered by this population is IE.

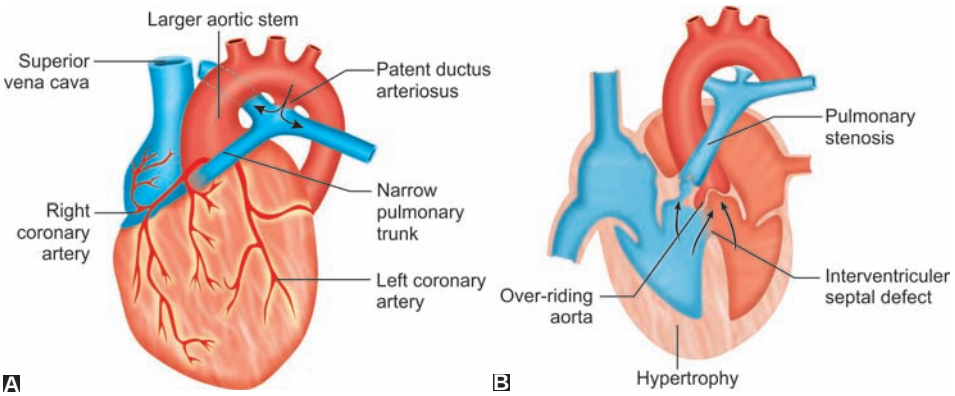
In addition to cyanosis, other physical examination may reveal the following:

- Finger clubbing (Fig. 63A)
- Normal pulse
- Normal BP
- Bulging of left anterior hemithorax due to RVH
- Left parasternal right ventricular impulse can be seen and felt
- Systolic thrill in left third and fourth parasternal space
- Loud harsh systolic murmur along left parasternal border which is ejection in type in upper left parasternal border and holosystolic in left lower sternal area
- Murmur is due to right ventricular tract obstruction causing turbulence
- Second heart sound is single.

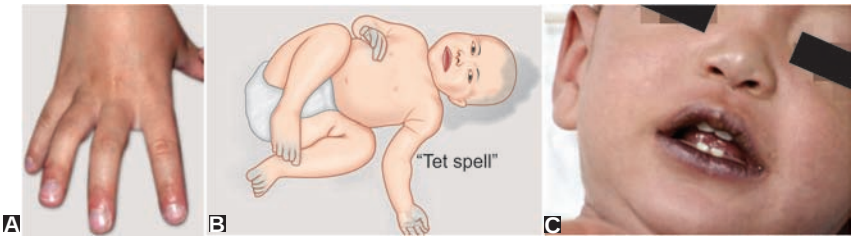
The electrocardiogram will demonstrate RAD and prominent right ventricular forces, with large R wave in the anterior precordial leads and large S wave in the lateral precordial leads.

The classical chest radiograph will demonstrate a boot-shaped cardiac silhouette (Fig. 64).

This is due to upward displacement of the right ventricular apex as a consequence of the RVH, and a narrowing of the



Figs 62A and B: Tetralogy of Fallot. (A) Surface view; (B) The four components of the defect: Pulmonary stenosis, over-riding aorta, interventricular septal defect and hypertrophy of the right ventricle



Figs 63A to C: Child with Tetralogy of Fallot. (A) Clubbing; (B) Exhibiting bluish skin during episodes of crying or feeding; (C) Showing overt central cyanosis

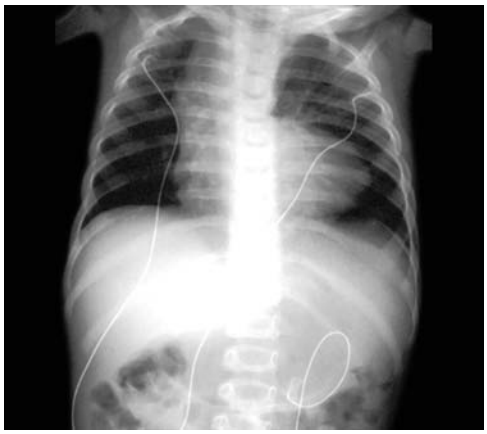


Fig. 64: Chest X-ray of tetralogy of Fallot upward and outward apex boot-shaped cardiac silhouette with oligemic lung field

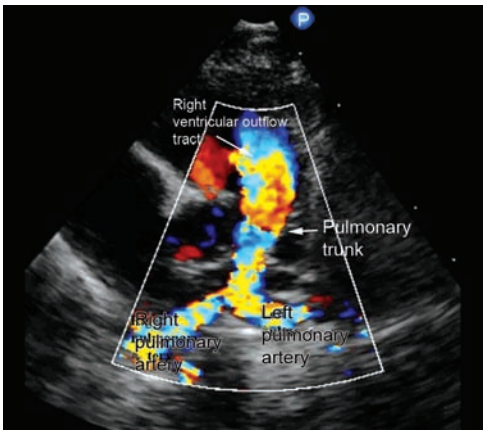


Fig. 65: Color Doppler has been used, and demonstrates turbulence and acceleration of the flow of blood in the right ventricular outflow tract, originating at the level of the deviated outlet septum. The turbulence continues into the hypoplastic pulmonary trunk and pulmonary arteries

mediastinal shadow due to the hypoplastic pulmonary outflow tract.

Diagnosis is confirmed with echocardiography. The severity of the subpulmonary obstruction, its dynamic component, the size of the right and left PAs, and any additional sources of flow of blood to the lungs will all be delineated. The degree of aortic override, the size of the interventricular communication, as well as the presence of other associated lesions, will be identified. Cardiac catheterization is now rarely needed due to the high sensitivity and specificity of echocardiographic images.

Etiology and Genetic Counseling

The etiology is multifactorial. Associated chromosomal anomalies can include trisomies 21, 18 and 13, but recent experience points to the much more frequent association of microdeletions of chromosome 22. The deletion, manifested by varying degrees of palatal abnormalities, dysmorphic facies, learning disabilities, immune deficiencies, and hypocalcemia, is frequently referred to as the DiGeorge Syndrome. The risk of recurrence in a family is approximately 3%. Associations with maternal intake of retinoic acid during the first trimester, poorly controlled diabetes, and untreated phenylketonuria has also been described.

MANAGEMENT

Medical Therapy

- Maintain Hb greater than 14 gm/dL (by using oral iron or blood transfusion)
- β-blockers to be given in highest tolerated doses (usual dose 1–4 mg/kg/day in two to three divided doses).

Management of the Hypercyanotic Spell

Parents at home with a child suffering such spells are taught to place their child in the knee-to-chest position in an effort to increase SVR and promote systemic venous return to the right heart. Medical management will consist of establishing immediate intravenous access to allow prompt administration of fluids, which will improve right ventricular preload. Oxygen should be initiated to decrease peripheral pulmonary vasoconstriction, and improve oxygenation once flow of blood to the lungs is reestablished. Subcutaneous morphine should be administered to decrease the release of catecholamines. This will increase the period of right ventricular filling by decreasing the HR, and promote relaxation of the infundibular spasm. Alternatively, intravenous esmolol infusion (shortacting β-blockers) can be used. If the patient remains hypercyanotic after these measures, he/she should be paralyzed and intubated, with phenylephrine administered intravenously to increase SVR.

Surgical Management

In the current era, definitive therapy for TOF is surgical (adequate, complete relief of any right ventricular obstruction along with closure of the VSD).

Timing of Surgery

- Stable, minimally cyanosed: Total correction at 1–2 years of age or earlier according to the institutional policy
- Significant cyanosis (SaO_2 <70%) or history of spells despite therapy
  - Less than 3 months: Systemic to PA shunt

– More than 3 months: Shunt or correction depending on anatomy and surgical centers' experience.

COMPLETE TRANSPOSITION OF THE GREAT ARTERIES

In this anomaly, the aorta arises from the morphological RV, and the PA arises from the morphological LV (i.e. there is ventriculoarterial discordance). The aorta also tends to be on the right and anterior, and the great arteries are parallel rather than crossing as they do in the normal heart. Because the systemic and pulmonary circulations run in parallel, there has to be a communication between the two, either with an ASD, a VSD, or at the great arterial level (PDA) to support life. These connections allow systemic blood to enter the pulmonary circulation for oxygenation and allow oxygenated blood from the pulmonary circuit to enter the systemic circulation. The most common associated lesions are VSD (which occurs in almost half of the cases), pulmonary outflow tract obstruction, and less commonly, coarctation of the aorta (5%) (Fig. 66).

CLINICAL FEATURES

D-TGA is one of the most common cyanotic defects seen in newborns, and when the ventricular septum is intact, it is usually cyanotic in the first day of life. If circulatory mixing occurs via a patent ductus, physiological closure of the ductus causes abrupt cyanosis and clinical deterioration.

- Usually mild tachypnea only (unless CHF)
- No murmur (unless VSD or PS murmur)
- Loud and single S_2 (aortic valve very anterior and pulmonary valve further posterior)
- CHF due to left-sided overload (a later feature).

ELECTROCARDIOGRAPHY

Nonspecific, usually normal; however, RV hypertrophy may be noted after first week of life.

CHEST X-RAY

- Egg on a string (narrow superior mediastinal silhouette) (Fig. 67)
- Increased pulmonary vascular markings
- But, egg on string and increased vascular markings may not be seen in neonate!
- Concave pulmonary trunk seen sometimes
- Heart size normal or slightly increased.

MANAGEMENT

- Prostaglandin E1 to keep PDA open
- Treat CHF if present
- Cyanotic babies may be treated percutaneously with a Rashkind atrial balloon septostomy to create a more sizable ASD, which may dramatically improve their oxygenation until definitive surgery can be performed.

Definitive

Jatene arterial switch: Usually done at approximately 2 weeks of life if no VSD because LV still remains sufficiently hypertrophied to support systemic pressure load. If presented beyond 2 weeks, the LV mass have may regress and may be insufficient to support systemic BP. If VSD presents, switch procedure may be delayed.

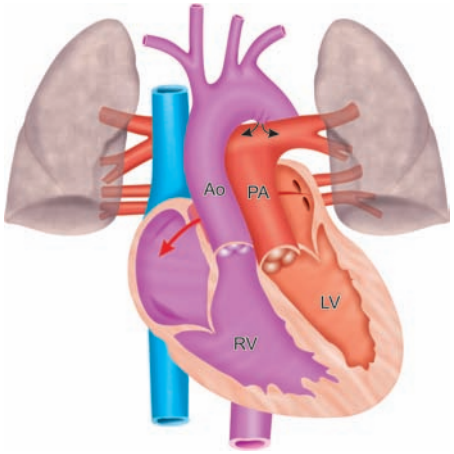


Fig. 66: Diagrammatic anatomy of transposition of great arteries (TGA)
Abbreviations: Ao, aorta; LV, left ventricle; PA, pulmonary artery; RV, right ventricle

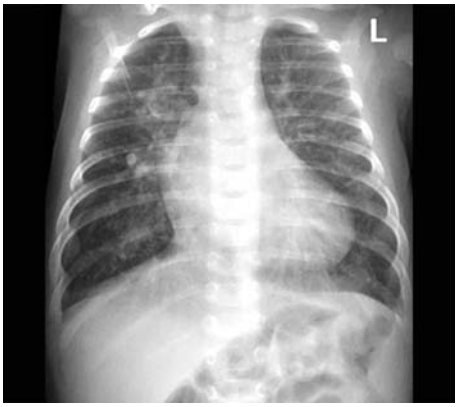


Fig. 67: Chest X-ray of transposition of great arteries (TGA) showing increased pulmonary vasculature, narrow mediastinal shadow giving the appearance of egg on string

TRICUSPID ATRESIA

This defect is relatively frequent among the cyanotic congenital diseases although not as often as TOF or transposition of the great arteries. The 30% of the cases will be associated to transposition of the great arteries.

ANATOMY

The anatomy is characterized by:

- Total atresia of the tricuspid valve
- Atrial septal defect (patent foremen ovale, ostium secundum)
- Occasionally, a common atrium maybe seen
- Left ventricular hypertrophy
- Ventricular septal defect is present in most cases
- Marked hypoplasia of the RV (Fig. 69)
- Transposition of the great arteries and atresia of the PA is not unusual in this congenital disease. In other cases, the PA may be normal or only a hypoplastic vessel (Figs 70 and 71).

Diagrammatic anatomy of normal heart (Fig. 68) compared to other CHDs associated with tricuspid atresia are shown in Figures 70 to 72.

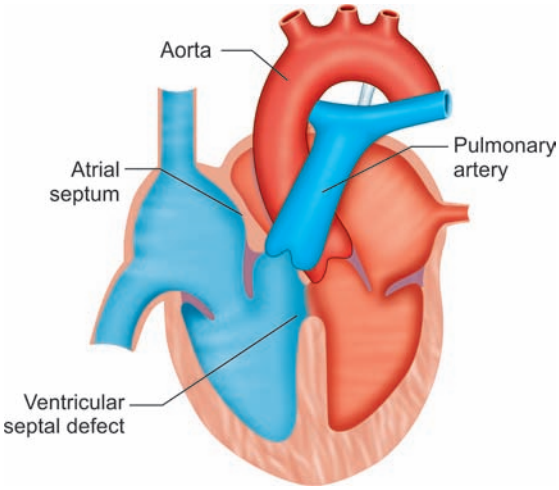


Fig. 68: Normal heart

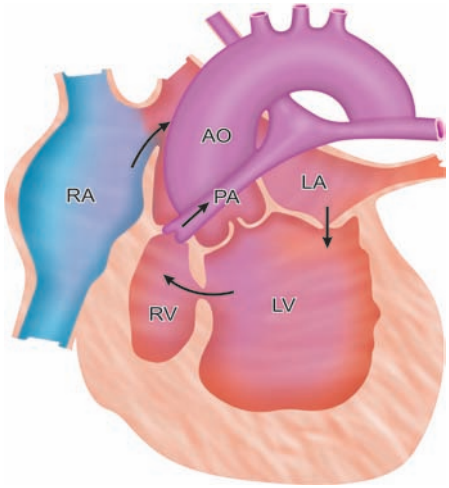


Fig. 71: Tricuspid atresia with pulmonary artery hypoplasia and ventricular septal defect. Note that the relation between the aorta and the pulmonary arteries is normal

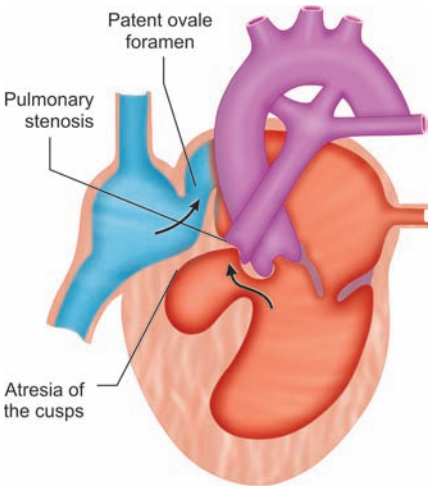


Fig. 69: Tricuspid atresia showing small right ventricle and large left ventricle

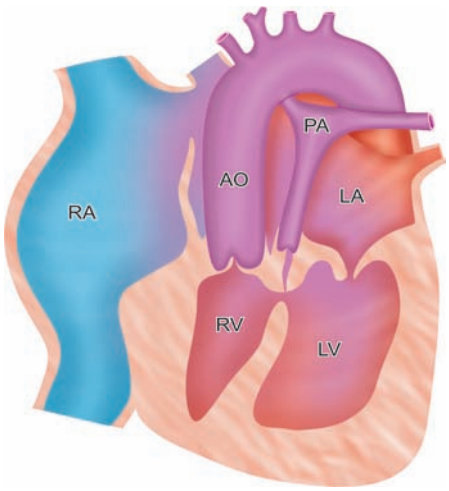


Fig. 72: Variety of tricuspid atresia with incomplete transposition of the great arteries and infundibular pulmonic stenosis

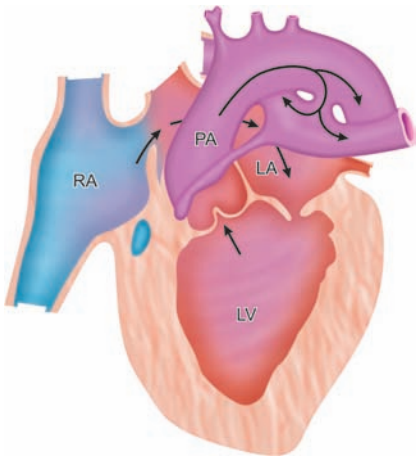


Fig. 70: Tricuspid valve and pulmonary valve atresia. Diagrammatic representation of the anatomy and pattern of circulation. The so called "four-chamber view" or -"apex view" in real-time echocardiography may be tremendously helpful in tricuspid valve atresia

ELECTROCARDIOGRAPHY

Electrocardiography is characteristic with LVH and left axis deviation (Fig. 73).

CLINICAL VIEWPOINT

- This is typically a cyanotic CHD with LVH and one of the few situations where the combination of cyanosis and left axis deviation in the electrocardiogram may be seen
- The patient may present clubbing of the fingers, dyspnea and anoxic crisis.
- Early cardiac insufficiency with cyanosis and cerebral vascular accidents is common finding
- The auscultation of these patients is rather atypical, having murmurs of different significance depending upon the importance of the associated malformations and shunts present.

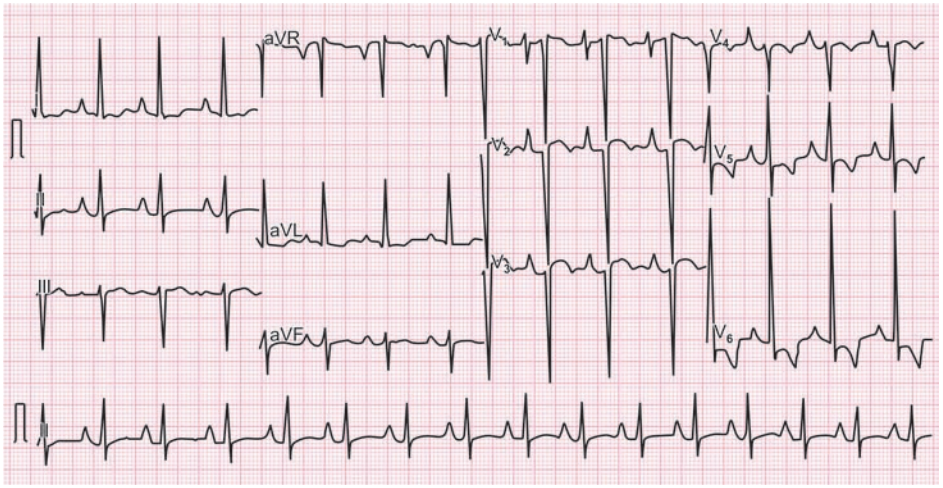


Fig. 73: Electrocardiography of tricuspid atresia showing left ventricular failure (LVF) (tall R in V_6) and left axis deviation as evidenced by negative QRS in AVF and tall R in lead-1 characteristic of tricuspid atresia

SURGICAL TREATMENT

The surgery attempts, in most cases, to alleviate the problem and not pretend a total, complete anatomical correction.

PROCEDURES

Glenn operation: Side-to-side anastomosis at the SVC with the right PA. Ligation of the SVC at the junction with the RA is necessary. The surgery is usually attempted when the patient is older than 6 weeks. If surgery is necessary before 6 weeks of age, side-to-side anastomosis between the right PA and the ascending aorta is preferred.

TRUNCUS ARTERIOSUS

- Associated with DiGeorge syndrome and infants of diabetic mothers
- Increased risk right aortic arch and interrupted aortic arch.

PATHOPHYSIOLOGY (FIG. 74)

- One arterial blood vessel leaves the heart from a single semilunar valve and gives rise to pulmonary and systemic (and coronary) arteries
- Truncal valve stenosis and regurgitation common (valve may have 2, 3 or 4 cusps): Stenosis places increased pressure load on both right and LVs and regurgitation increases SV
- Large VSD always present
- Not ductal dependent unless aortic arch is interrupted
- Branch PA and coronary artery stenosis can occur.

CLINICAL FEATURES

Cyanosis and CHF are hallmarks

- Cyanosis is mild-to-moderate
- Presentation may be subtle with only mild cyanosis and tachypnea
- CHF usually not present during immediate neonatal period
- Increased pulmonary blood flow (PBF) associated with decreased cyanosis and increased CHF (Fig. 75)

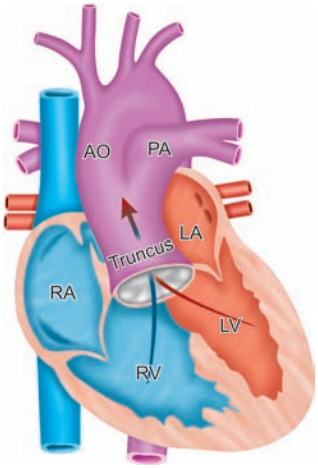


Fig. 74: Anatomy of truncal arteriosus (diagrammatic)
Abbreviations: Ao, Aorta; LA, left auricle; LV, left ventricle; PA, pulmonary artery; RA, right auricle; RV, right ventricle

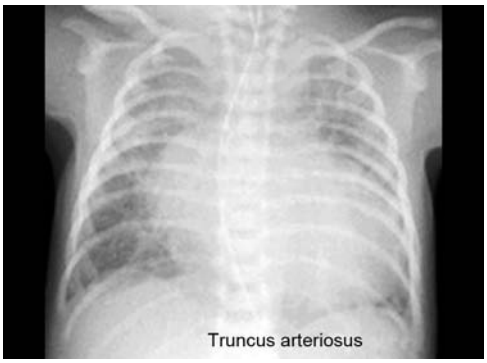


Fig. 75: X-ray chest showing cardiomegaly with pulmonary plethora

- Decreased PBF associated with increased cyanosis and decreased CHF
- Wide pulse pressure (with low diastolic pressure)
- Loud pansystolic murmur and single S_2 (increased flow across truncal root + valve may be stenotic)
- Stenotic truncal valve opening may be associated with mid-systolic click
- If missed in immediate neonatal period, may present with tachypnea and diaphoresis with feedings.

MANAGEMENT

- Avoid supplemental oxygen unless severe hypoxia present (decreased PVR leads to excessive PBF)
- Treat CHF if present (furosemide and digoxin)
- Echocardiography: Must examine for associated defects (aortic arch, truncal valve abnormalities, coronary artery stenosis)
- Evaluate for 22q11.2 deletion for DiGeorge syndrome or Shprintzen syndrome Velocardiofacial syndrome (VCF): Both DiGeorge and VCF syndrome map to same locus).
  - Fluorescence in situ hybridization
  - Check for hypocalcemia (be aware of seizures that may occur)
  - Consider initial immunodeficiency workup
  - Evaluate parents for VCF syndrome
  - Early (neonatal period) surgical repair.

TOTAL ANOMALOUS PULMONARY VENOUS RETURN

All [as opposed to some, as in partial-anomalous pulmonary venous return (APVR)] pulmonary veins, with fully oxygenated blood, follow an abnormal route returning to the RA via various paths instead of the LA; ASD required for right-to-left shunt to provide blood to LV and provide systemic blood flow.

Most common association is with asplenia syndrome and single ventricle.

Pathophysiology

There are three types of TAPVR (Figs 76A to C).

Two clinical types based on whether obstructive or nonobstructive.

Obstructive

- Mostly infracardiac, some supracardiac with vertical vein compressed between LPA and left main bronchus
- Clinical: Cyanosis, severe respiratory distress, shock and acidosis, no murmur
- Chext X-ray: Respiratory distress syndrome (RDS)-like, pulmonary edema (CHF) [increased pneumonia virus of mice (PVM)] from pulmonary venous hypertension
- Management: PGE1, oxygen, treat CHF, may need extra-corporeal membrane oxygenation (ECMO), urgent surgery.

Nonobstructive

- Mostly cardiac or supracardiac (Fig. 76)
- Clinical: Mild-moderate cyanosis, may have CHF secondary to increased PBF
- Chest X-ray: Pulmonary edema, (increased PVM), "snowman" (Fig. 77) silhouette (supracardiac only). Normal of small heart with pulmonary edema in infracardiac variety (Fig. 78)
- Management: Oxygen, treat CHF, elective surgery.

Ebstein's Anomaly (Fig. 79)

- Very uncommon (<1% of all CHD)
- High association with maternal lithium use.
- Increased risk for pulmonary hypoplasia due to large right heart in utero.

Pathophysiology:

- Tricuspid valve leaflets are displaced into RV and may obstruct the right ventricular obstruction tract (RVOT)
- The portion of the RV above the displaced leaflets become "atrialized"
- Tricuspid valve regurgitation and/or tricuspid stenosis
- Increased RA pressure results and right-to-left shunting occurs at atrial level.

Clinical features:

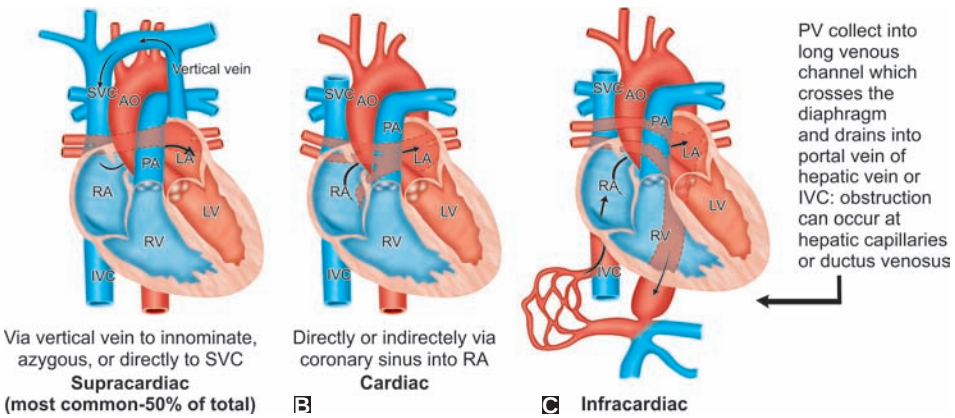
- Can have severe cyanosis secondary to decreased PBF
- Often without murmur
- Hepatosplenomegaly
- Supraventricular tachycardias (SVTs) (20% with WPW) common; can have RBBB and 1st degree AV block also.

Chest X-Ray

Massive cardiomegaly and pulmonary oligemia are characteristic (Fig. 80).

MANAGEMENT

- Mild forms require no specific treatment, and the infants generally do well
- Ductal dependent if severe RVOT obstruction; therefore, PGE1
- However, PDA (retrograde) flow in PA may make antero-grade flow more difficult and the RV may fill by pulmonary regurgitation
- Biventricular repair is possible depending on anterior tricuspid leaflet
- One and half ventricle repair (tricuspid valve repair with cavopulmonary anastomosis)
- Fontan or transplant may be the only alternatives in severe cases.



Figs 76A to C: Three types of total anomalous pulmonary venous return (TAPVR). (A) Supracardiac; (B) Cardiac; (C) Infracardiac

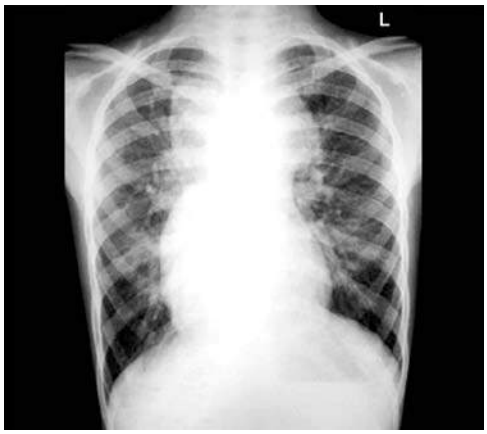


Fig. 77: Cardiomegaly with an enlarged right atrium and widening of the mediastinum (snowman or figure of 8 appearance), increased pulmonary arterial blood flow

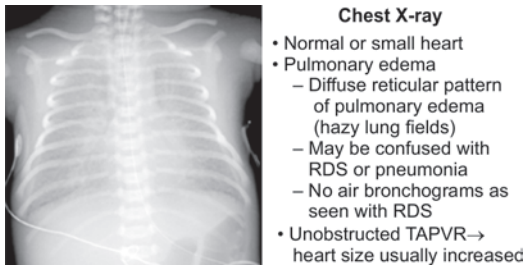


Fig. 78: Characteristics X-ray of infracardiac of Total Anomalous Pulmonary Venous Return (TAPVR)
Abbreviation: RDS, respiratory distress syndrome

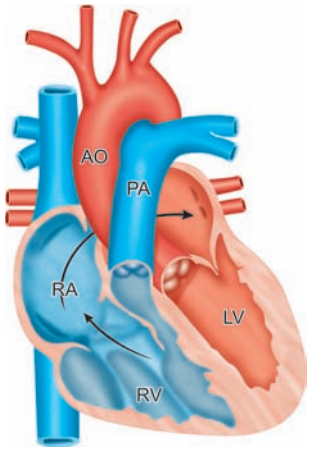


Fig. 79: Ebstein's anomaly (diagrammatic)
Abbreviations: Ao, aorta; LV, left ventricle; PA, pulmonary artery; RA, right auricle; RV, right ventricle

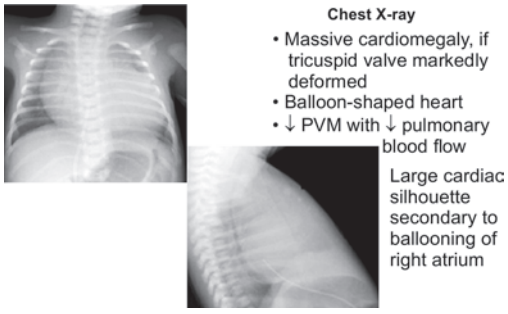


Fig. 80: Characteristic chest X-ray of Ebstein's anomaly

CONGENITAL HEART DISEASES: WHEN TO OPERATE?

EXTENT OF PROBLEM OF CONGENITAL HEART DISEASES

- Incidence: 6–8/1,000 live births
- About 40% critical: Need intervention in infancy
- Handful of centers available for intervention
- 1% children receive appropriate care.

Timely Diagnosis and Referral

These are essential and depend upon:
- Recognition of the problem in neonate
- Beside testing:
  - Hyperoxia test
  - Peripheral pulsations
  - Four limb blood pressure
- Life-saving interventions—PGE
- Knowledge of prognosis and counseling.

Timely Intervention

Timely intervention is required as:
- Too late may cause development of ventricular dysfunction
- Irreversible pulmonary vascular disease
- Inoperable
- Too early may cause high-risk surgery, poorer long-term results.

INTERVENTION FOR LEFT-TO-RIGHT SHUNTS

Atrial Septal Defect

- Usually asymptomatic
- Attention because of murmur—elective closure at 3–5 years of age
- Options: Surgical/device closure
- 10% have symptoms of CHF in infancy
- Need early closure if CHF develops.

Large shunt will require early consideration for intervention as evidenced by:
- Presence of diastolic flow rumble
- Cardiomegaly on chest X-ray
- Echo evidence of right ventricular volume overload
  Problems with ASD such as:
  - Right ventricular volume overload
  - Pulmonary vascular obstructive disease
  - Arrhythmia.
- Atrial septal defect with pulmonary artery hypertension (PAH) in children with:
  - Large defects
  - Additional lesions
  - Left ventricular inflow abnormalities
  - Pulmonary vein stenosis.

Such conditions need early closure by surgical/device.

Ventricular Septal Defects

- 1.5–3.5 per 1,000 live births
- 20% of congenital cardiac defects
  - Clinical presentation depends on size
  - Large VSDs: CHF, PAH, FTT
  - Small VSDs—murmur

Timing of intervention:
- Large VSD with PAH
  - Surgical closure of VSD by 6 months
- Small VSD do not require surgery prophylaxis IE
- Ventricular septal defects VSD with prolapsed AV with aortic incompetence—early surgery
- Moderate VSDs:
  - Moderate VSD, moderate PAH, CHF surgery at 6–12 months of age
  - Moderate VSD, mild PAH, no CHF surgery at 1 year of age
  - Moderate VSD, no PAH, >2:1 left to right shunt, surgery at 2–3 years of age.

Patent Ductus Arteriosus

- Large PDAs: CHF, PAH
- Small PDAs: Murmurs.

Patent Ductus Arteriosus Closure

- All auscultable PDAs to be closed due to risk of IE
- Preterm infants: Indometacin 0.2 mg/kg initial dose
- Large ductus: Early surgical closure in first year of life
- Small to moderate PDA transcatheter/surgical closure at presentation.

Atrioventricular Septal Defect

- Complete, partial transitional
- Complex AVSD—Early surgery at 8–12 weeks
- Partial/transitional: 2–5 years of age.

Left-sided Obstructive Lesions

Coarctation of Aorta

  - Severe coarctations present in infancy due to CHF
  - Associated with other complex lesions or syndromes like Turner's.

Management:
- Critically ill neonates
  - Prostaglandin E1: 0.01–0.1 mg/kg/minute
  - Emergency repair either surgery or balloon dilatation
- Coarctoplasty to be done when diagnosed to avoid residual hypertension
- Surgical repair—primary coarctations at less than 6 months of age
- Balloon dilation—native coarctations at greater than 6 months of age
  - Recoarcts/coarctations with CHF
  - Long-term follow-up is essential.
    - Pseudoaneurysms, recoarts, persistent hypertension.

Valvar Aortic Stenosis

- 15% present by 1 year with CHF
- Critical aortic stenosis (AS) in neonate present with cardiogenic shock
- Options: Surgical valvotomy/balloon aortic valvotomy (BAV)
- Moderate-to-severe AS-BAV at presentation.

Subaortic Stenosis

- Subaortic membrane or thick fibromuscular ridge, associated with AR
- Surgical repair if PG is above 50 mm Hg or new onset of AR
- Surgical myomectomy + resection of membrane
- Associated valvar AS—needs Ross/Ross Konno procedure.

Hypoplastic Left Heart Syndrome

- Rare CHD—Hypoplasia, absence of LV, MV, AV
- Fatal, if left untreated
- Neonatal presentation depends upon:
  - Patency of PDA
  - Restriction of ASD
  - Ratio of PVR to SVR.

Management

Stabilization on presentation by PGE:
- Two options: Three staged Norwood procedure or cardiac transplantation
  1. First palliative: Blalock-Taussig (BT) shunt with neoaortic reconstruction at first week of life with Damus K repair.
  2. Second stage: BDG or hemi-Fontan at 6–12 months of age.
  3. Third stage: Completion of Fontan at 3–5 years of age.

Right Ventricular Obstruction Tract Anomalies

- Pulmonary valve stenosis
- Balloon pulmonary valvuloplasty (BPV) if PSG is greater than 50 mm Hg
- Surgery for dysplastic pulmonary valve/infundibular pulmonary stenosis.

CYANOTIC CONGENITAL HEART DISEASE

Reduced Pulmonary Blood Flow

Tetralogy of Fallot Physiology

- Good intracardiac anatomy—Intracardiac repair (ICR) at 1 year of age
  - Adequate PV annulus
  - Good sized PA
  - Normal coronary anatomy
  - No associated defects.

Palliative treatment:
- Blalock-Taussig shunt:
  - Less than 6 months of age
  - Cyanotic spells
  - Unsuitable anatomy.
- Balloon pulmonary valvotomy.

Other variants:
- Tetralogy of Fallot with PA
  - Need early intervention
  - Unifocalization with shunt initially
  - Closure of VSD, RV-PA conduit at later stage.
- Double outlet right ventricle (DORV) with PS.
  - Needs to be treated on similar grounds
  - Rastelli repair—RV-PA conduit at 4–5 years of age
  - TGA, VSD with PS—Rastelli repair.

CYANOSIS WITH INCREASED PULMONARY BLOOD FLOW

Transposition of Great Vessels

- If ASD is restrictive—Balloon atrial septostomy

- PGE1: 0.01–0.1 mg/kg/minute
- Balloon atrial septostomy
- Arterial switch operation—up to 4 weeks
- Senning repair: 6–12 months of age.

Truncus Arteriosus

- One great vessel from the heart
- PA arises from aorta
- Medical management with decongestive treatment
- Corrective repair to be done before 6 months, preferably 4–6 weeks of life, VSD closure, RV-PA conduit
- May need replacement of conduit after 3–6 years.

Total Anomalous Pulmonary Venous Connection

- Obstructive total anomalous pulmonary venous connection (TAPVC), infradiaphragmatic
  - Need urgent surgery on presentation
- Supracardiac nonobstructive TAPVC
  - Behave like large ASDs
  - Nonurgent surgery
  - Needs corrective repair electively.

ACQUIRED CLINICAL CONDITION AFFECTING CARDIOVASCULAR SYSTEM

RHEUMATIC FEVER

Rheumatic fever is a systemic disease affecting several organ systems, including the heart. It is a sequel of group A beta-hemolytic streptococcal infections, usually tonsillopharyngitis, developing in less than 1% of infected patients. Rheumatic fever usually develops 10 days to 2 weeks following a streptococcal pharyngitis that almost always is associated with fever above 101°F (38.3°C), sore throat and cervical adenitis. The pathogenesis of the systemic manifestations is unknown.

Pathophysiology

The pathogenic link between a group "A" streptococcal infection of the upper respiratory tract and an attack of acute rheumatic fever, characterized by organ and tissue involvement far removed from the pharynx, is still not clear. One of the major obstacles to understanding the pathogenesis of acute rheumatic fever and rheumatic heart disease has been the inability to establish in animal model. Several theories of the pathogenesis of acute rheumatic fever and rheumatic heart disease have been proposed, but only two are seriously considered: the cytotoxicity theory and the immunologic theory.

The cytotoxicity theory suggests that a group A streptococcal toxin may be involved in the pathogenesis of acute rheumatic fever and rheumatic heart disease. Group A *streptococcus* produces several enzymes that are cytotoxic for mammalian cardiac cells. For example, streptolysin O has a direct cytotoxic effect on mammalian cells in tissue culture, and most of the proponents of the cytotoxicity theory have focused on this enzyme. However, one of the major problems with the cytotoxicity hypothesis is its inability to explain the latent period between an episode of group A streptococcal pharyngitis and the onset of acute rheumatic fever.

An immune-mediated pathogenesis for acute rheumatic fever and rheumatic heart disease has been suggested by the clinical similarity of acute rheumatic fever to other illnesses produced by immunopathogenic processes and by the latent period between the group A streptococcal infection and the acute rheumatic fever. The antigenicity of a large variety of group A streptococcal products and constituents, as well as the immunologic cross-reactivity between group A streptococcal components and mammalian tissues, also lends support to this hypothesis. Common antigenic determinants are shared between certain components of group A streptococcus (e.g. M protein, protoplast membrane, cell wall group A carbohydrate, capsular hyaluronate) and specific mammalian tissues (e.g. heart, brain, joint). For example, certain M proteins (M1, M5, M6 and M19) share epitopes with human tropomyosin and myosin. Additionally, the involvement of group A streptococcal superantigens such as pyrogenic exotoxins in the pathogenesis of acute rheumatic fever has been proposed.

Diagnosis of Acute Rheumatic Fever

Essential Criteria

Evidence of recent streptococcal infection as indicated by:
- Increased antistreptolysin "O" titer (↑ASO)
- Positive throat culture
- Recent scarlet fever.

Two major or one major and two minor criteria in the presence of essential criteria are required for diagnosis of rheumatic fever.

Exceptions to the Jones Criteria

A presumptive diagnosis of rheumatic fever may be made without strict adherence to the criteria in at least three circumstances:
1. Chorea, which may be the only manifestation.
2. Carditis and its sequelae in patients presenting long after an episode of acute rheumatic fever.
3. Previous history of rheumatic fever and a recent streptococcal infection, but care must be taken that the diagnosis of the previous episode of rheumatic fever was carefully made according to the Jones criteria.

In any of these situations, other etiologies must be excluded by appropriate testing. As with all such diagnostic criteria, strict adherence to the Jones criteria may lead to under diagnosis of acute rheumatic fever. In the modern era, this is particularly pertinent when considering the increased identification of valvulitis by echocardiography, which is not evident by physical examination (Table 3).

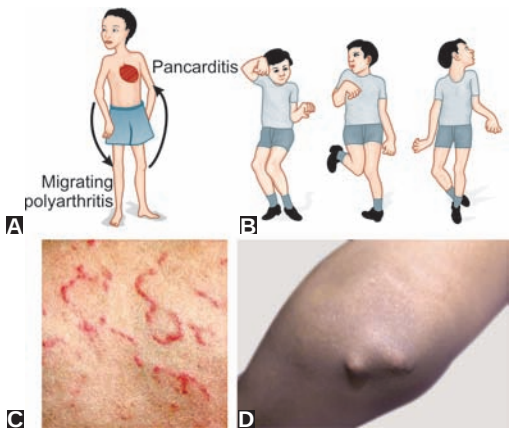
Major Criteria

Carditis:

Carditis can involve any layer of the heart. Pericarditis can occur in this disease and can be suspected by the occurrence of chest pain that may be referred to the abdomen or shoulders. It is diagnosed by finding a pericardial friction rub on auscultation, ST segment elevation/depression on the electrocardiogram, or thickened pericardium or effusion by echocardiogram.

Cardiac enlargement or cardiac failure without evidence of valvar anomalies is evidence of myocardial involvement. Rarely, cardiac failure occurs from myocardial involvement itself. Various degrees of heart block, gallop rhythm and muffled heart sounds are other manifestations of myocarditis. Prolonged PR interval in itself is not a criterion for carditis.

Table 3: Modified Jones criteria for the diagnosis of acute rheumatic fever
Major criteria (Figs 81A to D)
Carditis*
Arthritis
Chorea*
Erythema marginatum
Subcutaneous nodules
Minor criteria
Arthralgia
Prolongation of the PR interval
Elevated acute phase reactants (e.g. ESR, CRP, WBC)
Fever
Other
Previous history of rheumatic fever*
Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; WBC, white blood cells *See exceptions noted.



Figs 81A to D: Five major criterias of rheumatic fever. (A) Migrating polyarthritis and pancarditis; (B) Sydenhams chorea; (C) Erythema marginatum; (D) Subcutaneous nodules

Valvulitis is the most serious manifestation of carditis because it can lead to permanent cardiac sequelae. Both the aortic and MV may be involved acutely.

Acute hemodynamic overload leads to LVF and increase mortality and morbidity of rheumatic fever and rheumatic heart disease.

Three types of murmurs may be present that suggest acute rheumatic fever:

1. An apical holosystolic murmur of mitral insufficiency is the most frequently occurring murmur, which is evidence of endocarditis.
2. At times a mid-diastolic murmur or delayed diastolic murmur (Carey Coombs murmur) may also be heard at the apex. The origin of this murmur is unknown, but it is perhaps related to turbulence either from the valvulitis or from the blood flow into a dilated LV.
3. An early-diastolic murmur of aortic insufficiency may be found during the acute episode but is a more frequent late manifestation.

Aortic stenosis does not occur during the acute episode of rheumatic fever.

These valvular abnormalities, particularly aortic and mitral insufficiency, may be demonstrated by echocardiography and color Doppler.

Arthritis:

Arthritis is usually a migrating polyarthritis; several joints may be involved, often sequentially, but at a given time there may be involvement of only one joint. Usually the large joints are involved. Diagnosis of arthritis rests on finding warm and tender joints that are painful on movement. The changes are never permanent. Younger the child with acute rheumatic fever the less the arthritis and older the patient the more the arthritis.

Chorea (Figs 81B and 83):

Chorea is a late manifestation of rheumatic fever and often develops several months after the streptococcal infection. At that time, other manifestations of rheumatic fever may not be found and signs of acute phase reactants like raised ESR and raised CRP return to normal. The presence of chorea alone is sufficient for the diagnosis of rheumatic fever, as there are virtually no other causes in childhood, although lupus must be excluded. Chorea is more common in females and prior to puberty.

Chorea is characterized by involuntary, nonrepetitive, purposeless motions, often associated with emotional instability. The parents may complain that their child is clumsy, is fidgety, cries easily, or has difficulty in writing or reading.

Classic physical findings of chorea may not exist. The milkmaid (or grip) sign describes the fibrillatory nature of a hand grasp. Other findings are related to exaggerated muscle movements, such as the hyperextension of the hands or apposition of the backs of the hands when the arms are extended above the head. Although lasting for months in some children, it is not usually permanent.

Erythema Marginatum (Fig. 81C):

Although major criteria for acute rheumatic fever, it is rarely found in children of Indian subcontinent. Also dark complexion of children in these regions helps not to recognize its signs. It is an early manifestation and predominantly seen over trunk. Erythema marginatum is a fleeting, characteristic cutaneous finding. It is characterized by pink macules with distinct sharp margins; these change rapidly in contour. Warmth tends to bring out these lesions.

With time the center fades, while the margin persists as a circular or serpentine border.

Subcutaneous Nodules

Subcutaneous nodules are a rare manifestation of rheumatic fever, occurring late in the course of the disease. These are nontender, firm, pea-like nodules over the extensor surfaces, particularly over the knees, elbows and spine. They have a strong association with carditis.

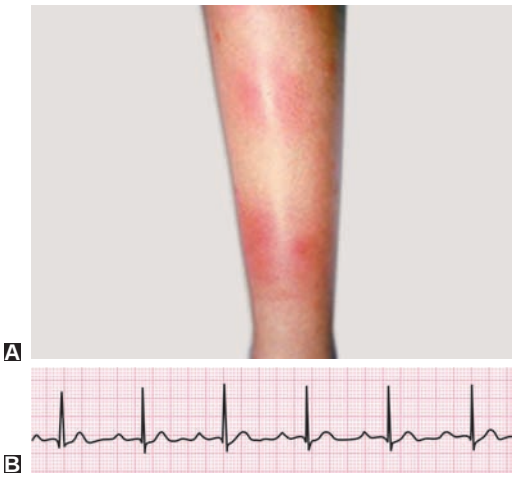
Minor Criteria (Figs 82A and B)

Arthralgia:

The symptom of painful joints without subjective evidence of arthritis may be used as a minor criterion, if arthritis has not been used as a major one.

Prolongation of the PR Interval:

This can be used as a minor criterion, if carditis has not been used as a major one.



Figs 82A and B: (A) Erythema nodosum; (B) Prolonged P-R interval in ECG, two minor criteria for diagnosis of rheumatic fever

Acute-phase Reactants:

Laboratory evidence of acute inflammation, such as elevated ESR or CRP, meets requirements for a minor criterion.

Fever:

The temperature is usually in the range of 101–102°F.

Previous history of rheumatic fever or rheumatic heart disease.

Erythema Nodosum

Tender erythematous nodules usually on the shins.

Differential Diagnosis of Acute Rheumatic Fever (Fig. 83)

Arthritis
• Rheumatoid arthritis • Reactive arthritis (e.g. Shigella, Salmonella, Yersinia) • Serum sickness • Sickle cell disease • Malignancies • Lyme disease • Gonococcal infection
Carditis
• Viral myocarditis • Viral pericarditis • Infective endocarditis • Kawasaki disease • Congenital heart disease • Mitral valve prolapsed • Innocent murmurs
Chorea
• Huntington's chorea • Wilson disease • Systemic lupus erythematosus • Cerebral palsy (dyskinetic) • Tics • Hyperactivity

Investigations

Laboratory

Acute phase reactants consist of polymorphonuclear leukocytosis, increased sedimentation rate and presence of CRP. The leukocyte count is usually 10,000–15,000/mm^3.

C-reactive protein is a β-globulin, which is increased uniformly in all patients with acute rheumatic fever. It subsides rapidly if a patient is on steroids. Absence of CRP is strongly against the diagnosis of acute rheumatic fever. Presence of CRP, however, is not diagnostic since it becomes positive in many other infections.

Prolonged PR Interval in the EKG

Prolonged PR interval is a non-diagnostic criterion since it can get prolonged in many infections. It is also not diagnostic of carditis.

Essential Criteria

The essential criteria include evidences for recent streptococcal infection. The most useful is the presence of antibodies against the streptococci. The most common in use is the antistreptolysin "O" titer.

Positive throat culture for streptococci is relatively uncommon when a patient presents with acute rheumatic fever. Positive throat culture can also not be equated with the diagnosis of rheumatic fever. Positive throat culture means that streptococci are present in the throat. The third feature suggestive for the diagnosis of recent streptococcal infection is the presence of residuals of scarlet fever. The desquamation of skin of palms and soles indicates that the patient has had scarlet fever within the previous 2 weeks.

Echocardiography

It is a very sensitive investigation for the diagnosis of rheumatic carditis. Features indicative of rheumatic carditis consist of annular dilatation, elongation of the chordae to the anterior leaflet of the MV causing prolapse and lack of coaptation of the two leaflets resulting in mitral regurgitation.

Though the revised Jones criteria do not include echocardiographic and Doppler findings for the diagnosis of carditis, these investigations have improved the recognition of carditis, which at times is not possible clinically.

Treatment

There is no specific treatment. Management is symptomatic combined with suppressive therapy.

Bed Rest

During the acute febrile period of the illness, bed rest is a must. Then gradual increases in activity should be allowed, provided that there is no recurrence of signs or symptoms. Serial determination of ESR is helpful in reaching decisions concerning activity levels. The return to full activity may be achieved by 6 weeks in patients with arthritis as the only major criterion; but in those with carditis, 3 months is advisable.

Salicylates

Salicylates are the preferred medications to reduce the inflammatory response, and they produce a prompt improvement in arthritis. However, evidence does not suggest that aspirin improves the natural history of carditis or valvulitis.

Temperature associated with rheumatic fever returns to normal within a few days. Aspirin is administered in a dose sufficient to achieve a blood salicylate level of approximately 20 mg/dL (1.45 mmol/L); usually this dosage is about 75–100 mg/

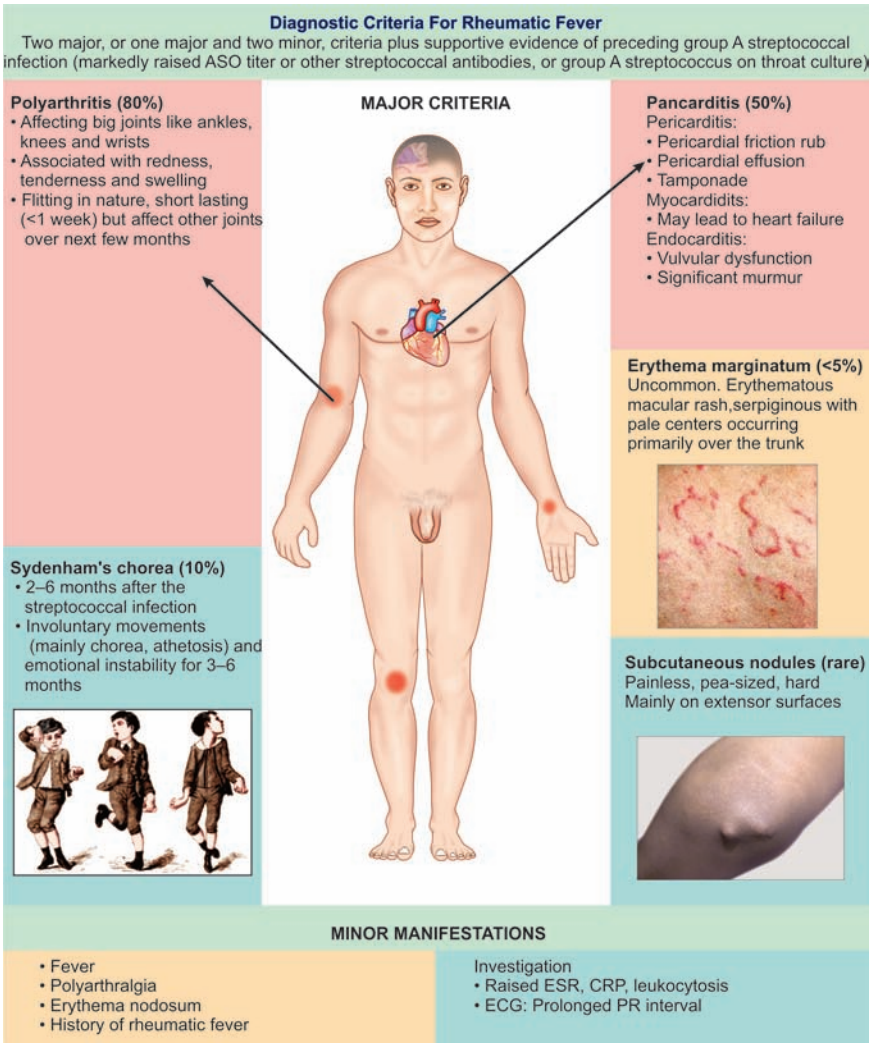


Fig. 83: Major and minor manifestation of rheumatic fever
Abbreviations: ASO, antistreptolysin O; ESR; erythrocyte sedimentation rate; CRP, C-reactive protein; ECG, electrocardiography

kg/day. Salicylates are continued until the ESR is normal, and then the dosage is tapered. Usually for duration of 12 weeks.

Corticosteroids

Steroids have been used in the treatment of acute rheumatic fever, but there is no evidence that they are superior to aspirin in preventing cardiac valvar damage. Steroids may, however, lead to a more prompt reduction in symptoms than does aspirin. Since steroids are more hazardous, their use should be reserved for patients with severe pancarditis.

Penicillin

After obtaining throat cultures, the patient should be treated with penicillin. Initially the patient is given therapeutic doses of penicillin, 400,000 units of procaine penicillin, intramuscularly, twice daily for 10 days. This is followed by treatment with benzathine penicillin 1.2 million units every 21 days or 0.6 million units every 15 days.

Treatment of Carditis

Patients who have carditis with CCF have higher mortality if aspirin is used compared to steroids. In selecting the suppressive drug for an individual patient, the following guidelines are followed:

- If a patient had carditis with CCF, the use of corticosteroids is mandatory
- Carditis without CCF: One may use either steroids or aspirin; steroids are preferred
- If the patient does not have carditis, it is preferable to use aspirin.

Treatment of Chorea

Chorea is a late manifestation. By the time a patient presents with chorea, the sedimentation rate as well as the ASO may be normal. The patient as well as the parents should be reassured and told about the self-limiting course of the disease. The patient should be provided complete physical and mental rest. Phenobarbitone 30 mg thrice daily is given. Other drugs, including chlorpromazine, diazepam, diphenhydramine or promethazine can be administered.

Prevention of Acute Rheumatic Fever

The aim of physicians should be the prevention of the initial episode of rheumatic fever by recognition and proper treatment of group A beta-hemolytic streptococcal infections. Only by adequate treatment of such infections can rheumatic fever be prevented. The throat of any child with the symptoms and findings of tonsillopharyngitis should be tested, because

the absolute clinical differentiation of streptococcal versus viral infection is not possible. However, 30–80% of sore throats resulting in rheumatic fever can be asymptomatic.

Two types of tests are available: Culture and rapid screening tests. Rapid streptococcal tests that detect the group A carbohydrate antigen are highly specific, so positive results do not demand additional culture. But the rapid tests vary in sensitivity, so a negative result should be backed up with culture. If beta-hemolytic streptococcus is present, the throat culture becomes positive within 24 hours. The aim of treatment of this infection is the eradication of the streptococcus.

Primary Prophylaxis

Rheumatic fever cannot be prevented in patients with streptococcal pharyngitis treated by adequate doses of oral penicillin for 10 days. As such intramuscular benzathine penicillin is mandatory for prevention of rheumatic fever.

Benzathine penicillin, 600,000 IU for children weighing less than 60 pounds (27.3 kg) and for larger children and adults, 1.2 million U, intramuscularly in a single dose.

Oral penicillin however can be given to children who have needle phobia and showing non-compliance of taking injectable penicillin. Penicillin V, 250 mg (400,000 IU) orally twice to three times daily for 10 days for children and for adolescents and adults, 500 mg (800,000 IU).

Penicillin-allergic patients may receive erythromycin or other macrolides, but resistance is a problem in some parts of the world. First-generation cephalosporins may be used, but tetracyclines and sulfonamides are not advisable for acute streptococcal eradication.

Secondary Prophylaxis

Once patients have had an episode of rheumatic fever, they are at higher risk of developing a second episode, particularly within the first 5 years; however, some added risk continues throughout life. Since rheumatic fever develops following a streptococcal infection, preventive measures are directed at eliminating such infections in susceptible individuals.

Secondary prophylaxis is giving long-acting benzathine penicillin. The dose is 1.2 million units once every 3 weeks or 0.6 million units every 15 days, depending on patient age and muscle mass. The injection is painful and some patients get fever for 24–36 hours following the injection.

Ideally, penicillin prophylaxis should continue life-long or at least until the age of 35 years particularly if associated with carditis or rheumatic heart disease. The least satisfactory approach is to give for 5 years from the last attack of rheumatic fever.

Oral penicillin can be given but unreliable and long-term daily compliance is a problem.

Penicillin V, 250 mg orally twice a day. Patients allergic to penicillin, should receive erythromycin.

Long-term Care

After the acute episode of rheumatic fever, the patient should be seen periodically. The purposes of these visits are to:

- Emphasize the continuing need of penicillin prophylaxis for rheumatic fever
- To emphasize the need for additional prophylaxis against bacterial endocarditis at the time of dental work or other procedures; and
- To observe for the development of valvar rheumatic heart disease.

In half of the patients with evidence of valvar abnormality during the acute episode, the murmurs disappear; but over a period of years, the other half may develop more severe cardiac manifestations, such as mitral stenosis, mitral insufficiency or aortic insufficiency. These patients may ultimately require a cardiac operation or intervention.

RHEUMATIC HEART DISEASE

In the pediatric age group, the sequelae of rheumatic fever consist of mitral, aortic and tricuspid valve disease. The MV involvement manifests predominantly as mitral regurgitation and much less commonly as mitral stenosis. The aortic valve and tricuspid valve involvement presents exclusively as aortic and tricuspid regurgitation respectively.

MITRAL REGURGITATION

Mitral regurgitation is the most common manifestation of acute as well as previous rheumatic carditis.

Hemodynamics

Mitral regurgitation results in a systolic leak of blood to the LA. Blood reaches LA during ventricular systole but during diastole it can pass freely across MV, keeping mean atrial pressure almost normal. Therefore no dyspnea or tachypnea occurs. There is no increase in pulmonary venous pressure and no pulmonary congestion. Mitral regurgitation provides two exits for the left ventricular blood—the forward flow through the aortic valve into the systemic circulation and the backward leak into the LA. The forward output becomes insufficient during exertion. This decrease in the systemic output results in fatigue, the most common symptom of significant mitral regurgitation. With failing LV, the left ventricular diastolic pressure increases, the left atrial and pulmonary venous pressure increase and pulmonary congestion appears. There is an increase in PAP and features of PAH appear. Thus presence of features of PAH in a patient having pure mitral regurgitation suggests severe mitral regurgitation, or failing left ventricular myocardium, or acute mitral regurgitation.

An important adjustment consists of decrease in the SVR to help increase the forward flow. The maximum ejection of blood into the aorta takes place during early systole. The combination of these two factors results in an increased systolic and decreased diastolic pressure in the systemic circuit. The pulse pressure is, therefore, increased resulting in the small water hammer pulse of mitral regurgitation.

Clinical Features

History

Easy fatigability without dyspnea on exertion. Dyspnea on exertion is a late feature when PH occurs.

General Examination

- Increased pulse rate, wide pulse pressure (small water hammer pulse) respiratory rate— normal or increase in PH
- Precordium—hyperkinetic, visible apex beat
- Thrill—systolic thrill only less than 10% cases due to backward regurgitation in LA. A diastolic thrill, however,

may be felt at mitral area, due to increased flow across MV.

On Auscultation

- First heart sound: Soft or inaudible
- Second heart sound: Widely split, but not fixed (change with respiration)
- Third heart sound: May be heard at apex.

Added Sound

Pansystolic murmur at apex is diagnostic. Radiation occurs to axilla and as far as left sternal border. A diastolic flow murmur may be heard at mitral area.

Differential Diagnosis

- Atrial septal defect, ostium premium type
- Coarction of aorta with mitral regurgitation (congenital)
- Papillary muscle dysfunction associated with left ventricular dilatation
- Marfan's syndrome
- Anomalous origin of left coronary artery from PA.

Investigation

- Chest X-ray: Cardiac enlargement due to LVH
- ECG: Sinus tachycardia and evidence of LVH
- Echocardiogram: Evidence of LVH and left atrial hypertrophy
- Doppler echocardiography can quantitate mitral regurgitation.

Treatment

- Medical: Digoxin, diuretic, vasodilators and penicillin prophylaxis.
- Surgical: In severe mitral regurgitation, if cardiothoracic ratio is greater than 55%. MV repair or prosthetic valve replacement. Concomitant anticoagulant is required.

MITRAL STENOSIS

Rheumatic mitral stenosis is less common than mitral regurgitation in children. Pediatric mitral stenosis constitutes 10% of all rheumatic mitral stenosis patients.

Hemodynamics

Mitral stenosis results in obstruction to flow of blood across the MV during left ventricular diastole. The atrium compensates for this obstruction by increasing its pressure. The increase in pressure results in hypertrophy of the left atrial wall. However, the LA is a thin-walled chamber and the capacity for its hypertrophy is limited. The increase in LAP prevents decrease in the blood flow across the MV. Since there are no valves between the LA and the pulmonary veins, the increased LAP is transmitted to pulmonary veins as well. The increased pulmonary venous pressure results in pulmonary capillary engorgement and pulmonary congestion, which produces dyspnea, the most common symptom of mitral stenosis. The PAP therefore increases. Clinically, the PAH is recognized by accentuation of the pulmonary component of the second sound. The RV hypertrophies.

With mild or moderate mitral obstruction, the forward flow through the MV remains normal. With severe mitral obstruction, the forward flow through the MV is diminished. If the flow to the LV decreases, the cardiac output diminishes and peripherally one feels a small volume pulse. The diminished cardiac output in severe mitral stenosis is recognized on the bedside as cold extremities, with or without peripheral cyanosis and a small volume pulse. The right ventricular hypertension can result in tricuspid regurgitation, which is seen in 30% patients with moderate to severe mitral stenosis.

Clinical Features

Boys develop twice as clinical features as girls. It is unusual before the age of 5 years. Clinical history includes dyspnea on exertion, shortness of breath, cough, hemoptysis, paroxysmal nocturnal dyspnea, attacks of acute pulmonary edema and atypical angina.

Examination

General Examination

Low volume pulse increased respiratory rate.

- Pricordium: Quiet.
- On palpation: Left parasternal heave suggestive of RVH may be felt. Liver may be palpable and pulsatile, particularly if tricuspid regurgitation is present.

On Auscultation

- First heart sound: Accentuated.
- Second heart sound: Normally split, with loud pulmonary component.

Added Sound

Delayed diastolic murmur with late diastolic accentuation is diagnostic. The diagnostic murmur is preceded by an opening snap.

Bilateral lung basal crepitation may be heard in pulmonary contestation and right ventricular failure associated with severe mitral stenosis.

Investigation

- Electrocardiography: Evidence of RVH with RAD and P mitrale.
- Chest X-ray: Normal-sized heart, with evidence PH and evidence of left atrial enlargement.
- Echocardiogram: Shows decreased EF slope, paradoxical posterior leaftlet motion, left atrial enlargement and PAH. 2D echocardiography can identify the narrowed mitral opening. Doppler echo provides transmitral gradient accurately, noninvasively.

Treatment

Treatment essentially surgical.

- Medical: Digitalis and diuretic should be given. Digitalis decrease HR, increase left ventricular and left atrial contractibility.
- Surgical: Closed mitral valvotomy is the best surgical approach.
- Balloon valvoplasty: Mitral valvoplasty may also be done using a balloon, which is introduced through femoral vein,

passed through atrial septum, positioned in the MV and inflated to reopen stenosed MV.

AORTIC REGURGITATION

Aortic valve involvement in rheumatic heart disease results in aortic regurgitation. Rheumatic AS has not been described in the children. Clinically pure aortic regurgitation, without associated MV disease, is rare. Pathologically pure rheumatic aortic valve disease is almost unknown.

Hemodynamics

Aortic regurgitation is a backward leak from the aorta into the LV during diastole. This increases the volume of blood reaching the LV. The LV increases in size to accommodate the extra volume. The size of the LV is thus directly related to the degree of aortic leak, unless there is myocardial disease. Because of the backward flow of blood, the forward flow is impaired. This is compensated by peripheral vasodilatation as well as increased ejection from the LV during early part of the systole. However, significant AR result in low forward output. The peripheral pulse pressure is wide because of the increased systolic and lowered diastolic pressure. Signs of wide pulse pressure in the form of exaggerated arterial and arteriolar pulsations are present unless the AR is mild. If the left ventricular myocardium is failing, the left ventricular diastolic pressure goes up and results in an increase in LAP and pulmonary congestion.

Clinical Features

Aortic valve disease is more common in boys compared to girls. The symptom is palpitation. Fatigue is not an early symptom. The pulse pressure is wide. The diastolic BP may be recorded as zero with severe aortic regurgitation. Prominent carotid pulsations, visible arterial pulsations over the extremity vessels and visible pulsations of the abdominal aorta are evidences of wide pulse pressure from any cause. Holding the middle of the forearm or leg and elevating it discloses a sharply rising and abruptly failing pulse (Corrigan pulse or water hammer pulse).

If the stethoscope is put over the brachial or the femoral artery without applying any pressure, pistol shot-like sounds may be heard in moderate or severe aortic regurgitation. A systolic murmur may be heard if pressure is applied to partially occlude the artery proximal to the chest piece and a diastolic murmur if pressure is applied distally. This combination of systolic and diastolic murmurs is the Duroziez's sign.

Examination of the precordium will reveal apex displaced downward and outward. The apex is forcible or heaving. Diastolic thrill may be palpable at the upper left or right sternal border. The first sound is soft and the aortic component of the second sound may be audible or may be masked by the regurgitant diastolic murmur. The murmur of AR is a high-pitched, decrescendo diastolic murmur starting with the aortic component of the second sound. The murmur is best heard along the left sternal border and radiates to the apex and even beyond the apex. With large aortic leaks, there is also an ejection systolic murmur at the second right interspace, conducted to the neck and not infrequently associated with a systolic thrill. The systolic murmur is the result of a large SV, passing across rough valves. The does not indicate AS.

The ECG shows increase in left ventricular voltages with deep "S" waves in V1 and tall "R" waves in V6. There are also deep "Q" waves in left chest leads with tall "T" waves. Chest X-ray shows left ventricular cardiomegaly and dilated ascending aorta. Echocardiogram shows enlarged LV, dilated aorta and flutter of anterior mitral leaflet. A Doppler study quantitates the severity of vulvar lesion.

Differential Diagnosis

The differential diagnosis of rheumatic AR includes: Conditions associated with a wide pulse pressure like PDA, arteriovenous fistulae, VSD with aortic regurgitation, ruptured sinus of valsalva, anemia and thyrotoxicosis.

Management

Significant aortic regurgitation, if associated with either angina-like chest pain or signs of LVF, can only be managed surgically. Surgical treatment consists of aortic valve replacement, by either homograft or a prosthetic valve. Better surgical results are claimed in patients whose cardiothoracic ratio is less than 60%.

AORTIC STENOSIS

Rheumatic AS is usually not seen in children.

TRICUSPID REGURGITATION

Features indicative of tricuspid regurgitation are seen in almost 20–50% patients with rheumatic heart disease. In an individual patient, it is difficult to decide whether the tricuspid regurgitation is organic or functional.

Hemodynamics

Tricuspid regurgitation results in a systolic backflow of blood from the RV to the RA. The systolic leak thus results in a systolic murmur and volume overload of the RA as well as the RV. The volume overload results in an increase in the size of the RA as well as the RV, which is displaced downward and outward. Usually all patients with tricuspid regurgitation also have PAH. In patients with rheumatic heart disease, the tricuspid regurgitation may be associated either with mitral stenosis or with mitral regurgitation. If the tricuspid regurgitation is associated with mitral stenosis, it may be either organic or functional due to PAH. If, on the other hand, the tricuspid regurgitation is associated with dominant or pure mitral regurgitation, it is most likely organic.

Clinical Features

It is possible that with the onset of tricuspid regurgitation the dyspnea may be relieved to some extent in patients with mitral stenosis. The patients may give history of pain in the right hypochondrium. Specific features of tricuspid regurgitation consist of:

- Prominent V waves in the jugular venous pulse
- Systolic pulsations of the liver, and
- A systolic murmur at the lower left sternal border increasing in intensity with inspiration.

In addition to the above features, there are signs of PH and MV disease. The pansystolic murmur of tricuspid regurgitation

may be heard from the lower left sternal border to the apex. Since the LV is displaced backward, the mitral stenosis murmur may be audible only in the axilla or may not be heard at all.

Patients with tricuspid regurgitation almost always show severe RVH on ECG. Contrast echocardiography and Doppler can document and quantitate the severity of tricuspid regurgitation as well as findings of left-sided disease.

Management

All patients with findings of tricuspid regurgitation should be put on anticongestive (diuretics) measures whether the tricuspid regurgitation is associated with mitral stenosis or with mitral regurgitation. Patients with mitral stenosis may lose all evidence of tricuspid regurgitation following mitral valvotomy. Patients with tricuspid regurgitation in association with mitral regurgitation generally have severe mitral regurgitation. If, there is an evidence of deterioration or lack of improvement during follow-up, the patient may have to be sent for MV repair or replacement.

DIAGNOSTIC PROBLEMS ASSOCIATED WITH RHEUMATIC HEART DISEASE

There may be too major diagnostic problems associated with rheumatic heat disease

- Is the heart lesion is due to acute rheumatic fever with or without previous rheumatic heart disease?
- In a febrile patient, is it IE or active rheumatic fever?
- Cardiac lesion associated with active or inactive rheumatic fever?

If the patient has well-documented cardiac findings then the appearance of a new murmur or a significant increase in a pre-existing murmur is very suggestive for active rheumatic fever. History of arthralgia or arthritis within a period of less than 12 weeks is suggestive of active rheumatic fever especially if associated with elevated sedimentation. The difficulty arises in those patients who have relatively low levels of the ASO titer. In such cases, unless serial serum sample are available, it is difficult to decide whether or not there has been a rise in the level of the ASO titer.

In a Febrile Patient, is it Active Rheumatic Fever or Infective Endocarditis?

The diagnosis of IE should be suspected in any cardiac patient who has unexplained fever of 7–10 days in the presence of embolic phenomena. Embolic phenomena, however, are rarely diagnosed unless the central nervous system is involved.

Patients with IE have loss of appetite, general weakness, malaise, headache and loss of weight. They may show petechiae, splinter hemorrhages, Roth's spots, clubbing and splenomegaly.

Investigations show normocytic normochromic anemia with Hb level of 7–10 gm/dL. The leukocyte count is less than 10,000/cubic mm in 50%; thrombocytopenia may occur. Urine examination shows mild albuminuria and microscopic hematuria. The diagnostic investigation is blood culture.

Echocardiogram is a highly sensitive noninvasive technique for identifying endocarditis. Vegetations of 2 mm or more can be detected.

If the separation of rheumatic activity from IE is in doubt because of negative cultures or low levels of ASO titer, it is best to give a therapeutic trial. Since IE is more serious, the patient should first be treated for this condition.

INFECTIVE ENDOCARDITIS

Infection of the endocardial lining of the heart is called IE. The most common site of infection is generally a diseased valve from where the infection can spread to the mural endocardium or the vascular endothelium. IE has significant morbidity and mortality at times changing the prognosis of an otherwise benign lesion markedly. It should be considered as a medical emergency since it can damage the valves, the myocardium and other parts of the body like the brain and the kidneys.

Predisposing Factors

Infective endocarditis predominantly occurs in a diseased heart. In children, the common underlying disease could be CHD including MV prolapse syndrome or rheumatic heart disease. The most common congenital lesions involved in IE are those with a VSD or aortic valve disease. Thus isolated VSD, VSD with aortic regurgitation. Fallot's tetralogy, tricuspid atresia, valvar AS or a bicuspid aortic valve in coarctation of the aorta are generally the most common lesions associated with endocarditis. It is rare in ASD of the secundum type. Endocarditis affects the mitral or aortic valve in patients with rheumatic heart disease. Patients with prosthetic valves or those with recent cardiac surgery are prone to endocarditis. Infections anywhere in body, e.g. pyoderma, tooth abscess, ear infection, urinary infection or osteomyelitis may result in endocarditis.

The most common predisposition for endocarditis in children is poor dental hygiene.

Pathogenesis

The pathogenesis of endocarditis depends upon the invasiveness and virulence of the infective organisms. The infection generally starts at a jet lesion, that is where the high pressure jet in a VSD or AS hits the endocardium or the endothelium. The right ventricular mural endocardium or the tricuspid valve in VSD, aortic endothelium in AS or coarctation of the aorta, ventricular surface of the aortic valve in AR are the usual sites.

Bacteremia resulting from an infection such as a boil, furuncle, otitis media or initiated by an intervention such as cardiac or urinary catheterization or dental extraction is necessary for the initiation of endocarditis. Bacteremia may also result from simple day to day events such as brushing teeth. Bacteria that are deposited on the endocardium are covered by fibrin and platelets forming vegetations. Almost any species of bacteria and some species of fungi can cause endocarditis. *Streptococcus viridians, Staphylococcus aureus,* Enterococci, *Pseudomonas aeruginosa* and some Gram negative bacilli are responsible for endocarditis. Fungal endocarditis may occur in hospitalized patients with indwelling central venous catheters.

Clinical Features (Fig. 84)

The presence of unexplained fever of 7–10 days duration in a patient with known heart disease should raise the suspicion of endocarditis. Identification of endocarditis by the organism is preferable, as it helps in deciding the choice of antibiotics as well.

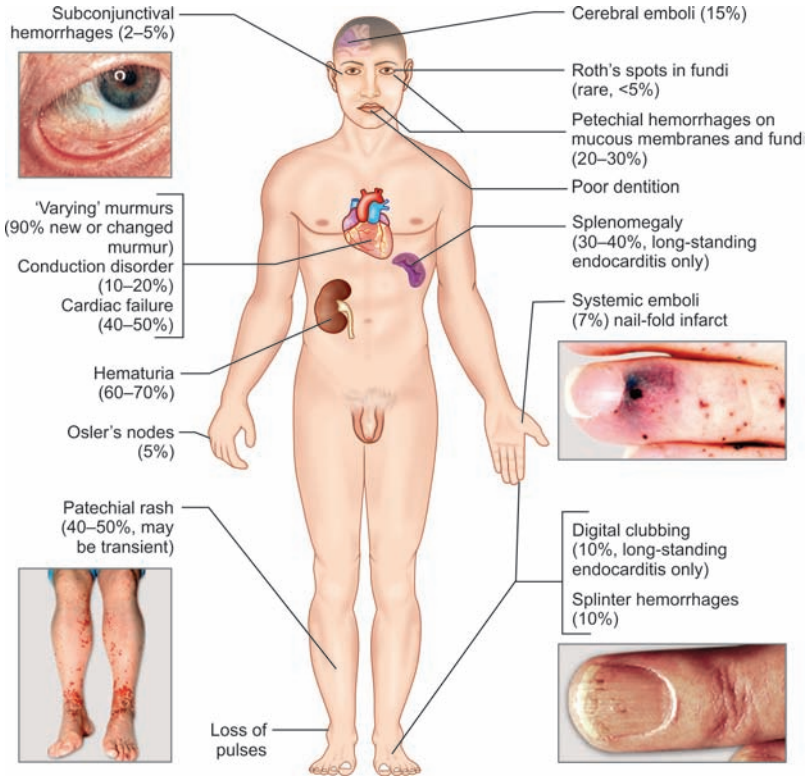


Fig. 84: Diagram and clinical pictures of infective endocarditis

Infective endocarditis is rare below the age of 2 years. The clinical features are divided into:

- Indicating the presence of an infection
- Indicating involvement of the cardiovascular system
- Indicating the presence of an immunological reaction to infection. The features indicating the presence of infection consist of fever, chills, rigors, night sweats, general malaise, weakness, loss of appetite and weight loss.

Features indicative of the involvement of the cardiovascular system may be absent in the initial stages. The acute occurrence of left or right HF, development of a new murmur or change in a pre-existing murmur and features suggesting embolic events (e.g. hemiparesis from stoke, hematuria from renal infarct, left flank pain from splenic infarct and gastrointestinal hemorrhage from mesenteric embolism) is suggestive.

Features of immunological response consist of arthralgia, mylagia, petechiae, Osler's nodes, clubbing, splenomegaly and microscopic hematuria. Splinter hemorrhages are hemorrhagic spots under the nails, though suggestive, are not specific for endocarditis as they can result from minor injuries. Petechiae over the skin or mucous membranes and conjunctiva are seen in about 50% patients. Petechiae in the retina are called Roth's spots. Osler's nodes are tender erythematous nodules over the pulp of finger tips, but are relatively rare. Clubbing and splenomegaly tend to appear 3 weeks after the onset of endocarditis.

In the acute form, the symptoms progress rapidly with high fever, chills and rigors. Perforation of valve cusps results in acute aortic or mitral regurgitation with progressive downhill course and death within 6 weeks from the onset.

Patients with endocarditis of the right side such as the tricuspid or the pulmonary valve throw emboli to the lungs. The embolic episodes to lungs may present as repeated episodes of pneumonitis or septic infarcts resulting in lung abscesses.

Postoperative endocarditis is classified as early (within 60 days) and late (after 60 days). Early endocarditis is due to pyogenic organisms (staphylococcus, pseudomonas, gram negative bacilli) introduced at the time of operation. The patients have high fever with chills and rigors and features of septicemia. Late endocarditis is like native valve endocarditis and the most common organisms are *S. viridans* and gram negative bacilli. The patients tend to follow the subacute course. Cardiac surgery is an important risk factor for gram negative endocarditis. Prosthetic valve endocarditis may also be early or late; fungal infection of prosthetic valves is associated with high mortality.

The risk of fungal endocarditis has increased especially following cardiac surgery and in intensive care settings. *Candida* is the most common fungus responsible.

Diagnosis

A positive blood culture, in a patient with underlying heart disease, suspected to have endocarditis is confirmatory for the diagnosis. Three blood cultures, each of 10 mL, taken with meticulous aseptic precautions every half hour are recommended. It has been shown that three blood cultures shall detect over 95% cases with a positive blood culture. Unfortunately in most cases (upto 50%), patients with endocarditis have negative blood cultures, the commonest cause being previous antibiotic therapy.

Other investigations which provide supportive evidence for diagnosis are:

- Normocytic normochromic anemia: Hb level around 10 gm/dL.
- White cell count: In subacute presentation, leukocyte counts are normal in approximately 50% patients. In acute endocarditis, leukocyte counts are usually elevated.
- Platelet count may be reduced.

- Elevated sedimentation rate.
- Microscopic hematuria and albuminuria are present in 90% cases.
- Immunological investigations for low complement levels and circulating immune complexes. Specific antibodies against causative organism may be increased, e.g. high ASO titer in streptococcal endocarditis. Rheumatoid factor is positive in approximately 50% cases.

Echocardiography is a sensitive diagnostic tool for detecting vegetations (Fig. 85), including in patients with culture negative endocarditis. Echocardiography also identifies complications like ruptured chordae, perforated cusps and flail cusps resulting from endocarditis. The presence of vegetations correlates well with the diagnosis of IE. If vegetations can be demonstrated, the probability of having endocarditis is around 94%. If vegetations are absent, the probability of not having endocarditis is 92%.

Treatment

If the blood culture is positive, the choice of antibiotics is dictated by the antibiotic sensitivity. Patients allergic to penicillin should receive cefazolin or ceftriaxone. Patients allergic to both penicillin and cephalosporins should be treated with vancomycin. Endocarditis secondary to infection with *S. aureus* is treated with the combination of cloxacillin and an aminoglycoside or combination of vancomycin with an aminoglycoside. Fungal endocarditis is treated with either amphotericin alone or its combination with flucytosine. Surgical excision of the infected valve may be necessary.

Culture negative Endocarditis

The choice of treatment lies between a combination of ampicillin with an aminoglycoside or combination of cloxacillin and an aminoglycoside.

Prophylaxis

The most important factor in prophylaxis against endocarditis is good dental hygiene and this should be strongly encouraged in all children with CHD. Antibiotic prophylaxis will be required for:

- Dental treatment, however trivial
- Surgery which is likely to be associated with bacteremia (e.g. appendicectomy, ENT surgery).

> Antibiotic prophylaxis against bacterial endocarditis must be given to all children with CHD (except secundum ASD) before dental extraction or any potentially septic operation

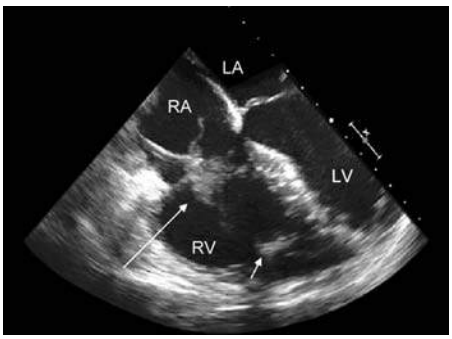


Fig. 85: Transesophageal echocardiography four-chamber view shows multiple vegetations on the tricuspid valve (long arrow) and pacing leads (short arrow)
Abbreviations: LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle

Summary of Clinical Signs

- Fever
- Anemia and pallor
- Splinter hemorrhages in nailbed clubbing (late)
- Necrotic skin lesions
- Changing cardiac signs
- Splenomegaly
- Neurological signs from cerebral infarction
- Retinal infarcts
- Arthritis/ arthralgia
- Hematuria (microscopic).

CARDIOMYOPATHIES

Incidence, pathophysiology and clinical features of some cardiomyopathies are depicted in Table 4.

IMPORTANT PEDIATRIC CARDIAC ARRHYTHMIAS

SUPRAVENTRICULAR TACHYCARDIA (SVT)

Infants and children tolerate arrhythmias less well than adults as they are more dependent on HR for cardiac output and have less reserve.

Between 30% and 40% of children who present with supraventricular tachycardia do so within the first few weeks of life. Their presentation is variable. Supraventricular tachycardia can be the cause of unexplained hydrops of the fetus or can result in sudden profound cardiovascular collapse in the newborn period. More usually neonates and small infants will present with symptoms of increasing tachypnea, poor feeding and pallor which have developed over a few days. Occasionally supraventricular tachycardia is intermittent and a strong index of suspicion must be maintained if the diagnosis is not to be missed. The older child more usually presents with a history of palpitations (Fig. 86).

Classification of Supraventricular Tachycardia (Anatomical sits of origin and ECG findings of various SVT are provided in Figures 86 and 87 respectively)

Junctional Tachycardias

Atrioventricular re-entry tachycardia (AVRT).

Orthodromic AVRT

Tachycardia involving a circuit utilizing the AV node in the antegrade limb and an accessory connection between ventricle and atrium as the retrograde limb.

Antidromic AVRT

Tachycardia involving a circuit utilizing an accessory connection as the antegrade limb and the AV node as the retrograde limb.

Atrioventricular Nodal Re-entry Tachycardia

Tachycardia involving a circuit of the two limbs which are intimately associated with the AV node. The atria and ventricles are activated as offshoots of the circuit. The common type of atrioventricular nodal re-entry tachycardia (AVNRT) is

Table 4: Incidence, pathophysiology and clinical features of some cardiomyopathies

	Hypertrophic	Dilated	Restrictive
Incidence and association	• IDMs, postnatal steroids • Noonan, Pompe, Hurler	• Carnitine deficiency • Myocarditis • Postarrhythmia • Post severe hypoxia	• Least • Common idiopathic
Pathophysiology	• Global or localized obstructive or nonobstructive diastolic function a major feature	• Decreased ventricular inotropic function during systole with LA dilation also	• Stiff ventricles • Abnormal diastolic function
Clinical	• Asymptomatic with normal exam may have CHF, harsh systolic murmur	• CHF, poor distal perfusion • S4 gallop • MR murmur	• No murmur
CXR	• Normal vs increased heart size	• Increased heart pulmonary edema	• Normal
Management	• Inotropes versus volume (depends whether obstructive or nonobstructive); usually provide adequate preload with volume	• Treat CHF • Consider anticoagulation • May need transplant	• Medical treatment • Transplant

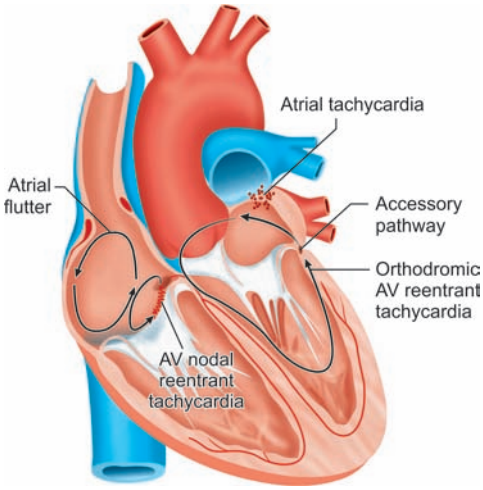


Fig. 86: Anatomical sites (diagrammatic) of origin and pathway of supraventricular tachycardia

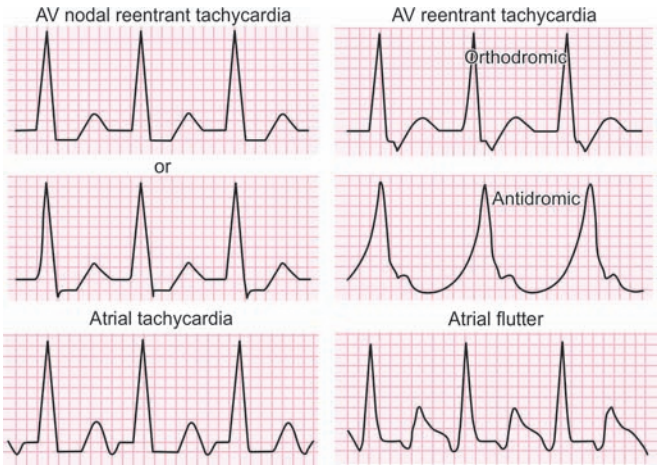


Fig. 87: Electrocardiographic findings of various types of supraventricular tachycardia

typified by slow conduction antegradely and fast conduction retrogradely, the uncommon type by fast conduction antegradely and slow conduction retrogradely.

Long R-P Tachycardia

Tachycardia involving a circuit utilizing the AV node as the antegrade limb and a slow conducting pathway as the retrograde limb. The latter may be an accessory connection in close association with the AV node, in the posteroseptal position or remote from the AV node.

Atrial Tachycardias

Tachycardia characterized by discrete atrial activity on the surface electrocardiogram with varying ventricular response resulting either from a micro re-entry circuit or ectopic focus confined within the atria.

Atrial Flutter

Tachycardia characterized by a saw tooth undulation of the baseline on the surface electrocardiogram probably resulting from conduction around a re-entry circuit within the atria.

Atrial Fibrillation

Tachycardia characterized by chaotic low voltage "fibrillatory" waves on the surface electrocardiogram with an irregular ventricular response, resulting from disordered atrial activity.

Wolf-Parkinson-White syndrome

Pre-excitation syndrome predisposing to SVT. This is due to an abnormal re-entry circuit that includes the AV node and an accessory conduction pathway connecting atrium to ventricle on the right or left lateral cardiac border, or within the ventricular septum. It may be associated with Ebstein's anomaly, post-surgical repair, and cardiomyopathy. Characteristic ECG of Wolf-Parkinson-White (WPW) syndrome is given in Figure 88.

Clinical Features

Sudden onset (and cessation) lasting from a few seconds to hours; HR: 250–300 beats/minute. SVT is well-tolerated in older children, but HF may occur in young infants. Often precipitated by intercurrent (febrile) illness.

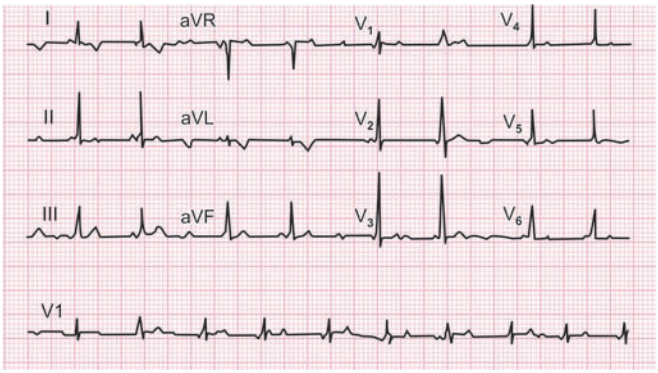


Fig. 88: Electrocardiography shows short PR interval and delta wave (slow upstroke of QRS complex) characteristic of WPW syndrome

Diagnostic Investigations

A resting 12-lead electrocardiograph (ECG) should be recorded. Patients with a history of sustained arrhythmia should always be encouraged to have at least one 12-lead ECG taken during the arrhythmia. An echocardiographic examination should be considered in patients with documented sustained SVT to exclude the possibility of structural heart disease, which usually cannot be detected by physical examination or 12-lead ECG. An ambulatory 24-hour Holter recording can be used in patients with frequent (i.e. several episodes per week) but transient tachycardias (Fig. 89).

Treatment

Vagal Maneuvers

They are easy to perform, quick, safe and often successful. Immersion of an infant's face in cold water (Fig. 90), to elicit the diving reflex, appears to be very effective. Some older children will actively participate in vagal maneuvers, particularly if it is not their first attack. Others are too frightened and attempts at immersing their face in cold water do little to improve this. Anatomical substrate relevant to supraventricular tachycardia (SVT), ECG findings of various types of SVT and ECG changes after Valsalva's maneuvers or by drug treatment are provided in Figures 91 to 93. If vagal maneuvers fail, drug treatment may be considered. Adenosine is a new drug with many attractive characteristics. It acts by slowing AV nodal conduction thus disrupting a re-entry circuit. Initial dose of 50 µg/kg followed by increments of 100 µg/kg up to a maximum of 300 µg/kg in infants and 400 µg/kg in children. It has a rapid onset of action and is effective within 10–20 seconds of being given intravenously in approximately 86% of junctional tachycardias. It has a short half-life of 10–15 seconds with little transient side-effects, which occur in one-third of patients treated and rarely require intervention. Additionally adenosine is not negatively inotropic in this form and so may be given to an infant or child in low cardiac output without fear of exacerbating this. Moreover if adenosine is administered to a child with ventricular tachycardia by mistake, it will not precipitate ventricular fibrillation. Indeed a bolus of adenosine can be used in the difficult situation of a wide complex tachycardia as a diagnostic aid to help distinguish ventricular from supraventricular tachycardia (Fig. 93). The main disadvantage of using adenosine is that in approximately 30% of cases, the tachycardia will reinitiate.

Flecainide exerts profound effects on the accessory connection as well as the AV node. Flecainide is negatively inotropic and can be proarrhythmic. It should therefore be given slowly over at least 10 minutes (2 mg/kg) with careful attention to the electrocardiogram and BP.

Other drugs used are amiodarone IV, propanolol IV and verapramil IV (over 1 year of age) (Table 5). See Flow chart 4 for drugs with their doses. Other therapeutic options available when dealing with the acute situation are direct current (DC) cardioversion or pacing, either via an esophageal or transvenous electrode. Use 1 J/kg in the first instance. Flow chart 4 shows the management of SVT.

Chronic Therapy

Patients with well-tolerated episodes of PSVT that will always either terminate spontaneously or can be broken easily by the patient do not require chronic prophylactic therapy. Selected patients may be treated only for acute episodes. For patients whose PSVT is not well-tolerated or not easily broken, either catheter ablation or chronic drug therapy may be appropriate.

CATHETER ABLATION

Catheter ablation is an attractive alternative for patients who either desire to avoid or are unresponsive or intolerant to drug therapy. In patients with manifest preexcitation and tachycardia mediated by accessory pathways, radiofrequency ablation of the accessory pathways results in the prompt disappearance of the delta wave and prevents further episodes of tachycardia (Figs 94 and 95).

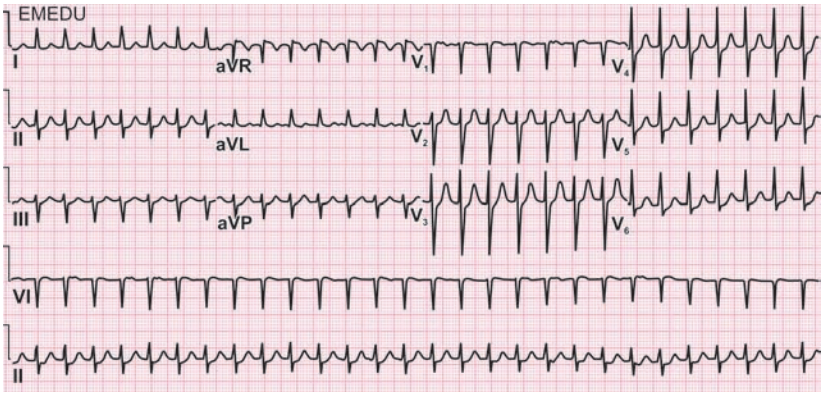


Fig. 89: Electrocardiograph of supraventricular tachycardia

Fig. 90: Immersion of an infant's face in cold water with ECG monitoring to treat SVT

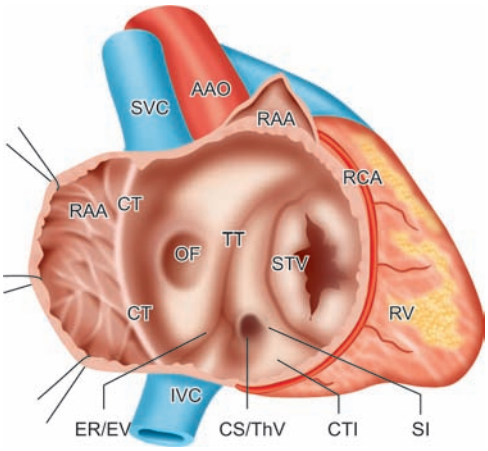


Fig. 91: Anatomical substrate relevant to supraventricular tachycardia *Abbreviations:* RA, right atrium; CTI: cavotricuspid isthmus; IVC, inferior vena cava; STV, septal tricuspid valve; CS, coronary sinus; SI, septal isthmus (is often the target for ablation); AVN, atrioventricular node, ER/EV, Eustachian valve and/or ridge; TT, tendon of Todaro.

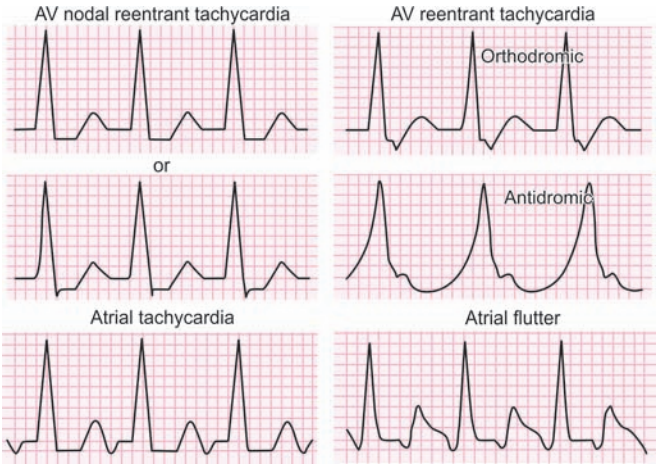


Fig. 92: ECG findings of various types of supraventricular tachycardia

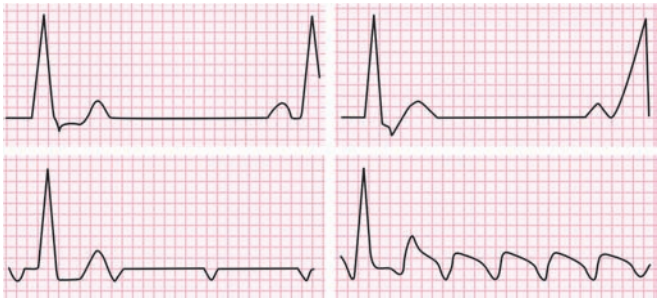


Fig. 93: Electrocardiography changes before and after Valsalva's maneuvers or adenosine

Flow chart 4: Algorithm for the management of supraventricular tachycardia

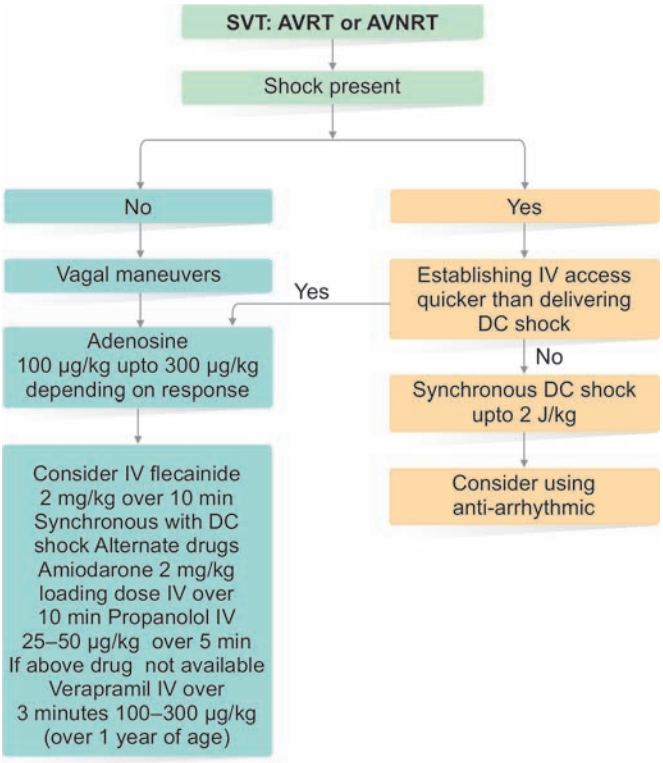


Table 5: Long-term antiarrhythmic drug therapy for supraventricular tachycardia

Tachycardia	First choice	Second choice	Third choice
Atrioventricular nodal reentrant and atrioventricular reentrant (concealed bypass tract)	Calcium channel blockers, β-blockers, digoxin	Flecainide, propafenone* ** Quinidine, procainamide, dispyramide* ***	Amiodarone
Wolff-Parkinson-White syndrome	Flecainide, propafenone* Quinidine, procainamide, dispyramide***	Beta-blockers, calcium-channel blockers**	Amiodarone, sotalol
Sinus-node reentrant	Calcium-channel blockers, β-blockers, digoxin	Flecainide, propafenone* ** Quinidine, procainamide, disopyramide** ***	-
Unifocal atrial reentrant	Flecainide, propafenone* Quinidine, procainamide, dispyramide***	Amiodarone, sotalol	-
Automatic	β-blockers, calcium-channel blockers, digoxin	Flecainide, moricizine**	Amiodarone
Multifocal atrial	Magnesium and potassium supplements	Metoprolol, verapamil**	-

*For patients with no associated heart disease
**To be used in combination with a first-choice drug
***For patients with associated heart disease

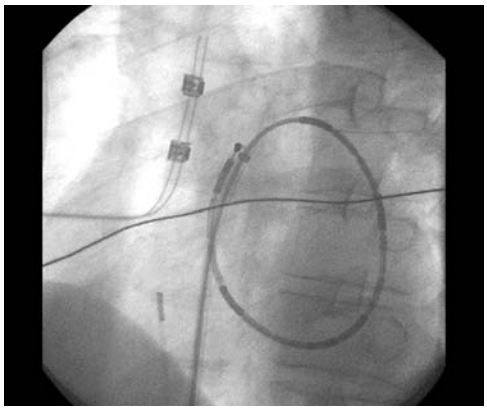


Fig. 94: Catheter ablation

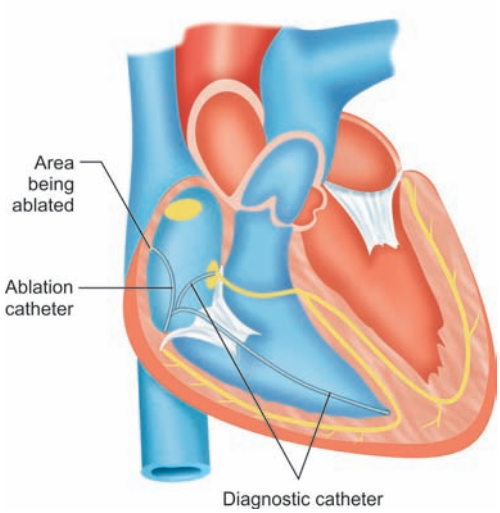


Fig. 95: Catheter ablation (diagrammatic)

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12 Pediatric Neurology

HISTORY TAKING

Obtaining satisfactory history often provides better clue than examination or investigation for diagnosis and management of a neurological disease.

History taking should be interactive. Doctor should cross check, whether he understood, what the patient or care giver told. Doctor should ask the patient or care giver, whether he (doctor) understood is the same as the patient told to doctor. School-age children should be given an opportunity to speak to doctor alone.

History of Presenting Complaints

Children may present with symptoms of following neurological conditions and disorders:

- Paroxysmal episodes: Seizures, migraine
- Pain: Headache (migraine)
- Movement disorders: Ataxia, chorea
- Altered consciousness: Intracranial infections (meningo-encephalitis)
- Developmental delay: Falling off from normal development [cerebral palsy (CP)]
- Developmental regression: Loss of already achieved developmental skill (neurodegenerative disorders).

However, the above neurological features should be obtained by taking history carefully. Doctor should listen carefully what the patient said and try to rationalize the history in a broader way before jumping to describe the complaint as a specific pathological term. For example, if the mother complains that her child falls frequently and the doctor term it as seizure disorder, dyspraxia or ataxia, then he has closed his thinking for wide range of simple nonorganic cause of balance problem including simple problem like fall due to generalized weakness. On the contrary, some parents will use ill understood misleading medical term like telling doctor that their child has absence seizure, which should be gently discouraged.

For acute onset clinical problem, it is usually better to start at the beginning of the history like asking the parents when the child was reasonably well. For very long-term problem, it may be more useful to start with present situation and fill in backward. If a child of 5-year-old with CP presents with convulsion, listen the presenting problem and then go back how it started. Currently, the child presented for the first time with convulsion. However, the child was not normal before. The problem started when he developed meningitis at 1 year age, followed by developmental delay and he cannot stand at this age. Later at 4 year age he developed occasional seizure.

The time course over which the symptoms have evolved is particularly informative in relation to probable pathology. Slowly progressive disorders like slow growing cerebral tumor usually progress over several years while cerebrovascular events have a sudden onset.

Birth History Relevant to Neurological Condition

Birth history is important and should be taken in detail. Preterm, very extremely low-birth weight babies are more vulnerable to develop CP and developmental disorders. Ask simple questions. Was your baby born in due time (expected date of delivery) and what was his/her birth weight? If cannot remember, did he/she looked very small when he/she was born? Clinical events during birth are also important. Ask the parents whether their baby cried immediately after birth, which is relevant to birth asphyxia, which may later lead to CP. Take history whether the baby suffered from sepsis or meningitis. Ask the parents whether their baby developed severe jaundice (hyperbilirubinemia) requiring phototherapy or exchange transfusion which may be relevant to kernicterus, etc. which are relevant to later development of central nervous system (CNS) disorder. Ask the parents simply whether their baby was discharged from hospital normally after birth, or did the baby require prolonged stay in the hospital particularly in neonatal intensive care unit requiring ventilatory care. Prolonged ventilation care may cause pulmonary as well as CNS problem.

Developmental History

It commonly is an underemphasized but useful part of neurological history taking. Ask when the child was able to sit without support, and age of learning, age of crawling and walking. Ask about speech development, including vocalizing, babbling and speaking meaningful words. Inquire if there is any age-matched problem with language and communication (relevant to autism)? Can the baby respond to sound? Distinction between developmental delay (achieving developmental skills later) and developmental regression (loss of achieved skills) can be obtained by taking careful history.

Cognitive Development

- Pointing at an object of his/her interest like dog or cat and inviting others for shared attention to look at the same object. Also vocalizes to bring the object to him/her. Established by 18 months.
- Symbolic toy test: Using representational toys (animals, dolls and cars) and function of use like showing toy aeroplane flying or kicking small football established by 18 months. It also assesses early language development.

EXAMINATION OF CENTRAL NERVOUS SYSTEM

Try to start examining the child with minimum touch, then more touch without disturbing the child and in the form of game. Details of neurological examination of neonates and young infants are mentioned later, in this chapter and also in newborn examination (*See* Chapter 1).

Older children undergo the full adult neurological examination by making it a game. Pay particular attention to gait, spine, head size and skin for neuromuscular stigmata.

EXAMINATION OF PERIPHERAL NERVOUS SYSTEM

It comprises assessment of appearance, postures, gait, tone, power, reflexes, coordination and sensation.

Appearance and Posture

Look for muscle balk, inspection of feet (equinus posture), neurocutaneous stigmata, (depigmented spot, cafe au lait spot, etc.) visible fasciculation and limb asymmetry. Look for involuntary involvement (chorea, tic, etc.). Note whether stance is broad based (cerebellar problem). Spastic children take attitude of flexion.

Gait

Gait can provide clue for diagnosis of neurological conditions without touching or disturbing the child. Although, it is easily straightforward to recognize when a gait is normal but when the gait is abnormal, it can be challenging to find what is wrong. Neurological diseases typically give one of several gestalt gait appearances that enable to recognize underlying neurological condition. Remove the clothes as far as underwear, if the child is happy.

Neurological Gait: Gestalt

Spastic hemiparesis: Equinus posture of the foot. Tendency to catch a toe on the floor either resulting in leg swing laterally during swing phase (circumducting gait) or it is compensated by hip flexion. Affected upper limb is flexed at elbow (Fig. 1).

Soft Neurological Signs

A soft neurologic sign which include fog's test and tandem test may be defined as particular form of deviant performance on a motor or sensory test. Minimal choreoathetoid movements in the fingers of extended arm are normal up to 4 years age. However, gross abnormal movement and posture, particularly if such movement and posture are asymmetric or one sided of body is usually abnormal. Any asymmetric abnormal movement and posture on motor or sensory test after 7 or 8 year is abnormal. Symmetric deviant performance on motor (Fog's test) or sensory test can occur above 4-year child with motor coordination disorder (clumsy child) but asymmetric performance occur in CP. It helps clinical diagnosis of occult (apparently normal) hemiplegia. Persistent and positive tests of more than one soft neurological signs or positive signs of one test performed in different ways of same test increases the sensitivity of positivity of the test. For example persistent deviant performance on Fog's test on walking on heal toe, inner and outer side of feet increases the sensitivity of positive Fog's test.

How to Elicit Subtle Hemiparesis?

This can be elicited by performing Pronator drift test and Fog's test in the following ways:

Pronator Drift

A useful technique to screen subtle hemiparesis is to ask a child to stand still for 20 seconds with arm outstretched or in pulled up position with palms outward and eyes closed. Mild pyramidal weakness results in pronator drift, a downward drift and pronation of affected arm (Figs 2 and 3).

Fig. 2: A normal child showing no pronator drift

Fig. 1: Left-sided hemiplegia showing flexion of hip and elbow of affected side

Fig. 3: A left side hemiphagic child showing pronator drift

Fog's Test

Elicit associated movements (soft neurological sign) in the upper limbs, when the child is asked to heel walk, toe walk on everted or inverted feet (Fig. 4). In the 4-year-old child the upper limb normally mirror the pattern of the movement on the lower limb. This becomes much less marked or has disappeared entirely by 9–10 years. Asymmetries which are marked and reproducible point to hemisyndrome on the exaggerated side. Therefore an 8-year-old child with subtle spastic right-sided hemiplegia not observed by gait and posture can show exaggerated-associated movements (increased flexion or extension, etc.) and excessive posturing of right upper limb (nondominant), when the child is asked to walk on inverted or everted feet (Fig. 5). This will help to perform subsequent neurological examination like deep reflexes, when right side will show hyperreflexia in comparison to left. Identification and elicitation of hyperreflexic deep reflexes of affected side in subtle hemiplegia, sometimes may pose difficulty without performing Fog's test or pronator drift initially. Excessive posturing, which is bilaterally exaggerated for the child's age, points to an underlying developmental dyspraxia or clumsiness which is unlikely to be pathological.

Fig. 4: A normal child performing Fog's test by walking on tip toe showing no exaggerated upper limb movements

Fig. 5: A child with right-sided hemiplegia performing Fog's test by showing exaggerated movement and posture of right upper limb

Spastic paraparesis or diplegic gait: Legs are adducted across midline when viewed from in front ("Scissor gait"): Knees scraping together and bilateral toe walking and crouched stance due to bilateral flexion contracture.

Flaccid foot drop: Ask the child to walk on heel. It cannot perform due to weak dorsiflexion (tibialis anterior). Tendency to step "high" on the affected side flexing the hip to lift the foot clear of the floor.

Proximal weakness (e.g. Duchenne dystrophy): Look for the muscle bulk (increase hypertrophied calf muscle) and for marked lumbar lordosis. Exaggerated rotation and throwing of the hips to each side with each step results in *waddling gait*. The ability to climb layers is limited. Perform Gower maneuver (assessment of proximal muscle strength) which is positive in extreme proximal muscle weakness [Duchenne muscular dystrophy (DMD)].

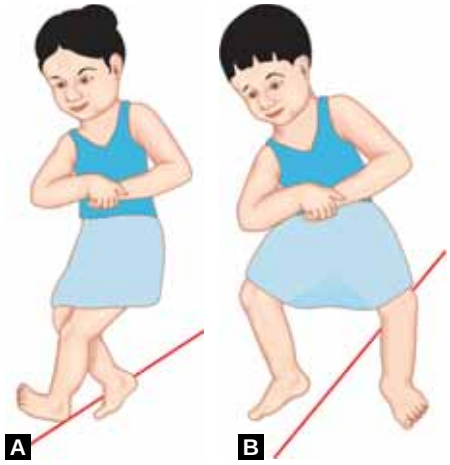
Dystonic gait: Can be extremely variable and extremely bizarre. Dystonic gaits are typically accompanied by sustained posturing of arms, trunk, head and neck. Involvement of one foot or ankle, due to abnormal contraction caused by sustained contraction of agonists and antagonistic muscles.

Ataxic gait: Usually broad-based gait (Fig. 6). Ask the child to walk in a straight line with hands folded and then quickly around. A child with truncal ataxia cannot perform quickly (cerebellar dysfunction). This is also called Tandem test (Figs 7A and B). Sensory ataxia is similar to cerebellar ataxia but markedly worse with the eyes closed.fs

TONE

Next look for muscle tone. Muscle tone is a state of tension or contraction found in the healthy muscles. For clinical purposes, it may be defined as resistance felt when a joint is moved passively. Younger children can find it hard to just relax which can cause misleading impression of increased tone. Increased tone can be pyramidal (*spastic*) or extrapyramidal (*dystonic*) in nature. The two may coexist, particularly in CP. Spasticity is linked to sensation encountered when opening a clasp knife and is called "clasp knife" type of hypertonicity. It is characterized by rapid buildup in resistance owing to the first few degree of passive movements and then as the movement continues there is sudden lessening of resistance. It is a type of hypertonicity, when increased tone is produced by rapid stretching of muscle,

Fig. 6: A child with ataxic gait with broad-based walking and outstretched upper limb



Figs 7A and B: (A) Straight line walking test (Tandem test) for eliciting truncal ataxia in normal child (normal child); (B) Showing a child with truncal ataxia who is unable to walk on straight line with upper arm folded in front of chest

by rapidly flexing and extending the muscle at joints. Spasticity is therefore also called a form of hypertonicity, which is stretch sensitive. Spasticity is velocity dependent with increase in resistance to passive muscle stretch.

Spasticity is divided roughly into two types: (1) Phasic spasticity; (2) Tonic spasticity.

Phasic spasticity: Muscles are hypertonic on rapid stretch. Its significance lies in the fact that, a child with upper motor (pyramidal) lesion occasionally look hypotonic (particularly if undernourished), but surprisingly with hyper-reflexic jerk (hypotonic are usually associated with hyporeflexia and vice versa). If muscles are not stretched rapidly, hypertonicity (phasic) may be missed out.

Tonic spasticity is characterized by hypertonicity with slow stretch.

Spasticity commonly and more easily detected in passive movements of the knee joint than it is in the upper limb. Two maneuvers should be done. Rapid passive movement and slow passive movement of knee or elbow joint, and to feel whether it is hypertonic on rapid (phasic spasticity) or slow stretch (tonic spasticity). Spasticity is associated with exaggerated tendon reflex.

Although spasticity is velocity dependent, but tone of spasticity unlike dystonic hypertonicity, does not change with change in posture, emotion or touch. It usually affects the flexor and adductor muscles, (as opposed to extensor muscles, affected by dystonia), giving rise to attitude of flexion and flexion deformity of joints.

Spasticity may complicate CP. Consequences include:

- Pain and discomfort
- Loss of function, e.g. mobility
- Contracture
- Difficulty with care, e.g. in the groin area.

Spasticity is treated to ameliorate one or more of these, not for its own sake. Realistic goals should be agreed prior to treatment and are the criteria against which success is assessed.

Spasticity Scale

Modified Ashworth Scale

A six point criteria is used to quantify degree of spasticity. It is simple and widely used but not entirely reliable as speed of movement is not specified.

Phasic spasticity
- 0 = No increase in muscle tone
- 1 = Slight increase in tone, with catch and release or minimal resistance at end range.
- 2 = Minimal resistance through range following catch, but body part is easily moved.

Tonic spasticity
- 3 = More marked increased tone throughout range
- 4 = Considerable increase in tone, passive movement difficult
- 5 = Affected part is rigid in flexion/extension (Difficult to distinguish from dystonic hypertonicity)

Dystonia or rigidity is the term used to describe resistance to passive movement, which is sustained throughout range of movement and unlike spasticity is velocity independent, and associated with fixed change in muscle, tendon and joints. It is due to disease of basal ganglia. This phenomenon gives rise to sensations reminiscent of those produced by bending a lead pipe, called lead pipe rigidity. When tremor is superimposed on rigidity, the resistance to passive movement is jerky increased as if a ratchet were slipping over the teeth of a cog. This is called cogwheel rigidity, and commonly felt in Parkinsonism. Extrapyramidal (basal ganglia) and cogwheel rigidity are most easily detected at the wrist when relatively slow manipulation is employed.

Measurement scale of dystonia is not as well-established as spasticity. The Barry-Albright dystonia scale was developed for children. Five point-ordinal scale served for the following body parts—eyes, mouth, neck, trunk and each limb.

0 – Normal
1 – Slight body part affected less than 10% of tone
2 – Mild body part affected less than 50% tone, not interfering with function
3 – Moderate body part affected more than 50% of tone and/or interference with function
4 – Severe body part affected more than 50% of tone, prevents or severely limits function.

Unlike spasticity, dystonic hypertonicity is velocity independent, but changes with posture, emotion, tactile stimulation. Tone may be increased in dystonic CP child, when the child sleeps on supine position but tone may be decreased on prone position which is important for postural management of dystonic CP. A child with CP may throw himself into severe dystonic rigidity when he/she cries or emotionally upset. A predominantly dystonic infant may show persistent primitive reflexes like exaggerated galant and perez reflex and overperformance of progression reflexes like stepping and walking reflexes, unlike spastic CP. A child with dystonic hypertonicity usually takes the posture of extension, as opposed to flexion attitude of spastic child. Tendon reflexes are also not increased in comparison to spastic child. Persistent primitive reflexes like asymmetric tonic neck (ATN) reflex are also more associated with dystonic CP.

Difference between Spastic and Dystonic Hypertonicity

In CP there may be mixed pattern. However, one may be more dominant than other (Table 1).

Hypotonia: This is harder to assess in younger children. Posture may be more useful indicator of decrease tone in early infancy.

Table 1: Difference between spastic and dystonic hypertonicity

Spasticity	Dystonicity
Stretch sensitive and velocity dependent	Velocity independent and not stretch sensitive
Usually affects flexor and adductor muscles of joints	Usually affects extensor muscles of joints
Posture: presents attitude of flexion and adduction	Posture: attitude of extension
Tone: does not change with change of posture, emotion or tactile stimulation	Tone: may change with change in posture, emotion and tactile stimulation. Usually more hypertonic on supine position.
Reflexes: exaggerated tendon reflex	Reflexes: no exaggerated tendon reflexes
Knee flexion: flexor withdrawal of positive planter reflex	Knee extension: extensor withdrawal of planter reflex

They feel floppy, with poor head control, head leg and truncal instability. Putting hands under armpit, it may slip under armpit while trying to lift the child (Fig. 8).

Hypotonia is often demonstrated by hyperextensibility of joints. Hyperextension of more than 9° at knee and more than 10° at elbow is significant hyperextension suggestive of hypotonia and lax joints (Fig. 9). Similarly hyper-reflexion at wrist allows thumb to touch the dorsum of the forearm, which is normally not possible, is suggestive of significant hypotonia. When thumb is closed in closed fist, it protruded beyond medial border of hand (Steinberg sign), a diagnostic test of Marfan syndrome, where hypotonicity and hyperextensibility coexist. When child is asked to touch his or her nose with tongue, a child with hypotonia and hyperextensibility can do it, which a normal child cannot perform.

If the child is hypotonic, look for visible fasciculation and wasting of muscle. Fasciculation is produced by spontaneous contraction of large group of muscle fibers or a whole motor unit. It suggests lower motor neuron lesion.

POWER

Younger children often struggle to understand what is wanted of them in formal power test is done by requesting the child to pull the examiner towards the child, while the examiner resists such action to request, such as pull against me. Testing of power of group of muscles can be done by asking the child to contract a group of muscles as powerfully as possible and thus move a joint and then maintain the deviated position of the joint while the examiner tries to restore the part to its original position. Examine shoulder abduction on each side simultaneously then elbow flexion on each side before elbow extension. Formal examination of power in legs is best performed in supine position.

Proximal weakness of shoulder and hip girdle (usually associated with complaints of difficulty in raising head from pillow, combing hair, raising arms above head and climbing stairs) usually implies muscle disease. In severe proximal muscle weakness, Gower sign will be positive (Fig. 10). Remember, the key feature that makes a Gower sign positive is not so much the "walking up legs" which may be absent if the proximal weakness is mild. *The child is required to turn from supine lying to prone position as a preclude to getting up.* The child will have difficulty rising from the floor (Gower's maneuver) where the child climbs up his thigh with his hands to get up off the floor. Proximal weakness of the body usually implies muscle disease while distal weakness as evidenced by difficulty in opening caps of bottles, turning keys, buttoning clothes usually occurs in neuropathic disease or in dyspraxic child.

Grading of Muscle Power

The evaluation of muscle power should be recorded quantitatively using the grading recommended by the Medical Research Council (MRC).

0 – No active movement
1 – Visible or palpable active contraction with active movement

Fig. 8: A floppy infant showing slipping through hands at armpit on vertical suspension

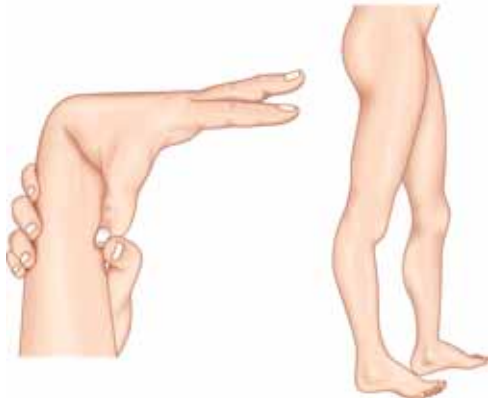


Fig. 9: Figure showing hyperreflexion of wrist at thumb, allows thumb to touch dorsum of hands and hyperextension at right knee joint

Fig. 10: Figure showing Gower's maneuver with Gower sign positive

2 – Movement which is possible with gravity eliminated
3 – Movement which is possible against gravity
4 – Movement which is possible against gravity plus resistance but which is weaker than normal
5 – Normal power

Since this is a relatively crude scale, it is acceptable to subdivide grade-4 into 4 +, 4 and 4–, thus improving sensitivity.

In younger child, assessment of power may be difficult. Try to assess power in the form of playing game with child and appreciating the child, while you observe, whether the child can lift (power level at least 3) his/her limbs and can kick or fist you against resistance (power level 4 to 5).

REFLEXES

The successful elicitation of a deep tendon reflex requires the muscle belly to be relaxed yet moderately extended. Attention to optimal limb position is thus helpful. Young children may also be disconcerted by the idea of being hit! For both these reasons examination of reflexes in the upper limb can be helped by your holding the arm, placing a finger or thumb over the tendon and striking your own finger or thumb. With the child's hands on his/her lap, press firmly with your thumb over the biceps (C_5) tendon just above the elbow and strike your thumb (Fig. 11). Elicited jerks are often as much felt (through your thumb) as seen. Supinator reflexes ($C_{5, 6}$) can be elicited by striking your finger placed just proximal to the wrist over the radial side of the partially supinated forearms as it rests in the child's lap or for bigger children directly hitting on supinator tendon as shown in Figure 12.

Triceps ($C_{6, 7}$) may require a slightly different approach: hold the arm abducted at the shoulder to 90° and with the forearm hanging down passively, and strike the tendon directly as you won't have a hand free (Fig. 13).

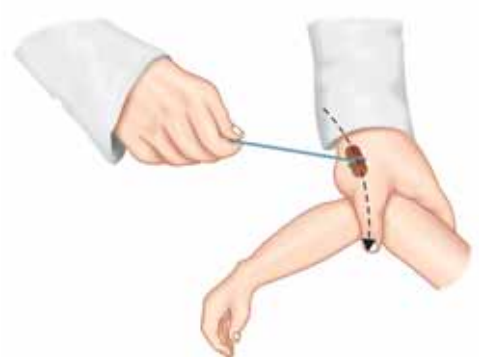


Fig. 11: Eliciting bicep reflex (C_5)

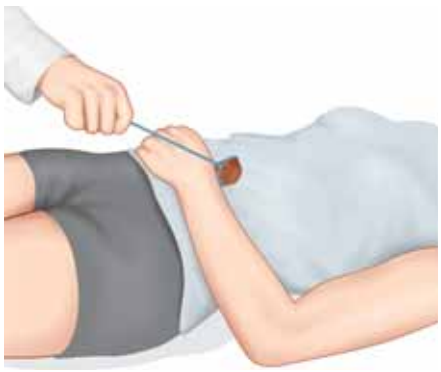


Fig. 12: Eliciting supinator reflex ($C_{5, 6}$)

Knee Jerk ($L_{3, 4}$): It can be elicited in various ways depending on age of the child. In younger children adequate relaxation of quadriceps, muscles for elicitation of knee jerks can be assured with both child and examiner being seated and facing each other (Fig. 14). Put the child's feet either up on the front edge of your chair (Fig. 15) or on your knees (Fig. 14). In young infant it can be elicited in supine position (Fig. 16). Feel the patellar tendon by thumb and placing thumb on tendon, strike your thumb with the hammer in young infant (Fig. 16). In big child patellar tendon can be hit directly (Figs 14 and 15). Look jerks, by looking at brisk contractions of quadriceps and sudden extension of knee joints.

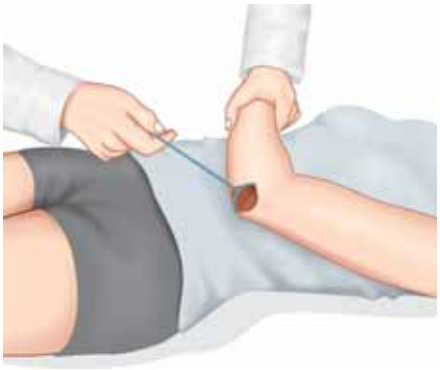


Fig. 13: Eliciting triceps reflex ($C_{6, 7}$)

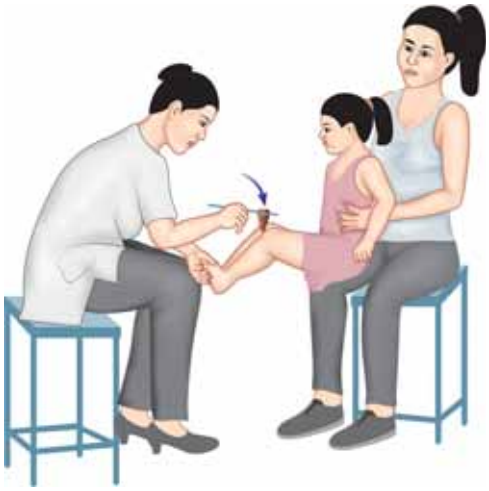


Fig. 14: Eliciting knee jerk ($L_{3, 4}$) in young child while both child and examiner being seated and facing each other

Fig. 15: Eliciting knee jerk in young child in sitting position while legs are hanging from sitting position

Fig. 16: Eliciting knee jerk in young infant. Relax quadriceps by flexing the knee with one hand and placing the thumb on the patellar tendon. Strike your thumb with the hammer in your free hand. Look for quadriceps contraction or feel the contraction with the hand on the infant

When tendon reflexes are pathologically exaggerated, they often spread beyond the muscles stimulated by nerve concerned and adjoining muscle of same side or even opposite limb may show brisk contraction (cross hyperreflexia). For examples in spastic CP, hyperreflexic knee joint in one side may be associated with brisk contraction of adductor muscle of opposite side (Cross adduction) (Fig. 17).

Hyperreflexia is usually associated with hypertonia. Exaggerated hyperreflexic knee jerk not only can be elicited by striking patellar tendon, but also by striking hammer lower down the patellar tendon, e.g. on shin of tibia. Therefore if hyperreflexic knee jerk is expected, start striking gently on shin of lower tibia and gradually step up striking shin gently and finally strike patellar tendon (Fig. 18). In hyperreflexic knee jerk, hyperreflexia may start well below down the patellar tendon due to *extended afferent* (usually seen in spastic CP). Observe at what level below patellar tendon, the quadriceps start contraction. Also look for cross adduction in such case.

Similarly finger flexion often accompanied biceps and supinator jerks, when they are pathologically exaggerated.

Hoffman Sign

It is another manifestation of hyperreflexia. It is elicited by first flexing the distal interphalangeal joint of the patient's middle finger and then flicking it down further so that it springs back to normal. When tendon reflexes are hyperactive the thumb quickly flexes in response to this maneuver.

Tendon reflexes are exaggerated in upper motor neuron disease (pyramidal). Children with spastic CP are usually associated with hyperreflexic tendon reflexes.

Fig. 17: Exaggerated knee jerk with hitting the left patellar tendon and showing contraction of adductor muscle of hip of opposite side (right) due to cross adduction (see arrow)

Fig. 18: Eliciting knee jerk in upper motor neuron lesion with hyper-reflexia with suspected extended afferent. Picture shows striking hammer on shin of lower tibia and gradually stepping up in order to identify the point where hyper-reflexia begins below patellar tendon (dots and arrow marks) for extended afferent

Clonus

When the tendon reflexes are exaggerated as a result of corticospinal lesion, there may be clonus. To test for ankle clonus, bend the patient's knee slightly and support it with one hand, grasp the fore part of the foot with the other hand and suddenly dorsiflex the foot. The sudden stretch causes brief reflex contraction of the calf muscles, which then becomes relaxed, continued steady stretch causes a regular oscillation of contraction and relaxation which is called clonus. There may be clonus with minimal or no stretch, called spontaneous clonus. Sustained clonus or spontaneous clonus is abnormal and is evidence of an upper motor neuron lesion (Fig. 19).

Grading the Reflexes

The tendon reflexes are graded as follows:

0 – Absent
1 – Present
2 – Brisk
3 – Very brisk with extended afferent and cross hyperreflexia
4 – Clonus

Ankle Jerk (S_1, S_2)

In supine posture, place the lower limb on the bed so that it lies everted and slightly flexed. Then with one hand slightly dorsiflex the foot so as to stretch the Achilles tendon and with hammer on other hand, strike your hand which dorsiflexed the child's foot or if the child is big (> 5 years) strike the tendon directly on its posterior surface of tendoachilles. A quick contraction of calf muscle results (Fig. 20).

Planter Response (S_1)

Planter responses are elicited in usual manner. A firm but gentle striking stimulus to the outer edge of the sole of the foot evokes initial dorsiflexion (extension) of large toe and fanning of the other toes, which is positive Babinski sign, characteristic of pyramidal lesion; but it is normal below 18 months of age. For positive Babinski sign, always look for initial upward movement of hallux, as it may undergo flexion following brief dorsiflexion, and falsely interpreted as negative Babinski sign (Fig. 21).

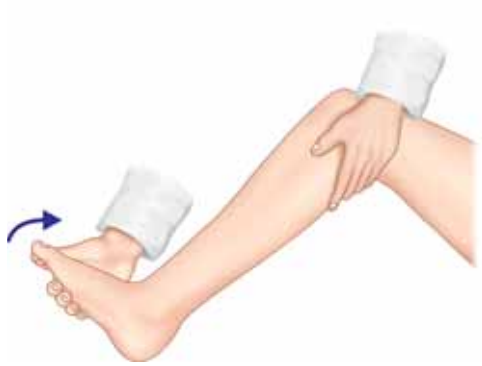


Fig. 19: Testing for ankle clonus

Fig. 20: Eliciting ankle jerk in a small infant, with one hand dorsiflexing in the foot while with hammer on the other hand striking the hand of the examiner which dorsiflexed the child's foot

Fig. 21: Eliciting the planter reflex (S_1) showing extensor response

Diminished or absent tendon reflexes: Diminished or absent tendon reflexes: Usually associated with hypotonia, associated with lower motor neuron disease [Guillain-Barré syndrome (GBS), spinal muscular atrophy (SMA), etc.]. The significance of depressed tendon reflexes needs to be interpreted by comparison between the responses obtained on two sides and between the amplitude of the jerks in the arms and those in the legs. If normally brisk contractions are seen in the arm and the very poor responses are evoked at knee and ankles, then it is possible that the later findings are pathological.

Reinforcement: In bigger child if no response is obtained after routine tendon tap, the absence of reflexes should be confirmed by reinforcing the jerk. Tendon reflexes are increased in amplitude (i.e. potentiated or reinforced) by forcible contraction of muscles remote from those being tested. To reinforce the knee and ankle jerks, the patient may be asked forcibly to close the hands. An alternative procedure requires the patient to hook the fingers of the hand together and then forcibly attempt to pull one away from the other without disengaging the fingers (Fig. 22).

Abdominal reflexes are elicited by scratching the skin along a dermatome toward the midline. They may be absent in 15% of the normal population and may be normally asymmetrical. They can help localize thoracic spinal cord lesion, though they are less reliable than sensory level to pin prick.

SENSATION

If indicated assess sensation by asking them to close their eyes and say "yes" every time they feel your touch. Pain and temperature sensation (testing spinothalamic tract) may be difficult in children, but if possible should be carried out by two

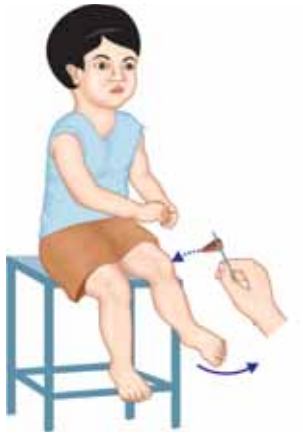


Fig. 22: Reinforcement in eliciting the knee jerk

point discrimination. Loss of spinothalamic and preservation of dorsal column (touch and proprioception) is an important sign of Syringomyelia.

Joint position sense may be assessed at a single joint in the older child in the usual manner, but it is more useful to screen for compared proprioception by performing the Romberg test (looking for increased body sway in standing with eye closed).

COORDINATION OR ATAXIA

Truncal Coordination: Measure of Cerebellar Function

Ask the child to walk on a straight line, with heel of one foot just in front of toe of other foot (heel-toe walking) keeping upper arms folded in front of chest, so that the child cannot compensate possible balance problem by freed upper arms. Child with truncal coordination (cerebellar vermis lesion) problem cannot perform. It may be found in a child with motor coordination disorder. This is called Tandem test (Figs 7A and B).

Peripheral in-coordination (Finger-nose test): Ask the child to move his index finger from tip of his nose to the tip of your index finger, and back to the tip of his nose. Ask to do it repeatedly. Emphasize the accuracy not the speed, whether finger lands precisely on tip of the nose. If this movement is performed naturally and smoothly and without random errors, coordination (peripheral) is normal. If finger cannot touch tip of nose, rather goes past nose (past pointing dysmetria), then incoordination (cerebellar hemisphere) is present.

Intention tremor: It is characteristic of damage of posterior lobe of the cerebellum. The patient's hand is steady at rest but develops a tremor as it approaches its target, e.g. as it approaches tip of his nose or tip of examiner's index finger.

CRANIAL NERVES

Olfactory Nerve (I)

Rarely tested in children, may be tested in condition associated with anosmia (Kallmann syndrome).

Optic Nerve (II)

Visual Acuity Test

If the child is small (<3 years), look at the child's eye. Do they fix and follow? Move an interesting toy and watch child's eye

movement. Note the ability of the child to reach small items, which are safe if ingested (sweet gems).

Fields

In older children, visual field can be tested by confrontation with both eyes open. Isolated nasal visual field defects (without temporal field defect) are rare. Thus a binocular approach is an effective screen. If defects are identified, then test each eye separately. In infant gross field preservation can be inferred by refixation reflex: the child refixing on a target as it moves from central into peripheral vision in each direction (Fig. 23).

- Lesion in (A), i.e. lesion is anterior to optic chiasm (optic nerve) causes one-sided visual filed deficit.
- Lesion in (B) gives bitemporal hemianopia
- Lesion in (C) homonymous hemianopia from a lesion in the contralateral optic tract
- Lesion in (D, E) temporoparietal lobe lesions result in partial deficits, rarely precisely quadrantanopic
- Lesion in (F) a branch of the middle cerebral artery supplying the area of occipital cortex relating to the macula allows posterior cerebral artery lesions affecting the occipital cortex to result in "macular sparing".

Fundoscopy

Examination of fundus is particularly difficult in infants. In younger children (age 5–7), it should be performed in the form of playing a game involving child and mother. Ask them to sit in your clinic where child will sit in front of you while mother will sit behind you. Ask mother to make funny face to help child to fix his/her eyes on her and not on your ophthalmoscope. Fundoscope in toddlers requires an assistant to attempt to secure attention and patience.

View the child's right eye with your right eye and vice versa so as not to block the view of nonexamined eye with your head and prevent fixation on a distant target. Keep your glasses on if worn but remove the child's glasses. Darkening the room (e.g. drawing curtains) helps pupillary dilatation, but very dark room may cause distress and prevents the child fixing on the target.

Optic neuritis (papillitis) and papilledema have very similar appearance (Fig. 24). Visual loss is prominent in papillitis and is the usual presenting complaint. Pale optic disk (Fig. 25) is suggestive of optic atrophy.

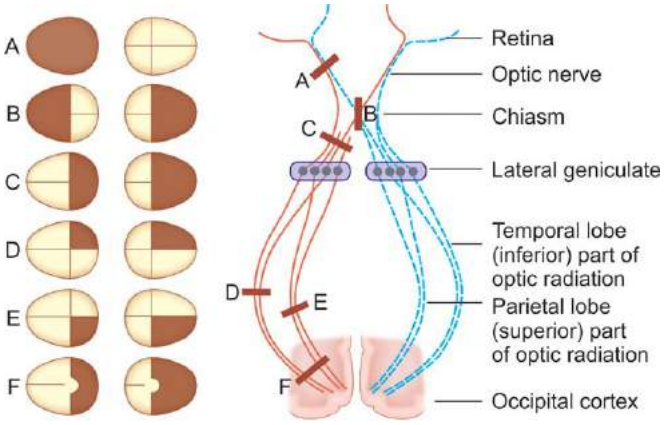


Fig. 23: Visual field

Look for: Pupillary size, shape, color and pupillary reflexes. Pupil should be inspected.

Anisocoria

Deciding which the abnormal pupil is can be difficult. A dilated pupil may be due to a partial third cranial nerve lesion usually associated with eye deviation inferolaterally and/or eye lid closure (Fig. 26).

- A small pupil again associated with ipsilateral ptosis is likely to represent a unilateral Horner's syndrome (Fig. 27).

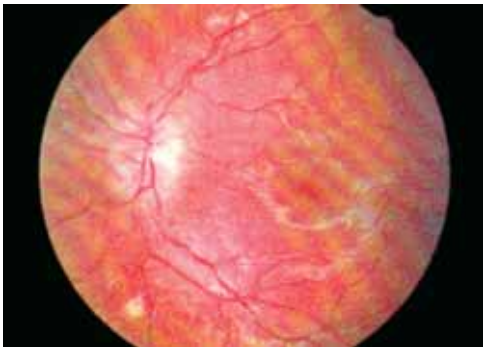


Fig. 24: Optic disk swelling: Advanced papilledema

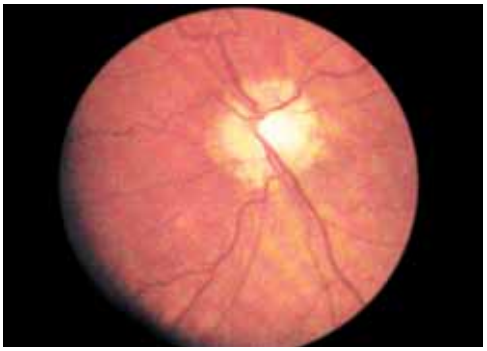


Fig. 25: Optic atrophy (pale optic disk)

Fig. 26: Left congenital ptosis

Fig. 27: Right Horner's syndrome with ptosis and small pupil of right eye

- Isolated anisocoria is usually benign, although often a cause of anxiety. Pupil is larger and reacts to light poorly, but contracts briskly on accommodating to a near target.

Pupillary (light) reflexes and afferent pupillary defect: If a light is shown on eye, the pupil of the same side (direct light reflex) as well as on the opposite side contracts (consensual light reflex). A nonreactive pupil can arise from a lesion either in the afferent (optic nerve) or the efferent (third nerve) limb of pupillary light reflex. Due to bilateral consensual nature of the pupillary light reflex, an eye with an interrupted optic nerve but intact third nerve will still constrict when the opposite eye is illuminated.

Head trauma is one context where recognition of an APD is crucial, the optic nerve can be involved in orbital fractures and give rise to a dilated pupil (due to an APD) that might otherwise be interpreted as a third nerve lesion (efferent pupillary defect) and a sign of ipsilateral uncal herniation.

Leukokoria (white pupil) and red reflex: Pupil looks dark when looked from outside. A white pupil may be due to lentil opacity (cataract), corneal opacity (xerophthalmia), vitreous hemorrhage and retinoblastoma (Fig. 28). In such conditions, normal red reflex (viewed from arm's length distance with the ophthalmoscopic lens at zero) will also be absent. Normal red reflex appearance varies in different ethnic groups, if in doubt, check the appearance in the mother.

Cranial Nerve III, IV and VI

The third, fourth and sixth cranial nerve nuclei and their interconnections span the pons.

Inspection

- Note the presence of broad epicanthic folds or a nasal bridge that can give the appearance of a pseudo squint
- Observe for ptosis
- Note pupil size: Small with ptosis on same side of Horner's syndrome (Fig. 27) and dilated in third nerve palsy (Fig. 29). Look for aniridia or absence of iris (associated with Wilms' tumor), Colobomas

Fig. 28: Right leukokoria due to retinoblastoma

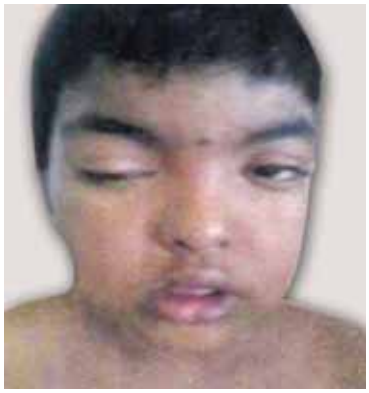


Fig. 29: Ptosis due to third nerve palsy

- Note symmetry of position of light reflex (the dot of light due to the reflection of the ophthalmoscope light on the iris or cornea) when examining for red reflex or simply by shining a light in the eyes from in front of the face. This is very useful in detecting subtle nonalignment of eyes in the neutral position. Normally dots of light reflex should be at the same position in each cornea.

Eye Movement

- In a younger child, observe spontaneous eye movements
- In an older child test smooth pursuit of slowly moving target and eye movements
- In an infant eye movement can be observed by inducing nystagmus. A rotating striped drum will induce optokinetic nystagmus.

Strabismus

A squint or strabismus is an abnormality of ocular movement such that visual axes do not meet at the point of fixation.

Depending on weakness of ocular muscles squint is divided into (1) Paralytic and (2) Nonparalytic (concomitant) squint.

Depending on external appearance of squint, it is again divided into (1) Latent and (2) Manifest squint.

Paralytic squint occurs due to weakness of one or more of the extraocular muscles, when eye fails to move at all or fails to move through its normal angular excursion.

In nonparalytic (concomitant) squint, the eye movement is normal and the angular deviation of the visual axes is the same in whatever position the eye moves.

Latent Squint and Manifest Squint: Test by Cover Test (Fig. 30)

In doubtful case of nonparalytic squint, as to which eye is affected, a cover test can be done. In latent squint, the squinted eye looks normal and light reflex slightly nasal to center. Cover test identifies the affected eye. Cover affected eye, it turns in

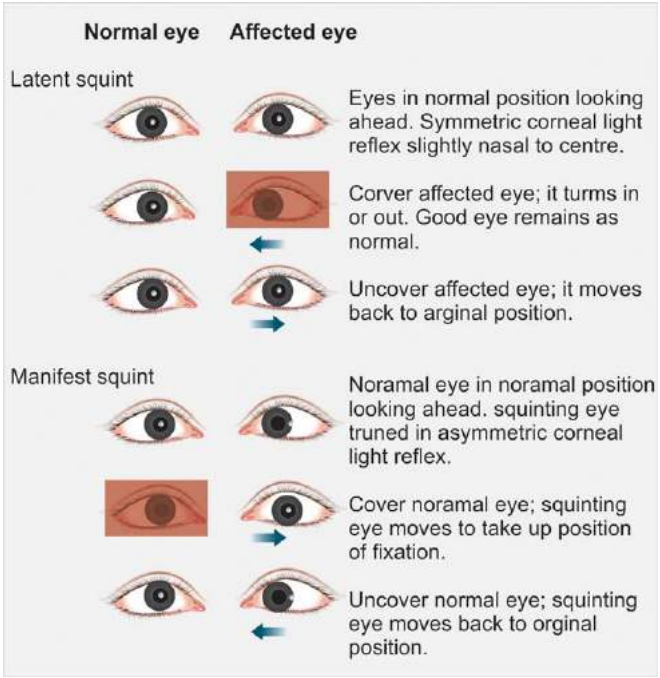


Fig. 30: Cover test

or out. Good eye remains at normal. Uncover affected eye. It moves back to original position, thereby identifying the affected eye.

Abnormal conjugate eye movements:

- Down with sun setting in raised intracranial pressure (RICP), in hydrocephalus (Fig. 31)
- To one side toward the irritable lesion (seizure, frontal lobe lesion)

Abnormal Disconjugate Eye Movement

- Squint
- Cranial nerve palsies
- Nystagmus
- Head tilt

Diplopia (Double Vision)

Older children should be asked specifically whether they see double vision when they are deviated by movements of eye, both conjugate and when they move each eye separately. Paralytic eye movements (paralytic squint) are associated with diplopia. Diplopia will be worst when attempting to look in the direction of affected eye movement.

Diplopia is often distressing and children may cover or occlude the eye and dislike having it open.

Cranial Nerve V

Usually not routinely tested in pediatric practice particularly in younger children

Corneal reflex: Approach with a wisp of cotton wool from the side to avoid a blink due to visual threat. Touch the cornea over the inferolateral quadrant of the iris. Note whether a blink is noted.

Cranial Nerve VII

Watch the facial movements. Do not overlook asymmetric crying facies for facial nerve involvement in neonate and young infant.

Ask the child to imitate facial expressions (grimaces, frown, smile, forced eye closure). Examine the symmetry of movements (Fig. 32). The child should normally be able to bury their eye lashes in forced eye closure. Distinguish upper motor neuron involvement of the seventh cranial nerve (minimal

Fig. 32: Cranial nerve palsy: VII nerve palsy (right) with deviation of angle of mouth to unaffected left side

effect on eye closure or eyebrow elevation) from lower motor neuron lesion (typically marked effect on eye closure).

Cranial Nerve VIII

For hearing (VIII) say something with your hand covering your mouth and see if the child responds appropriately.

Formal hearing is normally clinically checked for the first time between 6 months and 8 months of age.

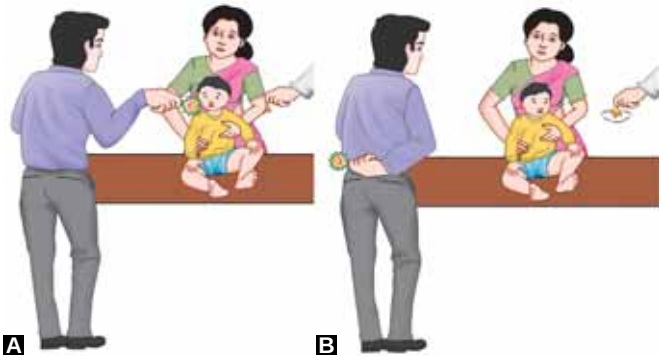
Distraction Test

To carry out distraction test (Figs 33A and B), the baby sits on the mother's lap or on a table held by mother, facing forward. It helps if an assistant can sit facing them to distract the child with toys, etc. (but not funny noises). The examiner makes soft noises to one side or the other behind the mother and the child and out of the child's line of vision, while the assistant in front hides the toy. The sounds used by examiner are a special high frequency rattle, a bell, a spoon in a cup and the rustle of tissue paper or whisper. At 6 months age a baby should turn to the source of sound when it is about 45 cm from the ear. By 9 months a baby reacts more quickly and localizes the sound at a distance of 90 cm.

There are special techniques like acoustic cradle, brain stem auditory evoked potential, cochlear echo, etc. Babies can be screened with these tests even in new born period. But these are only done in those babies who are at risk of impaired hearing, as for example when there is family history of impaired hearing; babies received ototoxic drugs like aminoglycoside, etc.

In children over 18 months, stycar animal picture performance test can be done for screening hearing. The child is asked to point various animals, which are familiar to him/her. If the child can hear examiner voice he/she will point the animal in the picture.

Fig. 31: Downward conjugate movement of eye due to raised intracranial pressure in hydrocephalus



Figs 33A and B: Hearing response test (distraction test) (A) Child vision is fixed to an object shown by attendant in front; (B) The child is distracted by another sound and turns to ringing bell (showing hearing response) performed by another attendant as the first attendant conceals the object in front simultaneously

For hearing and middle ear disease in older children Rinne tuning fork testing is reliable in children as young as 5 if performed carefully.

Hold the fork against the mastoid until the child reports that they have just stopped being able to hear it and then check whether they can still hear it, next to their ear (should be able to: air conduction should be better than bone conduction).

Cranial Nerve IX, X (Palatal and Bulbar Function)

Cranial nerve IX and X are not usually tested elaborately in routine pediatric neurological examination unless specifically indicated as it can produce lot of discomfort to apprehend child and the child may become uncooperative for rest of other examinations.

Does the child dribble excessively? Ask a healthcare provider to watch the child swallow and listen to his/her articulation of speech (IX, X).

Gag reflex: The gag reflex tests sensory and motor components of IX and X cranial nerves. In the conscious child, it is rarely necessary to elicit a gag reflex formally to assess palatal and bulbar function: this can be inferred from observation of feeding and swallowing behavior.

In neurologically comatose patient, involvement of IX and X nerve can be tested by gag reflex. Touching the posterior wall of pharynx evokes its constriction and elevation. This is the gag reflex whose afferent arm is the glossopharyngeal nerve and whose efferent path is the vagus nerve.

Cranial Nerve XI, XII

Children love to stick out their tongues and shrug their shoulder (XI, XII). Ask them to demonstrate it, if he is big enough to do it.

NEUROLOGICAL AND DEVELOPMENTAL ASSESSMENT OF NEONATES AND YOUNG INFANT

(See Neonatal Examination, Chapter 1 and Child Development in Chapter 5)

COMBINED NEUROLOGICAL AND DEVELOPMENTAL ASSESSMENT IN NEONATE AND INFANT

Developmental and few primitive reflexes assessment should be done along with neurological examination, in neonates and young infants in particular, as many developmental problems and abnormal primitive reflexes may be due to underlying primary neurological problems. Neurological and developmental examination should be done sequentially by examining the child in supine lying initially, followed by pulling to sitting, standing, ventral suspension and finally lying on prone position and this should be done at a stretch and not in haphazard manner like supine to sitting then standing and back to lying without going through ventral suspension and lying on prone position.

Neurological examination with developmental and primitive reflexes in new born and early infancy should be started with observation followed by minimum touch and then with more touch. More disturbing examinations which may upset the child, like Moro reflex should be done later.

*Children not sitting by 9 months should be referred for evaluation.

In Supine Lying (Figs 34 to 36)

- Note alertness
- Note head shape, dysmorphic features, neurocutaneous stigmata
- Palpate fontanel
- Examine range of eye movements, fixation and following of bright object in front of eye
- Note symmetry of cry in facial nerve palsy (Fig. 34)
- Note spontaneous antigravity limb movement (power)
- Note the posture. In Erb's palsy (the most common peripheral nerve injury in neonate), the arm is held extended, internally rotated with flexion at the wrist of affected side as if a waiter in a restaurant is taking a tip from a customer (Fig. 35).

Primitive Reflexes

A number of early or primitive reflexes are reliably demonstrated in normally developing infant that disappear by 4–6 months. Abnormal reflexes (absence of symmetric or persistent neonatal reflexes beyond normal period) are suggestive of underlying neurological disorder.

In supine lying position the following primitive reflex can be elicited:

Grasp Reflex

Fingers or toes grasp an object placed on the palm or sole.

Rooting Reflex

Head turn toward a tactile stimulus placed near the mouth.

Fig. 34: Asymmetric facial cry due to left-sided facial palsy

Fig. 35: Position of the right upper arm due to Erb palsy showing typical waiter's tips sign due to brachial nerve damage

Asymmetric Neck Reflex

Lying supine, if the head is turned, a fencing posture is adopted with the outstretched arm on the side to which the head is turned (Fig. 36B).

- Deep tendon reflex (Not reliable at this stage, but asymmetry is important)
- Bicep reflex (C_5/C_7) is absent in Erb's palsy
- Measure the head circumference.

Gentle arm traction to observe head lag

From supine lying pull to sit and note head lag

In sitting, note the need for support (Figs 37A to C)
By 3 months, there is no head lag and infant hold head upright when held sitting.

Significant head lag beyond 2 months is abnormal.

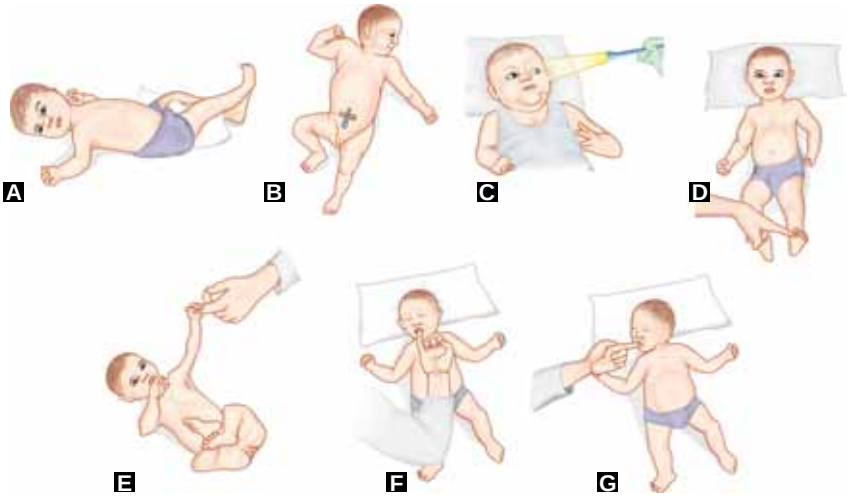
Sitting (Figs 38A to E)

At 6 months an infant sits in tripod fashion (sitting with own support on hands). By 7 months an infant should sit without support. To achieve this, the baby must have developed two reflexes:

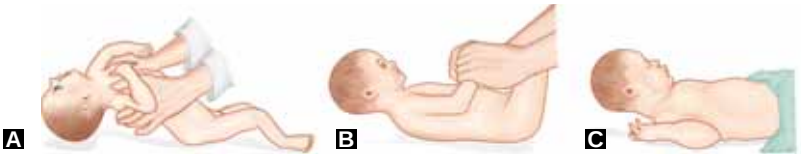
- Righting reflex: To position head and body back to the vertical on tilting
- Lateral parachute reflex: Support of body with hand, when tilted laterally on the side.

Standing (Figs 39A to E)

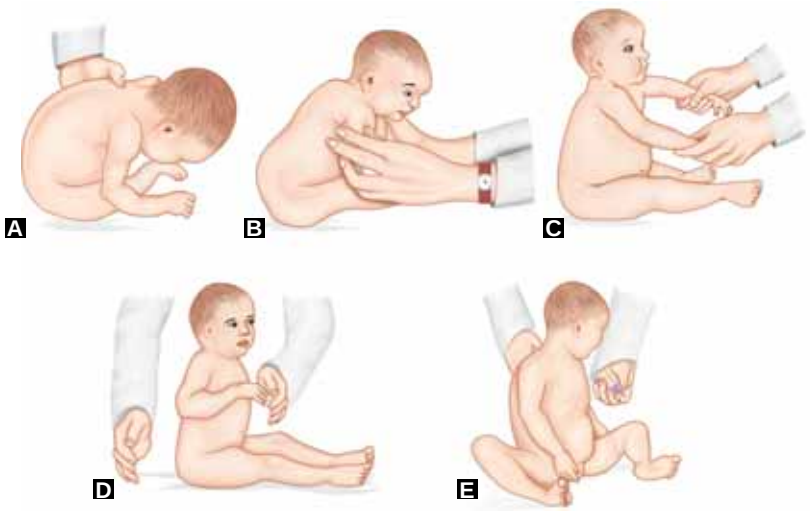
Lift the infant vertically by holding infant's shoulder with examiner's hands before placing the infant's feet on the table. Observe for scissoring (spastic diplegia). Also look for doggy paddling of lower limbs. Then place the infant's feet on the



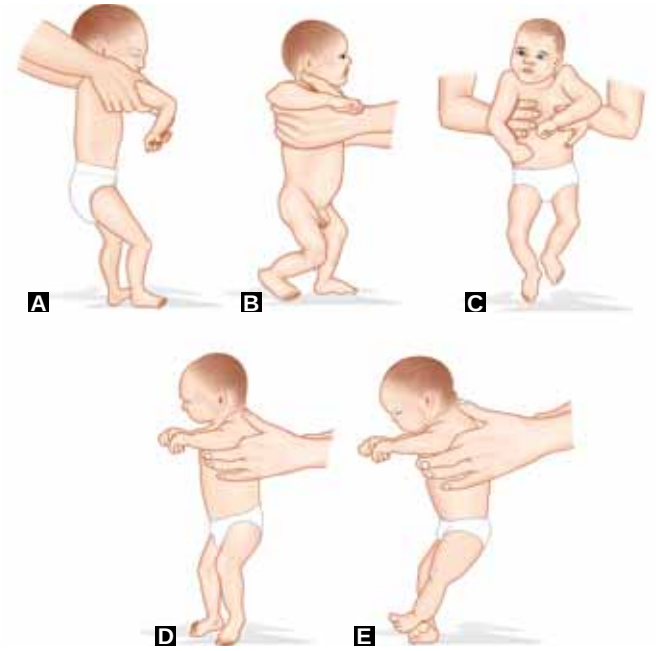
Figs 36A to G: Figures showing neonatal reflexes in supine position (A) Normal child in supine position showing normal antigravity movement; (B) A neonate showing asymmetric tonic neck reflex; (C) Showing visual fixation and following by 6 weeks; (D) Planter grasp; (E) Normal palmar grasp; (F) Rooting reflex; (G) Sucking reflex



Figs 37A to C: Showing head lag at various stage of development (A) Showing head lag in neonate; (B) Tonic elbow flexion and head lifting at 4 months; (C) A normal 6-months-old showing spontaneous lifting of head



Figs 38A to E: Figures showing sitting positions at various stages of development (A) Newborn; (B) Sitting position 2 months. Head held up slightly: (C) Sitting position 4–5 months back much more straight; (D) Sitting position 7 months sitting unsupported for short time; (E) Sitting position at 11 months showing pivoting movement



Figs 39A to E: Standing position: (A) Examiner at standing position examining muscle tone at armpit; usually baby resists slipping by increasing tone. Floppy child will show slipping at armpit due to decrease tone; (B) Showing standing position at 3 months (12 weeks) baby bearing some weight on legs; (C) The child showing stepping position examination by lifting; (D) Showing normal position of the lower limbs apart from each other; (E) Showing scissoring of the lower limbs due to spasticity of lower limb in CP

table and look whether the child can bear weight on feet and can normally bounce on his/her feet (usually a child can bear full weight on feet at 6 months and bounce on his/her feet).

Placing and Stepping Reflex

Infant held vertically, will step on to a surface when dorsum of foot is placed on it, followed by an up step by the other foot.

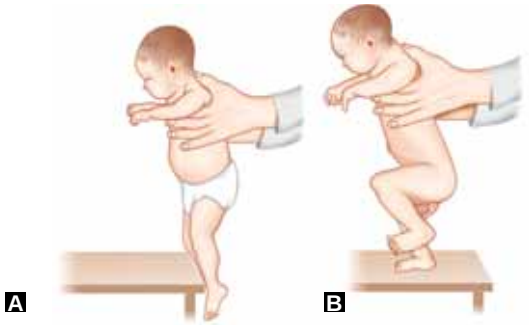
There will be persistence (>6 month) or overperformance (<6 months) of placing and stepping reflexes in CP. Normally, the reflexes disappear by 6 months (usually present up to 3–4 months). In hypertonic (dystonic predominant), placing the child on the table in standing posture and by giving gentle push from back, the CP child will be seen to quickly walk across the table (overperformance of progression reflex) (Figs 40 A and B).

Ventral Suspension

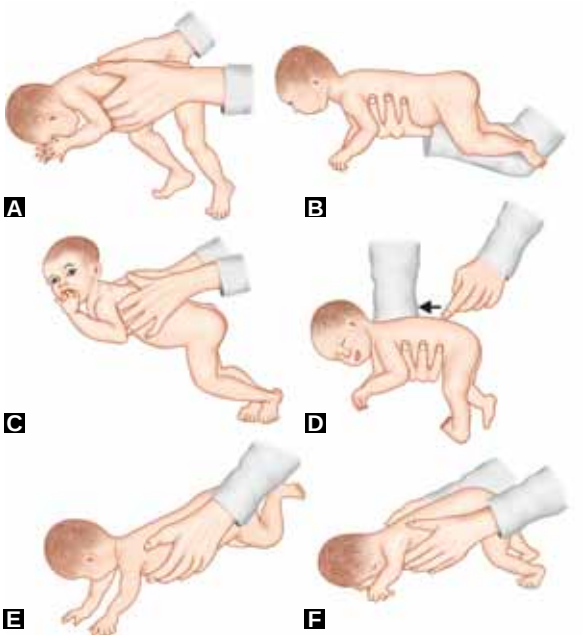
After standing, put the infant on ventral suspension. Look whether the child can lift the head from trunk. In both hypotonic (floppy) and hypertonic (dystonic child) baby, there will be head lag on pulling to sit from supine position. However, in ventral suspension, in floppy child, the child cannot lift his/her head above trunk, where as in hypertonic or in normal (> 6 weeks) child, head will be seen to be lifted above trunk. While in ventral suspension look and feel the fontanelle and spine, for evidence of neural tube defect (spina bifida). Also look for evidence of spina bifida occulta (tuft of hair, dimple, lipomatous lesion, etc. around lumbosacral spine) (Figs 41A to F).

Galant and Perez Reflex (Fig. 41D)

While in ventral suspension, elicit galant and perez reflex by pressing gently over and just lateral to the spine and from the



Figs 40A and B: Placing and stepping reflex: (A) Placing reflex. By touching dorsum of the feet with the margin of table the normal child will step up over the table; (B) The child showing stepping reflex. There may be abnormal performance of the reflex in neurological development disorders



Figs 41A to F: Ventral suspension**.** (A) Showing normal considerable head lag at 2–3 weeks; (B) Head in the same plane as rest of the body at 6 weeks; (C) Head held well beyond plane of rest of the body at 8–10 weeks; (D) Showing Galant reflex and Perez reflex (stroking along the spinous process): there may be overextension of trunks and flexion of hip in dystonic CP; (E) Showing normal downward parachute reflex with protective extension of upper limbs; (F) The child showing no parachute reflex due to neurological problems

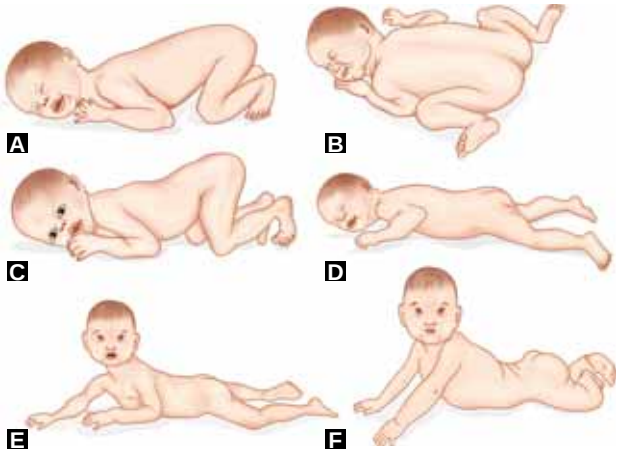
bottom to the top. Usually there will be arching and lateral movement of trunk respectively during the test, in infants up to 3–4 months. Overperformance during these periods or persistence of these reflexes beyond 6 months usually occurs in CP.

Downward Parachute Reflex

In ventral suspension bring down the baby with head facing down toward the floor to elicit parachute reflex (Figs 41E and F).

Lying on Prone Position (Figs 42A to F)

After ventral suspension put the infant on prone position. Look whether the child can lift head on lying position and move it from side to side (6 weeks).

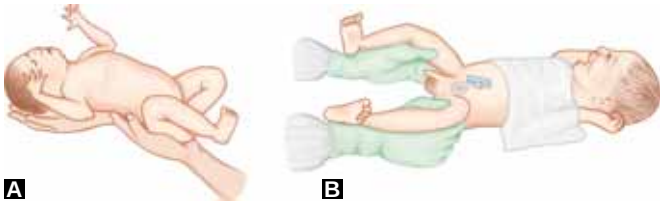


Figs 42A to F: (A) Prone newborn baby, pelvis high, knees drawn up under abdomen; (B) Premature baby with hyperabducted hip due to hypotonia; (C) Prone, 3–4 weeks, pelvis high, some extension of hip and knees; (D) Prone, 6–8 weeks, pelvis low legs extended; (E) Prone, 4 months, weight on forearm; (F) Prone, 5–6 months, weight on extended arm

Moro Reflex (Startle Reflex) (Fig. 43A)

Since Moro reflex can upset the child and can spoil subsequent neurodevelopmental examination, it is better to do it at the end of all examinations. It is performed by inducing sudden extension, which produces symmetrical extension of limbs followed by flexion. It is usually present up to 3–4 months. Persistence of Moro beyond 6 months is unusual and suggestive of CP. Symmetry of movements is also important to observe. Asymmetry of movement can be observed in erb palsy. Similarly ATN reflex can be seen later, instead of initial supine position as it may also disturb the infant and can spoil subsequent examination.

In supine position non-neurological examination like screening for congenital dislocation of hip (ortolani and Barlow test) can be done (Fig. 43B).



Figs 43A and B: Moro reflex. (A) Baby extending and adducting upper limbs, opening the hands; (B) Examination of hip for stability of hip joint (Ortolani and Barlow test), though not genuinely a part of neurodevelopmental system

INVESTIGATION OF CENTRAL NERVOUS SYSTEM

There are many neurological investigations including number of newly developed expensive and invasive investigations to diagnose pediatric neurological conditions. However, investigations should be done rationally and it is of fundamental importance in pediatric neurology to perform test depending on sensitivity and specificity of test.

Sensitivity: False negative is absent or rare in highly sensitive investigations, good for screening test for a disease.

Higher the sensitivity of a test, lower the chance of false negative. However, few individuals, who do not have the disease, may show positive test (false positive), which are excluded by test with high specificity. In a highly sensitive test all negative tests usually can be excluded.

Specificity, i.e. false positive is absent or rare in a test of high specificity

Higher the specificity of a test lower the chances of false positive.

THE PRINCIPLE OF PEDIATRIC NEUROLOGY INVESTIGATION

Neurologically relevant tests of satisfactory sensitivity and specificity are done considering the following factors:

- There are enough clinical grounds to suspect a clinical condition for which relevant investigations is required to support or confirm clinical diagnosis.
- Also when the investigation results will help management decision or help offering genetic counseling. However, test may be done to know the diagnosis and prognostication even when no treatment of the disease exists for parental peace of mind.

IMAGING MODALITIES USED IN PEDIATRICS

Cranial Ultrasound

Noninvasive imaging modality particularly suited for the detection of ventriculomegaly and intracerebral hemorrhage in neonates (before closure of the anterior fontanelle), and young infants. It is also useful to diagnose hypoxic ischemic encephalopathy and acute stage of periventricular leukomalacia (PVL) in preterm neonate with intraventricular hemorrhage (IVH) (Fig. 44).

Computerized Tomography

- It is an X-ray-based technique delivering a radiation dose of higher magnitude than a standard chest X-ray
- Main advantages are speed (important if a child is critically ill) and its efficacy for many neurosurgical management decisions. Due to its speedy performance it is well-suited for children as they cannot remain quiet for long time
- Spiral CT is particularly useful but with an even higher radiation dose than conventional CT
- As an X-ray technique, it is better suited than magnetic resonance imaging (MRI) to study the bony skull which includes fracture. CT thus has major role in the early

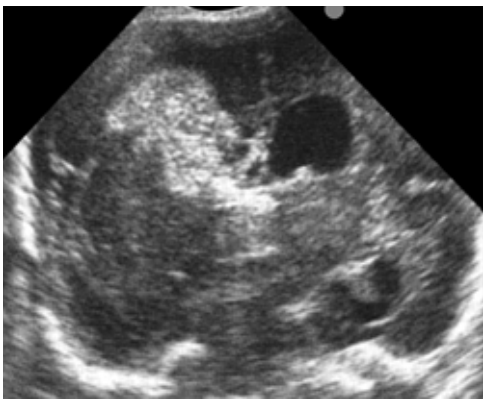


Fig. 44: Coronal ultrasound scan showing large right intraventricular hemorrhage with hemorrhagic parenchymal infraction

management of neurotrauma. It can effectively detect intracranial calcification and craniosynostosis.

White (or light gray) structures on CT comprise strongly X-ray attenuating substances and in practice are either: Blood, bone, calcification or contrast.

Areas of reduced X-ray attenuation in the brain parenchyma (appearing darker gray) are typically due to edema.

Cranial CT scan provides useful information on calcification, brain atrophy, hydrocephalus, hemorrhage, infarction, cerebral abscess (with contrast enhancement) and arteriovenous malformation (AVM). CT thus retains a major role in the early management of neurotrauma (Figs 45 and 46).

Drawback of Computed Tomography

Computed tomography has poor resolution for lesion causing focal epilepsy and cannot detect mesial temporal sclerosis (MTS).

CT angiography: Intravenous contrast by a high velocity injector followed by CT scan can provide better evaluation of large vessel diseases particularly carotid and it is superior to MRI in this respect. It is also useful in diagnosing cerebral AVM and cerebral hemorrhage (Fig. 47).

Magnetic Resonance Imaging

Magnetic resonance imaging uses a magnetic field for imaging. Therefore, it has the advantage to avoid ionizing radiation.

Magnetic resonance imaging is superior to CT in the sense that it provides improved soft tissue contrast and high anatomical resolution.

Image acquisition is however, prolonged (typically 20–30 minutes duration for full study) and claustrophobia can make young children uncomfortable and uncooperative.

- Oral sedation is widely used in toddlers because of limited anesthetic resources but is controversial
- General anesthetic is safe and guarantees images unaffected by movement artifact
- Neonates and infants can typically be scanned in spontaneous sleep after a feed.

Sequences of Magnetic Resonance Imaging

Many different MRI sequences are used to detect various brain pathologies.

Axial-T1-weighted: In T1 sequence gray matter looks gray and white matter white. CSF looks black (low signal). Optimal for defining soft tissue anatomy (Fig. 48).

Axial-T2-weighted: Normal T2 appearances change strikingly through the first year of life.

- It is sensitive to the presence of water. Pathologically, areas of high T2 signal intensity reflect edema, e.g. due to inflammation or tumor. CSF is brighter white
- Most of the brain pathology can be detected in T2 (Fig. 49).

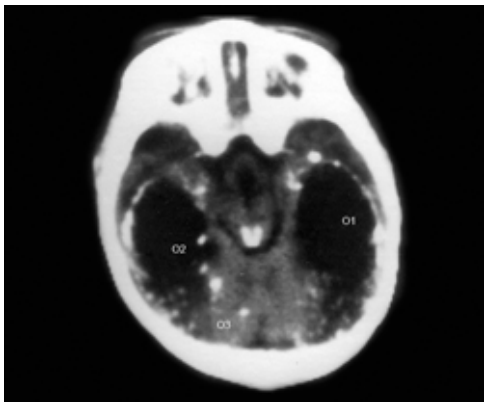


Fig. 45: CT scan showing periventricular calcification with hydrocephalus

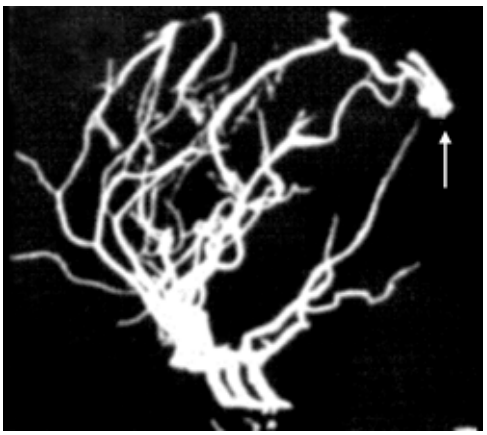


Fig. 47: Computed tomography angiography showing aneurysm due to arteriovenous malformation (arrow mark) with bleeding in a 7-year-old child

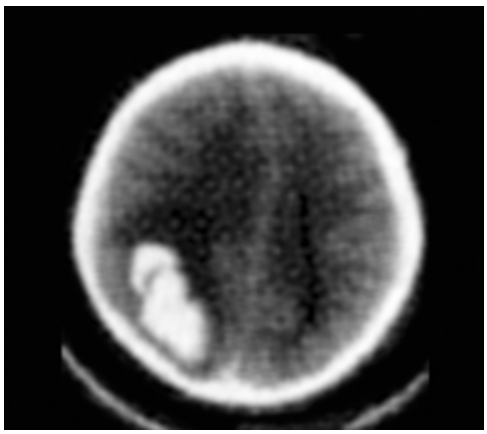


Fig. 46: CT scan showing right-sided parieto-occipital intracranial bleeding in a child due to ruptured aneurysm of arteriovenous malformations

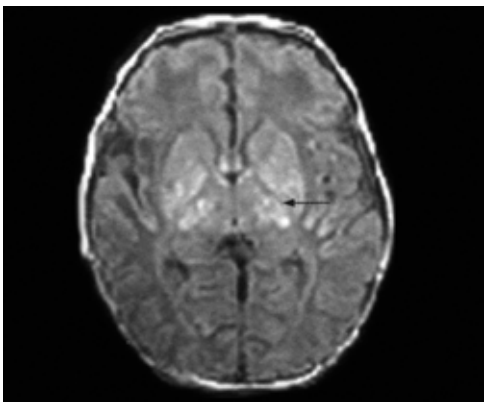


Fig. 48: Axial T1-weighted images showing abnormally increased signal intensity in the basal ganglia and thalami (arrow) in a birth asphyxia child

Diffusion-weighted imaging: It quantifies the degree to which water can diffuse in tissue; which indicates cytotoxic edema or creation of increased intracellular space for diffusion. Its clinical implication lies in the fact that it can identify cerebral ischemia or infraction earlier than other sequences of MRI or CT, which can help to undertake early medical intervenient like thrombolysis.

Magnetic Resonance Imaging Angiography/ Venography

It is the means of noninvasive imaging of large arteries and veins. It is useful for excluding venous sinus thrombosis.

Functional Magnetic Resonance Imaging

Signals dependent on the levels of deoxyhemoglobin in a region are used to infer local increases in blood flow, which in turn is taken as an indication of increased local neuronal activity. This can be used to localize a seizure focus (Fig. 50).

Cerebral Angiography (Digital Subtraction Angiography)

It is the "Gold standard" angiography for the evaluation and treatment of cerebrovascular disease. Invasive catheterization (typically percutaneously via femoral artery) and injection of radioopaque contrast to visualize arterial tree by X-ray (Fig. 51).

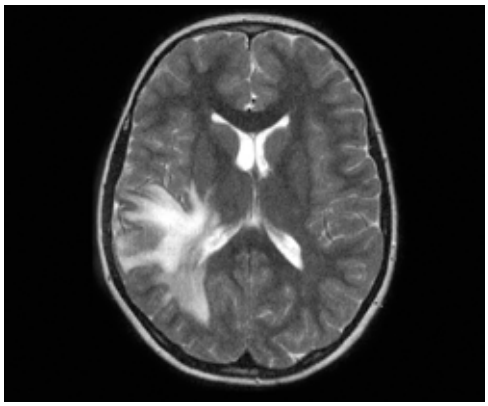


Fig. 49: T2 Magnetic resonance imaging with FLAIR axial image: Typical T2-weighted image showing white cerebrospinal fluid in lateral ventricle: Gray matter is lighter gray than white matter. The large area of high T2 signal in right parietooccipital white matter reflects water (cerebral edema) indicating inflammation

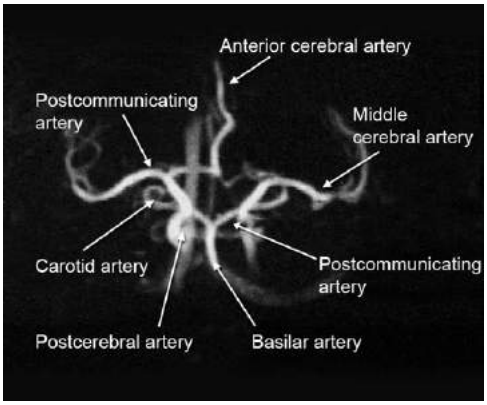


Fig. 50: This is a normal study of magnetic resonance angiography, a noninvasive technique for visualization of the neck and intracranial vessels

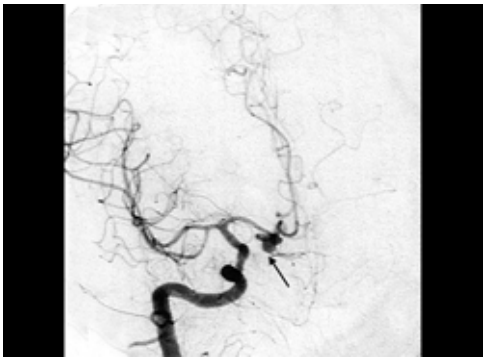


Fig. 51: Oblique right carotid angiogram with digital subtraction showing a multilobulated anterior communicating artery aneurysm (arrow)

Positron Emission Tomography

It is a functional imaging technique using radiation detectors to localize the uptake of positron-emitting isotopes in different brain regions. It has a role in identifying the location of seizure foci in evaluation of candidates for epilepsy surgery.

PRINCIPLES OF NEUROPHYSIOLOGY

ELECTROENCEPHALOGRAPHY

What is an Electroencephalography?

It is an aid to diagnosis, which has to be interpreted in the context of the clinical history. Electroencephalography (EEG) records the difference in electrical potentials generated by neurons in two locations against a time base. Electrical potentials generated are attenuated by up to 90% by the CSF, skull and scalp. They are of low amplitude (10–200 μV) and must be amplified and filtered before they can be interpreted.

Best quality recordings are obtained by cleaning and preparing the scalp prior to electrode placement. This minimizes resistances and abnormal tracing of EEG due to artifacts. It involves twenty minutes recording system documenting relevant clinical events. Activation procedures include *hyperventilation and photic* stimulation.

Electrode Placement

- Standard positions designated using the international "10–20 System". Even numbers refer to right-sided electrodes, odd numbers to left-sided electrodes.
- F, frontal; Fp, fronto-polar; P, parietal; C, central; T, temporal; O, occipital; Z, midline; A, auricular
- Typically up to 16 pairs of electrodes (or individual electrodes versus a reference) are displayed in a montage suitable for the particular clinical question at hand.

INDICATION FOR ELECTROENCEPHALOGRAPHY

In the Management of Epilepsy

Do use the EEG when it is expected to help determine seizure type and epilepsy syndrome in individuals in whom epilepsy is suspected to assess the risk of seizure recurrence in individuals presenting with a first unprovoked seizure.

An EEG should be performed only to support a diagnosis of epilepsy. If an EEG is considered necessary, it should be

performed only after the second epileptic seizure but may in certain circumstances, after a first seizure where the history is strongly suggestive of epilepsy (Fig. 52).

In General Acute Neurology

One often forget the role of EEG in general acute neurology when it is considered as an "erythrocyte sedimentation rate (ESR) of the brain" or more accurately the cerebral cortex. The presence of normal age-appropriate background rhythms is a strong indicator of intact cortical function suggesting cortical sparing in any process under evaluation.

Photic stimulation (Fig. 53) and hyperventilation should remain part of standard EEG assessment which increases the sensitivity and increase the yield of specific abnormalities. The individual and family and/or caretaker should be made aware that such activation procedures may induce a seizure and they have a right to refuse.

Special Procedures

When a standard EEG has not contributed to diagnosis or classification, a sleep EEG should be performed. In children, a sleep EEG is best achieved through *sleep deprivation* (Fig. 54).

Long-term video or ambulatory EEG may be used in the assessment of individuals who present diagnostic difficulties after clinical assessment and standard EEG. This is usually only helpful when the events occur daily.

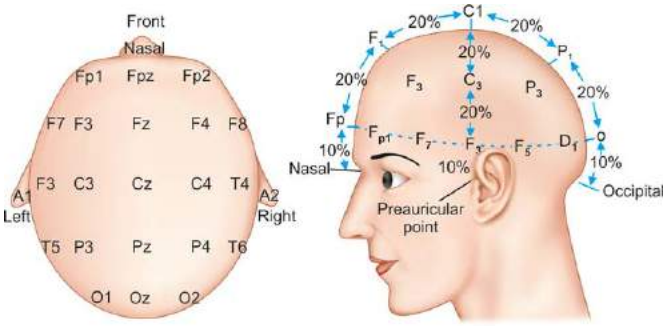


Fig. 52: 10–20 system electroencephalography montage

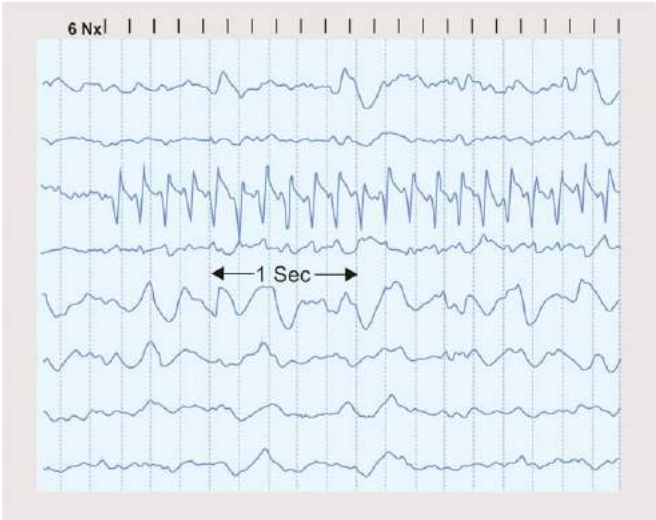


Fig. 53: Photic stimulation response showing frontal time locked myoclonic potential

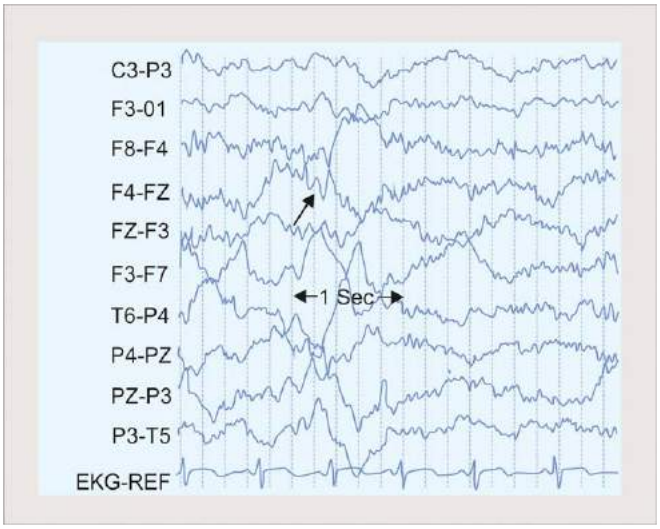


Fig. 54: Vertex waves and sleep spindles 13–14 Hz (/second) are seen in a child in drowsy-state, when alpha-wave disappear and delta-wave starts.Also beta activity increases

Video EEG has an important place in the assessment of children for epilepsy surgery, total records help define the site of seizure origin

Basic Electroencephalography Characteristics and Reading Reports

Separate consideration is given to the background (a general indicator of cortical function) and paroxysmal activity (related to epilepsy).

Background Rhythms

Recorded rhythms are evaluated by their rate, amplitude (μV), symmetry and morphology. The various recorded rhythms includes fast activity beta rhythms at 14–20 Hz (cycles/second), alpha rhythms at 8–13 Hz, theta rhythms at 4–7 Hz and slow rhythms or delta at 1–3 Hz. Activity faster than beta is an artifact from the scalp muscles.

Both with age and the child's arousal level, normal background rhythm frequencies increase and amplitudes decrease with age. An alpha rhythm on eye closure should be present by age 8 (8 Hz by 8 years). A technical report will follow each record along with an opinion on the relevance of the findings to the clinical situation. Comment should be made on whether the background rhythms are appropriate for the child's age and on any asymmetries.

Paroxysmal Activity

Many EEG may show normal nonspecific abnormalities such as an excess of dysrhythmic or slow wave (Fig. 55) activity in posterior areas.

These findings are so common in the general population that they offer little or no support for a diagnosis of epilepsy: beware of over-interpreting them. More supportive of epilepsy would be persistent sharp (Fig. 56), spike, or spike-wave complexes. An ictal record, capturing a seizure and demonstrating spike-wave discharge during the seizure is the only truly diagnostic finding. A persistent slow wave (Fig. 57) focus may indicate an underlying structural lesion.

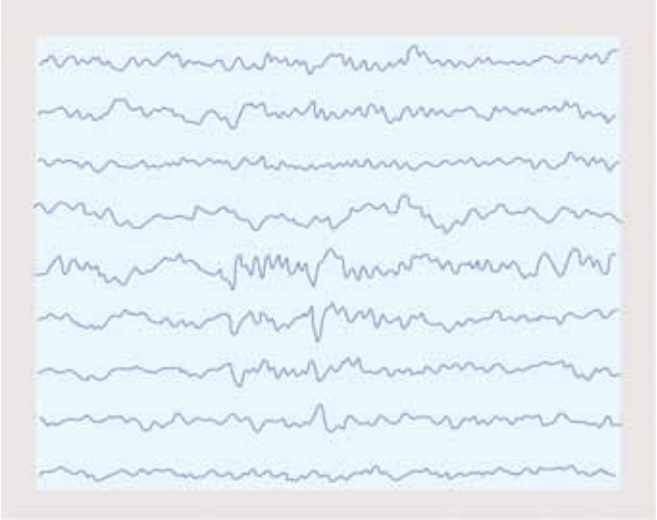


Fig. 55: Slow wave in a normal electroencephalography

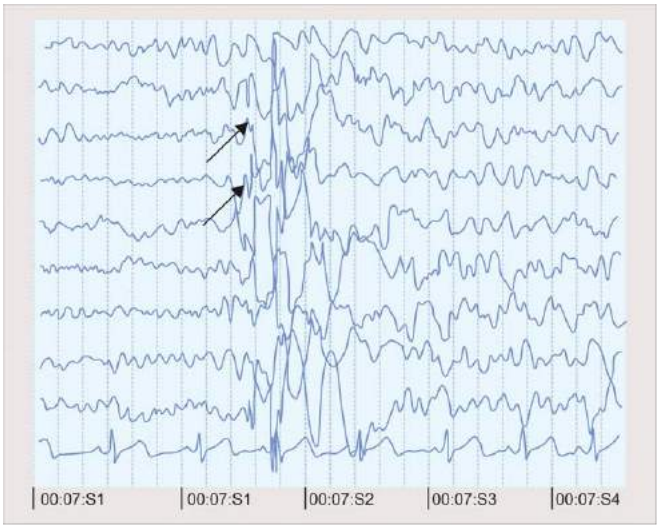


Fig. 56: Polyspikes characteristics of seizure disorder

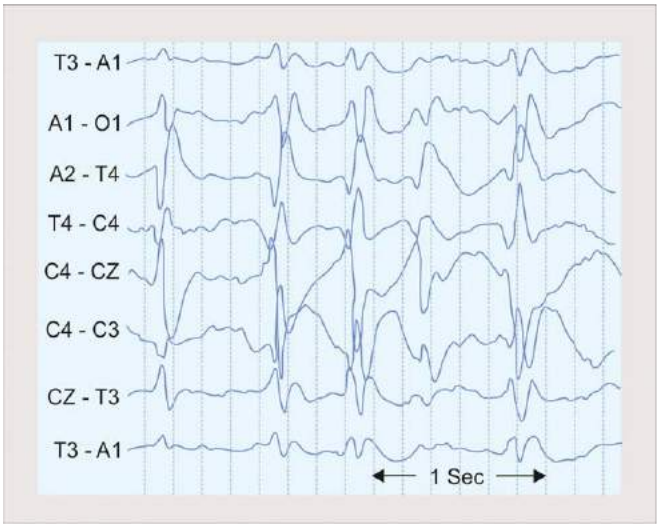


Fig. 57: Persistent slow wave characteristics of seizure disorder (The electroencephalography of child suffering from Lennox-Gastaut syndrome)

Potential Pitfalls of using an Electroencephalography

- Individuals who have never had any seizure (such as army recruits who have undergone routine EEG) may have epileptiform abnormalities on EEG
- Interictal EEGs are commonly normal in individuals with epilepsy
- Normal range of waves on EEG tracing varies with age: In particular physicians without specific experience of neonatal EEG may report normal neonatal EEG appearances as pathological
- Epileptiform spikes are common in conditions such as CP and birth asphyxia even when there is no history of seizures.

Neurophysiological Testing of Central Sensory Pathways

Visual Evoked Potential

- Uses a reversing checkerboard (or, if no response, strobe flash) typically 128 stimulate at 3 Hz with scalp electrodes placed 2 cm above the anion and 4 cm to the left and right of this point
- The large volume of macular fibers means that this is essentially a test of retinocortical conduction of the central retina
- A five-component waveform is seen
- The amplitude is typically variable and affected by visual acuity (VA), the integrity of the visual pathway and stimulus type
- The latency of the visual evoked potential (VEP) (reflecting conduction velocity of fastest fibers) is much more constant and repeatable. As with peripheral nerves, slowed conduction reflects demyelination.

Clinical Application

- Optic nerve lesion:
  - Demyelination (e.g. optic neuritis). Abnormal and markedly delayed wave form
  - Compression (e.g. craniopharyngioma or optic nerve glioma in neurofibromatosis).
- Macular disease:
  - Ischemic
  - Toxic lesion results in disturbance of waveform and delayed conduction. Aids monitoring of progression.

Electroretinogram

- Recorded by measuring the potential difference between electrodes from a contact lens electrode or a skin electrode applied close to the eye and a reference electrode on the forehead. A strobe flash is the stimulus. As the rapidity of flashes increases a flicker retinogram (FRG) is obtained.
- Electroretinogram (ERG) is a combination of rod- and cone- system responses. In light-adapted retina, the response is dominated by the cone system. In the dark-adapted state, there will be a pure rod response.

Clinical Application

- To determine the function of rods and cones, the function of the outer retinal layers and to determine the retinal level of a pathological insult

- Rod function typically is lost early in retinitis pigmentosa
- In early detection of retinopathy associated with neurodegenerative conditions
- Ophthalmic artery occlusion.

Nerve Conduction Studies

Some children smile through the procedure, others scream. A low threshold for sedation is advised.

Measures amplitude, latency, configuration and conduction velocities of motor, sensory or mixed nerves (Fig. 58).

Conduction velocity is dependent on the diameter and degree of myelination of the neuron. In the newborn infant the velocity is only about one-half the adult level and does not reach adult level until 3–5 years of age (at times later). Nerve conduction velocity is delayed in GBS helping to exclude alternative diagnosis.

ELECTROMYOGRAPHY

Procedure

This is uncomfortable but best done on someone able to cooperate by contracting individual muscle groups.

- Muscle tissue is normally relatively electrically inactive at rest. As voluntary effort increases, individual action potentials summate and become confluent to form a "complete interference pattern" and the baseline disappears
- A loudspeaker system is used to allow electrical activity to be heard: Aural impressions can be informative.

The main role of electromyography (EMG) is to help differentiate neuropathies and myopathies (Fig. 59).

Neurogenic Change (Denervation) (Fig. 59B)

- The interference pattern is reduced so that the EMG baseline becomes partially visible.
- High amplitude polyphasic fasciculation potentials of long duration also occurring at rest indicates anterior horn cell disease (notably spinal muscle atrophy)
- Individual motor unit potentials are either normal or of large amplitude, long duration and polyphasic. They indicate collateral reinnervation by surviving neurons with an increased territory.

Myopathic Changes (Fig. 59C)

Random loss of muscle fibers results (low amplitude full interference pattern) in low amplitude EMG with polyphasic short duration potentials. Sounds like "crackles" on a loudspeaker.

Myotonia

The sound is characteristic, described as resembling a "dive bomber" or accelerating motorcycle.

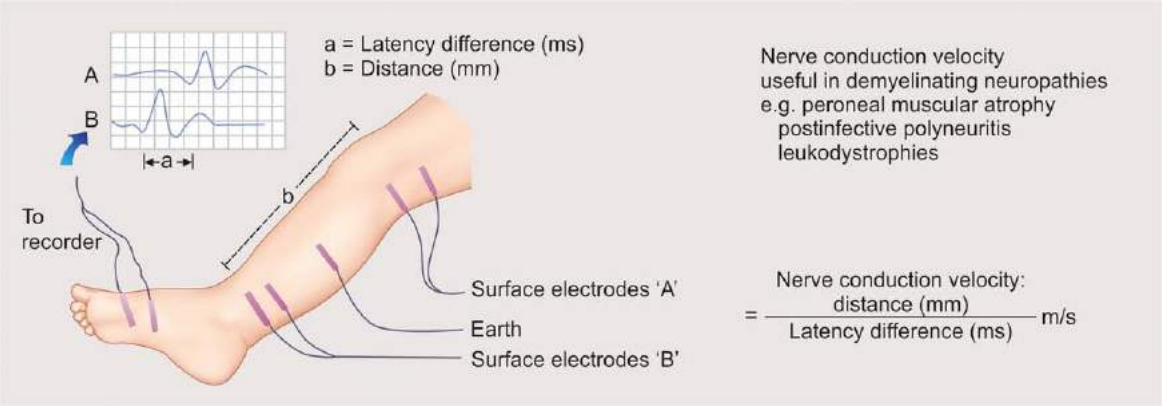
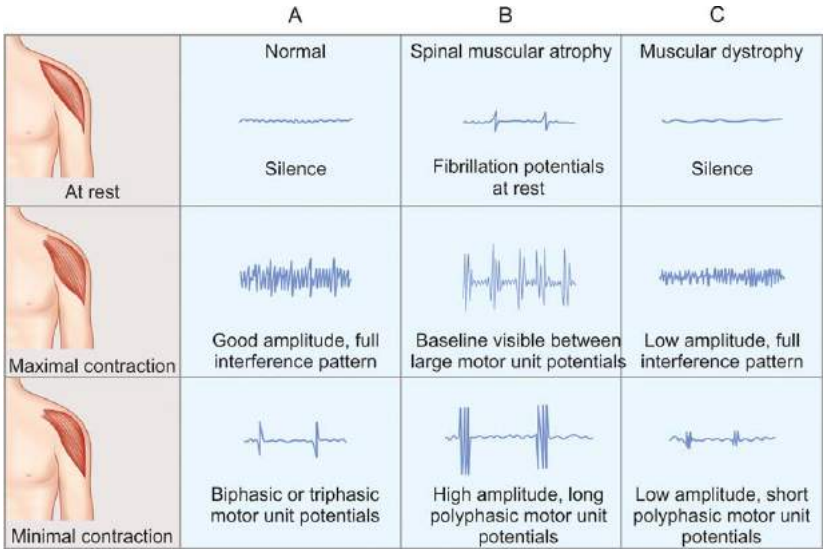


Fig. 58: Procedure of nerve conduction study



Figs 59A to C: Two abnormal electromyography patterns

Cerebrospinal Fluid

Pediatric neurology does involve a number of potentially unfamiliar but important investigations like CSF.

Cerebrospinal fluid is required mostly to exclude intracranial infection, caused by bacterial, viral (aseptic), tubercular and other infections. It involves cytology, microbiological and biochemical studies. When there is excess of polymorphs (normal less than 1 mm^3), elevated protein (greater than 400 mg/L), reduced CSF glucose (CSF glucose is usually less than 1.0 mmol below blood sugar so this will need to be measured at same time) and bacteria is detected on Gram staining then bacterial meningitis is diagnosed. Alternatively, the picture may be that of excess of lymphocytes, elevation of CSF protein (400–1,000 mg/L), a normal CSF glucose and negative Gram stain, then the diagnosis is likely to be viral meningitis.

The likely findings on microscopy (Gram stain) are:

- Gram negative intracellular diplococci—meningococci
- Gram positive diplococci—Pneumococci
- Gram negative coccobacilli—*Haemophilus influenzae (Hib)*
- Gram negative bacilli—*E. coli*. This is almost entirely limited to first year of life.

Tuberculous meningitis: Positive Ziehl-Neelsen for acid fast bacilli.

The diagnosis will usually be confirmed on culture and identification. Previous antibiotic therapy may prevent growth. In that case rapid antigen screening [reflux asystolic syncope (RAS)] can detect antigen of bacteria commonly involved in bacterial meningitis. RAS is done using ELISA or latex or counterimmunoelectrophoresis.

Polymerase chain reaction: May be required for *meningococcus*, *herpes* and tuberculous meningitis. Culture of CSF for bacterial and tuberculosis may be required in suspected case.

C-reactive protein (CRP) of CSF is usually high in bacterial meningitis.

Muscle Biopsy

Muscle biopsy may be required to differentiate between myopathic and neuropathic disorders. In myopathic disorders muscle biopsy may show variation of fiber size, splitting of fibers and internal nuclei. In neuropathic disorder, muscle biopsy will show small groups of uniformly small atrophic fiber.

EPILEPSY IN CHILDREN

Epilepsy is the most common neurologic disorder that affects 50 million people worldwide of which 40 million live in developing countries. Over 60% of epilepsy has its onset in childhood.

WHAT IS THE EPIDEMIOLOGY OF EPILEPSY?

Incidence: 50/100,000/year in developed countries.

100–190/100,000/year developing countries.

Prevalence: 4–10/1,000 persons.

Prevalence of active epilepsy: 6–10/1,000 persons.

There are many clinical conditions particularly in children, which mimic epilepsy but actually not genuine epilepsy. On the other hand consequence of false positive and false negative diagnosis can be serious, although even in specialist centers the rate of false positive diagnosis of epilepsy is as high as 10–15%. It is, therefore, important to be familiar with epilepsy and various paroxysmal conditions which mimic epilepsy and to be familiar with different terms and definitions associated with epilepsy.

What is Pediatric Epilepsy?

Recurrent (≥2) unprovoked epileptic seizures occurring 24 hours apart in a child more than 1 month old.

What is Epileptic Seizure?

A clinical manifestation presumed to result from an abnormal and excessive discharge of a 'set -of neurons in the brain, manifested clinically by sudden and transitory abnormal phenomena like alteration of consciousness, motor, sensory, autonomic or psychic events.

Types

- Provoked/symptomatic: Preceding insult present
- Unprovoked: No such preceding insult.

Active Epilepsy

At least one epileptic seizure in past 5 years irrespective of antiepileptic drug (AED) treatment.

Epilepsy is more common in developing countries than developed countries because of:

- Increased perinatal problems: Hypoxic ischemic encephalopathy (HIE), sepsis, bilirubin encephalopathy
- Increased neuroinfections: Meningoencephalitis, malaria, febrile encephalopathy, systemic sepsis, inflammatory-granuloma, etc.
- Increased head injury.

What is Convulsion, Aura, Ictal, Postictal, Tonic, Clonic, Tonic-Clonic, Absence, and Atypical Seizure?

Convulsion: Attack of involuntary muscle contractions which may be sustained (tonic) or interrupted (clonic). They may be epileptic or nonepileptic.

Aura: Is the earliest portion of a seizure recognized by the patient; it is actually an "ictal" event and has a localization value. Details of aura can often point out the focus of origin. Children may not be able to describe the aura properly and may just express the feeling as "something happening inside" or "something funny". Association of aura suggests a focal origin.

Ictal Period

It is the time when clinical features of seizures and EEG changes are associated with neuronal firing. If the seizures are generalized, there is associated loss of consciousness.

Generalized seizure: Arise from both cerebral hemispheres simultaneously. Occasionally focal seizures with a very rapid secondary generalization (partial seizure with secondary generalization) may be clinically mistaken for "generalization seizure".

Generalization tonic-clonic seizures (Figs 60A and B): These are extremely common and may be "primary generalized" or may follow a partial seizure with a focal onset (secondary generalization).

Postictal Period (Fig. 61)

It is the time when the neurons stop firing and clinical events as well as EEG return to normal. Clinical manifestations of the postictal period vary with the seizure type. Usually go into unarousable sleep and if disturbed the child may be irritable.

Absence Seizure

Typical absence seizures are characterized by sudden, transient lapses of consciousness without loss of postural control and without any significant motor activity. Absence is never associated with any aura. There is no postictal state (Fig. 62).

Atypical absence seizure: The lapse of consciousness is usually of longer duration, and less abrupt in onset and cessation. There are minor myoclonic movements of the face, fingers or extremities, and all times, loss of body tone.

Figs 60A and B: A child with (A) Tonic; (B) Clonic

Fig. 61: A child in postictal sleep

Fig. 62: Seizure manifested by blank staring look without loss of postural control in absence seizure

What is Epileptic Encephalopathy?

Definition: Conditions where medically intractable seizures and/or epileptiform discharges are associated with a progressive decline in cognitive and behavioral function.

Definition of Childhood Epileptic Syndrome

Childhood epileptic syndrome (CES) is a term applied to epilepsy condition in which there are common clusters of characteristics such as age, type, EEG and prognosis. They may have different etiologies.

Most of the CES are age specific: The CES seen in neurodevelopmentally normal children are often different, than those seen in children with neurologically abnormal and developmental delay.

Thus an early approach involves consideration of the: (1) age (2) neurodevelopmental status of the child and (3) type of the seizure. This will lead to presumptive diagnosis of CES which should later be confirmed by EEG.

Depending on CES under consideration further test include neuroimaging, metabolic and genetic test.

What are the Etiologies of Epilepsy?

- Idiopathic: Genetic in origin
- Intrauterine infection: *Toxoplasma gondii*, rubella virus, cytomegalovirus, herpes simplex virus (HSV) infections (TORCH), HIV
- Abnormal brain development: Neuronal migration defect
- Perinatal insults
- Central nervous system infections
- Brain injury
- Brain tumor
- Neurometabolic, neurodegenerative diseases and neurocutaneous disorders like tuberous sclerosis (Fig. 63), neurofibromatosis (Fig. 64), Sturge-Weber syndrome (Figs 65 and 66)
- Chromosomal disorders: Fragile X, Trisomies.

International Classification of Epileptic Seizures—International League against Epilepsy

Partial Seizures

- Simple partial seizure (consciousness not impaired) with
  - Motor signs (focal motor → Jacksonian march, postural, phonatory)

Fig. 63: Tuberous sclerosis depigmented spots

Fig. 64: The boy with neurofibromatosis showing café-au-lait macule, left-sided ptosis due to neurofibroma of upper eye lid, presented with recurrent attack of generalized seizure

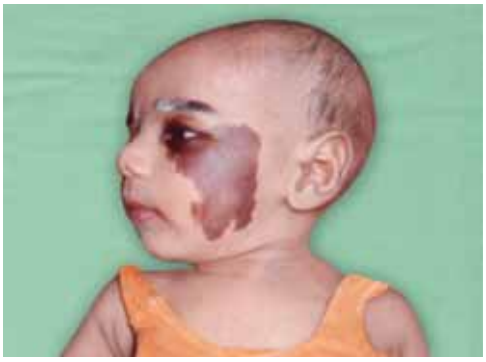


Fig. 65: Picture showing portwine stain of Sturge-Weber syndrome

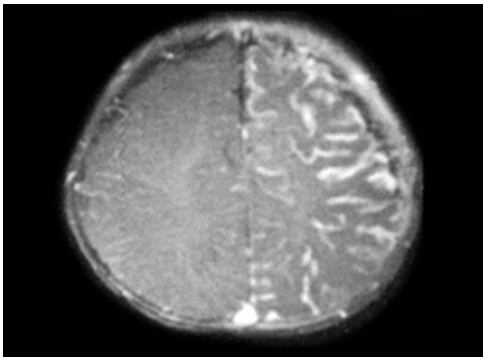


Fig. 66: Computed tomography scan showing tramline calcification in Sturge-Weber syndrome associated with epilepsy

  - *Sensory:* General and special sense, like delusion, hallucination
  - *Autonomic symptoms and signs:* Flushing of face, piloerection, etc.
  - Psychic symptoms (dysphasia, dejavu, dreamy state, anger, fear)
- *Complex partial seizure* (consciousness impaired)
  - Simple partial onset followed by impairment of consciousness
  - Impairment of consciousness from onset
- Simple partial seizures evolving to generalized tonic-clonic seizure (GTCS)
  - Simple partial seizure evolving to GTCS
  - Complex partial seizures evolving to GTCS.

Generalized Seizures (Convulsive or Nonconvulsive)

- Absence: Typical/atypical
- Myoclonic
- Clonic
- Tonic
- Tonic-clonic
- Atonic.

Unclassified

- Neonatal seizure, e.g. subtle seizure
- Infantile spasm.

Generalized Epilepsies and Syndromes

Generalized epilepsies and syndromes are:

- Idiopathic:
  - Benign neonatal familial convulsion
  - Benign neonatal convulsion (fifth day fit)
  - Benign myoclonic epilepsy of infancy
  - Childhood absence seizure
  - Juvenile absence
  - Juvenile myoclonic epilepsy
  - Generalized tonic-clonic seizures on awakening
- Symptomatic:
  - Early myoclonic encephalopathy
  - Early infantile epileptic encephalopathy (EIEE)
- Cryptogenic or symptomatic:
  - West syndrome
  - Lennox-Gastaut syndrome (LGS)
  - Myoclonic-astatic epilepsy (Doose syndrome)
  - Myoclonic absence epilepsy.

Undetermined are:

- Neonatal seizures (subtle seizure)
- Severe myoclonic epilepsy of infancy (Dravet syndrome)
- Landau-Kleffner-syndrome (LKS)
- Continuous spike-waves during slow wave sleep.

Special syndromes are:

- Febrile convulsions
- Isolated SE
- Seizures accompanying acute toxic/metabolic events, alcohol, drugs, nonketotic hyperglycinemia, eclampsia.

Epileptic syndromes are grouped into two age groups:

1. Epileptic syndromes in infancy (1–2 years): Presenting in 1–2 years of age.
2. Epileptic syndromes presenting in 2–12 years of age

Epileptic Syndromes in Infancy (1–2 years)

Presenting in:

First month	:	Early infantile epileptic encephalopathy Early myoclonic epilepsy
First Year	:	Infantile spasm Severe myoclonic epilepsy (Dravet syndrome) Benign familial/ + nonfamilial seizures Myoclonic astatic epilepsy (MAE) (Doose syndrome)
First 3 years	:	Benign myoclonic epilepsy
Variable	:	Generalized epilepsy with febrile seizure + Hemiconvulsive-hemiplegia-epilepsy

- Benign
  - Benign childhood epilepsy with centrotemporal spikes (BCECT)
  - Benign occipital epilepsy
- Intermediate
  - Childhood absence epilepsy (CAE)
  - Generalized epilepsy with febrile seizure plus (GEFS+).
- Severe or catastrophic
  - Early infantile epileptic encephalopathy
  - Lennox-Gastaut syndrome
  - Landau-Kleffner syndrome
  - Myoclonic astatic epilepsy
  - Continuous spike-wave in slow sleep.

SOME SELECTIVE EPILEPSY AND EPILEPTIC SYNDROME

Benign Epilepsy of Childhood with Central-temporal Spikes (BECTS) Synonym; Rolandic, or Benign Rolandic Epilepsy

Onset: 3–13 (mean 7–9 years)

Characteristics: Seizure occurs mostly within hours of falling asleep. Involvement of face with or without oropharyngeal symptoms, such as difficulty with speech, gurgling, drooling, etc.

Family history of epilepsy is often present.

Asymptomatic sibling may show characteristic EEG.

Electroencephalography: Characteristic (Fig. 67) blunt high voltage centrotemporal spike followed by slow waves, which are activated maximally by sleep.

Prognosis: Generally recover by 15–16 years.

Treatment: Antiepileptic drug not mandatory.

For frequent seizure carbamazepine (CBZ) or oxcarbazepine can be used.

Early Infantile Epileptic Encephalopathy or Ohtahara Syndrome

This is a devastating epilepsy with:

- Recurrent tonic spasms, at times myoclonus
- Electroencephalography shows a burst suppression pattern.

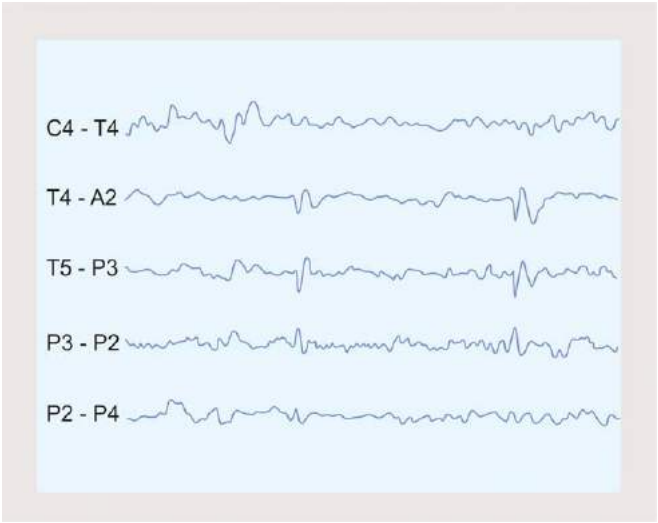


Fig. 67: Electroencephalography showing blunt centrotemporal spikes in a child with benign childhood epilepsy with centrotemporal spikes

- Magnetic resonance imaging often reveals serious developmental anomalies
- *Treatment*: Most AEDs and steroids are infective
- *Course*: Progressive neurologic deterioration occurs and about half the cases die within a few months. Survivors have severe disabilities and may later develop West syndrome or LGS (Fig. 68).

INFANTILE SPASM AND WEST SYNDROME

This is a devastating age-specific epilepsy characterized by infantile spasm (Salam fit), neurodevelopmental impairment and hypsarrhythmia on EEG.

Age of onset 4–6 months with male preponderant but may occur at any time below 2 years.

- Tonic spasm—sudden jerks with sustained held posture for a second or occurring in clusters (Fig. 69)
- Spasm may be either predominantly flexor or predominantly extensor
- There may be associated variable encephalopathy
- West syndrome refers to the combination of infantile spasm and EEG appearance of hypsarrhythmia
- Most children have underlying neurodevelopmental impairment secondary to various etiologies

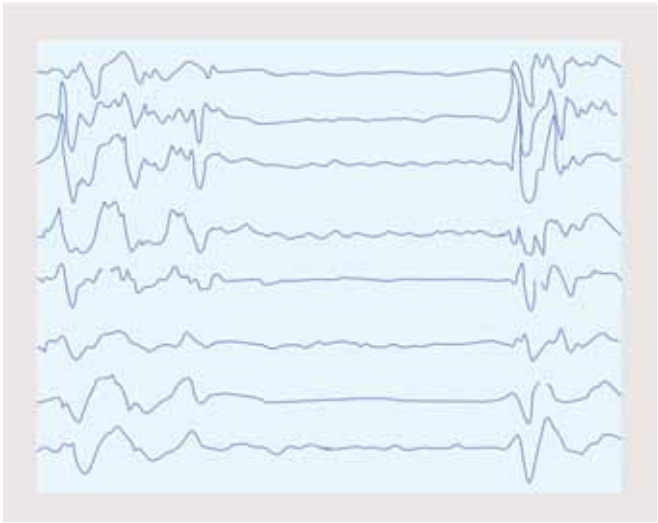
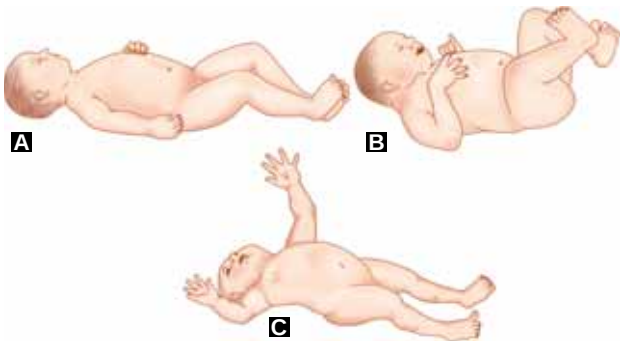


Fig. 68: Burst suppression pattern in early infantile epileptic encephalopathy



Figs 69A to C: Clinical features of infantile spasm. (A) Infantile spasm during remission time; (B) Sudden flexion of neck (Salam fit), upper and lower limbs; (C) Sudden extension of neck, upper and lower limb predominantly extensor type of infantile spasm. In both types, the positions are held for seconds or the spasm may occur in clusters

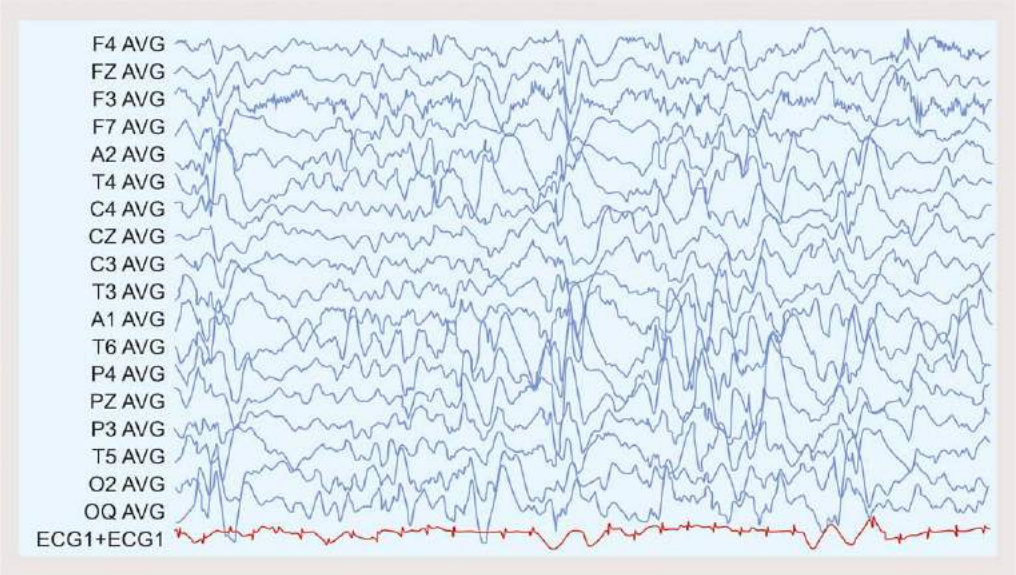


Fig. 70: Hypsarrhythmia high-amplitude slowing and multifocal spikes

- Electroencephalography shows hypsarrhythmia which consists of chaotic high voltage slow waves, multiple spikes and sharp waves (Fig. 70)
- Modification and variation of hypsarrhythmia may occur. These include presence of local abnormalities burst suppression, slow waves without spikes, or asymmetry
- *Etiology types*: It may be symptomatic, cryptogenic, or idiopathic—possible genetic. Most (over 80%) are symptomatic and a wide variety of underlying disorders may be associated. Neurocutaneous syndrome (Fig. 63), CNS malformation, CNS infections are often associated. Neuroimaging reveals cerebral atrophy, periventricular leukomalacia, cerebral dysgenesis, tubers (Fig. 71) and other abnormalities.

Causes of Infantile Spasm

Prenatal

Cerebral dysgenesis: Polymicrogyria, schizencephaly, focal cortical dysplasia, other neuronal migration disorders, microcephaly.

Neurocutaneous syndrome: Tuberous sclerosis (Figs 63 and 71), Sturge-Weber (Figs 65 and 66), incontinentia pigmenti congenital infections (TORCH).

Perinatal

Hypoxic: Ischemic encephalopathy.
C*entral nervous system infections*: Meningitis, encephalitis

- Intracranial hemorrhages
- Trauma.

Postnatal

Central nervous system infections: Meningitis, encephalitis.

Neurometabolic: Phenylketonuria (PKU), nonketotic hyperglycinemia, Maple syrup urine disease, mitochondrial disorders.

- Degenerative disorders.

Idiopathic

Evaluation: Detailed history and thorough neurodevelopmental assessment should be done. General examination particularly skin must be looked at closely for ash leaf macules of tuberous sclerosis, port-wine stain for Sturge-Weber syndrome. Neuroimaging is indicated in all cases depending on etiology.

Magnetic resonance imaging for cerebral dysgenesis.

CT for calcified tubers (Fig. 71), calcification in congenital infection (TORCH).

Treatment: The most effective treatments are adrenocorticotropic hormone (ACTH), oral corticosteroid and vigabatrin (VGB) (particularly in tuberous sclerosis).

Adrenocorticotropic hormone: 40 U/m^2 single dose IM daily for 2 weeks.

Increase ACTH till response up to 60 U/m^2 daily, then alternate day for 4 weeks and then stop.

or

Prednisolone: 2 mg/kg/day in two doses for 4 weeks followed by half dose for 4 weeks, then one-fourth dose for 4 weeks.

Vigabatrin: 100–150 mg/kg/day in two divided doses for 2–3 months.

Surgery: Antiepileptic surgery (AES) may be required for retractable seizure.

Prognosis: Poor, mortality up to 20–30%. Of the survivors almost 75% develop psychomotor retardation. Many later develop LGS.

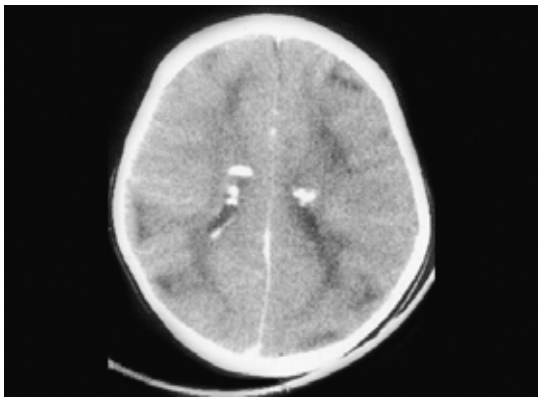


Fig. 71: CT scan showing calcified tubers

LENOX-GASTAUT SYNDROME

This severe childhood epileptic syndrome has an onset 1–8 years, with a peak between 3 years and 5 years.

Tonic seizures are the hallmark, but atonic atypical absence and myoclonic also occur. Tonic seizures are activated by sleep and often lead to fall (Fig. 72).

Nonconvulsive status is common (50–90%).

Etiology

Most cases are symptomatic with previous CNS insult/epilepsy (60%), West syndrome (30–40%) and associated with mental retardation.

Electroencephalography (interictal) shows abnormal slow background with generalized slow spike/poly spike-waves 1.5–2.5 Hz (Fig. 73).

Treatment

Valproate and lamotrigine (LTG) are the drugs of choice. Topiramate (TPM) has also been reported to be effective. Benzodiazepines (BDZs) such as clonazepam (CZP) may be needed additionally. The seizures are resistant to most AEDs, and a complete control is rarely achieved.

Fig. 72: Characteristic tonic seizure of Lennox-Gastaut syndrome

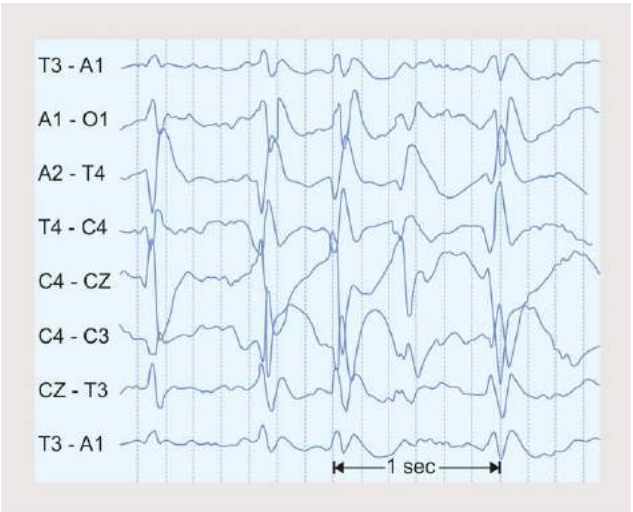


Fig. 73: Slow spike wave complex in Lennox-Gastaut syndrome

Steroids: Adrenocorticotropic hormone 40 IU per day reduces seizures but has a high relapse rate; ketogenic diet (KD) improves seizure control in about one-third to half cases.

Surgery: Antiepileptic surgery may be required when medical treatment fails.

Prognosis

Prognosis for cognitive behavior and seizure control is generally poor.

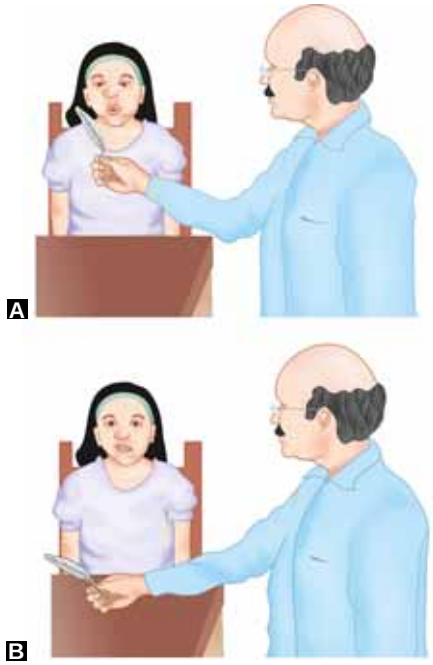
Childhood Absence Epilepsy

- This is seen most often in school age (4–10 years) with a peak at 6–7 years and is more common in girls
- Use of term "petit mal" is discouraged as it is used indiscriminately in any seizure other than grand mal seizure or GTCS
- It is characterized by brief (typically < 5 seconds) arrest of speech and activity. Subtle perioral or flickering of eyelids may be seen
- Hundreds of such absence episode can occur in a day
- There is strong genetic component with a family history in one-third of the cases
- Clinically this epileptic seizure can be elicited in an outpatient clinic by hyperventilation test. The child is asked to blow repeatedly a feather placed in front of the child until respiratory alkalosis occurs when perioral or periocular flickering will be seen (Figs 74A and B)
- Generalized tonic-clonic seizure can occur infrequently. Families should be warned about it.

Electroencephalography shows 3Hz/second generalized Spike-Waves (Fig. 75).

Treatment: The drugs of choice are valproate, ethosuximide and LTG.

Course: The outcome in typical CAE is generally good and most cases remit by puberty. Good prognostic factors include—



Figs 74A and B: (A) Showing hyperventilation test by repeated blowing of feather which results in brief perioral and periocular flickering; (B) diagnostic of childhood absence epilepsy

normal IQ, normal EEG background, absence of other seizure types, no SE.

LANDAU-KLEFFNER SYNDROME ASSOCIATED WITH CONTINUOUS SPIKE-WAVES DURING SLOW-SLEEP

- This may be part of nonconvulsive status epilepticus (NCSE)
- This epilepsy usually starts during early childhood with a peak between 4 years and 5 years age
- Insidious onset of a severe receptive and expressive language disorder leading to aphasia
- The child has various seizure types during sleep and atypical absence when awake
- Electroencephalography shows continuous diffuse spike waves during slow wave (non REM) sleep for almost 85% of the sleep time (Fig. 76)
- Treatment: Often resistant to most AEDs. Management is like in LGS
- Outcome: It lasts for months to years and the prognosis is guarded.

Juvenile Myoclonic Epilepsy

- This occurs in normal children with onset around puberty 12–18 years with a 2:1 female to male ratio
- It is characterized by the occurrence of myoclonic jerks, within 20–30 minutes after awakening in the morning with no loss of consciousness
- The seizures are precipitated by sleep deprivation and hand activities
- Later, about 90% cases also have GTCS on awakening, with peak at about 16 years
- Genetics: 17–50% have family history of epilepsy.

The inter-racial EEG shows bilateral symmetric diffuse spike waves and polyspike waves 4–6 Hz which increases

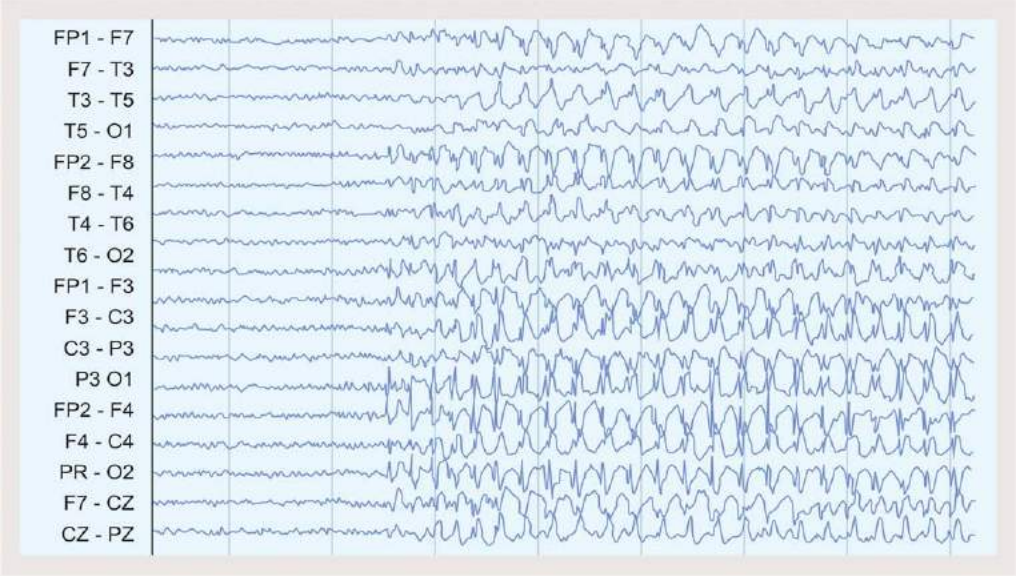


Fig. 75: Generalized 3 Hz spike-wave complexes typical of absence epilepsy

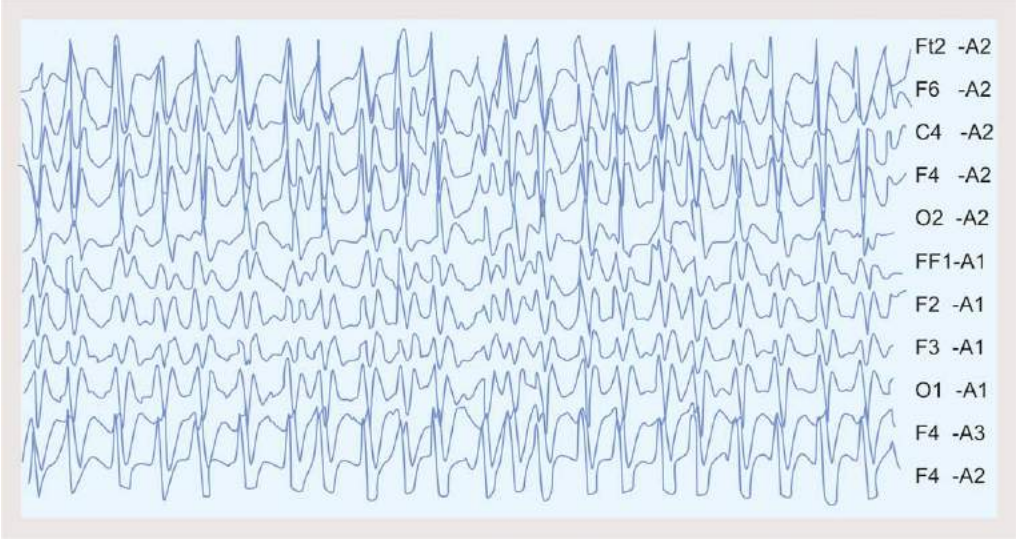


Fig. 76: Electroencephalography showing continuous slow spike-waves in a child with characteristics of continuous spikes and waves during sleep

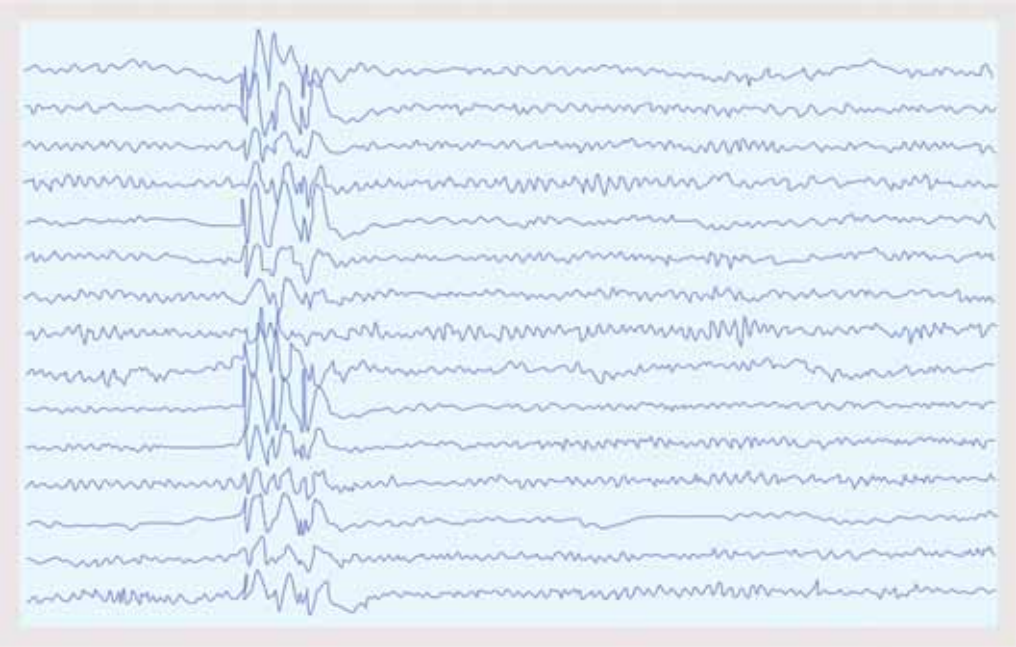


Fig. 77: EE showing 4–6 Hz spikes and spike waves in juvenile myoclonic epilepsy with normal background activity

with photic stimulation. Background activity is always normal (Fig. 77).

Treatment

Valproate is the drug of choice and controls seizure in 85% cases; however, the relapse rate is very high on stopping the drug. LTG is found effective and preferred in some adolescent girls because of the risk of polycystic ovarian disease with valproate.

Lifestyle Modification

Factors that precipitate juvenile myoclonic epilepsy such as sleep deprivation, early awakening, flickering lights and fatigue should be avoided.

LOCALIZATION-RELATED EPILEPSY

Temporal Lobe Epilepsy (Complex Partial Epilepsy)

- The onset is in childhood or in young adults
- The seizures are partial, generally simple but may be complex and may be secondary generalized. The complex partial seizures consist of automatisms such as lip smacking or chewing movements. There is postictal confusion, and amnesia with gradual recovery. The attacks generally last from few to several minutes. Autonomic and/or psychic and sensory symptoms are common particularly epigastric sensations
- Absence of awareness or responsiveness to surroundings
- Memory deficit may occur
- There is often a history of febrile seizure in infancy
- Electroencephalography shows localized (temporal) seizure focus (Fig. 78)
- Magnetic resonance imaging shows MTS (Fig. 79).

Treatment

- Oxcarbazepine (OXC) or carbamazepine (CBZ) are the drugs of choice
- *Course*: The seizures are generally well-controlled with AEDs, but may be refractory in 20–30% cases. Temporal lobectomy may be required for such cases.

Diagnosis of Epilepsy

- Mainly clinical:
  - Details history taking
  - Identification of seizure types: from
    - Patient's statement
    - Observer description
    - Family video images
- Supplemented/supported by:
  - Electroencephalography
  - Neuroimaging like CT scan and MRI brain.

Role of interictal electroencephalography: EEC recorded during interictal period will help in:

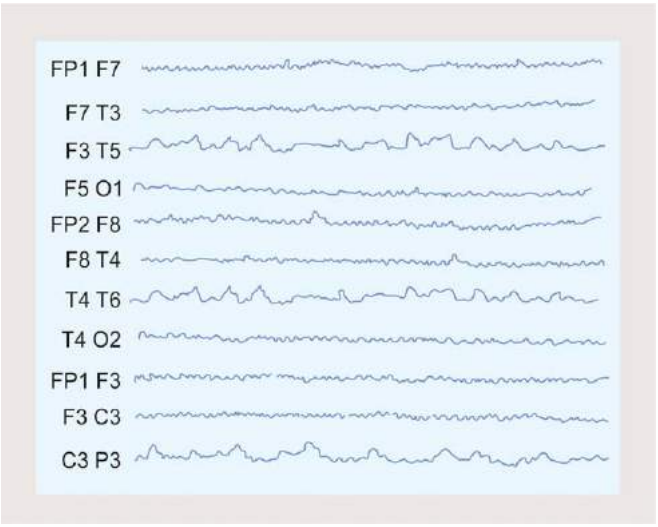


Fig. 78: Electroencephalography showing temporal spike (T3-T5, T4-T6) in temporal lobe epilepsy

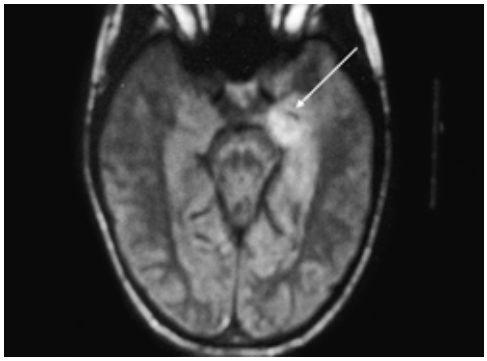


Fig. 79: Mesial temporal sclerosis (MTS) showing small hippocampus and small temporal lobe

- Confirmation of diagnosis
- Defining type of epilepsy: Partial versus generalized
- Identification of epileptic syndromes: LKS, West syndrome, Rolandic, LGS, CAB where EEG is always abnormal (Table 2)
- Planning of drug management
- Planning of epilepsy surgery.

Electroencephalography also helps in:

- Evaluation of first seizure: Risk of seizure recurrence can be predicted
- Monitoring AED withdrawal: Guide decision but presence of occasional brief epileptiform discharges should not preclude withdrawal of AED in seizure-free patient.

Sensitivity of electroencephalography: First EEG 30–55%, Serial EEG: 80–90%

- Sensitivity increases by photic stimulation, sleep deprivation
- Up to 3.5% of normal children EEG may be abnormal.

Role of Neuroimaging in Epilepsy

- To identify structural lesions that cause certain epilepsies
- Magnetic resonance imaging of brain better than CT scan: Indications of MRI in children are:
  - Partial epilepsy (history, examination, EEG)
  - Seizures continue in spite of first line medication (Fig. 80)
  - Epilepsy before the age of 2 years.

Table 2: Choice of antiepileptic drug in different epileptic syndromes

Epileptic syndromes	First line drugs	Second line drugs
Infantile spasms	Steroids, vigabatrin	SVA, TPM, CZP, CLB
Lenox-Gastaut	LTG, SVA, TPM	CLB, CZP, LEV
Landau-Kleffner	SVA, Steroids, LTG	TPM, LEV
BECTS	CBZ, OXC, SVA, LTG	TPM, LEV
Mixed benign myoclonic epilepsy of infancy	SVA	
Severe myoclonic epilepsy of infancy	SVA, TPM, CZP, CLB	LEV, Stiripentol
Myoclonic-astatic	SVA, TPM, CZP, CLB	LTG, LEV

Abbreviations: CLB, clobazam; CBZ, carbamazepine; PHT, phenytoin; SVA, sodium valproate; OXC, oxcarbazepine; LTG, lamotrigine; TPM, topiramate; NTZ, nitazoxanide; LEV, levetiracetam; NTZ, nitazoxanide.

Principles of Epilepsy Management

Step 1 : Confirm diagnosis of true seizures
Step 2 : Establish seizure type and epilepsy syndromes
Step 3 : Evaluate need for treatment initiation: First versus second seizure, widely apart seizure, benign versus malignant epileptic syndromes.
Step 4 : Select AED based-on seizure type and epilepsy syndromes: considerations are spectrum, efficacy, adverse reaction, drug interaction, tolerability, compliance, age sex, weight, life style, psychiatric and other comorbidities
Step 5 : Start monotherapy with chosen first line drug in low dose, titrate ↑ slowly ("Start low go slow" policy) till seizure control/maximum pharmacological dose/ maximum tolerated dose appears. (↑ slowly over weeks depending on nature of AED and urgency of situation).
Step 6 : Seizure persists

- Switch to another monotherapy (alternative first line or second line) if first drug is ineffective or poorly working
- Add-on therapy (combination with different mechanism of action) with a second drug if first drug is partly effective and well-tolerated (Flow chart 1).

Indications of Antiepileptic Drug (AED) on First Seizure

Usually, antiepileptic drug (AED) should be advised if seizure is recurrent. However, AED should be advised on first seizure in following conditions:

- Neurological deficit
- Underlying cerebral lesion epileptogenic of focal lesion
- Who have a high risk of epilepsy syndrome
- Abnormal EEG done within 24 hour of first-seizure
- Seizure type: Atonic, tonic, as á morbidity/mortality
- Partial seizure as recurrences is more
- Status epilepticus.

Properties of an Ideal Antiepileptic Drug

- High oral efficacy without seizure aggravation
- Good tolerability and no teratogenicity
- No or minimal drug interaction
- Once or twice daily dosing
- Range of formulation available
- Low cost and high cost effectiveness.

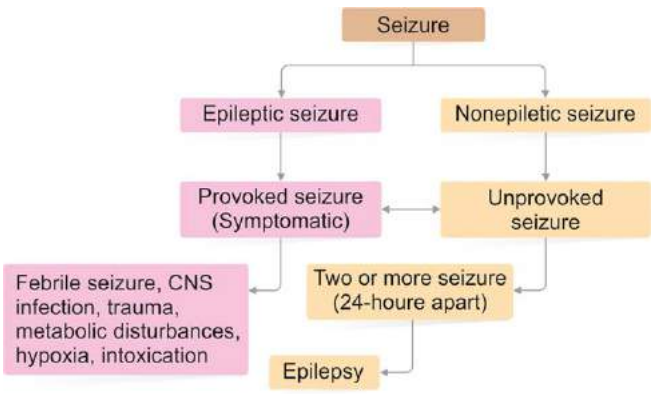
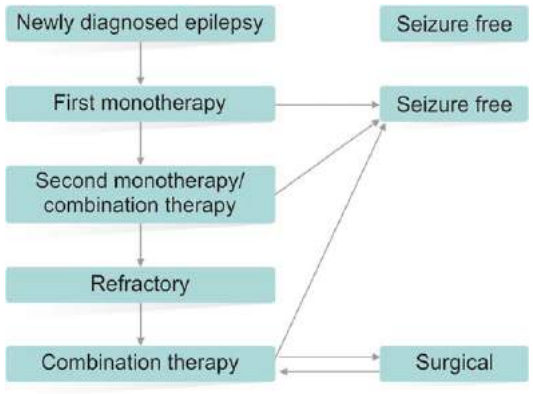


Fig. 80: Algorithm for evaluation of seizure

Flow chart 1: Treatment pathway for newly diagnosed epilepsy



Antiepileptic Drugs

(For details see therapeutic medicine chapter): Broadly divided into:

- Older AED:
  - Phenobarbitone (PB)
  - Carbamazepine
  - Sodium valproate (SVP) or SVA
  - Ethosuximide
  - Benzodiazepine:
    - Clobazam (CLB)
    - Clonazepam
    - Nitrazepam (NZP).

Advantages: Effectiveness against many seizure types and epileptic syndrome and relatively cheaper (Table 3).

Disadvantages: Adverse effect of older AEDs contribute to more than 40% of initial treatment failure, variable pharmacokinetics, hepatic enzyme induction lead to troublesome drug-drug interactions (Table 4).

Newer Antiepileptic Drugs

Ten new AEDs available since 1990s.

1. Vigabatrin
2. Oxcarbazepine
3. Lamotrigine
4. Topiramate
5. Levetiracetam (LEV)
6. Zonisamide
7. Gabapentine (GBP)
8. Tiagabine (TGB)
9. Pregabalin (PGB)
10. Folbamate (FBM).

Table 3: Choice of antiepileptic drug in different epileptic seizures

Seizure	First line	Second line
Partial	CBZ, PHT, SVA, PB	OXC, LTG, TPM, other new AEDs
GTCS	SVA, CBZ, PHT, PB	TPM, LTG, OXC, LEV
Absence	SVA, CZP, CLB	LTG, TPM, LEV
Myoclonic	SVA	LTG, TPM, LEV
Atonic/Tonic	SVA	CZP, CLB, NTZ, LTG, TPM
Mixed	SVA	

Abbreviations: CBZ, carbamazepine; PHT, phenytoin; SVA, sodium valproate; PB, potassium bromide; OXC, oxcarbazepine; LTG, lamotrigine; TPM, topiramate; LEV, levetiracetam; NTZ, nitazoxanide.

Pharmacological properties of newer antiepileptic drugs:

- Effectiveness same
- Less adverse effects
- Tolerability high
- Reduced drug-drug interaction
- Effectiveness against refractory epilepsy (RE) is better
- Usually noninducer of liver enzyme except, OXC, TPM and FBM can do so in high doses
- Reserved for refractory cases not responding to older AEDs/intolerant (Table 5) (Either as first line or second line adjunctive therapies).

Myoclonic and absence seizure aggravating agents:

- Carbamazepine
- Oxcarbazepine
- Phenobarbitone
- Gabapentin
- Vigabatrin
- Tiagabine
- Pregabalin
- Lamotrigine (myoclonic seizure only).

Table 4: Efficacy of older antiepileptic drug for different seizure types

Seizure	PB	PHT	CBZ	SVA	ESM	BDZ
Partial	+	+	+	+	0	+
2^0 GTCS	+	+	+	+	0	+
GTCS	+	+	+	+	0	+
Absence	0	+	+	+	+	?
Myoclonic	?+	+	+	+	0	+
Atonic/Tonic	?	0	0	+	0	+

+ = efficacy, ?+ =- probable efficacy, 0 = ineffective, - = worsens seizure, ? = unknown
Abbreviations: GTCS, generalized tonic-clonic seizure; PB, potassium bromide; PHT, phenytoin; CBZ, carbamazepine; SVA, Sodium valproate; ESM, Ethosuximide; BDZ, benzodiazepine

Table 5: Efficacy of newer antiepileptic drug for different seizure types

Seizure	Partial	2oGTCS	GTCS	Absence	Myoclonic	Atonic/ Tonic
VGB	+	+	+	+	?+	?
OXC	+	+	+	+	+	0
LTG	+	+	+	+	+	0
TPM	+	+	+	+	+	+
LEV	0	0	0	+	0	0
ZNS	+	+	+	?	+	+
GBP	+	+	+	+	+	0
TGB	+	+	?	+	+	0
PGB	+	+	?	?	?	
FBM	+	+	?+	?+	?+	+

+ = efficacy, ?+ =- probable efficacy, 0 = ineffective, - = worsens seizure, ? = unknown
Abbreviations: GTCS, generalized tonic-clonic seizure; VGB, vigabatrin; OXC, oxcarbazepine; LTG, lamotrigine; TPM, topiramate; LEV, Levetiracetam; ZNS, zonisamide; GBP, gabapentin; TGB, Tiagabine; PGB, pregabalin; FBM, Felbamate.

Side-effects of Antiepileptic Drugs

Cognitive and behavioral side-effects of AEDs according to frequency:

High	Low
BP/BDZ > PHT > CBZ > SVA > Newer AEDs	

Stevens-Johnson Syndrome

Skin reaction is common to aromatic AEDs like PB, PHT, CBZ and LJG. There is an 80% chance of cross sensitivity among these compounds, especially in children (Fig. 81).

Incidence of *Stevens-Johnson syndrome* for:

- *Phenobarbitone* : 20/100,000
- *Carbamazepine* : 60/100,000
- *Phenytoin* : 90/100,000
- Phenobarbitone may cause hyperactivity and impulsivity. It may also cause Vit-D and Vit-K deficiency
- Phenytoin may cause gum hypertrophy. A good oral hygiene is required to avoid it. PHT also causes acne, hirsutism Vit-D and Vit-K deficiency
- Valproate may cause alopecia hepatotoxicity, increased liver enzymes and liver failure particularly in younger children with multiple AED. It may also cause undue weight gain
- Carbamazepine may cause nausea, vomiting, ataxia, water retention and syndrome of inappropriate antidiuretic hormone [syndrome of inappropriate antidiuretic hormone (SIADH)] like syndrome
- Benzodiazepine (diazepam, CZP, NZP) may cause sedation, ataxia, depression and hyperactivity. Tolerance develops rapidly and withdrawal symptoms are more associated with this group
- Lamotrigine may cause skin rash and retinopathy.

Goals of Antiepileptic Drug Treatment

- Complete seizure control with no or minimal side-effects
- Maintenance of normal lifestyle
- Reduce morbidity and mortality.

International League against Epilepsy Guideline for Antiepileptic Drug Level Monitoring

- Base line level: After initiation of AED
- To check compliance: Once or twice yearly
- Seizures not controlled despite an adequate dose
- Expected toxicity
- After each AED change
- Management of drug interactions during polytherapy
- Special clinical condition; SE, organ failure
- Blood level judged on single sampling may be misleading.

Duration of Treatment and Drug Withdrawal

- Withdrawal: If remain seizure free for 2 years

Fig. 81: Stevens-Johnson syndrome. Bullous lesions, with severe involvement of mucous membranes, conjunctivitis and malaise

- Withdraw one drug at a time
- Gradual withdrawal over 6–12 weeks
- Longer withdrawal for BDZ (6 m/more): As withdrawal symptoms are more common.

Outcome after Treatment

Prognosis

- Seventy percent becomes seizure free → 5–10% responders subsequently relapse and remain uncontrolled
- Thirty percent are "difficult to treat/control" from outset.

Recurrence after Discontinuation of Antiepileptic Drugs

- Seventy percent remains seizure free
- Predictors of recurrence after discontinuation of AED:
  - Focal seizure
  - Neurological dysfunction
  - Underlying remote symptomatic etiology
  - Age at onset: Children versus adolescent/adult more in lower age group
  - Influence of drugs: PB, withdrawal seizure more
  - Mental retardation
  - Presence of spike on prewithdrawal EEG (controversial).

Probability of Subsequence Seizure after First Seizure

First afebrile seizure (GTCS and partial seizure) needs to be addressed.

- Chance for recurrence of second seizure after first episode: 50%
- Chance for recurrence of third seizure after second seizure: 80%
- Most (80%) of the recurrences occur within first year and 90% within first 2 years
- Overall recurrence rate for second seizure is 50%
- Recurrence rate for first partial seizure: 80%.

REFRACTORY EPILEPSY IN CHILDREN

There is small group of children (20–30%) who will continue to have seizure even after trial of two or three appropriate AEDs given in adequate dose. These cases are often labeled as having refractory or intractable or drug resistant epilepsy.

Factors associated with increased risk of intractable epilepsy:

- Age less than 1 year
- Remote symptomatic epilepsy:
  - Cerebral palsy
  - Mental subnormality
  - Other neurodevelopmental disorders
  - Central nervous system infections—pyogenic and tubercular meningitis, encephalitis
- Epileptic syndromes—Infantile spasm (West syndrome), LGS, myoclonic seizure, etc.
- Microcephaly
- Symptomatic neonatal seizures
- Neurometabolic, neurodegenerative diseases, MTS
- Family history of epilepsy
- Initial very frequent seizures
- Focal slowing on EEG.

APPROACH TO A CHILD WITH REFRACTORY EPILEPSY

- Exclude pseudoresistants due to wrong diagnosis like pseudoseizure
- Exclude factitious seizure or fabricated-induced illness (FII)
- Determine the cause of intractability
- Perform complete clinical evaluation
- Do appropriate investigations
- Chalk out long-term plan
- Counsel the parents
- Consider non-antiepileptic drug option
- Consider AES.

CLINICAL EVALUATION

A meticulous history taking together with relevant diagnosis tests are essential to diagnose true RE. First of all one have to be sure the diagnosis is correct, i.e. whether the condition is at genuine seizure or not. The parents may have misconception about seizure and frequently describe shivering associated with fever as convulsion or jitteriness as convulsion. Sometime, parents give imaginary description (fictitious) of seizure. More dangerously parents particularly mother may manufacture (FII) history of false seizure in such a way that the healthcare providers have to believe it as seizure. In fact seizure is the most common form of FII or Munchausen's by proxy in western countries and recognized form of child abuse. Take note of mother's behaviors (usually aggressive, complaining) during consultation and take note of parent-child interaction. More information can be gathered from community health worker or concerned general practitioner.

Exclude pseudoseizure and other paroxysmal events like gastroesophageal reflux (GER), syncope breath holding attack, cardiac arrhythmia (supraventricular tachycardia), etc. Parents may be asked to show video footage of seizure of their child which can be available from their mobile phones.

Take family history of seizure disorder, onset of seizure, developmental history and history of intracranial infection.

TREATMENT HISTORY

- Asked about drug doses, compliance. Ask the patient to practically show the drug being given and how they are being administered
- A thorough CNS examination should be done for any neurological deficit. Look for micro or macrocephaly, neurocutaneous signs
- Admit the patient if possibility of prescribing drug at appropriate dose fails to control seizure or keep them under close supervision
- Patients are asked to take drugs in presence of healthcare providers, observed for any seizure directly or through video and by video EEG. Serum levels of AED are estimated. If there is no seizure for a week and serum of anti-epileptic drugs estimated are within normal range then refractory (RE) due to noncompliance is suggestive. If there is seizure with recommended AED with subtherapeutic AED level then doses are increased to highest tolerable therapeutic level. If there is still seizure with normal AED blood level than the drug/drugs are not working for the child and genuine drug resistance is diagnosed. Management outline of refractory seizure are mentioned in Figure 82 and Flow chart 2 shows the protocol for management of refractory seizure.

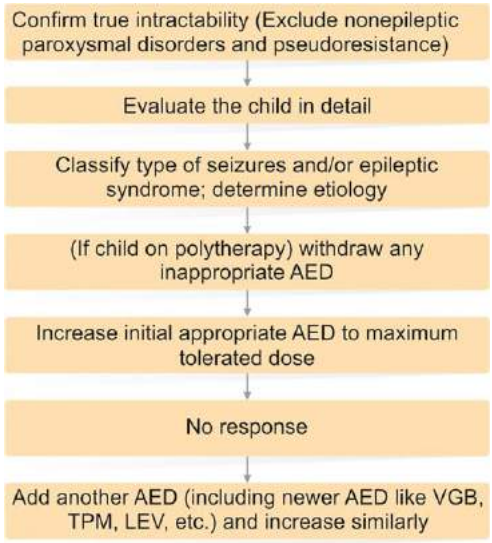
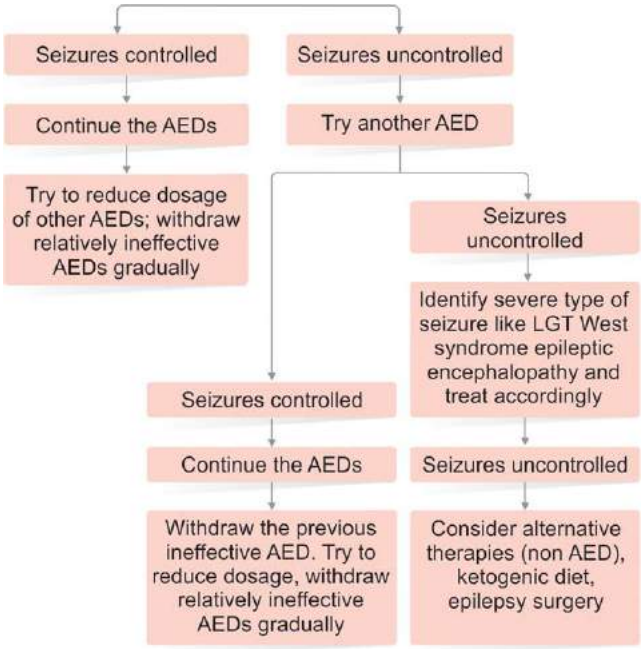


Fig. 82: Management outline of refractory seizure
Abbreviations: AED, antiepileptic drug; LGT, low grade tumors.

Flow chart 2: Protocol for management of refractory seizure



Strategy for Monotherapy Switchover in Refractory Seizure

- No conclusive evidence for choosing between alternative monotherapy and switching to combination therapy when first-line monotherapy fails. Recommendation is to decrease dose of first drug and adding second drug or
- Start second drug → build up to an adequate or maximum tolerated dose and only then taper off the first drug slowly
- If second drug is unhelpful, taper either first or second depending on relative efficacy, side-effects or tolerability
- Consider combination therapy if seizure continues after attempts with monotherapy. If first combination is not effective, a sequence of combinations with potential complementary mode of action can be tried (dual/triple)
- If trials of combination not beneficial, revert to regimen (mono or combination) that provided best balance between tolerability and reducing seizure frequency

- First/second monotherapy improves control but does not produce seizure freedom: an AED with different but multiple mode of action should be added
- Most (60–70%) responds to monotherapy either old/newer AED, combination therapy increases 10–15% more chance of control
- Around 30–40% will need combination therapy
- Outcome is better when a second drug is added immediately after the first drug fails, rather than waiting to see whether first drug works.

PRINCIPLES OF COMBINATION THERAPY

- Around 30–40% need combination therapy to control seizure
- Combinations are prescribed who remain unresponsive to monotherapy
- Combine either two appropriate first line or one first line and a second alternate line/newer AED
- Antiepileptic drugs with different mechanisms of action: Sodium channel blocker + GABAergic drugs, e.g. PB, BDZ, VGB and TGB
- Similar spectrum of activity but different adverse event profiles + TPM
- Drug interactions are more common in hepatic enzyme inducing AED's like PB, PHT, CBZ
- Sodium valproate is an enzyme inhibitor
- Drug-drug interactions are unlikely for nonhepatic enzyme inducing AED's: GBP, LEV, PGB
- Better combinations: VPA + LTG, LTG + TPM, GBZ + TGB, BP + PHT
- Bad combinations: PHT + CBZ, CBZ + LTG.

NONEPILEPTIC ATTACK DISORDERS/ NONEPILEPTIC EVENTS

A large number of children produce paroxysmal events which are genuinely not epileptic and quite frequently diagnosed as epilepsy. These are called nonepileptic event (NEE). NEE, however can also occur in epilepsy (Table 6).

Nonepileptic event can be psychological, physiological process or psychosocial, due to psychogenic process.

BREATH-HOLDING SPELLS

Breat- holding spells (BHS) can be very frightening for parents and are sometimes mistaken for "epileptic attacks".

Table 6: Some nonepileptic events—age-wise distribution

Infants	Toddler	Older children
• Breath holding spells • Benign myoclonus of infancy • Self-gratification behavior • Gastroesophageal reflex/Sandifers syndrome • Benign paroxysmal torticollis • Paroxysmal dystonia	• Breath holding spells • Benign paroxysmal vertigo/torticollis • Benign myoclonus • Self-gratification behavior • Head banging • Sleep disorders • Sandifers syndrome	• Syncope of various types • Migraine • Day dreaming • Tics • Pseudoseizures • Paroxysmal movement disorders • Sleep disorders (night terrors, narcolepsy and catalepsy) • Hyperventilation panic/ anxiety attacks

Incidence: Breath-holding spells are reported in about 4–5% children.

- *Age*: Typical BHS occurs in between 6 months and 18 months of age and 80% cases occur before 18 months of age.
- *Genetic*: There is often family history in up to 30% of cases

Types: There are two types: (1) cyanotic spells and (2) pallid spells

- Cyanotic spells: Are three times more common than pallid spells
- Pathophysiology: A possible mechanism is the mechanical defect involving lung volume maintained during intrapulmonary shunting giving rise to rapid onset of hypoxemia. Central and peripheral neural respiratory controls are normal.

Clinical Features

Breath-holding spells occur in neurodevelopmentally normal children.

They are precipitated by emotional stimuli such as anger, cry, denial or frustration. When a child is denied something or physically hurt, the child cries rigorously usually for less than 15 seconds than becomes silent and holds the breath in expiration. The apnea is associated with rapid onset of cyanosis followed by brief limpness and unconsciousness (Figs 83A and B). Rarely there may be clonic movement or seizure may occur. Recovery usually occurs within 1 minute with the child having a few gasping respiration and then return to regular breathing and consciousness.

How to Differentiate Breath Holding Spells from Epilepsy?

In BHS cyanosis due to hypoxia occurs first followed by brief unconsciousness and/or convulsion. On the other hand, usually in epilepsy convulsion unconsciousness occurs first followed by cyanosis due to subsequent hypoxia.

Breath-holding Spells: Pallid Spells?

Pathophysiology usually occurs due to excessive vagal tone leading to cerebral hypoperfusion. These attacks are now considered as reflex anoxic seizures or RAS.

Clinical Features

Pallid BHS are usually provoked by sudden fright or pain, by sudden striking of head or a startle. A child may gasp and cry for only a very brief period of time, then becomes quiet, loses consciousness and becomes pale. Limpness and sweating are commonly seen. The child typically regains consciousness in less than 1 minute but may sleep for several hours after the episode.

Laboratory test and EEG are usually not indicated.

Treatment

- Most important aspect is to reassure the family that the spells are benign

Figs 83A and B: (A) The child crying vigorously in extended position with holding of breathing during expiration followed by brief apnea and limpness; (B) Characteristic of breath-holding attack

- As soon as the child starts holding the breath, the parents should try to interrupt the apnea by giving a stimulus (flick/pinch) on the buttocks or soles of the child
- The parents should not make a "big issue" of the attack. If the attack is precipitated soon after "demand" then that should not be fulfilled after the attack; also the child should not be pampered after the attack, as this leads to reinforcement.

Role of Anemia and Iron Therapy in Breath-holding Spells

Iron deficiency may play role in the pathophysiology of breath holding spells because iron is important for catecholamine metabolism and neurotransmitter function. Iron therapy should be initiated in a child who has developed breath-holding spell associated with iron deficiency with or without iron deficiency anemia.

Pseudoseizure/Nonepileptic Psychogenic Seizure

Various terms has been used like pseudoseizure/nonepileptic psychogenic seizure, hysteric seizure, functional seizure, pseudoepilepsy, etc. In psychiatry literature, the term somatoform disorder, which includes convulsion disorder or dissociative disorder is also used.

Incidence

Varies from 6% to 10% because variable diagnostic criteria are used by different authors. Pseudoseizure may occur in the absence or presence of epilepsy.

- About 10% of patient with epilepsy have pseudoseizure
- They occur more often in adolescent than in childhood and are more often seen in females than in males
- They may present in various ways such as convulsive movements, tonic posturing, limpness/inability to move, unresponsiveness and myoclonic movements
- It may at times be difficult to differentiate pseudoseizure from true epileptic seizures. The important fact is that consciousness is preserved in pseudoseizure (Fig. 84) or psychogenic seizure. Those with convulsive movement can be differentiated from GTCS by the fact that nonepileptic epilepsy generally have either bizarre or coarsely rhythmic movements (with prominent thrusting of pelvis or trunk in older children), some children can be asked to act the attack or stop the attack when they are having one and they can usually do it
- Unresponsiveness without marked motor manifestation is one of the most common ictal characteristics of nonepileptic seizure
- Increase psychosocial stress and significantly higher number of life events in the preceding year are found to characterize children with nonepileptic seizure (Table 7).

Figs 84A and B: Pseudoseizure: (A) A young girl showing convulsion (mimicking myoclonic seizure) with bizarre movement without losing consciousness; (B) Same girl few seconds after convulsion playing videogame

Key Points of Nonepileptic Events

- Nonepileptic events must always be considered and excluded before making a diagnosis of epilepsy
- Breath-holding spells and RAS are often confused with epilepsy particularly when there are associated brief clonic movements; parental reassurance is important. EEG and AEDs are not required
- Syncopal attacks are commonly confused with seizures in older children. The presence of precipitating factors, warning symptoms, associated pallor and sweating favor the diagnosis of syncope (Table 8)
- Psychogenic seizures are not uncommon in children
- Preservation of consciousness, bizarre movements, ability of children to re-enact the events and at times to stop the attack on command are some of the factors that help differentiate these from true seizures
- A meticulous history is the key factor in distinguishing NEEs from epileptic seizures
- Further confirmation is done by a good physical examination, (particularly observation of the event), EEG and video EEG monitoring in some difficult cases.

Table 7: Difference between epilepsy and nonepileptic attack disorder

	Epilepsy	**NEAD**
Age of onset	All ages	Usually adolescent, late childhood
Sex	F = M	F:M = 3-4:1
H/O, psychiatric illness	Nil	Common
Precipitating factor	Missing dose, sleep deprivation	Emotional dysfunction
Occurrence	Waking in presence of others	Waking or sleep
Onset	Sudden	Gradual
Duration	Brief	Prolonged, minutes
Movements	Tonic-clonic	Bizarre
Eye	Open	Forcibly closed
Tongue bite	Side of tongue	Tip of tongue
Mouth	Open	Grinding teeth
Injuries	Frequent	Rare
Stereotypic attack	Always	Divergent pattern
Amnesia of event	Yes	Variable
1o or 2o gain	Rare	Common
Induced by suggestion	No	Common
Postictal EEG	Slowing	Normal
Postictal Prolactin	Elevated	Normal

Abbreviation: NEAD, nonepileptic attack disorder

Table 8: Difference between epilepsy and syncope

	Epilepsy	Syncope
Precipitating factor	Rare	Common
Occurrence	Awake, sleep	Awake
Onset	Abrupt	Gradual
Duration	60–90 seconds	10–15 seconds
Jerking limbs	Yes	Occasional
Facial color	Flushed	Pale
Perspiration	Hot, sweaty	Cold, clammy
Postictal recovery	Slow	Rapid
Postictal confusion	Common	Uncommon
EEG	Positive	Negative

Abbreviation: EEG, electroencephalography

Self-Stimulation Behavior

Masturbation is not uncommon in infants and toddlers particularly in girls between the ages 2 months and 3 years.

- These children have repetitive stereotyped episodes of tonic posturing often with arching of back and sometimes crossing of legs (Fig. 85) with copulatory movements; however, the child does not manually stimulate the genitalia
- The child suddenly becomes flashed and perspires
- The child gets irritated if the activity is interfered
- The examination is otherwise normal and the child is active and normally playful
- For someone familiar with the behavior, differentiation form epilepsy is not difficult
- *Treatment*: Parents often feel embarrassed because of the child's behavior and need considerable reassurance that there is nothing wrong with their child and that the activity will subside by 3 years of age and no specific therapy is required.

Management of Nonepileptic Attack Disorders

- Organic conditions must be excluded before making a diagnosis of pseudoseizure
- Appropriate psychology or psychiatry consultation should be sought
- Sexual abuse must be actively looked into, in case of young girls with pseudoseizure. Often the abuse is by one of the male family member, or friend or relative

Fig. 85: Showing self-stimulating behavior (masturbation) in a girl with tonic posturing with crossing of legs with copulatory movements (better identified on video)

- The patient and the family should be educated about the illness in causation and outcome
- Supportive psychotherapy and confrontation has been found useful in over 75% patients
- Anxiolytics or antidepressants may be needed in addition to psychotherapy in some cases.

Sleep Disorders

Nonrapid Eye Movement Sleep Disorders

Night terror are frightening events that occur during partial arousal from nonrapid eye movement sleep

Age affected: Peak between ages 5 years and 7 years and resolution usually by adolescence. Prevalence approximately 3% of children.

Clinical features:

- Night terror typically occurs only once in a night. It occurs usually within 1–2 hours of falling sleep. They are characterized by mark autonomic nervous system activation like tachycardia, tachypnea, tremulousness, nervousness, panicked state and sweating. There may be uncontrolled shouting, screaming and facial expression of terror or intense fear.
- Duration: Usually a few minutes
- Episodes stop rather abruptly, with the child rapidly returning to a deep sleep
- Typically the child does not remember the event next morning.

Management:

- Parental reassurance and guidance
- Child should not be sleep deprived
- Medication should be reserved for rare complex cases
- Medication used with success includes BDZs and tricyclic antidepressants.

Rapid Eye Movement Sleep Disorder

- *Nightmare*: In nightmare the child gets up frightened after a bad dream and then becomes fully awake
- *Sleep paralysis*: The child is unable to move for a brief period and feels very frightened.
- *Narcolepsy and catalepsy*: This is characterized by paroxysmal attacks during which the child gets uncontrollable sleep during the day, which is sometimes associated with transient loss of muscle tone (catalepsy)
  - The incidence of narcolepsy is 1:2,000; it generally starts during adolescence
  - Children with narcolepsy are easily aroused and becomes continuously alert whereas a convulsion is followed by a deep sleep, postictal drowsiness and lethargy
  - *Treatment*: Stimulants have been used however, modafinil acetamide 200 mg/day PO is better than stimulants
- Cataplexy is differentiated from epilepsy by the fact that the children with cataplexy have sudden loss of muscle tone and fall to the floor because of laughter, stress, or frightening experiences.

Treatment: The child should be advised to have intermittent short period of sleep. Stimulants such as amphetamine and methylphenidate are required in some cases.

STATUS EPILEPTICUS

CONVULSIVE AND NONCONVULSIVE

Status epilepticus (SE) in children is a common emergency and required early recognition and aggressive treatment. There are two types of SE: (1) Convulsive status epilepticus (CSE), and (2) nonconvulsive status epilepticus.

Convulsive status epilepticus is defined as a continuous generalized convulsion or repeated convulsive seizure without full recovery of consciousness in between, lasting 30 minutes or longer. Convulsion continuing for five or more than 5 minutes is called impending SE. CSE may occur at any age but is more common in children below 2 years.

Causes of CSE include febrile seizure, intracranial infection and epilepsy, subtherapeutic anticonvulsant level, withdrawal or change of AEDs, cerebral hypoxia and metabolic disorder. Febrile seizure is the most frequent case of CSE all over the world. However, intracranial infection probably is the most common cause of CSE in Indian subcontinent.

A significant brain damage and morality is associated with CSE. However, mortality and morbidity depend on underlying etiology. CSE associated with febrile seizure usually has better prognosis than CSE associated with symptomatic or idiopathic seizure disorder.

A seizure that has not stopped spontaneously by 5 minutes (impending SE) is less likely to do so, therefore start drug treatment quickly. The algorithm of SE is useful for most children over 4 weeks of age. Children with epilepsy and recurrent episodes of CSE may have their own individualized CSE treatment algorithm (Tables 9 and 10).

After emergency therapies, useful diagnostic tests include FBC and white blood cell differentials, if not done already brain imaging (CT, MRI, EEG, LP, anticonsultant levels, toxicology screen if indicated), metabolic investigations including ammonia (if indicated).

OUTCOME AND PROGNOSIS

- Factors that determine outcome include the age of the child, underlying etiology, rapidity of SE control and adequacy of care. The time from seizure onset to initiation of treatment is inversely correlated with termination of seizure.
- Convulsive status epilepticus associated with fever has better prognosis than CSE associated with symptomatic or idiopathic seizure disorder (Table 11).

The mortality of SE ranges from 3% to 10% in children and the morbidity is twice this. The mortality is higher with symptomatic SE, and in children with refractory SE it is about 20%. Neurological sequelae-motor or cognitive deficits and subsequent epilepsy are found in almost a third of survivors.

The key points of convulsive status epilepticus are discussed in Table 12.

NONCONVULSIVE STATUS EPILEPTICUS

Nonconvulsive status epilepticus also known as subclinical SE is diagnosed with EEG and should be considered with prolonged postictal state or unexplained alternation in consciousness. In less acute form it may present with unexplained regression of motor, speech, cognitive and behavior problem with excessive

Table 9: Treatment algorithm of convulsive status of epilepticus (for detail drug dose see Chapter 22)

Time (minutes)	Drug treatment	Supportive treatment
0		• Start O_2 and ensure adequate respiration • Consider intubation
2–3	No vascular access Diazepam 0.5 mg/kg/PR or midazolam 0.5 mg/kg buccal	• Start an intravenous line with normal saline • Draw blood for glucose, hepatic and renal function, FBC with DC, electrolytes, calcium, magnesium and blood gases • Obtain urine for routine dipstick
3–5	Vascular access Diazepam: 0.3 mg/kg or lorazepam 0.1 mg/kg infused over 2 minutes	Start second IV line with normal saline for simultaneous administration of a second medication and IV fluids
7–8	Phenytoin/fosphenytoin: 20 mg/kg/ dilute in saline and infuse at a rate of not more than 1 mg/kg/minute	25% DA: 2 mL/kg or 10% DA 5 mL/kg IV push Pyridoxine: 100–200 mg of IV push in children < 18 months of age Monitor blood pressure, ECG
15	IV phenobarbitone: 20 mg/kg	Monitor, BP, respiratory rate, heart rate
20	If available IV valproate: 30 mg/kg, if seizure controlled 5 mg/kg/hour for 6 hours. Alternatively IV levetiracetam (30 mg/kg IV slowly) diluted in 5% dextrose infusion can be tried	Transfer to PICU, prepare for intubation, ventilation, get EEG
20	If valproate not available or valproate fails to control seizure diazepam/midazolam infusion, diazepam: 0.01 mg/kg/minute, maximum 0.1 mg/kg/minute. Midazolam: 0.2 mg/kg (200 µg/kg) loading followed by infusion of 2 µg/kg/minute with increment of 4 µg/kg/minute every 30 minutes till seizure control, up to 20 µg/kg/minute or more can be given	Cardiorespiratory monitoring
60	Thiopental-load with 3–4 mg/kg and given over 2 minutes followed by an infusion at 0.2 mg/kg/minute. Increase the dose every 3–5 minutes by 0.1 mg/kg/minute (until control and the EEG is isoelectric)	Start mechanical ventilation

Abbreviations: FBC, fluidized bed combustion; PICU, pediatric intensive care unit; EEG, electroencephalography; ECG, electrocardiography

Table 10: Salient features of antiepileptic drugs used for control of status epilepticus (for detail of drug dose see Chapter 22)

Shorter term/acute cessation of seizure						
Drug and Route	**Dose**	**Maximum**	**Rate**	**Repeat**	**Risks**	**Comments**
Lorazepam (IV, SL, IO)	0.1 mg/kg	4 mg	<2 mg/ minute	q 10 minute x 2	Hypotension, respiratory depression	Must be refrigerated and diluted before administration
Midazolam (IV/ Buccal)	0.1–0.2 mg/kg	5 mg	<2mg/ minute	Increased by 0.4 mg/kg every 30 minute	-do-	IV prep, can be given buccal
Diazepam (IV,IO)	0.3 mg/kg	10 mg	<2mg/ minute	q 5 minute x 2–3	-do-	Administer as close to vein as possible without dilution
Diazepam (PR)	0.5 mg/kg	10 mg		q 5–10 minute	-do-	Use undiluted IV preparation
Longer-acting anticonvulsants/acute cessation and prevention (not previously on medications)						
Phenytoin (IV, IO) Fosphenytoin	20 mg/kg 18 mg/kg	1,000 mg (30 mg/kg)	1 mg/kg/ minute	May give additional 5 mg/ kg IV if unable to stop seizure	Hypotension, arrhythmia, need to be on cardiac monitor	Must be given in nonglucose containing solution
Phenobarbital (IV)	20 mg/kg	600 mg (30 mg/kg)	1 mg/kg/ minute		Respiratory depression, especially if diazepam has been used	First choice in neonates

Abbreviations: IV, intravenous; SL, sublingual; IO, intraosseous; PR, per-rectum

Table 11: Management of complications of status epilepticus

Problems	**Treatment**
Circulatory support	(IV fluids) inotropes and hemodynamic monitoring
Acidosis	Support circulation with fluids and vasopressors, ventilation and control of seizures
Metabolic	Correction of hypoglycemia, hypocalcemia, hyponatremia
Pulmonary edema	Ventilation, diuresis, vasoactive drugs
Cerebral edema	Head elevation; normoventilation, IV mannitol
Hyperpyrexia	Cooling blankets, IV fluids, tepid sponging
Renal failure	Dialysis and other appropriate management

Table 12: Key points of convulsive status epilepticus

Convulsive status epilepticus is a life-threatening emergency
The outcome is directly related to the time at which treatment is initiated and related to underlying cause of CSE
The most common cause of refractory SE in Indian subcontinent is CNS infections
Prompt and aggressive management with a preset protocol is essential
Newer AEDs such as IV valproate/IV levetiracetam has been used successfully in CSE and may be considered in situations where facilities for ventilation are not readily available
Abbreviations: AED, antiepileptic drugs; CNS, central nervous system; IV, intravenous.

inconsolable cry, undue demanding attitude and sleepiness, less responsive, less or hyperactive. Many cases of NCSE are often misdiagnosed as neurodegenerative disorder by clinicians due to its presentation as developmental regression of motor, speech and cognition (Fig. 86).

Nonconvulsive status epilepticus children usually occur in setting of severe epilepsy, such as LGS and Dravet syndrome. It hardly occurs denove.

Various types of NCSE include (1) Electrical SE (2) absent status (3) complex or simple partial status (4) myoclonic (controversial).

Electrical status epilepticus without any motor manifestations: This is usually seen in situations, such as continuous spike wave discharges during sleep which occurs commonly in children with epileptic encephalopathies.

ABSENCE STATUS EPILEPTICUS

Absence SE is a term used to denote a clinical state of diminished awareness associated with generalized spike-wave discharges on EEG. It is classified into typical and atypical.

Typical: Absence SE is associated with generalized (synchronous/symmetric) 3-Hz spike-wave discharges. Isolated impairment of consciousness is seen; occasionally there is slight jerking of eyelids. Response to IV BDZ is good and the SE stops immediately.

Atypical absence SE: Occurs much more frequently and is seen in children with symptomatic and/or cryptogenic generalized epilepsies particularly in children with LGS, West syndrome (infantile spasm), MAE and severe myoclonic epilepsy of infancy.

Clinical Presentations

- Impairment of consciousness and awareness
- Unusually delayed response to questions and commands
- Cognitive decline manifesting as worsening of school performance
- Loss of motor skill already achieved
- Loss of interest in, or contact with surroundings
- Feeding difficulties with excessive drooling

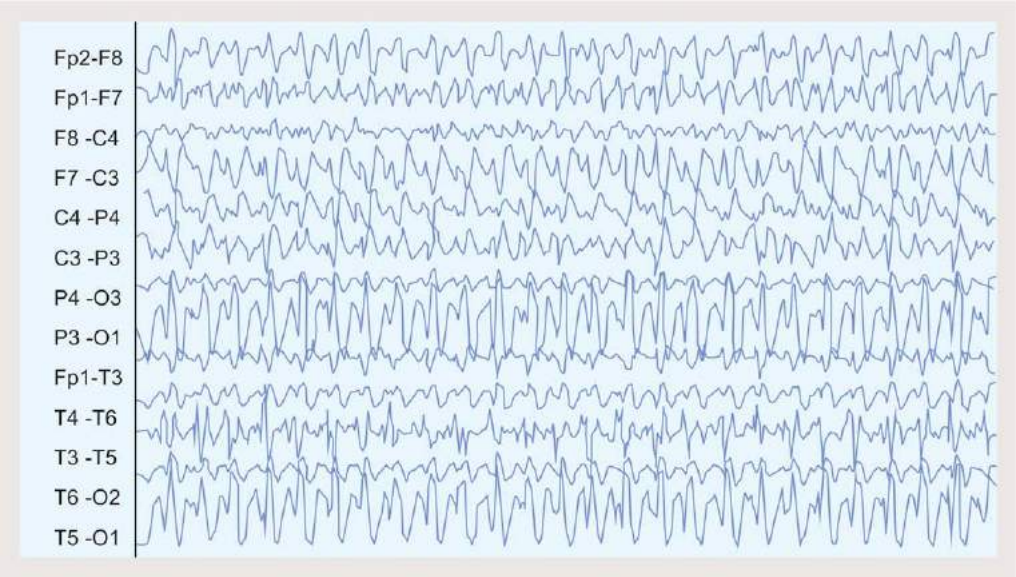


Fig. 86: Electroencephalography feature of nonconvulsive status epilepticus showing continuous 2–2.5 c/s spike wave complexes in a child of 7 years

- Hypotonia leading to difficulty in sitting, walking (pseudoataxia), holding objects.

Nonconvulsive status epilepticus decreases during wakefulness and increases during drowsiness. The clinical features may be very subtle and difficult to distinguish from pre-existing cognitive problems. Thus, the diagnosis is often delayed. Video-EEG monitoring with cognitive testing may be necessary to identify ictal events.

COMPLEX PARTIAL STATUS EPILEPTICUS

Complex partial status epilepticus (CPSE) is characterized by prolonged confusion, impairment of consciousness, lack of interaction, staring, speech arrest, staring behavior and automatisms. Focal motor activity may occur. At times it may be difficult to differentiate from absence status.

Occasionally, CPSE may be the first manifestation of epilepsy.

Electroencephalography: Abnormality reflects the pattern of individual complex partial seizures. Spike and slow wave activity may be seen in the temporal or occipital regions.

Complex partial status epilepticus should be considered in all children with unexplained prolonged change in behavior.

Treatment

Nonconvulsive status epilepticus is not life-threatening but is associated with neurologic morbidity. EEG monitoring is usually required to determine when the status has stopped.

Treatment of absence status epilepticus: Typical absence status responds rapidly and completely to intravenous BDZs. VPA is also effective. Continuous IV infusion of midazolam may be required.

Atypical absence status epilepticus is often very resistant to treatment. VPA or oral steroids or ACTH may be effective, but relapse may occur.

Outcome of absent status epilepticus: Typical absence has a good prognosis. Atypical absence SE has a poor prognosis, often with intractable epilepsy and cognitive deterioration. Long-term prognosis is determined primarily by the underlying etiology.

Treatment and Prognosis of Complex Partial Status Epilepticus

- Most cases respond to intravenous PHT and BDZs
- Long-term prognosis is determined primary by the underlying etiology.

Complex Partial Status Epilepticus

Long-term complications include neurologic and behavioral problems, particularly memory deficits, following CPSE.

Key Points

- Children with unexplained regression of motor, speech, cognitive and behavior state, particularly associated with previous history of seizure should be suspected of NCSE
- Nonconvulsive status epilepticus occurs mostly in children with severe epilepsy particularly LGS
- Diagnosis requires a high index of suspicion and EEG confirmation.

NONANTIEPILEPTIC DRUG TREATMENT AND NONPHARMACOLOGICAL MANAGEMENT OF PEDIATRIC EPILEPSY

Seizure control is achieved in approximately 75% of children treated with conventional AED, but nonconventional (or nonstandard) medical treatments, surgical procedures, dietary approaches, and other nonpharmacological treatment approaches may have a role to play in those with intractable seizures or in AED toxicity. In addition there is increasing concern amongst parents and carers about the unwanted side-effects of conventional AEDs, often fuelled by the media and internet chat rooms. Nonepileptic drugs used either alone or as an adjunct therapy may reduce the need of conventional AED with its unwanted side-effects.

NONANTIEPILEPTIC DRUG MEDICAL TREATMENT

- Steroids (ACTH)
- Intravenous immunoglobulins
- Vitamins (pyridoxine, pyridoxal phosphate)
- Melatonin.

Corticosteroids

Adrenocorticotropic hormone in children with West syndrome (infantile spasms) was used in 1958, but since then corticosteroids have been used for many other drug-resistant epilepsy syndromes. ACTH is unavailable in UK and hydrocortisone is used in France. Corticosteroids may also be useful for exacerbations of seizures or episodes of NCSE in other epileptic encephalopathies, including severe myoclonic epilepsy in infancy (also known as Dravet syndrome), LGS, cryptogenic epilepsy syndromes, or Rasmussen's encephalitis. Corticosteroids have also been reported to be successful (as monotherapy or in combination with SVA) in LKS.

Immunoglobulins

Intravenous immunoglobulin (IVIG) has been used for the treatment of Rasmussen's syndrome and seizure exacerbations in West syndrome and LGS. Several regimens have been used with varying doses and duration, ranging from 100 mg/kg to 1,000 mg/kg given for 1, 2, or 3 consecutive days and then repeated after 1, 2, or 3 weeks. As with corticosteroids, there is no clear mechanism of action. It is a very expensive option, particularly if treatment is maintained with repeated courses, and is therefore a relatively uncommon treatment choice.

Role of Vitamins in Epilepsy

There are two general indications for vitamin supplementation in epilepsy. The first is for replacement therapy in inherited metabolic defects, including pyridoxine-dependent seizures, biotinidase deficiency, and folinic acid responsive neonatal seizures. The second is where vitamin may reduce seizure frequency through a presumed anticonvulsant role, possibly by "resetting" the inhibitory gamma aminobutyric acid (GABA).

Vitamin B6 (Pyridoxine)

This is the treatment of choice in the rare recessive pyridoxine-dependent seizure syndrome. The diagnosis is clinical and should be considered in all babies with intractable seizures under the age of 18 months. It can also be used as nonreplacement therapy in severe refractory seizure presumed to be due to other causes like hypoxic ischemic encephalopathy. Patients can either be tested by giving 100 mg of pyridoxine intravenously/orally while undergoing EEG monitoring or given a 3-week course of oral pyridoxine (100–200 mg daily).

Pyridoxal Phosphate: Pyridoxal phosphate is the major activated form of vitamin B6. It appeared to be most effective in children with intractable infantile spasms. However, the medication is expensive, difficult to administer and may be poorly tolerated due to vomiting. The recommended oral dose is 50 mg/kg/day for a minimum of 2 weeks. It may act as an anticonvulsant, particularly in neonatal seizures and EIEE (Ohtahara syndrome).

Melatonin

It is frequently prescribed for sleep disorders in children with a range of developmental disorders. Some anecdotal reports have suggested that melatonin may improve seizure control, particularly in myoclonic and nocturnal seizures.

Key Points

- Adrenocorticotropic hormone and steroids can be tried in refractory seizures not responding to appropriate AEDs particularly in children with LGS and LKS
- Trial of pyridoxine is given in children up to 2 years of age with refractory seizures not responding to AEDs, where the cause of seizures is not known.

DIETARY MANIPULATION

- Ketogenic diet
- Classical KD
- Medium-chain triglyceride (MCT) diet.

Dietary Changes for the Treatment of Epilepsy

Ketogenic Diet

The KD is effective for resistant complex epilepsies such as LGS.

The KD mimics fasting by having a high fat and low carbohydrate content which promotes prolonged ketone production. There are broadly two types of KD, the first "classical diet" and a modified version, the MCT diet. The MCT diet begins with either no or a shorter fasting and allows more dietary choices, but it probably causes more unacceptable gastrointestinal side effects. Indications for the KD in children include intractable epilepsy or unacceptable AED toxicity, or both. It is most practical and effective in younger children (aged 1–10 years) due to better compliance and also appears to be more effective in the generalized rather than the focal epilepsies. If effective, children often have improved cognition and behavior through a direct effect of reducing clinical and electroencephalographic seizure frequency.

How to Start Ketogenic Diet?

- It is generally planned to reduce total calorie intake and provide calories through fats versus protein and carbohydrates in a ratio of 4:1 or 3:1.
- Energy intake is calculated at 75% and fluids at 80% of the daily recommended intake for age.
- It is prepared using a combination of fats including oils and protein, carbohydrate and water.
- Some children respond to a liberalized KD that uses MCT, instead of long chain triglycerides. Coconut oil can be used as MCT.
- The child is hospitalized and is first made to fast to produce ketosis, during this time only water and sugar-free drinks are given. After 24–36 hours the urine shows ketones. The diet is then started.

Side-effects

Side-effects are renal stone, constipation, initial vomiting and dehydration, lack of weight gain, acidosis, hypoglycemia and decrease bone density.

Antiepileptic Surgery

- Antiepileptic surgery offers a realistic and potentially very effective and even curative therapeutic option for a significant number of children with drug-resistant temporal and extratemporal lobe epilepsy
- Any surgical procedure should be considered sooner rather than later, and
- Children undergoing a surgical option require detailed pre-, intra- and postoperative assessments, expertise, and care and this must be in place before any surgical procedure can and should be undertaken.

NONPHARMACOLOGICAL TREATMENTS OF EPILEPSY ALONG WITH ANTIEPILEPTIC DRUG

Sleep Hygiene

Sleep deprivation is well recognized as a precipitant for seizures (and most epilepsies), particularly in the idiopathic generalized epilepsy syndromes and temporal lobe epilepsy. Interictal EEG discharges are promoted by sleep deprivation, possibly by increasing neuronal excitability. Patients with epilepsy should therefore be advised to have good sleep hygiene. They should try to ensure regular and consistent sleep and if they go to bed later than usual, they should try to get up later the next morning. They should also avoid exhaustion and fatigue.

Lifestyle Changes

Exercise: Participation in exercise should be recommended for children with epilepsy, providing they are adequately supervised. This is intended to have an impact on quality of life and social inclusion rather than seizure control. Exercise is difficult for many children with epilepsy due to their motor problems and learning disabilities, but this should not preclude their attempts to participate in games and sports activities whenever possible (Fig. 87).

Psychological Approaches

Techniques to Abort Seizures or Reduce Seizure Frequency

Avoidance: The most common reflex epilepsy is that triggered by visual stimuli (flickering lights or specific visual patterns or both). Most common reflex seizures are in patients who are photosensitive as part of their epilepsy syndrome (particularly in juvenile myoclonic epilepsy) or who have pure photosensitive epilepsy. If photosensitivity is documented following intermittent photic stimulation on an EEG recording, measures to try to avoid seizures should be advised including sitting more than 2.5 meter away from the television in a well-lit room. Children should also avoid playing video games in a darkened room or when they are excessively tired. Covering one eye can also be used when a patient is exposed to other visual stimuli, such as flashing lights.

Avoidance to prevent complication of seizure (Fig. 88):

- Playing on open roofs
- Swimming without attendant
- Climbing trees and risky activities
- Cycling on crowded roads
- Cooking or staying near open fire.

Fig. 87: Showing activities which are allowed and encouraged in epilepsy

OTHER TECHNIQUES TO AVOID SEIZURE

Relaxation Techniques

The role of relaxation techniques in adults and children with intractable epilepsy has been discussed in a recent Cochrane review. Successfully taught relaxation techniques might indirectly improve seizure control in a number of children with epilepsy (for example, through improved sleep).

Promotion of Emotional Well-being

Stress management: Stress is considered to be a precipitant for seizures and yoga is believed to induce relaxation and therefore stress reduction. During yoga, meditation is believed to awaken dormant divine energy in the body which can heal disorders. However, there is no high quality scientific yoga in management of epilepsy is scarce.

Fig. 88: Showing activities which are not allowed and discouraged in epilepsy

Reduction in psychiatric comorbidity: Anxiety, depression and psychosis may complicate epilepsy. These symptoms may be part of the epilepsy syndrome or iatrogenic arising as a consequence of surgery or the use (or withdrawal) of AEDs. Pediatricians should seek help from the local child and adolescent psychiatry teams if severe symptoms of depression or psychosis develop, as occasionally neuroleptic and antidepressant medication may be indicated to control these often very disabling symptoms.

Coping strategies for living with epilepsy: Psychological treatments that focus on the emotional impact of seizures are now considered as standard management practice in adult patients. Techniques include both individual and group/family counseling and psychotherapy. Cognitive behavior therapy (CBT) is another useful approach. Patients are taught coping skills to try to recognize and control their symptoms. However, these are only useful in older child or teenager and their families.

Educational Interventions

Educational programs for adults and children with epilepsy can result in a significant improvement in the knowledge and understanding of epilepsy, coping with epilepsy and concordance (adherence) with medication.

KEYPOINTS OF NONPHARMACOLOGICAL TREATMENT OF EPILEPSY

Lifestyle Changes

- Avoidance of sleep deprivation
- Avoidance of fatigue and exhaustion
- Exercise

Psychological Approaches

- Techniques to abort seizures (avoid flickering light, avoid TV watching and video watching in dark room, allow adequate relaxation)
- Promotion of emotional well-being and stress management (yoga)
- Reduction of psychiatric comorbidity (anxiety or depression)
- Coping strategies for living with epilepsy (CBT, counseling, psychotherapy and educational interventions)

CONCLUSION

Seizure control is achieved in approximately 75% of children treated with conventional AEDs. Nonconventional AED treatments and nonpharmacological approaches may have a role in those with intractable seizures or AED toxicity. Many of the psychological approaches are largely common sense and are already incorporated into our current practice, including, for example, avoidance techniques and lifestyle advice.

FEBRILE SEIZURE

A febrile seizure (FS) is defined as an epileptic seizure occurring in association with pyrexia in a neurodevelopmental normal child less than 5 years of age (between 6 months and 5 years) in the absence of a confirmed or suspected CNS infection. Pyrexia is defined as temperature more than 37.5°C.

Febrile seizures are the most common provoked seizure and 3–5% children experience them. There is a genetic predisposition with a 10% risk if the child has a first degree relative with a febrile seizure. In majority of cases viral infections are implicated.

Seizure is not related to degree of fever and quite frequently occurs during early part of febrile spike when temperature is not very high. It sometimes so happen that seizure occurs before parents can realize that their child has developed fever and parents frequently narrate that seizure occurred when the child had no fever and they found their child febrile immediately after seizure took place. Febrile seizure is usually generalized tonic-clonic (convulsive) type. However, it may be nonconvulsive type like staring look, conjugate deviation eye or brief loss or consciousness. That is why the term febrile convulsion is discouraged and instead the term febrile seizure is currently used. Febrile seizure is usually benign and does not cause brain damage. However, first attack of febrile seizure is associated with 30–40% chance of further febrile seizure. This is more likely, the younger the child, the shorter the duration of febrile illness before seizure (pre-seizure fever duration), the lower the temperature at the time of seizure and if there is a positive family history of seizure.

TYPES OF FEBRILE SEIZURE

Febrile seizures (FS) are two types:

- Simple FS
- Complex or atypical FS.

Characteristic of Simple Febrile Seizure

- Generalized seizure
- Seizure duration is short, usually less than 5 minutes
- Usually not occurs in series or repeated in the same illness
- No temporally or permanent neurological deficit after seizure
- Postictal phase is usually absent or brief
- Not associated with brain damage or subsequent intellectual problem.

Chance of developing epilepsy in simple FS is 1–2% similar to the risk for all children.

Characteristics of Complex Febrile Seizure

- Focal seizure or focal onset
- Seizure duration is prolonged, usually more than 15 minutes
- Occurs in series or repeated in same illness
- May be associated with prolonged or transient neurological deficit like Todd's paralysis following seizure attack
- Postictal phase of drowsiness or impaired level of consciousness is prolonged
- More associated with brain damage or subsequent intellectual problem
- Chance of developing later epilepsy is high (4–12% in complex FS).

In determining the prognosis or etiology of seizure associated with fever role of duration and quality of postictal phase are frequently underemphasized. Patients after seizure attack go through a phase of unarousable sleep, confusion or rarely coma, called postictal phase which may last from 5 minutes to 10 minutes up to hours. However, in many children postictal is either shorter or they do not at all go through postictal phase.

It is mention worthy that seizure duration may not affect postictal or recovery time. A brief seizure may be followed by prolonged postictal phase with delayed recovery from postictal sleep. Children recover more quickly from simple febrile seizure in comparison to complex febrile seizure or acute symptomatic seizure who recovers more slowly. It is generally thought that failure to recover as expected from seizure attack should prompt consideration of a sinister etiology like brain damage or intracranial infection (provided rescue drugs like BDZ were not given previously at home or by medical care givers).

EVALUATION OF A CHILD FEBRILE SEIZURE

History taking, examination and investigation are done to assess current clinical status, including fever, ongoing seizure, hydration status, etc. to know the underlying cause of FS and to exclude possible alternate clinical diagnosis particularly meningitis.

Characteristic clinical features include:

- Brief tonic-clonic seizure with brief or no postictal phase and not associated with neurological deficit. Generally seizure occurs in the initial stage of fever.
- Parents may give similar history of seizure associated with fever, which is also suggestive of FS and usually exclude meningitis.
- Family history of febrile seizure may be present.
- Although mostly viral illness, history taking and examination may be suggestive of bacterial infection like invasive diarrhea (*Shigella dysenteriae*), acute follicular tonsillitis, acute suppurative otitis media, etc. and lower respiratory tract infection.

The examination should include assessment of hydration status, status of airway, record of temperature, level of consciousness, examination of fontanel, examination of throat for tonsillitis and ear for otitis media. Evidence of signs of meningism should be looked for.

Neurological examination should be done for possible neurological deficit due to complex FS or primary neurological lesion. Postictal phase should be meticulously observed for its duration and level of consciousness during postictal phase.

INVESTIGATION

- Blood, complete blood count (CBC), ESR, CRP
- Others depending on clinical condition
- Urine RE M/E and culture
- Stool RE M/E for invasive diarrhea.

Lumbar puncture (LP) and CSF study: Not routinely done. It should be done if meningitis is suspected.

The decision to do lumbar puncture (LP) in FS is crucial and sensitive. Although generally safe procedure, if done without valid reason, it may hurt sensitive parents who may become critical. On the other hand if not done when indicated, genuine potentially catastrophic but treatable diagnosis of intracranial infection will be missed out.

INDICATION OF LUMBAR PUNCTURE IN FEBRILE SEIZURE

1. First febrile seizure in a child below 1 year, as it is difficult to exclude meningitis at this age, because sings of meningism are usually absent
2. Prolonged seizure (>15 minutes) duration or febrile convulsion compatible with SE
3. Focal seizure

4. If seizure occur in series or more than one seizure in single episode
5. Neurological deficit detected after seizure
6. Prolonged (> 30 minutes) postictal sage, without rescue drugs
7. Unfavorable clinical response, i.e. initially behaved like febrile seizure, but later (on subsequent hours or days), deterioration of clinical condition which include level of consciousness
8. Signs of meningism (neck rigidity, positive Kernig's sign)
9. First febrile seizure in older children does not merit an LP unless clinical signs of CNS infection are present.

Recurrent febrile seizure does not merit LP. However, multiple seizure in same episode with impaired level of consciousness in between attack, deserve consideration of LP to exclude meningoencephalitis.

Is LP mandatory in febrile child with bulging fontanel?
Scientific evidence suggests most febrile children with bulging fontanel, without neck stiffness, without impaired level of consciousness (including lethargy or agitation), without focal seizure do not predict bacterial meningitis. Most infant with fever and bulging fontanel have benign and self-limited diseases like upper respiratory infections, viral diseases, roseola infantum and aseptic meningitis. In such case LP is not mandatory, or should be done assessing the overall condition of child with FS, suggesting to do LP.

Parents should be properly counseled in simple language about the procedure of LP and the necessity to perform LP in febrile seizure. They should be told about the safety and minimal risk of LP. The parents should be advised not to be present during the procedure as it may be distressing for them.

Electroencephalography and Neuroimaging

Electroencephalography is usually not required as an abnormal EEG does not alter the management of febrile seizure. Similarly neuroimaging is not usually done in simple febrile seizure.

Conventional Pediatric Practice of Management of Febrile Seizure

Management of FS widely practiced (not all well-supported by scientific evidences) at home, community level and at hospital are the following:

- Prompt reduction of temperature with antipyretic and hydrotherapy (tepid sponging)
- Antipyretics: Paracetamol orally 15 mg/kg/dose 6 hourly, or per-rectum (if cannot swallow) by suppository. Anti-inflammatory antipyretic like ibuprofen 20 mg/kg/day in three divided doses can be given. Combined paracetamol and ibuprofen are better at reducing fever than paracetamol alone, due to synergistic action. Alternating the drugs may achieve better fever control over the course of illness. It may also help to reduce paracetamol poisoning from overdose due to frequent administration
- Aspirin should be avoided due to risk of Reye's syndrome.

Physical Management of Febrile Seizures

- These include tepid sponging, removing clothing and cooling the environment with fans and improved ventilation, along with antipyretic treatment
- Supportive: Adequate airway and oxygen should be ensured. Rectal and axillary temperature should be recorded frequently
- Parents should keep antipyretics and BDZ at home.

Control of Seizure by Anticonvulsants

Parents and community physicians should give anticonvulsant if they occur.

Quick acting and relatively safe anticonvulsants are recommended. BDZs are recommended agents for prehospital use. Diazepam 0.3–0.5 mg/kg/dose rectally can be given. Buccal midazolam is gaining popularity as an alternative and there is evidence that it is more effective than per-rectum diazepam in terminating seizure. In hospitalized patients IV diazepam can be given (0.2–0.3 mg/kg/dose) by slow push (maximum 5 mg/dose).

Convulsion if present during presentation to attending doctor or other healthcare providers should be terminated as early as possible. It should be kept in mind, that although FS generally benign in nature, it is the most common cause of CSE in children and if not terminated earlier, seizure control becomes difficult subsequently.

In hospitalized patients intravenous line should be started to maintain hydration, to give medication and to obtain blood for investigation. Possibility of meningitis should be excluded by LP if indicated.

OUTCOME AND PROGNOSIS OF FEBRILE SEIZURE

Febrile seizure recurs in 30–40% cases. In most cases seizure is short lived. However, seizure may be prolonged (complex FS) and febrile seizure is the most common cause of CSE in infants and young children. Prolonged FS is associated with hippocampal edema in patients investigated within 48 hours of an episode of CSE. It may follow later with focal epilepsy, as hippocampus injury evolves into MTS. However, adverse effect of CSE due to prolonged FS is much less than CSE due to other etiologies like acute symptomatic or idiopathic epilepsy.

There are numerous evidences to suggest that children who develop seizure with lower degree of fever have lower threshold and therefore high recurrence rate of febrile seizure, while those with high fever over 40°C have fewer recurrences.

Complex FS is more associated with later development of cognitive and behavior impairment, permanent neurological defect and subsequent epilepsy.

Febrile Seizure Prophylaxis

Prophylaxis of FS is indicated if:

- Febrile seizure is recurrent
- Seizure occurring at lower degree of fever
- If first seizure occurred in infancy
- There is a family history of FS or epilepsy
- Prolonged febrile seizure
- If the child later found to be developmentally abnormal.

There are evidences to suggest after prolonged febrile seizure, the risk of epilepsy is much higher, about 10 times the general population. In such child, the subsequent epilepsy, if occurs, is more often focal than general. According to definition of FS a child should be developmentally normal as a prerequisite of FS. However, if the child is later found to be developmentally delayed or shows neurological abnormality, than he/she is more likely to develop epilepsy later.

Prophylaxis is of two types: (1) Intermittent, (2) Continuous.

Intermittent Prophylaxis

It is the more desirable form of prophylaxis.

Benzodiazepines are used. Oral or rectal diazepam or oral CLB are used. Buccal midazolam is also used.

Diazepam (0.3–0.5mg/kg), orally or rectally is used 8 hourly, at onset of fever, up to 48–72 hours as seizure recurrence risk is high in first 48 hours. CLB orally 1 mg/kg, single dose can also be used.

Continuous Prophylaxis

It is indicated in the event of failure of intermittent prophylaxis, in atypical FS or family history of epilepsy. SVA (10–20 mg/kg/day) or phenobarbitone (3–5 mg/kg/day) is effective. The duration of therapy should be for 1–2 years or until 5 years of age, whichever comes earlier.

Carbamazepine and PHT are not effective.

Evidence-based Management of Febrile Seizure (Not Yet Widely Practiced)

There is a significant contrast between scientific evidence on one hand with concept and practice of febrile seizure on the other hand.

Management of Fever

Do we need antipyretic to treat fever in FS?

Fever is often considered by parents and doctors as major and harmful sign of illness. Fever phobia, an exaggerated fear of fever in their children is common among parents. The parental concern leads to increased use of antipyretic by healthcare providers. In addition, there is often a widespread perception among pediatricians that fever is dangerous. Antipyretics are parent's and pediatrician's preferred method of managing fever.

However, recent researches have shown that fever has overall inhibiting effect on growth of bacteria and replications of viruses. It enhances immunological process, including activity of IL1, T helper cell and B cell and immunoglobulin synthesis. Therefore fever has protective role and moderate fever (<40°C) is beneficial.

Febrile seizure is usually benign and there is now abundant evidences that antipyretic do not prevent febrile seizure. Fever is not responsible for febrile seizure. Some changes at neuronal level of brain mostly induced by viral infection triggers seizure at lower degree of fever or even before temperature rises. Numerous studies have shown that children who develop seizure with lower degree of fever have lower seizure threshold and therefore high recurrence rate of febrile seizure, while those with high fever over 40°C have lower recurrence.

On the other hand, there are known adverse effects of antipyretics such as gastrointestinal bleeding (ibuprofen), liver (paracetamol) and renal failure.

There is also no evidence to suggest alternating antipyretic (paracetamol and ibuprofen) can prevent febrile seizure.

Antipyretic however can be given to improve child well-being, which should be properly assessed. If the child is active and playful with fever, there is no need for antipyretic. It can be given to reduce symptoms like pain, discomfort, lethargy, or when there is high fever over 40°C.

Evidence-based educational interventions are the best way to treat and prevent fever phobia and reduce unnecessary use of antipyretics.

Is physical management necessary?

There are evidences to suggest that physical measures like tepid sponging, removing clothes and cooling the environment by fanning is necessary to reduce fever in febrile seizure. It has only short-term effect and can reduce temperature insignificantly. It may produce unpleasant sensation to child with shivering and excessive crying without medical benefit. The main indication of physical therapy is in hyperthermia.

Use of seizure prophylaxis, is it necessary?

The main concern of recurrent febrile seizure is future development of epilepsy. However, there is no substantial evidence to suggest that recurrent seizure is more associated with later development of epilepsy than general population in neurodevelopmentally normal child. Studies have shown a lack of association between duration of first febrile seizure and risk of subsequent epilepsy. Therefore to prevent future epilepsy, use of febrile seizure prophylaxis to prevent febrile seizure in childhood which is generally benign in nature, has little or no value. Even some evidences suggest the prolonged seizure, and duration of seizure of more than 30 minutes (CSE), which is one of the features of complex FS, is also not more associated with later development of febrile or nonfebrile seizure disorders, in neurodevelopmentally normal child.

However, fever coupled with seizure produces a lot of anxiety and panic to parents and caregivers feel nervous or feel unethical not to offer prophylaxis. Evidence-based educational interventions can help to prevent fever phobia and FS phobia and can help genuine evidence-based practice of management of fever and febrile seizure, provided by healthcare providers, at least by pediatricians.

INTRACRANIAL INFECTION

Infections of the CNS are classified as meningitis or encephalitis according to whether the pathology predominantly affects the meninges and CSF or the brain parenchyma. In meningitis, the brain surface is usually involved and meningoencephalitis would be a better term. In contrast, encephalitis may exist with little or no evidence of inflammation in the CSF.

The term encephalomyelitis including acute disseminated encephalomyelitis (ADEM) is used for brain inflammation caused by usually postinfection autoimmune response, rather than direct invasion by pathogens. Noninfectious causes of meningitis and encephalitis include drugs, vasculitis and malignancy.

MENINGITIS

Acute meningitis is mostly bacterial, but acute viral aseptic meningitis also occurs.

Chronic meningitis may be caused by infection with bacteria, especially *Mycobacterium tuberculosis*, but also by rickettsia, fungi and parasites in the immunocompromised host. Tuberculous meningitis discussed in Pulmonology (*see* Chapter 9) along with pulmonary tuberculosis.

Acute Bacterial Meningitis

Acute bacterial meningitis (ABM), a major cause of mortality and morbidity in young children, occurs both in epidemic and sporadic pattern.

Incidence and Etiology

the epidemiology is changing as a result of immunization pattern. Host factors are also important (e.g. immuno-compromised individuals).

Age-specific Etiology of Acute Bacterial Meningitis

Neonatal period (3 months): *E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Streptococcus pneumoniae, Staphylococcus aureus, Salmonella* species.

Group B *Streptococcus* is one of the most common pathogen in western countries but rare in Indian subcontinent. *Listeria monocytogens* is also a frequent pathogen in western countries.

From 3 months to 3 years: *Haemophilus influenzae, Streptococcus pneumoniae* and *Neisseria meningitidis* are the most common pathogen.

Beyond 3 years: *Haemophilus influenzae* (up to 5 years) and *Neisseria meningitidis* are the most common bacterial pathogen involved in meningitis.

Pathogenesis

Bacterial infection of the meninges usually follows bacteremia. It may also come from distant septic focus like pyoderma, empyema, osteomyelitis and from near septic focus like otitis media, infected paranasal sinuses.

Recurrent meningitis can occur in unresolved fracture skull, congenital dermal sinus, congenital cyanotic heart disease, tetralogy of Fallot, congenital immunodeficiency disease including defect of polymorph and immunoglobulin.

Pathology

bacteria from circulation enter the CSF, probably across the choroid plexus and capillaries enter the CSF, an area of impaired host defense, where the bacteria multiply. This generates an immune response and an inflammatory cascade killing the bacteria but also causing brain injury.

Additional Mechanisms

Direct toxic effect of agents released by bacteria and/or by immune mechanism.

Development of vasogenic agent and cytotoxic edema, resulting in RICP and cause diminished perfusion. The leptomeninges are infiltrated with inflammatory cells and cortex of the brain shows edema. The exudates from destroyed ependymal cells collect at the base of brain as purulent exudate may lead to brain abscess. The exudate may block the foramina of luschka and magendie, resulting in hydrocephalus.

Inflammation of cerebral vessels also occurs, resulting in vasculitis, thrombophlebitis, leading to decreased perfusion of brain with infarction, causing neurological sequelae (pathogenesis of brain damage).

Hypotension and Septic Shock Associated with Meningitis

As mentioned earlier meningitis usually follows or is associated with concomitant bacteremic septicemia. Most of the damage of host tissues is caused by host immune response, triggered by endotoxin released by bacteria, causing meningitis, particularly produced by *Meningococcus* bacteria. Endotoxin activates host macrophage which triggers an intense inflammatory process, by producing proinflammatory cytokines including tumor necrosis factor-α and interleukin 1β (IL-1β), IL-6, etc. These cytokines not only damage brain tissue but are also involved in causing microvascular damage and increased capillary permeability leading to hypovolumia and hypovolemic shock. The complex pathophysiology of septic shock and intravascular fluid depletion with hypovolumia in meningitis, particularly in association with meningococcemia are:

- Increased vascular permeability
- Pathological vasoconstriction and vasodilatation
- Loss of thromboresistance and intravascular coagulation
- Profound myocardial dysfunction.

Pathogenesis of Shock Associated with Adrenal Hemorrahge

Shock associated with adrenal hemorrhage is characteristic and different from other septic shock not associated with adrenal hemorrhage. Meningitis associated with fulminant meningococcemia may cause diffuse adrenal hemorrhage without vasculitis and causes clinical manifestation of adrenal crisis called Waterhouse-Friderichsen syndrome (WFS) and may lead to death. An abnormal mass in abdomen, anemia, shock, unexplained jaundice or scrotal hematoma may be presenting features. Less frequently it may occur due to septicemia caused by other bacterial pathogens.

Syndrome of Inappropriate Antidiuretic Hormone

Syndrome of inappropriate antidiuretic hormone (ADH) may occur in ABM causing dilutional hyponatremia.

Applied Pathology

Cerebral Edema and Raised Intracranial Pressure

Direct toxic agents and vasogenic agents released by bacteria and inflammation of cerebral cortex by proinflammatory cytokines produced by host response, causes cerebral edema and ICP. These features are also associated with brain tissue damage. This is the rationale of giving dexamethasone, in early stage of meningitis in an attempt to reduce tissue damage by blocking above mechanism.

Raised ICP may cause reduced cerebral perfusion with impaired consciousness, papilledema and reversible sixth nerve palsy due to pressure effect manifested by convergent squint.

Inflammatory exudate may cause subdural fluid collection (subdural effusion), particularly in meningitis associated with *Haemophilus influenzae* type-B meningitis. Inflammatory exudate may become purulent causing brain abscess (Fig. 89). Purulent exudate collects at base of brain and can block foramina of Luschka and Magendie, resulting in internal hydrocephalus (Fig. 90).

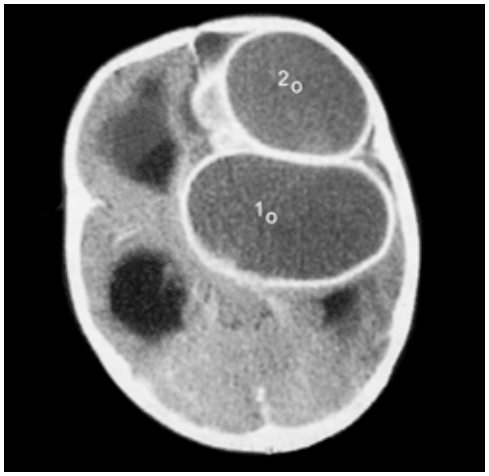


Fig. 89: CT scan of brain abscess following pyogenic meningitis

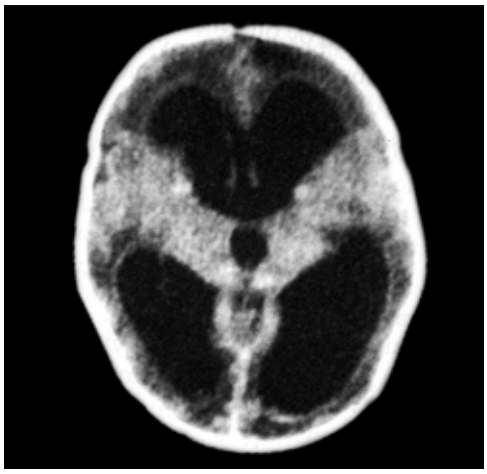


Fig. 90: CT scan of brain. Hydrocephalus (ventriculomegaly) following acute meningitis

Cranial Nerve Palsy, Blindness, Deafness, Hemiplegia

Inflammation of blood vessels (vasculitis) and thrombophlebitis may compromise blood supply to brain with infarction of brain tissue, including cranial nerve like optic nerve and VIII nerve causing blindness and deafness respectively. Brain damage may occur as a result of direct toxic effect of bacteria and more importantly by host immune response, releasing proinflammatory cytokines. Decreased cerebral perfusion as a result of increased ICP, also contributes to brain damage due to cerebral infarction.

Brain Damage

Damage of motor cerebral cortex, internal capsule or pyramidal tract may result in contralateral hemiplegia, meningitis in early infancy may cause CP.

Brain injury may be associated with convulsion and later development of seizure disorder.

Clinical Feature of Acute Bacterial Meningitis

Symptoms

- Triad of fever, headache and neck stiffness
- May be associated with photophobia, irritability and myalgia
- There may be convulsion and impaired sensation (Fig. 91).

Signs

- Meningism with neck rigidity, positive Brudzinski and Kernig sign (Figs 92 and 93)
- Bulging fontanel
- Generalized hypertonia
- Impaired level of consciousness
- Raised BP, due to RICP may be associated with convergent squint due to pressure on sixth nerve (false localizing sign)
- Seizure (30%), cranial nerve signs (15%), other focal neurology (10%)
- Hypotonia with septic shock (particularly with septic shock due to meningococcal infection)
- Petechial/purpuric rash in meningococcus (Fig. 94).

Meningitis in Neonates and Young Infants

Bacterial meningitis in new born and in the first year of life has many atypical features. Neck rigidity and Kernig sign are seldom present.

Fig. 91: Some important clinical features of meningitis

Fig. 92: Testing for meningeal irritation (neck rigidity)

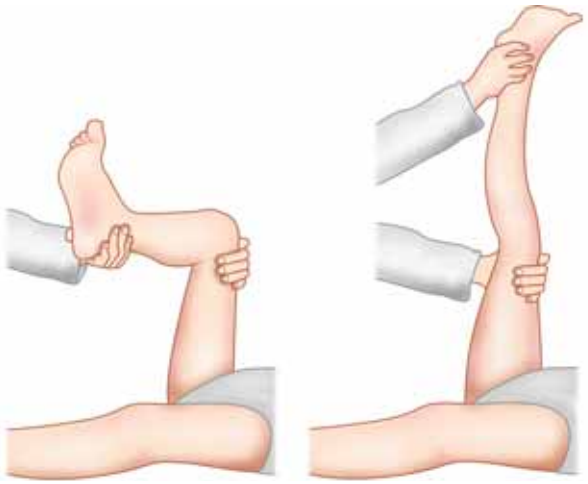


Fig. 93: Testing for meningeal irritation (Kernig's test)

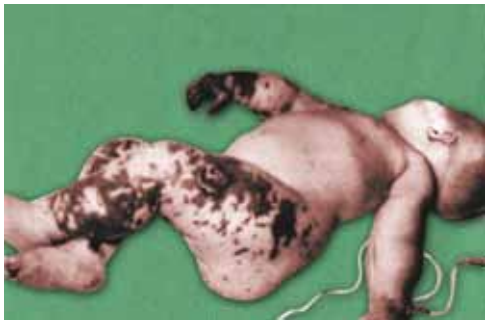


Fig. 94: Meningococcal septicemia with purpuric skin rash with head retraction suggestive of meningitis

Symptoms and signs which arouse suspicion of bacterial meningitis are: (1) presence of sepsis, (2) vacant stare, (3) alternating irritability and drowsiness, (4) persistent vomiting and fever, (5) shock, circulatory collapse, (6) convulsion and neurological defect of various types associated with fever or hypothermia.

Causes of Reappearance of Fever Few Days after Fever Remission

- Drug fever: High dose of antibiotic may cause drug fever
- Intravenous line infection
- Hospital-acquired infection
- Infected subdural effusion
- Complicated by brain abscess
- Vasculitis, thrombophlebitis
- Immune-mediated arthritis, myocarditis.

Causes of Reappearance of Seizure after Initial Seizure Control

- Subdural effusion
- Brain damage due to infarction due to cerebral vasculitis, thrombophlebitis
- Hyponatremia associated with SIADH
- Hypoxic ischemic encephalopathy associated with decreased cerebral perfusion due to RICP and decreased systemic hypotension, associated with concomitant septic shock.

Complication of Acute Bacterial Meningitis

Immediate Complication

- Septic shock
- Cerebral edema
- Raised ICP
- Vasculitis: thrombophlebitis with brain infarction and brain damage
- Subdural effusion
- Cerebral abscess (Fig. 89)
- Hydrocephalus (Fig. 90)
- Syndrome of inappropriate ADH.

Late Complication

- Hemiplegia
- Cerebral palsies, if meningitis occurs in neonate and young infant
- Cranial nerve palsies
- Blindness due to optic nerve damage
- Deafness due to eighth nerve damage, particularly associated with Hib type B infection
- Epilepsy
- Psychomotor delay
- Cognition and learning difficulty (LD)
- Behavior disorder.

Investigations

- Blood
- Complete blood count, ESR, CRP, blood culture.

Lumbar Puncture and Cerebrospinal Fluid Study

Measure pressure and send for microbiological investigations including Gram staining, cytology and biochemistry. The CSF has elevated pressure, is turbid with an elevated cell count, often more than 1,000/mm^3 and mostly polymorphonuclear. Proteins are elevated above 100 mg/dL and sugar in the CSF is reduced significantly to below 50% of blood sugar or below 40 mg/dL.

In partially treated meningitis, CSF may be clear with predominant lymphocytes, culture negative and sugar may be normal.

Rapid Antigen Screen

RAS is done to identify rapidly, the common bacterial infections causing meningitis. Besides being rapid, they are unaltered by previous antibiotic use. RAS can be done not only from CSF, but also from blood and urine.

Polymerase Chain Reaction

Polymerase chain reaction (PCR) helps in the diagnosis of bacterial infection, particularly *meningococcus*. Its significance lies in the fact that it can identify bacterial antigen even when CSF is cleared off bacteria by prior antibiotic use. PCR not only can diagnose the involved bacteria rapidly (4–6 hours) but also can measure bacterial DNA load and disease severity. Successful outcome of meningitis is dependent on aggressive antimicrobial and supportive intensive care treatment. Bacterial DNA load, obtained by PCR can help taking appropriate strategy. PCR is also useful in diagnosing of meningitis caused by herpes simplex, enterovirus and tuberculosis, etc.

Computed Tomography/Magnetic Resonance Imaging

Not done for diagnosis of meningitis. However, if consciousness is significantly altered and/or there are focal neurological signs, it is done to exclude abscess, subdural effusion.

X-Ray Chest/Sinus X-Ray

If clinically indicated.

DIFFERENTIAL DIAGNOSES

Febrile Seizure

Febrile seizure particularly complex febrile seizure may be confused with meningitis and vice versa. Febrile seizure is more difficult to exclude in young infants, particularly below 1 year age, where signs of meningitis are usually absent. Febrile seizure usually occurs between 6 months and 3 years and the child is usually normal in between seizure. In doubtful cases LP and CSF study should be done, which will show normal study.

Meningism

There are some clinical conditions, which are associated with meningism and may be confused with meningitis, for

example upper lobe pneumonia, acute cervical lymphadenitis, retropharyngeal abscess. There are no neurological sign and CSF is normal. Toxemia associated with generalized infection like typhoid fever, so called typhoid encephalopathy may be confused with meningitis.

Viral Meningitis

Clinical presentation may resemble ABM. However, CSF is clear, mild pleocytosis and lymphocytes predominance. Sugar is normal, with mild elevation of protein. PCR may show viral antigen.

Tuberculous Meningitis
(see TB Section in Pediatric Pulmonology in Chapter 9)

Usually insidious and associated with lethargy and low grade fever. Neurological features like convulsion, altered level of consciousness, cranial nerve lesion may be present. However, there may be history of contact with adult tuberculosis and evidence of systemic tuberculosis, with positive X-ray chest finding of pulmonary tuberculosis and positive Mantoux test. CSF is clear and a cobweb coagulation is formed on standing. The cell count is increased but unlike ATM, lymphocyte dominant, and sugar is less diminished than pyogenic meningitis.

Management of Acute Bacterial Meningitis (ABM)

It consists of:

- Aggressive antibiotic therapy
- Symptomatic treatment
- Optimum supportive management including intensive care and nursing care
- Management of complications.

Initial Empiric Antibiotic

- Choice depends on the age of the child, local epidemiology and resistance pattern and local microbiological advice
- Typical regime based on third generation cephalosporin (ceftriaxone or cefotaxime)
- In neonate consider adding aminoglycoside for Gram-negative cover and ampicillin for *Listeria* in endemic area. For avoidance of cholestatic jaundice in neonate ceftriaxone is avoided and cefotaxime or ceftazidime is preferred
- Once the pathogen is identified, treatment can be tailored to known sensitivities
- A combination of ampicillin (200 mg/Kg/day) and chloramphenicol (100 mg/Kg/24 hours) for 10–14 days is also effective as initial empiric choice.

Steroid Therapy

Dexamethasone has been shown to decrease the inflammatory response; decrease ICP and reduce mortality and the severity of both acute and long-term neurological and auditory complications (associated with *H. influenzae* infection). However, anti-inflammatory effect can decrease CSF penetration of certain antibiotics and delay sterilization of the CSF.

Therefore, dexamethasone should be given for short duration and ideally be started before (at least 15 minutes before) the first dose of antibiotic. Dexamethasone in a dose of 0.15 mg/kg IV 6 hourly for 2–4 days is recommended. Steroid is not recommended to treat neonatal meningitis.

Specific Antimicrobial Therapy

Meningococcal and pneumococcal meningitis: Benzyl penicillin 400,000–500,000 units/kg/day, 4 hourly. Ceftriaxone 100 mg/kg/day or cefotaxime 150 mg/kg/day is also effective.

The prevention of penicillin resistance pneumococci (PRP) is rising. Those PRP can also be resistant to β-lactam (cephalosporin) and carbapenem as they will act on penicillin binding protein. The drug of choice therefore is combination therapy with vancomycin.

H. influenzae meningitis: Ceftriaxone IV, 100 mg /kg/day is used as a single agent. Alternatively combination of ampicillin (300 mg/kg/ day, IV, 6 hourly) and chloramphenicol 100 mg/kg/day in four divided doses (6 hourly) may be administered.

Gram-negative rods are most commonly found in neonates and early infancy. Ceftriaxone (postneonatal)/ceftazidime/cefotaxime should be used. An aminoglycoside may be added for better efficacy. Cheaper alternative consists of a combination of ampicillin and aminoglycoside.

Staphylococcal meningitis: Vancomycin IV (40 mg/kg/days) in 3–4 divided doses is the treatment of choice, if methicillin (Methicillin-resistant *Staphylococcus aureus*) or penicillin resistance is suspected.

Listeria: Not common in Indian subcontinent. Commonly found in neonate and early infancy. Ampicillin (300 mg/kg/day, 6 hourly) and aminoglycoside (gentamicin, amikacin or netilmicin) are preferred.

Pseudomonas: A combination of ceftazidime and aminoglycoside is used. Meropenem or cefepime are good broad spectrum agents, useful if above drugs fail.

Duration of Antibiotic Theory

Duration of treatment is 7–10 days. Around 10–14 days treatment may be required in Hib and *Pneumococcus* meningitis. Consider imaging of brain for effusion/empyema. Consider repeat LP.

Symptomatic Treatment

Convulsion (stepwise management): Administer diazepam 0.3 mg/kg (maximum 5 mg) IV or midazolam (0.1 mg/kg).

Buccal midazolam can also be used but not easily available in developing countries.

Phenytoin (18 mg/kg over 30 minutes IV) with ECG monitoring, subsequently 5 mg/kg/day PO or IV until antibiotics are continued.

If persistent seizure: To be managed in pediatric intensive care unit (PICU).

Midazolam is administered at initial loading dose of 0.2 mg/kg IV followed by continuous infusion at 2 µg/kg/minute, with increment of 4 µm/kg/minute every 30 minutes (PICU settings only) till seizure is control. Up to 20 µg/kg/minute or more can be given. Maintenance infusion rate is usually 5–20 µg/kg/minute.

Alternatively:
Thiopentone 4 mg/kg over 2 minutes in intubated patients.

Increased Intracranial Pressure

Clinical features of increased ICP are impaired level of consciousness, systemic hypertension and relative bradycardia, unequal dilated or poorly reacting pupil, focal neurological sings and papilledema (late sign).

Do not attempt LP. Osmotic diuresis with 0.5 g/kg of mannitol as a 20% solution is administered within 30 minutes, every 4–6 hours for a maximum of 6 doses.

If no response:
- Call anesthetist and contact PICU
- Intubation and ventilate to control $PaCO_2$ (4–4.5 KPa)
- Urinary catheter and monitor output
- NG tube.

Management of Hypotension and Septic Shock Associated with Meningitis

Meningitis particularly, due to *Meningococcus* infection is frequently associated with hypotension and septic shock. The mechanism involved is discussed in pathogenesis part of meningitis. Signs of early compensated shock include:
- Tachycardia
- Cool extremities
- ↑ Capillary refill time (>4 seconds)
- Unexplained metabolic acidosis (base deficit >5 mmol/L)
- Hypoxia on arterial blood gas
- Confused state
- Poor urine output
- Hypotension (late sign).

Septic shock associated with adrenal hemorrhage causing clinical manifestations of adrenal crisis called Waterhouse-Friderichsen syndrome (WFS) has been discussed in pathogenesis part of septic shock of this chapter.

Correction:
Oxygen (10 L/minute), bedside glucose.

Volume resuscitation: Pulse boluses of isotonic saline (0.9% sodium chloride) or colloid (4.5% human albumin/gelofusine/hemaccel) 20 mL/kg IV or intra osseus.

Repeat preferably colloid or NS (20 mL/kg) if necessary. Up to 60 mL/kg of fluid can be given in the first hour. Re-evaluate airway, breathing and circulation (ABC) after each bolus fluid resuscitation. However, after 40 mL/kg of fluid resuscitation if shock still persists; than endotracheal intubation and mechanical ventilation will be required to maintain adequate oxygenation and ventilation as pulmonary edema is likely to develop. In addition early elective intubation and ventilation by positive end-expiratory pressure (PEEP) improve the outcome of septic shock and reduces the risk of fatal pulmonary edema.

Inotropes: Dopamine or dobutamine at 10–20 μg/kg/minute. Make up 3 × weight (kg) mg in 50 mL of 5% dextrose and run at 10 mL/hour = 10 μg/kg/minute.

Mild adrenal insufficiency may occur in many children suffering from septic shock. This is, however, different from severe adrenal insufficiency due to adrenal hemorrhage associated with WFS. Such patients are usually not responsive to inotropes and adrenal hyporesponsiveness to endogenous steroid should be suspected. In such cases, use hydrocortisone (1 mg/kg/6 hourly). This is however different from use of hydrocortisone in genuine WFS syndrome where high dose of hydrocortisone should be used. Steroid alone has no role in improving hypotension or shock associated with meningitis or septicemia. Dexamethasone, practiced in early part of meningitis in order to facilitate antibiotic efficacy and to prevent complications of meningitis has no role in improving hypotension associated with septic shock.

Algorithm of Shock Management Associated with Meningitis (In Addition To Appropriate Antibiotic)

- Airway, breathing and circulation and oxygenation (10 L/minute)
- Volume resuscitation
- Fluid bolus preferable colloid or NS (20 mL/kg) and review
- Repeated fluid bolus prefer colloid if necessary
- Observe closely for response/deterioration
- Do not attempt LP.

After 40–60 mL/kg of fluid resuscitation still signs of shock:
- Will require elective intubation and ventilation
- Call anesthetist and contact PICU
- Continue boluses of 10–20 mL/kg of fluid
- Start intubation and ventilation
- Nasogastric tube and urinary catheter
- Add IV inotropes (dopamine, dobutamine)
- Add IV hydrocortisone if adrenal hyporesponsiveness is suspected
- Anticipate pulmonary edema and consider PEEP.

The above mentioned management will depend on availability of facilities. If PICU care is not available send the patient to appropriate center having PICU care with appropriate transport facilities for transfer of sick child.

Management of Shock Associated with Waterhouse-Friderichsen Syndrome

Treatment of adrenal in sufficiency associated with WFS must be immediate and vigorous. In clinical suspicion investigation should be done to measure serum electrolyte, glucose ACTH, cortisol (aldosterone and renin if facilities are available). Intravenous administration of 5% glucose in 0.9% saline solution should be given to correct hypovolumia, hypoglycemia and hyponatremia. If hyperkalemia is severe intrarectal potassium binding resin (kayexalate exelate) or intravenous infusion of glucose and insulin should be given. Unlike septic shock not associated with adrenal insufficiency, high dose of IV hydrocortisone has vital role. Hydrocortisone should be given 4 mg/kg IV 6 hourly for 24 hours with gradual tapering in subsequent dosages. After initial resuscitation cortisol replacement is usually required in most patients. Oral prednisolone (0.5–1 mg/kg/day) may be given. ACTH level may be measured to measure adequacy of glucocorticoid replacement. If mineralocorticoid deficiency is present, fludrocortisone (florinef) is given orally in a dose of 0.1–0.3 mg/kg daily.

Fluid Management of Acute Bacterial Meningitis (ABM)

Do not assume hyponatremia always indicates SIADH. Fluid restriction may further compromise cerebral circulation. So before restricting fluid check plasma and urinary sodium, osmolality and urine output.

Nursing care: Optimum nursing care is essential for holistic management of ABM. The oral cavity, eyes, bladder and bowel should be taken care of. Retention of urine is managed by gentile suprapubic pressure or a hot water bottle. Bed sores are prevented by repeated change of posture in the bed and application of methylated spirit on the skin. Soft foam rubber mattress or cushion is used to prevent pressure on bonny points.

Supportive Care

Supportive care including intensive care is also very important part of management of ABM.

TREATMENT OF COMPLICATIONS

Subdural Effusion and Empyema

Drainage of the subdural space alone with intensive antibiotic therapy.

Hydrocephalus

Ventriculomegaly may occur in the acute phase and generally regresses. Ventriculoperitoneal (VP) or ventriculoatrial shunt is rarely required.

Management of Long-term Complications, Through Follow-Up and Rehabilitation

All cases of bacterial meningitis should be followed up for early detection and management of long-term postmeningitis sequelae like seizure disorder, CP, hemiplegia and other neurological deficits and provide appropriate rehabilitation. Auditory and visual evaluation should be carried out at the time of discharge and 6 weeks later. They should be followed longitudinally for early detection of behavior, cognition disorder and learning difficulties.

New Treatments

Early recognition, antibiotic, prompt treatment of RICP, shock and supportive intensive care are still mainstays of treatment for ABM. Because of the continued high mortality and morbidity, attempts to improve outcome have focused on development of adjunctive treatments that may modulate the inflammatory process. The most promising treatment that has been evaluated includes the antiendotoxin agent protein (bactericidal permeability-increasing protein).

Prevention (Vaccines)

Haemophilus influenzae type-b infection can be prevented by immunizing with Hib vaccine. The incidence and mortality for Hib meningitis is decreasing where Hib vaccines are routinely given to children.

Meningitis due to *meningococcus* can be prevented by giving *meningococcus* AC vaccine. However, it cannot protect from group-B *meningococcus* which is more frequent than A and C, in UK, although there is a recent shift from B to C. Tetravalent (A, C Y, W135) conjugate vaccine now available in Indian subcontinent is effective in preventing invasive meningococcal infections of this serotypes.

Prevention of Pneumococcal Meningitis

Invasive pneumococcal diseases including meningitis were prevented by seven valent pneumococcal conjugate vaccines. In developing countries, some published studies showed that seven valent vaccines may not cover majority of serotypes of *Pneumococcus* in developing countries. PHiD-CV (polysaccharide and nontypeable *H. influenzae* protein D conjugate vaccine, PCV-10) and 13 valent pneumococcal conjugate vaccine (PCV-13) are now available in South Asian countries. It is very promising vaccine in prevention of invasive pneumococcal infections which include meningitis and pneumonia in children of developing countries.

Measles, mumps and rubella (MMR) vaccine can prevent measles, mumps-induced meningitis. Similarly BCG can prevent disseminated tuberculosis including tuberculous meningitis.

Chemoprophylaxis

There are no robust evidences to suggest that prophylactic antibiotic can prevent secondary cases.

However, followings antibiotic can be tried to prevent ABM in household contacts. *H influenzae*, rifampicin 20 mg/kg/day single dose for 4 days.

Meningococcus: 20 mg/kg/days in two divided doses for 2 days.

VIRAL MENINGITIS

- Common cause of meningitis
- Causative agents: Enterovirus responsible for 85% of cases:
  - Echovirus
  - Coxsackie virus
  - Poliovirus
  - Mumps virus.

CLINICAL FEATURES

- Fever, headache following flu-like illness
- Not toxic look
- Drowsiness uncommon.

Look for other clinical features to give clue to etiology, e.g. in mumps: parotitis, orchitis; in echovirus, conjunctivitis, myopathy; Coxsackie: Hand, foot, mouth disease, myocarditis pericarditis; Polio: typical paralysis follows febrile condition.

CEREBROSPINAL FLUID FINDINGS

- WBC: 10–1,000 (usually < 300 Í 106/L)
- Lymphocytes mainly but may be neutrophilic in first 48 hours of illness
- Protein: Normal or mildly elevated (0.5–1 g/L)
- Glucose: Normal, but may be decreased in mumps meningitis

Blood count, FBC: Normal, CRP: Normal or mildly elevated, serum amylase increased in mumps infection.

DIFFERENTIAL DIAGNOSIS

- Partially treated bacterial meningitis
- Tuberculous meningitis
- Febrile seizure
- Collagen vascular disease
- Autoimmune disease.

TREATMENT

Supportive, usually full recovery within 2 weeks.

Encephalitis

Encephalitis is defined as an inflammatory process of the CNS with dysfunction of brain. Encephalitis is most commonly viral. Viral encephalomyelitis is usually associated with aseptic meningitis. Viral encephalitis is classified as:

- Acute viral encephalitis
- Postinfections encephalomyelitis

- Slow virus infection of CNS, subacute sclerosing panencephalitis long after flowing measles infection.

Acute Viral Encephalitis

Most common cause in children is HSV-1 mostly

Other causes include:

- Herpes virus: Herpes zoster, or Varicella Zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes virus (HHV-6).
- Measles, mumps and rubella virus
- Arbovirus: Japanese B encephalitis, West Nile encephalitis, tick born encephalitis
- Rabies.

Clinical Features of Encephalitis

Fever, headache and altered level of consciousness. There may be focal neurological signs like ocular palsies, hemiplegia and speech problem. It may have insidious onset with abnormal behavior that can be mistaken for psychiatric illness.

Few important and common viral encephalitis are considered further.

VIRAL (MENINGO) ENCEPHALITIS

Herpes Simplex Encephalitis

- Herpes simplex 1 (HSV1) and herpes simplex 2 (HSV2) are most commonly involved
- Herpes simplex 1 most commonly involved after neonatal period
- Among various infections caused by HSV1, encephalitis is uncommon
- However, Herpes simplex encephalitis (HSE) is the most common cause of viral encephalitis in western countries but globally Japanese encephalitis (JE) virus is most frequently involved
- Beyond the neonatal period majority of cases are due to HSV1
- One-third primary infection two-third reactivation
- In neonate HSV2 is the most common and is blood born causing multiorgan infection and diffuse encephalitis
- Herpes virus cases fulminant hemorrhagic and necrotizing encephalitis with severe edema and necrosis particularly in temporal lobe.

Clinical Features

- Age: One-third HSE occurs between 6 months and 20 years.

Acute or insidious onset with:

- Headache, fever, reduced consciousness
- Focal neurological sign primarily temporal lobe neuro-ogical sign and symptom.

Differential Diagnosis

- Other intracranial infections, meningitis, brain abscess
- Acute disseminated encephalomyelitis
- Noninfectious encephalopathy: Metabolic disorder, traumatic brain injury.

Diagnostic Investigation

Unfortunately diagnostic investigations are normal in early stage when treatment is most effective.

Cerebrospinal fluid finding:

- Similar to other viral meningitis but may get normal in first 48 hours of illness. Lymphocytic pleocytosis
- Protein may be up to 6 g/L
- Polymerase chain reaction of CSF: Viral DNA/RNA. Diagnostic method of choice with sensitivity and specificity more than 95% but may be negative if LP is done less than 48 hours or more than 14 days after onset of illness.

Neuroimaging:

Reveals abnormalities after 3–5 days:

- Cranial CT scan: Low density area of mass effect localized to temporal lobes (Fig. 95)
- Magnetic resonance imaging of brain: T2-weighted MRI—Abnormal signals from temporal lobe. Insular cortex, frontal lobes and cerebellum may be involved.
- Electroencephalography: Defuse slowing of the background, focal abnormalities and later characteristic periodic lateralized epileptiform discharge may appear which is diagnostic (Fig. 96).

Treatment

Treatment should be started earlier if HSE is a diagnostic possibility as it is effective if given in early viral replication phase.

Acyclovir 10 mg/kg IV 8 hourly for 21 days if HSV infection is confirmed to prevent relapse.

Other treatment: Treat seizure, RICP and other complication.

Prognosis: Two-third of survivors have significant sequelae.

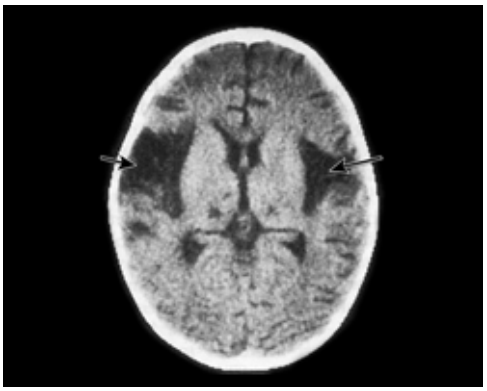


Fig. 95: Herpes simplex encephalitis: The CT scan shows gross atrophy loss of neural tissue in the temporoparietal regions (arrows)

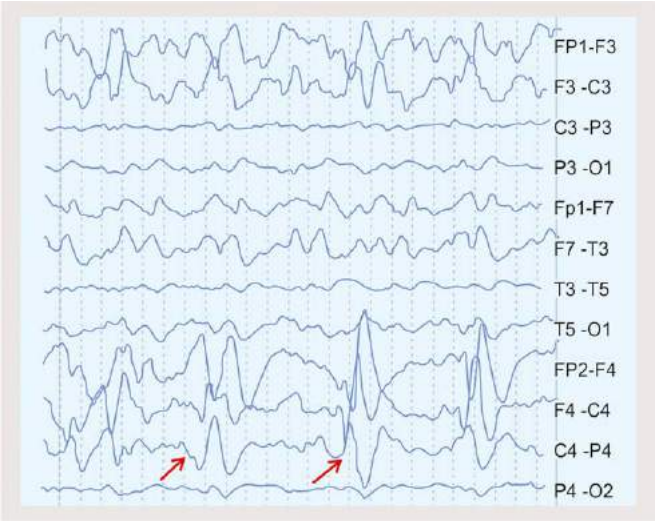


Fig. 96: Periodic lateralizing epileptiform discharges in HS E

JAPANESE ENCEPHALITIS

Japanese encephalitis is a vector born viral disease (*flavivirus*) that occurs in South Asia, South East Asia, East Asia and Pacific. The annual number of human death is 10,000–15,000 and estimated global impact from JE in 2002 was 7,09,000 disability adjusted life years (DALY's). The disease can cause irreversible neurological damage.

EPIDEMIOLOGY

Virus: Zoonotic *flavivirus* requiring a bite from an infected mosquito to produce human encephalitis.
Vector involved: Mosquito Culex-Culex tritaeniorhynchus.

Virus reservoir: Wadding water birds (e.g. herons and egrets) pigs, horse, donkeys and human.

Japanese encephalitis outbreaks: Monsoon and post monsoon (July, August) associated with rainfall, rice cultivations.

Endemic countries: India (Uttar Pradesh, Andhra Pradesh, Maharashtra, Assam), Nepal, Thailand, Indonesia, Malaysia, Philippines, Vietnams and Sri Lanka.

CLINICAL COURSE

- Asymptomatic and mild form
- Symptomatic:
  - Common age: 5–15 years
  - Nonspecific febrile illness (fever, nausea, headache)
  - Encephalitis manifests as:
    - Altered sensorium, seizure, focal neurological deficit
    - A wide variety of movement disorder (Parkinsonism features)
    - Thalamic involvement manifested as-

  Dystonia (most important clinical features)
  Restricted eye movement, opsoclonus.
  On examination: Cogwheel rigidity
- Recovery of consciousness:
  - Frequently followed by Parkinsonism features (tremor, bradykinesia, postural instability)
  - Marked axial dystonia (opisthotonus, teeth clenching, oculogyric crisis) (Fig. 97).

LABORATORY INVESTIGATION

Diagnosis: Mainly done by IgM, antiJE, antibody in CSF of patients.

Detection of virus in CSF by reverse transcription PCR.

Fig. 97: Oculogyric crisis in a child with encephalitis (suspected Japanese encephalitis)

Radiological Finding

- Radiological changes mainly restricted to thalamic region
- CT and MRI of brain
- High intensity lesion on the thalamus and basal ganglia giving the appearance of pediatric autoimmune, neuropsychiatric disorders associated with streptococcal (PANDA) (giant PANDA sign) (Fig. 98).

DIFFERENTIAL DIAGNOSIS

- Bacterial meningitis
- Other viral encephalitis (herpes)
- TB meningitis
- Cerebral malaria
- Acute disseminated encephalomyelitis.

Therapy

- No specific antiviral therapy is currently available
- Management is symptomatic and supportive
- Seizure control by anticonvulsant
- Management of increased ICP (fluid restriction, mannitol)
- Treatment of Parkinsonism
- Fluid and electrolyte balance
- Nutrition management: Proper feeding
- Nursing
- Monitoring: Glasgow coma scale (GCS) monitoring.

PROGNOSIS

- Mortality due to JE is 20–30%
- Neurological sequelae:
  - 20–25% moderate
  - Up to 30% severe.

PREVENTION

- Environmental management for vector control:
  - Alternate wetting and drying rice field (intermittent irrigation)
  - Chemical control (insecticide): Organophosphorus, pyrethroids only marginally effective. Insecticidal resistance develop quickly
- Vaccines: Main pillar of JE control is multiple vaccines
  - Live attenuated vaccine for human—two types:
    - First type: Yellow fever derived chimeric vaccine
    - Second type: Attenuated SA 14–14-2 virus strain

  Two doses, first at 9 months, second dose 16–18 months.
  Efficacy with two doses: 50–80%.

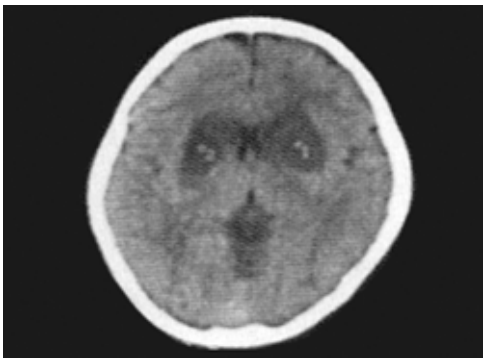


Fig. 98: CT scan of brain of a child suffering from Japanese encephalitis showing bilateral hypodense basal ganglia with giant PANDA sign

ENCEPHALOPATHIES

The term encephalopathy implies cerebral dysfunction due to circulating toxins, poisons, abnormal metabolites or intrinsic biomedical disorders affecting neurons but without inflammatory response.

Etiology of Encephalopathies

- *Postinfections*: Typhoid, *Shigella*, malaria, Reye syndrome
- Hypoxic ischemic encephalopathy: Following prolonged seizure, cardiorespiratory arrest
- Acute disseminated encephalomyelitis, heat hyperexia postvaccinal, allergic
- *Metabolic:* Diabetic acidosis, uremic coma, hepatic coma, bilirubin encephalopathy of newborn, inborn error of metabolism.
- *Fluid and electrotype disturbance:* Hypernatremia, hyponatremia, water intoxication, alkalosis, acidosis.
- *Toxic:* Heavy metals (lead, mercury, arsenic), insecticides, malignancies.

Clinical Manifestations

Clinical features are frequently similar to encephalitis due to inflammation of brain. However, clinical features of underlying cause may be obtained by taking careful history and clinical examination. Every effort should be made to arrive at precise underlying etiology, account of recent illness or exposure to toxins. One should look, whether the child is suffering from treatable course like the typhoid encephalopathy, *Shigella* and malaria. Also take history, whether the child is a known diabetic or has been suffering from hepatic or renal disorder or inborn error of metabolism.

Diagnosis

Serum electrolyte, blood sugar, urea, blood ammonia, liver enzymes, prothrombin time, metabolic screening, serum lactate and urine analysis should be done. LP and CSF study should be done if there is no evidence of RICP. The CSF fluid is examined biochemically, cytologically and for viral and bacteriological culture to exclude possible meningoencephalitis. Toxicological studies should be done in suspected cases. Serum lead level should be estimated if there is a possible exposure of the child to lead contained environment.

Demyelinating Diseases Mimicking Encephalopathy or Encephalitis

Acute Disseminated Encephalomyelitis

- Demyelinating disease, which includes ADEM is relatively common in pediatric neurological practice
- Typical ADEM affects young children with peaks in toddles often severe and at 7–10 years
- Usually there is a significant encephalopathy component with confused or drowsy state with seizure (Fig. 99)
- Bilateral optic neuritis may occur
- Cerebrospinal fluid is usually normal, or may show mild pleocytosis, mildly elevated protein
- Magnetic resonance imaging (with enhancement) may show multiple hypodense areas in white matter of brain and spinal cord (Fig. 100).

Fig. 99: A child with acute disseminated encephalomyelitis with impaired sensorium

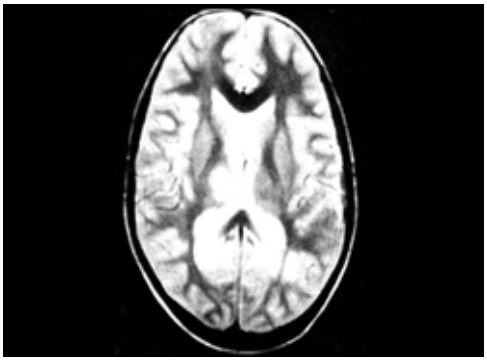


Fig. 100: Magnetic resonance imaging of acute disseminated encephalomyelitis showing a multiple large confluent centrifugal white matter lesion

Nonencephalopathic Demyelinating Disease

Other demyelinating diseases are multiple sclerosis (MS), optic neuritis, neuromyelitis optica, Schilder's disease. They do not fall under differential diagnosis of encephalitis or encephalopathy.

Multiple Sclerosis

- Usually occurs in older children (> 10 years)
- Usually spontaneous onset, no preceding infection
- Sings are often white matter related with spasticity and weakness
- Unilateral blurring vision with unilateral optic neuritis
- Multiple sclerosis has relapsing and remitting nature
- Radioimaging usually shows more discrete areas of demyelination with periventricular lesion.

Prognosis: Risk of relapse with age of onset more than 10 years.

OTHER DEMYELINATING SYNDROME

Optic Neuritis

- Marked visual impairment with orbital pain
- Typical age is more than 7 years
- Fundoscope showing optic disk swelling (bilateral), may be mistaken for papilledema
- Visual evoked potential is abnormal
- Recovery of VA usually occurs in 75% of cases
- Steroid therapy may shorten the time of recovery.

Neuromyelitis Optica (Devic's Disease)

Relapsing bilateral optic neuritis with myelitis. A specific NMD antibody has recently been identified (detectable in serum and CSF) that distinguishes Devic's disease from multiple sclerosis (MS).

Transverse Myelitis

Acute disseminated encephalomyelitis-like process confined to one or more segments of the spinal cord resulting in acute or subacute onset signs of severe spinal cord dysfunction often with prominent painful sensory disturbances like paresthesia leading to sensory loss. The child may present as initially as acute flaccid paralysis (AFP) with sphincter disturbance. It may resemble GBS. All children will require MRI to exclude surgically remediable cause of cord compression.

Treatment is typically high dose methylprednisolone and rehabilitative spinal care.

Treatment of Demyelinating Diseases as a Whole

Acute

Steroids appear to hasten the rate of recovery. However, there is no evidence to suggest that steroid affects the long-term prognosis and relapses risk. Pulsed methylprednisolone and/or few weeks of oral prednisolone are often used in the acute phase, particularly in ADEM.

Immunomodulatory Drugs in MS

Treatment options:

- Interferon β. Reduce the relapse rate
- Azathioprine
- Mitoxantrone.

NEURODEVELOPMENTAL DISORDER

DEVELOPMENTAL DELAY

Cerebral Palsy

Cerebral palsy is a group of disorders of the development of movement and posture causing activity limitation that are attributable to nonprogressive lesion of developing fetal or infant brain. Although the lesion is fixed, the clinical manifestations emerge overtime in the early years of life as child development is dynamic and different movement patterns are acquired later. Thus an affected infant is often floppy and hypotonic up to age of 6 months and then become hypertonic. Cerebral palsy is the most common cause of motor impairment in children.

Although CP emphasizes motor deficit but associated problems of hearing, vision and cognitive function are common.

ETIOLOGY, RISK FACTORS AND PATHOLOGY

Multiple etiologies and risk factors often interact, hence the term, causal pathway to describe complex process. Causal mechanisms by which the developing brain may be damaged are well recognized and include hypoxia-ischemia infection, inflammation and bilirubin toxicity.

Ascertain risk factors by taking careful history including antenatal and birth history (discussed under the head history taking), examination and investigation, particularly MRI (discussed under the head examination and investigation).

It is useful to categorize the causes of CP into prenatal perinatal, postnatal and postneonatal.

Prenatal (Maternal/Fetal/Placental)

Intrauterine infections with TORCH infections

Chorioamnionitis: Ascending infection may trigger a fetal immune response causing inflammation which damage the fetal brain and initiate premature labor.

Placental insufficiency:

- Maternal diseases, like UTI, hypertension
  Multiple pregnancy: As a risk factor this increases the likelihood of low birthweight and preterm birth.
- Small for gestational age.

Perinatal

Premature delivery: 20% of children with CP are born at less than 32 weeks. Rates are markedly increased in extreme prematurity (<25 weeks), higher in boys. Preterm infants are especially vulnerable to brain damage from PVL secondary to ischemia and/or severe IVH. The rise of survival of extremely preterm infant has been accompanied by an increase in survivors with CP.

Birth asphyxia: Perinatal hypoxic-ischemic brain damage accounts for 15% of cases of CP in infants born in term, although, it is difficult to exclude a contribution from prenatal factors.

In developing countries the documentation of birth asphyxia is difficult as most deliveries are domiciliary. However, it is an important preventable cause of CP.

Ascribing CP to perinatal asphyxia or hypoxic ischemic encephalopathy has medicolegal implications. To provide strong evidence in favor of perinatal asphyxia causing CP, the following factors will help:

- History of moderate to severe neonatal encephalopathy (Sarnat grade II and III)
- Near term (>34 weeks) delivery
- Neuroimaging showing diffuse cortical atrophy
- Cerebral palsy of spastic quadriparesis or dyskinetic type
- Umbilical artery acidosis (Ph <7.0 and base deficit >12 mm/L), or fetal scalp/early newborn acidosis of similar degree.

In combination of any of the following:

- Abnormal fetal heart rate on tachograph
- Difficult delivery or history suggestive of hypoxemic event around the time of labor. More relevant to home delivery in developing countries
- Low APGAR score (<7 at 5 minutes)
- Need for resuscitative measure at delivery.

Hyperbilirubinemia with kernicterus (bilirubin encephalopathy): It is an important cause of CP in developing countries. Dyskinetic CP is more associated with kernicterus.

Other important perinatal causes:

- Neonatal meningitis
- Perinatal cerebral hemorrhage causing hemiplegic CP
- Perinatal thrombophlebitis.

Postneonatal (During Infancy)

- Intracranial infections: Meningitis encephalitis
- Traumatic injury of brain: Accidental, nonaccidental injury (NAI)
- Hypoxic ischemic encephalopathy

- Hemorrhagic stroke
- Post-cardiopulmonary arrest.

Classification of Cerebral Palsy

It can be classified, based on:

- Dominant movement disorder and limb movement (classic pattern)
- In relation to clinical care or multiaxial classification
- Severity of CP (mild, moderate and severe).

Classic Patterns

It is a useful classification for epidemiology but inadequate for clinical care.

Spastic hemiplegia (33–38%): Upper limb predominant.

Spastic diplegia (35–43%): Lower limb predominantly affected. Majority occurs in preterm infants caused by damage to periventricular white matter which carries the fibers for motor cortex of lower limbs.

Spastic quadriplegia (6%): Spasticity of all four limbs and associated with severe cognitive defect. Associated with severe prolonged intrapartum asphyxia in term infants.

Dyskinetic (dystonic and athetoid, 7–15%): Selective damage to basal ganglia may occur in term infants, with severe short-lived asphyxia, leading to athetoid CP. Choreoathetosis associated with bilirubin encephalopathy is rare in industrialized countries, but still not uncommon in developing countries. Dystonia when present as an important component of hypertonicity along with spasticity in spastic CP, however, is not considered as dyskinetic CP.

Ataxic CP

Most of these infants are born in term and have genetic disorders, often associated with cerebellar hypoplasia.

Multiaxial Classification

This helps routine clinical care, facilitates communication, guides investigations and helps progression. Each of the following axes are evaluated and recorded and utilized in clinical care.

Type of movement disorder: Records not only presence of spasticity but the often under-recognized concurrent dystonia, dyskinesia, athetosis and ataxia.

- Pattern of anatomical involvement:
  - Body part involved, degree of symmetry
  - Severity of motor impairment: Quantify spasticity, strength, contracture deformity, coordination.
- Comorbidities: Learning disability, visual and hearing impairment, epilepsy
- Functional abilities of daily living: Transfer, self-care, etc. Standard measurement tools are available
- Known etiology and risk factors: Nature and timing, prenatal, perinatal and postnatal
- Known neuroimaging findings: White matter injury, cerebral malformations, etc.

DIAGNOSTIC APPROACH OF CEREBRAL PALSY (CP)

Take relevant antenatal, perinatal and postnatal history like preterm delivery, history suggestive of perinatal asphyxia (delayed cry, significant resuscitation measure at birth), severe neonatal jaundice requiring exchange transfusion, history of intracranial infection in neonate and early infancy, etc.

Clinical features depend on type, stages and at what age the patients have presented; the earlier the diagnosis and management, the better is the prognosis. Therefore, it is better to pick up patients as early as possible. Although, CP cannot be diagnosed confidently in neonates and early infancy, at risk infants should be closely monitored and followed up.

In Neonatal Period (Clinical Features Indicating Risk of Developing CP)

Risk groups: Birth asphyxia, LBW and preterm babies; Neonatal meningitis, highly jaundiced patients.

Abnormal behavior in neonates: Poor cry, poor activity, abnormal respiration with apnea or irregular respiration, seizure.

Hemisyndrome: Asymmetric tone, asymmetric reflexes, "asymmetric power (not moving on one side of extremities)". About 10–20% of hemisyndrome neonates, later come out as CP. Clues to detect CP are the followings:

Postneonatal and Early Infancy

- 3 months: Does not lose grasp reflex and hands are not open. Cannot hold a rattle placed in hands and play with it.
- 4 months: Cannot release following grasp reflex.
- 5 months: Cannot reach out to catch object.
- 6 months: Do not develop manipulative skill.
- 6–12 months: Equinus tendency in the leg, tendency of crossing (scissoring) at lower limb (Fig. 101).

Overperformance or persistent neonatal or primitive reflexes: Palmer grasp, planter grasp, Moro reflex, ATN reflex, gallant reflexes, Perez reflexes, etc. (Figs 102A to C).

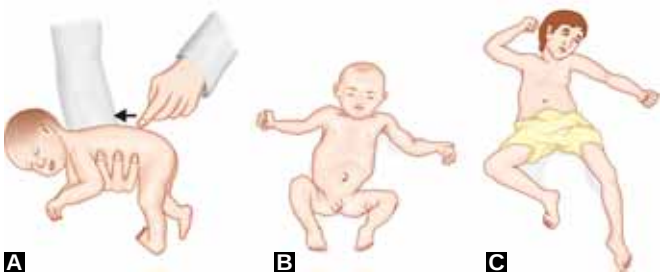
Absence of normal reflexes: Landau reflexes, righting reflex, parachute reflexes (protective reflexes) like lateral, vertical and downward parachute reflexes, at 6 months, 9 months and 12 months respectively (Fig. 103).

ESTABLISHED CEREBRAL PALSY

Presentation depends on type of CP.

- Spastic CP: This variety is mainly hemiplegia and diplegia.
- Hemiplegic variety usually present as hemisyndrome in neonate. Posture: Attitude of flexion. Gait: Hemiplegic gait

Fig. 101: Picture showing scissoring at lower limb



Figs 102A to C: Figure showing overperformance and persistent galant, Moro and ATN in cerebral palsy (A) Galant reflex; (B) Moro reflex; (C) Asymmetric tonic neck reflex in CP

Figs 103A and B: (A) Normal; (B) Absent Downward parachute reflex in cerebral palsy

Fig. 104: Picture showing left-sided hemiplegic cerebral palsy with flexion of upper limb and tip toe walking (hemiplegic gait)

with tip toe walking. Planter reflex: Babinski positive with flexor withdrawal. Affected hand remains fisted even after one year. Distal part limb more affected than proximal. Defective volitional skill and fine motor movement, therefore, more affected like splaying of hand in reaching an object. Upper limb in a state of flexion (Fig. 104) and lower limb in a state of extension. Hand hyperpronated with pronator catch. Feet: Equinovarus deformity.

- In subtle (occult) hemiplegia, Fog's test and pronator drift test should be done to detect the affected limb.
- In "Fog's test" when the child is asked to heel-walk, toe-walk or walk on inverted or everted feet, the child will show exaggerated movement and posture of upper affected (nondominant) limb (Figs 105A to D).

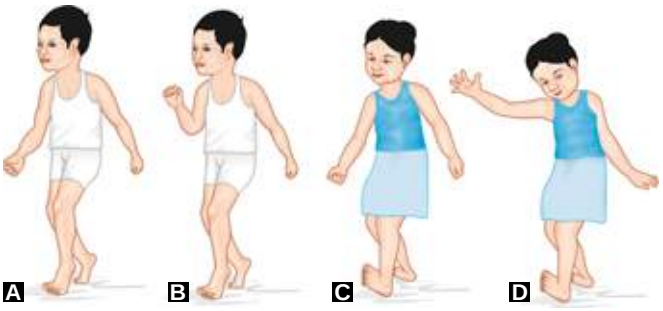
PRONATOR DRIFT TEST

In pronator drift test when the child is asked to stretch out his/her upper limbs up, the affected upper limb will be flexed at elbow and pronated at wrist (Fig. 106).

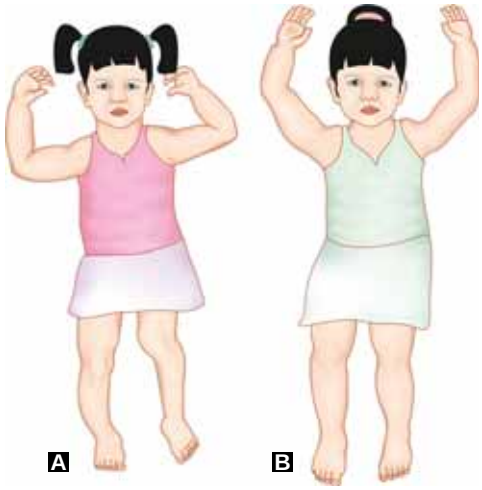
In diplegic CP, both lower limbs are more spastic than upper limb. Spasticity causing scissoring of lower limbs (Fig. 107).

In spastic quadriplegia the posture takes crouched position (Figs 108A and B).

Plantar reflexes are extensor in all spastic CP and deep reflexes are exaggerated, in all varieties of spasticity.

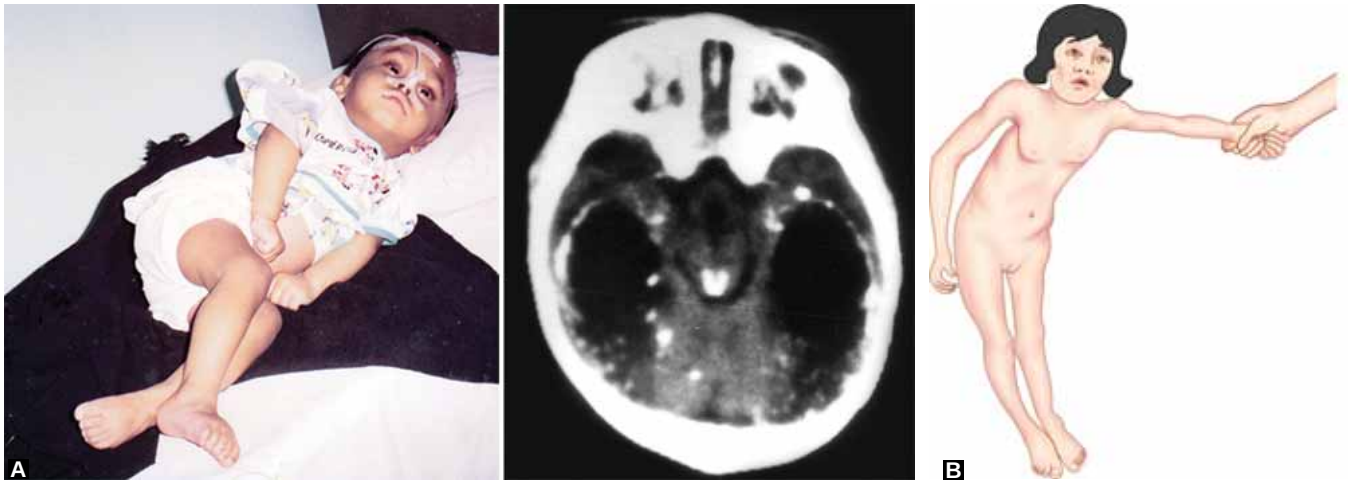


Figs 105A to D: Fog's test in different ways. (A) A boy with occult right-sided hemiplegia showing normal posture while walking. The same child; (B) Showing exaggerated movement and posture of right upper limb when asked to walk with inverted feet suggestive of right-sided hemisyndrome (hemiplegia); (C) Showing a girl walking normally on heel; (D) Showing another girl with exaggerated movement and posture of right upper limb when asked to walk on heel, a positive fog's test suggestive of right-sided hemiplegia



Figs 106A and B: (A) Showing positive pronator drift test with flexion at elbow and hyperpronation of left wrist in comparison to right, suggestive of left-sided hemiplegia. The normal child; (B) Showing no such abnormality

Fig. 107: Diplegic cerebral palsy showing scissoring of lower limbs



Figs 108A and B: (A) Showing spastic quadriplegia with scissoring of lower limbs and fisting of both hands in a child with congenital cytomegalovirus infection. The CT scan showing enlarged ventricles and periventricular calcification; (B) Picture showing wind swept deformity and crouched position due to spastic quadriplegia

Tone is increased in spastic CP: Increased tone may cause contracture deformity. Quantify and measure fixed deformity of joints. Quantitative measurement of tone (modified ashworth) is discussed under the head neurological examination . Tone should be elicited by both rapid stretch and slow stretching maneuver at joints, preferably at knee joint to differentiate between phasic and tonic spasticity (discussed under the head neurological examination).

Elicit deep tendon reflexes: Hyperreflexic deep reflexes are elicited. Look for cross hyperreflexia with cross adduction (Fig. 109) and for extended afferent (discussed under the head neurologic examination).

Look for contracture deformity of joints both for positional and fixed deformity. If fixed deformity is present measure the degree of deformity, to assess severity and for management purpose (Fig. 110).

There is usually concomitant dystonia along with spasticity and one may dominate other. It is important to assess distonic element for management purpose which includes physiotherapy and drug therapy (Table 13).

In ataxic cerebral palsy (10% of CP): The patient may present with following features:

- Floppy baby with hypotonia
- Increased joint angle with positive Scarf sign, hyper–extension of joints (knee more than 9° extension, elbow more than 10° extension).
- Poor head control.
- Tendon reflexes: Pendulous.
- Walking delayed up to 1–12 years.
- Poor balance with broad-based staggering gait with arm swaying out like walking on balancing pole (Fig. 111A).
- In subtle ataxic (truncal) gait: Ataxia can be demonstrated by Tandem test (walking on a straight line, with hand folded in front of chest) which the patient cannot perform smoothly (Fig. 111B).

Volitional ataxia can also be demonstrated, in these patients by eliciting intention tremor, past pointing dysmetria, dysdiadochokinesia, etc. (Fig. 112).

It should be remembered that to diagnose ataxic CP, ataxia must be chronic and nonprogressive in addition to their disorder of movement posture and tone which is due to nonprogressive lesion of immature brain. If ataxia is progressive then alternate diagnosis (neurodegenerative disease) should be considered.

TEST FOR VOLITIONAL ATAXIA

In dyskinetic CP (10% of CP): Patient usually passes through initial neonatal hypertonic (opisthotonus) phase followed by hypotonic, dystonic and later stage of nonprogressive involuntary movement (dyskinetic) phase. If, however, progressive dyskinesia is present then it will fall under diagnosis of neurodegenerative disorder (Fig. 113).

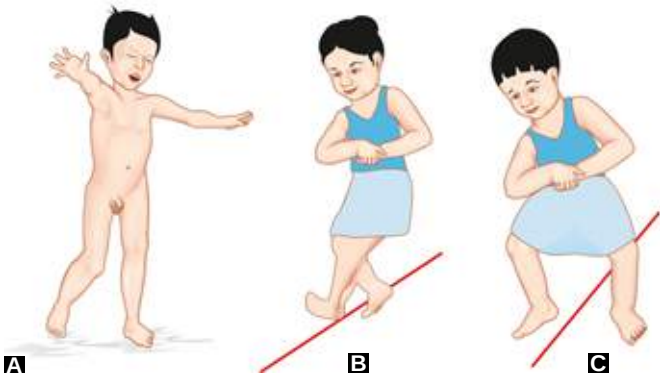
Fig. 109: Spastic cerebral palsy child showing cross adduction of right lower limb due to hyperreflexic left knee jerk

Fig. 110: Measuring range of joint movements and fixed flexion deformity of knee joint by goniometer

Table 13: Clinical features to differentiate between dystonic and spastic phase of hypertonic cerebral palsy (Characteristic features of dystonic and spastic CP)

Dystonic (extrapyramidal)	Spastic (cortical)	
1. Appearance and duration: Usually present up to 7–8 months but may persist for long time	1. Appears usually after 7 months	
2. Nature of hypertonicity: Cogwheel type hypertonicity	2. Spastic	
	Phasic	Tonic
	Clasp-knife type (Hypertonic with rapid stretch)	Led pipe type (Hypertonic on slow stretch)
3. Tone: Velocity independent, but varies with posture, emotion or exertion	3. Tone: Velocity dependent, but not varies with posture, emotion or exertion	
4. Posture: In a state of extension	4. Posture: Flexion, adduction and internal rotation (lower limb). Flexion and hyperpronated upper limb	
5. Primitive reflexes: Persistent primitive reflexes more common, particularly ATN, Moro, Galant, Perez reflex and overperformances of stepping and placing reflex	5. Less common	
6. Deep reflexes: Mildly exaggerated, no clonus	6. Greatly exaggerated, particularly in phasic spasticity. Clonus present Moderately exaggerated in tonic spasticity. Clonus present	
7. Deformity: Usually no fixed deformity	7. Present more in tonic spasticity. Scissoring of lower limb (Bilateral adductor spasm). Dislocation of hip, equinovarus (fixed) deformity of lower limb	
8. Plantar: Extensor withdrawal (extended at knee)	8. Flexor withdrawal (flexion at knee) but positive Babinski.	

Abbreviation: ATN, acute tubular necrosis.



Figs 111A to C: Test for truncal ataxia. (A) Ataxic child walking with broad-based staggering gait with poor control; (B) Showing ataxic CP child unable to walk on straight line with upper arm folded in front of chest (Tandem test); C) A normal child walking smoothly on straight line

Fig. 112: Ask the child to touch a finger or toy with his finger. He cannot perform smoothly and may show tremor before touching (intention tremor)

In addition to choreoathetosis, other important features of dyskinetic CP are persistent feeding difficulty, deafness (post-kernicterus) and poor dentition (Fig. 114).

Fig. 113: Dyskinetic child showing dystonic hyperextended neck and extended right elbow and stiff hand

Association of Cerebral Palsy

- Cognitive impairment
- Epilepsy
- Visual impairment
- Hearing loss
- Speech disorder
- Behavior disorder, psychiatric problem
- Orthopedic deformity.

Prevention

- Prevention of prematurity by appropriate antenatal and perinatal care

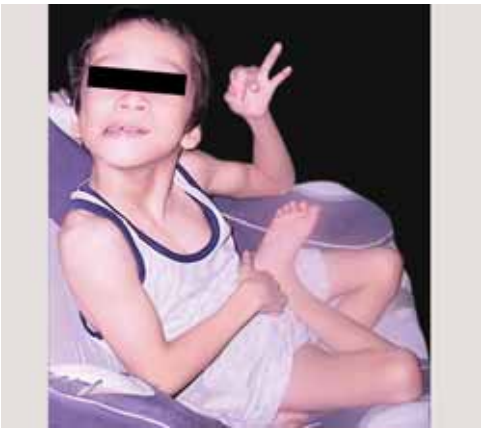


Fig. 114: Dyskinetic cerebral palsy showing choreoathetoid movement

- Prevention and optimum management of birth asphyxia
- Adequate and optimum treatment of neonatal septicemia, meningitis, seizure
- Prevention and optimum treatment of hyperviscosity, dehydration
- Prevention and optimum management of biochemical abnormality—hypoglycemia, hyponatremia, etc.
- Vaccination with Anti-D to Rh-negative mothers
- Exchange transfusion with significant hyperbilirubinemia
- Prevention of congenital rubella by combination vaccines (containing rubella vaccine like measles and rubella (MR), measles, mumps and rubella combinations vaccine (MMR).

Investigation

Investigations are done to determine etiology and exclude alternate diagnosis. Investigations may include:

Cranial ultrasound: Helpful in early neonatal period to identify IVH, HIE (Fig. 115).

Cranial CT: Identifies small congenital malformation, hemorrhage, periventricular leukomalacia. Intracranial calcifications associated with TORCH infections are better identified by CT than MRI (Fig. 116).

Cranial MRI: Optimal modality for older children as it defines cortical and white matter abnormalities and myelination at high resolution.

Normal brain imaging does not exclude CP but suggest pursuit of a metabolic or genetic etiology.

Electroencephalography: If seizures are suspected.

Karyotyping: To exclude chromosomal abnormalities.

TORCH screen: Congenital infection.

Metabolic: Plasma amino acid, urine amino acid and organic acid

Lysosomal enzyme study: To exclude enzyme positive neurodegenerative and storage disorders.

Thyroid function test and creatine phosphokinase: If relevant as a cause of developmental delay.

Nerve conduction study: Hereditary neuropathy can present as toe walking and tight tendo-Achilles.

Cerebrospinal fluid study: Cerebrospinal fluid lactate (if mitochondrial disorder is suspected). CSF glycine (in intractable neonatal seizure in nonketatic hyperglycinemia).

Role of MRI of Brain

This is the single most useful investigation, recommended for children with CP, particularly term infants. MRI brain lesions have diagnostic and prognostic implications. Some important MRI findings associated with CP and its clinical significance are mentioned below:

Periventricular leukomalacia: MRI with FLAIR (fluid attenuated inversion recovery) where CSF signal is specifically suppressed shows typical features of PVL. PVL is occasionally reported after perinatal ischemic injury at-term, causation is not established.

Irregular lateral ventricle enlargement and reduced white matter thickness, particularly seen posteriorly, clinically associated with lower limb predominant spasticity (spastic diplegia). There is predominant dystonia in some preterm infants. Epilepsy is less common than in cortical lesions. Assess for visual impairment and specific learning disorders.

Porencephaly: This is a focal periventricular cyst, a remnant of fetal/neonatal periventricular hemorrhage. Timing of cerebral insult is at-term and in late gestation.

Delayed myelination, hypomyelination: Usually nonCP causes leukodystrophy, neurometabolic disorder (biotinidase deficiency, menkes, etc.).

Hypoxic ischemic encephalopathy: Characteristically causes an early high T_2 signal and later atrophy in the putamen and thalamus (Fig. 117).

Cystic encephalomalacia (Fig. 118): Multiple subcortical cyst and gliosis occurs with increased T_2 signal in remaining white matter. There is separation in the cyst. This suggests perinatal injury near term, or early postnatal injury.

Significant cortical atrophy (Fig. 119): A thin cortex/subcortex results in compensatory ventriculomegaly with deepening of

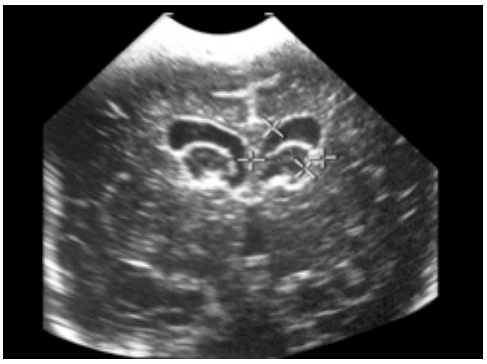


Fig. 115: Cranial ultrasound showing intraventricular hemorrhage

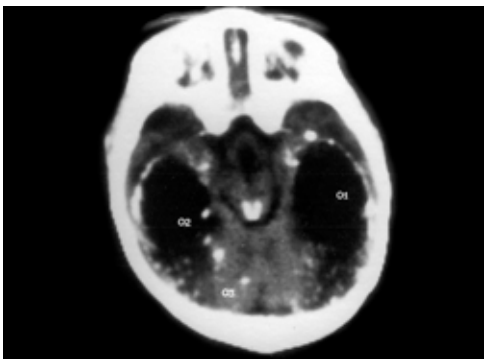


Fig. 116: CT scan showing periventricular calcification with hydrocephalus

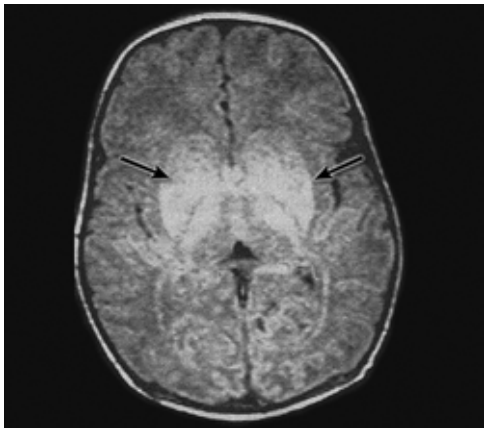


Fig. 117: MRI of brain of a neonate suffering from birth asphyxia showing abnormal (white) signal in the basal ganglia and thalami (arrows)

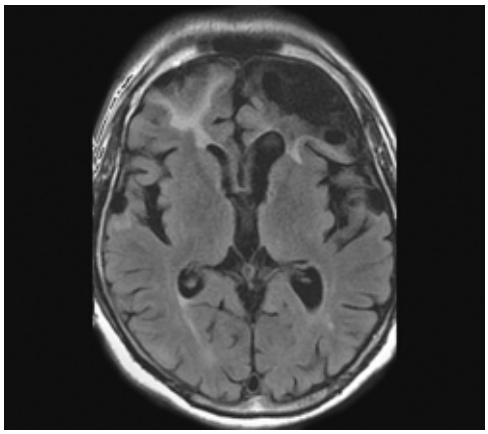


Fig. 118: Computed tomography scan showing cystic encephalomalacia

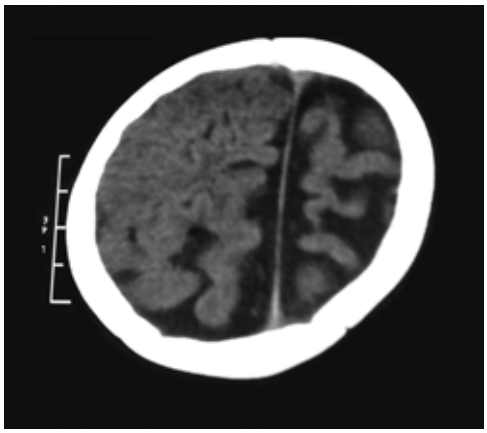


Fig. 119: CT scan showing brain atrophy with deepening of sulci and increased extraventricular cerebrospinal fluid space in a child with CP

sulci. It is the result of severe neonatal encephalopathy due to an intrapartum hypoxic event. It is associated with spastic total body involvement CP and cognitive disability. It may also result from postneonatal hypoxic events.

Schizencephaly: This is a cerebral dysgenesis due to neuronal migration disorder, where specific genes are implicated. It is associated with early hemiplegia, quadriparesis, epilepsy and learning disability.

Lissencephaly (Fig. 120): Cerebral dysgenesis associated with CP causing seizure disorder and learning disability.

Cerebellar Hypoplasia and Atrophy

A nonprogressive lesion (ataxic CP) may be distinguishable from progressive lesion (degenerative CNS disorder). Hypotonia usually precede ataxia.

Hypoplasia and Agenesis of Corpus Callosum

A thin hypoplastic corpus callosum may be secondary to PVL and extensive cortical lesion (Fig. 121). Agenesis of corpus callosum suggests an early gestational insult, typical genetic cerebral dysgenesis.

Treatment

There is no cure of CP as brain damage cannot be repaired. A multidisciplinary approach is implemented to relieve symptoms, improve prognosis, improve function and activities in CP children. According to international classification of functioning (ICF) of WHO model for care of disabled child, which include CP children, management of CP should address:

- Improvement of impairment of function of disabled body parts
- Improvement of activities in the environment where the disabled child lives and participation in real life situation, which includes performance of social roles. Therefore, two major components of management are medical and social. A disabled child's participation at social level can dramatically improve child's condition, without any change of impairment. In situations where we can do little to reduce impairment, devoting energy to improving the environment in which the impaired child lives may have much greater effect on participation. A nondiscriminatory attitude or legislation may be required in this regard.

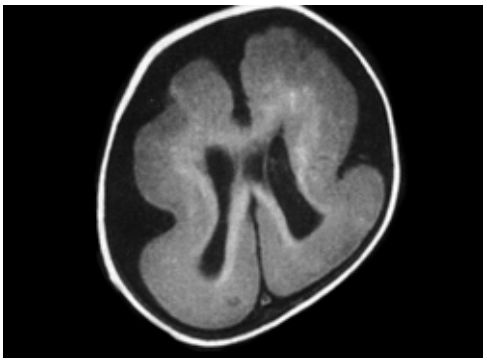


Fig. 120: MRI shows lissencephaly

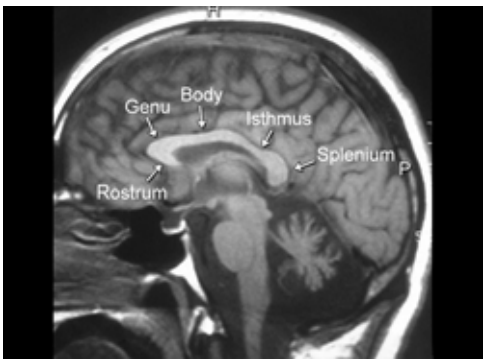


Fig. 121: CT scan showing agenesis of corpus callosum

Management includes:
- Medical and surgical management
- Physical management
- Educational
- Psychosocial support
- Counseling.

Aims of Management

Prevention of deformity thereby improving functional abilities in real life, overcoming feeding problem, treatment of epilepsy, improvement of communication and thereby increasing participation in real life and rehabilitation.

Professionals Involved

Pediatrician, physiotherapist, occupational therapist, speech and language therapist (SALT), ophthalmologist, community medical officer, educational psychologist, orthopedic surgeon and social worker.

Management of Spasticity and Contracture

Spasticity is treated to ameliorate pain and discomfort, to improve mobility, to reduce discomfort and to prevent contracture associated with it. Spasticity can be treated by physical therapy, drugs, appliances or combinations of all.

Assessment of motor impairment and function should be interdisciplinary involving physiotherapist, analysis of videotaped movements and decision making. Identify and measure if possible the following:
- Degree of spasticity, by spasticity scale consisting of 0–5 grades (modified Ashworth scale discussed under the head neurological examination).
- Concomitant presence and degree of dystonia (Barry Albright scale discussed under the head neurological examination) contributing to hypertonia
- Fixed joint, tendon bone deformity (Achilles contracture, scoliosis)
- Gross motor function [i.e. gross motor function classification system (GMFCS)]
- Coordination and fine motor
- Perceptual and cognitive problem like visual impairment
- Abilities and disabilities in daily life, i.e. self-care.

Management to improve motor function depends on above mentioned factors. Concurrent spasticity and dystonia may complicate hypertonic CP. Physical management also varies depending on which type predominates. Spasticity and dystonia scales are mentioned under the head neurological examination. GMFCS is a very simple and well-recognized classification of mobility in CP. Routine use in clinics is feasible. It is more reliable in children over 2 years. Five point scales, (I mild to V severe) are used as follows (Fig. 122):

I. Walks without associated restrictions: Limitation only in more gross motor skill.
II. Walks without assisted device: Limitations walking outdoors and in the community
III. Walks with assisted mobility device: Limitations walking outdoors and in the community
IV. Self-mobility with limitations: Children are transported or use of power mobility outdoor and in the community
V. Self-mobility is severity limited even with assisted device.

Limitations in daily living are not just due to motor impairments. Disability measures integrate the effect of

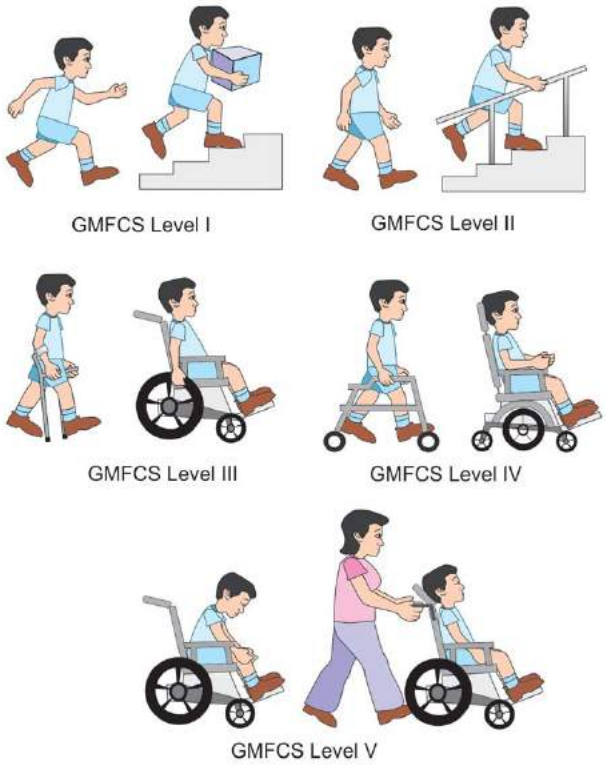


Fig. 122: Picture showing various levels of gross motor functional classification system

comorbidities like scoliosis, cognitive defects, perceptual defects (visual impairment) and behavior disorder.

Physical management consist of muscle strengthening exercise: Recent studies suggest training antagonists of shortened muscle improve function. Muscle stretching exercises comprise slow manual stretching aimed at preventing shortening of muscles and stiffness of joints.

Positioning

Frequent repositioning can prevent contracture. If this is not possible, prolonged period of immobility should be in an optimal position. Predominantly dystonic should avoid supine position and better placed in prone elevated position to reduce tone.

Splints

Night splints provide prolonged stretching to prevent contracture. Day splints also prevent contracture, but are also intended to improve function by joint stabilization.

Serial Casting

Casting has a similar effect to splinting but ensures compliance. Serial casting can help lengthen muscle, sometimes in collaboration with botulinum toxin injection.

MEDICAL MANAGEMENT OF SPASTICITY (FIG. 123)

Muscle Relaxant

Baclofen and diazepam are frequently used as muscle relaxant. Both of them have side effects in the form of impairment of

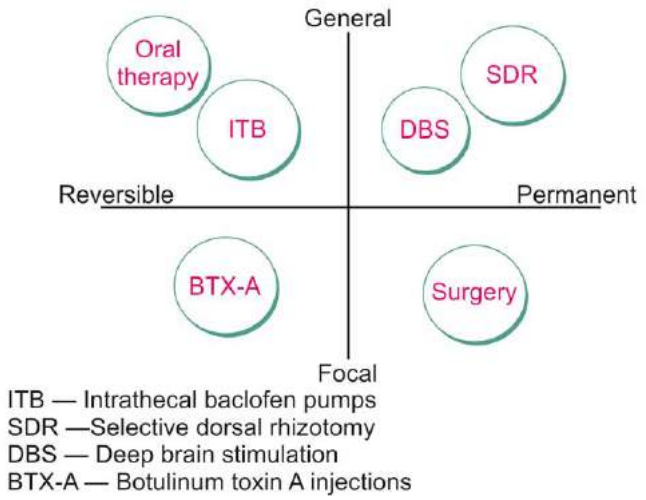


Fig. 123: Medical management of tone problem

alertness. Intrathecal baclofen can achieve higher CSF level without systemic side effects.

Botulinum Toxin

Botulinum toxin A (BT-A) offers a targeted antispasticity treatment in children with CP without causing loss of sensation. BT-A is safe and easy to administer and can be given as an outpatient procedure and results in an improvement in walking. The use of intramuscular botulinum toxin derived from *Clostridium botulinum*, to block intramuscular transmission in spastic muscles, has become common place in recent years. Its prime use has been in the calf muscles to overcome dynamic equinus of the ankle in children with hemiplegia or diplegia. The technique is simple and successfully paralyze muscles. Common sites of injections are calf muscles, hamstrings and adductors of hip. The injection site can be identified by vision and palpation. Application of topical anesthetic cream is suggested for younger children.

It has expanding role in planning surgical intervention in both lower and upper limbs.

Botulinum toxin type A has been found useful in the management of intractable drooling of saliva associated with many children with CP.

Surgical Management

Selective Dorsal Rhizotomy (Fig. 123)

Selective dorsal rhizotomy (SDR) is regarded an important treatment option for children with CP in USA, Australia and Canada. Disinhibition of the spinal reflex resulting from an upper motor neuron lesion is thought to be the basis of spasticity in a child with spasticity. Selectively dividing portion of the dorsal lumbosacral roots of the spinal cord and thus interrupting the spinal reflex arc on the sensory side lead to reduction in spasticity without causing paralysis.

Children who have early SDR have favorable long-term outcome. SDR is clearly a powerful procedure for combating crouch gait and knee stiffness. Significant functional improvement as measured by gross motor function measure occurs after SDR.

Ideal candidates for SDR are children aged 3–10 with severe spastic diplegia without associated ataxia, dystonia or athetosis.

Side effects include bladder problems and paresthesia.

Intrathecal Baclofen

Unlike the oral preparation, baclofen delivered intrathecally [intrathecal baclofen therapy (ITB)] escape the blood-brain barrier which accounts for its greater efficacy. It is an agonist of GABA receptor. It produces effects by activating GABA receptor and GABA is a major inhibitory transmitter. Increased GABA either from disorder of GABA metabolism or therapeutically provided results in hypotonia or decreased muscle tone along with other function. Hypotonia produced by increased GABA is exploited by Baclofen to reduce muscle tone in hypertonic CP.

Intrathecal pumps offer much lower doses of Baclofen because they are designed to deliver the medication directly to the spinal fluid, rather than going through the digestive and circulatory system. They are often preferred in spastic patients such as those with spastic diplegia as very little of the oral dose actually reaches the spinal fluid. However, only 70–80% of children with spastic cerebral palsy (CP) respond to intrathecal baclofen (ITB). Intrathecal baclofen has been shown to be beneficial in children with a notable dystonic element of hypertonic CP, but not dystonia associated with dyskinetic CP.

Judicious use ITB offers greater comfort by reducing spasticity and ultimate bony deformity. It also facilitates easier nursing, thus improving the quality of life of spastic children.

Deep Brain Stimulation (Fig. 123)

In young people with severe dystonic quadriplegic CP, implanting quadripolar electrodes within the basal ganglia of the brain can deliver a continuous electrical signal to the target nuclei. The globus pallidus interna is usually targeted and by doing this aberrant signals from the damaged locomotor driving system are felt to be made more organized. The insertion of this "brain pacemaker" has led to the improvement in dystonia rating scales between 5% and 40%, as well as the general quality of life.

Orthopedic Surgery

For many years the mainstay of surgical treatment for children with CP was tendon lengthening, bony fusions and derotation osteotomy. These include lengthening of Achilles tendon, adductors tenotomy, psoas and hamstring lengthening in one session. Such programs have done little for child's self-esteem, his socialization or his education and gradually being replaced by multisurgical approach.

Multilevel Surgery

A comprehensive surgical prescription should be based on the best evidence available from both clinical and gait analysis. Multilevel surgery is a good option in the hemiplegic and diplegic child where cognition and emotional maturation are adequate to comply with postoperative rehabilitation. This surgery should be undertaken at the start of adolescent growth spurt. Until then child should be treated with physiotherapy and orthotics.

Ventriculoperitoneal or ventriculoatrial (VA) short neurosurgery: rarely required for hydrocephalus-associated CP.

Orthoses and Role of Occupational Therapist and Physiotherapist

Abnormalities of body posture both between body segments and with respect to gravity are common with CP. Orthoses broadly addresses these aspects by application of external force to correct the relation of segments, between body and gravity or both.

Both physiotherapist and occupational therapist work together, borrowing each others skill, as to the requirement of various orthoses.

Various orthoses or aids that prevent deformities are ankle foot orthoses (AFO) to prevent equinous deformity of feet (Fig. 124) and chest braces to prevent scoliosis (Fig. 125).

Wedges and rolls are excellent in helping the floppy child develop spinal and head control.

Mobility aids: Walkers, crawlers rollators may be useful for floppy children. Wheel chair use depends on individual assessment and recommendation from therapist.

Aids that help to improve developmental skills:
Feeding: Special sticking mats or dycem mats (sticky mats that stop plates sliding about) may be used, with high chair (Fig. 126). Feeding dishes and beakers have been designed for children with poor motor skill.

The Role of the Speech Therapist in Feeding Problem

They must be involved early in suspected CP children. In their initial assessment they evaluate tongue, palate and mouth movements and advise over feeding problems.

Fig. 124: A child using ankle foot orthoses

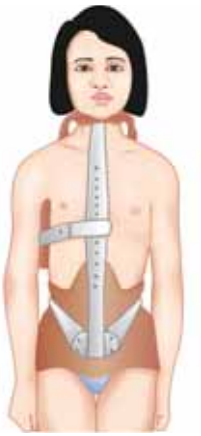


Fig. 125: Brace to manage scoliosis (Milwaukee)

Fig. 126: A spastic child with braces sitting in locally made high chair, note the convergent squint

Seizures: Antiepileptic drugs.

Athetosis/dystonia: Antiparkinsonian drugs.

Excessive drooling: Anticholinergic drugs like glycopyrrolate (glycopyrronium bromide). Injectable botulinum toxin in intractable cases may be tried.

Feeding Assessment and Management

Feeding problems often associated with CP are:

- Poor intake
- Prolonged time to feed
- Vomiting and GER and aspiration.

Assessment consists of assessment of nutritional status, particularly anthropometric assessment which includes assessment of weight for height Z score to identify wasting. Simple measures like assessment of skin-fold thickness and measurement of mid upper arm circumference (MUAC) by MUAC tapes are useful.

Assessment of aspiration is obtained from history of cough during feed. An experienced SALT can better assess aspiration by observing abnormal responses like persistent primitive reflex which include rooting and sucking reflexes.

Reflux is diagnosed by repeated vomiting after feed. Spasm and arching after feed can suggest Sandifer syndrome. Investigations for reflux include barium meal, endoscopy and pH probe, video fluoroscopy to observe pharyngeal phase and involuntary esophageal phases of swallowing, radioisotope milk scan where child is given usual milk mixed with technetium, when radioactivity in the lungs indicates aspiration.

Treatment of Feeding Problems

An upright position (postural management) is paramount during feeding. The SALT and occupational therapist can advise on feeding problems associated with overperformance of primitive reflexes and advice on thickening of feed.

- Dietician can advise on supplementary food
- Nasogastric (NG) feeding may be necessary in inadequate feeding
- Percutaneous endoscopic gastrostomy may be required if NG feeding fails to meet adequate nutritional intake.

If postural management and thickening of feed fail to prevent reflux, drug treatment (ranitidine, omeprazole, domperidone and erythromycin) is given. In intractable cases laparoscope fundoplication is considered.

Education and Learning

A team specialized in children with special needs provides education and learning support. Many children with CP have normal or above normal intelligence, although full expression of their potential may be limited by their motor disability. Environmental stimulation is required with particular emphasis on the development of concepts of color, number, position, size, etc. as perceptual difficulties are associated with CP. A nursery placement is desirable by 3 years of age. It is desirable that CP children with normal on near normal intelligence should be integrated in mainstream school. The decision to send the child to a type of school depends upon level of handicap of the child, the learning ability of the child, the special resources that are needed, location of the school which should permit easy access for the child with limited mobility. An educational psychologist and community pediatrician can help in this regard.

Psychosocial Support

Disable children including spastic children require psychosocial support for participation and function in social life, as per current WHO model of ICF for care of disable children. A congenial environment for disabled children can help in this regard. Personal and family support should be extended to them. A nondiscriminative and helpful attitude should be shown to them. Various aids and appliances should be available to them through social service department, department of health handicap/rehabilitation center, local charities (rotary international, inner-wheel club, etc.). For disabled children including CP children, there are "societies for spastic children" or "societies for disabled children" in many countries, where the parents of CP can meet each other and exchange their experience and views of their disabled children. These help to reduce their misery when they find that they are not the only parents who have physically challenged children. There are leaflets and booklets available in the society through which parent gather new informations involving management of their disabled children. Sports for CP children of various forms are also arranged by such or similar organizations, which bring a lot of fun to such children and help to increase their self-esteem.

Benefits

Many social welfare countries provide benefits to parents of CP in the form of weekly attendance allowance, which is usually available for the child since 2 years of age. In addition mobility allowance is given if the physically challenged child cannot walk by 5 years age. Other funds like family fund are given to such parents.

Short-term relief of distress to parents is provided through shared care or short-term stay at social service premises or residential nursery in some countries.

Counseling and Disclosure of Diagnosis

The parents should be properly counseled about the nature of the disease and expected prognosis and how to take care of the child in various stages of their development. Disclosure of the diagnosis of CP may cause profound distress to parents. Counseling should be done sympathetically and realistically showing regards to parents concern. It should be disclosed better by attending consultant pediatrician, if possible accompanied by physiotherapist who will be involved in child's continuing care. Parental acceptance of diagnosis is related to observed degree of clarity and frankness of the professional's consultation. Disclosure of diagnosis requires professionals to plan ahead so that the appropriate environmental, people, information and immediate follow-up support can be in place.

Parents should be told together. Where a parent is single or not available, the suggestion of bringing another family member should be made. The parents should be told in a private place, where the consultation will be undisturbed.

Parents should be told directly, but sympathetically with clarity about medical conditions in detail and parents given as much time as they wish to ask questions. The manner the professionals deliver the diagnosis is very important and should reflect sympathy, honesty and openness.

Once a firm diagnosis is made parents will appreciate general information about the condition and about the feelings which other parents may have had at such time, about support group and about range of services which may be available in their locality.

PROGNOSIS OF CEREBRAL PALSY

Prediction of Severity by Age of Presentation

More severe CPs are predicted if they present early during neonatal (hemisyndrome) or postneonatal period. Children showing clinical features of CP at late infancy or early childhood have usually milder form of CP. Such children are found already walking on toes (toe walking).

PREDICTION OF COMORBIDITY ASSOCIATED WITH CEREBRAL PALSY

Epilepsy, cognitive impairment, being nonverbal along with severe motor disability are more associated with CP, due to neonatal encephalopathy, cerebral dysgenesis or intracranial infections. Their quality of life is worse than children with CP without such comorbidity.

Walking and Mobility

Spastic hemiplegic child can walk before 2 years. In contrast spastic quadriparetic children are unlikely to walk. If a spastic child can sit by age 3 years, there is more than 70% probability of walking without assistance by 6 years. If a child can roll but cannot sit by 3 years there is less than 25% probability to walk by 6 years.

Life Expectancy

Majority of children with CP (80–90%) can survive up to adulthood. However, cognitive impairment is more associated with early death.

DEVELOPMENTAL DELAY AND DEVELOPMENTAL REGRESSION

Developmental regression is the term when a child losses developmental skill which he/she achieved before, whereas developmental delay is the failure to achieve developmental skill in time matched for child's age. CP is typical example of developmental delay where the child learns to sit or work lately in comparison to corresponding peers. When two parameters of development are delayed (motor delay plus visual impairment for example) it is called *global delay*.

Development delay is usually a static condition of CNS, whereas developmental regression is usually progressive neurological disorder. The developmental regression is more serious condition compared to developmental delay. Improvement of development usually can be done in development delay by multidisciplinary approach, while in most developmental regression particularly due to neurodegenerative disorders, in spite of all efforts developmental disorders are progressive. It is, therefore important to differentiate between developmental delay and developmental regression by taking careful history, clinical examination and relevant investigation.

However, recognition of progressive developmental disorder may be difficult to differentiate from global developmental delay, if developmental regression occurs before 4 years of age. In late onset it can be more easily differentiated.

CAUSES OF DEVELOPMENTAL REGRESSION

Developmental regression usually occurs in neurodegenerative disorders. Other conditions which may cause developmental regression include:

- Cerebral tumor
- Uncommon epileptic syndrome: Infantile spasm, LGS, nonconvulsive SE, etc.
- Hydrocephalus
- Congenital and acquired hypothyroidism
- Inborn error of metabolism (PKU, galactosemia).

Neurodegenerative Diseases

The neurodegenerative diseases encompass a large group of genetic disorder with less than 1/1,000 live birth. Inheritance is usually autosomal recessive (AR) and so risk is greatly increased by consanguinity. The disorders are classified into: White matter disorder and gray matter disorder.

White matter disorders: Genetic and acquired

Genetic leukodystrophies:

- Metachromatic leukodystrophy (MLD): A defect in arylsulfatase. Present in second year of life with regression, peripheral neuropathy and later hypotonia.
- Krabbe disease: Autosomal recessive disorder. Defect in galactocerebrosidase. Globoid cells are found. Early onset with severe spasticity and irritability.

Adrenoleukodystrophy: Accumulation of very long chain of fatty acid (VLCFA) in all tissues due to mutation in ABCD1 gene. Cerebral form has onset age between 5 years and 10 years with cognitive and behavioral problem followed by abnormal gait. Measurement of VLCFA is diagnostic. Bone marrow transplantation is beneficial in early presymptomatic stage.

Rare Form

Pelizaeus-Merzbacher syndrome: X-linked recessive. Early hypotonia, spasticity and nystagmus with diffuse symmetrical demyelination.

Alexander Disease

Presents in first year of life with hypotonia and megalocephaly. Sporadic mutation in glial fibrillary acidic protein genes encoding glial fibrillary acid protein is responsible.

Acquired White Matter Disease

Infective:

- Subacute sclerosing panencephalitis
- Aids encephalopathy
- Creutzfeldt-Jakob disease.

Inflammatory:

- Acute disseminated encephalomyelitis
  - Nutritional
- Thiamine deficiency, B_{12} deficiency.

Toxic: Lead poisoning drugs.

Gray matter disorders: Affecting the cortex with cognitive decline and seizure. They include following:

Sphingolipidoses

- GM2 gangliosidoses, Tay-Sachs and Sandhoff (enzyme positive)
- GM1 gangliosidoses (enzyme positive)
- Mucopolysaccharidoses (MPS): Sanfilippo, MPS III.
- Neuronal ceroid lipofuscinosis: Batten disease (enzyme negative)
- Rett syndrome.

Various types of MPS and their characteristic features are discussed in Table 14.

Clinical Assessment of Degenerative Disorders

This comprises:

- History
  - Physical examination including fundoscopic
  - Developmental assessment
  - Assessment of phenotype and behavioral syndrome
  - Differential diagnosis and identification of secondary disabilities
  - Targeted test (relevant selected test).

History

History taking is the cornerstone for diagnosis of developmental regression and to differentiate from developmental delay, particularly from global developmental delay.

Perinatal History

Substantiate neonatal events from parental reporting or from past history. Contemporaneous case notes or discharge summaries where possible should be obtained. Acquired brain insult such as perinatal hypoxia, intracranial infections are important causes of developmental delay and help to differentiate developmental delay from developmental regression.

Table 14: Various types of mucopolysaccharidoses and their characteristic features

	Bony changes	Liver spleen	Mental retardation	Corneal clouding
Hurler	++	+	++	+
Hunter	++	+	+	-
Sanfilippo	±	±	++	-
Morquio	+++	-	-	+

Following histories regarding developmental disorders are important:

- Age of onset: Infantile, late infantile or juvenile
- Family history: Consanguinity, unexplained death
- Development: Static or regressive
- Seizure: Suggestive of gray matter disorder
- Open question about: How the child plays can be revealing, supplemented with more direct inquiries as to exactly what the child does and how they play with toys and what their range or restriction in interest is.
- Specific inquiries about a range of developmental domains should be made including hand function (Rett syndrome) and personal care, vision, hearing, communication, feeding, social communication, behavior and cognition.
- It is always important to allow parents to elaborate their child's positive attributes, strength and achievements.
- History taking should end with open question to parents as to whether they have missed any important matter to discuss.

Examination

General Examination

- Look for facial dysmorphism: Specific syndrome (MPS) (Fig. 127)
- Look for seizure (myoclonus)
- Large head: Alexander disease Tay-Sachs disease
- Corneal clouding: Hurler syndrome.

Fundoscopy: Cherry red sport (Tay-Sachs), optic atrophy (MLD), retinitis pigmentosa (refsum disease, A β-lipoproteinemia) (Fig. 128).

Higher CNS function: Cognitive impairment in gray matter disorder.

Thorough developmental assessment (Gross and fine motor, hearing, vision, social development).

Peripheral Nervous System

Prominent ataxia: Batten disease, MLD, Pelizaeus Merzbacher syndrome.
Pyramidal track signs/spasticity: White matter disease.
Extrapyramidal features: Battens, Wilson's, Hallervorden Spatz.

Investigation of Degenerative (Developmental Regression) Disorders

Although many neurodegenerative diseases have no specific treatment, investigations for diagnosis is important for:

- Genetic counseling
- Predict prognosis
- Providing contact with support group.

Fig. 127: A child with mucopolysaccharidoses showing coarse facial features, macroglossia and claw hands

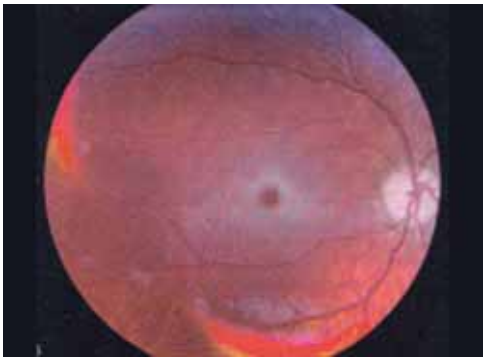


Fig. 128: Cherry red spot on fundoscopy in Tay-Sachs disease

Targeted investigations should be done, guided by clinical suspicion.

Useful investigations include:

- Peripheral blood film: Vacuolated lymphocytes are hallmark of batten disease.
- Thyroid function test: Serum T4, TSH
- Cranial MRI: Identifies cortical malformation, tumor, leukodystrophies
- Neurophysiology: EEG, ERG and VEP. Useful in diagnosis of NCL
- White cell enzymes: Lysosomal enzymes can be measured in peripheral blood white cells in enzyme positive degenerative disorders (Krabbe disease, MLD).
- Genetic analysis: Karyotype, DNA analysis, mitochondrial DNA deletions and mutation
- Biochemistry: Plasma lactate, amino acid, ammonia, urine amino acid, organic acid.
- Muscle biopsy: Paroxysmal disorders VLCFA, respiratory chain enzyme analysis for mitochondrial disorders.

Treatment

There are some conditions where developmental regression can be improved if early diagnosis and proper timely intervention are done. Developmental regression in hypothyroidism can be improved if treatment given before brain damage occurs. Some inborn error of metabolism like PKU, galactosemia, etc. can be treated with dietary exclusion of offending amino acid or monosaccharide. Specific treatments available for some disorders include enzyme replacement therapy, bone marrow transplant and substrates reduction therapy.

Any other case, where specific treatments are not available, management is multidisciplinary and supportive.

DEVELOPMENTAL COORDINATION DISORDER (DCD) OR DYSPRAXIA

DEFINITION

There is no well consensus of precise definition of developmental coordination disorder (DCD). The broadly agreed definition of DCD or dyspraxia is the inability to plan, organize and coordinate motor function as expected for the age of the child in the absence of any known neurological or intellectual impairment. Dyspraxia is literally defined as breakdown of praxis (action) and the inability to utilize voluntary motor abilities effectively in all aspects of life, from play to structured skill tasks. The motor coordination difficulties interfere with

academic achievement and or activities of daily living and not due to physical disorder such as CP.

Developmental coordination disorder or dyspraxia is a developmental disorder involving organization, planning and execution of physical movement with a developmental rather than acquired origin.

Developmental coordination disorder and dyspraxia are synonymous. Other terms used:

- Clumsiness or clumsy child syndrome
- Minimal brain disorder
- Motor LD
- Disorder of attention and motor perception.

Normal or Abnormal Developmental Coordination Disorder?

Difficulty to draw a line between normal and abnormal DCD may sometimes be difficult as it may be found otherwise in many normal children.

It is abnormal if the difficulties have functional effect and adversely affect school and leisure activities.

- Incidence: Considered as "hidden problem" with an estimated prevalence of 10%.
- M:F- 4:1
- Predisposing factors: Prematurity, extremely low birth-weight, retinopathy of prematurity (ROP), premature rupture of membrane, Apgar score less than or equal to 5 minutes at birth.

Comorbidities associated with DCD:

- Poor self-esteem
- Learning (dyslexia) problem
- Disorder of attention and motor perception.

Presenting Features

Developmental coordination disorder manifests functionally in aspects of daily life. Presenting features depend on age of development:

Preschool child:

- Delayed developmental milestone with:
  - Crawling, walking and speech delay
  - Difficulty with dressing, poor ball skill, immature art work.

School aged:

- Slow immature and laborious handwriting
- Difficulty in copying from blackboard
- Difficulty in dressing, shoe laces and riding bike
- Difficult in handling cutlery
- Problem with school progress (reading, copying, solving mathematics)
- Behavior problems (low self-esteem, attention deficit disorder).

Nonspecific:

- Parents may complain about the child as:
  - Difficult child
  - Awkward child
  - Something not quite right for the child.

EXAMINATION

A thorough neurological and physical examination to exclude underlying neurological, muscle disorder and other medical disorder.

Clinical Testing for Motor Coordination

- Difficulty in unscrewing and screwing (Fig. 129)
- Difficulty in hand eye coordination task such as ball catching, threading beads (Fig. 129).

Fog's Test (Also Discussed Under the Head Neurological Examination)

Bilateral exaggerated posturing and associated movements of upper limbs (Figs 130 and 131) may be demonstrated in dyspraxic child when the child is asked to heel walk, toe walk or walk on inverted or everted feet. In neurological disorder on the other hand like subtle hemiplegia or hemisyndrome, there will be exaggerated unilateral movements of upper limb (affected side) only (Fig. 132).

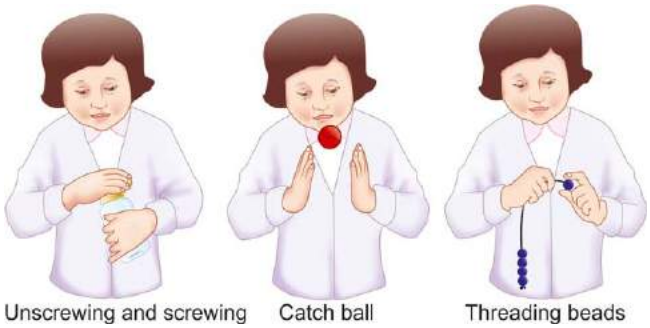


Fig. 129: Clinical testing for motor coordination

Fig. 130: Normal postures and movement on heel walking in a normal child

Fig. 131: Bilateral exaggerated posturing of upper limbs in dyspraxic child

Fig. 132: Unilateral (right) exaggerated posturing of upper limbs in hemisyndrome (right)

Test to Distinguish from Ataxia (Cerebellum)

Past pointing dysmetria with intention tremor is incompatible with diagnosis of dyspraxia but suggests cerebellar lesion.

Management

Developmental coordination disorder with significant functional effect should be referred for further assessment and management to:

- Physiotherapist
- Occupational therapist
- Educational support: Educational psychologist and clinical psychologist may be involved for associated comorbidities.

Therapeutic Intervention

Two main methods of treatment:

1. Task oriented approach: To improve specific task through practice
2. Process-oriented therapy: Concentrate on developing sensory modalities involved in motor performance such as sensory integration approach.

Other management includes:

- Improving self-esteem
- Psychological support.

Prognosis

Failure to diagnose and address DCD with its comorbidities has major consequences in adult life with:

- Unemployment
- Poor interpersonal skill
- Psychiatric disorder
- Avoidance of physical activity
- Substance misuse and criminality.

MOVEMENT DISORDER

Although movement disorders have been recognized in children over centuries, the interest in movement disorder in children has been only recent. In contrast to movement disorder in adults, most movement disorders in children fortunately are self-limiting, lasting for months or few years.

DEFINITION

Movement disorder is defined as any abnormal, unwanted involuntary movement with preserved sensorium and consciousness and not related to convulsion.

A broad spectrum of congenital and acquired brain diseases (usually involving basal ganglia and cerebellum) can result in movement disorder. The most important cause of disorder movement in childhood occurs in CP. Genetic inflammatory, neoplastic and toxic pathological process may present as movement disorder and manifest as ataxia or paroxysmal dyskinesia like chorea, dystonia and tics.

Movement disorders are classified according to speed, reason and suppressibility of the movement. The childhood movement disorders are difficult to classify based on the type of movement because observation has been the mainstay of diagnosis. The problem is that many of the disorders have several manifestations, such as bradykinesia with rigidity and tremor (Parkinson disease). At any given time of clinical examination one manifestation may be prominent and misleading to the clinician. Evaluation of movements using videotaping at the clinic or home has been of great help in evaluation of movement disorder.

Ataxia

Ataxia is the inability to coordinate movement and posture. Depending on onset of ataxia it may be acute or chronic. Chronic is again divided as chronic progressive (neurodegenerative disease) and chronic nonprogressive or static (ataxic CP). Ataxia may manifest as (1) truncal ataxia, and (2) volitional ataxia or both.

Acute Ataxia

Onset within hours:

- Intoxication: Carbamazepine, antihistamine
- Hypoglycemia:
  - Prolonged starvation (Extreme small for date child are more vulnerable)
  - Teenage alcohol ingestion, more common in western countries.

Onset within days:

- Inflammation:
  - Postinfectious cerebellitis (varicella, coxsackie)
  - Acute disseminating encephalomyelitis.

Within weeks:
Raised ICP due to space occupying lesion, posterior fossa tumor.

Episodic ataxia:

- Genetic:
  - Maple syrup urine disease
  - Organic aciduria
  - Urea cycle disorder
  - Mitochondrial disease
  - Basilar migraine.

Chronic Progressive Ataxia

It is one of the clinical features of neurodegenerative disorders mostly genetic.

Autosomal recessive: Friedreich ataxia, ataxia telangiectasia.

Metabolic disorders: Menkes disease, PKU.

Tay-Sachs disease

Autosomal dominant: Spinocerebellar ataxias.

X-linked: Rett syndrome

Demyelination: Multiple sclerosis.

Brain tumors: Cerebellar astrocytomas, ependymomas.

Chronic Static Ataxia

Hypotonic CP (cerebellar hypoplasia), chronic static ataxia

Dandy-Walker malformation, Joubert syndrome, fetal alcohol syndrome.

CLINICAL EVALUATION

History

The time of onset is important. Acute and chronic progressive and nonprogressive have different etiology.

History should be taken whether ataxia occurred over hours, days, or weeks and whether the ataxia is episodic and recurrent or progressive.

Physical Examination

Evidence of recent infection like skin lesions of chickenpox should be looked for. Skeletal deformity like *pes cavus* (Friedreich ataxia) should be looked for.

Thorough neurological examination should be done.

- Tone: Hypotonia in ataxic CP
- Cerebellar signs: Nystagmus, dysarthria, dysmetria
- Sensory function: Romberg's test (unsteadiness worse with eyes closed) is positive in sensory ataxia
- Raised ICP: Papilledema
- Spinocerebellar degeneration: Absent tendon reflexes and upgoing (extensor) plantar responses.

CLINICAL SYNDROMES

Friedreich Ataxia

Friedreich ataxia is the most common of the hereditary recessive ataxias.

Onset is usually at puberty with ataxia and clumsiness. Examination reveals reduced or absent deep tendon reflexes, reduced joint position and vibration sensation, and extensor plantar responses (Fig. 133A) with *pes cavus* (Fig. 133B). Other musculoskeletal abnormalities include distal muscle weakness with preserved intellect, progressive kyphoscoliosis. Other complications include cardiomyopathy, optic atrophy, diabetes and deafness. Genetic testing is available for diagnosis.

Figs 133A and B: (A) Friedreich ataxia with plantar extensor; (B) and *pes cavus*

Ataxia Telangiectasia

This is the most common cause of inherited progressive ataxia which begins at about 2 years of age and progressive to loss of ambulation by adolescence.

It is an AR disorder caused by a defect in DNA repair associated with immune deficiency, predisposition to malignancy, especially after exposure to ionizing radiation, and telangiectasia.

Dystonia and choreoathetosis are prominent early features. Difficulty in fixating the eyes on an object with overshooting of the target and refixating by use of lateral movement of the neck called oculomotor apraxia and horizontal nystagmus are frequently the presenting features.

Telangiectasia usually develops in sun-exposed areas such as bulbar conjunctiva (Fig. 134) behind the pinnae and the shoulders.

Diagnostic investigations include serum α-fetoprotein which is raised in 95% chromosome fragility tests. Reduced secretory IgA, IgG2, IgG4, IgE and increased frequency of chromosomal breaks are the laboratory abnormalities.

Death is usually by infection or tumor dissemination.

Paroxysmal Dyskinesias

The paroxysmal dyskinesias are a group of conditions characterized by sudden episodes of purposeless and involuntary movements which are difficult to differentiate particularly in children. The movements may include one or combination of the following depending on the speed rhythm and compressibility of the movement.

Chorea, Athetosis, Dystonia, Ballismus

The paroxysmal dyskinesias are a group of conditions characterized by sudden episodes of involuntary movements. The movements may include any combination of:

- Chorea: irregular jerky movements
- Athetosis: slow, writhing motions
- Dystonia: twisting, patterned movements with distorted posturing
- Ballismus: uncontrollable flinging movements of an arm or leg or both.

Chorea

Chorea is purposeless, jerky irregular movements. Sydenham's chorea (SC) is the classical post-streptococcal neurological disorder occurring weeks to months after group A β-hemolytic streptococcal infection and is one of the major diagnostic criteria of rheumatic fever. However, in addition to rheumatic fever which has disappeared in industrialized countries long before, chorea can also occur in streptococcal infection

Fig. 134: Ataxia telangiectasia showing telangiectasia on bulbar conjunctiva

which is prevalent globally without causing rheumatic fever. A new post-streptococcal brain syndrome has recently been proposed and termed pediatric autoimmune, neuropsychiatric disorders associated with streptococcal (PANDAS) infections (Fig. 135).

Patients with PANDAS are characterized by the acute onset of chorea or tics or dystonia or combination of all along with comorbid neuropsychiatric syndromes particularly obsessive compulsive disorder (OCD).

Recognition that chorea, tics and dystonia may occur as immune-mediated complications of β-hemolytic *Streptococcus* (BHS) infection suggests that spectrum of post-streptococcal autoimmune basal ganglia disorders may be broader than previously described. It is perhaps not surprising that a variety of movement disorders may occur in the context of post-streptococcal neurological disease. Rarely do basal ganglia syndromes result in one extrapyramidal phenotype.

The phenotype expression of paroxysmal dyskinesias may depend on other variables including the specific corticostriatal circuits involved, developmental status, genetic predisposition and patient sex. There is phenotypic similarity between post-streptococcal CNS syndromes including chorea and common neuropsychiatric disease such as tic disorders, Tourette syndrome, attention-deficit hyperactivity disorder (ADHD) and OCD.

In poststreptococcal dyskinesias antibasal ganglia antibodies (ABGA) appear to be prevalent during active phase of the disease and decrease during remission.

Antibasal ganglia antibodies estimation by western immunoblotting has been found to be potentially useful diagnostic marker in post-streptococcal neurological disorder including chorea where streptococcal infection has either been implicated as an initial trigger or associated with exacerbations.

TREATMENT

In paroxysmal dyskinesias movement disorders which includes chorea, due to its immune-mediated phenomenon immunosuppressive like short course of steroid may be given empirically where estimation of ABGA cannot be done.

Oral penicillin in addition may be helpful. Neuroleptic agents can be used to control behavior disorder associated with chorea.

Huntington's chorea: This is not a paroxysmal dyskinesia of childhood but a rare progressive degenerative disorder of CNS of unknown etiology and inherited as an autosomal dominant trait. Rigidity and dystonia are more prominent in children than chorea, that involved the proximal muscles and number of patients have general tonic clonic seizure and more than 50% are resistant to AEDs. The progressive intellectual and motor decline in children with Huntington's chorea is unresponsive to pharmacological treatment. However, anticonvulsant can be tried and neuroleptic agent can be used to control behavior and chorea. Children tend to survive for a shorter time (5–10) years than adult (10–15) years, so that they are unable to reproduce and genetically transmit the disease.

Dystonia

Dystonia in children is the disorder of basal ganglia and is characterized by contraction of opposing agonist and antagonist group of muscles of limb and axial musculature causing abnormal posture with twisting and repetitive movements. The movements are involuntary, sometimes painful and may affect entire body, a single muscle or a group of muscles.

ETIOLOGY

Primary Dystonias (Genetic 50%)

- Dystonia 1 (dystonia muscularis deformans, primary torsion dystonia)
- Dopa-responsive dystonia, Segawa syndrome
- Huntington disease
- Wilson disease.

Secondary Dystonias

- Drugs: metoclopramide, phenothiazines usually acute onset (Fig. 136)
- Perinatal hypoxia-ischemia: cerebral palsy
- Carbon monoxide poisoning, stroke and trauma.

CLINICAL CLASSIFICATION

Dystonias are classified according to the muscles affected into:

- Generalized dystonia
- Segmental dystonia: affecting two adjoining parts
- Hemidystonia and focal dystonia: spasmodic torticollis, blepharospasm.

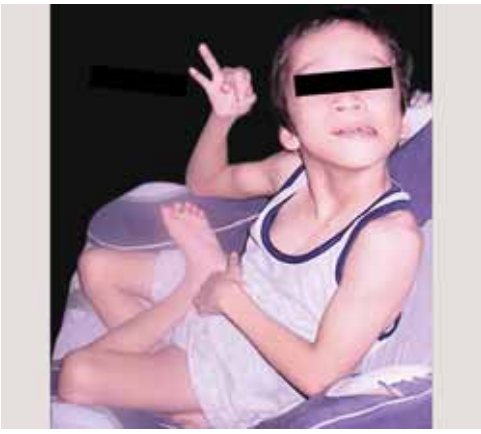


Fig. 135: A child showing choreoathetoid movement

Fig. 136: A child with acute onset dystonia with oculogyric crisis

CLINICAL FEATURES

- Muscle spasms lead to abnormal posturing and discomfort.
- Dystonia 1, dystonia muscularis deformans
- Autosomal dominant with onset in childhood or adolescence of involuntary posturing of trunk, neck or limbs
- Dopa-responsive dystonia
  Autosomal dominant with onset in first 5 years. It is caused by defect in an enzyme in the pathway for dopamine synthesis.

MANAGEMENT

- Medication: Antimuscarinics, GABAergic muscle relaxants (BDZs, baclofen), levodopa, antiepilepsy drugs and botulinum toxin in focal dystonia
- In acute dystonia particularly drug-induced acute extrapyramidal disorder IV procyclidine works dramatically (Figs 136 and 137)
- Surgery: Selective denervation.

TICS

Tics are involuntary and purposeless movement or utterance that is sudden, periodic and repetitive. The tic disorder is known movement disorder in children. Tics can range from simple blinking of eyes of facial twitching to extreme ones like abnormal gestures and vocalization. It is most common in school age children. According to DSM IV disorder, it is classified into transient, chronic, Tourette syndrome or tic disorder not otherwise classified. Tics can also be classified as motor tics, vocal tics and Tourette syndrome.

Motor Tics

- Simple: Eye blinking, grimacing, shrugging, frowning
- Complex: Hopping, clapping, touching objects, kissing, squatting, echopraxia (imitating movements), copropraxia (rude gestures).

Vocal Tics

- Simple: Coughing, clearing throat, sniffing, whistling
- Complex: Repeating words or phrases, unusual rhythms, tone or volume, coprolalia (rude or socially unacceptable words or phrases)

Fig. 137: The same child few minutes after IV procyclidine administration

- Tourette syndromes is the severest of the tic disorders presenting between 2 years and 21 years of age and inherited as autosomal dominant, the gene having mapped to chromosome 18q 22.1. The syndrome is characterized by motor tics, vocal tics, obsessive compulsive behavior and attention deficit disorder with hyperactivity. Not all of them may be present in a single patient, the symptoms waxing and waning and exacerbated by stress and anxiety. Dopaminergic antagonist like haloperidol and antipsychotics like quetiapine are useful in relieving symptoms. Psychotherapy has also a role in the management.

TREMOR

Tremors are rhythmic oscillatory involuntary movements observed at rest or with movement. They are common in children and are a benign form of movement disorder as parkinsonism with resting tremor is uncommon in children.

Fine tremor denoting high anxiety or exaggerated psychological tremor is much more commonly seen. It is also seen due to sympathomimetic drugs for asthma (salbutamol) or AEDs (carbamazepine, valproate).

Benign essential tremor which is classically intentional is a common cause of tremor in children. It is transmitted as autosomal dominant and family history is often positive. Head nodding, vocal tremor and severe body tremor while standing may be seen. Counseling of the parents and occasionally β-adrenergic blocking agents such as propanol may be useful.

OPSOCLONUS MYOCLONUS SYNDROME

This is one of the proximal movement disorders which mimic myoclonic seizure disorder. There is abnormal movement of eyes together with myoclonic movement of limbs resembling epilepsy (Fig. 138). They are distinguished from epilepsy by retained consciousness and presence of precipitating factors. It is characteristically associated with neuroblastoma. Ultrasonogram of whole abdomen, MRI, brain and adrenal glands should be done to exclude neuroblastoma.

Fig. 138: A child with opsoclonus myoclonus with abnormal multidirectional eye movements with retained consciousness

Treatment

Methylprednisolone or immunomodulators may be useful.

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome is characterized by a classical triad of progressive motor weakness, areflexia and elevated CSF protein without pleocytosis. Landry published the

first modern description of an illness likely to be an acute inflammatory demyelinating polyneuropathy (AIDP) in 1859. In 1916 Guillain-Barré and Strohl further enlarged the clinical description and first reported the characteristic CSF finding, albuminocytological dissociation that is elevation of CSF proteins with normal CSF cell count. GBS is the most common cause of acute flaccid paralysis in childhood in countries with established immunization program. The diagnosis is generally relatively straight forward for experienced clinicians, but occasionally can be a challenge even to the most experienced.

PATHOPHYSIOLOGY

The mechanism is an immunological cross reactivity secondary to a prodromal illness within the previous 4 weeks, typically upper respiratory tract infection or gastroenteritis. Implicated organisms are mycoplasma, EBV, CMV, VZV, campylobacter, mums, hepatitis A and varicella.

Clinical Subtypes and Variants

The main types include AIDP, acute motor axonal polyneuropathy, acute motor and sensory axonal neuropathy and Miller Fisher syndrome (MFS).

DIAGNOSIS

The diagnosis of GBS is based primarily on the clinical evaluation and exclusion of important possible alternate diagnosis. Classically in GBS the weakness starts in the lower limb then follows an ascending course over hours or days. Paralysis is usually symmetrical. Although minor asymmetry is not uncommon, gross asymmetry is a rare phenomenon.

Supportive investigations include CSF examination and nerve conduction studies. Occasionally MRI reveals enhancement of spinal nerve roots, indicating radicular inflammation in GBS. However, MRI is more important to exclude possible alternate diagnosis, like acute transverse myelitis, ADEM. This is important as both the emergency treatment and prognosis for these disorders are different from isolated GBS.

The operational diagnostic criteria for GBS are mentioned below:

Features required for diagnosis:

- Progressive motor weakness of more than one limb
- Areflexia of hyporeflexia (loss of ankle jerk and diminished knee and bicep reflex will suffice if other features are consistent with the diagnosis).

Features Supportive of Diagnosis

- Progression of weakness stops less than 4 weeks into illness
- Relative symmetry
- Mild sensory involvement
- Absence of fever at onset
- Cranial nerve involvement, facial weakness developed in approximately 50% of patients
- Autonomic disturbance (↑BP)
- Recovery, begins 2–4 weeks after progression.

Cerebrospinal fluid: Elevated protein after first week, less than 10 lymphocytosis.

Nerve conduction abnormalities (slowing).

Features Casting Doubt on the Diagnosis

- Marked persistent asymmetry in motor function
- Persistent bladder or bowel disturbance
- Discrete sensory level
- Complete ophthalmoplegia.

Various Phases of Guillain-Barré Syndrome

Guillain-Barré syndrome can be divided into five distinctive clinical phase:

Phase 1 : First 24 hours from presentation
Phase 2 : Disease progression
Phase 3 : Plateau phase
Phase 4 : Initial recovery
Phase 5 : Rehabilitation.

There are varieties of clinical presentation

- Ascending flaccid paralysis
- Respiratory distress in 50% cases: Monitor vital capacity by peak flow meter
- Bulbar and ocular involvement
- Autonomic disturbance: Constipation, urinary retention, incontinence, excessive sweating, hypertension, arrhythmia
- Myelopathy: Pain paresthesia, paraparesis, sphincter disturbance (Fig. 139).

INVESTIGATION

Cerebrospinal fluid: Raised protein from second week with absence of lymphocytes (< 10). However, especially in children, LP is not always necessary to make a definite diagnosis.

Nerve conduction study: Slow nerve conduction.

MRI: Enhancement of nerve root. It is usually done if possible alternative diagnosis is suspected.

DIFFERENTIAL DIAGNOSIS

It is imperative to exclude conditions that require immediate specific treatment, especially spinal cord compression. Important differential diagnosis of GBS, are follows:

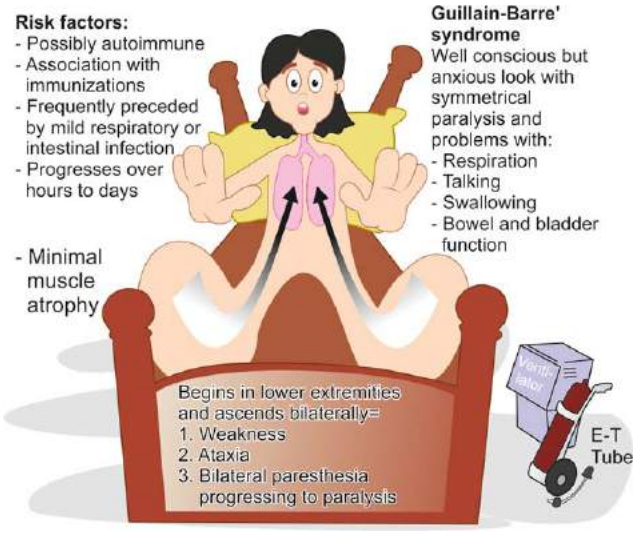


Fig. 139: Showing clinical presentation of Guillain-Barré syndrome

Spinal Cord Lesion

Acute transverse myelitis (ATM), tumor, compression of cord due to trauma or congenital anomalies and poliomyelitis

Peripheral Neuropathies

Toxic: Heavy metal poisoning, vincristine organophosphate poisoning.

Infection: HIV, diphtheria, lyme disease.

Inborn error of metabolism: Porphyria.

Neuromuscular Function Disorder

Myasthenia gravis, botulism, myopathies, tick paralysis, periodic paralysis, dermatomyositis.

ATM presents with well-defined sensory level. Sphincter dysfunction more frequently found in ATM then GBS. CSF will show marked pleocytosis in comparison to GBS. Nerve conduction study is usually normal in ATM.

Spinal cord tumor and trauma can be evaluated by MRI study.

Poliomyelitis and other paralytic condition due to enteroviruses are usually distinguishable by presence of fever, asymmetry of weakness and lack of sensory involvement.

Myasthenia syndrome can be distinguished by electrophysiological nerve stimulation or a test dose of IV edrophonium (tensilon test).

Assessment and Management of a Child with Suspected Guillain-Barré Syndrome

Divided into four staging:

1. Primary assessment and management accordingly
2. Secondary assessment and its management accordingly
3. Symptomatic management
4. Definitive care.

PRIMARY ASSESSMENT AND MANAGEMENT

Primary assessment ABCD:

- Airway: Respiratory distress
- Breathing: Respiratory rate, work of breathing
- Circulation: Heart rate, BP, arrhythmia
- Disability: Conscious level (usually preserved).

Resuscitations during Primary Assessment

Life-threatening conditions should be treated during primary assessment. Oxygen suction bag and mask ventilation and intubation and artificial ventilation may be required in impending respiratory failure.

Circulation: IV access, fluid therapy.

Secondary Assessment

Detailed neurological examination: Examine in anatomical manner.

Head	:	Level of consciousness, according GCS.
Face	:	Cranial nerve involvement, evidence of bulbar involvement.
Chest	:	Respiratory (respiratory distress) and cardiovascular (arrhythmia) examination. Perform bed side vital capacity.
Abdomen	:	Palpable bladder, sensory level, constipation, abdominal reflex.
Spine	:	Swelling, deformity, bruising, tenderness.
Extremities	:	Look for power (MRC grading), tendon reflex, tenderness peripheral sensation.

Symptomatic Treatment

Symptomatic treatment is an essential part of the management of GBS. Careful monitoring of vital functions, avoidance of aspiration pneumonia and tube feeding along with assisted ventilation has considerably decreased the mortality rate. Children should be admitted to a PICU if they have one or more of the followings:

- Flaccid tetraparesis
- Severe rapidly progressive course
- Reduced vital capacity at or below 20 mL/kg
- Bulbar palsy with symptoms
- Autonomic cardiovascular instability that is persistent or labile hypertension or arrhythmia
- Severe pain and discomfort.

DEFINITIVE CARE

Immunotherapy

Although GBS is generally self-limiting with gradual recovery in majority of patient with supportive care, immunotherapy has definite requirement in severe GBS by reducing the severity of tissue injuries by immunomodulation at various levels. Also IVIG hastens recovery compared to supportive care alone.

Intravenous Immunoglobulin

The conventional dose of immunoglobulin is 400 mg/kg/day intravenously for 5 days. Response is best observed if treatment is offered within 3–4 days of onset.

Corticosteroid: There is no role of corticosteroid in the treatment of GBS in children. They can sometimes even make things worse or slow the recovery. However, intravenous methylprednisolone along with IVIG may hasten recovery but does not significantly affect long-term outcome.

Plasmapheresis

Plasmapheresis has remained the gold standard treatment for GBS over the last 20 years. Continuous flow plasma exchange machine may be superior to intermittent flow machine and albumin or fresh frozen plasma as the exchange fluid.

Pain Management in Guillain-Barré Syndrome

Pain or discomfort is present in 50–80% of children with GBS. Pain can be managed by giving:

Nonsteroidal anti-inflammatory drugs (NSAID): Ibuprofens with an antacid for example omeprazole or ranitidine may be added to neutralize adverse gastrointestinal effect of NSAID.

- Antiepileptic drugs: Carbamazepine or gabapentin are effective adjuvant treatment for neuralgic pain.

Opioids

- Severe pain may need oral or parenteral opioids.
- Patients within intensive care unit or ventilatory support are best managed with continuous subcutaneous or opioid infusion.

Disadvantages:

- Tolerance
- Respiratory depression
- Potential for physical dependence.

Prevention of Pain

- Air mattress
- Turning postures and appropriate comfortable positioning of limbs
- Padding of elbows and knee
- Continuation of enteral feeding, effective antacid like omeprazole
- Preventing constipation
- Identifying, relieving and preventing urinary retention.

Communication and Child-friendly Atmosphere

The child is usually fully aware and conscious of the surrounding despite paralysis. Everything that is said in front of the child is likely to be heard, even if sedated in PICU. It is important that the child is kept informed of what is happening and should be reassured by familiar voices and faces. A calm and reassuring atmosphere is essential. The environment should be as child friendly as possible.

Speech and language therapists and occupational therapists should be involved early. They will assess the patient's need for augmented and alternate communication devices if required.

Rehabilitation

Rehabilitation remains a very important aspect of the management of a child with GBS. A better outcome may be achieved by multidisciplinary, holistic approach to behavioral attitudes, coincidental medical disorders, anxiety, depression and social problems. Good communication with the child's school should be maintained throughout the illness and during recovery.

Outcome

Prognosis depends on time taken in progression of disease. If rapid progression up to completion takes small duration (few days) prognosis is more guarded if rapid progression up to completion takes small duration (few days) than taking longer time of disease progression up to completion.

- After 1 years: Up to 15% may be unable to walk
- After 3 years: Up to one-third have lifestyle alteration
- Overall mortality is less than 5%.

ACUTE FLACCID PARALYSIS

It refers to floppy limb paralysis, at least in one limb with acute onset (< 4 weeks) in a child aged less than 15 years, where no initial well-defined or obvious cause such as trauma or electrolyte imbalance is detected or when the condition is not present from birth or when polio is suspected in a person of any age with paralytic illness. On examination tone is diminished but sensation is not affected.

Acute flaccid paralysis is classified into four groups, based on four levels of motor unit namely muscle, neuromuscular function, motor fibers and anterior horn cells. Localization of disorder in the motor limit can be done based on clinical feature.

Common causes of AFP include poliomyelitis, GBS, transverse myelitis and traumatic neuritis.

ACUTE FLACCID PARALYSIS SURVEILLANCE

Acute flaccid paralysis should be considered as public health emergency. All suspected AFP cases must be immediately reported regardless of final diagnosis. The aim of AFP surveillance is to detect poliovirus transmission. All the confirmed AFP must be investigated, which include:

- A complete investigation form, which is available in government health facilities
- Two stool specimen with adequate volume (8–10 g), collected 24–48 hours apart and within 14 days of paralysis for poliovirus study and sent to appropriate centers (WHO accredited laboratories).

Outbreak response efforts should be started promptly without waiting for the laboratory results, which might take up to 8 weeks. Surveillance is carried out for all cases of AFP, not just for poliomyelitis. All cases that are classified as "discarded not polio" require thorough justification and should be reported with the final diagnosis (Table 15).

NEUROMUSCULAR DISORDER AND FLOPPY INFANT

Neuromuscular disorders affects any part of the pathway from anterior horn cell to skeletal muscle fiber and include involvement of:

- Anterior horn cell
- Peripheral nerve
- Neuromuscular junction
- Skeletal muscle.

Neuromuscular disorder can be genetic or acquired. Depending on site of lesion involved and mode of acquiring it is classified as follows (Table 16):

The main clinical presentation of neuromuscular disorders is floppiness. Floppiness is associated with following features:

- Hypotonia
- Weakness.

HYPOTONIA

- Decrease in muscle tone
- Poor head control, head lag and truncal instability
  When held in the air under arms, infant will slip through
- Acute hypotonia: Acute systemic disease
- Chronic hypotonia: May present in perinatal period or late
- Central hypotonia (upper motor neuron): Deep reflexes increased. Initially present with hypotonia followed by hypertonia in later infancy. Around 60–80% infants who are floppy, the etiology is central
- Peripheral hypotonia: Peripheral nerve, neuromuscular junction or muscle.

Weakness: Implies peripheral cause with decrease in muscle power (Table 17).

How to assess weakness: Lying in supine position whether the child has enough antigravity power to hold the limbs in the air?

Approach to Diagnose and Assess Floppy Infant

History

Maternal history: Systemic disease, unrecognized myotonic dystrophy. Congenital myotonic dystrophy (congenital dystrophia myotonica), although autosomal dominant but

Table 15: Differential diagnosis of acute flaccid paralysis

Feature	Poliomyelitis	Guillain-Barré syndrome	Transverse myelitis	Traumatic neuritis
Progression to full paralysis	24–48 hours	Hours to day	Hours to 4 days	Hours to 4 days
Fever onset	High, always present at the onset of paralysis	No	Present before paralysis	No
Flaccidity	Acute, asymmetrical, proximal	Acute, symmetrical, distal, ascending	Acute, symmetrical, lower limbs	Acute, asymmetrical
Muscle tone	Diminished	Diminished	Diminished in lower limbs	Diminished
Deep tendon reflex	Decreased or absent	Absent	Absent early; hyperreflexia late	Decreased or absent
Sensation	Severe myalgia and back ache, no sensory change	Cramps, tingling, hypoanesthesia of palms and soles	Anesthesia of lower limbs with sensory level	Pain in gluteal region
Cranial nerves	Only when bulbar and bulbospinal	Often present, affecting nerves VII, IX,X, XI, XII	Absent	Absent
Respiratory insufficiency	Only when bulbar and bulbospinal	In severe cases	Sometimes	Absent
CSF examination	High leukocytes, normal or slightly elevated protein	Less than 10 leukocytes, high protein	Cellular or acellular; normal or slightly increased protein	Normal
Bladder dysfunction	Absent	Transient	Normal	Never
EMG at 3 weeks	Abnormal	Normal	Normal	May show abnormality
Nerve conduction velocity at 3 weeks	Normal	Abnormal	Normal	Abnormal
Sequelae at 3 months	Severe, asymmetrical atrophy, skeletal deformities appear later	Symmetrical atrophy of distal muscles, recovery in milder cases	Diplegia, atrophy after years, recovery in milder cases	Moderate atrophy in affected limb

Abbreviations: EMG, electromyography; CSF, cerebrospinal fluid.

Table 16: Classification of neuromuscular disorders

Site	Genetic	Acquired
Anterior horn cell	Spinal muscular atrophy	Poliomyelitis
Peripheral nerve	Hereditary sensory motor neuropathy	Guillain-Barré syndrome
Neuromuscular junction	Congenital myasthenia syndrome	Myasthenia gravis
Muscle	Congenital myopathy	Inflammatory myopathy
	Muscular dystrophies Metabolic myopathy	Viral myopathies Endocrine myopathy

Table 17: Conditions of floppiness with and without associated weakness

Floppiness with obvious weakness	Floppiness without obvious weakness
Werdnig Hoffman disease Congenital myotonic dystrophy Congenital myasthenia syndrome Congenital myopathy Glycogen storage disease Congenital muscular dystrophy	Cerebral palsy (early hypotonia) Chromosomal disorders: Down syndrome, Prader-Willi syndrome Nutritional: severe malnutrition, rickets Endocrine: Hypothyroidism, neurometabolic, Tay-Sach disease, Menkes syndrome Connective tissue disorders (Ehlers-Danlos syndrome) Benign congenital hypotonia

is usually derived from mother only. Mother may notice myotonia on hands, when she finds difficulty to release hand after shaking hands (handshake myotonia) or feeling myotonia at hands while washing cloths by hands.

Family history: Consanguinity, infant deaths.

Delivery: Apgar score (muscle tone), requirement for resuscitation, cord gases.

Postnatal course: Feeding difficulty, alertness, spontaneous activity, respiratory distress [spinal muscular atrophy (SMA)].

Floppiness course: Deteriorating overtime (SMA) or improving (benign congenital hypotonia).

Examination (Clinical Evaluation)

This is directed toward distinguishing floppiness:

- With weakness (paralytic): Peripheral cause
- Without weakness (nonparalytic): Central cause.

Examination of Face

Look for dysmorphic facies: Open mouth, tented upper lip, lack of facial expression and restricted ocular movement are characteristics of myopathic facies. Compare with mother who may have similar facies (myotonic dystrophy). Shaking hand, mother finds difficulty in releasing hand in myotonic dystrophy.

Posture

- Look for fasciculation (SMA)
- Frog leg posture and paucity of spontaneous movements
- Waddling gate with positive Gower sign in older children characteristic of DMD

- Power: Decreased in paralytic type. Muscle strength in usually normal in central cause.
- Tone: Poor head control, head lag and truncal instability. When held in the air under arms, infant will slip through (Figs 140). When held in ventral suspension the child cannot lift his head above horizontal plane (Figs 141 and 142). Usually has poor axial and limb tone in peripheral type. Increase in central type. Evidence of scissoring, fisting of hand in central type. In central cause of floppiness there is often notable poor axial tone, but relatively good limb tone. History of cerebral insult (HIE) are often found in central cause.
- Reflexes: Decreased in paralytic or peripheral type. Increase in central (upper motor neuron type).

Other Characteristics Findings on Clinical Examination

- Anterior horn cell (SMA): Generalized weakness decrease or absent reflexes, fasciculation looks alert.
- Peripheral nerve: Weakness, distal more than proximal, decreased or absent reflexes.
- Neuromuscular junction: Weakness with ptosis, extraocular muscle involvement. Normal reflexes.
- Muscles: Weakness more in proximal than distal, reduced reflexes.

Fig. 140: Normal child showing resistance at armpit to prevent slipping through hands on vertical suspension with well-flexed upper limbs

Fig. 141: A floppy infant showing slipping through hands at armpit on vertical suspension

Fig. 142: Evidence of hypotonia on ventral suspension

Fundoscope

Cherry red spot in retina (neurodegenerative disorder) should be looked for.

For peripheral hypotonia:
Serum creatine phosphokinase: Elevated in more muscle disorders, should be measured in all late walkers.

Neurophysiology: Nerve conduction and EMG

Distinguishes myopathic, neurogenic, myotonic and myasthenic etiologies

Muscle biopsy: Needle or open biopsy. Histology, Mt DNA immunohistochemistry

DNA analysis: Specific test are available for some disorders including SMA, congenital myotonic dystrophy.

Management

Specific treatment is not available for most of disorders and management consists of:

- Medical management associated with disorders
- Educational
- Physiotherapy and occupational therapy including appliances (AFO)
- Orthopedic complication management
- Psychosocial
- Nutritional
- Genetic counseling.

MUSCULAR DYSTROPHIES

MYOTONIC DYSTROPHY
(*Dystrophia Myotonica*)

Incidence: 18,000 live birth.

Genetics: The common form of myotonic dystrophy is MD1.

- It is an autosomal dominant disease transmitted from mother and caused by expansion of CTG triplet repeats in the 3'- untranslated region of the last exon of DMPK. Congenitally affected infants usually have a huge expansion of the triplets with more than 1,000 repeats.
- Occur in affected babies born to woman who also have myotonic dystrophy with onset usually in adult life, which may be mild or undiagnosed.

CLINICAL FEATURES

- Mild form: Present with presenile cataract
- Congenital form: Reduced fetal movement, polyhydramnios
- Neonatal period: Severe hypotonia, feeding difficulty, facial weakness, arthrogryposis. The affected mother may be asymptomatic.

CLINICAL EXAMINATION

Handshake examination: Myotonia can be indirectly examined in mother by handshake examination. This manifests as slow release of handshake or difficulty releasing the tightly clasped fist. Mother may give history of myotonic contraction of hand while washing cloths. Although autosomal dominant but mostly comes from mother. Facies of mother and affected child look similar (Fig. 143).

Classical Form

Adolescent and adults present with muscle wasting and weakness and percussion myotonia. Other clinical features include cataract, testicular atrophy and male pattern of boldness in woman.

Diagnostic test: MD1 gene testing

Treatment: Supportive including physiotherapy and occupational therapy

- Learning support: For LD
- Medical treatment: For cardiac and visual impairment
- Genetic counseling: Important since there are likely to be other affected family members.

DYSTROPHINOPATHIES

The severity from milder variety called Becker to severe form called DMD depends on quantity of residual functional dystrophin.

Etiology and Pathology

Mutations in the DMD genes on P21 band of X chromosome (XP21) encoding dystrophin cause a range of phenotypes from severe DMD to milder Becker dystrophy (BMD) depending on level of remaining functioning dystrophin.

The DMD gene extends over 79 exons and a 2.5 mb genomic region. Approximately 60% of affected individual have deletion of one or more exons of gene.

Dystrophin: Dystrophin places an important role in anchoring the cytoskeleton to the plasma membrane and protects the sarcolemma during contraction. Dystrophin is expressed in skeletal and smooth muscle, brain and peripheral nerves. Boys with DMD have little or no functional dystrophin whereas in the milder case like BMD dystrophin may be reduced in amount or altered in size.

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy, an X linked recessive disorder, is the most common hereditary neuromuscular disease associated with decreased production of dystrophin.

- Incidence: 1/3,500 live birth
- Inheritance: X-linked recessive, one-third new mutation
- Gene involved:
  - Xp21 dystrophin gene
- Family history: Similar clinical problem in maternal uncles and sibling may be present
- Clinical features:
  - Age of onset: Less than 5 years
  - Delayed gross motor development (delayed walking, running)

  On examination:
  - Waddling lordotic gait
  - Normal sensorium but intellectual impairment
  - Calf hypertrophy (Fig. 144)
  - Symmetrical proximal weakness of muscles with sparing of the facial extraocular and bulbar muscle
  - Positive Gower sign (Fig. 145)
  - Weakness of limb girdle (lower more than upper)
  - Clinical evidence of cardiomyopathy
  - Clinical evidence of respiratory involvement.

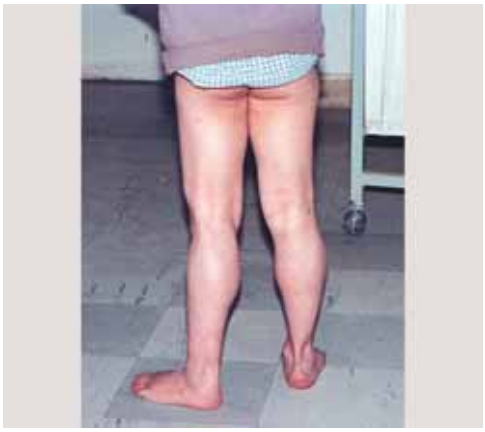


Fig. 144: Calf hypertrophy in Duchenne muscular dystrophy

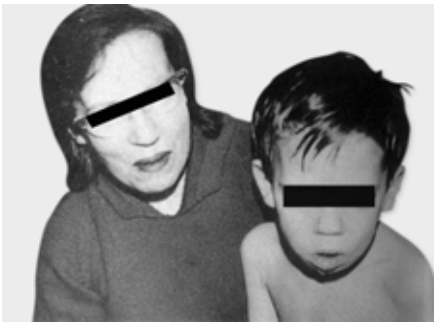


Fig. 143: A child with myotonic dystrophy with relatively immobile facies, note the mother has similar facies

Fig. 145: Gower sign in a Duchenne muscular dystrophy child

Gower Sign

Child should be able to independently stand from sitting position without using upper limbs. With weak lower limb muscles, the child may crawl hands up thighs (climbing up on legs) in order to stand up.

Natural History and Prognosis

- Cardiomyopathy (onset after 10 years)
- Respiratory involvement during treatment, important cause of mortality
- Wheel chair for mobility by 8–12 years.

Life span: Variable, into late twenties. Death mostly due to pulmonary insufficiency and respiratory infections. Ten percent deaths are attributable to cardiac dysfunction.

Diagnosis Investigations

Diagnosis is suspected on clinical presentation and markedly elevated (> 1,000) of serum CK.

Confirmation Requires

Genetic testing: Gene deletion up to 70% cases.

Other investigations: As indicated.

Chest X-ray: Cardiomegaly with CT ratio more than 0.5 (Fig. 146).

ECG: RVH with increased R (>4 mm in V1) and increased RS more than 1 in V1 (Fig. 146).

Echocardiogram:
- Decrease ejection fraction
- Decrease deceleration time: 150 milliseconds suggestive of diastolic dysfunction.

Lung function test: Forced vital capacity, flow-volume, forced expiratory volume 1.

Muscle biopsy: Absence of dystrophin in immunohistochemistry with monoclonal antibody to dystrophin.

Management

Consist of general management, supportive and symptomatic management, medical treatment including cardiac management, management of complication, nutritional including management of obesity and genetic counseling.

Medical Treatment

- Steroids: 0.75 mg prednisolone with 10 days on and 10 days off. More useful in boys from 7 years to 10 years.
- Benefits: Prolongation of walking, possible benefits to respiratory and cardiac function
- Side effects: Weight gain, osteoporosis.

Management of Complications

Cardiac:
- Look for evidence of cardiac failure
- Cardiac assessment annually
- Annual 24 hours ECG to screen for arrhythmia from 10 years of age
- Consider ACE inhibitors in cardiac failure in DMD including in female carriers.

Respiratory:
- FVC: A 40% FVC predicts sleep hypoventilation and the first sign of impending hypoventilation. In nocturnal hypoventilation nasal mask intermittent positive-pressure ventilation is indicated.
- Nutritional: Both undernutrition and obesity occurs. Involvement of nutritionist is required.
- Physiotherapy: Physiotherapy for prevention of contracture and prolongation of walking. Use of appliances like AFO may be required.
- Supportive care: Supportive care including family support. Involvement with supportive group or society (Duchenne society) helps relieve parental distress.
- Genetic treatment: Still at research level.
  - Exon skipping in Duchenne dystrophy
  - Aim to convert Duchenne to Becker by modifying the splicing of the dystrophin gene.

Becker muscular dystrophy:
- Incidence: 1/300–1/600 males
- Presentation: Similar as DMD but variable severity and onset (5–15 years)
- Clinical course: Slow progression, wheel chair mobility by more than 16 years
- Life expectancy: 40 years to normal
- Diagnosis: Gene test and biopsy: Patchy dystrophin staining.

Limb girdle dystrophy:
- A heterogeneous group of disorder. Related to structural protein
- Incidence: 1/10,0000–20,000
- Inheritance: 90% AR, 10% autosomal dominant
- Creatine phosphokinase: 10–100 times elevated.

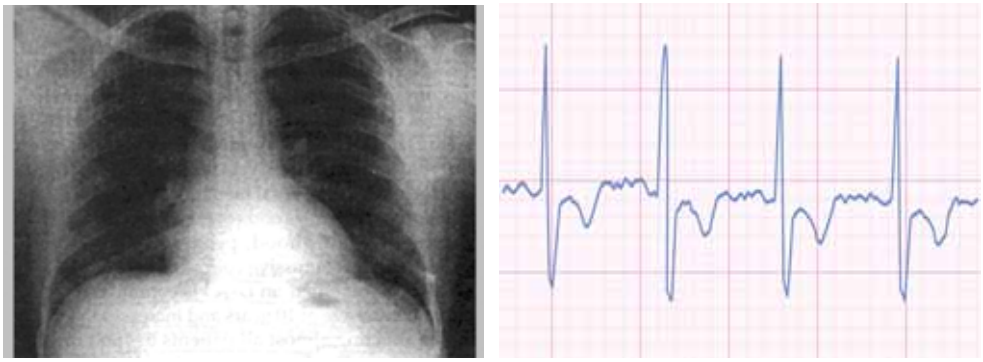


Fig. 146: X-ray chest and ECG of 8-year-old boy with Duchenne muscular dystrophy showing cardiomegaly (with a CT ratio of 0.5) and classical pattern of tall are in V1 respectively

Clinical presentation:
- Onset: 2–20 years
- Slow progressive weakness and atrophy of shoulder and pelvic girdle muscles
- Waddling gait with increased lumbar lordosis
- Some affects CNS, vision and hearing.

Complications:
- Dilated cardiomegalopathy can occur in LGMD2F1
- Arrhythmia in LGMD1B.

Facioscapulohumeral dystrophy:
- Inheritance: Autosomal dominant
- Onset: Variable. Usually initially affects facial muscles with facial weakness (eyes and mouth) followed by weakness of shoulder muscles causing scapular winging
- Later pelvic and tibial muscles.

NEURAL TUBE DEFECTS AND HYDROCEPHALUS

Neural tube defects (NTDs) arise from failure of closure of the neural tube on or before 28 days of gestation and encompass a range of malformations involving the brain or spinal cord and adjacent meninges, bones and skin.

ETIOLOGY AND PATHOGENESIS

Fusion of the edges of the neural groove starts cranially and progresses caudally, the anterior neuropore closing at about 25 days and the posterior neuropore posing at 27 days. The causes of NTDs are multifactorial and include both genetic and environmental factors. Risk factors include:
- Maternal diabetes
- Folic acid deficiency: It is established that periconceptual folic acid supplementation can prevent some NTDs
- Genetic factors: A family history of NTDs increases risk
- Antiepilepsy drugs: Increased risk in pregnant women taking AEDs, SVA, PHT or CBZ.

CLASSIFICATION

Dysraphism is a synonym for NTD.
- Spinal dysraphism:
  - Cranial dysraphism: Anencephaly and encephalocele
  - Spina bifida cystica: Meningocele, myelomeningocele ± Chiari II malformation
- Spina bifida occulta
- Diastematomyelia
- Dorsal dermal sinus.

Spina Bifida

This is a common and important congenital defect resulting from failure of closure of the posterior neuropore, which normally occurs around the twenty-seventh day of embryonic life.

The most common and most severe form is a meningo myelocele (Fig. 147) in which elements of the spinal cord and nerve roots are involved. It may occur at any spinal level but the usual site is the lumbar region. The baby is born with a raw swelling over the spine in which it is either exposed or covered by a fragile membrane. The cord is at risk of further damage from infection, drying out or other direct physical trauma.

Meningocele

These are less common and less serious. The sac of CSF is covered by meninges and skin and contains no neural tissue.

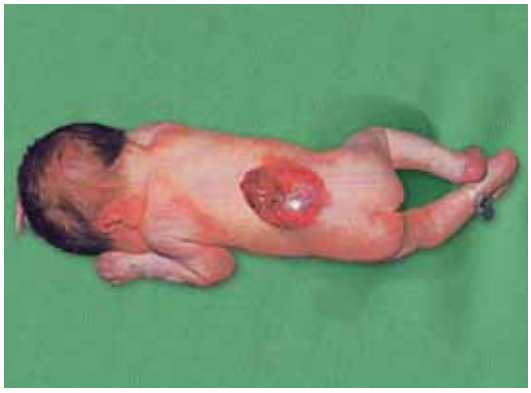


Fig. 147: A case of spina bifida myelomeningocele

Encephaloceles

Encephaloceles are protrusions through the skull usually in the occipital region. They are uncommon, and if large are likely to be associated with severe brain damage.

Spina Bifida Occulta

This is of little importance. Although there is failure of fusion of the posterior neural arches of the vertebrae, the membranes and cord do not project through it and are nearly always normal. The site of the cleft may be marked externally by a nevus, or a tuft of hair. There are usually no neurological disturbances. In 10% of children, X-rays show a gap in the neural arch, but many of these have cartilaginous fusion rather than spina bifida occulta.

The main physical problems from meningomyelocele are:
- Legs: Partial or complete paralysis below the level of the lesion, with associated sensory loss. Secondary hip dislocation and leg deformities occur, especially talipes (club foot).
- Head: Associated hydrocephalus with possible brain damage
- Bladder: Neuropathic bladder with overflow incontinence and recurrent urinary tract infections leading to kidney damage.

In addition, paralysis of the anus will be present if the relevant spinal cord segments or roots are involved. The emotional and social problems for the child and family are massive, varying from the frequent hospital admissions and attendances to the problems of providing suitable education for a paraplegic deformed child.

Antenatal Screening

Antenatal screening detects 85% of NTDs. Maternal serum α-fetoprotein levels at 16–l8 weeks are raised in anencephaly or spina bifida.

Ultrasonogram is recommended for all at-risk women: Positive serum α-fetoprotein, or previously affected child.

Ultrasonogram detects anencephaly from twelfth week and spina bifida from 16 weeks to 20 weeks. The 20 weeks anomaly scan will show ventriculomegaly, vertebral arch defects and talipes. Amniocentesis to measure amniotic fluid α-fetoprotein and acetylcholinesterase levels provide additional confirmation and MRI is increasingly used to define the lesion.

Postnatal Management

Eighty percent are lumbosacral.

Magnetic resonance imaging identifies contents of the defect and associated cranial malformations. CT scan allows visualization of the bony defect and anatomy.

The newborn with an open myelomeningocele should be positioned prone and the defect covered with a sterile saline dressing. Closure of the defect is usually done together with placement of ventriculoperitoneal shunt and administration of antibiotics.

Long-term management is multidisciplinary and requires attention to the many complications which occurs as these patients survive into adult life:

- Hydrocephalus: VP shunt; infections or blockage are frequent complications
- Kyphoscoliosis: It may require spinal stabilization
- Cord tethering syndrome
- Renal compromise secondary to neurogenic bladder is the leading cause of death after the first year of life
- Neuropathic bowel
- Cognitive impairment is common. Seizures in 10–30%.
- Trophic skin lesions.

Spina Bifida Occulta

Bony spina bifida occulta at L5-S1 is a common incidental finding on radiographs and not usually associated with symptoms or signs. No action is necessary.

HYDROCEPHALUS

Definitions and Variants

- Hydrocephalus: Increase in volume of CSF spaces in the brain particularly the ventricles (ventriculomegaly) associated with increased ICP and classical signs and symptoms.
- Ventriculomegaly: Radiological appearance of increased ventricular volume not necessarily implying increased pressure or symptoms (e.g. could be due to parenchymal atrophy).

Variants of Hydrocephalus

- *Obstructive (noncommunicating)*: Obstruction to CSF flow in the ventricular system before reaching the subarachnoid space
- *Communicating*: Decreased absorption of CSF from arachnoid villi and subarachnoid spaces; or increased CSF production (choroid plexus papillomas)
- *Normal pressure hydrocephalus*: Ventricular dilatation, no parenchymal atrophy and normal CSF pressure with chronic symptoms (classically gait disturbance, cognitive deterioration and incontinence in the elderly). Not known to occur in children.

Etiology

Causes of hydrocephalus are congenital or acquired (Fig. 148).

Congenital Hydrocephalus

- Malformations:
  - Aqueduct stenosis: 10% neonatal cases
  - Dandy-Walker malformation: 2–4% neonatal cases with vermis hypoplasia and cystic dilatation of fourth ventricle
  - Arnold-Chiari malformations I and II: Associated with NTDs
- X-linked hydrocephalus: Including Bickers-Adams syndrome of aqueduct stenosis, mental retardation, thumb deformity
- Congenital toxoplasmosis.

Acquired Hydrocephalus

- Intraventricular hemorrhage in preterm infants
- Mass lesions: Posterior fossa tumors, cysts, abscesses
- Infections: Bacterial meningitis
- Increased venous sinus pressure in achondroplasia, craniosynostosis, venous thrombosis
- Iatrogenic: Hypervitaminosis A.

Early Infancy

- Accelerated head growth; occipitofrontal circumference crossing the centiles (may also be seen with benign external hydrocephalus); Greater than 1 cm per week in neonates.
- Bulging fontanel (even when upright and settled)
- Cranial sutures widened
- Prominent scalp veins
- Sun-setting eyes (Fig. 149)
- Parinaud syndrome
- Irritability, poor feeding
- Delayed development including abnormal visual behavior.

Later Childhood

- Macrocephaly, may be an isolated finding in arrested hydrocephalus
- Headache
- Vomiting

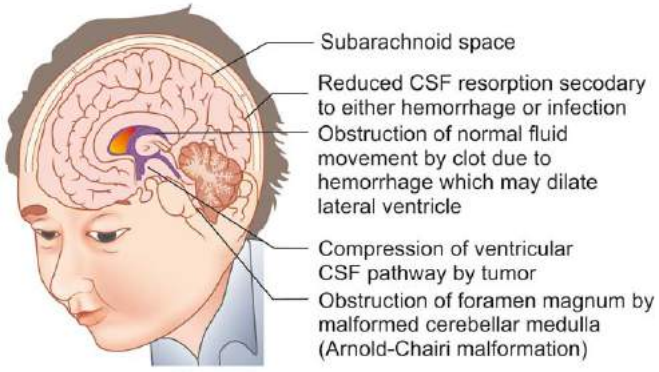


Fig. 148: Mechanism of development of hydrocephalus

Fig. 149: A child with hydrocephalus showing sun-setting eyes sign and dilated scalp vein

- Lethargy and somnolence
- Visual disturbance (check VA and fields)
- Papilledema is not reliable: Often absent in acute decompensation.

Antenatal Detection

There has been a reduction in the incidence of congenital variants due to termination after fetal detection of gross ventriculomegaly and myelomeningocele.

Fetal ventriculomegaly defined by lateral ventricle width at 20 weeks gestation: 10–15 mm = mild, more than 15 mm = severe (ventricular size independent of gestational age >20 weeks).

Differential Diagnosis

Macrocephaly may resemble hydrocephalous. Macrocephaly may be found in normal children in familial large head (Fig. 150). Macrocephaly may also occur in pathological condition like megalocephaly (central neurofibromatosis, Alexander disease, etc.), chronic subdural effusion, hydranencephaly (Fig. 151), etc.

Management

Brain imaging options include cranial ultrasound if fontanel is open, cranial CT for acute assessment of ventricular size, and cranial MRI. MRI allows better definition of posterior fossa contents and evaluation of cerebral malformations.

Fig. 150: A child with large head (familial) with normal development. Parents also have large heads

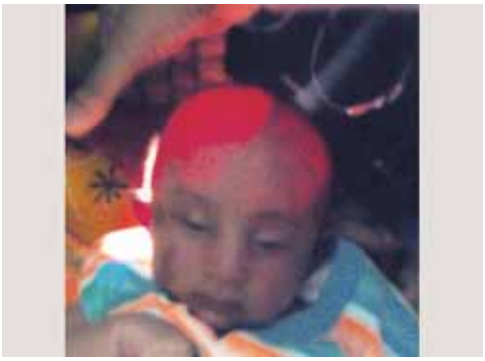


Fig. 151: An infant with hydranencephaly showing positive transillumination

Treatment

- Diuretics (furosemide, acetazolamide)
- Repeated ventricular taps and LP
- Other methods: Intraventricular fibrinolysis
- Around 20–30% of those with grade 3 or 4 IVH needing repeated CSF removal eventually require a shunt.

Progressive Ventricular Dilatation in Neonates (See Chapter 1)

Surgical treatment: Surgical intervention is required in most cases of symptomatic hydrocephalus with RICP. VP shunting is the most common procedure. A silastic tube is placed into the ventricles to drain the CSF info the peritoneal cavity. Shunts may become blocked, infected, or outgrown (Figs 152 and 153).

Endoscopic third ventriculostomy is an option in selected patients and avoids risks of infection and overdrainage.

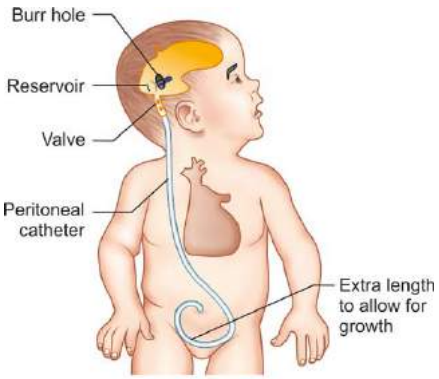


Fig. 152: Ventriculoperitoneal shunt. Currently most commonly practiced

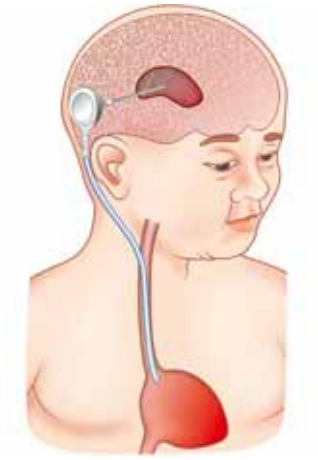


Fig. 153: Ventriculoatrial shunt not practiced nowadays due to need for reoperation with child growth and higher complications

COMA AND DECREASED LEVEL OF CONSCIOUSNESS

Coma: It is a state of profoundly reduced conscious level.
Decreased level of consciousness: It is defined as modified GCS less than 15 or being responsive only to voice or pain.

ETIOLOGY

Traumatic: Accidental and NAI of brain.

Nontraumatic:

- Intracranial infection and inflammation
  - Meningitis, encephalitis, brain abscess, shunt infection
- Postinfectious: ADEM, cerebellitis
- Hypoxic ischemic: Birth-related cardio/respiratory arrest, hypotension
- Epilepsy: Postictal, NCSE, subtle motor SE
- Metabolic: Hypoglycemic, renal failure, hepatic failure, diabetic ketoacidosis, hyperammonemia
- Toxic: Opioids, barbiturates, lead, heavy metal poisoning.

Infective Causes

- Acute bacterial (*Pneumococcus, Haemophilus influenzae, N. meningitidis*) meningitis.
- Mycobacterial: Tuberculous meningitis
- Viral meningitis (encephalitis): Herpes simplex, JE
- Parasitic: Cerebral malaria.

PRIMARY ASSESSMENT

For approach to identification of etiology.

Clue to Know the Etiology

- Fever gives clue to infective origin
- Traveling or inhabitant in endemic zone of infection: Malaria, JE
- Coma due to SE: History of epilepsy
- Acute disseminated encephalomyelitis: 1–2 weeks after viral or other infection
- History of pica: Lead poisoning
- Retinal hemorrhage with bulged fontanel: NAI
- Unusual smell from body and urine with unexplained death in siblings: Suggestive of inborn error of metabolism (hyperammonemia).

General Examination

- Fever (absence makes intracranial infection unlikely)
- Evidence of trauma: Bruising or scalp swelling.

Neurological Examination

Look for signs of meningism (neck rigidity, Kernig sign), RICP, fundi (papilledema or retinal hemorrhage), abnormal posturing, focal neurological signs.

Determination of Level of Consciousness

Coma level should be rapidly assessed using the modified GCS mentioned in Table 18. Signs or increased ICP should be looked for if GCS is deteriorating or less than 12. Also signs of herniation syndrome should be looked for by examining brain stem reflex.

Significance of Early Reorganization of Raised Intracranial Pressure

- It reduces cerebral perfusion pressure (mean arterial pressure—ICP), which causes cerebral ischemia
- Difference of pressure in different compartment of brain causes herniation syndrome causing mechanical damage of brain.

Examination of Brainstem is Required to Identify Such Condition

Pupil response to light: Pupil size and responsiveness to light needs to be checked. Temporal herniation is evidenced by unilateral dilated pupil with impaired response to light (due to third nerve palsy).

Dolls eye (oculocephalic) reflex (Figs 154 and 155): Normally when the head of an unconscious person is moved to one side, there is counter rolling of the eyes of the other side (dolls eye movement), but the movement may be disconjugate, lost unilaterally or absent with brainstem lesion.

Table 18: Modified Glasgow coma scale

	>5 years	<5 years
Eye opening		
4	Spontaneous	Same as >5 years
3	To voice	
2	To pain	
1	None	
Verbal		
5	Orientated	Alert, babbles, coos, words or sentences normal
4	Confused	Less than usual ability cries
3	Inappropriate words	Cries to pain
2	Incomprehensible sounds	Moans to pain
1	No response to pain	No response to pain
Motor		
6	Obeys commands	Normal spontaneous movements
5	Localizes to supraocular pain	Localizes to supraocular pain or withdraws to touch in infant <9/12
4	Withdraws from nailbed pressure	Withdraws from nailbed pressure
3	Flexion from nailbed pressure	Flexion from nailbed pressure
2	Extension to supraocular pain	Extension to supraocular pain
1	No response to supraocular pain	No response to supraocular pain

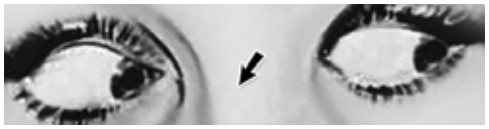


Fig. 154: Counter rolling of eyes in unconscious person opposite the direction of head tilting (doll's eye movement)

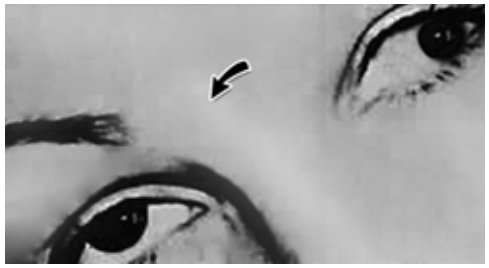


Fig. 155: Disconjugate movement of eyes with head tilting due to possible brainstem injury

Emergency Management of Child in a Coma

- Initial management follows the ABC.
- Check capillary blood glucose immediately as hypoglycemia is an important remedial cause of altered consciousness
- Assess GCS
- Assess brainstem function (pupillary reflex, dolls eye reflex)
- Examine fundi:
  - Papilledema (Fig. 156) in RICP (not always present particularly if suddenly increased) (Fig. 156)
  - Presence of venous pulsation
  - Retinal hemorrhage (NAI)
  - Macular star (hypertensive encephalopathy) (Fig. 157).

LP: If the working diagnosis in intracranial infection (meningitis, encephalitis) or cause not obvious and the child is either less than 12 months age or GCS is more than 12 then perform LP and start IV third generation cephalosporin and IV acyclovir.

Cerebrospinal fluid should be analyzed by gram staining microscopy, culture, protein, glucose, RAS for common microorganism, PCR for HHV1 and other viruses (JE) if indicated.

Contraindications of LP include:

- Glasgow coma scale (GCS) less than or equal to 8 or deteriorating
- Focal neurological signs, abnormal posturing
- Pupillary abnormalities
- Signs of RICP
- Bleeding diathesis
- Clinical evidence of meningococcemia, e.g. shock.

CT: Consider emergency cranial CT when the working diagnosis is RICP, intracranial abscess, traumatic brain injury or cause of altered sensorium remains uncertain.

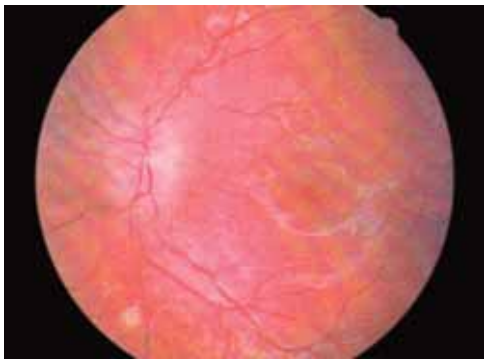


Fig. 156: Optic disk swelling: Advanced papilledema

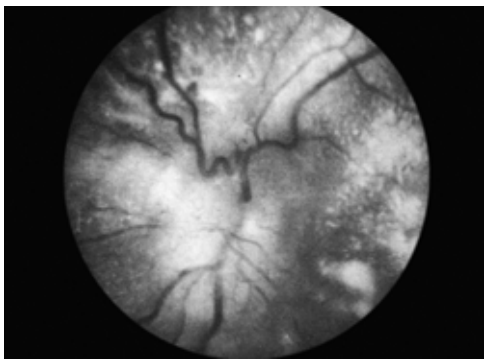


Fig. 157: Hypertensive retinopathy in a 7-year-old boy with renal disease

A normal cranial CT does not exclude acute RICP. The decision to perform LP in a child with reduced conscious level should be made by experienced pediatrician who has examined the child.

Intubation and Ventilation

- If GCS is less than 8 or evidence of herniation
- Inadequate respiration: Oxygen saturation less than 92% despite high flow oxygen therapy
- Signs of RICP shock: Persisting despite volume replacement of more than 40 mL/kg.

Other Investigation

Blood

- Glucose, gases, urea and electrolyte
- Full blood count, blood film, CRP, coagulation screen
- Blood culture (if febrile)
- Liver function tests, plasma ammonia, plasma lactate
- Plasma and urine for toxicology, organic and amino acids
- Plasma/serum/urine: Save for later analysis.

CT (Nonemergency) with Contrast

If brain abscess is suspected

Electroencephalography: Detect NCSE.

Other Management

- Liaise with local PICU and neurosurgeon and arrange transfer if necessary
- May need urinary catheterization and arterial line.

Management of Raised Intracranial Pressure

- Head position:
  - Maintain head in midline and tilted up to 30°
  - Minimal handing and suction
- Fluid: Maintain good circulatory volume. Observe for SIADH or cranial diabetes insipidus. Careful fluid balance, 6 hourly urine and serum osmolality
- Osmotic diuresis: Mannitol 0.5–1 g/kg given IV bolus over 20 minutes with careful attention following bolus to avoid hypovolemia
- Intravenous dexamethasone given before or with first dose of antibiotic in bacterial meningitis is not used to decrease
- Raised intracranial pressure and its role in decreasing RICP is controversial.
- Seizure:
  - Treat obvious seizure as it may cause RICP
  - Prophylactic barbiturate, controversial
- Ventilate to normocapnea: Hyperventilate/bag for RICP spike
- Hydrocephalus: Consider VP shunt or ventriculotomy. Discuss with neurosurgeon
- Hypothermia: Mild hypothermia (core temperature 32°C) may be useful in neonatal HIE, stroke, head injury
- Cerebrospinal fluid drainage or surgical decompression may be useful in persistent RICP
- Other management of coma depends on underlying cause: Appropriate antibiotic for optimum time in pyogenic meningitis, in SIADH considers fluid restriction, etc.

HEARING

Hearing is the perception of sound (where perception is the mind's reaction to a sensation). Therefore, hearing is not only the reception of sound by the ears and its transmissions to the temporal lobes of the brain by a complicated network of nerve pathways and relay stations, but is also the perception of that sound by the brain.

Ear is an important organ not only for hearing but also for balance. For speech and language development satisfactory hearing is essential.

LISTENING

Listening is paying attention to the sounds heard with the object of interpreting their meaning.

Language

Language is a code or a set of symbols with which we can communicate our thoughts or ideas.

Speech

Speech is the use of systematized vocalizations to express the verbal code.

SOUND TO BE PERCEIVED AS HEARING

Sounds are vibrations transmitted through an elastic solid, liquid or gas, capable of detection by human organ of hearing. Sounds have two characteristics features:

- Loudness or intensity: Measured in decibels (dB)
- Pitch or frequency: It is measured as Hz cycles per second. A sound of single frequency is a pure tone.
  Threshold: A threshold sound is one which is just audible.

Loudness in dB of some sound:

- Calm breathing : 10–20
- Whisper : 30
- Speech: 30–40
- TV or radio : 60
- Dog barking : 80
- Overhead jet : 110–140
- Gunshot at 1 m : 140
- Pain threshold : 140

Hearing loss is defined as the following threshold:

- Less than 20 dB : Normal
- 20–40 dB : Mild
- 40–70 dB : Moderate
- 70–95 dB : Severe
- More than 95 dB : Profound.

Consequences of hearing deficit:
Unilateral hearing loss:

- Poor sound localization
- Difficulties in noisy environment.

Bilateral hearing loss:

- Up to 50 dB: Delayed language development
- More than 70 dB:
  - No spontaneous language development
  - Delayed in writing and reading skills
  - Delayed psychosocial development
  - Cognition development is otherwise normal.

Two types of hearing loss:

- Conducted hearing loss: More common. Typically a high frequency loss selectively affecting discrimination of consonants and intelligibility of speech. Common causes are:
  - Acute otitis media (Fig. 158)
  - Otitis media with effusion (Fig. 159)
  - Ear wax.

Otitis Media with Effusion

Prevalence has two peaks: at 1 year and again at 3–5 years. There is an accumulation of fluid behind an intact tympanic membrane in otitis media with effusion.

Risk factors: Craniofacial abnormalities, cleft palate, Down syndrome, seasonality (winter), bottle feeding. Associated with hearing loss ranging from 20 dB to 40 dB, may affect speech and language development.

Treatment option: Adenoidectomy, insertion of grommet (Fig. 160), hearing aide rarely.

Sensory Neural Hearing Loss

It occurs due to hair cell damage in the cochlea. It is less common but more serious than conductive hearing loss. Most of them are irreversible.

Genetic (up to 50% of congenital deafness): They are divided into (1) Nonsyndromic and (2) Syndromic.

Nonsyndromic

- Dominant of recessive variety
- Connexin 26 mutation is the most common cause of nonsyndromic deafness.

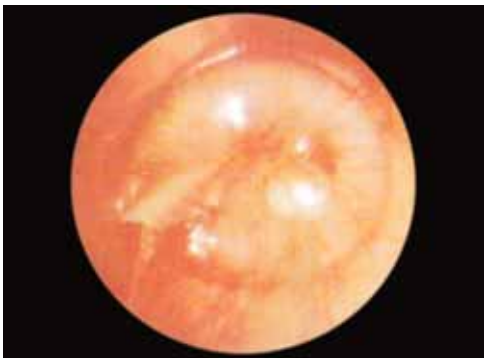


Fig. 158: Ear drum of acute otitis media congested and bulging

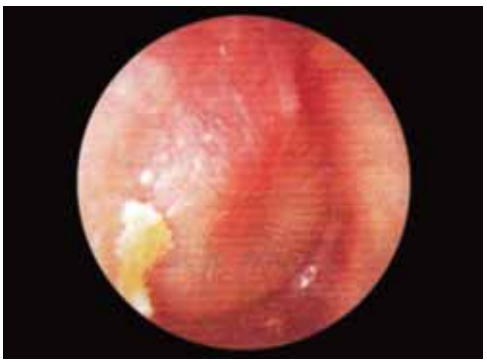


Fig. 159: Otitis media with effusion

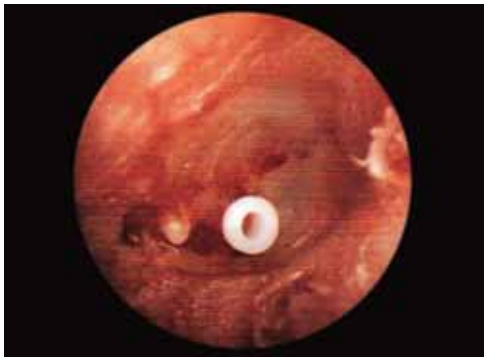


Fig. 160: Inserted grommet

Fig. 161: Waardenburg syndrome with white forelock and deafness (note the hearing aid in left ear)

Syndromic

- Dominant: Waardenburg syndrome (Fig. 161) with pigmentary abnormalities, Crouzon (craniosynostosis with oxycephaly prominent forehead proptosis)
- Recessive: Pendred syndrome (with goiter), Usher syndrome (with retinitis pigmentosa), Jervell syndrome (with ECG abnormality).

Acquired

- Prenatal: Intrauterine infections (CMV, rubella)
- Perinatal: Birth asphyxia, hyperbilirubinemia, prematurity
- Postnatal:
  - Infection: Meningitis, mumps, measles
  - Drugs: aminoglycoside
  - Head injury.

Mixed Hearing Loss

This occurs when a conductive loss is imposed on sensory neural loss. Hearing assessment shows air conduction threshold to be poorer than abnormal bone conduction threshold (Tables 19 and 20).

VARIOUS SCREENING AND DIAGNOSTIC TESTS FOR ASSESSMENT OF HEARING IN CHILDREN AT VARIOUS AGES

Early Identification of Hearing Loss

Newborn hearing screening program [Otoacoustic emission (OAE) and auditory brain steam response].

The primary justification for early identification of hearing impairment in infants relates to impact of having impairment on speech and language acquisition, academic achievement and social and emotional development. The first 3 years of life are most important for speech and language development. It is estimated that approximately 1.5–6 in every 1,000 newborns suffer from permanent congenital hearing impairment. It has been estimated that 10–20/1,000 neonates have an established risk factor and of this group of risk factors 2.5–5% have sensory neural hearing impairment.

There is robust evidence that identification and remediation of hearing loss, when done before 6 months of age for newborn infants who have developed variable degree of hearing deficits. Enable them to perform significantly higher on vocabulary, communication, intelligence, social skills and behavior. American Academy of Pediatrics (AAP) in 1999 advocated universal newborn screening program and remedial intervention which is being practiced in most of the developed countries.

Hearing screening involved in all newborns with special attention to the high-risk group which include the following:

- Family history of hereditary childhood sensory neural hearing loss
- Intrauterine infection such as CMV rubella toxoplasmosis, herpes
- Birthweight less than 1,500 g

Table 19: Auditory behavior and vocalizations in infancy

Age	Auditory behavior	Vocalizations
0–6 weeks	Eye widening, eye blink, stirring or arousal from sleep, startle, to noises of 70 dB SPL	Cries and physiological sounds. No phonated sounds.
6 weeks to 4 months	Eye widening, eye shift, eye blinking, quieting, beginning rudimentary head turn by 4/12 to noises of 60 dB SPL	Cooing and gurgling in response to overtures By 3/12 "true babbling" (the pleasurable repetition of sounds in the parents' absence and the increase of these sounds in the presence of the parents)
4–7 months	Head-turn on lateral plane toward sound; listening attitude to noises 40–50 dB	Babbling at first consists of vowel sounds. At 5/6 months the repetitive production of consonant vowel sequences begins
7–9 months	Direct localization of sounds to side when sounds of 30 dB made at ear level	Speech like babble reinforced by parents. Nonspeech like babble decreases 7–8/12.
9 months to 1 year	Direct localization of sounds to side and below and indirectly to sounds above ear level at 30 dB	Meaningful consonant vowel utterances reinforced
1 year	Direct localization of sounds to side, above and below at 25–30 dB	First meaningful word at 1 year.

Abbreviation: SPL, sound pressure level

Table 20: Speech and language milestone in infant and child

Month/year	Comprehension	Expression
3–6 months	Responds to speech	Babbling, cooing
9 months	Responds to name imitates lip smacking	Babbles with two syllables ('da-da')
12 months	Plays "peek a boo", waves	Imitates, points, 1–2 words
18 months	Understands simple commands objects by name	6–20 words
2 years	Understands two word commands (e.g. "feed teddy")	50 words, joins two words. Join in nursery rhymes
2.5 years	Asks questions	200 words. Uses pronouns (T, "me")
3 years	Understands three word commands (e.g. "give me a doll, teddy, and cup") Understands prepositions	Tasks in short (3–4 words) sentences. Asks "what" and "who" questions
4 years		Asks "why", "when", "how" questions counts up to 20 by rote

- Ototoxic medications including aminoglycoside
- Bacterial meningitis
- Apgar score 0–4 at 1 minute or 0–6 at 5 minutes
- Hyperbilirubinemia at serum level requiring exchange transfusion
- Craniofacial anomalies including those with morphological abnormalities of the pinna and air canal (Treacher-Collins)
- Mechanical ventilation lasting 5 days or more
- Stigmata or other findings associated in the sensory neural and/or conductive hearing loss.

Ideally two tier screening programs should be done. Infants are first screened with, OAE. Infant who fail OAE are screened with auditory brainstem response (ABR) which is more expensive. Screening test takes only about 3–4 minutes if the baby is in neutral sleep. Older babies may require sedation (Fig. 162).

Otoacoustic emissions are used to assess structural integrity and are physiologic measurement of the response of outer hair cells of the cochlea to acoustic stimuli. Therefore, OAE are used to assess the outer, middle and inner ear portions of the auditory systems.

In the test a small ear piece is inserted in the air canal. This produces a sound that evokes an echo or emission from the ear if the cochlea is normal.

Auditory brainstem response assesses the auditory function from the eighth nerve through the auditory brainstem. ABR testing helps in assessing the whole system, from periphery to the auditory nerve and brainstem.

Both OAE and ABR serve as a first objective screening test for normal cochlear function.

The ABR and OAE are tests of structural integrity. Therefore, even if ABR and OAE test results are normal hearing cannot be considered definitely normal until a child is mature enough for a reliable behavioral audiogram.

Any infants who demonstrate delayed auditory and/or communication skill development, even if he/she passes newborn hearing screening should receive an audiological evaluation to rule out hearing loss.

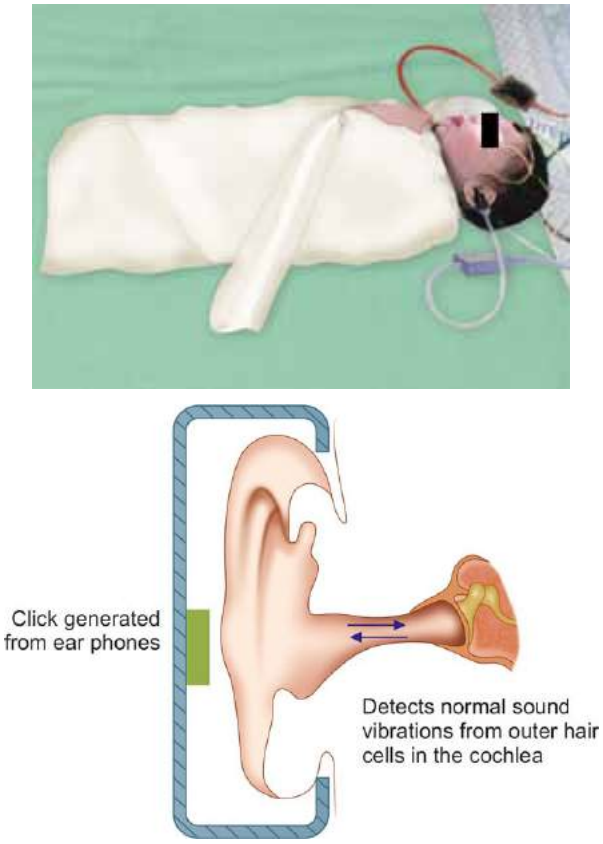


Fig. 162: Newborn hearing screening by otoacoustic emission

SCREENING TEST FOR OLDER INFANTS AND CHILDREN

Screening at 6–12 Months

Distraction Test

(Also discussed in Neurology Examination section of Pediatric Neurology)

This has been the mainstay of hearing screening but has been replaced by universal neonatal screening. It is a diagnostic test for hearing. It is performed between 6 months and 12 months of age but preferable 6–9 months of age. The test (Figs 163A and B) is based on the principle that normal response is observed when sound is presented to an infant and the infant then turn their head to locate the source of sound. Two testers are required: the first tester presents the sound out of the infant's line of vision while the other holds the infant's attention in a forward direction. The test involves delivering of frequency-specific stimulus presented at a quiet level (35 dB) to the side and slightly behind the infant seated on a parent's knee. The child will turn the head to sound produced by first tester, when second tester removes the object of attention (Fig. 163B). Distraction test requires a behavior response and therefore a direct test of hearing sensitivity.

Visual Reinforcement Audiometry (10–18 Months)

For younger children who are unable to understand instruction (<2 years) visual reinforcement audiometry is

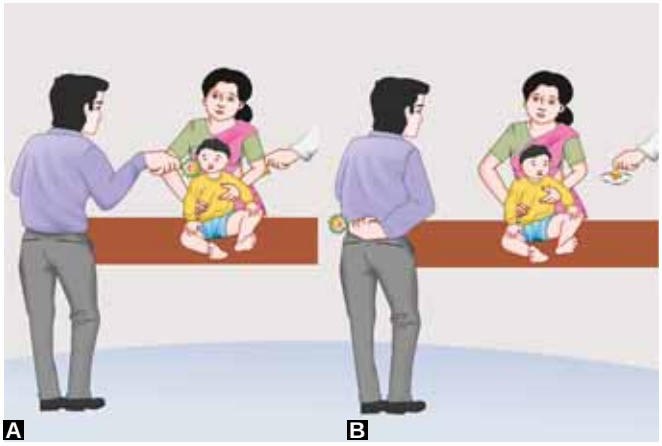
very useful. It is suitable screening test in children between 10 months and 18 months. While an assistant plays with the child, sound of a specific frequency are emitted from speaker. When the child turns to it, the tester lights up a toy placed on the speaker, to reinforce the sound with a visual reward (child is encouraged).

Speech Discrimination Test (20–36 Months)

Child is asked to identify miniature toys or pictures when tester calls them by name. The pictures of toys are chosen so that the sound may easily be confused, for example: ship, brick, chick and fish. The words must be within the vocabulary of the child to be tested and it is first necessary to know that the child knows the names of the pictures or toys. The tester should be 6 feet away from the child and lip must be covered (Fig. 164).

Performance Test (30–36 Months)

The child is conditioned to perform some motor act in response to sound stimulus. For instance the child is conditioned to drop a toy into a box at the command go. "Go test" is used for low frequency. Once the child is conditioned the tester can reduce the test sound down to threshold level, behind the visual field of child. The sound 'Ah!' can be used for high frequency. Clue to the child must be avoided.



Figs 163A and B: Hearing response test (distraction test)

Fig. 164: Speech discrimination test using miniature toy. Testers mouth should be covered to prevent lip reading

Pure Tone Audiometry (5 years) by Sweep Test

The sweep test: The sweep test is widely used for auditory screening at 5 years old in school. The sweep test is used to register children to hear test sound at 20^{o} level.

Pure tone audiometry: Threshold audiometry is usually possible in children more than 5 years to assess severity of hearing loss and nature of hearing loss. Pure tone audiometry allows distinction between conductive, sensory neural and mixed pattern of hearing loss.

Tympanometry

Tympanometry is a convenient and rapid method of detecting middle ear disease. It requires little cooperation from the child and can be performed at any age. It is able to identify children with fluctuating conducting hearing loss which may be missed on a simple sweep test. Tympanometry can give a good indication of the function in the middle ear.

Assessment of Hearing

History:

- Pregnancy, delivery (illness congenital infection)
- Neonatal history: Neonatal sepsis, requirement of intensive care, use of antibiotics (gentamycin)
- Postnatal history: Meningitis, head injury
- Family history: Congenital deafness, consanguinity (Pendred syndrome, Waardenburg syndrome).

Physical Examination

Facial dysmorphism:

- Ear abnormalities (Treacher-Collins, Goldenhar syndrome)
- Eye sign: Usher and Refsum (retinitis pigmentosa)
- Skeletal abnormality: Klippel-Feil syndrome (cervical vertebral fusion, low hair line webbed neck), Crouzon (oxycephaly, proptosis prominent forehead)
- Skin, nail or hair disorder (Waardenburg syndrome).

Fundoscopic Examination

To find eye signs associated with deafness: Retinitis pigmentosa in Usher syndrome and Refsum syndrome, chorioretinitis in congenital CMV infection.

Assessment of Development

Especially hearing, speech, language and communication development.

Neonatal period:

- Startles and blinks at sudden noise
- Neonatal screening by OAE ± ABR
- Less than 2 months: The child startles, blinks or cries to loud noise sound during assessment or at home
- Around 2–6 months: Turn to voice or smiles and quieten to voice
- Around 6–12 months: Turn immediately to sound on each side. Response to name at 12 months.
  - Distraction test: Distraction test for hearing response can be carried out at this stage
- Around 10–18 months: Visual reinforcement audiometry can be carried out at this stage.
- Around 2–3 years: Speech discrimination test with miniature toys or pictures can be carried out at this stage.

Table 21: Screening and diagnostic

Age	Screening	Diagnostic
0	Assessment of risk factor: • Otoacoustic emission • Auditory brainstem response	Response audiometry (rarely done) Cortical evoked response Brainstem evoked response
6–12 months	Infant distraction test at minimum sound level (30 dB)	Distraction test at measured sound level
12–18 months	Visual reinforcement testing at 40 dB	Visual reinforcement testing at measured sound level an impedance testing
>2 years (24–36 months)	Speech discrimination test (toy or picture discrimination at 40 dB)	Pure tone audiometry using play technique
>2 ½ years (30–36 months)	Performance test with condition Go game at 30 dB	Performance test with measures sound level • Go game • Free-field audiometry
5 years	Pure tone audiometry screening by sweep test	Scored word list via headphones from cassette tape Impedance testing

- Two and a half years to 3 years: Performance test or play audiometry test can be carried out at this stage. Child is conditioned to perform in response to sound without using hand sign.
- Five years: A pure tone audiogram is delivered to each air separately via headphones. Each sound is loud at first and reduced to establish hearing threshold (Table 21).

Hearing Assessment in Children (0–5 Years)

Investigation

Primary Investigation

- Audiogram
- Audiogram of first degree relatives of affected child (Figs 165 and 166)
- X-ray skull: For calcification as found in congenital CMV and toxoplasmosis
- ECG: For evidence for prolonged QT interval in Jervell syndrome
- Ophthalmological: For diagnostic (retinitis pigmentosa, chorioretinitis) and correction of refractory errors
- Urine: Microscopic hematuria in Alport syndrome. For evidence of CMV (owl's eye appearance epithelial cell).

Further Investigations as Indicated

- TORCH screen (CMV, rubella)
- Full blood count
- Thyroid function test
- Metabolic
- Renal ultrasound
- Chromosomes:
  - Karyotyping
  - Genetic analysis: Connexin 26 mutation (common cause of recessive nonsyndromic deafness)
- MRI: Cochlea/internal auditory meatus
- Vestibular investigation/ERG.

Management

Refer for Assessment

- If failed hearing screen
- Parental worry about hearing.

Management of hearing loss is multidisciplinary and may include ENT and genetic referral, cardiologist, SALT and social workers.

Treatment options include hearing aids and cochlear implantation which can provide hearing for children who are profoundly deaf which allows speech to be heard at 32–45 dB level.

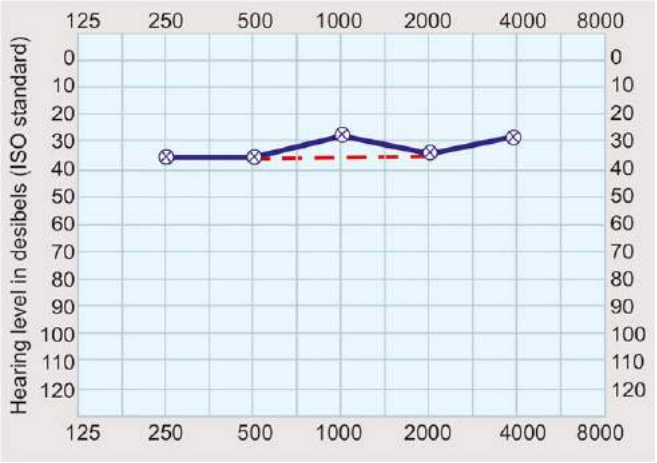


Fig. 165: Audiogram showing bilateral conductive deafness

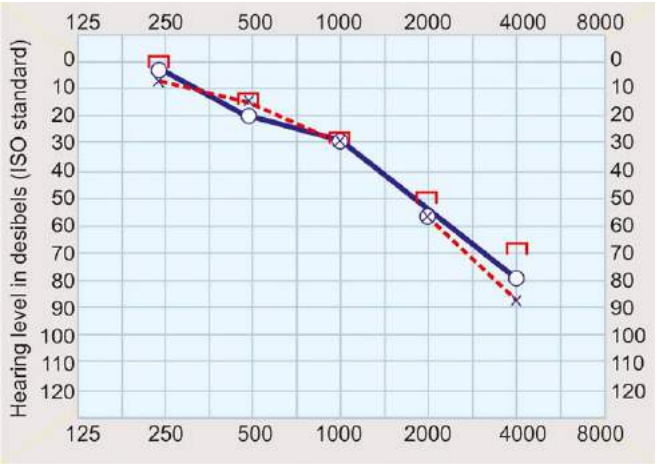


Fig. 166: Audiogram showing bilateral sensory neural deafness

VISUAL IMPAIRMENT

There are two main types of visual impairment:

1. Low vision: Partially sighted
2. Blind: Severely sight impaired.

The WHO definitions are:

Low vision: Visual acuity less than 6/18 but equal to or better than 3/60 in the better eyes with best correction or visual field less than 20°.

Blind: Visual acuity less than 3/60 or visual field loss less than 10° in the better eye with best correction.

GLOBAL BURDEN OF VISUAL IMPAIRMENT

About 160 million globally is visually impaired and about 40 million (25%) is blind. Ninety percent of the world's visually impaired live in developing countries and 50% of it is potentially preventable.

Primary Causes Vary According to Socioeconomic Conditions

Low income countries:
- Corneal scarring: Vitamin A deficiency, measles, trachoma, ophthalmia neonatorum
- Cataract: Congenital rubella (Fig. 167)
- Meningitis
- Onchocerciasis (river blindness).

Middle income countries:
- Congenital cataract and glaucoma
- Retinopathy of prematurity.

High income countries:
- Retinopathy of prematurity
- Genetic diseases: Retinoblastoma, albinism
- Cortical visual impairment
- Optic nerve hypoplasia.

Amblyopia

It is the permanent loss of VA in an eye that has not received clear images in the sensitive period of visual development (in the first decade of life). Most commonly due to squint but may also develop with refractive errors and cataract. It is also called dull eye or lazy eye.

Visual Development

- At birth: Most babies can fix and follow horizontally
- Six weeks: Both eyes move together and will follow a light source
- Three months: Visual acuity is 6/60, a baby should watch their hands and notice toys
- Six months: A baby reaches for toys and passes from one hand to the other.

Fig. 167: A 1-year-old child with congenital rubella syndrome wearing glasses for low vision after cataract surgery. Note also a hearing aid in the right ear for correction of hearing deficit

Clinical Suspicion of Visual Impairment

- Not smiling responsively by 6 weeks post-term
- Lack of eye movements with parents
- Visual inattention
- Random eye movement
- Nystagmus
- Photophobia
- Squint
- Loss of red reflex from cataract
- A white reflex in the pupil (leukocoria), which may be due to retinoblastoma, cataract or ROP.

Visual Assessment

Birth:
- General observation: Eye movement
- Ophthalmoscopy:
  - Red reflex: Dark spot in the red reflex can be due to cataract corneal abnormalities or vitreous opacities
  - The red reflex may be absent in dense cataract
  - White reflex (leukocoria or white pupil): Cataract, retinoblastoma or ROP
- Around 6–8 weeks: Optokinetics (nystagmus demonstrated by looking at moving stripe target) present in normal vision
- Two years: Identification of pictures
- Three years onward: Letter matching on the single letter chart, e.g. Sheridan Gardiner chart
- Five years: Identification of letters on Snellen chart.

MANAGEMENT

- General management: Multidisciplinary team in supporting parents and child like any other child with disability.
- Medical:
  - Early surgical treatment in the neonatal period for cataract. Careful follow-up of very preterm babies for ROP
  - Correction of refractory errors
- Treatment of amblyopia:
  - Regular orthoptic monitoring with ongoing correction of refractory error in the weaker eye is required
  - Correct refractory error with appropriate glasses
  - Eye patching: Attempts to reverse amblyopia by covering the better eye to force the weaker or lazy eye to work
  - Ocular muscle surgery
- Developmental and educational:
  - Full developmental and audiological assessment by a specialist team followed by appropriate educational provision in accordance with assessment
- Social: Disability benefit and social service benefit
- Genetics:
  - Up to 50% of severe visual impairment is genetical
  - Genetic assessment and appropriate genetic counseling to prevent is therefore necessary
- Prevention: In developing countries:
  - Prevention of night blindness: High potency vitamin A supplementation to child at 9 months along with

measles vaccine and vitamin A supplementation along with national immunization for polio eradication/or deworming on separate fixed dates
- Provide vitamin A supplementation in severe acute malnutrition and measles
- Awareness of risk to premature infants undergoing intensive care (ROP)
- Rubella immunization (to prevent cataract)
- Hib vaccine and pneumococcal conjugate vaccine (PCV), to prevent meningitis-induced blindness
- Good diabetic control of children with juvenile diabetics to prevent diabetic retinopathy and cataract.

Secondary Prevention

Early identification and treatment of correctable causes like cataract, amblyopia and squint.

SQUINT (STRABISMUS)

Squint is common in childhood. This is the term used to describe a misalignment of the eyes or visual axis. It interferes with binocular single vision which depends on correct alignment and similar image clarity of both eyes from the newborn period.

CAUSES OF SQUINT

- Visual loss
- Refractory errors
- Ophthalmoplegia (central or peripheral)
- Idiopathic.

Various Terms Used in Eye Movement Related to Squint

- Monocular movement: Abduction, adduction
- Binocular movement:
  - Conjugate movement: Eye move in same direction, include left gaze, right gaze
  - Disconjugate movement: Eye move in opposite directions, include convergence (esotropic or inward and exotropic or outward).

TYPES OF SQUINT

Paralytic Squint

When one eye considered separately is not capable of a full range movement, then it is called paralytic squint. These are less common and reflect pathology in the cranial nuclei or nerves (III, IV and VI), neuromuscular junction, extraocular muscles or orbit. Cranial nerve palsy causes divergent (III) squint, vertical squint (IV) or convergent squint (VI). A VI nerve palsy may be associated with RICP (false localizing sign).

Restrictive syndrome: Paralytic squint causing mechanical restriction due to developmental anomalies includes:

- Mobius syndrome: Congenital absence of VII and VI nerves due to mid brain lesion
- Brown syndrome: Restriction of superior oblique tendon as it traverses the trachea causing failure to elevate the affected eye
- Duane syndrome: Absence of abducens (VI nerve) nucleus. Absence of abduction of lateral rectus causing convergent squint.

Nonparalytic Squint

- When considered separately each eye is capable of full range of movement.
- Common in children:
  - At birth: Normal exotropic (nonparalytic deviation)
  - Up to 3 months: Normal esotropic or exotropic deviation
  - Around 1–5 years:
    - Normal accommodative esotropia (conver gent) but often due to refractory errors (Fig. 168)
    - Secondary esotropia (convergent) associated with visual impairment in pathological conditions like cataract, retinoblastoma, corneal scar, ROP.

Other Types of Screening

- Latent squint: A squint that is controlled by subconscious effort and is not always apparent. In certain situation such as fatigue the control is lost and the latent squint will become more obvious
- Manifest squint: Constant squint
- Pseudosquint: This arises when wide epicanthic fold and broad nasal bridge give the appearance of squint which is excluded by cover test which will be normal and the light reflex central.

CLINICAL EVALUATION

History

- From parents: History of intermittent squint. Diplopia infrequent complaint
- Expreterm baby
- Spastic children (CP) more vulnerable.

Examination

- Posture: Abnormal head posture (torticollis)
- Look for epicanthic fold
- Narrow or wide interpupillary distance (hypertelorism, Fig. 169)
- Test for VA and eye movement (fixation and following).

Screening Test

- Corneal light reflex

A penlight is shone in the child's eye from 30 cm. If there is a misalignment the reflection is not in the same spot in each eye (Fig. 170).

Cover test (Discussed under the head Neurological Examination)

Fig. 168: Bilateral nonparalytic esotropic squint (convergent) in a child

Fig. 169: Hypertelorism causing pseudosquint

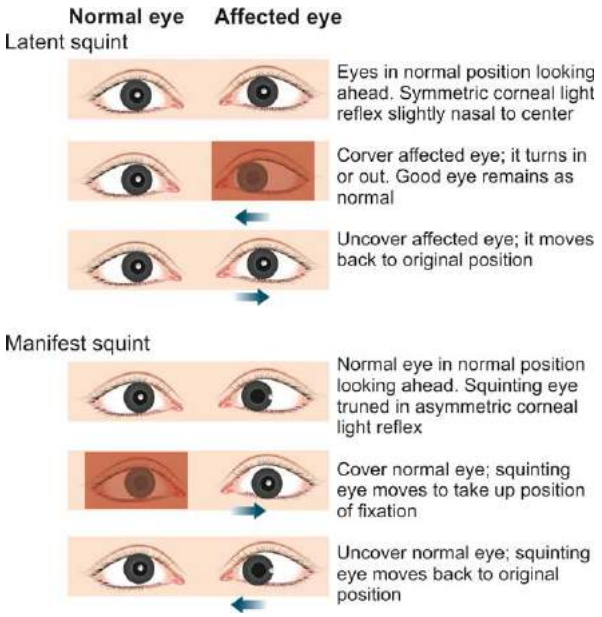


Fig. 170: Cover test

Management

Treatments are usually under the supervision of orthoptist in cooperation with ophthalmic surgeon. A child must be seen by an ophthalmologist if squint is:

- Paralytic
- Divergent
- Persistent beyond 3 months.

Management strategies include:

- Correction of any refractory error: Wear glasses
- Occlusion
- Patching or penalization (atropinization) of the good eye to prevent any treat amblyopia
- Eye muscle exercise
- Surgery: Only after full assessment and treatment of the positive factors, deviation persists and no further improvement is anticipated.

PTOSIS

Drooping of one or both eyelids from birth is common. It is essential to distinguish congenital from acquired.

CAUSES OF PTOSIS

Congenital

- Idiopathic:
  - Most common "cause"
  - Seventy percent unilateral (Fig. 171)
  - Eye movements normal

May have Marcus-Gunn "jaw-winking" phenomenon (synkinesis)

- Causes other than idiopathic:
  - Horner's syndrome
  - Myasthenia gravis
  - III nerve palsy
  - Syndromes associated with ptosis, e.g. Noonan, Saethre-Chotzen.

Acquired

- Horner's syndrome
- Myasthenia gravis (Fig. 172)
- III nerve palsy
- Migraine
- Trauma
- Infection/inflammation of lid or orbit
- Mitochondrial myopathies.

Fig. 171: A congenital idiopathic unilateral (right) ptosis in a child

Fig. 172: A child with bilateral ptosis in myasthenia gravis (Tensilon test was positive)

Myasthenic Syndromes

Classified in three main types: (1) Myasthenia gravis; (2) Transient neonatal myasthenia; (3) Congenital myasthenia syndromes.

Myasthenia gravis:

- It is most common in females between 18 years and 25 years.
- Incidence: 2/1,00,000.

It is an autoimmune disease in which antibodies are formed against to either the acetyl choline receptor or muscle specific kinase (MusK).

Clinical Features

- The hallmark of the condition is fluctuating, fatigue weakness
- At onset 50% of patients have ptosis, eventually more than 80% developing it
- A myasthenic crisis with paralysis of respiratory muscles may be triggered by infection, fever, emotional stress, surgery, pregnancy or overexertion.

On examination reveals fatigable weakness as evidenced by poor sustained shoulder abduction with arms outstretched and proximal weakness:

- Reflexes normal or brisk.

Diagnostic Investigation

- Edrophonium test: IV edrophonium (tensilon) is given which improves muscle weakness within 1 minute
- Ice-pack test for evaluation of ptosis: If neuromuscular junction dysfunction is being considered in a child with ptosis, hold in ice-pack firmly over one eye for 2 min. Improvement in the ptosis (i.e. better elevation of the eyelid) relative to the opposite (control) eye strongly suggests myasthenia as the cause of the ptosis.
- Acetyl choline receptor antibodies are present in more than 50% of cases
- X-ray test ± CT or MRI: To identify thymoma.

Treatment

Options:

- First line: cholinesterase inhibitor such as pyridostigmine
- Steroids: Prednisolone may be used in conjunction with anticholinesterase but may cause initial deterioration.
- Plasmapheresis and IVIG: Use for myasthenic crisis and preoperative thymectomy
- Thymectomy: Done in case of thymoma.

LEARNING DIFFICULTIES (DISABILITIES)

The term LD is currently used as previous term of learning disabilities believed to be more offending term. The following are the characteristics of the learning difficulties.

- Unexpected underachievement in adequate educational settings
- Learning difficulty is not a single disability but a category composed of disabilities in one or more skill domains: listening, speaking, basic reading (decoding and word recognition), reading comprehension, writing, arithmetic calculation and mathematical reasoning
- Approximately 5% of children in industrialized countries are identified as some type of LD
- Not caused primarily by cultural, educational, environmental and socioeconomic factors or by other disabilities (mental deficiency, visual or hearing impairments, or emotional disturbance)
- Factors associated with increased risk for LD include first degree relative with dyslexia, lead exposure and prenatal cigarette exposure
- The commonest specific learning disability is known as dyslexia.

DYSLEXIA

Figure 173 is representing dyslexia.

Definition

Developmental dyslexia is a neurodevelopmental learning disability characterized unexpectedly poor reading and underachieved scholastic performance relative to child general intelligence and not explained by other factors such as socioeconomic background or gross neurological deficit. The DSM IV defines dyslexia as academic skill-specific learning disorder. Developmental dyslexia is known to have a considerable genetic component but the mechanism causing dyslexia is unknown.

Incidence

It is an important cause of learning disability. Dyslexia affects four out of five children with LD. The overall incidence of dyslexia is not known. In UK 5–10% of children have dyslexia.

Etiology

The exact etiology is unknown and the mechanism causing dyslexia is not clear. Not caused primarily by educational, cultural, environmental or socioeconomic factors, i.e. underprivileged children of developing countries and well-served children of industrialized countries are equally affected in similar frequency.

Factors Associated with Increased Frequency

- First degree relative with dyslexia
- Prenatal cigarette exposure
- Lead exposure.

Fig. 173: Dyslexia

Factors Associated with Decreased Frequency

Familial high blood pressure-associated negatively with dyslexia.

Although mechanism involved in dyslexia is unclear it seems increasingly clear that dyslexia is a neurobiological syndrome characterized by both structural and functional brain differences. Evidence of phospholipid metabolism has been implicated in dyslexia like other neurodevelopmental disorders like autism. Phospholipid present in neuronal membrane can affect neural function. Abnormal phospholipid metabolism with fatty acid deficiencies are more associated with dyslexic children. Phospholipid activating factor is a neuroimmune mediator with multiple functions including cell signaling, vasodilatation and stimulation of leukocyte adhesion.

Process Involved in Dyslexia

Cognitive process required for reading are involved: The domain of impairment includes:

- Decoding—which involves converting letter strings into sound sequence
- Linguistic comprehension
- Encoding—spelling out.

The dyslexic child may have associated expressive language difficulties, DCD and ADHD.

Clinical Features

Dyslexia is a chronic persistent developmental disorder.

- Infancy:
- Difficulty in manipulating language sound
- Poor phonologic awareness
- Early childhood:
  - Difficulty in identifying words
  - Difficulty in reading
  - Difficulty of breaking words into component sound and again resynthesizing them
- Later childhood:
  - Reading is slow and inaccurate
  - Spelling are poor, mirror imaging of words may occur, e.g. "b" for "d" (Fig. 174)
  - Avoidance of reading.

Important clues to detect dyslexic:

- Mispronunciation
- Delayed language
- Word finding difficulties.

Diagnosis

Diagnosis is educational with discrepancy between ability (IQ) and scholastic achievement. Early predictors are difficulties in naming numbers, letters and naming pictures.

Associated DCD and language difficulties should be assessed.

Management

Pediatrician role is to consider the diagnosis and to exclude other diagnosis.

Dyslexia support societies are often helpful.

Fig. 174: Mirror imaging of words in a dyslexic child

Fig. 175: Special reading program using animal pictures attached to words to understand words in dyslexic child

Specialist Advice and Support from Education

- Special reading programs need to be designed including use of computers (Fig. 175)
- Allowance given to weakness of children, e.g. oral test instead of written test when problem of written expression
- Recurrent practice of weak skills
- Children are helped to develop skills to breakdown spoken words into smaller units of sounds
- Provision of extra time in school may be arranged to learn decoding or encoding words
- Curriculum modification may have to be done to suit dyslexic child
- Examination may have to be taken orally instead of written.

Prognosis

Dyslexia is a chronic developmental disorder and not a transient phenomenon. If severe, it can lead to low self-esteem and school refusal. Long-term outlook depends on severity of disorder together with support required for education. Many dyslexics are known to have successfully completed studies.

PERVASIVE DISORDERS

It encompasses impairment and deviance of reciprocal social interaction, language and communication. It is difficult to say whether there is global increase or decrease in pervasive disorders, which includes autism as apparent increase of such disorders in recent past may be due to increased awareness of this condition among child health providers and another allied departments, among parents. Changes in diagnostic criteria and classification system may at least have contributed to reported increased rates of autism spectrum disorders (ASDs) in epidemiological research. In developing countries, these serious developmental disorders are not well-appreciated and not picked up early until recently when concerned stake holders have started recognizing the condition increasingly.

SPECTRUM OF PERVASIVE DEVELOPMENTAL DISORDERS

Autistic disorders (core autism): Severe defect in reciprocal social interaction, communication, language and behavior.

Asperger syndrome: Clumsy, not retarded without speech problem, but restricted socialization, narrow range of interest.

Rett's syndrome: It is a specific disorder found in girls only with developmental regression, lack of hand use and use of stereotypic hand movement.

Childhood disintegrated disorders: A massive developmental regression takes place in previously normal child when he or she reaches at an age of 4–10 years. There is no neurodegeneration of brain or psychosis like schizophrenia.

Pervasive developmental disorder otherwise not specified: It is the disorders in children with autistic behavior who do not fulfill the criteria for any other criteria in the spectrum.

AUTISM SPECTRUM DISORDERS

Since its original description by Leo Kanner in 1943, autism has come to be recognized as a neurodevelopmental disorder that manifests in infancy or early childhood and encompasses both delays and deviance in a "triad" of behavioral domains: reciprocal social interaction, communication, and restricted and repetitive behaviors and interests. Autism is thought to be the cornerstone of a spectrum of disorders, commonly referred to as ASDs. It is a part of pervasive behavioral disorder which consists of:

- Autistic disorder (core autism)
- Pervasive disorders otherwise not specified
- Asperger's syndrome
- Childhood disintegrated disorders.

The spectrum of ASD runs from individual of all ages who are severely impaired to those considered high functioning. The term high function is misleading in that an individual with high intellectual ability can still be significantly impaired in terms of social skills.

The last two are very rare disorders.

Though associations have been shown between increased rates of ASD and genetic, chromosomal, and/or brain abnormalities, no biological marker adequately accounts for a significant minority of cases with reasonable specificity. Therefore diagnosis is currently based on behavioral phenotype alone.

ETIOLOGY AND EPIDEMIOLOGY

Complex interaction between multiple genetic and environmental factors is involved in ASD (i.e. gene-gene or gene-environmental interactions). Autism spectrum disorder is highly genetic. Around 60–90% of monozygotic twins are concordant for autism spectrum disorder, compared with about 10% for dizygotic twins.

Around 10–15% of ASD are associated with some known genetic disorders like Fragile X syndrome (about 3%), tuberous sclerosis (about 2%), and maternal duplication of 15q1-q13 (2%), and deletions and duplications of 16p11 (about 1%).

CLINICAL FEATURES OF AUTISM

Core symptoms of ASDs affect domains of socialization, communication, and behavior. Clinical signs are usually present by age 3 years, but typical language development might delay identification of symptoms. The core domains are given in Tables 22 to 24.

Table 22: Core domains of autism

A.	**Socialization**
	• Impaired use of nonverbal behaviors to regulate interactions • Delayed peer interactions, few or no friendships, and little interaction • Absence of seeking to share enjoyment and interests • Delayed initiation of interactions • Little or no social reciprocity and absence of social judgment
B.	**Communication**
	• Delay in verbal language without nonverbal compensation (e.g. gestures) • Impairment in expressive language and conversation, and disturbance in pragmatic language use • Stereotyped, repetitive, or idiosyncratic language • Delayed imaginative and social imitative play
C.	**Restricted, stereotyped, and repetitive patterns of behavior**
	• Preoccupation with stereotyped or restricted interests or topics • Adherence to routines, rigidity, and preservative behavior • Stereotyped, repetitive motor mannerisms, and self-stimulatory behavior • Preoccupation or fascination with parts of items and unusual visual exploration

Table 23: Early signs and symptoms

Qualitative abnormalities in communication	
	• Delay or lack of development of spoken language that is not accompanied by an attempt to compensate through the use of gesture or mime • A lack of babbling • A lack of pointing to express interest or a lack of spontaneous pointing • Odd speech patterns, words or phrases, echolalia, unusual tone and pitch
Qualitative abnormalities in social interaction	
	• Poor eye contact • Failure to follow gaze • Limited social smiling—does the child spontaneously smiles in greeting? • Limited imitation of others (also seen in play) • Poor use of gestures—for example, shakes head, nods, waves and claps • Failure to show an interest • Does the child show things of interest?—for example, brings toys to parent? • Does the child respond to others' emotions? • Limited pretend and imaginative play • Limited social play—for example, peekaboo, pat a cake
Restricted and repetitive interests and behaviors	
	• Repetitive play—for example, lining up cars • Unusual interests, interest in nonfunctional elements of play material • Oversensitivity to household noises • Extreme adverse reaction to change in routine • Motor mannerisms or stereotyped behavior—for example, hand flapping • Sensory hypo/hypersensitivity
Source: Adapted from the National Autism PC of UK	

Psychiatric, Neurodevelopmental and Behavioral Comorbidities

Disturbances of behavior, attention, activity, thought and emotion are common in children with ASD and/or developmental difficulties.

Table 24: Behavioral features of autism spectrum disorders
Reciprocal social interaction
• Absence of joint attention (i.e. failure to show interest, share a focus of attention and follow gaze) is highly suggestive of core autism • Inadequate facial expressions, including lack of social smiling and limited use of gestures, e.g. shaking head, nodding, waving, clapping
Communication
Failure to acquire language as expected
Interests and activities
• May have a preoccupation with an interest that is abnormal in intensity, content or both • Stereotypes (hand flapping, finger flicking, rocking, head banging and twirling) or mannerisms are commonly seen but are not always evident before the age of 3 years • Hypo- or hypersensitivity to environmental stimuli, e.g. loud noises, insensitivity to pain, or fascination with smells, textures or colors of food or fabrics
Regression
Regression most commonly affects language, usually at less than 10 word stage, therefore, occurring between 18 months and 24 months of age
Learning disabilities
learning disabilities (IQ less than 70) affects 70–80% of individuals with ASD
Epilepsy
Epileptiform EEGs are common in autism, both with and without regression, and studies have shown that 10% of children with autism have an epileptiform EEG without any clinical evidence of seizures

Psychiatric, behavioral and neurodevelopmental comorbidities associated with autistic spectrum disorders are as follows:

- Attention-deficit hyperactivity disorder
- Tourette syndrome/tic disorder
- Dyspraxia/DCD
- Dyslexia
- Obsessive-compulsive disorder
- Specific phobias
- Anxiety
- Depression/mood disorder
- Sleeping difficulties
- Feeding difficulties.

Other Comorbid Symptoms

Following are the comorbid symptoms observed in ASDs.

Gastrointestinal:

- Food selectivity
- Gastroesophageal reflux
- Constipation.

Sleep:

Sleep disruption.

Differential Diagnosis of Autism Spectrum Disorder

- Global developmental delay
- Learning difficulties
- Hearing problems
- Visual impairment
- Specific language disorders
- Selective mutism
- Reactive attachment disorder
- Lack of opportunity for interaction
- Rett syndrome (if features of regression).

Some medical conditions are associated with ASD:

- Tuberous sclerosis
- Fragile X
- Down syndrome
- Neurofibromatosis
- Phenylketonuria (untreated)
- Fetal alcohol syndrome
- Smith-Lemli-Opitz syndrome
- CHARGE syndrome
- Duchenne muscular dystrophy
- Congenital rubella
- Iron-deficiency anemia.

Differences between autism, pervasive developmental disorder not otherwise specified (PDD-NOS) and Asperger's syndrome are discussed in Table 25.

Diagnosis

The diagnosis of ASD depends on carefully obtained history and observation in several settings emphasizing core behavioral features.

The diagnosis of core autism is stable in third even second year of life. Diagnosis of broader range of ASD is less reliable. Diagnostic uncertainty should not however exclude a child from early social/communication intervention program strategy.

Use of two research quality, gold-standard assessment methods based on DSM criteria, the autism diagnostic observation schedule (ADOS) and the revised autism diagnostic interview (ADI-R), have improved accuracy and reliability of diagnosis. The ADOS is a semi-structured standardized assessment for social behavior, communication and imaginative play, and is used in research and clinical settings. To diagnose individuals with intellectual disability is difficult because behaviors might not be specific to ASDs; the ADOS diagnostic algorithm was revised to address these issues. The time needed for administration of the ADI-R (1–3 hours) precludes its use in many clinical settings.

Assessment of Autism Spectrum Disorders

Specialist assessment:

- A multidisciplinary approach is required to cover all aspect of ASD.
- All professionals involved in diagnosing ASD in children and young people should consider using either ICD-10 or DSM-IV.
- Autism spectrum disorders should be part of the differential diagnosis for very young (preschool) children displaying absence of normal developmental features, as typical ASD behaviors may not be obvious in this age group.
- The use of an appropriate structured instrument may be a useful supplement to the clinical process to help identify children and young people at high risk of ASD.
- If, on the basis of initial assessment, it is suspected that a child or young person may have ASD, they should be referred for specialist assessment.

Table 25: Differences between autism, pervasive developmental disorder-not otherwise specified and Asperger's syndrome

	Autism	PDD-NOS	Asperger's syndrome
Age of recognition (diagnosis*)	1–6 years (2–5 years)	Variable	> 3 years (6–8 years)
Regression	About 25% (social or communication)	Variable	No
Sex ratio (male:female)	2:1	Male > Female (variable)	4: 1
Socialization	Poor; >2 DSM-IV criteria	Variable	Poor
Communication	Delayed, deviant; might be nonverbal	Variable	No early delay; qualitative and pragmatic difficulties later
Behavior	More impaired than in Asperger's syndrome or PDD-NOS (includes stereotypy)	Variable	Variable (circumscribed interest)
Intellectual disability	> 60%	Mild to severe	Mild to none
Cause	More likely to establish genetic or other cause than in Asperger's syndrome or PDD-NOS	Variable	Variable
Seizure	25% over lifespan	Roughly 10%	Roughly 10%
Outcome	Poor to fair	Fair to good	Fair to good

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; PDD-NOS, pervasive developmental disorder-not otherwise specified
*Average age at diagnosis
Source: Data adapted from Volkmar and Pauls, 4th edition.

- Specialist assessment should involve a history-taking element, a clinical observation/assessment element, and the obtaining of wider contextual and functional information.
- Autism spectrum disorders-specific history-taking instruments may be considered such as ADOS or ADI-R as a means of improving the reliability of ASD diagnosis.
- Autism spectrum disorders-specific observational instruments may be considered by the healthcare professionals for better diagnosis of ASD.
- A comprehensive evaluation of speech, language and communication skills should be done in all children and young people with ASD. This may help to take appropriate intervention.
- Assessment of intellectual, neuropsychological and adaptive functioning should be considered in children and young people with ASD.
- Physical examination: Where relevant, physical examination should be done
  - Examination of physical status, with particular attention to neurological and dysmorphic features should be noted
- Investigations: Investigations include:
  - Electroencephalography
  - Karyotyping and fragile X DNA analysis
  - Examination of audiological status
  - Investigations to rule out recognized etiologies of ASD
- General healthcare intervention

  Medical and emotional problem associated with ASD should be treated accordingly by healthcare professionals.
- Occupational therapy and physiotherapy assessments may be offered when required.

Investigations

Investigations are required to exclude organic diseases. These are based on clinical presentation and should be performed if clinically suggestive.

The investigations are:

- Karyotyping and Fragile X testing for all individual
- Neuroimaging and electroencephalography: If clinically indicated
- Assessment of gastrointestinal tract
- Investigation for assessment of hearing and visual impairment.

Management

Management should be multidisciplinary and take a behavioral and educational approach, as well as providing information and support to the family in the form of a family care plan. Early social and communication-based intervention programs are effective in the management of ASD.

Nonpharmacological Intervention

Management of core symptoms of ASD is as follows:

Socialization

Intervention to support social communication should be considered for children with ASD with the most appropriate intervention being assessed on individual basis.

Educational curricula:
Treatment and education of autistic and related communication handicapped children (TEACCH), strategies for teaching based on autism research (STAR), parent training, and inclusion with trained shadow.

Communication and language:
- Interventions to support communication in ASD are indicated, such as the use of visual augmentation such as pictures and objects.
- Didactic and intensive training.

Social-skills training:
Social skills training and social stories.

Behavioral treatment:
- Behavioral interventions should be considered to address a wide range of specific behaviors in children and young people with ASD, both to reduce symptom frequency and severity and to increase the development of adaptive skills.
- Behavioral therapy should be considered for children and young people with autism who experience sleep disturbance
- Behavioral interventions are: discrete trial instruction, pivotal response training, and relationship development intervention.

Communication

Communication intervention:
Within a comprehensive program (e.g. pivotal response training, or other center), social pragmatics approach, and parent training.

Augmentative and assistive communication:
Picture exchange communication system, sign language, and assistive technology (e.g. vocal output devices).

Behavioral (e.g. play, reciprocal communication)
Floor time/developmental, individual differences, relationship-based approach, applied verbal behavior.

Educational:
TEACCH, STAR.

Behavior

Behavioral intervention:
Discrete trial instruction, and other comprehensive programs using applied behavior analysis.

Psychopharmacology:
Selective serotonin reuptake inhibitors, anticonvulsants, atypical antipsychotics, α-2 agonists.

Role of Occupational Therapy

Children affected with ASD may be benefited from occupational therapy such as providing advice and support in adapting environments, activities and routines in daily life.

Dietary Management

Young children with ASD display significant food selectivity and dysfunctional feeding behavior. Restricted diets may be adversely affect growth and deficiency disorders. Advice on diet and food intake for such children should be sought from dietician.

Pharmacological Intervention

Pharmacological intervention should only be taken by the experienced doctor with appropriate training in dealing with psychotropic drugs and capable of managing and providing support as required if adverse effects arise from such drugs.
- Methylphenidate
  May be used for ADHD-associated ASD
- Desperidone
  May be considered in ASD with aggressive behavior or tantrums
- Melatonin
  May be considered in ASD children with significant sleep problem.

Support Group for Autistic Children

Various autistic societies are present in western countries to support autistic children and their parents. The magnitude of suffering of families of autistic children is significantly more in developing countries than developed countries. It is not only the autistic children who suffer but also their parents who often have to refrain from leading a normal life. Lack of adequate service for autistic children of developing countries hinders proper management of such children.

Prognosis

As ASDs are lifelong neurodevelopmental conditions, behaviors and presentation vary over time with a tendency for progress in all domains, although there is huge individual variation. Determinants of outcome include severity of behaviors, cognitive abilities and useful speech. The majority of individuals remain functionally impaired. Many individuals require specific supports; some adults with higher functioning ASD may be able to live independently and obtain employment but at the present time few adults appear to achieve their full potential. The best predictors of good outcome are development of speech by age 5 and normal IQ.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER

Attention-deficit hyperactivity disorder is a neuro-development condition or pervasive disorder of attention control, usually with hyperactivity and impulsivity. ADHD is responsible for a high morbidity exerting impact on the lives of the affected children, their families and schools, and society (Fig. 176).

DEFINITION OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER

Attention-deficit hyperactivity disorder (ADHD) is a mental health disorder. According to Diagnostic and Statistical Manual 4th Edition (DSM IV), ADHD is currently defined as "a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals of comparable levels of development."

ETIOLOGY

The evidence for ADHD as a neurobiological condition is well-substantiated. Neuropsychological and neuroimaging studies implicate frontal networks or frontostriatal dysfunction as the underlying neural substrate and catecholamine. Deregulation of the underlying pathophysiological substrate. Specific dopamine receptor and transporter genes may increase susceptibility.

Fig. 176: Attention-deficit hyperactivity disorder

COMORBIDITIES

During initial and subsequent assessment several comorbidities associated with ADHD should be taken into account. Some may mimic aspects of ADHD and diagnosis may be difficult. If in doubt, extended assessment or a tertiary opinion is indicated. The important comorbidities are:

- Autistic spectrum disorder/Asperger syndrome
- Dyspraxia/disorder of attention, motility control and perception
- Dyslexia
- Developmental delay/LD
- Tourette/tic disorders
- Oppositional defiant disorder/conduct disorder
- Epilepsy or epileptic syndromes
- Genetic/neurodevelopmental syndromes with behavioral phenotypes
- Child maltreatment.

CLASSIFICATION

The American Psychiatric Association's DSM-IV criteria for the disorder are: six out of nine symptoms of inattention and/or six out of nine symptoms of hyperactivity/impulsivity with noted impairment prior to 7 years of age, in two or more settings, and with clinically significant impairment in social, academic, or occupational functioning. DSM-IV categorizes ADHD into subtypes:

- Predominantly hyperactive/impulsive subtype
- Predominantly inattentive subtype, and
- Combined hyperactive/impulsive and inattentive subtype.

CLINICAL FEATURES AND DIAGNOSTIC CRITERIA

- Preschool children:
  - Reduced play intensity and duration
  - Motor restlessness
  - Associated developmental deficits in motor coordination and language
  - Oppositional defiant behavior is common
- School age children:
  - Play activities lack rich diversity and extension of imaginative play
  - Impaired ability to listen to language reduces:
    - Social interaction
    - Ability to follow complex instructions
    - Ability to engage in extended reciprocal conversation
  - Difficulty with starting and finishing tasks
  - Poorly sustained attention and easy distractibility
  - Difficulty in waiting, reduced awareness of danger, increased frequency of accidents
  - Behavior immature, silly or rude
  - Hyperactivity both motor and vocal with unusual noises
- Adolescents
  - Difficulties in planning and organization become more evident
  - Motor restlessness reduces, inattention persists
  - Increasing self-awareness—secondary emotional problems may mask symptoms
  - At risk of increased aggressive antisocial and delinquent behavior, alcohol and drug problems and accidents
  - Increasing academic underperformance
  - Behavior described as lazy or unmotivated (compounded by unrecognized specific areas of learning deficit).

DSM-IV diagnostic criteria for attention deficit/hyperactivity disorder is given in Table 26.

DIAGNOSIS

Attention-deficit hyperactivity disorder is a clinical diagnosis and the cornerstone of diagnosis is the clinical history.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses of ADHD are mentioned in the Table 27.

TREATMENT OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER

The AAP guideline includes five recommendations regarding treatment of ADHD:

1. Approach and treat ADHD as a chronic health condition
2. Collaborate with partners in designing and evaluating treatment plans and outcomes
3. Provide medication management
4. Provide periodic systematic follow-up
5. Evaluate treatment failure as needed.

Attention-deficit hyperactivity disorder cannot be cured but the core symptoms, associated impairments and complications can be actively managed by a combination of approaches termed "multimodal treatment". Objectives of multimodal treatment in ADHD are to:

- Reduce core symptoms of ADHD
- Reduce comorbid symptoms
- Reduce the risk of further complications
- Educate the child about the disorder
- Educate the adults about the disorder
- Adapt the school and home environment to the patient's needs
- Enhance coping skills of parents and teachers
- Change maladaptive views.

Multimodal treatment includes:

- Pharmacotherapy alone
- Behavior-based treatment alone
- A combination of pharmacotherapy and behavioral treatment and
- Community-based treatment.

Table 26: DSM-IV diagnostic criteria for attention-deficit/hyperactivity disorder

A. Either 1 or 2
1. Six or more of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level
Inattention
• Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities • Often has difficulty sustaining attention in tasks or play activities • Often does not seem to listen when spoken to directly • Often does not follow through instructions and fails to finish school work, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions) • Often has difficulty organizing tasks and activities • Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework) – Often loses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books, tools) – Often is easily distracted by extraneous stimuli – Often is forgetful in daily activities
2. Six or more of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level
Hyperactivity
• Often fidgets with hands or feet or squirms in seat • Often leaves seat in classroom or in other situations in which remaining seated is expected • Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness) • Often has difficulty quietly playing or engaging in leisure activities • Often is "on the go" or acts as if "driven by a motor" • Often talks excessively
Impulsivity
• Often blurts out answers before the questions have been completed • Often has difficulty awaiting turn • Often interrupts or intrudes on others (e.g. butts into conversations or games)
B. Some hyperactive-impulsive symptoms or inattentive symptoms that caused impairment were present before 7 years of age
C. Some impairment from the symptoms is present in two or more settings (e.g. at school or at home)
D. There must be clear evidence of clinically significant impairment in social, academic or occupational functioning
E. The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder and are not better accounted for by another mental disorder (e.g. mood disorder, anxiety disorder, dissociative disorder, or personality disorder)
Based on these criteria, three types of ADHD are identified: 1. ADHD, combined type: If both criteria 1A and 1B are met for the past 6 months 2. ADHD, predominantly inattentive type: If criterion 1A is met but criterion 1B is not met for the past 6 months 3. ADHD, predominantly hyperactive-impulsive type: If criterion 1B is met but criterion 1A is not met for the past 6 months

Table 27: Differential diagnosis of attention-deficit hyperactivity disorder

Developmental disorder
• Language disorder • Learning disability • Intellectual disability • Autism spectrum disorders • Developmental coordination disorder
Psychiatric disorders
• Anxiety disorder • Attachment disorder • Mood disorder • Oppositional defiant disorder • Post-traumatic stress disorder
Medical disorders
• Lead intoxication • Anemia • Prematurity • Sleep apnea • Medication adverse effects • Seizure disorder • Substance abuse • Sensory deficits • Fetal alcohol syndrome • Tourette syndrome
Genetic disorders
• Klinefelter syndrome • Fragile X syndrome • Turner syndrome • 22q11.2 deletion syndrome • Williams syndrome • Neurofibromatosis I • Inborn errors of metabolism

Pharmacotherapy

Pharmacotherapy consists of stimulants and nonstimulant drugs. For most children, stimulant medication is highly effective in treating the core symptoms of ADHD. AAP recommends following guideline for initiating pharmacotherapy in school-aged children:

- Initiate treatment with a stimulant medication from the amphetamine or methylphenidate group. If one stimulant group does not work, switch to the other.
- Dosing of stimulant medication is not weight-dependent. Start with a low dose and titrate until ADHD symptoms are manageable, maximum dose is reached, or adverse effects prevent additional titration.
- Initiation of treatment with an extended-release preparation of medication often is preferred
- Use of parent and teacher ADHD rating scales is helpful during the titration phase and periodically thereafter to determine response to medication and to monitor adverse effects
- Monitoring of growth impairment by measuring height and weight is essential in each visit
- Follow-up is usually at 1 month interval. If a child who has ADHD shows full remission of symptoms and normative functioning, behavior therapy may not need to be added to the regimen. Additional laboratory investigation or electrocardiography is not recommended unless clinically indicated.

Stimulant Medications

- Stimulant medications are the first line of treatment for ADHD
- They are highly efficacious in reducing symptoms.
- More than 80% of children having ADHD respond to stimulants.

Stimulants consists of methylphenidate and amphetamine compounds. They are available in short-, intermediate-, and long-acting formulations.

Mode of action of stimulant drugs: They enhance CNS catecholamine action, probably by increasing the availability of dopamine and norepinephrine at the synaptic cleft level in the frontal corticalstriatal circuits that regulate attention, arousal and impulse control.

Nonstimulant Medications

- Second-line drug for the treatment of ADHD
- Less effective in treating ADHD symptoms when compared with stimulants
- Atomoxetine is the nonstimulant, second-line drug.

Atomoxetine:

- It is a selective inhibitor of the presynaptic norepinephrine transporter in the CNS.
- It increases norepinephrine and dopamine concentrations, especially in the prefrontal cortex.

Behavioral Therapy

- Directed at manipulating the physical and social environment to modify behavior
- Should avoid focusing on negative behaviors and instead of promoting positive behaviors
- Can be used in the home and school
- May be recommended as an initial treatment when ADHD symptoms are mild and cause minimal impairment, when the diagnosis is uncertain, when the family chooses not to use medication for the child, or as an adjunct to medication treatment
- Additional forms of therapy, such as cognitive-behavioral therapy or family therapy, although not proven to be effective in the management of core ADHD symptoms, may be appropriate in the treatment of comorbid problems or family interaction difficulties
- Children with more prominent features of hyperactivity may require planned opportunities for controlled movements.

FOLLOW-UP

- With the advancing age ADHD does not resolves, so the children with ADHD requires a long time follow-up
- Long-term follow-up includes adherence to treatment as well as monitoring of growth and adverse effects of medication used.

PROGNOSIS

- Attention-deficit hyperactivity disorder often persists into adulthood. Up to 85% of children with ADHD continue to have impairment in adolescence and up to 60% in adulthood
- Hyperactivity component of the disorder often decreases with age, but the other symptoms of inattention and impulsivity persist
- Outcomes have been found to be dependent on:
  - The quality of the symptoms
  - Existing comorbidities
  - Socioeconomic status and history of treatment.

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13 Child Abuse and Child Protection

DEFINITION OF CHILD ABUSE

It is an ill-treatment to children perpetrated by adults which is unacceptable by a given culture at a given time. A physical or emotional ill-treatment, which is generally acceptable in the culture of Indian subcontinent may not be acceptable in western countries where it can be considered as child abuse. Even in same country or society, definition of child abuse varies from time to time. For example, ill-treatment to children that might have been acceptable (nonabusive) in Victorian England was not acceptable during the time of Dickens, who expressed his disapproval of much what he described in his famous novel "Oliver Twist". In the novel he expressed the story of an orphaned boy who started his life in a warehouse in London who suffered all categories of abuse. Once again in terms of standard in same England in the year 2012, many of the acceptable child care practices described in Oliver Twist constitute child abuse.

A child may be abused in the family, in an institutional setting and rarely by strangers.

TYPES OF CHILD ABUSE

- Physical
- Emotional
- Sexual
- Derivational
- Fabricated-induced illness (FII).

Two other conditions involving inadequate child care include:

- Neglect
- Child labor.

Deprivational Abuse and Neglect

Deprivational abuse is deliberate withholding of food or other necessities of life, including love from a child. Forced isolation, deliberate food deprivation or the withholding of love are used deliberately as punishment, sadistically or to induce illness. On the other hand, neglect is non-deliberate failure to supply needs of the child.

Physical child abuse and deprivational abuse although are two distinct entity, the two may go together. For example, a little girl of 4 years, beaten by an iron rod (a physical abuse) by her psychopath stepmother, was later locked up in an isolated room for 3 days and denied any food to take, which is a form of deprivational abuse, which followed physical abuse.

Physical Abuse

Physical abuse involves any activity that causes physical harm to a child, for example shaking, burning, hitting and suffocating. It can be classified in two ways:

1. Depending on the type of injury.
2. Depending on the motive and degree behind inflicting injuries.

Presentation Depending on the Type of Injury

Bruise: Bruise remains the commonest form of physical abuse (Figs 1 and 2). The characteristics of abusive bruises are the following:

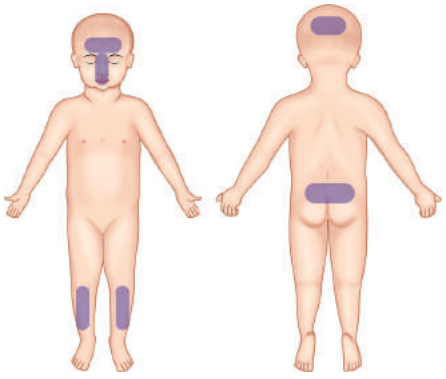

Fig. 1: Sites of accidental bruising

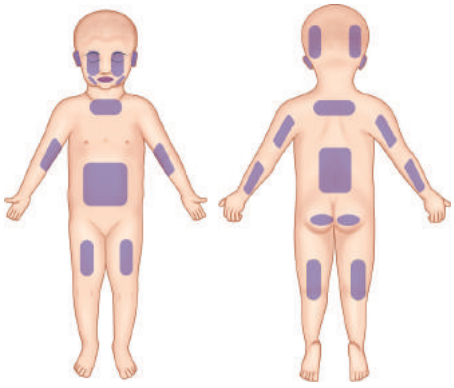

Fig. 2: Sites of abusive bruising

Table 1: Difference between accidental and abusive bruises

Accidental bruise	Abusive bruise
T-shape across forehead	Periorbital, ear, nose and cheeks
Bruise over bony prominence like over knee and sheen of tibia of lower limbs (Fig. 1)	Away from bony prominence, e.g. thigh and forearms (Fig. 2)
Bruises without petechiae	Bruise with petechiae strongly suggestive of abusive bruise (if coagulation disorder excluded)

- Bruises in a child who is not independently mobile
- Symmetrical bruised eyes (periorbital bruise)
- Unusual sites of bruise, like bruises of ear or mouth or cheek, are characteristics of abusive bruise. Bruises in lower limbs in toddlers are characteristics of fall during normal walking or running (Table 1) and not characteristics of abusive bruise
- Bruises of different ages (different color of bruise)
- Linear bruise on buttocks or backs
- Bruises away from bony prominences
- Finger marks on legs, arms or chest often associated with rib fracture
- Bruises on soft tissue of face
- Uncommon sites for accident. For example, genitalia, neck and chest
- Distinct pattern of bruising, for example, kicks and hand print marks.

Burns and scalds: In western countries, scald is a common type of burn, whereas in developing countries flame burn (from cooking gas cylinder or stove) is much frequent. Children are also vulnerable to accidental burn or scald. Accidental scald are usually "pull over scald" where the child pulls down a container of hot liquid on themselves producing scalds on face, upper limb, anterior trunk and neck. The burns are usually asymmetrical, with irregular age and irregular burn depth. Hot curry or warm water may also directly hit anterior abdominal wall of a child (Fig. 3).

In contrast to accidental scald, the usual sites of intentional burn are on buttocks, perineum and lower limbs due to forced immersion in hot water. There may be burn or scald in hands and feet called "gloves and stocking burn" (Fig. 4).

Fracture: Characteristics of abusive fracture are following:

- Fracture of bones of children not yet walking should be suspected of abusive fracture
- Multiple fractures in various bones
- Combination of evidences of recent and past fractures
- Typical metaphysial fracture of long bones (due to twisting and shaking) and deposition of new bones under periosteum along the shaft (Fig. 5)
- Fractures in ribs, particularly multiple rib fracture
- Spiral or oblique fracture of long bones
- Linear fracture of scalp particularly parietal bone with or without underlying chronic subdural effusion.

Classification of Child Abuse by Motive Rather than Type of Injury

As far as child protection is concerned, motive behind child abuse is sometimes more important than actual physical injury. Classification by motive is as follows:

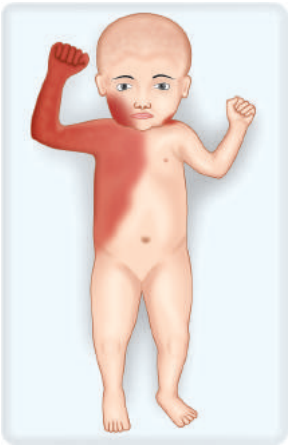

Fig. 3: Common site of accidental scald

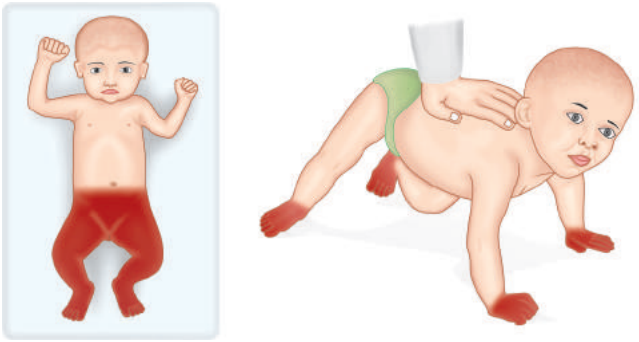

Fig. 4: Common sites of abusive scald

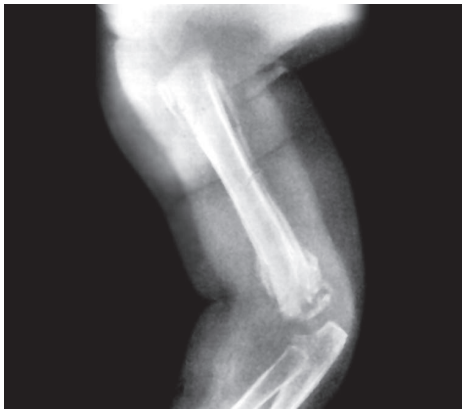

Fig. 5: Typical metaphysical fracture of humerus with fragmentation of bones and formation of new bones due to physical abuse

- *Grade A*: Ill-treatment undertaken for gain by disturbed, dangerous and manipulative individual
- *Grade B*: Impulsively done active abuse undertaken because of socioeconomic pressure, lack of resources, education and support
- *Grade C*: Universal mild ill-treatment, behavior undertaken by all normal caring parents in all societies.

Investigation for Physical Abuse

Skeletal survey and other imaging:

- All children below 2 years suspected of physical abuse should have full skeletal survey done
- X-ray: Particularly in children below 18 months
- CT or MRI of brain: In infants and children who are present with irritability and coma.

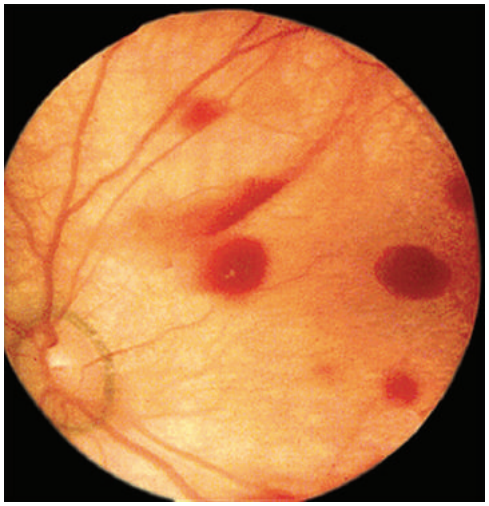

Fig. 6: Fundoscopy showing retinal hemorrhage due to shaking injury

Coagulation screen:

- Coagulation screening should be done if extensive and unusual bruising or unexplained cerebral hemorrhage is present
- Exclude clotting disorders: Bleeding time (BT), clotting time (CT), partial thromboplastin time (APTT), prothrombin time and platelet count.

Ophthalmological examination: By ophthalmologist for retinal hemorrhage due to shaking injury (Fig. 6).

Sexual Abuse

This is defined as forcing or enticing a child or a young person to take part in sexual activities including prostitution whether or not, the child is aware of what is happening. These activities include physical contact, penetrating or non-penetrating or non-contact sexual activities like involving children in pornographic activities.

Perpetrator who gains sexual gratification from the abuse is usually a family member (intrafamilial abuse) like cousins, stepfather, etc. or a non-family member, frequently family visitor like house tutor. Perpetrators are usually male.

Presentation

- Evidence of urinary tract infection (UTI), vulvovaginitis
- Sexually transmitted infections—chlamydia, trichomonas, gonorrhea
- Pregnancy
- Vaginal bleeding in prepubertal children.

Behavior Abnormalities Associated with Child Abuse

- Withdrawal
- Aggression
- Self-harm
- Adult sexual behavior
- Deterioration of school performance
- Secondary bed-wetting or fecal soiling.

Physical Signs

- Unexpected pregnancy
- Tear in hymen, vaginal bleeding, bruising around genitalia
- In boys: Bruising of genital area, urethral injury, torn of frenulum of penis.

Anal Signs (Both Girls and Boys)

Reflex anal dilatation (due to sodomy), anal fissure, gaping anus and swelling of anal margin.

Emotional Abuse

Definition

Persistent, emotional ill-treatment of a child that results in severe impairment in emotional development.

Neglect

- Neglect is defined as unintentional failure to supply the needs of a child. It should be differentiated from deprivational abuse where withholding needs of a child, like food, care or love, is deliberate. Neglect is a non-deliberate failure to provide the child needs by responsible persons. This definition explicitly excludes abuse which always stands for acts of commission
- Neglect is directly related to education, awareness and resources available to caretakers. It usually results from impoverished circumstances and life stresses affecting the family. Parents may be unaware of the needs of the child due to lack of education. Usually caretakers who neglect are innocent. Lack of resources available to caretaker also causes neglect of child, although he/she may be aware of the satisfactory child care practice. For example, a young unsupported mother who is burdened with several young children may fail to feed and look after her children adequately as she has to go out for job, leaving children at home uncared and neglected. The situation may prevent children to go to school.

Malnutrition as a consequence of neglect: Malnutrition is a glaring example of neglect. Thirty-five percent of world children are nutritionally stunted. Malnutrition involves neglect since nutritional needs of children are not met due to inability of parents to purchase appropriate and adequate food or lack of nutritional education. However, all parents of such children want their children to grow well and their neglect in such case is non-deliberate.

Another consequence of neglect: Although neglect is not as dangerous as physical or deprivational abuse, severe neglect requires protection. Some children who are neglected may seek attention and love elsewhere. Emotionally neglected children particularly girls are vulnerable to abusive sexual relationship.

Although seems similar, deprivational abuse and neglect can be differentiated as shown in Table 2.

Fabricated-induced Illness (FII)/Münchausen Syndrome by Proxy (MSBP)

Definition

It is the condition where the child's illness has been deliberately fabricated or induced by the carers and the child has suffered harm as a result. The essentials of FII are:

- A parent (mostly mother) fabricate illness in a child
- The child is presented persistently for medical care
- The perpetrator denies the etiology of the child's illness

Table 2: Differences between neglect and deprivational abuse

Neglect	Deprivation abuse
1. Non-deliberate failure to meet the needs of a child	1. Deliberate or malicious failure to supply the needs of a child
2. No ill motive behind inadequate child care	2. Ill motive (for personal gain) of perpetrators behind deprivational abuse
3. Can be negated by other people	3. Other people cannot negate deprivational abuse
4. Related to poverty, lack of education, stressful condition	4. Such relationship seldom present
5. Frequently not aware of consequence of neglect	5. Knows consequence of abuse (hitting a child is harmful)
6. Neglect, by definition, is done by an innocent person	6. Deprivation abuse is done by dangerous, sadistic or psychopathic personality person

- Symptoms and signs of illness cease when the child is separated from the perpetrator.

Various Terminologies are Used Interchangeably

- Fictitious: Unreal, imaginary, where factitious specially contrived, not genuine
- Fabricated: Constructing, manufacturing, false story of illness
- Münchausen syndrome by proxy (MSBP) is the most recognizable journalistic term of FII

Fabricated induced illness is now an established form of child abuse. The disease is not present in a child but is present particularly in a mother. A perpetrator mostly mother has characteristic personality. These are follows:

- Sense of insecurity in mother especially separated or divorced mother are more vulnerable
- Attention seeking behavior of mother
- Frequently changes doctor (doctor shopping)
- Complaining, hostile and aggressive in their interaction with healthcare providers
- Takes discharge from hospital against medical advice.

Passive Role of a Child

- The child usually adopts a sick role, frequently dictated by mother
- It affects image as an ill or disabled person which may seriously harm the child emotional and social development
- Other form of abuse may coexist in the family.

Healthcare Role in FII

Training in pediatrics does not equip doctors and healthcare personnels efficiently to deal with FII. Most common scenario is that:

1. Physician inadvertently but avoidably harms the child by over investigating and overtreating
2. Providing the carers to continue the deception.

Types of FII Induced in a Child

Seizure has been reported to be the most common form of FII. Others include:

- Hematuria (often mixing mother's blood in child's urine)
- Bleeding per rectum
- Hematemesis
- Poisoning
- Smothering
- Narrating exaggerated symptoms leading to unnecessary investigations and medications
- Death may occur in extreme situation (up to 10%) like from poisoning.

A child at one extreme of the spectrum may present with illness that may be consciously induced, for example poisoning. On the other hand, a child may be presented with exaggerated normal symptoms like "my child has loose motion with frequency of more than 1,000 times in last 24 hours, whereas in reality he/she passed only 4 times loose motion in last 24 hours."

Early Diagnosis of FII

Improving outcome by child protection intervention may be difficult, if the abuse is not detected early.

- Identify a secular relation between symptoms and mother's presence
- If possible collaborate with concerned general practitioner or family physician or health visitor if present
- Take detailed family medical history
- Look for vulnerability for FII, like frequent medical visit without reasonable cause
- Interview with father separately. If he refutes mother's complaint, then it goes in favor of FII
- A video surveillance covertly taken may be required to identify the genuinity of alleged medical complaints
- Foster high index of suspicion of those who are allegedly unresponsive to usual treatment.

Investigation

Avoid unnecessary investigations.

- An electroencephalography (EEG) may be done, if seizure is presenting complaint
- Drug levels (antidepressants, anticonvulsants, etc.) and toxicological screen may be done, particularly if presented with seizure
- Resist attempts by carers to escalate investigations or treatment or seek inappropriate second opinion.

Support to Children

- Psychiatrist opinion is available to assess parent-child relationship and to assess psychological damage incurred on a child
- Assess the magnitude of harm in terms of number of days of school absence or number of hospital admission
- Shift consultation from child to mother in order to change her misconception of illness of her child
- If parents cannot be dissuaded then child protection needs to be initiated
- Social service professional should be involved and fully informed
- A period in to foster care (where available) may be required
- Doctors who made the diagnosis should be involved for adoption of strategy of initial child protection.

CHILD PROTECTION

Definition

The decisive action taken to safeguard children from harm is called child protection.

Most countries of the world, particularly developing countries, do not have adequate system to identify and protect children from abuse, despite all except two countries being signed up to the United Nations Convention on the Rights of the Child.

Role of Healthcare Providers in Child Protection

All healthcare providers have responsibility toward children to ensure them care, support and services. They need to promote child health and development. Child protection involves following:

- Recognizing children in need
- Assessing need of children and increasing capacity of parents to meet their children's need
- Planning and providing support for vulnerable children and families
- Planning support for children at risk of significant harm
- Providing medical health to abused children.

Ethical and legal practice of doctors (wherever feasible) in suspected children who are in immediate serous damage from child abuse.

Reporting

It is important to share information with other colleagues. Contact:

- Social service or Directorate of Women and Social Welfare
- Police.

Reporting may override consideration such as confidentiality. Reporting does not need parental permission. However, parents should be informed about steps to be taken unless there is a likelihood of harm to child.

The child safety is of equal importance with their medical treatment. If hospitalization is not required, child should not be discharged without a clear plan and decision about the place of safety. Police should be immediately informed if their parents/carers attempt to remove the child from the hospital before decisions for safety place of child is made.

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14 Infectious Diseases

IMMUNIZATION IN CHILDREN

Standard Immunization Schedule Suitable for Middle-income and Low-income Countries

Standard vaccinations are given ideally in addition to mandatory vaccines given by extended program for immunization (EPI) to protect children from infectious diseases which have significant disease burden for the country with significant morbidity and mortality. However, attempt should be taken to integrate the additional new vaccines with immunization schedule of EPI of a country, particularly with the timing of EPI vaccines without causing increasing burden of multiple visits to vaccination center or avoiding multiple needle pricks if possible.

Vaccination Ideally Given at Birth

At birth, BCG, oral polio vaccine (OPV) and first dose of hepatitis B (HepB) vaccine should ideally be given. OPV given at birth is considered as OPV-0 vaccine. HepB vaccines first dose preferably should be given at birth. It is mandatory to give first vaccine at birth if mother is HBsAg positive (along with hepatitis B immunoglobulin).

Vaccines Given at 6 Weeks (First Dose of Penta plus OPV/Pentaxim/Hexa, PCV, Rotavaccine HepB Monovalent)

Pentavalent vaccine containing DwPT, HIb, HepB called penta plus OPV (first dose) or pentavalent containing DaPT, Hib, IPV (Pentaxim) or hexavalent vaccine containing DaPT, HIb, HepB, IPV (Infanrix).

Pentavalent vaccine (combination vaccine) given by EPI called penta contains whole-cell pertussis vaccine, hence called DwPT while pertussis vaccine containing acellular pertussis vaccine is called DaPT which is commercially available as pentavalent vaccine (Pentaxim). Pentavalent vaccine (Pentaxim) differs from penta of EPI in that it contains inactivated poliovaccine (IPV) given as combined vaccine with DaPT-Hib as IM injection (DaPT-Hib-IPV) not orally. Pertussis vaccine which it contains is acellular hence called DaPT which is less reactogenic in comparison to vaccine given by EPI as penta. Unlike penta of EPI Pentaxim containing acellular pertussis does not contain HepB vaccine. Acellular pertussis containing pentavalent combination vaccine (DaPTHiBIPV) is less reactogenic but more expensive and does not contain HepB vaccine. Hence, Pentaxim is not suitable for mass vaccination by EPI in developing countries.

Hexavalent vaccine or Hexa (Infanrix) contains six vaccines (DaPT, IPV, Hib, and HepB). Like Pentaxim, Hexa also contains acellular pertussis vaccine and hence less reactogenic but more expensive. Therefore, it is also currently not suitable for mass vaccination by EPI in developing countries.

At 6 weeks, second dose of HepB vaccine is given whose first dose was given at birth. If not given at birth, first dose of HepB vaccine is given at 6 weeks, either as a monovalent vaccine or with HepB containing combination vaccine [penta, hexa (infanrix)].

At 6 weeks, first dose of primary series pneumococcal conjugate vaccine (PCV) is also given. All above vaccines given at 6 weeks are in consistentce with EPI schedule of first primary vaccine which helps to vaccinate children in one visit. Similarly, such vaccines are given at 10 and 14 weeks.

Vaccines Given at 10 Weeks and 14 Weeks

Second and third dose of DwPT-HepB-Hib (penta) plus OPV/DaPT-Hib-IPV (Pentaxim) or hexavalent vaccine like DaPT-Hib-IPV HepB (Infanrix) are given respectively. Second and third dose of HepB vaccine are given at 10 and 14 weeks when first dose is given at 6 weeks in combination vaccine with penta or hexa. But if first vaccine of HepB vaccine is given at birth then second dose should be given at 6 weeks (as monovalent or combination vaccine) and third vaccine should be given at 6 months, if HepB is given as monovalent vaccine. If given in combination vaccine (penta/hexa), it can be given at 10–14 weeks. If HepB vaccine is given at birth and parents wish to give HepB vaccine alongwith HepB containing combination vaccine, it can also be given at 6, 10 and 14 weeks. No problem of total 4 vaccines of HepB if given at 0, 6, 10 and 14 weeks.

Primary series vaccines of PCV second and third dose are also given at 10 and 14 weeks.

Other Vaccines Given at ≥6 Weeks

Rotavirus vaccine (rotarix) oral: First dose is given at minimum age of 6 weeks. Second dose is given ≥4 weeks after first dose, but not exceeding 32 weeks.

Vaccine given at ≥6 months: *Flu vaccine (inactivated trivalent vaccine) given once a year.

Vaccine which can be given at 9 months: Measles/MR (IM/SC) + OPV (4th dose) + Vit A (100,000 IV).

Vaccines Given at ≥1 Year

- *Hepatitis A (HepA) vaccine IM first dose. Second dose at least 6 months after first dose
- Varicella virus vaccine SC. Second dose at least 6 months after first dose, preferably at 4 years
- Cholera vaccine (Shancol) first dose, second dose 2 weeks after first dose.

Vaccines Given at 15 Months

Measles/MMR 1, pneumococcal conjugate vaccine, booster.

Vaccines Given at 18 Months

First booster dose of:

- Pentavalent vaccine (DwPT-Hib-HepB or Penta) plus OPV/DaPT, IPV, Hib (Pentaxim) or Hexa/Infanrix (DaPT-Hib-IPV-HepB), and Hepatitis A second dose
- Vaccines given at ≥2 years: Typhoid vaccine IM. Revaccinate every 3–4 years.

Vaccines Given at 4 Years (Range 4–6 Years)

- Second dose of MMR
- Second booster of DwPT-Hib-HepB (Penta) plus OPV DaPT Hib IPV (Pentaxim)/DaPT-Hib-HepB-IPV (Hexa, Infanrix).

Immunization schedule for children is shown in the Table 1.

Parents should be advised to bring their children at vaccination centers in due time as per vaccination schedule mentioned above. However, for some obvious reasons parents frequently fail to report to vaccination centers in time. Not infrequently parents are misinformed that their children cannot be vaccinated once they have failed to attend vaccination center to vaccinate their children in due time. It is not necessary that vaccination schedule should be strictly maintained. Although it is advisable to vaccinate children in due time according to schedule, there is range of time for different vaccination during which vaccination can be given. Immunization schedule with range is given in Table 2.

Hepatitis B Vaccine: What Dose Schedule?

- HepB vaccine: It is the only vaccine in infant immunization which can be given in different schedules/doses
- For routine immunization, 3 doses: Birth, 6 weeks and 6 month are ideal
- For babies born to HBsAg –ve mothers. HBIG within 12–24 hours of birth along with birth dose of HepB vaccine
- For babies born to HBsAg -ve mothers. 6 weeks, 10 weeks and 6 months schedule may be followed if given as monovalent vaccine. If given as combined vaccine (Penta/Hexa) then subsequent vaccine can be given at 6, 10 and 14 weeks in one prick
- If given at birth as monovalent vaccine and parents wish to give hepatitis B vaccine in combination vaccine (Penta/Hexa) later, subsequent vaccine can be given at 6, 10 and 14 weeks along with combined vaccine. One additional vaccine (total 4) given in that fashion will not be a problem
- Immunology of 6, 10 and 14 weeks schedule given with combination vaccine: Current studies show it is comparable with immunogenicity of 0, 1 and 6-month schedule. Seroconversion and seroprotection is excellent and is 96%. EPI also provides similar schedule of HepB vaccine as combined vaccine (Penta). Immunogenicity at different schedule is comparable
  - 0, 1 and 6 months: 96–98%
  - 0, 1 and 2 months: 96%
  - 0, 6 and 14 weeks: 95–96%
  - 6, 10 and 14 weeks: 97%
  - 2, 4 and 6 months: 99%
- Booster doses are usually not required for HepB vaccine.

Figure 1 shows why booster doses are not mandatory for HepB vaccine.

- HepB vaccine in preterm low birth weight babies: If HepB vaccine is given to a newborn with birth weight less than 2 kg, its immune response remains doubtful. In such case, it is considered as 0 vaccine and 3 further (total 4) vaccines subsequently should be given starting from postnatal neonatal period.

Pneumococcal Conjugate Vaccine and Its Dose Schedule

Newer PCV vaccines containing more serotype causing invasive pneumococcal disease are currently available. PCV 10 and PCV 13 are currently available. For primary series vaccine, three doses are given at 6, 10 and 14 weeks with same timing of Penta, Pentaxim or Hexavaccine. A booster dose is given at 12–15 months (total 3 + 1 = 4). If not given below 6 month, but started between 7 and 11 months then 2 doses are given, second dose 4 weeks after first dose. A booster dose is given after 12 months (total 2 + 1 = 3). If given between 12 and 23 months, 2 doses are given. Second is given 2 months after first dose. No booster is required. If given ≥24 months up to 5 years, only one vaccine is given.

MR, MMR and Measles Vaccine

Measles and rubella (MR) vaccines is given at 9 completed months (270 days) according to current EPI schedule (Table 3). It is followed by measles vaccine at 15 months according to EPI schedule. At 9 months previously practiced measles vaccine can be given if MR not available. MMR vaccine can be given before 12 months of age. In that case, it is not considered as a valid dose. Two doses of valid MMR vaccine ideally should be given, first dose at 15 months and other at 4–6 years of age. Second dose, however, may be given at least 2 weeks after first dose. Second dose is not a booster dose.

VIRAL INFECTIONS

Seasonal Influenza and Pandemic Flu

Seasonal influenza (H3N2) and pandemic flu (H1N1 2009) are discussed together because they frequently share common microbiological, clinical features, preventive and treatment approach.

Influenza viruses are responsible for respiratory infection and are important cause of mortality and morbidity among persons of all ages worldwide. Influenza virus is a single-stranded RNA virus which includes influenza virus A, B, and C. Most seasonal local outbreaks and all worldwide outbreaks

Table 1: Immunization schedule for children

Vaccination Records						
Name of vaccine	**Approx. age**	**Scheduled date**			**Date of vaccination**	**Remarks and signature**
BCG	Birth					
Oral polio 0	Birth					
Hepatitis B I	Birth					
Hepatitis B II	6 weeks					
DPT I	6 weeks					
Oral polio I/IPV	6 weeks					
Hib I	6 weeks					
Rotarix I	6 weeks					
Pneumococcal vac I	6 weeks					
DPT II	10 weeks					
Oral polio III/IPV	10 weeks					
Hib II	10 weeks					
Rotarix II	10 weeks					
Pneumococcal vac II	10 weeks					
DPT III	14 weeks					
Oral polio III/IPV	14 weeks					
Hib III	14 weeks					
Pneumococcal vac III	14 weeks					
Hepatitis B III	6 Months					
Influenza I	6 Months					
Influenza II	7 Months					
Measles/MR	9 Months					
Oral polio IV	9 Months					
Hepatitis A	1 Year					
Chicken pox I	1 Year					
Cholera vaccine (Shanchol)	1 Year					
Cholera vaccine (Shanchol)	2 weeks after 1st dose					
Pneumococcal vac booster	15 M					
MMR vaccine I	15 M					
Hepatitis A 2nd dose	18 M					
Hib booster	18M					
DPT booster I	18 M					
Oral polio V/IPV	18 M					
Typhoid	2 Years					
Meningococcal vaccine	2 Years					
Chicken pox II	4 Years					
MMR vaccine II	4 Years					
DPT booster II	5 Years					
Oral polio VI/IPV	5 Years					
Hepatitis B booster (optional)	5 Years					
Human papilloma virus (cervical cancer) vaccine	10 Years	1st	2nd	3rd		

(pandemic) are due to influenza A. The last pandemic was seen in 2009. In April 2009, a novel influenza A virus (H1N1) emerged from Mexico and spread to other parts of the world through human-to-human transmission. It spread so rapidly that by June 11, 2009, the WHO declared it as pandemic. Though 2009 H1N1 pandemic officially ended in August 2010, it is expected to be a predominant influenza virus responsible for influenza diseases over the next few flu seasons.

Microbiology

Influenza A, the most common virus is diverged and characterized by combination of their hemagglutinin (HA)

Table 2: BPA (immunization subcommittee) recommended immunization schedule for children with range, 2013

Age / Vaccine	BCG / At birth	6 wk	10 wk	14 wk	18 wk	6 mo	9 mo	12 mo	15 mo	18 mo	2–3 yr	4–6 yr
BCG, OPV (0) HepB-1(monovalent)	✓											
Penta (DwPT-Hib-HepB) combined + OPV 1)		1st	2nd	3rd					Booster I			Booster II
Pentaxim (DaPT-Hib-IPV) combined		1st	2nd	3rd					Booster I			Booster II
Hexa (DaPT-Hib-IPV-HepB) combined		1st	2nd	3rd					Booster I			Booster II
Hepatitis B vaccine (either of two schedules can be given, if not given as combined vaccine)	1st	2nd				3rd						
		1st	2nd			3rd						
PCV (primary series vaccine): IM		1st	2nd	3rd				Booster				
Rotavirus vaccine (rotarix)		1st	2nd									
Measles/MR/MMR (IM/SC), oral polio							1st					
MMR (IM/SC)								1st				2nd
Hepatitis A vaccine (IM)								1st			2nd	
Varicella virus vaccine subcutaneous								1st				2nd
Typhoid vaccine: IM											Typhoid (2–3 yearly)	
Cholera vaccine (oral)								Cholera 1 and 2 (Shanchol)				
Flu vaccine (IM)						Influenza (yearly)						
Meningococcal vaccine											Meningococcal	

Abbreviations: DwPT, Diphtheria whole-cell pertussis tetanus; DaPT, Diphtheria acellular pertussis tetanus; OPV, Oral polio vaccine; IPV, Inactivated poliovaccine; Hib, Hemophilus influenzae type B; PCV, Pneumococcal conjugate vaccine (PCV 10, PCV 13); MR, Measles, rubella; MMR, Mumps measles rubella

and neuraminidase (NA) proteins. There are 16 HA and 9 NA subtypes of influenza A, of them H1-3 and N1-2 are the principal antigenic types found in human. Unlike most respiratory viruses, influenza virus has evolved efficient mechanism that promotes antigenic variability. Point mutation in the surface protein gene in influenza, particularly the HA gene can occur at a high rate during viral replication. Recent data also demonstrate that antigenic changes favorable to virus can occur in nonimmune individuals particularly in children merely through binding to host cell receptors. This gives rise to new influenza strain of same HA type, a phenomenon termed antigenic drift.

The influenza genome is segmented allowing for reassortment of genome segment, so that one influenza strain such as H3N1 can acquire a completely new HA or NA gene such as H1 or N1 resulting a new virus subtype such as H1N1 or H1N2. These dramatic and sudden changes influenza serotype can result in pandemic influenza. Variability in influenza antigenicity necessitates development of new influenza vaccines. Globally, the common circulating influenza A virus from 1994 to 2005 was H3N2 (90.6%); however, this distribution changes significantly with the emergence of 2009 H1N1 pandemic virus between April 2009 and March 2010. In the USA, 98% of the influenza types were pandemic H1N1 strains. The 2009 H1N1 virus strains are now predominant seasonal influenza A strains.

Epidemiology

Influenza is one of the most common and important respiratory illness affecting all ages. In temperate countries, it exhibits a seasonal pattern with peak activity during winter months. The epidemic characteristics are less apparent in tropical countries. In tropical countries, although influenza A predominates, epidemics of influenza B can occur. The virus is stable humidity and cold temperature, conditions that favors its transmission. These in addition to indoor crowding that occurs in winter month could explain the seasonal pattern of influenza infection. The virus grows to high-titer respiratory secretion promoting efficient transmission in persons in close contact via large particle droplet generated by coughing and sneezing. Small particle air-borne transmission in the vicinity of the infected person may also occur. Seasonal influenza viruses infect 5–15% of global population per year resulting in 250,000–500,000 death annually. Among human influenza virus, influenza A (H3N2) causes the largest number of hospitalization and death.

Seasonal influenza epidemics from 1976 to 2004 were responsible for more than 200,000 annual hospitalization and more than 30,000 of influenza-associated death annually in the USA.

The influenza death toll is expected to be higher during pandemic compared with local epidemic due to large number of person infected and the lack of protective immunity against new virus subtypes. Pandemic occur infrequently (11 have occurred in past 300 years) can be devastating. The 2009 H1N1 flu was the first pandemic flu of the century. Global pandemic in the previous century (20th) were in 1918–1919 (Spanish flu), 1957–58 (Asian flu H2N2, >100,000 deaths), 1968–70 (Hong Kong Flu, 700,000 deaths). Despite initial concern about a high lethality rate with the last novel 2009 H1N1 strain, most illness caused by H1N1 virus was mild and self-limited. Overall case fatality was less than 0.5%.

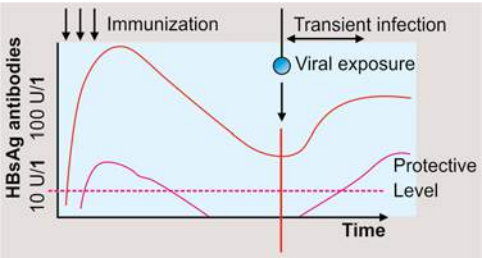


Fig. 1: HBsAg antibody titer following HepB vaccination

Incubation Period

2–5 days.

Clinical Features of Seasonal and Pandemic Flu

- Abrupt onset with fever (>90%), dry nonproductive cough (>80%), nasal congestion, headache, nonexudative sore throat
- Systemic or lower respiratory illness are frequently found both in H3N2 and H1N1. But generally more common in H3N2. Affected patient may frequently present with severe acute respiratory illness (SARI) and children may present with clinical features of severe pneumonia like tachypnea and chest in drawing
- Constitutional symptoms like myalgia, malaise, prostration
- In previously healthy individuals, symptoms typically subside within 5–8 days, but may be protracted in high risk or immunocompromised patients.

The risk factors for H1N1 Influenza are similar to those of seasonal influenza, which are following:

- Previous history of chronic lung diseases and hyper-responsive airway diseases like bronchial asthma
- Severely immunosuppressed patients (e.g. those receiving treatment for malignancies, hematopoietic or solid organ transplant recipients) presenting with an acute respiratory illness
- Children younger than 2 years and adults >65 years

Table 3: Immunization schedule according to EPI

Name of the vaccines	At birth	First dose	Second dose	Third dose
BCG	✓			
Penta (DwPT-Hib-HepB)		6 weeks	10 weeks	14 weeks
OPV		6 weeks	10 weeks	14 weeks
PCV (Given in few selected centers)		6 weeks	10 weeks	14 weeks
MR + OPV + Vit A 100,000 IV		9 months (270 completed days)		
Measles		15 months		

- Morbid obesity
- Pregnancy, particularly in pandemic influenza.

Persons with influenza may develop primary influenza pneumonia or secondary bacterial infection. Primary influenza pneumonia characterized by diffuse interstitial infiltrates and high mortality. Secondary bacterial pneumonia may complicate influenza. *Staphylococcus aureus* or *Streptococcus pneumonia* infection, often with empyema may occur 7–21 days following resolution of infection. The increase susceptibility to bacterial infection is due to increased adherence of bacteria to the influenza virus infected respiratory epithelium, decrease mucociliary clearance and impaired function of neutrophil, macrophage, monocytes and lymphocytes. Children with bronchial asthma may develop acute exacerbation of asthma due to flu virus infection and may require hospitalization.

Other Nonrespiratory Complications

- Encephalopathy
- Pericarditis
- Myositis
- Rhabdomyolysis with renal failure.

Central Nervous System Complications

- Encephalitis
- Myelitis
- Guillain-Barré syndrome
- Postinfectious encephalitis.

Reye's syndrome which is associated with a variety of viral infections is perhaps most severe postinfectious complication of influenza. It occurs primarily in children and manifests as neurological impairment including delirium, seizure, coma, vomiting, respiratory arrest, liver dysfunction with fatty infiltration.

Case Definition of 2009 H1N1 (Pandemic Flu)

United States Centers for Disease Control and Prevention defines swine flu as:

- Influenza-like illness (ILI) is defined as fever [temperature of 100°F (37.8°C) or greater] with cough or sore throat in the absence of a known cause other than influenza
- A confirmed case of pandemic H1N1 influenza A is defined as an individual with an ILI with laboratory-confirmed H1N1 influenza A virus detection by real-time reverse transcriptase polymerase chain reaction (rRT-PCR) or culture.

Incubation Period

The estimated median incubation period is approximately 1.5–3 days.

Transmission of Pandemic and Seasonal Flu

Person-to-person transmission: Influenza viruses can be transmitted through sneezing and coughing via large-particle droplets in both seasonal and pandemic flu. Other source of transmission is certain other bodily fluids (e.g. diarrheal stool). The 2009–2010 pandemic of H1N1 influenza A infection demonstrated sustained human-to-human transmission, as suggested by the large numbers of patients with respiratory illnesses identified within a short period of time at various locations around the world. The seasonal flu also spread from human-to-human but transmission is within localized community.

Hospitalized patients acquire nosocomial infection from healthcare providers and from patients to healthcare providers.

Viral Shedding

Shedding of pandemic H1N1 influenza A was observed to begin the day prior to symptom onset and often to persist for 5–7 days or longer in immunocompetent individual. Longer periods of shedding may occur in children (especially young infants), elderly adults, patients with chronic illnesses, and immunocompromised hosts. Delayed clearance of virus from the nasopharynx was observed in patients who developed acute respiratory distress syndrome or who had fatal disease. Maximum amount of virus is shredded during the first 2–3 days of illness.

Role of Pigs in Pandemic Flu

Pigs play an important role in interspecies transmission of influenza virus. Susceptible pig cells possess receptors for both avian (alpha 2-3-linked sialic acids) and human influenza strains (alpha 2-6-linked sialic acids), which allow for the reassortment of influenza virus genes from different species if a pig cell is infected with more than one strain.

Clinical Manifestations of 2009 H1N1 (Pandemic) Influenza and Influenza AH3 (Seasonal Flu)

The signs and symptoms of influenza caused by pandemic influenza A virus were similar to those of seasonal influenza, although gastrointestinal manifestations appeared to be more common with pandemic H1N1 influenza A and respiratory symptoms more commonly associated with H3N2 seasonal flu.

Center for Disease Control (CDC) categorizes the severity of pandemic flu (H1N1) as following:

- Mild or uncomplicated illness: Mild or uncomplicated illness is characterized by fever, cough, sore throat, rhinorrhea, muscle pain, headache, chills, malaise, and sometimes diarrhea and vomiting, but no shortness of breath and little change in chronic health conditions
- Progressive illness: Progressive illness is characterized by typical symptoms plus signs or symptoms such as:
  - Chest pain
  - Poor oxygenation (e.g. tachypnea, hypoxia, labored breathing in children)
  - Cardiopulmonary insufficiency (e.g. hypotension)
  - Central nervous system (CNS) impairment (e.g. confusion, altered mental status)
  - Severe dehydration
  - Exacerbations of chronic conditions (e.g. asthma, chronic obstructive pulmonary disease, chronic renal failure, diabetes, or other cardiovascular conditions)
- Severe or complicated illness
  - Severe or complicated illness is characterized by signs of lower respiratory tract disease (e.g. hypoxia requiring supplemental oxygen, abnormal chest radiograph, mechanical ventilation), CNS findings (encephalitis, encephalopathy)
  - Complications of hypotension (shock, organ failure)
  - Myocarditis or rhabdomyolysis
  - Invasive secondary bacterial infection based on laboratory testing or clinical signs (e.g. persistent high fever and other symptoms beyond three days).

Investigations

Investigations for seasonal influenza AH3 during community outbreak is usually not required. Investigation should be done if available and if indicated and should be done earlier to help clinician to treat earlier with antiviral drugs. Investigations are also done for epidemiological interest.

- Real-time reverse transcriptase (rRT): Real-time reverse transcriptase (rRT) PCR is the most sensitive and specific test for the diagnosis of pandemic H1N1 influenza A virus infection. Viral PCR for seasonal H3N2 can be done but rarely required for clinical purpose particularly in developing countries
- *Isolation of pandemic H1N1 influenza A virus using culture* is also diagnostic, but culture is usually too slow to help guide clinical management. A negative viral culture does not exclude pandemic H1N1 influenza A infection. Viral culture of seasonal flu H3N2 is diagnostic and can be done if indicated
- Rapid antigen tests: Certain rapid influenza antigen tests that are commercially available can distinguish between influenza A and B viruses, but cannot distinguish among different subtypes of influenza A (e.g. pandemic H1N1 influenza A versus seasonal H1N1 or H3N2 influenza A)
- Immunofluorescent antibody testing: Direct or indirect immunofluorescent antibody testing (DFA or IFA) can distinguish between influenza A and B, but does not distinguish among different influenza A subtypes
- Chest X-ray: On chest radiograph, the H1N1 and H3N2 virus affected subjects show infiltrates suggestive of pneumonia or acute respiratory distress syndrome
  X-ray chest may show patchy consolidation or ground glass opacities with or without consolidation; there may be lower lung zone predominance and the most commonly affected regions are the peripheral and central perihilar areas
- Other biochemical and hematological change may be evident:
  - Elevated alanine aminotransferase
  - Elevated aspartate aminotransferase
  - Anemia
  - Leukopenia or leukocytosis
  - Thrombocytopenia or thrombocytosis
  - Elevated total bilirubin.

Complications of Pandemic and Seasonal Flu

Individuals with certain medical conditions, those at the extremes of age, and pregnant women are at increased risk for influenza complications.

- Respiratory complications
  - Rapidly progressive pneumonia
  - Respiratory failure
  - Acute respiratory distress syndrome
  - Multisystem organ failure
- Bacterial superinfection with *Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus aureus, Streptococcus mitis,* and *Haemophilus influenzae*
- Neurologic complications
  - Seizure is the most common complication
  - Other complications include confusion, unconsciousness, acute or postinfectious encephalopathy, quadriparesis, encephalitis, and severe acute disseminated encephalomyelitis.
- Muscles: Acute myositis

Management of Influenza

Management of influenza consists of:

- Supportive
  - Rest at home
  - Plenty of drinks by mouth
  - Antipyretics and analgesics if required
- Antiviral therapy: Discussed later
- Antibacterial therapy
  Secondary bacterial pneumonia not infrequently associated with influenza. Antibiotic should be given accordingly
- Treatment of complication: As per guideline of specific complication.

Post-exposure Chemoprophylaxis and Antiviral Treatment of Seasonal Flu (H3N2)

- Either oseltamivir or zanamivir is recommended for antiviral prophylaxis
- The drugs used for prophylaxis of influenza are not substitute for vaccine which remains the most effective way of preventing influenza
- Drug used for prophylaxis and treatment of influenza are oseltamivir and zanamivir.

Who will receive chemoprophylaxis and antiviral therapy: Oseltamivir and zanamivir are generally recommended for prophylaxis and treatment of seasonal flu. Either oseltamivir or zanamivir is recommended in postexposure prophylaxis when influenza is highly circulating in the community, in at risk patients who are not effectively protected by influenza vaccine and who have been in close contact with someone suffering from influenza like illness in the same household or residential settings. They should be given within 48 hours of exposure. It can be offered irrespective of vaccination status in a risk patient living in long-term residential setting.

At-risk patients of age >65 years are those who have one or more of the following:

- Chronic respiratory disease including asthma and chronic obstructive pulmonary disease
- Chronic heart failure
- Chronic renal disease
- Chronic neurological disease
- Diabetes mellitus
- Immunosuppression.

For prophylaxis, oseltamivir can be given in following dose:

- Adult or children >12 years: 75 mg once daily for 10 days
- For children <12 years: 3 mg/kg once daily for 10 days
- For children between 1 and 3 months: 2.5 mg/kg once daily for 10 days
- For children <1 month of age: 2 mg/kg once daily for 10 days.

Drug Treatment (Antiviral) of Seasonal Flu

When influenza is highly circulating in the community either oseltamivir or zanamivir is recommended for treatment of influenza at risk patient (mentioned above) who should start treatment within 48 hours of onset of symptoms of flu or flu-like illness.

Dose for antiviral treatment:

- Adult or children >12 years: 75 mg twice daily for 10 days
- For children <12 years: 3 mg/kg twice daily for 10 days

- For children between 1–3 months: 2.5 mg/kg twice daily for 10 days
- For children <1 month of age: 2 mg/kg twice daily for 10 days

Chemoprophylaxis and Treatment of Pandemic Flu

This is due to that fact that the guideline for chemoprophylaxis and treatment of seasonal flu does not cover the circumstances of a pandemic or impending pandemic or a widespread epidemic of a new strain of influenza to which there is little or no immunity in the community.

Indications for Prophylaxis for Pandemic Flu

The United States Centers for Disease Control and Prevention stated that postexposure antiviral prophylaxis could be considered for adults and children who had close contact with a confirmed or suspected case and also fell into one of the following categories:

- Adults who are at high risk for complications of influenza (e.g. individuals with certain chronic medical conditions or who are greater than 65 years of age)
- Pregnant women and women who are up to two weeks' postpartum (including following pregnancy loss)
- Children who are <5 years of age or who are at high risk of complications of influenza
- Healthcare workers and emergency medical personnel.

Indications for Antiviral Therapy in Pandemic Flu

Prompt (within 48 hours of onset of symptoms) initiation of antiviral therapy is recommended for children, adolescents, or adults with suspected or confirmed influenza (pandemic) infection with any of the following features:

- Illness requiring hospitalization
- Progressive, severe, or complicated illness, regardless of previous health status
- Previous history of chronic lung diseases and hyper-responsive airway diseases like bronchial asthma
- Severely immunosuppressed patients (e.g. those receiving treatment for malignancies, hematopoietic or solid organ transplant recipients) presenting with an acute respiratory illness.

Center for Disease Control also recommends that early treatment (preferably within 48 hours of onset of symptoms) be considered in patients with suspected or confirmed influenza infection who were at high risk for complications: Children <5 years of age, particularly those <2 years of age.

Antiviral agents:

- Oseltamivir
  - Adult and children >12 years: Oseltamivir of 75 mg twice a day for 5 days
  - Children 1–12 years: 3 mg/kg twice daily for 5 days
  - Children 1–3 months: 2.5 mg/kg for twice daily 5 days
  - Children below 1 month: 2 mg/kg twice daily for 5 days
- Zanamivir
  - Inhaled zanamivir 5 mg once daily for 10 days can also be given
  - Intravenous zanamivir: Intravenous zanamivir is the preferred agent for patients with oseltamivir-resistant pandemic H1N1 influenza A infection. The intravenous formulation is considered appropriate for those who are unable to use inhaled zanamivir (e.g. critically ill patients, patients with a history of bronchospasm).

Nonpharmacological Prophylaxis of Influenza

Important steps are:

- Frequent hand washing with soap
- Avoiding touching eyes, nose and mouth
- Covering mouth and nose during coughing and sneezing with handkerchief and throw it into the bin
- Avoiding close contact (less than 3 feet) with people with respiratory symptoms
- People affected with influenza like symptoms should stay at home and avoid coming within 3 feet with other people.

Influenza Vaccine

Influenza vaccine is the mainstay of prevention of influenza. In influenza, immune response is provided by surface antigen specially HA antigen. Antibody to one influenza type or subtype or antigenic variant confers little or no protection against older influenza types or subtypes. It is a frequent phenomenon due to antigenic drift. Influenza vaccines are targeted against an antigen, which is prone to change, therefore, vaccines must be reformulated annually based on the changing pattern of influenza virus. In February and September of each year, for the Northern and Southern hemispheres respectively, the influenza virus strains to be included in the coming season's vaccines are selected. To elicit broad serum IgG responses against surface HA and NA proteins of circulatory strains, two strains of influenza A (one H3N2 and one H1N1) and one of influenza B are selected and mixed in each vaccine. If significant change occurs after this, as occurred in 2009, the vaccine may not provide protection against circulating influenza strains. At the beginning of H1N1 pandemic, the WHO recommended for vaccine strains in May 2009, but the virus replicated poorly in embryonated chicken eggs, leading to vaccine shortage. Cell culture based vaccine is more rapid and may be used for persons with egg allergies.

Currently available seasonal influenza vaccines include the trivalent inactivated vaccine (TIV) and live attenuated influenza vaccine (LAIV). Both vaccines contain same antigenic variants of influenza A and influenza B viruses which are predicted by WHO.

Seasonal influenza vaccines are unable to protect against 2009 H1N1 influenza due to antigenic variation. It is observed that no cross reactive antibodies to 2009 H1N1 influenza virus developed in children receiving seasonal influenza vaccine. Specific monovalent H1N1 influenza vaccines have been developed. Similar to season influenza vaccine both inactivated or live attenuated formulation against Influenza A (H1N1) are available.

Eligible Candidate for Vaccination

During the initial period of 2009 outbreak, the CDC Advisory Committee on Immunization Practice (ACIP) recommended prioritywise vaccination to five groups considered at the highest risk of influenza complications. These are:

- Pregnant women
- Close contact of children less than 6 months of age
- Healthcare personnel
- Children and young adults 6–24 years of age

- Persons 25–64 years of age with underlying medical conditions that is associated with increased influenza mortality and morbidity.

After the pandemic of 2009, influenza vaccine is recommended in all children with risk factors and also where the vaccine is requested by parents (after discussing the benefit and limitations of the vaccine).

Children at risk are:

- Congenital or acquired immunodeficiency
- Chronic cardiac, pulmonary, renal, liver, hemato–logical diseases and diabetes mellitus
- Children on long-term aspirin therapy
- Any neurological disease that might cause respiratory compromise or impair the ability to handle secretions.

Dosing Schedule

The dosing schedule for the influenza virus has been given in Table 4.

Which Strain should be Used for 2011–12 Influenza Season?

In the US, these are A/California/7/2009 (H1N1) like, A/Perth/16/2009 (H3N2) like, and B/Brisbane/60/2008 like antigens. The influenza A (H1N1) vaccine virus strain is derived from a 2009 pandemic influenza A (H1N1) virus.

When to Vaccinate

Preferably given before peak influenza season, i.e. winter (December to March) in temperate countries and in rainy season in tropical countries. Influenza occurs all over the year, but more frequently in rainy season. Therefore it is better to vaccinate before onset of rainy season (from June to August). In India IAP recommends offering influenza vaccine just before the onset of rainy season. The current trivalent inactivated influenza vaccine incorporates the 2009 pandemic strains also, hence avert the need of a separate A(H1N1) vaccine.

Is it efficacious?

When the vaccine strain is identical or matches the strain of circulating influenza virus, it provides protection about 70–100% among healthy adults and 30–60% in elderly and young children.

Both TIV and LAIV are effective in children and adults but advantage of one over another is difficult to prove due to insufficient data.

It was found that the immunogenicity of 2009 H1N1 monovalent vaccine is similar to typical seasonal influenza vaccine.

Vaccination in Children

Younger children are at high risk for acquiring and transmitting influenza infections. Administration of TIV and LAIV in healthy children showed 55–70% reduction in laboratory-confirmed cases of influenza. Vaccination of children in schools can reduce the incidence of influenza among family contacts and the community at large.

Adverse Effects of Vaccination

- Trivalent inactivated vaccine
  - Mild soreness of arm at the site of vaccination for 1 to 2 days
  - Fever, malaise, headache, arthralgia
  - Hypersensitivity to vaccine component
- Live attenuated influenza vaccine
  LAIV is well-tolerated. Mild respiratory symptoms like rhinorrhea, sore throat, nasal congestion may develop.

Contraindications for Vaccination

- Both vaccines are contraindicated in patients who are allergic to eggs
- Live vaccine should not be administered to immunocompromised individuals and in pregnancy.

Pandemic Flu

An epidemic of influenza-like illness occurred in Mexico in March 2009. The WHO issued a statement on the outbreak of "influenza-like illness" in the confirmed cases of A/H1N1 influenza had been reported in Mexico, and that 20 confirmed cases of the disease had been reported in the US. The disease spread rapidly through the rest of the spring, and by May 3, a local of 787 confirmed cases had been reported worldwide. On June 11, 2009, the ongoing outbreak of influenza A/H1N1, commonly referred to as "swine flu", was officially declared by the WHO to be the first influenza pandemic of the 21st century and a new strain of influenza A virus subtype H1N1 was first identified in April 2009.

In November 2009, a worldwide update by the WHO stated that "199 countries and overseas territories/communities have officially reported a total of over 482,300 laboratory confirmed cases of the influenza pandemic H1N1 infection that included 6,071 deaths". By the end of the pandemic, there were more

Table 4: Dosing schedule of influenza virus

Vaccine type	Age group	Dose	Route
Inactivated	6–35 months	0.25 mL, 1 or 2 doses, 4 weeks apart	Intramuscular
	>36 months	0.5 mL, 1 or 2 doses, 4 weeks apart	
	>9 years	0.5 mL, 1 dose	
Live attenuated	2–49 years	0.2 mL sprayer, 1 or 2 doses, 4 weeks apart	Intranasal

than 18,000 laboratory confirmed deaths from H1N1. Due to inadequate surveillance and lack of healthcare in many countries, the actual total number of cases and deaths were likely much higher than reported. Experts, including the WHO, have since agreed that an estimated 284,500 people were killed by the disease, about 15 times the number of deaths in the intial death toll.

Seasonal Flu (Influenza A H3) Epidemic

Among human influenza viruses influenza A H3N2 caused largest number of hospitalization and death. Seasonal influenza epidemics from 1976 to 2004 were responsible for more than 200,000 annual hospitalization and more 30,000 influenza associated death annually in USA. There are much less data available on influenza burden in low income countries.

In temperate climates, seasonal epidemics occur mainly during winter while in tropical regions, influenza may occur throughout the year, causing outbreaks more irregularly.

Influenza occurs globally with an annual attack rate estimated at 5–10% in adults and 20–30% in children. Illnesses can result in hospitalization and death mainly among high-risk groups. Worldwide, these annual epidemics are estimated to result in about 3–5 million cases of severe illness, and about 250,000 to 500,000 deaths.

In industrialized countries, most deaths associated with influenza occur among people aged 65 years or older.

The precise effects of seasonal influenza epidemics in developing countries are not known, but research estimates indicate that a large percent of child deaths associated with influenza occur in developing countries every year.

Avian Influenza (H5N1)

The emergence of a novel influenza A virus strain in 1918 caused a global influenza pandemic with an estimated 50–100 million deaths worldwide.

In 2003, Influenza A (H7N7) infection occurred in the Netherlands among persons handled infected poultry during an outbreak of avian flu among poultries. On February 1, 2004, the WHO reported two fatal cases of human H5N1 infection in Vietnam and Thailand, which was caused by highly pathogenic avian influenza H5N1 infection. From 2003 to 2012 globally 592 persons were infected by bird flu of which 349 died.

Most human cases of "highly pathogenic" H5N1 virus infection have occurred in people who had recent contact with sick or dead poultry that were infected with H5N1 viruses. About 60% of people infected with the virus died from their illness. Unlike other types of flu, H5N1 usually does not spread between people. There have been no reported infections with these viruses in birds, poultry or people in the United States. H5N1 is an avian (bird) flu virus that has caused outbreaks in domestic poultry in parts of Asia and the Middle East. Because H5N1 is so deadly to poultry, it is considered "highly pathogenic," or highly disease-causing. Since 2003, 650 human infections with highly pathogenic H5N1 viruses have been reported to the WHO by 15 countries. About 6% of these people died from their illness.

In 2011, 62 human H5N1 cases and 34 deaths were reported from five countries—Bangladesh, Cambodia, China, Egypt and Indonesia. Six countries—Bangladesh, China, Egypt, India, Indonesia and Vietnam—have widespread and ongoing infections in their poultry. Poultry outbreaks have occurred in other countries recently as well.

Thailand has begun a phase 1 clinical trial to test an H5N1 avian, or bird, influenza vaccine in a needle-free, nasal spray form. This is a result of international collaboration with health agencies around the world, including the US department of health and human services, Biomedical Advanced Research and Development Authority (BARDA). This is the first step in testing the new vaccine in humans.

Epidemiology

The current outbreak of highly pathogenic avian influenza, which began in South-East Asia in mid-2003, is largest and most severe on record. Despite the death or destruction of an estimated 150 million birds, the virus is now considered endemic in many parts of Indonesia and Vietnam and in some parts of Cambodia, China, Thailand and Lao.

In early August 2004, Malaysia reported its first outbreak of H5N1 in poultry, becoming 9th Asian nation affected. Russia reported its first H5N1 outbreak in poultry in late July 2005, followed by reports of disease in adjacent parts of Kazakhstan in early August.

Pathogenesis

Influenza viruses are enveloped RNA viruses that have a segmented genome and display great antigenic diversity. Influenza A and B viruses have two major antigenic surface glycoproteins embedded into the membrane, the hemagglutinin (HA) and neuraminidase (NA) that induce antibody responses in humans. Influenza virus strains are classified by their core proteins (i.e. A, B or C), species of origin (e.g. avian, swine), geographic site of isolation, serial number, and for influenza A, by subtypes of HA and NA.

Influenza A is responsible for frequent, usually annual outbreaks or epidemics of varying intensity, and occasional pandemics, whereas influenza B causes outbreaks every two to four years. Although 16 HA (H1-H16) and nine NA (N1-N9) virus subtypes occur in their natural reservoir of aquatic birds, only three hemagglutinin subtypes have caused widespread human respiratory infection (H1, H2, and H3), suggesting a degree of host specificity. The H1N1 influenza virus that caused the 2009 pandemic represented a quadruple reassortment of two swine strains, one human strain, and one avian strain of influenza.

Transmission

On present understanding, H5 and H7 viruses are introduced to poultry folks in their low pathogenic form. When allowed to circulate in poultry population, the viruses can mutate, usually within a few months, into highly pathogenic form. This is why the presence of an H5 or H7 virus in poultry is always for concern, even when the initial signs of infection are mild. Recent events make it likely that some migratory birds are now directly spreading the H5N1 virus in its highly pathogenic form.

Human influenza (H5N1) is transmitted by inhalation of infectious droplets and droplet nuclei, by direct contact, and possibly by indirect (fomite) contact.

For human influenza A (H5N1) infections, bird-to-human is the predominant route of transmission.

- Animal-to-human: Common for those who handle poultry
- Human-to-human: Though rare, instances of limited human-to-human transmission of H5N1 and other avian influenza viruses have occurred in association with outbreaks in poultry and should not be a cause for alarm. In no instance has the virus spread beyond a first generation of close contacts or caused illness in the general community. Data from these incidents suggests that transmission requires very close contact with an ill person.

Does the Virus Spread Easily from Birds to Human?

No. Though only few human are affected, this is a small number compared with the huge number of birds affected and the numerous associated opportunities for human exposure, especially in areas where backyard folks are common. It is not presently understood how infection occurs in humans, causing serious illness. It is a new virus for human (H5N1 have never circulated widely among people), and it has infected more than 100 humans in 2006, killing over half of them.

Changes Needed for H5N1 to Become a Pandemic Virus

The virus can improve its transmissibility among humans via two principal mechanisms. The first is a "reassortment" event, in which genetic material is exchanged between human and avian viruses during coinfection of a human or pig. Reassortment could result in a fully transmissible pandemic virus, announced by a sudden surge of cases with explosive spread.

Implications for Human Death

The widespread persistence of H5N1 in poultry populations poses two main risks for human health. The first is the risk of direct infection when the virus passes from poultry to humans, resulting in very severe disease. Unlike normal seasonal influenza, where infection causes only mild respiratory symptoms in most people, the disease caused by H5N1 follows an unusually aggressive clinical course, with rapid deterioration and high fatality. Primary viral pneumonia and multiorgan failure are common. A second risk, of even greater concern, is that virus, if given enough opportunities, may change into form that is highly infectious for humans and spreads easily from person to person. Such a change could mark the start of a global outbreak (pandemic); however, fortunately human-to-human transmission is currently rare.

Clinical Features

The clinical manifestations of avian influenza are variable.

Avian Influenza H5N1

WHO reports 60% case fatality in more than 400 human cases of H5N1 influenza. Most patients with H5N1 infection give a history of recent exposure to dead or ill poultry. H5N1 infection can result in mildly symptomatic illness to life-threatening disease.

The clinical presentation may depend on the duration of exposure and the virulence of the virus.

Incubation Period

Following exposure to infected poultry, the incubation period for human H5N1 infection is seven days or less, and is often two to five days.

In clusters of human-to-human transmission, the incubation period is typically three to five days.

Clinical Manifestations

Respiratory illness is the most common manifestation, but patients with solely gastrointestinal or central nervous system involvement have also been described. A striking feature of the avian influenza H5N1 outbreaks is the predominance of children and young adults.

- Fever, cough, dyspnea, bilateral pulmonary infiltrates, lymphopenia, and increased aminotransferases [aspartate aminotransferase (AST); alanine aminotransferase (ALT)]
- Respiratory symptoms may be accompanied by gastrointestinal symptoms, headache, myalgia, sore throat, rhinorrhea or uncommonly conjunctivitis or bleeding gums.

Laboratory Diagnosis of H5N1 Avian Influenza in Human

Diagnosis of H5N1 avian influenza:

- Viral culture in appropriate biocontainment
- Polymerase chain reaction assay for avian influenza A (H5N1) RNA
- Immunofluorescence test for antigen with the use of monoclonal antibody against H5A fourfold rise in H5-specific antibody in paired serum samples
- Serologic testing-virus neutralization, ELISA, and Western blotting.

Treatment

- Supportive
- Including ventilatory support in respiratory failure
- Antiviral therapy
  Neuraminidase inhibitors like oseltamivir and zanamivir are also effective against avian influenza. The optimal dose and duration of antiviral therapy for H5N1 influenza have not been established. Recent studies showed that neuraminidase inhibitors may have the role in prevention of healthy adults and post-exposure prophylaxis among the household contact.

Prevention of Avian Influenza

In addition to nonpharmacological health measure including respiratory health measures, following measures should be taken:

- Avoidance of handling of poultry and poultry meat during an outbreak
- Mass incineration of poultries (affected flock).

Prevention by vaccination: Multiple avian influenza vaccines are currently being evaluated and one vaccine, manufactured by Sanofi-Pasteur, has been approved by the United States Food and Drug Administration (FDA). It is now clear that oil-in-water emulsion adjuvant and whole virus pandemic vaccines offer advantages over conventional subvirion vaccines. Major problem with the development of an effective vaccine against avian influenza (and H5, in particular) has been poor immunogenicity in humans.

MEASLES

Epidemiology

Measles occurs worldwide; control efforts have substantially altered the global distribution.

In developed countries during the prevaccine era, ≥90 percent of children acquired measles by age 15. Following implementation of routine childhood vaccination at age 12–15 months, the age of peak measles incidence during epidemics in the United States shifted to six months of age. This is approximately the time at which transplacentally acquired maternal antibodies are no longer present if the mother has vaccine-induced immunity.

Microbiology

Measles is a single-stranded RNA paramyxovirus with one antigenic type. Humans are the only reservoir. Measles virus infects the upper respiratory tract and regional lymph nodes and is spread systemically during a brief, low-titer primary viremia. It is more prevalent in winter and spring. A secondary viremia occurs within 5–7 days when virus-infected monocytes spread the virus to the respiratory tract, skin, and other organs. The characteristic histologic finding is the presence of large, multinucleated giant cells (Warthin-Finkeldey cells) and syncytium formation in respiratory epithelia and reticuloendothelial cells. Virus is present in respiratory secretions, blood, and urine of infected individuals. Measles virus is transmitted by large droplets from the upper respiratory tract and requires close contact.

Incubation Period

Eight to twelve days from exposure to the onset of symptoms

Infective Period

Period of infectivity is from 1 to 2 days before symptoms (about 5 days before onset of rash) to 4 days after the appearance of the rash.

Mode of Transmission

Measles is highly contagious. Measles virus is typically transmitted by respiratory droplets, direct contact, or fomites. Infants less than one year rarely acquire measles due to passage of maternal antibodies.

Clinical Features

Stages of Infection

Classic measles infection can be subdivided into the following clinical stages: prodromal, eruptive, and convalescent.

Prodromal: The prodrome usually lasts for 2–3 days but may persist for as long as 8 days

The prodrome phase is defined by the appearance of symptoms which typically include fever, malaise, and anorexia, followed by conjunctivitis, coryza, and cough. The severity of conjunctivitis is variable and may also be accompanied by lacrimation or photophobia. The respiratory symptoms are due to mucosal inflammation from viral infection of epithelial cells. Fever is typically present; the pattern may be variable. Various fever patterns have been described; fever as high as 40°C can occur.

Koplik's spot: Patients may develop an enanthem known as Koplik's spots; Koplik's spots (Fig. 2) in patients with suspected measles, are considered pathognomonic for measles infection and occur approximately 48 hours before the characteristic exanthem appears. However, this enanthem does not appear in all patients with measles. These are 1 to 3 mm whitish, grayish, or bluish elevations with an erythematous base, typically seen on the buccal mucosa opposite the molar teeth, though they can spread to cover the buccal and labial mucosa as well as the hard and soft palate. They have also been described as "grains of salt on a red background". Koplik's spots subsequently may coalesce and generally last 12 to 72 hours.

*Eruptive phase***:** Starts on 4–5th day of illness when fever rises again. The exanthem of measles is a maculopapular (Fig. 3), blanching rash beginning on the face and spreading cephalocaudally and centrifugally to involve the neck, upper trunk, lower trunk, and extremities. The lesions may become confluent, especially in areas such as the face, where the rash develops first. The rash may also have some petechiae; in severe cases, it may appear hemorrhagic. In general, the extent and degree of confluence of the rash correlates with the severity of the illness in children. The palms and soles are rarely involved. The cranial to caudal progression of the rash is characteristic of measles but is not pathognomonic.

Other characteristic findings during the exanthematous phase include lymphadenopathy, high fever (peaking two to three days after appearance of rash), pronounced respiratory signs including pharyngitis, and nonpurulent conjunctivitis. Koplik's spots often begin to slough when the exanthem appears.

Clinical improvement typically ensues within 48 hours of the appearance of the rash. After three to four days, the rash darkens to a brownish color and begins to fade, followed by fine desquamation. The rash usually lasts six to seven days. Hyperpigmented skin lesion may persist long after active measles infection, and is an evidence of post measles infection. Hyperpigmented skin lesion may persist long after active

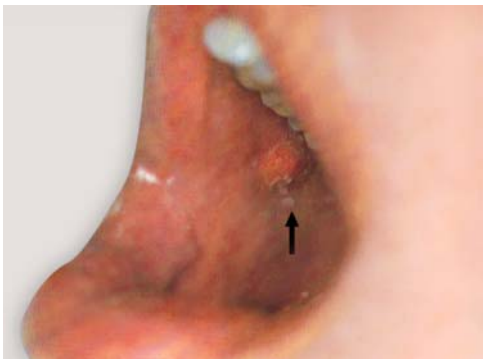


Fig. 2: Marked arrow shows the Koplik's spot

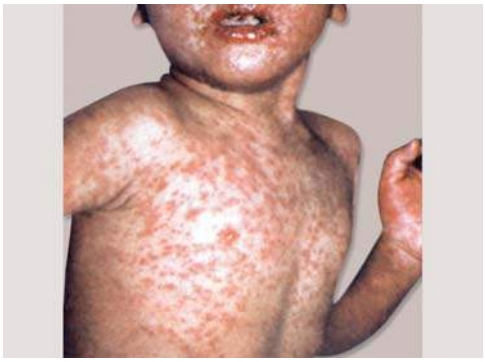


Fig. 3: Maculopapular rash on trunk

measles infection and an evidence of post measles infection (Fig. 4).

Convalescent phase: Cough may persist for one to two weeks after measles infection. The occurrence of fever beyond the third to fourth day of rash suggests a measles-associated complication. Immunity after measles infection is thought to be lifelong, although there are rare reports of measles reinfection.

Diagnosis

Mostly clinical depending upon history and clinical examination. Koplik's spot seen is pathognomonic. Post-measles desquamation and hyperpigmentation are too characteristics. Cases of modified measles and atypical measles could be confusing, when measles specific antibody in paired sera is useful.

Differential Diagnosis

- Other exanthematous immune-mediated illnesses and infections,
  - Rubella (rash is similar but prodrome is milder, there is a prominent retroauricular or suboccipital lymphadenopathy)
  - Adenoviruses
  - Enteroviruses
  - Epstein-Barr virus (characterized by sore throat, lymphadenopathy and splenomegaly)
- Exanthem subitum or Roseola infantum rash usually appears after disappearance of fever and erythema infectiosum (in older children)
- Mycoplasma pneumoniae and group A *Streptococcus* may also produce rashes similar to measles
- Kawasaki syndrome: It can manifest many of the same findings as measles but lacks discrete intraoral lesions (Koplik's spots) and a severe prodromal cough. Typically has elevated neutrophils and acute-phase reactant levels. In addition, the characteristic thrombocytosis of Kawasaki syndrome is absent in measles
- Drug eruptions (history of specific drug consumption).

Laboratory Investigations

- Complete blood count (CBC)
  Leukopenia, T-cell cytopenia, and thrombocytopenia may be observed during measles infection

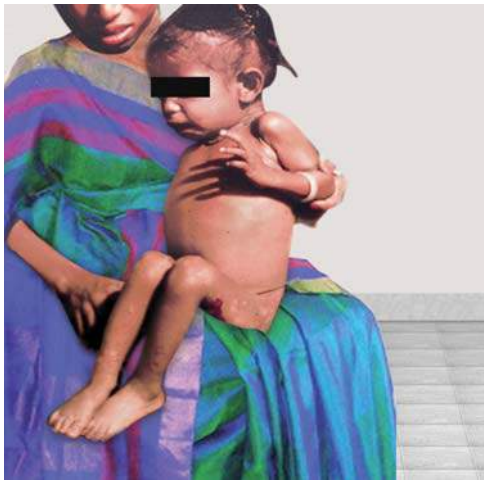


Fig. 4: Malnutrition following measles. Skin showing brownish discoloration

- Chest radiography may demonstrate interstitial pneumonitis
- Biopsy samples of lymphoid tissues before the appearance of the exanthem may demonstrate reticuloendothelial giant cells.
- Histologic analysis of enanthem or exanthem and cytologic examination of nasal secretions may also demonstrate epithelial giant cells.

Treatment

Mainly symptomatic and supportive with nutritional support

- Maintenance of hydration, oxygenation, and comfort are goals of therapy
- Antipyretics for comfort and fever control
- For patients with respiratory tract involvement, airway humidification and supplemental oxygen
- Ventilatory support may be required for respiratory failure due to croup or pneumonia
- Antiviral therapy is not effective in otherwise normal healthy patients
- Antibiotics are indicated in superadded bacterial infection in the convalescent phase.

Vitamin A in Measles

Vitamin A can reduce the severity and complications of measles. Published studies revealed that measles associated death increases about 24% in vitamin A deficient children.

Dose of Vitamin A

200,000 1U orally for children ≥1 year of age and 100,000 IU for children 6 months to 1 year of age, two doses on D1 and D2.

Patients suffering from measles should be offered protein and energy-dense diet and increment of two additional daily diets at least for 6 weeks to prevent subsequent malnutrition.

Complications

Case fatality from complications of measles, in developing countries is 4–6%. Risk groups for developing complications are:

- Immunocompromised hosts
- Pregnant women
- Individuals with vitamin A deficiency or poor nutritional status
- Individuals at the extremes of age.

Measles causes disseminated infection, so multiple systems and organs are affected.

- Pulmonary: Respiratory tract infections (most frequently occurs among patients <5 years and >20 years)
  - Interstitial pneumonia
  - Post-measles bronchopneumonia due to *Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae,* and *Staphylococcus aureus*
  - Laryngotracheobronchitis (croup both pre-eruptive croup and posteruptive croup)
  - Otitis media occurs in 5 to 10 percent of cases
  - Bronchiectasis
  - Flaring up of latent tuberculosis
  - Coinfection with other viruses like parainfluenza and adenovirus.
- Neurologic
  - Febrile seizure

- Encephalitis: Usually appears within a few days of the rash. It is associated with a CSF pleocytosis (predominantly lymphocytes), increased protein levels, and normal glucose
- Acute disseminated encephalomyelitis: Acute disseminated encephalomyelitis (ADEM) is a demyelinating disease that presents during the recovery phase of measles infection, typically within two weeks of the exanthem. ADEM is also known as postinfectious or postvaccination encephalomyelitis
- The major manifestations of ADEM include fever, headache, neck stiffness, seizures, and mental status changes such as confusion, somnolence, or coma. Other findings may include ataxia, myoclonus, choreoathetosis, and signs of myelitis, such as paraplegia, quadriplegia, sensory loss, loss of bladder and bowel control, and, in patients with myelitis, back pain. Analysis of cerebrospinal fluid generally demonstrates a lymphocytic pleocytosis and elevated protein concentration
- Subacute sclerosing panencephalitis
- Subacute sclerosing panencephalitis (SSPE) is a fatal, progressive degenerative disease of the central nervous system that occurs 7 to 10 years after natural measles infection
- Others

  Other neurologic complications associated with measles include acute measles-induced encephalopathy

- Malnutrition

  Measles is a common antecedent of malnutrition (Fig. 4), lasting for 2–4 weeks in healthy children and it can also increase the severity of malnutrition and can make previously existing nonsevere malnutrition to severe acute malnutrition (SAM), a potentially serious condition with high-case fatality.
- Eye manifestations
  - Measles-induced keratitis (a common cause of blindness)
  - Corneal ulceration
- Gastrointestinal
  - Gingivostomatitis
  - Diarrhea
  - Gastroenteritis
  - Hepatitis
  - Mesenteric lymphadenitis
  - Appendicitis.

In developing countries, measles-induced stomatitis and diarrhea can lead to worsening of nutritional status.

- Cardiac

  Cardiac complications of measles include myocarditis and pericarditis
- Immunosuppression: Measles infection can lead to systemic immune suppression and severe secondary infections, especially in the developing world. These effects are caused by direct infection of T cells by measles virus and by infection of dendritic cells, impairing their important antigen presenting/accessory function in T cell activation.

  Due to immunosuppressant properties, children suffering from bronchial asthma may get temporary relief of breathing difficulty as it behaves like steroid. However its adverse effects in such cases far outweigh its bronchodilator property. Similarly, children with nephrotic syndrome with measles may develop brisk diuresis as it also works here as steroid (immunosuppressant).

Prevention

- Isolate the patient during its infective period
- Measles vaccine given within 72 hours of exposure can prevent measles in contact as incubation period of vaccine measles virus is less than natural measles virus and produces immunity earlier than natural measles virus, due to earlier subclinical infection of attenuated vaccine virus.

Measles Vaccine

With the absence of an intermediary host, measles vaccine has generated a lot of interest for potential eradication. Hence the measles vaccination has a lot of importance at the national and international level. Maternal antibody provides protection for first 6 to 9 months of infancy. A number of live attenuated vaccines are available against measles either as monovalent measles vaccine or measles containing vaccine (MCV). The MCV are MMR (measles, mumps and rubella), MMRV (measles, mumps, rubella, and varicella) and MR (measles and rubella).

Two doses of measles vaccine are given. The first dose is given with MR (measles and rubella) in EPI schedule. The second dose is given at 15th month as monovalent measles vaccine according to EPI schedule. However instead of monovalent measles vaccine given by EPI, measles vaccine containing combination vaccine MMR (measles, mumps, and rubella) can be given at 15th month.

In areas with high measles transmission, the first dose of MCV (MR, MMR) should be administered at nine month. All unvaccinated children over nine month should receive their vaccine as soon as possible. In countries with low risk of measles transmission, the first dose may be administered at 12 months. The optimum timing for second dose is 15 to 18 months.

Measles vaccines are safe, effective, inexpensive and provide long lasting immunity. Hence all countries should aim at providing two doses of vaccine.

Measles Status: Global and Regional Targets

Millenium development goal aims to reduce deaths among children overall by two-thirds by 2015. Routine measles vaccination coverage was selected as an indicator of progress towards this goal because of the potential of measles vaccination to reduce mortality among children and considerations of measles coverage as a marker of access to children's health services. All six WHO regions have committed to eliminate measles. Then Americans achieved tha goal in 2002, the Western Pacific Region aims to eliminate measles by the end of 2012 and the European and Eastern Mediterranean regions targeted to eliminate measles by 2015. African region planned to eliminate it by 2020.

VARICELLA (CHICKEN POX)

Virology

Varicella zoster virus (VZV), included in the family *Herpesviridae*

Epidemiology

Varicella zoster virus infection occurs worldwide. Seroprevalence at age 20 is typically 95%. Primary infection with VZV causes chickenpox, which is primarily a disease of childhood, although it may occur at any age and is more severe in adults, with a

higher incidence of serious complications such as pneumonitis. Reactivation of latent VZV in sensory ganglia causes herpes zoster (shingles). The absolute incidence of zoster is higher in adults, but not if corrected for prior exposure to VZV.
Reservoir: Man

Mode of Transmission

Person-to-person, by direct contact or droplet spread from cases of chicken pox or herpes zoster.

Incubation Period

13–21 days.

Infectious Period

From 2 days before the onset of rash until the lesions are crusted. Scabs are noninfectious.

Fetal Infection

If infection occurs at less than 26-weeks gestation, there is a small risk of fetal malformation (microcephaly, hydrocephalus, limb hypoplasia, cutaneous scarring and ophthalmic defects). The risk is highest during the first trimester (3%). Infection just before or shortly after delivery may be followed by neonatal infection, which can be severe.

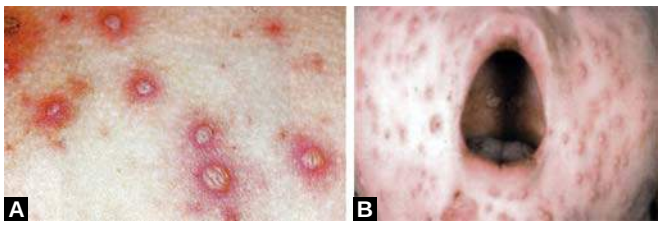
Infection in Neonates

Neonates of mothers who develop varicella <5 days before or shortly after delivery will not be protected by maternal IgG and may develop severe disseminated infection. They should receive VZIG (see below) and be monitored for 14–16 days for signs of infection, which should be treated promptly with aciclovir. Some recommend prophylactic acyclovir for these neonates. Herpes zoster during pregnancy poses no threat to mother or child, since by definition, the mother will have anti-VZV IgG and this will protect the neonate.

Clinical Features

- There is a mild prodrome of malaise, fever, headache and rhinitis.
- The rash develops as crops of vesicles (Fig. 5) each appearing on an erythematous base ("dewdrop on a rose petal"). Vesicles rapidly progress to umbilicated papules, pustules and scabs (Fig. 6). Distribution is typically central on head, trunk and arms, and also the palate or gums. New crops continue to appear for up to 7 days. Fever remains elevated for 4–5 days after onset of rash.

Pulmonary disease during varicella is often due to secondary bacterial pneumonia, usually with *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Staphylococcus aureus*. Staphylococcal septicemia may occur.



Figs 5A and B: (A) Vesicles on the skin with red base; (B) in oral cavity

Investigations

Light Microscopy of Vesicle Contents

Reveals multinucleate giant cells (Tzanck preparation); electron microscopy shows large numbers of herpes virus particles. Methods are available for the rapid detection of VZV antigens in vesicle fluid. Retrospectively diagnosis can be confirmed by serology.

CXR

CXR shows widespread patchy shadowing; may show military mottling. Residual pulmonary fibrosis and CXR calcifications may occur in survivors.

Differential Diagnosis

- Infectious vesicular rashes include:
  - Herpes simplex infection
  - Hand, foot and mouth disease
  - Disseminated gonococcal infection
- Noninfectious causes include:
  - Stevens-Johnson syndrome
  - Pemphigus
  - Pemphigoid

In atypical cases, vesicular impetigo due to *Staphylococcus aureus* or GAS can be confused.

Treatment

Supportive Care

- Antipyretic paracetamol and non-aspirin drug
- Plenty of fluid intakes
- Soothing agents like lotion calamine over the affected skin
- Antipruritic: In troublesome itching condition.

Antiviral Treatment (Not Usually Required)

Aciclovir shortens and reduces the severity of illness but must be given early (ideally <24 hours) to have a significant effect. Aciclovir is not recommended for routine use in immunocompetent children. Intravenous acyclovir is indicated in the following circumstances:

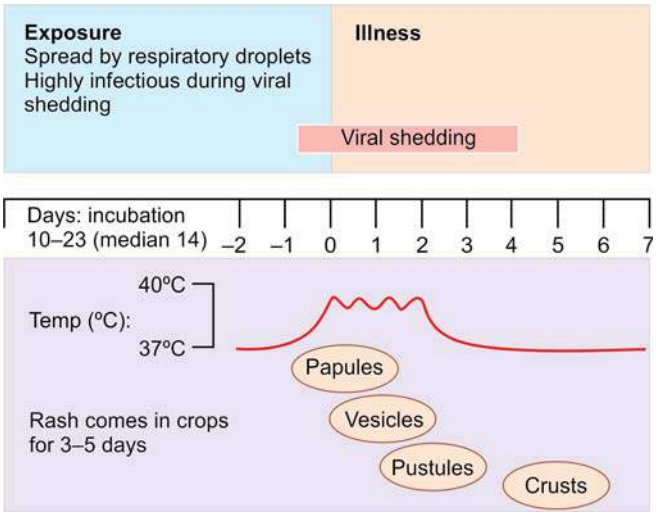


Fig. 6: Showing sequence of clinical features (fever and pleomorphic rashes during various stages of vericella infection)

- Immunocompromised patients (including those with AIDS)
- Neonates and if there is evidence of severe or disseminated disease (30 mg/kg in three divided dose IV for 10 days)
- In particular, ophthalmic disease, pneumonitis or encephalitis.

Complications

- Bacterial superinfection of the rash is common *Streptococcus* followed by *Staphylococcus*, sepsis, scarlet fever. In severe cases, varicella gangrenosum (*Streptococcus*)
- Hemorrhagic chickenpox
- Many patients have mild hepatitis
- Mucositis may cause dysuria
- Varicella *pneumonitis* is more common in immunocompromised patients
- It may progress rapidly, with hypoxia and tachypnea
- Encephalitis (cerebellitis): Chickenpox cerebellitis is an important cause of acute ataxia in children with good prognosis
  Other CNS complications:
  - GBS
  - Transverse myelitis
- Thrombocytopenia and disseminated intravascular coagulopathy: Occur very rarely and may cause hemorrhagic varicella, with bleeding into vesicles. All complications are commoner in the immunocompromised.

Prevention

Chicken pox is very contagious.

- Isolation
- Rest at home to keep away from close human contact until the lesions are crusted.

Vaccination

Live attenuated varicella-zoster virus (Oka strain), obtained from human diploid cell culture.

Indications

- A single dose of vaccine is recommended in children ≥12 months of age. For children ≥12 years, 2 doses at 4-week interval. Currently, however, 2 doses are recommended irrespective of age after 12-month age
- For active immunization, from age 12 months onwards at a dose of 0.5 mL, to be given subcutaneously
- Varicella and MMR vaccine can be given in same date at different sites, if not given they should be given at 4-weeks interval. They can be given combined by single injection MMRV vaccine at 12 months of age through 12 years of age. This MMRV vaccine may be used both first and second dose of MMR and varicella vaccine. Breakthrough infection may occur after first dose of varicella vaccine and manifests as modified chickenpox (milder form).

Contraindications

- Acute severe febrile illness
- Lymphocyte count <1200/cumm.

Adverse Effects

- Local reaction (pain, erythema)
- Generalized rash (maculopapular).

Role of Varicella Zoster Immunoglobulin (VZIG)

The Advisory Committee on Immunization Practices (ACIP) recommends administration of VZIG/VariZIG to newborns

- Whose mother has signs and symptoms of varicella around the time of delivery (5 days before or 2 days after)
- Premature infant born at >28 weeks of gestation who are exposed during the neonatal period and whose mothers do not have signs of immunity
- Premature infant born at <28 weeks of gestation or who weigh <1,000 grams at birth and were exposed during neonatal period, regardless of maternal history of varicella or vaccination.

MUMPS

The mumps virus causes an acute, self-limited, viral syndrome. Prior to the widespread use of an effective vaccine, mumps primarily occurred in young children attending primary grade school; mumps was also a leading cause of viral meningitis and the most common cause of unilateral acquired sensorineural deafness in children.

Virology

Mumps is caused by mumps virus. It is a member of paramyxovirus family. Mumps virus is a single-stranded RNA virus Humans serve as the only natural host for mumps virus.

The mumps virion possesses a helical core containing the genomic nucleocapsid portion, which is surrounded by an external glycoprotein envelope. The major surface glycoproteins provide two discrete functions: hemagglutination-neuraminidase activity and cell fusion activity. Only one mumps serotype has been identified.

Incubation Period

14–24 days.

Route of Transmission

By direct contact, air-borne droplets and fomites contaminated by saliva.

Infectious Period

Variable; usually 3–5 days before swelling of parotid gland and 3 days after the swelling subside.

Clinical Features

Twenty percent infections are asymptomatic. Mumps infection may occur with parotitis; in 30–40% of infection cases, there is bilateral involvement of parotid gland. In few cases, there may be involvement of other salivary gland (submandibular) without involvement of parotid gland. This makes mumps difficult to differentiate from acute pyogenic cervical lymphadenitis due to their close anatomical proximity.

Mumps infection is frequently accompanied by a nonspecific prodrome consisting of low-grade fever, malaise, headache, myalgias, and anorexia. These symptoms are generally followed within 48 hours by the development of parotitis, a classic feature of mumps infection. Symptomatic infection in adults is usually more severe than in children.

Parotitis

The swelling attains maximum size in 1–3 days, pushes the pinna upwards and outwards and subsides in 3–7 days. The swollen parotid is tender. Unilateral parotid swelling is common though other side may be affected (Fig. 7). Mumps virus may cause mumps meningitis without mumps parotitis, which makes clinical diagnosis of mumps meningitis difficult.

Fever is moderate. A maculopapular or erythematous rash may be seen.

Differential Diagnosis

Differential diagnosis of parotid swelling:

- Acute pyogenic cervical lymphadenitis
- Suppurative parotitis
- Viral infection like HIV, cytomegalovirus (CMV), influenza, parainfluenza 1, 2 and 3 and Coxackie
- Sialolactesis due to obstruction of parotid duct due to kinking or salivary duct calculus
- Recurrent parotitis
- Non-Hodgkin's lymphoma
- Mikulicz disease: Swelling of both parotids and lacrimal glands along with absence of tears and dryness of mouth.

Diagnosis

- Mostly clinical
- Isolation of virus from saliva, urine, spinal fluid or blood
- Viral culture
- Polymerase chain reaction
- Serology
  - Serum amylase: Serum amylase is frequently raised with mumps parotitis. The contribution of most of the serum amylase comes from salivary amylase rather than pancreatic amylase, and not due to mumps pancreatitis
  - Positive serum IgM for mumps
  - Significant rise in IgG titers between acute and convalescent specimens
  - Complement fixation test for mumps antibody: Detectable during salivary gland swelling and rises up to convalescence; may persist for 6–12 months.

Mumps Parotitis and Significance of Serum Amylase in Mumps Infection

An overenthusiastic tendency have been observed among clinicians to diagnose pancreatitis when children with mumps develop abdominal pain associated with increased serum amylase. Possibly, this complication is overdiagnosed in majority of cases. Mumps pancreatitis is probably less frequent complication than commonly thought. The possible over diagnosis of such less common but potentially serious conditions may create unnecessary panicky condition to parents and physicians, involving unnecessary costly investigations and treatment.

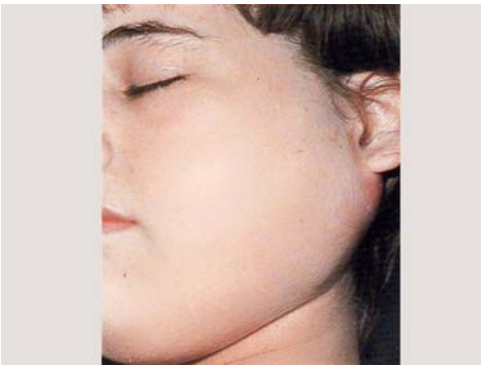


Fig. 7: Swelling of left parotid gland with lymphedema

Many children with mumps develop gastrointestinal symptoms like abdominal pain, vomiting, gastroenteritis reminding and tempting clinicians to diagnose potentially dangerous acute mumps pancreatitis especially when serum amylase is found raised. The serum amylase concentration may be elevated because of parotitis rather than pancreatitis and usually not increased in non-parotitis mumps (non-salivary gland involvement).

Published studies showed the magnitude of increased serum amylase depends on the degree of swelling of parotid gland due to mumps infection, being highest in huge swelling of parotid gland and lowest in mild swelling of parotid gland. The published studies also indicate that duration of increased serum amylase also correlates with degree of parotid swelling, not on the inflammation or duration of pancreatitis.

The sources of elevated serum amylase in mumps are salivary glands, pancreas and inflamed intestinal glands. A study found that serum amylase is increased in 70% cases suffering from mumps. A study of total serum amylase, lipase, and pancreatic isoamylase in patients suspected of having mumps pancreatitis suggests that almost all elevated total serum amylase were due to salivary amylase.

There should be no doubt that pancreas may be involved as part of illness of mumps, but in majority of cases, it is mild and subclinical form but overt clinical pancreatitis rarely occurs. If the diagnosis of mumps pancreatitis is based on the presence of abdominal pain, vomiting and increased serum amylase, only 5–10% of mumps parotitis may be associated with mild form of pancreatitis.

On the other hand, the highly elevated level of serum amylase associated with mumps infection, can be utilized as diagnostic test for mumps, particularly in doubtful cases, like submandibular mumps which makes it difficult to differentiate from acute cervical (submandibular) lymphadenitis where serum amylase level will be normal. It is more relevant in the context of resource poor developing countries where isolation of mumps virus or mumps specific antibody is difficult to perform.

Management

- Therapy for mumps parotitis is symptomatic and includes analgesics or antipyretics, such as acetaminophen
- Topical application of warm or cold packs to the parotid may also be soothing
- Patients who have meningitis or pancreatitis with nausea and vomiting may require hospitalization for intravenous fluids
- Patients with orchitis
  Treat symptomatically with bed rest, nonsteroidal anti-inflammatory agents, support of the inflamed testis, and ice packs.

Complications

The serious complications like meningitis, encephalitis, and orchitis, may occur in the absence of parotitis, which can delay accurate diagnosis of the clinical syndrome.

CNS Complications

There are some peculiarities of CNS involvement of mumps infection. Mumps is neurotropic virus and enters CNS via choroid plexus. CNS pleocytosis occurs in 40–60% of patients with mumps parotitis without significant meningitis and symptomatic CNS involvement occurs in 10–30% cases. On the other hand, mumps virus may enter CNS causing symptomatic meningitis without involving parotid gland and thereby without causing mumps parotitis. Aseptic meningitis is the commonest complication of mumps. It may present before, coincidentally with or after the illness. The CSF will show lymphocytic pleocytosis and the count may exceed 10,000 cells/μL. The protein may be elevated and glucose level is usually normal. However, the latter is often decreased in mumps meningitis. In this circumstances when mumps meningitis is not associated parotid swelling, it becomes difficult to distinguish mumps meningitis with pyogenic meningitis. Although mumps virus has higher affinity to affect CNS and CSF, mumps meningitis itself is usually benign. However, postinfectious mumps encephalitis is severe though complete recovery is usual.

- Meningoencephalitis
  Most frequent complication. Usually course is benign. CSF study shows lymphocytosis.
- Orchitis/epididymitis: In adolescent and adult males, epididymo-orchitis is second only to parotitis and a common finding in mumps. Similar to mumps meningitis without parotitis, orchitis can occur without parotitis. Involvement prepubertal male is extremely rare, but following puberty it occurs in 30–40% of male. In one-third cases, orchitis is bilateral. Atrophy of testes may occur but sterility is rare.

  Oophoritis is seen in postpubertal female but of lower incidence.
- Deafness: There may temporary or permanent sensorineural deafness; usually unilateral
- Other neurologic complications:
  - Encephalitis
  - Guillain-Barré syndrome
  - Transverse myelitis
  - Facial palsy
  - Deafness
- Pancreatitis: Clinical pancreatitis is rare. Characterized by severe epigastric pain, tenderness and increased serum pancreatic amylase, decreased serum lipase and serum calcium.
- Others: Nephritis, thyroiditis, myocarditis and arthritis.

Prevention

Mumps vaccine is effective in preventing mumps and its potential complications, including orchitis, aseptic meningitis, and pancreatitis.

Usually trivalent MMR (measles, mumps and rubella) is used for mumps vaccination along with measles and rubella.

The dosing schedules for both MMR and MMRV (measles, mumps, rubella and varicella) vaccines are the same. According to the Advisory Committee on Immunization Practices (ACIP) recommendations, MMR (or MMRV) vaccine should be given at ages 12–15 months and a second dose at 4–6 years of age.

Mumps (MMR) vaccine can be given at 9 months of age instead of measles vaccine. Another dose should be given at 15 months of age. This is not a second dose (but genuine first dose), but works on those, who will not respond to 9-month age due to persistent maternal antibody. Another dose is given at 4–6 years of age, which is genuine second dose not booster.

RUBELLA

Virology

Rubella virus is a member of the togavirus family, which includes two genera of small enveloped RNA viruses: alphavirus and rubivirus.

Rubella virus's positive-sense, single-stranded RNA encodes three structural proteins: C, E1, and E2. These proteins are encoded as a single precursor on a 24S subgenomic mRNA and cleaved by cellular peptidases. The capsid protein, C, surrounds the RNA of the virion while the glycosylated proteins, E1 and E2, form transmembrane spikes and serves as the major antigenic sites of the virus.

Incubation Period

- Usually 14–18 days (range 12–23 days)
- Viremia occurs five to seven days after inoculation, allowing the virus to spread throughout the body.

Period of Infectivity

Seven days prior to onset of rash to 7–8 days after its disappearance.

Transmission

Rubella is acquired via inhalation of infectious large particle aerosols and thus is augmented by close and prolonged contact with infected individuals. Initial replication occurs in nasopharyngeal cells and regional lymph nodes.

Other Mode of Transmission is Across the Placenta

Children between 5 years and 14 years are commonly affected; occurs mostly in spring. Maternal antibody protects infant up to first 6 months of life.

Transmission rate is 100% in closed institution and 50–60% among family members.

Clinical Features

Features of rubella depend on whether the disease is acquired or transplacental.

Acquired

Prodromal phase:

Mild catarrhal symptoms:

- Discrete rose spots on the soft palate. Discrete/confluent maculopapular rash starting from the face spreads to other parts of the body rapidly and clear by 3rd day with minimal desquamation (Fig. 8). May not be visible or appreciated in dark-skinned people.
- Mild fever, may be absent during rash
- Lymphadenopathy: Retroauricular, suboccipital, posterior cervical nodes start enlarging during prodrome
- Mild pharyngitis and conjunctivitis with photophobia
- In older girls, polyarthritis involving small joints of the hands may be present
- Sometimes fever and lymphadenopathy are the presentation without any rash.

Transplacental

In very early pregnancy, infection may cause abortion/fetal death. In infants born to mothers who had rubella, particularly during first 3 months of pregnancy with following consequences:

- Congenital rubella infection: Congenital rubella infection (CRI) encompasses all outcomes associated with intrauterine rubella infection (e.g. miscarriage, stillbirth, combinations of birth defects, asymptomatic infection)
- Congenital rubella syndrome: Congenital rubella syndrome (CRS) refers to variable constellations of birth defects (e.g. hearing impairment, congenital heart defects, cataracts/congenital glaucoma, pigmentary retinopathy, etc.).

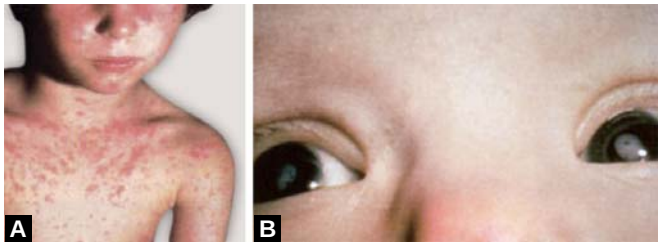
The risks of CRS following maternal rubella depend on the stage of pregnancy at which infection occurs:

- <10 weeks: risk is 90%
- 11–12 weeks: risk is 30%
- 13–20 weeks: risk is <10%
- >20 weeks: risk is very low.

Clinical Features

In neonates (Fig. 9):

- Intrauterine growth retardation
- Meningoencephalitis
- Large anterior fontanelle
- Hearing loss
- Cloudy cornea
- Cataract (Fig. 8B)
- Infantile glaucoma
- Retinopathy



Figs 8A and B: Rubella: typical scattered maculopapular (unlike confluent morbilliform rash of measles) rash on trunk (upper) in acquired rubella and congenital rubella syndrome with bilateral cataract (lower)

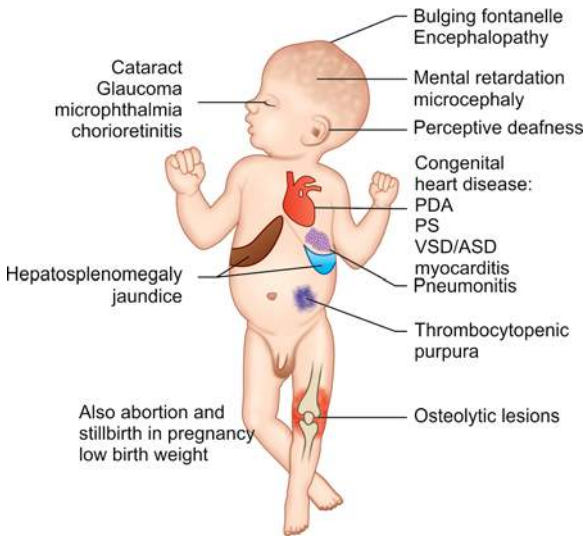


Fig. 9: Features of rubella syndrome

Case definition and classification criteria for congenital rubella syndrome (CRS)	
Clinical case definition	
An illness, usually manifesting in infancy, resulting from rubella infection in utero and characterized by signs and symptoms from following categories	
Category A	
• Cataracts/congenital glaucoma • Congenital heart disease most commonly PDA or peripheral pulmonary stenosis • Hearing impairment • Pigmented retinopathy	
Category B	
• Purpura • Hepatosplenomegaly • Jaundice • Microcephaly • Developmental delay • Meningoencephalitis • Radiolucent bone disease	
Laboratory criteria	
• Isolation of rubella • Demonstration of rubella specific immunoglobulin M (IgM) Infant rubella antibody level (IgG) that persists at a higher level and for a longer time than expected from passive transfer of maternal antibody (i.e. rubella titer that does not drop at expected rate of a twofold dilution per month • Polymerase chain reaction positive for rubella virus	
Classification	
Suspected	• A case with some compatible clinical findings but not meeting the criteria for a probable case • A case that is not laboratory confirmed and has either: – Any two complications from category A above, or
Probable	• One complication from category A and one from category B above and • Lacks evidence of other etiology
Confirmed	A clinically consistent case that is laboratory confirmed
Infection only	A case that demonstrates laboratory evidence of infection but without any clinical symptoms or signs

- Interstitial pneumonia
- Cardiac defects
- Hepatosplenomegaly
- Jaundice, hepatitis
- Diarrhea
- Radiolucent bone lesions (in the long bones)
- Petechiae and purpura (blueberry muffin lesions) (Fig. 10)
- Adenopathy
- Hemolytic anemia
- Thrombocytopenia

Many of these manifestations are transient and not necessarily specific for CRI. The risk of mortality is increased in neonates with severe defects (e.g. extreme prematurity, extensive meningoencephalitis, gross cardiac lesions or myocarditis with early heart failure, fulminant interstitial pneumonitis, and rapidly progressive hepatitis)

Fig. 10: Neonate suffering from rubella having blueberry muffin spot on skin

In infants and children: Structural defects in infants and children with congenital rubella syndrome (CRS). These generally result from defective organogenesis or scarring.

- Hearing loss: Nearly two-thirds of children with intrauterine rubella infection have long-term deafness, which is usually bilateral and sensorineural (Fig. 11)
- Cardiac and vascular anomalies: Approximately one-half of children infected during the first two months of gestation have congenital heart disease. They are:
  - Commonest
  - Patent ductus arteriosus and
  - Branch pulmonary artery stenosis
- Others
  - Pulmonary valvular stenosis
  - Aortic valve stenosis
  - Ventricular septal defect
  - Tetralogy of Fallot
  - Coarctation of the aorta
- Eye lesions
  - Cataracts (Fig. 8B): Occur in about one-quarter of infants with CRS
  - Infantile glaucoma is less frequent (cataracts and infantile glaucoma usually become apparent during the early weeks of life)
  - "Salt and pepper" retinopathy is caused by disturbed growth of the pigmentary layer of the retina.
    - Central nervous system abnormalities:
      - ◊ Microcephaly (27%)
      - ◊ Intellectual disability (formerly mental retardation; in 13%)
      - ◊ Motor delay
      - ◊ Behavioral disorders
      - ◊ Autism
      - ◊ Psychiatric disorders are less common.

Late Manifestations

Delayed manifestations of congenital rubella infection (CRI) occur in at least 20 percent of children with symptomatic congenital rubella infection. Some of the late manifestations may relate to subtle damage that is present but not detected in early life. Late manifestations include:

- Hearing loss: Permanent hearing loss is common. It is sensorineural and bilateral ranging from mild to profound
- Endocrine disorders:
  - Diabetes
  - Thyroid disease: Hypothyroidism, hyperthyroidism or thyroiditis
  - Growth hormone deficiency

Fig. 11: Child with congenital rubella syndrome who underwent definitive cardiac surgery and removal of cataract showing high hypermetropic glass and hearing aid visible on the right ear

- Eye problems: Pigmentary retinopathy, cataracts, glaucoma, keratic precipitates, keratoconus, corneal hydrops, microphthalmos (estimated to occur in 10–20 percent of cases), strabismus, and absorption of the cataractous lens.
  This damage can appear years or even decades after birth.
- Vascular effects: Fibromuscular proliferation of the intima, sclerosis of arteries, systemic hypertension secondary to renal disease, and subretinal neovascularization
  These lesions are potential causes of coronary, cerebral, and peripheral vascular disease in adulthood
- Progressive panencephalitis: Progressive rubella panencephalitis most commonly occurs in the second decade of life. It is slowly progressive and fatal. The initial findings are usually learning problems and ataxia
- Immune defects: Defects in specific antibody production, repeated infections, and defective T-cell response with associated autoimmune phenomena.

Diagnosis

Clinically, there is strong suspicion of acquired rubella, if the rash follows milder prodrome, is associated with significant retroauricular, suboccipital lymphadenopathy and polyarthritis.

Laboratory Investigations

Although the diagnosis of congenital rubella syndrome (CRS) may be suspected clinically, it is confirmed with laboratory tests. Laboratory evaluation should be performed before the child reaches one year of age, after which it is difficult to establish a diagnosis of congenital rubella infection.

- Virus isolation
- Serology: Demonstration of rubella-specific IgM antibody or infant IgG rubella antibody level that persists at a higher level and for a longer time than expected from passive transfer of maternal antibody
- Rubella virus PCR: It is difficult to establish a diagnosis of CRI in children older than one year of age. At this age, serologic testing usually is not diagnostic, and viral isolation is uncommon. Retrospective diagnosis of congenital rubella syndrome may be possible in children who are older than one year through:
  - Detection of persistent rubella RNA by PCR
  - Measuring lymphocyte response to rubella in vitro

- Measuring rubella IgG avidity (strength of antigen-antibody binding). Children with intrauterine rubella infection have low rubella-specific IgG avidity
- Measuring antibody response to rubella vaccination (in children with compatible manifestations but nondetectable antibody); children with congenital rubella syndrome generally do not respond to rubella vaccination.

Evaluation

The evaluation of a newborn with clinical findings compatible with intrauterine rubella infection (e.g. cataract, congenital cardiac defect) is the same as the evaluation for other intrauterine infections. It should include:

- Review of maternal history (evidence of rubella immunity)
- Assessment of physical stigmata consistent with the syndrome, including complete cardiac and neurologic examinations
- Complete blood count and platelet count
- Serum immunoglobulins [IgM >21 mg/dL (0.21 g/L) during the first week of life strongly suggests intrauterine infection (not specifically rubella); normal values do not exclude infection]
- Radiographs of long bones
- Ophthalmologic evaluation
- Audiologic evaluation
- Neuroimaging (e.g. ultrasonography, computed tomography)
- Lumbar puncture
- Echocardiography for all infants in whom congenital rubella syndrome is suspected, whereas others suggest cardiology consultation and echocardiography based upon clinical examination findings.

Treatment

Treatment consists of supportive care and symptomatic. No specific therapy for rubella infection is available. Interferon, isoprenisine have been used with limited success.

Prevention

The goal of rubella vaccination is to prevent congenitally acquired rubella. Immunization of all young children is required to reduce rates of CRS.

The World Health Organization recommends that the measles, mumps, rubella vaccine (MMR) be first given at 12–18 months of age, with a second dose at 36 months.

If a child has not received the second dose at school entry, it should be administered as soon as possible, but no later than 11–12 years of age. Pregnant women should be tested early in pregnancy for rubella immunity. Susceptible women should receive immunization after the child is born.

MMR can be given at 9 months of age instead of measles vaccine where measles transmission rate is high. However, MMR vaccine given before 12-month age is not considered as first vaccine. Another dose of MMR should be given at 12–15 months of age which is considered as genuine first dose. In order to complete the series, final dose should ideally be given between 4 years and 6 years of age. If started after 12 months of age, 2 doses are sufficient. In Indian subcontinent (India) rubella vaccine is given along with MMR vaccine. IAP recommends two doses of MMR at 12-15 months and 4-6 years. The second dose of MMR is to protect those who failed sero-convulsion against mumps and less commonly rubella with the first dose of the vaccine.

CYTOMEGALOVIRUS INFECTION

Cytomegalovirus (CMV) commonly infects people of all ages, races, and ethnic groups. Although most CMV infections are asymptomatic or cause mild disease, newborns and immunocompromised children are at great risk of developing serious disease.

Incubation Period

Unknown for horizontally transmitted CMV infections. Infection usually manifests 3–12 weeks after blood transfusions and between 1 and 4 months after tissue transplantation.

Virology

Cytomegalovirus is a DNA virus, a member of the herpes virus group.

Epidemiology

The prevalence of antibody to CMV is influenced by age, geography, cultural and socioeconomic status, and child-rearing practices. In developing countries, most children are infected by 3 years of age, whereas in developed countries, such as the United States or United Kingdom, as many as 60–80 percent of the population will be infected with CMV by adulthood. Seroprevalence generally correlates inversely with a country's socioeconomic development, with highest rates observed in developing countries throughout Africa and Asia.

Mode of Transmission

Transmission can occur via multiple routes:

- Perinatal
  Vertical transmission of CMV to an infant occurs by one of the following routes:
  - In utero by transplacental passage of maternal blood-borne virus
  - At birth by passage through an infected maternal genital tract, or
  - Postnatally by ingestion of CMV-positive human milk
- Close contacts: From close contact, the virus is shredded from upper respiratory tract and urine. Protracted viral shedding is much more common among children than immunocompetent adults.
- Blood or tissue exposure
  A major route of transmission is through transfusion of blood and blood product and transplantation of organs from seropositive donors
- Sexual: Seroprevalence rates are higher among patients with multiple sexual partners or a history of prior sexually transmitted diseases and that virus can be detected in the genital tract.

Clinical Features

In Adults and Adolescents

In many patients, it may remain asymptomatic or self-limiting; may present with fever, cough, headache, and back and limb

pain. The clinical picture may mimic infectious mononucleosis with lymphadenopathy, hepatosplenomegaly and occasionally jaundice. May present as hemolytic anemia and may cause pneumonitis in children with underlying chronic hepatic disorders, leukemia and other malignancies. Peripheral blood film may show atypical lymphocytes.

Congenital Cytomegalovirus Infection

Cytomegalovirus may affect fetus during pregnancy. The infected pregnant women may be asymptomatic and quiet often cannot give history of clinical features of CMV infection. Newborns acquire infection during utero, perinatal and postnatal life. Symptomatic infection occurred intrauterine life is more serious than acquired in perinatal or postnatal life. However, most of the infections of fetus are asymptomatic and only 5–15% of congenitally infected newborns will have symptoms at birth like IUGR, microcephaly, hepatosplenomegaly, jaundice, purpura, viral sepsis like syndrome with or without shock.

Various pathogens that infect the mother traverse the placenta and produce infection in the fetus. These infections are of interest because they can result in fetal wastage and serious permanent sequelae. The early clinical manifestations of these infections are similar to other congenital infection and hence the acronym "TORCH" (toxoplasma, rubella, cytomegalovirus, herpes). Herpes was coined to focus attention on this group of infection. Although majority of congenital CMV infection are silent and asymptomatic, some may show clinical jaundice, hepatosplenomegaly, IUGR, microcephaly (Fig. 12), purpuric rash, chorioretinitis or pneumonia. Approximately 20% of these children also have sensorineural hearing loss. Two-third of the symptomatic infant will develop neurological features with serious consequence as seizure, chorioretinitis, microcephaly, later development of hydrocephalus, cerebral palsy (Fig. 13) and mental retardation. Intracranial calcification can occur in congenital CMV and toxoplasmosis but in CMV it is usually periventricular and in toxoplasmosis is as diffuse cerebral calcification. Cerebral calcification is better seen in CT scan of brain (Fig. 14) than X-ray skull or MRI of brain. The clinical features are summarized below:

- Small size for gestational age (SGA), hepatosplenomegaly
- Petechiae and purpura of the skin
- Jaundice at birth
- Viral sepsis like syndrome.

Mononucleosis Syndrome

Cytomegalovirus-induced mononucleosis syndrome is usually observed in adults, but it may occur in adolescent, children and even infant. It may occur in both immunocompetent and immunocompromised host.

Typical CMV-induced mononucleosis is characterized by:

- Fever
- Severe malaise of approximately 1–4 weeks' duration
- Peripheral lymphocytosis with atypical lymphocytes; mildly elevated liver enzymes
- In some patients, headache, myalgias, and abdominal pain with diarrhea are prominent symptoms
- In premature infants with transfusion acquired CMV mononucleosis, prominent manifestations include shock, hepatosplenomegaly, pneumonitis, thrombocytopenia, and renal failure.

Fig. 12: A child with CMV with microcephaly at birth during newborn period

Fig. 13: The same child at 6 months showing microcephaly with spastic quadriplegia

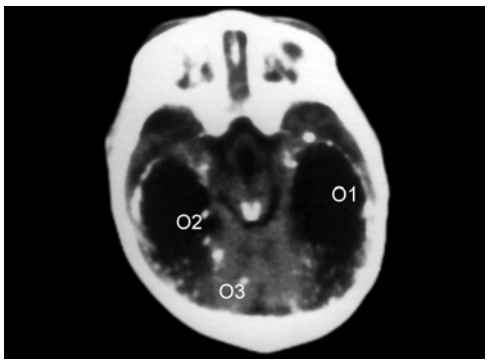


Fig. 14: CT scan of the child showing hydrocephalus with periventricular calcification

Differential Diagnosis

Differential diagnosis of symptomatic congenital CMV disease includes:

- Infectious causes:
  - Congenital toxoplasmosis
  - Congenital HSV infection
  - Congenital syphilis
  - Congenital rubella syndrome
  - Congenital infection with lymphocytic choriomeningitis virus
  - Congenital HIV infection
- Noninfectious causes:
  - Genetic disorders
  - Metabolic disease
  - Maternal exposure to drugs and toxins.

Perinatally Acquired CMV Infection

- Chlamydia pneumonitis
- Hepatitis B virus infection

- Infection with HIV
- Postnatally acquired infections with enteroviruses, adenovirus, and a variety of bacterial pathogens.

Laboratory Investigations

Detection of Infectious Agent

- Detection of CMV in urine by viral PCR. The test is definitive for CMV if done in first two weeks of life. If done later it may be due to perinatally or postnatally acquired infection which is not a serious condition.
- Virus detection from saliva and bronchial washing if available
- Imaging: CT scan of brain- showing periventricular calcification.

Serology

Elevated IgM CMV specific antibody in infants with seropositivity in mother (IgG and IgM) also diagnostic.

Determination of CMV IgG and IgM by:
- Complement fixation
- Hemagglutination inhibition
- Indirect fluorescent antibody assay
- Anticomplement immunofluorescence assay, enzyme-linked immunosorbent assay (ELISA)
- Latex agglutination and neutralization tests.

Treatment

Treatment of neonates with CMV infection is controversial, but may be considered in certain patients. Newborn who are likely to be benefited with antiviral treatment with ganciclovir include those with viral sepsis like syndrome, pneumonitis, retinitis or refractive thrombocytopenia

- Antiviral therapy
  To treat CMV infection, the antiviral drugs of choice are ganciclovir (10 mg/kg IV infusion in two divided doses for 2–3 weeks and may be continued 5 mg/kg/day until clinical features like retinitis, gastroenteritis regress). Likely toxic effects are bone marrow depression and live dysfunction. Other alternatives are valganciclovir, foscarnet and cidofovir
  - Potential candidate for antiviral therapy: Adult and pediatric immunocompromised hosts as well as for newborns with serious CMV disease
- Treatment of CMV-associated disease: Retinitis, pneumonitis, hepatitis, colitis, esophagitis, or encephalitis, in immunocompromised hosts usually involves a 2- to 3-weeks period of induction therapy with an intravenous antiviral medication, usually ganciclovir
- Cytomegalovirus hyperimmune globulin
  In conjunction with antiviral therapy CMV hyperimmune globulin may be used for patients with bone marrow transplant.

Prevention

General Health Measures

- All women contemplating pregnancy should know their CMV serologic status.
- Hygienic precautions reduce the risk of family transmission of the virus in pregnant women or those trying to become pregnant who are CMV seronegative to attempt to prevent the acquisition of primary CMV during pregnancy. These precautions include:
  - Avoiding kissing young toddlers and children on or near the mouth
  - Not sharing eating or drinking utensils, drinks, or food with toddlers or young children
  - Careful handwashing or using gloves after wiping noses, drool, and changing diapers
  - Avoiding intimate contact during the communicable period (when there is active viral shedding from saliva, genital secretions, or semen) with a sexual partner if the partner has documented CMV mononucleosis.

Blood Product, Human Milk, and Transplant Donor Selection

Whenever possible, CMV-seronegative recipients should receive transplants from CMV-seronegative donors, and all blood product transfusions should be from CMV-seronegative donors.

Passive Immunoprophylaxis

Although immune globulin or CMV hyperimmune globulin should not be used alone for the treatment of established CMV disease in immunocompromised patients, these preparations may be used to prevent the acquisition of serious CMV disease in selected immunocompromised patients.

Active Immunization

A variety of experimental CMV vaccines currently are in clinical trials and may be helpful someday in preventing CMV disease in newborns and immunocompromised patients.

HERPES SIMPLEX VIRUS INFECTION

Herpes simplex virus (HSV) belongs to the herpes virus family. Human infection occurs with herpes simplex virus 1 and 2 (HSV-1 and HSV-2) which are known as Human Herpes Virus 1 and 2 (HHV-1 and HHV-2). They are the most common cause of mucocutaneous lesions in immunosuppressed patients.

Microbiology

These viruses have characteristic neurotropism and latency in sensory ganglia. Persistence is associated with periodic reactivation and reappearance of infectious virus at mucocutaneous sites. The virions of HSV-1 and HSV-2 consist of an icosahedral protein capsid enclosing a core of double stranded DNA, surrounded by a protein tegument, and enclosed in a lipid-containing envelope. Glycoproteins present in envelope are important targets of the humoral and cellular immune responses (gB, gC, gD, and gG). The glycoproteins gE and gI function as immunoglobulin Fc receptors.

Incubation Period

2 days to 2 weeks.

Clinical Features

Neonates are affected usually with HSV-2, beyond neonatal period by HSV-1. HSV-2 is responsible for genital herpes where as cold sore is caused by HSV-1. Clinical features are as follows:

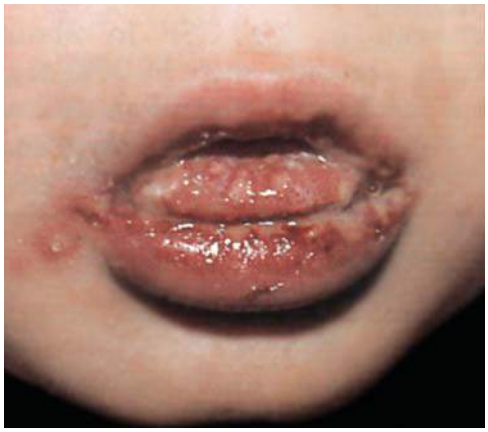


Fig. 15: Herpes gingivostomatitis showing vesicles and ulceration

- Orolabial infection
  Gingivostomatitis (Fig. 15)
  Grouped vesicles in tongue or lips are characterstics of HSV infection
  The gums are erythematous, mildly swollen, and ulcerated.
  Herpes stomatitis is not associated with encephalitis
- Genital infections
- Valvovaginitis: Rare in children
- Keratoconjunctivitis: Usually with HSV-1
- Cutaneous infection: Other than genital and orolabial infection HSV affects pulp and nail bed as "herpetic whitlow"
- CNS infection (discussed in detail in neurology chapter)
  It is a rare but severe complication. Unlike visible staphylococcal septic foci seen in skin and other body parts causing *Staphylococcal* septicemia or *Staphylococcal* pneumonia, overt visible herpes infection like herpes gingivostomatitis is not associated with herpes encephalitis. It is unclear that from where herpetic encephalitis develops. Herpetic encephalitis is caused by HSV-1 resulting from primary infection with HSV or reactivation. It is characterized by fever, altered consciousness, unusual behavior, and focal neurologic abnormalities, with signs and symptoms consistent with temporal lobe involvement
- Perinatal infection: Congenital infection occurs as a result of exposure to infected maternal genital secretion at delivery and includes skin lesions and scars, chorioretinitis, microcephaly, hydranencephaly and microphthalmia. Perinatal infection is caused by HSV-2 (also discussed in neonatology chapter)
- Other infections: In immunocompromised host HSV causes several unusual infections like visceral dissemination, esophagitis, tracheobronchitis, pneumonitis, and hepatitis.

Laboratory Investigations

- Viral culture
- HSV DNA PCR—highly sensitive and specific in herpes encephalitis
- Enzyme immunoassay
- Latex agglutination test.

Treatment

Acyclovir is the drug of choice. In case of herpes stomatitis usually do not require antiviral treatment except in immunocompromised child. The guideline for treatment of HSV infection with acyclovir is listed below:

- Encephalitis beyond neonatal period 10 mg/kg intravenous three times a day for 14–21 days
- Mucocutaneous infection in neonates 20 mg/kg IV three times a day for 14 days
- Disseminated or CNS infection in neonate 20 mg/kg IV three times a day for 21 days
- Primary genital:
  IV: 10 mg/kg four times a day for 5–10 days
  Oral: 200–400 mg five times a day for 5–10 days
- Recurrent genital 200 mg per oral five times a day for 5 days
- Mucocutaneous in immunocompromised host
  IV: 10 mg/kg three times a day for 7–10 days
  Oral: 200–400 mg five times a day for 7–10 days

Other alternatives to acyclovir are valacyclovir and famciclovir.

Complications

- After neonatal period, HSV infection yields minor morbidity and rarely life-threatening illness
- Fatal or serious outcomes occur in disseminated HSV infection in immunocompromised host and in herpes encephalitis. Progressive neurologic damage occurs in untreated encephalitis.

Prevention

- Infection control
  - Use of antiseptics, soap and hot water, or chlorine decreases the risk of transfer of virus in settings such as the home, spas, pools, wrestling meets, and hospitals
  - Use of condom during intercourse
  - Wearing of gloves during handling infected persons
- Chemoprophylaxis: Intravenous acyclovir is recommended in immunosuppressed patients receiving a bone marrow transplant or antileukemic chemotherapy. It is also indicated in HSV seropositive immunosuppressed pediatric patients.

TOXOPLASMA

Toxoplasmosis caused by *Toxoplasma gondii* is one of the important causes of perinatal/congenital infection.

Microbiology

It is an obligatory intracellular parasite.

Clinical Features

Toxoplasmosis in pediatric age group is classified into three categories: Congenital, postnatally acquired and ocular (which may be congenital or acquired).

Congenital

Asymptomatic acute infection in the mother results in congenital infection in neonate. Spontaneous abortion, prematurity and stillbirth may occur. The manifestation usually subclinical, when clinically apparent, the classic features are:

- Fever
- Hydrocephalus or microcephaly, hepatosplenomegaly
- Jaundice
- Convulsions, chorioretinitis (usually bilateral), cerebral calcifications, and

Table 5: Dose of antibiotic for the treatment of toxoplasmosis

Disease	Medication	Dosages	Duration of Therapy
Acute acquired—generally not treated unless severe persistent symptoms or vital organ damage or host is immunosuppressed	Pyrimethamine Plus	2 mg/kg/day for 2 days, then 1 mg/kg/day	4–6 wk or 2 wk after symptoms resolve for
	Sulfadiazine Plus	75–100 mg/kg/day divided twice daily (maximum 4 g/day)	
	Folinic acid	5–20 mg three times weekly	
Ocular, older child	Pyrimethamine Plus	2 mg/kg/day for 2 days, then 1 mg/kg/day (maximum 50 mg/day)	4–6 wk or 2 wk after symptoms resolve. Prednisone should be continued until resolution of sight-threatening active chorioretinitis
	Sulfadiazine Plus	75–100 mg/kg/day divided twice daily (maximum 4 g/day)	
	Folinic acid Plus	5–20 mg three times weekly	
	Prednisone	1 mg/kg/day divided twice daily	
Congenital	Pyrimethamine Plus	2 mg/kg/day for 2 days, then 1 mg/kg/day for 6 mo, then three times weekly (M-W-F) for 6 mo	1 yr
	Sulfadiazine Plus	100 mg/kg/day divided twice daily	
	Folinic acid Plus	5–10 mg three times weekly	
	Prednisone	1 mg/kg/day Divided twice daily	Until resolution of elevated CSF protein or sight-threatening active chorioretinitis

- Abnormal cerebrospinal fluid (CSF) (markedly increased protein and mononuclear pleocytosis)

Postnatally Acquired

Acquired toxoplasma infection is asymptomatic in most of the cases. Most commonly presents with lymphadenopathy and fatigue without fever. There may be encephalitis characterized by headache, disorientation and drowsiness.

Ocular

Bilateral retinal lesion is observed in congenitally active infection.

Chorioretinitis is the most common feature. Other ocular manifestations are:

- Microphthalmos (Fig. 16)
- Small corneas
- Posterior cortical cataract
- Anisometropia
- Strabismus
- Nystagmus.

Laboratory Diagnosis

- Detection of toxoplasma during acute infection
  - Toxoplasma tachyzoites in tissue or cytologic preparations of body fluids; lymph node histology
  - *Toxoplasma* cysts in the placenta, fetus, or neonate
- Toxoplasma gene detection by PCR
- Serological tests
  - IgG antibodies to Toxoplasma
  - Indirect immunofluorescent antibody (IFA) test
  - Agglutination tests
  - ELISA
  - CT scan of brain showing diffuse cerebral calcification (Fig. 17)

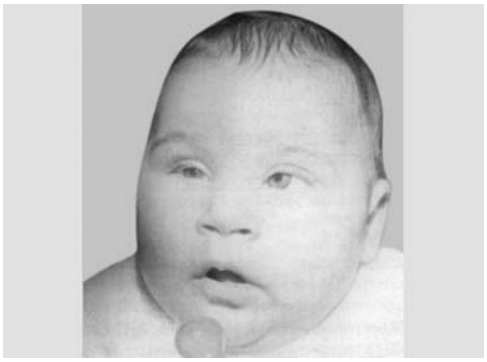


Fig. 16: An infant with chorioretinitis microphthalmia and strabismus

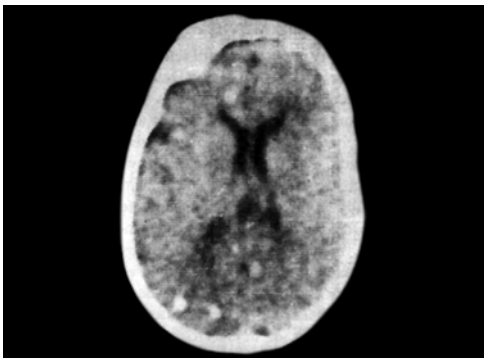


Fig. 17: CT scan of brain showing diffused calcification

Differential Diagnosis

Congenital Toxoplasmosis

Other perinatal or congenital infections

- Cytomegalovirus
- Herpes simplex virus (HSV)
- Rubella virus
- *Treponema pallidum* (syphilis)
- Human immunodeficiency virus type 1 (HIV-1)
- Lymphocytic choriomeningitis (LCM).

Postnatally Acquired

- Infectious mononucleosis
- Lymphoma.

Treatment

Drug treatment of toxoplasma infection is mentioned in Table 5.

Complications

Common are the neurological sequelae like mental retardation, convulsions, spasticity, diminished vision and palsies. Others are:

- Rash (maculopapular, petechial, or both)
- Myocarditis
- Pneumonitis and respiratory distress
- Hearing defects
- Erythroblastosis: like picture, thrombocytopenia, lymphocytosis, monocytosis
- Nephrotic syndrome.

Prevention

Prevention of Acquired Infection (Primary Prevention)

- Cook meat to medium [66°C (150°F)], smoke it, or cure it in brine
- Wash fruits and vegetables before consumption
- Avoid touching mucous membranes of the mouth and eyes while handling uncooked meat or unwashed fruits or vegetables
- Wash hands and kitchen surfaces thoroughly after contact with raw meat or unwashed fruits or vegetables
- Prevent access of flies, cockroaches, and other coprophagous insects to fruits and vegetables
- Avoid contact with materials that potentially are contaminated with cat feces, such as cat litter boxes, or wear gloves when handling such materials and when gardening
- Disinfect cat litter boxes for 5 minutes with nearly boiling water.

Prevention of Congenital Infection (Secondary Prevention)

- Identify women at risk by serologic testing. Treatment during pregnancy results in an approximately 50% reduction in the incidence of infection in infants
- Therapeutic abortion prevents birth of an infected infant—consider only for women who acquire infection in the first or second trimester.

DENGUE

Epidemiology

Dengue is one of the most important arbovirus infections in man. It has re-emerged as a major cause of morbidity and mortality in the tropics and subtropics, inhabited by more than two-thirds of people living on earth. Over 2.5 million cases of dengue hemorrhagic fever (DHF) and 40,000 deaths were officially reported between 1956 and 1990 in South Eastern Asia including Indian subcontinent, which is one of vulnerable areas of dengue hemorrhagic fever epidemics. At present, specific treatment against the disease is neither available nor are there effective vaccines. Untreated case fatality rates of severe disease could be as high as 30–40%.

The South East Asian region is known as "home" of dengue viruses had only sporadic outbreaks of dengue before World War II. In the two decades, during and after the war, epidemic dengue spread to Islands in the seas of Japan, Pacific Islands, Vietnam, Malaysia, Singapore, Indonesia, Southern American countries.

In the last 50 years, there has been 30-fold increase in the incidence along with geographic expansion to new countries, and in the present decade, from urban to rural settings. An estimated 50 million dengue infections occur annually and approximately 2.5 billion (more than 70%) of population at risk for dengue worldwide live in member states of the WHO South East Asia Region and western pacific region, which bear nearly 75% of the current global disease burden due to dengue.

This resurgence is due to unprecedented increase in population, unplanned urbanization, decay in public health infrastructure, lack of mosquito control, and last but not the least an increase in air travel.

Over the last 10–15 years, dengue fever (DF) has become a leading cause of hospitalization and death among children in the South East Asia Region (SEARO) of WHO, following diarrheal diseases and acute respiratory infections.

Today about 25 billion people (40% of the world population) live in areas where there is a risk of dengue. Dengue is endemic in at least 100 countries in Asia, the Pacific, the Americas and the Caribbean. The WHO estimates that 50–100 million infections occur yearly, including 500,000 DHF cases and 22,000 deaths, mostly among children.

No vaccine or specific antiviral therapy currently exists to address the threat of dengue. Early care detection and appropriate clinical management can reduce the mortality from severe dengue.

WHO global strategy for dengue prevention and control 2012–2020 indicated that surveillance and improved reporting of the dengue fever is essential to gauge the global situation. It has been hypothesized that dengue will increase in the future, including geographical expansion, incidence and reporting to WHO.

The Vector

The central facts of ecology of dengue fever are four distinct viruses (DEN 1–4) which are antigenically closely related and responsible for producing the disease. They are transmitted only by certain species of day-biting *Aedes* mosquitoes, particularly *Aedes aegypti* and that human beings constitute the cycle (main host) of infection by which the virus is perpetuated. The mosquito is also known as the tiger mosquito, due to the characteristic striped body appearance. It is a highly domesticated mosquito, lays eggs and produces larvae preferentially in artificial containers. Two peaks of biting activity are known for the mosquito, 2–3 hours after the day break and in the evening a couple of hours before sunset. The mosquito is a silent and fearless biter and does not buzz. It often feeds on several persons during a single blood meal in a short period of time. If infective, it can transmit the virus even while probing without taking blood meal (Fig. 18).

Fig. 18: *Aedes aegypti* mosquito

The virus survives in nature by two mechanisms: by transmission between infected vertebrate and mosquitoes and by vertical transmission in the mosquito. *Aedes aegypti* predominantly breeds indoor, in clean stored water, in ceramic jars or metal drums, water holding planters and outdoors in natural or artificial containers which trap rain water such as rubber tires, tin cans, plastic cups, bamboo internodes, coconut shells etc. *Aedes aegypti* mosquito can acquire the infection from febrile viremic patients. Once infective, a mosquito can serve as a vector for the rest of its life. A high degree of anthropophillia, multiple and interrupted blood feeding habits, and the urban location of breeding makes *A. aegypti* a highly efficient vector.

Aedes aegypti has a short (50–100 yards) flight range. They seldom disperse more than a few hundred yards from their place of birth. The geographical dispersion of dengue viruses is largely by the movement of viremic human beings. The "Jet age" air travel facilitates the quick geographic dispersion of dengue. An infected index case introduces viruses into a house hold infested with vector mosquitoes resulting in secondary cases. Crowded urban areas therefore, provide ideal opportunities for dengue transmission.

Hot, humid and rain are ideal condition for breeding of *A. aegypti*. Dengue endemic areas with mean temperature of 36°C during the rainy season have four times higher risk of dengue transmission compared to areas with mean rainy season temperature of 17°C. High temperature increases vector efficiency by reducing the period of viral replication in mosquitoes.

Dengue Virus Structure and Its Clinical Significance

The virus has three structural proteins (Capsid C, prM, the precursor of membrane M protein and envelope E) and seven nonstructural proteins (NS). The structural protein prM is involved in the severity of disease. In humans, dengue infections target monocytes/macrophages where, absent neutralization, heterotypic antibodies, perhaps directed at prM or domain I-II of the envelope protein (E) form immune complexes, attach to Fc receptors resulting in enhanced productive infection.

During the early stage of infection, when serological tests are negative, antigen detection envelope/membrane (E/M) antigen and nonstructural protein 1 (NS1) can be used to diagnose dengue infection.

Four serotypes DEN-1, 2, 3, and 4 have been identified for the virus. Each serotype provide specific lifetime immunity but only short time cross immunity. All serotypes can cause severe and fatal dengue. Dengue virus has an incubation period of 4–10 days, in human body (internal incubation period).

Unlike most of the infectious diseases prior infection with one dengue serotypes (DEN-1, DEN-2, DEN-3, DEN-4) confers only transient immunity to infection with heterologous serotypes. Therefore, individual infected with one serotype are susceptible to infection with the three other serotypes.

Current Concept of Pathogenesis and Pathophysiology of Dengue

Humans are the main host of the virus. Dengue virus circulating in the blood of viremic humans is ingested by female mosquitoes during feeding. The virus then infects the mosquitoe's midgut and subsequently spreads systemically over a period of 8–12 days. After this extrinsic incubation period, the virus can be transmitted to other humans during subsequent probing or feeding.

After an incubation period (internal incubation period) of 4–10 days, infection by any four virus serotypes can produce a wide spectrum of illness, although most infections are asymptomatic or subclinical. Primary infection produces lifelong protective immunity to the infecting serotype. For other serotype only a short-lived immunity (2–3 months) can be produced with no long-term cross protective antibody is achieved.

Symptoms and organ damage during active infection occur due to host immune response and direct damage of human organs and organelles by the virulent virus. Clinical features depend on different immune response, virulence of virus and genetic background of the individual infected with dengue virus (DV).

Three main pathological derangements occur during dengue, particularly in severe dengue. They are:

1. Vasculopathy
2. Coagulopathy
3. Thrombocytopathy (thrombocytopenia or abnormal platelet function)

Cytokine-induced tissue damage is an also important factor and a major final process of capillary damage and increased capillary permeability (vasculopathy) in the pathogenesis of dengue fever.

In vascular damage, autoimmunity is involved. Various autoantibodies are produced during dengue infection like endothelial antibody, IgM antiplatelet antibody. Endothelial antibody damages capillary endothelium. Endothelial cell apoptosis also occur induced by antibody produced by dengue virus. Anti-NS1 antibody also reacts with endothelial cells causing bleeding.

It has been recognized that serious form of dengue (DHF/DSS) is seen in children under 1 year of age who are born to mother exposed to dengue virus (DV) infection.

Pathogenesis Severe of Dengue Infection

In pathogenesis severe dengue following factors are involved:

- Human immune response of initiating antibody-dependent enhancement (ADE)
- Virulence of infecting virus strain
- Autoimmunity
- Genetic background of the infected person.

Antibody-Dependent Enhancement

With respect to the human immune response antibodies are double-edged swords with potential to neutralize viruses or enhance viral replication. ADE is a compelling theory that has been proposed to explain why some people develop dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).

In human severe dengue infection, dengue virus targets monocyte/macrophages where, absent neutralization, heterotypic antibodies, perhaps directed at prM of envelope protein (one of structural proteins) form immune complexes, attached to Fc receptor resulting in enhanced productive infection. In dengue illness virus-infected cell mass correlates directly with disease severity.

The ligation of monocyte/macrophage Fcγ receptors by immune complexes suppresses innate immunity, liberates IL-10, and bias Th 1 to Th 2 responses and results in increased productive infection per cell. Other proinflammatory vasoactive mediators like tumor necrosis factor (TNF), interleukins (IL-1, IL-2, IL-6), platelet-activating factor (PAF), complement-activating products (C3a and C5a), histamine etc. are also released. Simultaneous CD4+ T lymphocytes are induced to produce gamma interferon (*y*-IFN), lymphotoxin and various interleukins). All these cytokines which have complex interplay and act synergistically on vessel wall resulting in increased vascular permeability and hemorrhagic manifestation that characterize severe dengue.

Autoimmunity

In pathogenesis of vasculopathy one of the important factors of dengue is autoimmunity (endothelial antibody, anti-NS1 antibody) and endothelial apoptosis which in combination with *antibody-dependent enhancement* releases proinflammatory cytokines which cause vascular damage and increased capillary permeability which constitutes severe dengue pathogenesis. The pathogenesis and clinical expression of dengue also depends on virulence of dengue virus and genetic background of the infected patient.

Thrombocytopathy

Thrombocytopenia, which is almost universal in severe dengue, occurs due to multiple reasons. Initially it occurs due to marrow hypoplasia, which is also associated with leukopenia. Later on, as disease progresses, increased peripheral destruction and consumption (sequestration) particularly in liver also contribute to decreased platelet. IgM antiplatelet antibody, immune complex-mediated injury and DIC also contribute to thrombocytopenia. Leukopenia precedes thrombocytopenia in early stage of dengue infection.

Platelet dysfunction may occur without thrombocytopenia, induced by anti-NS1 antibody and direct infection by dengue virus.

In symptomatic stage of illness, the virus is present in blood, while its defervescence coincides with viral clearance.

During the acute phase of illness, the virus is present in the blood and its clearance from this compartment generally coincides with defervescence. In addition, innate host defence may limit infection by the virus.

Coagulopathy

The coagulation cascade of blood also show abnormality in severe dengue and is an important cause of hemorrhage with increased morbidity and mortality. Coagulation disorder occurs either due to mediators released from activated monocytes/macrophage or/with due to liver involvement by dengue due to vitamin K dependent clotting factors resulting in decreased production of vitamin K dependent clotting factors in liver. Complement factors production will be decreased. Levels of fibrinogen, prothrombin, factor II, VII, VIII, IX, X, XII are decreased. There is decrease in antithrombin III, Complement C3 and C5 are decreased but C3a and C5a are increased. Prothrombin time (PT), activated partial aPTT and TT are increased.

Dengue virus also induces plasminogen to produce plasmin. Increase plasmin results in hyperfibrinolysis leading to increased production of fibrin degradation product (FDP), therefore raising serum FDP, an important marker of DIC.

Dengue virus → induce plasminogen → plasmin → hyperfibrinolysis → FDP

In severe dengue, particularly in DSS, there is hemophagocytic syndrome. Due to hemophagocytic syndrome, RBCs are destroyed significantly. This is associated with increased serum ferritin. High serum ferritin in dengue is associated with increase mortality in children.

Viral Clearance

Humoral and cellular immune responses are considered to contribute to virus clearance via the generation of neutralizing antibodies and the activation of CD4+ and CD8+ T lymphocytes. In addition, innate host defence may limit infection by the virus.

Clinical Features

The symptomatic manifestation of dengue for all practical purposes are overlapping in nature and not differentiable at beginning, sometimes appears progressing from one category to another. So they are grouped into dengue syndrome.

Classification of Dengue

Previous WHO and Revised WHO Classification

A revised classification of dengue has been adapted recently by WHO. However, it will be useful to recapitulate earlier classification for better understanding of revised classification and for management according to new classification.

According to previous WHO classification, dengue virus infection may be asymptomatic or may cause undifferentiated febrile illness (viral syndrome), dengue fever (DF) or dengue hemorrhagic fever (DHF) including dengue shock syndrome (DSS). The clinical spectrum is given in Figure 19.

Undifferentiated fever: Dengue fever may present like viral flu-like illness.

Older children may have low-grade fever; may develop nausea, vomiting, retro-orbital pain, asthenia and myalgias. Maculopapular rashes appear during the fever or during defervescence.

Dengue fever: According to WHO, dengue fever is an acute febrile illness of 2–7 days' duration (sometimes with two peaks) with two or more of the following manifestations:

- Headache
- Retro-orbital pain
- Myalgia/arthralgia
- Bone pain (hence called breakbone disease)

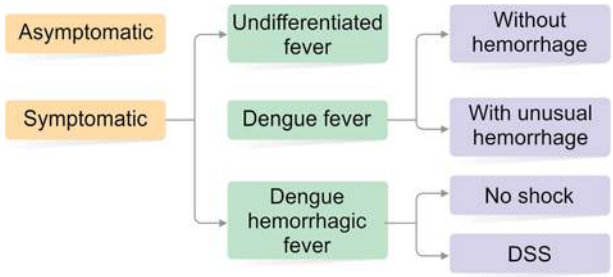


Fig. 19: Previous WHO classification of dengue virus infection

- Rash
- Hemorrhagic manifestations (petechiae and positive tourniquet test) (Figs 20 and 21)
- Leukopenia

Dengue hemorrhagic fever: The identification of a case of dengue hemorrhagic fever requires following criteria:

- Features of dengue fever at initial stage AND
- Hemorrhagic tendencies evidenced by at least one of the following:
  - Positive tourniquet test
  - Petechiae, ecchymoses, purpura
  - Bleeding from mucosa like Subconjunctival hemorrhage (Fig. 22), epistaxis (Fig. 23)
  - Hematemesis, malena
  - Bleeding from injection site
- Thrombocytopenia <100,000/mm^3
- Plasma leakage evidenced by at least one of the following:
  - Rise in hematocrit >20 percent
  - Fall in hematocrit >20 percent after IV fluids

Pleural effusion, ascites, hypoalbuminemia.

Tourniquet test (Fig. 21) is performed by inflating the sphygmomanometer cuff on the upper arm to midway between systolic and diastolic blood pressure for 5 minutes. A positive test is identified by appearance of more than 10 petechiae per 2.5 cm^2. The test may be negative during profound shock and usually becomes positive after recovery from shock.

Dengue shock syndrome: The identification of dengue shock syndrome requires DHF criteria and in addition a circulatory failure manifested by:

- Rapid and weak pulse
- Narrow pulse pressure (<20 mm of Hg)
- Hypotension for age (systolic pressure: <5 years: <80 mm of Hg; >5 years: <90 mm of Hg)
- Cold clammy skin, restlessness and profound shock
- Delayed capillary refilling (>2 sec).

Revised Classification of Dengue Infection (Figs 24 and 25)

The 1997's classification by the WHO for dengue into dengue fever and dengue hemorrhagic fever indicates that vasculopathy and the ensuing plasma leakage is the main determinant of severe disease (Table 6). A number of clinicians questioned the strictness of this scheme and the complexity of confirming DHF in clinical management as increase in clinically severe dengue cases which did not fulfill the criteria of the dengue hemorrhagic fever (DHF) and occasional dengue hemorrhagic fever which are not severe. This led WHO to initiate a prospective cohort in 7 countries which confirmed the difficulties in applying the DF/DHF/DSS criteria even in tertiary care hospitals, that DF/DHF/DSS do not represent levels of disease severity and that a clear distinction between

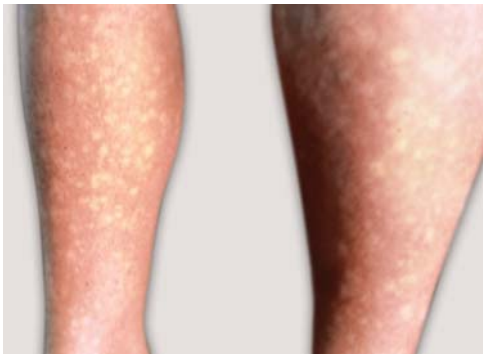


Fig. 20: Hemorrhagic rash in dengue

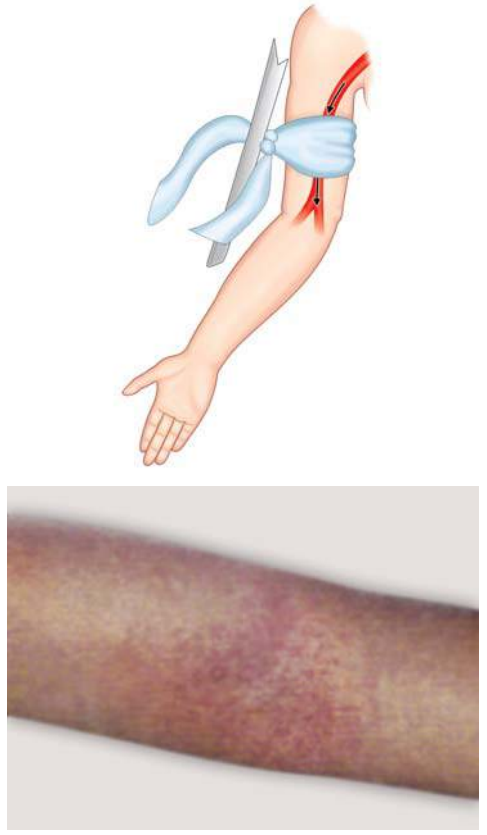


Fig. 21: Positive tourniquet test showing appearance of petechiae

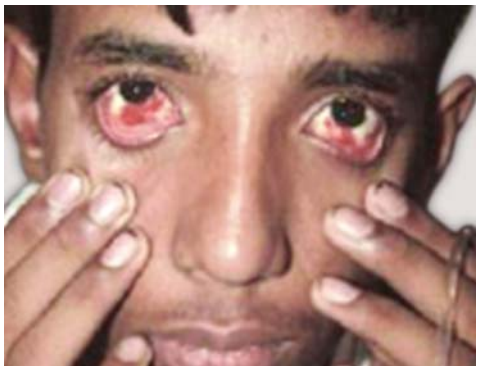


Fig. 22: Subconjunctival hemorrhage in DHF

severe dengue (defined by severe plasma leakage and/or severe hemorrhage and/or organ failure) and (nonsevere) dengue can be made using highly sensitive and specific criteria. In a global expert consensus meeting at WHO in Geneva/Switzerland in 2009, the evidence was reviewed and a revised scheme was developed, distinguishing dengue with or without warning signs and severe dengue (Fig. 25 and Table 7).

Criteria for diagnosing dengue (with or without warning signs) and severe dengue are presented in Figure 24. It must be kept in mind that occasional dengue patients without warning signs may develop severe dengue.

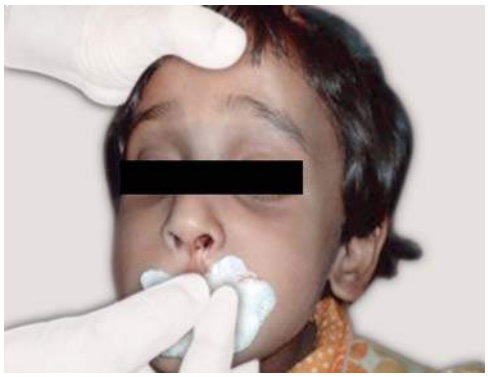


Fig. 23: Nasal bleeding in DHF

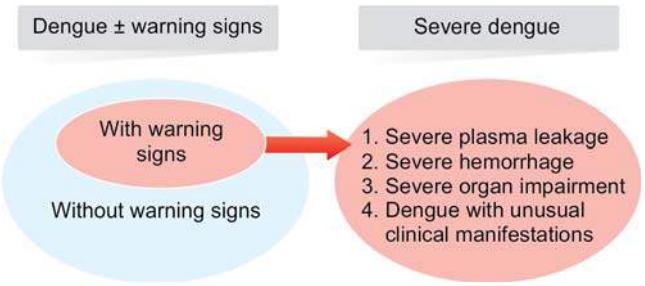


Fig. 24: Revised dengue classification according to severity

Warning signs: Dengue with warning sign is defined when nonsevere dengue has one or more of the following features:

- Persistent vomiting
- Mucosal bleed
- Abdominal pain and tenderness
- Liver enlargement >2 cm
- Clinical fluid accumulation
- Laboratory: increase in Hct concurrent with rapid decrease in platelet count

  Warning sign requires strict observation and intervention.

Modified 2011 Classification of Dengue

The revised classification WHO 2009 into dengue (D), dengue with or without warning sign (WS) and severe dengue (SD) emphasizes on WS which most of them are nonspecific and can be found in other disease as well. To exclude this nonspecific WS into the case definition of suspected dengue has made enormous increase, in suspected dengue patients causing overwhelming workload to all healthcare personnel. The modified WHO 2011 classified dengue clinical presentation into dengue fever (DF), dengue shock syndrome (DSS), dengue hemorrhagic fever (DHF) and expanded disease syndrome (EDS). DF patient have no plasma leakage that differentiate them from DSF/DSS. The classification emphasizes on plasma leakage which is the most important pathophysiological change that can lead to severe disease. Severe organ involvement, unusual clinical presentations like encephalopathy, convulsion, HUS, DIC, myocarditis, dyselectrolytemia, etc. are included in EDS.

Course of Disease

Dengue infection has a wide clinical spectrum that includes both severe and nonsevere clinical manifestation. After the incubation period of 4–10 days, the illness begins abruptly with high fever (febrile phase) followed by the critical and recovery phase.

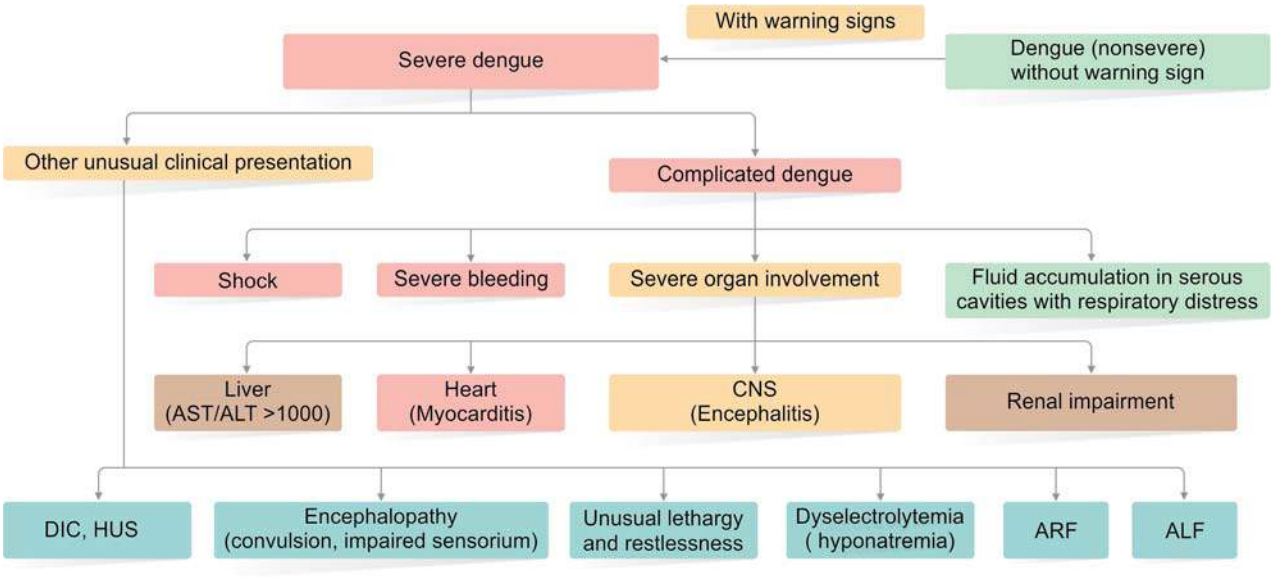


Fig. 25: Clinical features of dengue according to severity (revised classification)

Abbreviations: DIC, disseminated intravascular coagulation; HUS, hemolytic uremic syndrome; ARF, acute renal failure; ALF, acute liver failure

Table 6: Grades of dengue fever (DF)/dengue hemorrhagic fever (DHF) (according to earlier WHO classification)

DF/DHF	Grade	Symptoms	Laboratory
DF		Fever with two or more of the following signs: Headache, retro-orbital pain, myalgia, arthralgia	Occasional leukopenia Thrombocytopenia but nonconstant feature, no evidence of plasma loss
DHF	I	Above signs plus positive tourniquet test	Thrombocytopenia <100,000, Hct rise >20%
DHF	II	Above signs plus spontaneous bleeding (skin and mucus membrane)	Thrombocytopenia <100,000, Hct rise >20%
DHF	III	Above signs plus circulatory failure (weak pulse, narrow pulse pressure, hypotension, restlessness)	Thrombocytopenia <100,000, Hct rise >20%
DHF	IV	Profound shock with undetectable blood pressure and pulse	Thrombocytopenia <100,000, Hct rise >20%

Table 7: Criteria for dengue in clinical situation

Probable dengue	Warning signs	Severe plasma leakage leading to
• Live in dengue endemic area or travel to dengue endemic area • Fever and two of the following: – Aches and pains – Rash – Nausea, vomiting – Tourniquet test positive – Any warning sign – Leukopenia – In doubtful cases, laboratory confirmed dengue	• Persistent vomiting • Mucosal bleed • Abdominal pain and tenderness • Liver enlargement >2 cm • Clinical fluid accumulation • Laboratory: Increase in Hct concurrent with rapid decrease in platelet count Laboratory: Increase in Hct parallel with rapid decrease in platelet count • Patients with warning signs require strict observation and appropriate intervention if required	• Fluid accumulation causing respiratory distress • Shock • Lethargy, restlessness *Severe Bleeding* • As evaluated by clinician *Severe organ involvement* • Liver: AST or ALT >1,000 U/L • CNS: Evidence meningeal irritation, convulsion and impaired consciousness • Heart and other organs *Unusual clinical manifestation* • Convulsion • HUS • Dyselectrolytemia

Febrile Phase

As the clinical features are indistinguishable between severe and nonsevere dengue, therefore looking for warning signs is crucial to recognizing progression to severe dengue, in which lies the importance of revised classification of dengue. Patients characteristically develop sudden high-grade fever.

This phase usually lasts for 2–7 days. Severe headache, retro-orbital pain, generalized body ache, and myalgia are usually associated with fever. Some patients present with sore throat, conjunctival injection, congested pharynx, facial flushing and skin erythema. Anorexia, nausea, vomiting are common features. At this stage, clinician should look for warning signs as some patients from here later develop severe dengue (previous DHF/DSS) and early detection of warning signs may help to take timely intervention.

Although mild mucosal bleeding, like epistaxis and gum bleeding can occur at this stage, massive bleeding like massive vaginal bleeding and gastrointestinal bleeding is unusual in nonsevere dengue.

Critical Phase

It usually occurs on day 3–7 of illness, around the time of defervescence. The temperature may drop to normal or subnormal levels, when there may be increased capillary permeability in parallel with increase in hematocrit (Hct) level which heralds the onset of critical phase. The duration of clinically significant plasma leakage occur for 24–48 hours. However, patients with nonsevere dengue not progressing to severe dengue will not have significant plasma leakage.

Severe Dengue

Severe dengue is defined by one or more of the following:

- Accumulation of fluid in serous cavity (ascites, pleural effusion) causing respiratory distress
- Severe bleeding with or without shock
- Severe organ involvement like hepatic involvement, myocarditis/myopathy, renal involvement, CNS involvement
- Disease with unusual clinical manifestation like
  - CNS manifestation characterized by:
    - Convulsion
    - Impaired sensorium
  - Symptomatic dyselectrolytemia (hyponatremia)
  - Unusual lethargy or restlessness with or without shock.

Hypotension and Shock in Severe Dengue

These occur when plasma leakage is severe and intravascular fluid depletion worsens resulting in hypovolemic shock. It usually occurs in defervescence on day 4 or 5 of illness preceded by warning signs as mentioned above.

Two types of shock:

1. Initial compensatory shock
2. Decompensatory shock.

Compensated shock: In initial compensated shock, a normal systolic pressure is maintained due to compensatory peripheral vasoconstriction characterized by rapid pulse and cold clammy extremities and delayed capillary filling. The diastolic pressure on the other hand uniquely rises and pulse pressure narrows as peripheral vascular pressure increases. A pulse pressure

(difference between systolic and diastolic pressure) ≤ 20 mm of Hg is suggestive of shock in children in dengue. Due to normal systolic pressure, patient characteristically remains conscious and lucid in dengue shock syndrome (DSS). Therefore, patient of dengue shock is evidenced by narrow pulse pressure (≤ 20 mm of Hg), poor peripheral refill (>2 sec) and hypotension for age (systolic <80 mm of Hg in children <5, <90 mm of Hg in children >5 years). Therefore, peculiarities of compensated shock in dengue are:

- Systolic pressure may remain normal for a longer time
- Diastolic pressure increases which results in narrow pulse pressure (<20 mm of Hg)
- The patient may remain conscious and alert.

Decompensated (hypotensive) shock: If compensatory shock continues without treatment, decompensation occurs and both systolic and diastolic pressure fall abruptly. This is a difficult condition to manage. Prolonged hypovolemic shock is associated with organ hypoperfusion with hypoxia causing:

- Metabolic acidosis
- Multiorgan damage
- DIC
- Severe hemorrhage.

Severe Hemorrhage

Severe hemorrhage is an important component of severe dengue. It is unusual to develop severe hemorrhage only due to isolated thrombocytopenia or coagulation abnormalities. It usually occurs in association with prolonged shock which in combination with tissue hypoxia, metabolic acidosis, thrombocytopenia, coagulopathy results in disseminated intravascular coagulation (DIC). However, severe hemorrhage can occur without shock in some conditions like coexisting acid peptic disorders in females during menstruation or previous history of menorrhagia, and ingestion of drugs like ibuprofen, diclofenac, aspirin, etc.

Severe Organ Involvement

Liver: Liver may be infected directly by dengue virus or damaged by host immune response. Mild impaired liver function is usual phenomenon in dengue as evidenced by mild rise of (two- to threefold) liver enzymes which do not indicate severe liver involvement and consequently severe dengue. However, significant involvement may occur in severe dengue characterized by significant rise of liver enzymes (ALT/AST >1,000) with or without increased prothrombin time. Usually, liver impairment causes anicteric hepatitis with normal serum bilirubin and clinical jaundice is rare. Vitamin K dependent clotting factor synthesis in the liver may be significantly impaired contributing to bleeding diathesis. However, frank liver failure with hepatic encephalopathy is unusual clinical feature which indicates severe dengue (Fig. 24).

Heart: Myocarditis and severe cardiomyopathy may occur in severe dengue. Heart failure may develop due to myocarditis or fluid overload.

Kidney: Severe kidney involvement with abnormal kidney function test (KFT) can occur in severe dengue but frank established renal failure is rare which indicates severe dengue (Fig. 25).

Hemolytic Uremic Syndrome

It is rare complication which may indicate severe dengue.

Other Unusual Clinical Manifestation Suggestive of Severe Dengue

Encephalopathy

Characterized by impaired sensorium, convulsion can occur. In unusual case, dengue virus can cross blood brain barrier and can cause encephalitis.

As mentioned earlier, severe hepatic involvement may occur in severe dengue with severe encephalopathy. Similarly, in severe kidney involvement, there rarely may be acute renal failure. Significant and symptomatic dyselectrolytemia like hyponatremic convulsion can rarely occur which may indicate severe dengue.

Laboratory Investigations

Various blood and radiological abnormalities are observed in dengue. These include decrease in platelet (<100,000) count, WBC count (<5,000) and rise in Hct. Leukopenia precedes thrombocytopenia. Due to raised hematocrit, ESR is frequently unusually very low often touching zero. CRP is normal unless complicated by bacterial infection. *Low ESR and normal CRP can help differentiate from other common acute febrile bacterial sepsis like typhoid fever or bacterial sepsis where ESR and CRP raise significantly.* Abnormal coagulation profile is found in 80% of patients. Due to coagulopathy, there will be increased PTT, decreased fibrinogen. Prothrombin time is increased in liver involvement.

Diagnostic confirmation involves:

- Viral isolation
- Detection of viral antigen or viral antibodies or combination of all.

Virus and antigen of virus can be detected in early active phase. Viral isolation can be done by RT-PCR. For practical clinical purpose, antigen detection is convenient, quick and relatively easier. Two dengue antigens are currently detectable in clinical settings. They are envelope/membrane (E/M) antigen and nonstructural protein 1 (NS1) antigen. High concentration of dengue NS1 can be detected in the form of immune complexes in dengue patients after onset of illness up to 4–5 days. However, it can be detected 9 days after infection in gradually lower concentration.

Sensitivity and Specificity of Dengue NS1 Test

Dengue NS1 is a surrogate marker of viremia and therefore, very specific (specificity >91%). However, it is not highly sensitive. The sensitivity ranges from 40% to 71%. Therefore, almost all positive tests are positive for the disease. But negative NS1 test does not rule out dengue.

At the end of acute phase, dengue serological test is the choice of diagnosis. IgM and IgG antibodies are detected. IgM antibody is detectable earlier, it becomes detectable 3–5 days after the onset of illness. On 5th day, it is almost detectable, while it is >90% detectable after one week. IgG antibody is usually detectable at the end of first week. It continues to be detectable several months after illness. WHO recommends taking blood sample at first contact of suspected case. A second sample is taken at the time of discharge from hospital. A convalescent sample should be taken between 14 and 20 days of illness.

Other Biochemical Test

Serum protein estimation may show decreased serum protein and serum albumin which are the indicator of plasma leakage. Liver enzymes AST/ALT and prothrombin time are usually increased. Mild-to-moderate elevation of liver enzymes (AST/ALT) is found in dengue. A significant rise (AST/ALT >1,000) is found in severe involvement of liver and an indicator of severe dengue.

Coagulation screening (should be done if indicated):

- Serum prothrombin time and aPTT may be increased
- Serum C3 and C5 are decreased but C3a and C5a are increased.

Other tests (if indicated):

Serum electrolytes: May show hyponatremia

Kidney function test: Abnormal KFT may be found in severe involvement of kidney and HUS.

Radiological Investigations

X-ray chest and ultrasonogram (USG) of abdomen and chest are simple, noninvasive but are useful diagnostic tool in dengue.

- Chest X-ray can show pleural effusion. Chest USG is more sensitive and can detect small fluid collection not detected by X-ray chest. Pleural effusion is usually found more in right pleural cavity than in left
- USG can also detect hepatomegaly, splenomegaly and ascites. Most important area to explore is gall bladder area for diagnostic and prognostic purpose. Gall bladder can show sludge, acalculuos cholecystitis and gall bladder wall edema. Measurement of gall bladder wall thickness (GBWT) is useful for management purpose. GBWT of more than 3 mm on ultrasound can be considered as indicator for enough clinical evidence for hospitalization. GBWT is more than 5 mm in dengue often used as an indicator of impending hypovolemic shock with high sensitivity (>93%) and high specificity (>92%).

Differential Diagnosis of Dengue Fever

Several conditions may mimic dengue infection. These are as follows:

- During early febrile stage
  - Flu-like illness
    - Seasonal influenza
    - Early stage of typhoid fever
    - Chikungunya in endemic zone
  - Fever with rash
    - Measles, particularly when dengue is associated with morbilliform rash and conjunctival injection
    - Rubella, particularly when dengue is associated with rubelliform rash
    - Scarlet fever, when dengue is associated with scarletiform rash, sore throat, congested pharynx
    - Infectious mononucleosis, when dengue is associated with sore throat and congested pharynx.

Dengue presents with acute abdomen:

- Acute cholecystitis
- Acute appendicitis
- Acute viral hepatitis
- Diabetic ketoacidosis.

Convulsion:

- Febrile seizure
- Meningoencephalitis.

Other infection may mimic dengue:

- Malaria
- Typhoid
- Typhus
- Acute gastroenteritis
- Sepsis
- Septic shock.

Management of Dengue

Early clinical diagnosis and proper outpatient management including whom to admit or who will go home is the key to the management of dengue.

Basic Principle of Management

- *Practical and simple early clinical diagnosis of dengue infections* in patients with acute febrile illness; tourniquet test together with daily CBC to look for leukopenia and thrombocytopenia
- *Close follow-up of those suspected dengue cases* especially after day 3 of the illness for the early signs of plasma leakage
- *Health education to families and patients* about natural course of DHF and emphasize on warning signs, especially at the time of defervescence to come back to the hospital as soon as possible
- *Proper OPD triaging* of those suspected dengue cases at the time of follow-up; using fever ≥3 days, leukopenia and/or thrombocytopenia and warning signs as the screening parameters
- *Consider observation/admission for those patients who are likely to have plasma leakage/shock or those high-risk patients*
- *Dengue wards/unit/areas with mosquito-free environment* for suspected dengue patients and HDD/ICU for severe/complicated DHF/DSS/EDS cases. Proper monitoring is mandatory for all suspected dengue cases; monitor clinical, vital signs, Hct and urine output
- *Proper IV fluid management, types* (isotonic salt solution), amount (about maintenance + 5% dehydration) *rate* and *duration* including the use of proper colloidal solutions in patients with signs of fluid overload. The principle is to give IV fluid just enough to maintain intravascular volume
- *Management cases with complications/high-risk cases/cases that do not response to conventional IV fluid management.* The common complications are: acidosis, concealed bleeding, hypocalcemia, hypoglycemia and fluid overload
- *EDS* needs to be diagnosed early for proper management. Try to look for evidence of plasma leakage for DHF diagnosis
- *Steroid is proved not to be effective in DSS*
- *Inotropic drugs* are not indicated in DHF/DSS except for those with heart problems
- *Judicious transfusion of platelet;* No platelet transfusion prophylaxis
- *Detection of convalescence phase with proper management.* Aware of reabsorption period that extravasated plasma will return into the circulation
- Discharge patients when they have fulfilled the indications.

Patients can be grouped into three categories for management purpose depending upon clinical manifestations (history, physical examination, and presence of warning

signs, hemodynamic status), stage of illness (febrile, critical or recovery), severity of illness including warning signs and laboratory evidences (like initial full blood count, Hct and platelet).

- Group A: Outpatient management (can be sent home)
- Group B: Inpatient management (referred to hospital)
- Group C: Emergency treatment and urgent referral to appropriate health center preferably where intensive care (ICU) is available.

Group A: outpatient management (patients who can be sent home with advice): Ambulatory dengue patient who has general feeling of wellbeing, eating well, and tolerating food normally do not require hospitalization and can be sent home with advice. They should be reviewed daily if possible; particularly during defervescence time, blood should be tested for rising Hct or falling platelet and WBC. They should adhere to following action plan:

- Advise to take of plenty of fluid by mouth or take fruit juices, soup, coconut water, oral rehydration solution (ORS) or fluid containing salt and sugar. Avoid commercially available fruit juice as it contains preservatives. Caregivers should be advised to observe whether the patients are passing enough urine at least once in 6 hours
- Antipyretics like paracetamol can be given in high fever. Paracetamol can be given according to dosing mentioned below and should not be repeated in <6 hours.

Age	Dose (500 mg tab, 125 mg/5 mL syp)	mg/dose
<1 year	1/8 or 2.5 mL	62.5
1–4 years	¼ or 5 mL	62.5–125
≥5 years	½ or 10 mL	250

Prostaglandin inhibitors like clofenac and ibuprofen may trigger gastritis and bleeding and should be avoided.

Caregiver should be advised to bring the patient immediately to hospital or referral health centers if the patients' clinical condition deteriorates, particularly during defervescence time, develops warning signs like abdominal pain, persistent vomiting, or develops frank bleeding or evidence of bleeding like black tarry stool or coffee ground vomiting. The caregiver should also be asked to bring the patient if he/she does not pass urine for >6 hours of time or develop lethargy, irritability or restlessness.

Group B: Inpatient management (referred to hospital): Hospital admission and in-hospital management is required particularly when the patient approaches to critical phase (defervescence time) in the following condition:

- Dengue patient with warning signs
- Comorbidities like pneumonia and typhoid fever
- Congenital anomalies.

Plan of management will be:

- Obtain a Hct before fluid therapy
- Intravenous infusion of only isotonic fluid like 0.9% sodium chloride solution, Ringer's lactate or Hartmann solution in the following manner:
  - Start with 5–7 mL/kg/hr for 1–2 hours then
  - Reduce to 3–5 mL/kg/hr 2–4 hours
  - Reduce to 2–3 mL/kg/hr or less depending upon clinical improvement
- Reassessment of clinical status and Hct
  - If Hct rises minimally or static continue with same rate (2–3 mL/kg/hr) for 2–4 hours
  - If Hct rises rapidly or vital signs worsen then increase fluid rate to 5–10 mL/kg/hr for 1–2 hours
  - Reassess clinical status, repeat Hct and review fluid infusion
- Minimum IV fluid is given to maintain adequate perfusion and urine output 0.5 mL/kg/hr. IV fluid therapy is required for only 24–48 hours. The principle is to give IV fluid just enough to maintain intravascular volume (usually half of maintenance plus 5% deficit). If evidence of plasma leakage continue IV fluid for maintenance plus 5% deficit. Current policy is to give fluid by titrating according to monitored status and IV fluid may be required even for <24 hours (6–12 hours). Gradual reduction of IV fluid is required when critical phase is ending and decrease of Hct below baseline in a stable patient
- Close monitoring of following parameters should be ensured:
  - Vital signs
  - Detailed fluid balance
  - Peripheral perfusion (1–4 hourly)
  - Urine output (4–6 hourly)
  - Signs of fluid overload
  - Hct (before and after fluid replacement then 6–12 hourly)
  - Blood glucose
  - Other organ profile (renal function, liver function and coagulation profile).

Group C: Patients requiring emergency treatment and urgent referral: Patients who have features of severe dengue should be treated on emergency basis in hospital. As mentioned before features of severe dengue:

- Severe plasma leakage leading to dengue shock and/or fluid accumulation in serous cavities with respiratory distress
- Severe hemorrhage
- Severe organ impairment (hepatic damage, renal impairment, cardiomyopathy, encephalopathy or encephalitis) or expanded dengue syndrome (EDS) according to modified 2011 WHO classification
- Unusual clinical manifestations like:
  - Convulsion
  - Dyselectrolytemia
  - HUS
  - Encephalopathy.

This group of patients should be referred to hospital preferably where intensive care and blood transfusion facilities are available. Judicious fluid resuscitation is the mainstay of treatment.

The goals are:

- To improve central and peripheral circulation (improvement of blood pressure, tachycardia and pulse volume, warm and pink extremities, capillary refill time <2 seconds)
- To improve end-organ perfusion (i.e. stable conscious level, urinary output ≥0.5 mL/kg/hr)
- To decrease the metabolic acidosis.

These goals can be achieved with the strategy of larger fluid volume (e.g. 10–20 mL boluses) administration for limited period but without causing fluid overload and pulmonary edema

- Crystalloid: Crystalloid use during plasma leakage should be isotonic and should be just sufficient for effective circulation
- Plasma expanders
  - Hypertonic colloid: Dextran 40
  - Isotonic colloid: Plasma

  In hypotensive shock, associated with plasma loss should be rapidly and immediately managed with colloid solution
- Blood**:** Blood transfusion should be given only in cases with suspected/severe bleeding evidenced by decreased Hct.

Treatment of Shock

Compensated Shock (Normotensive Shock)

The management algorithm of compensated shock is given in Figure 26. Systolic pressure is maintained but reduced pulse pressure (<20 mm of Hg difference between systolic and diastolic pressure) and evidence of tissue hypoperfusion is noticed. During this management, patient's clinical situation is monitored and assessed routinely upon the following parameters:

- Vital signs
- Capillary refill time
- Fluid overload particularly if colloid is used
- Hematocrit
- Urine output.

Vital signs and peripheral perfusion should be monitored every 15–30 minutes until the patient is out of shock, then 1–2 hourly.

In compensated shock initial fluid resuscitation given with (Fig. 26) isotonic crystalloid 5–10 mL/kg over 1 hour. If clinical condition improves (A) fluid resuscitation is progressively reduced (Fig. 26A1) to ≤3 mL/kg/hr and maintained up to 24–48 hours duration (Fig. 26A2). If after initial improvement, patient again deteriorates give oxygen and estimate Hct. If it falls, consider fresh blood transfusion (Fig. 26A3) and if Hct rises consider second bolus of fluid, colloid preferably (Fig. 26A4). On the other hand, if with first fluid resuscitation with isotonic crystalloid there is no improvement (Fig. 26B) check Hct. If Hct rises (Fig. 26C), administer 2nd bolus dose of fluid (preferably colloid like plasma, albumin, dextran, Hemaccel) followed by progressive reduction of fluid (Fig. 26C1 and Fig. 26C2). However, if Hct falls (Fig. 26D), consider significant blood loss and give whole blood transfusion.

Uncompensated (Hypotensive) Shock

Patients with hypotensive shock should be managed aggressively. Hct and platelet should be checked initially in order to compare with subsequent Hct and platelet level during resuscitation.

In comparison to normotensive shock, initial bolus fluid replacement should be done quickly at higher bolus

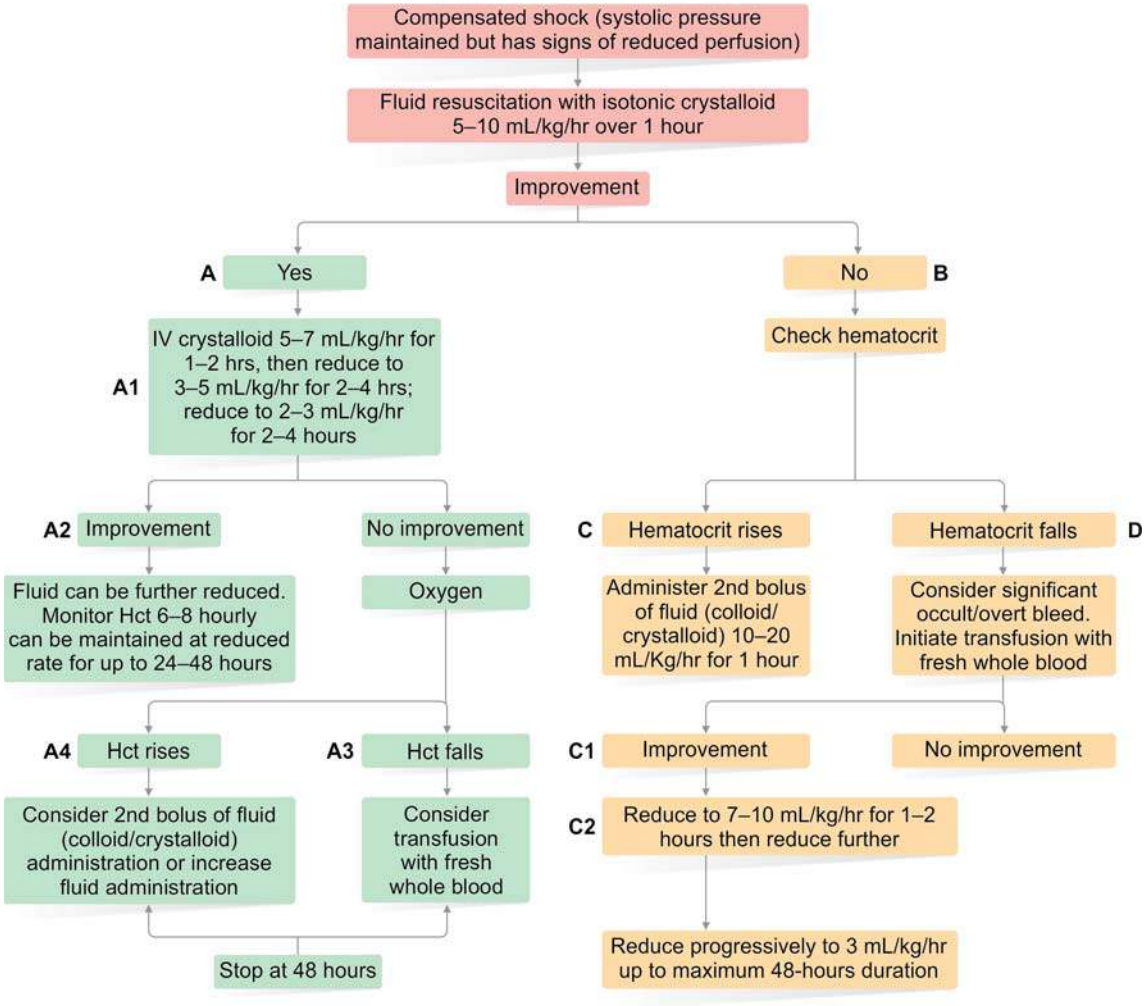


Fig. 26: Algorithm of fluid management in compensated shock

(20 mL/kg) and over a shorter period of time (within 15 minutes) to bring the patient out of shock as early as possible. Colloid is the fluid of choice for resuscitation as it less easily leaks out of capillaries and stays for a long time in intravascular spaces, thereby enabling maintain satisfactory arterial pressure for longer duration. In comparison to crystalloid, colloids are more frequently required in hypotensive shock than compensated shock.

In hypotensive shock (Fig. 27), the patient is given initially a bolus dose of either colloid or crystalloid 20 mL/kg in 15 minutes and if the patient improves with first bolus fluid administration then fluid is gradually reduced at ≤3 mL/kg/hr with maintenance of up to 24–48 hours' duration. Further, colloid administration is not mandatory and blood transfusion is not required if the patient improves (Fig. 27A1). However, if after initial improvement with first bolus fluid resuscitation, the patient shows no further improvement (Fig. 27A2), then further management depends upon the Hct status. If Hct falls (Fig. 27A3), then fresh blood transfusion is given (10–20 mL/kg); however, if the Hct rises (Fig. 27A4), a second bolus of colloid should be given at 10–20 mL/kg for 1 hour. Then colloid should be replaced by crystalloid and continued in decreasing manner as mentioned earlier.

The management of hypotensive shock not responding to initial bolus fluid administration (Fig. 27B) is different. They need their Hct to be checked first and subsequently for the second and third time if conditions later do not improve. If first Hct is decreased (Fig. 27D), then consider fresh whole blood transfusion. If Hct is raised, Hct a second bolus (colloid) (Fig. 27C) 10–20 mL/kg/hr for 1/2–1 hour followed by crystalloid in decreasing manner in 24–48 hours should be given as discussed before. However, during such resuscitation if the condition still remains unstable (Fig. 27C2), a second Hct estimation is done. If the Hct falls (Fig. 27C3), then blood transfusion is given as discussed above (Fig. 27D). If Hct rises, the third bolus dose of fluid (colloid) is given (Fig. 27C4) followed by crystalloid administration. If condition improves, the crystalloid fluid infusion is maintained up to 24–48 hours. After giving the third bolus, a third Hct estimation is done. Depending upon Hct level either fresh blood transfusion or another colloid should be given.

Oxygen should be given in hypotensive shock not responding to initial bolus fluid administration. Platelet transfusion is given in exceptional cases who are bleeding and have platelet count <10,000/cumm.

With above fluid therapy, the mortality can be reduced to <1% in hospitalized patients. Corticosteroids and other vasopressor drugs have no beneficial role in the management of severe dengue or dengue shock.

Treatment of Hemorrhagic Complications

Measures to be taken to mitigate hemorrhagic complications are:

- Strict bed rest to prevent trauma in patients with profound thrombocytopenia
- Avoidance of intramuscular injection
- Prophylactic platelet transfusion in case of severe thrombocytopenia (<10,000/cumm)
- Blood transfusion as soon as severe bleeding is suspected or evident.

Patients are at risk of major bleeding:

- Prolonged or refractory shock
- Liver or renal failure and/or severe persistent metabolic acidosis
- Using NSAIDs
- Pre-existing peptic ulcer disease (PUD)
- On anticoagulant therapy
- Any form of trauma even IM injection.

Treatment of Fluid Overload

Causes of fluid overload in management of dengue:

- Inappropriate use of large volume IV fluids or too rapid infusion
- Inappropriate transfusion of FFP, platelet concentrate and cryoprecipitate
- Continuation of IV fluid even after resolution of plasma leakage
- Comorbid illness including congenital heart disease, chronic lung and renal diseases.

Strategy to Combat Fluid Overload

The phase of disease and patient's hemodynamic status determines the management of fluid overload.

- Stable patient out of critical stage
  - Stop IV fluids but continue monitoring
  - If necessary oral or IV furosemide @ 0.1–0.5 mg/kg/dose once or twice daily or continuous infusion @ 0.1 kg/hr
  - Monitoring of serum potassium and correction of hypokalemia
- Hemodynamically stable patient but still in critical stage
  - Reduce fluid accordingly
  - Avoid diuretics
- Patient in shock plus low or normal Hct plus signs of fluid overload
  - Fresh whole blood transfusion as soon as possible
  - Avoid further infusion of large volume of IV fluids
- Patient in shock plus Hct
  - Repeated small boluses of colloid solution.

Is There Any Role of Platelet Transfusion or Corticosteroid in Dengue Fever?

There is no clear indication of platelet transfusion and corticosteroid therapy. Platelet transfusion is only considered upon clinical judgment. The WHO recommends platelet transfusion only if there is bleeding and platelet count <10,000/mm^3. However, the WHO does not include corticosteroid for the guideline of management of dengue.

Discharge Criteria

A patient suffering from dengue can be discharged from hospital when the following conditions are fulfilled:

- Visible clinical improvement
- Absence of fever for at least 24 hours without use of antipyretics
- No respiratory distress
- Return of appetite
- Adequate urine output, no vomiting, no bleeding
- Hematocrit return to normal and becomes stable.
- Platelet count >100,000/mm^3.

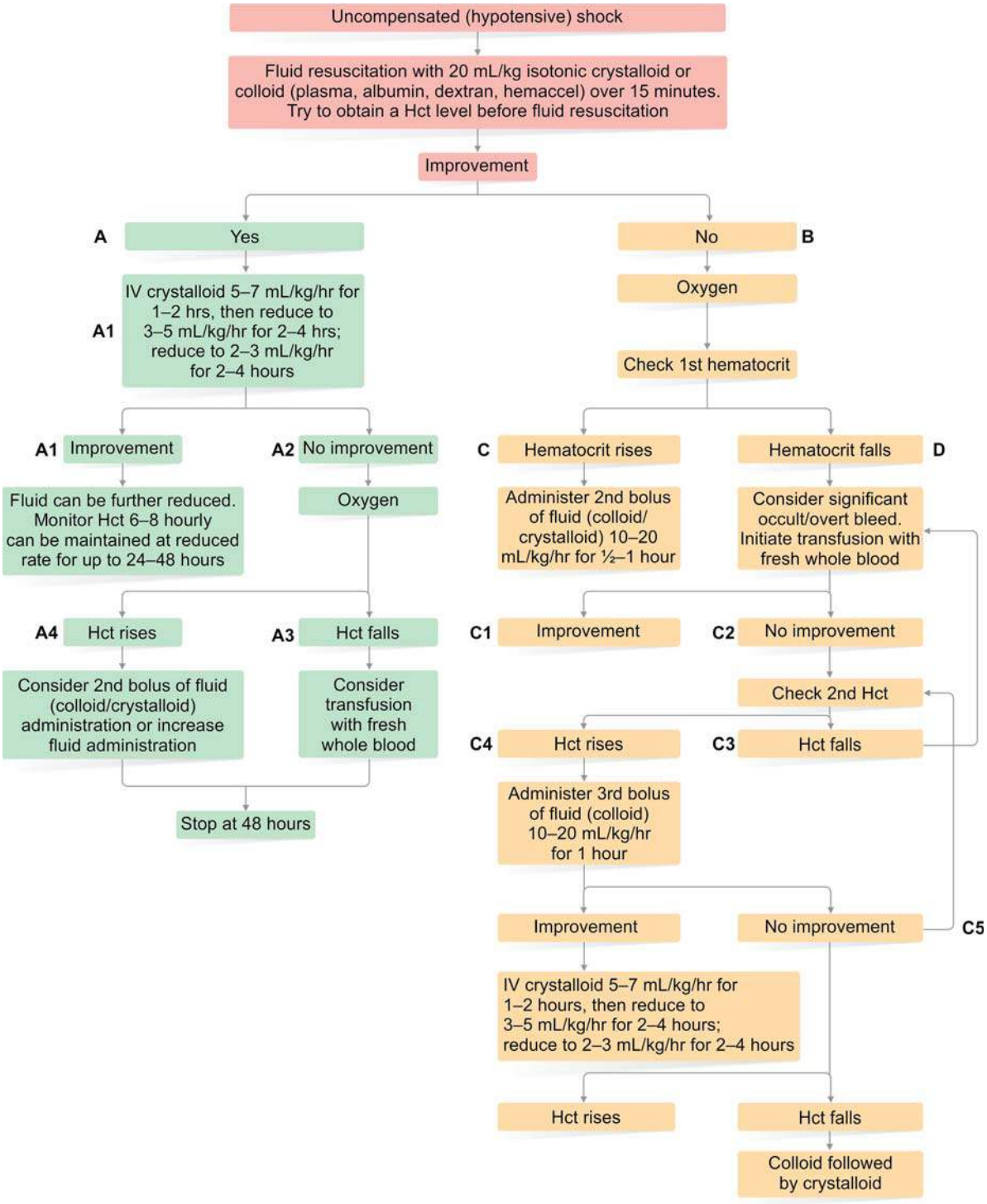


Fig. 27: Algorithm of fluid management in hypotensive shock

Prevention and Vaccination

Prevention

Vector control: Over the last four decades, several steps have been taken for environmental control, biological control and chemical control of dengue vector mosquito but still no universal consensus has been reached about the best method of control.

Insecticide spray with good community compliance were also not found to be affected strategy as it may not reach all breeding site of mosquito population. Environmental management which includes environmental modification, manipulation and changes to human habitats and behavior were also found to be ineffective as compliance and enforcement of environmental management schemes may be difficult to achieve. Biological control involves the involvement of organism that feed upon *A. aegypti* including invertebrate copepods introduced water storage tanks and larvivorous fish. However, this method is not found to be cost-effective.

Vaccines for Dengue

As all four dengue serotype cocirculate vaccines need to be tetravalent. Current candidate vaccines include:

- Live attenuated vaccine (LAV)
  - LAVs are now in phase 3 testing
- Chimeric live attenuated vaccine
- Inactivated or subunit vaccine and nucleic acid-based vaccine.

NIPAH VIRUS

Key Facts

- Nipah virus causes illness characterized by inflammation of the brain or respiratory diseases
- Case fatality of Nipah virus is very high
- Nipah virus can be transmitted to human from animals and can also be transmitted directly to human from human.
- Nipah virus can cause severe disease in domestic animals such as pigs
- There is no treatment or vaccine available for either people or animal
- Fruit eating bats of the pteropodidae are the natural host of Nipah virus.

Introduction

Nipah virus (NiV) first emerged in Malaysia and Singapore between 1998 and 1999 causing severe febrile encephalitis in human with mortality rate close to 40%. Since its initial outbreak there had been numerous outbreaks in India and Bangladesh, in which mortality rate rose to approximately 70%. Nipah virus (NiV) is an emerging zoonotic (a virus transmitted to human from animals) virus. In infected people, Nipah virus causes severe illness characterized by inflammation of brain (encephalitis) or respiratory diseases. It can also cause severe disease in animals such as pigs, resulting in significant economic losses for farmers.

Nipah virus is closely related to Hendra virus. Both are members of genus Henipavirus, a new class of virus in the paramyxoviridae family.

Although Nipah virus has caused only a few outbreaks, it infects a wide range of animals and causes severe disease and death in people, making it a public health concern.

Outbreak

Nipah virus was first recognized in 1999 during an outbreak among pig farmers in Malaysia. Since then, there have been another 12 outbreaks, all in South Asia.

Transmission

During the initial outbreaks in Malaysia, Singapore, most human infections resulted from direct contact with sick pigs or their contaminated tissues. Transmission is thought to have occurred via respiratory droplets, contact with throat or nasal secretion from infected pigs or contact with the tissue of sick animal. In Bangladesh and India outbreak, consumption of fruits and fruit products (e.g. raw date palm juice) contaminated by urine or saliva from infected fruit eating bats was the most likely source of infection (Fig. 28).

Nipah Virus in South Asia

During the last outbreak in Bangladesh and India, Nipah virus spread directly from human to human through close contact with secretion and excretions of infected people. From 2001 to 2008, around half of reported cases in South Asia were due to human-to-human transmission. In South Asia, from 2001 to 2011, there were 9 outbreaks of Nipah virus and case fatality on an average was 78%. In 2011, 24 people were infected with Nipah virus in Lalmonirhat district. Other endemic areas of previous year were Rajbari, Faridpur, Lalmonirhat, and Joypurhat.

In 2012, 6 persons suffered from Nipah virus and all hailed from Joypurhat district. Unfortunately, all of them died (case fatality was 100%).

Fig. 28: Potential source of Nipah virus infection is consumption of raw date palm juice contaminated by saliva of infected bat

Clinical Features

Human infections range from asymptomatic infection to fatal encephalitis. Infected people initially develop influenza like symptoms of fever, headache, myalgia, vomiting, and sore throat. This can be followed by dizziness, drowsiness, altered consciousness, convulsion, coma and other signs of acute encephalitis. Some people can also experience atypical pneumonia, a severe respiratory problem including acute respiratory distress. Encephalitis and seizure occur in severe cases, progression to coma within 24–48 hours.

Incubation Period

Interval from infection to onset of symptoms varies from 4 days to 45 days.

Most people who survive acute encephalitis make a full recovery but around 20% are left with residual neurological consequences such as persistent convulsion and personality changes. A small number of people who recover successfully relapse and develop delayed onset encephalitis. In the long term, persistent neurological dysfunctions are observed in more than 15% people. The case fatality rate is estimated at 40% to >80%. However, this rate may vary by outbreak depending on local capabilities for surveillance investigations and optimum supportive case management.

In Bangladesh in 2012 (up to March), 6 cases of Nipah virus were reported and all of them died (case fatality was 100%).

Diagnosis

Diagnosis is on the basis of typical history of consumption of date juice contaminated by infected bats, characteristics clinical findings of encephalitis and supported by relevant investigations which include:

- Serum neutralization
- Enzyme-linked immunosorbent assay (ELISA)
- Polymerase chain reaction assay
- Immunofluorescence assay
- Viral isolation by cell culture.

Treatment

There are currently no drugs or vaccine available to treat Nipah virus infection. Intensive supportive care with treatment of symptoms is the main approach to manage infected people.

Prevention

Controlling Nipah Virus in Domestic Animals

There is no vaccine available against Nipah virus. Routine cleaning and disinfection of pig farms with sodium hypochlorite or other disinfectant is expected to be effective in preventing infection. If an outbreak is suspected, the animal premises should be quarantined immediately sealing of infected animals with close supervision of burial or incineration of carcasses may be necessary to reduce the risk of transmission to people. Restricting or banning the movement of animals from infected farms to other areas can reduce the spread of the disease.

Reducing the Risk of Infection in People

- If possible, avoidance of taking date palm juice suspected of contamination of Nipah virus by fruit eating bats
- Freshly collected date palm juice should be boiled and fruits should be thoroughly washed and preserved before consumption
- Reducing the risk of human-to-human transmission: Close physical contact with Nipah virus infected people should be avoided. Gloves and protecting equipment should be washed when taking care of people. Regular handwashing should be carried out after caring for or visiting sick people
- Reducing the risk of animal-to-human transmission gloves and other protective clothing should be worn while handling sick animal or their tissue and during slaughtering and cutting procedure
- Special care should be taken in touching and handling the dead bodies during funeral, who died of Nipah virus infection.

POLIOMYELITIS

Virology

Poliovirus belongs to the Picornaviridae family, in the genus *Enterovirus.* The polioviruses are nonenveloped, positive-stranded RNA viruses and consist of three antigenically distinct serotypes (types 1, 2, and 3).

Incubation Period

Usually 8–12 days but range from 5 to 35 days.

Route of Transmission

Fecal-oral route; human are the only reservoir.

Clinical Features

Abortive Poliomyelitis

- Occurs 1–2 weeks after infection and lasts for 2–3 days; presents with a nonspecific influenza-like syndrome characterized by fever, malaise, anorexia, headache, sore throat, abdominal or muscular pain, and vomiting
- Recovers completely without any neurologic signs or sequele.

Nonparalytic Poliomyelitis

About 1% of patients infected with wild-type poliovirus, signs of abortive poliomyelitis are present, as are more intense headache, nausea, and vomiting, as well as soreness and stiffness of the posterior muscles of the neck, trunk, and limbs. Fleeting paralysis of the bladder and constipation are frequent.

It is divided into two phases:
1. First phase (minor illness).
2. Second phase (CNS disease or major illness).

The superficial reflexes, the cremasteric and abdominal reflexes, and the reflexes of the spinal and gluteal muscles are usually the first to diminish. Changes in the deep tendon reflexes generally occur 8–24 hours after the superficial reflexes are depressed and indicate impending paresis of the extremities.

When paralysis develops, the tendon reflexes become absent without affecting sensory system.

Paralytic Poliomyelitis (Fig. 29)

In this stage, central nervous system is greatly affected. Three clinically distinct conditions develop are:

1. Spinal paralytic poliomyelitis: The features are:
   - Severe headache
   - Fever occur with exacerbation of the previous systemic symptoms
   - Severe muscle pain
   - Sensory and motor phenomena (e.g. paresthesia, hyperesthesia, fasciculations, and spasms. Asymmetric flaccid paralysis or paresis (usually of proximal muscles than distal) occurs within 1-2 days
   - Bowel and bladder dysfunction ranging from transient incontinence to paralysis with constipation and urinary retention
2. Bulbar poliomyelitis: Dysfunctions of the cranial nerves and medullary centers. The clinical findings seen with bulbar poliomyelitis with respiratory difficulty (other than paralysis of extraocular, facial, and masticatory muscles include:
   - Nasal twang to the voice or cry caused by palatal and pharyngeal weakness
   - Inability to swallow smoothly
   - Accumulated pharyngeal secretions
   - Absence of effective coughing, shown by constant fatiguing efforts to clear the throat

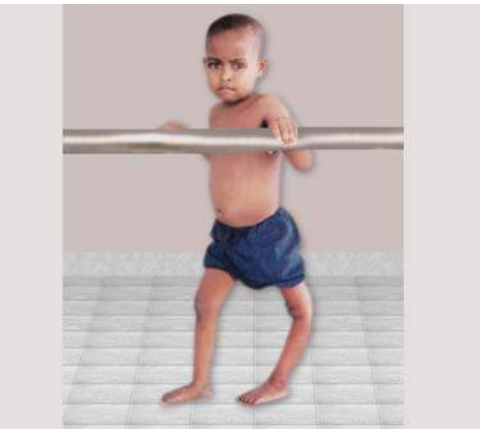


Fig. 29: Lower limb deformity in poliomyelitis

- Nasal regurgitation of saliva and fluids as a result of palatal paralysis
- Deviation of the palate, uvula, or tongue
- Involvement of vital centres in the medulla, resulting in irregularities in rate, depth, and rhythm of respiration; as cardiovascular alterations, including blood pressure changes (especially increased blood pressure), alternate flushing and mottling of the skin, and cardiac arrhythmias; and as rapid changes in body temperature
- Hoarseness, aphonia, and ultimately asphyxia due to paralysis of 1 or both vocal cords
- The rope sign, an acute angulation between the chin and larynx caused by weakness of the hyoid muscles

3. Polioencephalitis: Rarely occurs. Higher centers of the brain are severely involved.
   Presents with:
   - Seizures
   - Coma
   - Spastic paralysis with increased reflexes
   - Irritability, disorientation, drowsiness, and coarse tremors are often present with peripheral or cranial nerve paralysis.

Poliovirus mainly affects the following areas of CNS:

- The spinal cord (anterior horn cells chiefly and, to a lesser degree, the intermediate and dorsal horn and dorsal root ganglia)
- The medulla (vestibular nuclei, cranial nerve nuclei, and the reticular formation that contains the vital centers), The cerebellum (nuclei in the roof and vermis only)
- The midbrain (chiefly the gray matter but also the substantia nigra and occasionally the red nucleus)
- The thalamus and hypothalamus
- The pallidum
- The cerebral cortex (motor cortex).

The following areas are *not affected* by polioviruses:

- The entire cerebral cortex except the motor area
- The cerebellum except the vermis and deep midline nuclei
- The white matter of the spinal cord.

Laboratory Investigations

Stool Examination

The World Health Organization (WHO) recommends that the laboratory diagnosis of poliomyelitis be confirmed by isolation and identification of poliovirus in the stool, with specific identification of wild-type and vaccine-type strains. In suspected cases of acute flaccid paralysis, 2 stool specimens should be collected 24–48 hours apart within 14 days of onset of paralysis. Outbreak response effort should be started promptly without waiting for laboratory results which might take up to 8 weeks. All cases that are classified as "discarded" not polio require thorough justification and should be reported with the final diagnosis.

Adequate specimen specifies that its volume is about 10 g and arriving at WHO accredited laboratory in good condition. Good condition means no desiccation, or leakage, adequate documentation and evidence that the cold chain is maintained. Surveillance is carried out for all cases of AFP, not just for poliomyelitis.

Polioviruses may be isolated from 80–90% of specimens from acutely ill patients, whereas <20% of specimens from such patients may yield virus within 3–4 weeks after onset of paralysis. Because most children with spinal or bulbospinal poliomyelitis have constipation, rectal swabs may be used to obtain specimens.

CSF Study

- May be normal during mild illness.
- Pleocytosis may occur in CNS involvement. CSF protein content is normal or only slightly elevated at the outset of CNS disease but usually rises to 50–100 mg/dL by the 2nd week of illness.

Serological Test

Seroconversion or a fourfold or greater increase in antibody titer from the acute phase of illness to 3–6 weeks later.

Differential Diagnosis (Table 8)

- Guillain-Barré syndrome
- Transverse myelitis
- Traumatic paralysis.

Treatment

Supportive

The aims are:

- Limiting progression of disease,
- Preventing ensuing skeletal deformities, and preparing the child and family for the prolonged treatment required
- Prevention of permanent disability.

Abortive poliomyelitis:

- Analgesics, sedatives
- Nutritious diet
- Bed rest until fever subsides.

Nonparalytic poliomyelitis:

- Similar to abortive poliomyelitis. Firm bed is advised for bed rest
- Relief of pain with analgesics in conjunction with application of hot packs for 15–30 minutes every 2–4 hours
- Follow-up after 2 months to detect minor or residual effects that might cause postural problems in later years.

Paralytic:

- Hospitalization
- Complete physical rest in a calm atmosphere for the 1st 1–2 weeks
- A neutral position with the feet at right angles to the legs, the knees slightly flexed, and the hips and spine straight is achieved by use of boards, sandbags, and, occasionally, light splint shells
- Bladder care (catheterization if necessary)
- Maintenance of fluid, diet to provide adequate nutrition

In case of pure bulbar myelitis:

- Maintenance of airways
- Gravity drainage of accumulated secretions
- Monitoring for
  - Respiratory insufficiency
  - Blood pressure
- Tracheostomy if necessary (if there is vocal cord paralysis or constriction of the hypopharynx).

Table 8: Differential diagnosis of acute flaccid paralysis (AFP)

Feature	Poliomyelitis	Guillain-Barré Syndrome	Transverse myelitis	Traumatic neuritis
Progression to full paralysis	24–48 hours	Hours to a day	Hours to 4 days	Hours to 4 days
Fever onset	High, always present at onset of paralysis	No	Present before paralysis	No
Flaccidity	Acute, asymmetrical, proximal	Acute, symmetrical, distal, ascending	Acute, symmetrical, lower limbs	Acute, asymmetrical
Muscle tone	Diminished	Diminished	Diminished in lower limbs	Diminished
Deep tendon reflex	Decreased or absent	Absent	Absent early; hyper reflexia	Decreased or absent
Sensation	Severe myalgia and backache, no sensory change	Cramps, tingling, hypo-anesthesia of palms and soles	Anesthesia of lower limbs with sensory level	Pain in gluteal region
Cranial nerves	Only when bulbar and bulbospinal	Often present, affecting nerves VII, IX, X, XI, XII	Absent	Absent
Respiratory insufficiency	Only when bulbar and bulbospinal	In severe cases	Sometimes	Absent
CSF examination	High leukocytes, normal or slightly elevated protein	Less than 10 leukocytes, high protein	Cellular or acellular; normal or slightly increased protein	Normal
Bladder dysfunction	Absent	Transient	Present	Never
EMG at 3 weeks	Abnormal	Normal	Normal	May show abnormality
Nerve conduction velocity at 3 weeks	Normal	Abnormal	Normal	Abnormal
Sequel at 3 months	Severe, asymmetrical atrophy, skeletal deformities appear later	Symmetrical atrophy of distal muscles, recovery in milder cases	Diplegia, atrophy after years, recovery in milder cases	Moderate atrophy in affected limb

Specific

There is no specific antiviral therapy.

Prevention

General Measures

- Personal hygiene and healthy lifestyle prevents transmission of virus
- Provision for safe water supply, sanitation limits spread of poliovirus.

Vaccination

Vaccination is the only effective method of preventing poliomyelitis.

There are two types of vaccine are available

1. Inactivated polio vaccine (IPV)
2. Live attenuated Oral Polio Vaccine.

Both vaccines induce production of antibodies against the 3 strains of poliovirus. IPV elicits higher serum IgG antibody titers, but the OPV also induces significantly greater mucosal IgA immunity in the oropharynx and gastrointestinal tract, which limits replication of the wild poliovirus at these sites.

Available forms of polio vaccines: OPV is available as viral containing unit doses, usually 25 doses in ready-to-use liquid form. It is a live attenuated vaccine.

It is also available as combination vaccine containing IPV-DPT-HiB (Pentaxim) and IPV-DPT-HepB-Hib (Infanrix).

Schedule: OPV is given as 2 drops per orally. The first dose is given at birth to 15 days as zero doses OPV. Next 3 primary doses are given at 4 weeks interval starting at 6 to 8 weeks of age. 5 doses of polio vaccines are given within one year. The 5th dose is given at 9 months of age with measles vaccine.

Supplementary immunization: National immunization day is a mass campaign that aims to deliver 2 doses of OPV to all children less than 5 years in an entire country. All children are immunized regardless their prior immunization status. The two rounds are approx. a month apart and are normally conducted in cool dry season in order to facilitate the logistics and improve the immune response to vaccination. NIDs rapidly increase population immunity particularly intestinal secretary IgA to high levels that interrupts the circulation of wild poliovirus.

Efficacy and seroconversion: The efficacy of three doses of OPV in West is around 80–90%, whereas that in tropical countries, is only 60–70 percent.

There were initial concerns that IPV induces lower level of mucosal immunity than OPV and it does not get excreted in the stools of vaccine, so may be less efficacious in preventing wild virus circulation. But now studies have shown enhanced IPV (eIPV) induces adequate IgA formation in nasopharyngeal and intestinal secretion.

Advantages and disadvantages of OPV and IPV (Table 9): OPV is cheaper and being given orally is more acceptable. It leads to excellent herd immunity. Mass vaccination is easier with oral vaccine. IPV is available in injectable form and is costlier. OPV is preferred over IPV for routine and mass vaccination. On the other hand OPV is less efficacious in tropical countries as mentioned before. It has potential of vaccine associated paralysis (VAP). IPV is more efficacious, less thermolabile and

Table 9: Comparison of OPV and IPV

	OPV	IPV
Type	Live	Killed
Route	Oral	IM
Cost	Cheap	Costly
Storage	2–8°C (can be frozen)	2–8°C (strictly)
Doses (primary)	5	3
Side effects	Mild	Mild
Vaccine induced paralysis	+	–
Efficacy	++	+++
Pulsing	Possible	Difficult
Gut immunity	++	–
Herd immunity	++	–
Use in immunocompromised patients	No	Yes
Interference with virus isolation	+	–

no chance of vaccine induced paralysis. IPV has also currently shown to lead to local gut immunity as well as herd immunity. Good routine coverage of 5 primary doses of IPV can eradicate polio from a country. However, pulsing is easier with OPV than with IPV. Another major problem of use of OPV is emergence of circulating vaccine derived polioviruses (cVDPVs) which has property of wild virus. As long as OPV is in use, it is mandatory that very high immunization coverage must be maintained, so is to decrease the risk of emergence of cVDPV. Whereas VAP occur in individual cases, cVDPV can result in large outbreak.

Pulse polio immunization: It is a strategy of mass immunization by which one can eradicate poliomyelitis. Extra doses (pulses) of OPV are given to all children below 5 years of age in an area (country, state, city) at a time on a given day. Such pulses are repeated every year. The aim is to achieve 100% coverage.

Complications

Paralytic Poliomyelitis

- Acute gastric dilatation
- Severe malena may result from single or multiple superficial intestinal erosions
- Mild hypertension is common in the acute stage
- In the later stages, because of immobilization
- Hypertension
  - Dimness of vision
  - Headache
  - Light headed feeling
- Hypercalcemia
- Nephrocalcinosis
- Vascular lesions
- Myocarditis
- Acute pulmonary edema (occasionally, particularly in patients with arterial hypertension).

Prognosis

- Prognosis of inapparent, abortive poliomyelitis and aseptic meningitis syndromes is uniformly good, with death being exceedingly rare and with no long-term sequelae
- The mortality rate, in severe bulbar poliomyelitis, is about 60%, in less severe bulbar involvement it varies from 5% to 10%
- Death generally occurs from causes other than the poliovirus infection
- Mortality and the degree of disability are greater after the age of puberty.

Polio Status in Developing Countries

Polio cases have decreased by over 99%. Since 1988 from an estimated 350,000 cases then, to 406 reported cases in 2013. The reduction is the result of the global effort to eradicate the disease. In 2014, only three countries (Afghanistan, Nigeria and Pakistan) remain polio endemic. In most countries, the global effort has expanded capacities to tackle the disease.

In 1994, the WHO region of the America was certified polio-free, followed by the WHO Western Pacific region in 2000 and the WHO European region in 2002. On March 27, 2014 the WHO Southeast Asia region was certified polio-free, the transmission of wild polio virus has been interrupted in this block of 11 countries stretching from Indonesia to India.

Bangladesh is fortunate to have no polio case virtually from 2001, except in a window period in 2006 (Fig. 30).

RABIES

Epidemiology

Rabies is a major zoonotic infection throughout the world except Antarctica. Rabies infects domestic and wild animals and spreads to the human through close contact with infected saliva. More than 95% of human rabies infections come from dogs. Although all age group is susceptible, rabies is most common in children aged <15 years.

Virology

Rabies virus is the member of the family Rhabdoviridae under the genus Lyssavirus.

There currently are 7 known genotypes of Lyssavirus. Lyssavirus type 1 is the classic rabies virus. RNA of rabies virus encodes 5 proteins, including the G glycoprotein that carries the main antigenic site.

A lipoprotein envelope studded with glycoprotein spikes surrounds each virion. After inoculation, these glycoprotein projections attach to specific sites, such as the nicotinic acetylcholine receptors on plasma membranes of muscle cells.

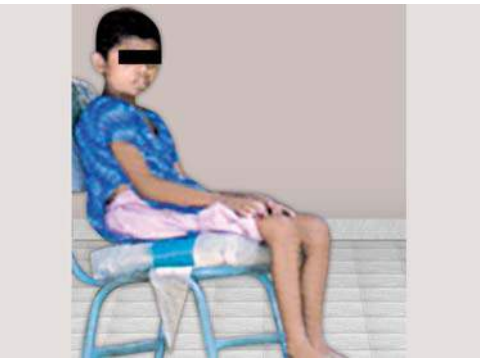


Fig. 30: Rahima Akter from Chandpur, Bangladesh is the first casualty case of polio after polio eradication since 2000

Pathogenesis

After deposition of Lyssaviruses in peripheral wounds, retrograde passage occurs from the periphery to the dorsal root ganglia and then to the brain. Viral replication occurs in the central nervous system (CNS). Lyssaviruses preferentially localize in the brainstem, thalamus, basal ganglia, and spinal cord. Spread from the CNS occurs along neural pathways to the heart, skin, and other organs, especially the salivary glands.

Factors that may increase host susceptibility to infection are:

- Infecting variant
- Size of the inoculum
- Concentration of local receptors
- Degree of innervation at the site of the bite
- Proximity of the bite to the central nervous system
- Host immunity and genetics.

All mammals are believed susceptible to viral infection although species differ in their relative susceptibility. Foxes, coyotes, wolves, and jackals are quite susceptible whereas opossums are relatively resistant.

Incubation Period

One to three months after exposure. Range of incubation period may vary from days to years.

Mode of Transmission

- Human infection occurs through a transdermal bite or scratch by an infected animal
- Other mode of transmission is person's mucosa or fresh skin wounds coming in contact with infected saliva
- Human-to-human transmission is extremely rare except for transplantation of an infected organ.

Peripheral nerves carry the virus to CNS, where it undergoes rapid multiplication and dissemination.

Clinical Features

In Animal

It is of either a paralytic (dumb) form or furious syndrome. Typical infections are characterized by behavioral changes and a rapid clinical course leading to coma and death. The prodromal phase starts with by nonspecific signs, like restlessness and malaise in rabid animal but later on they become vicious.

Dumb rabies (Fig. 31): It's a depressed encephalitic disease presents with Lethargy, selectively severe paralysis of throat muscles causing drooling of saliva because of difficulty in swallowing. Hydrophobia is uncommon in animal.

Furious rabies (Fig. 32): Characterized by an unusual state of alertness in which any visual or sound stimulation may incite an attack. Animals may roam indiscriminately, frequently feeding on stones, twigs, and other inanimate objects.

In domestic animals, the course is rapid and it takes about 7 to 10 days from onset of prodromal signs to death. Death occurs due to respiratory muscle paralysis.

Fig. 31: Dumb rabid dog

Fig. 32: Furious rabid dog

In Human

Rabies has two clinical forms. They are:

1. **Encephalitic or "furious" rabies**
   The prodrome consists of nonspecific flu-like symptoms including malaise, anorexia, irritability, low grade fever, sore throat, headache, nausea, and vomiting. Prodromal phase lasts from a few days to not more than a week.

   An acute neurologic syndrome of either encephalitic or paralytic rabies follows the prodrome and typically lasts for two to seven days. The manifestations of encephalitic rabies include:
   - Hyperactivity
   - Persistent fever
   - Fluctuating consciousness
   - Painful pharyngeal or inspiratory spasms, autonomic stimulation (hypersalivation), and
   - Seizures.

   Pharyngeal spasms upon encountering a draft of air (aerophobia) or when offered water (hydrophobia) are seen in nearly all patients with encephalitic rabies.
   There may also be non-neurologic manifestations such as cardiac arrhythmias and myocarditis. The myocarditis may reflect both the hyperadrenergic state and direct viral infection.
2. **Paralytic or "dumb" rabies**
   Paralytic rabies presents with quadriparesis with sphincter involvement, mimicking Guillain-Barré syndrome. These patients have little evidence of cerebral involvement until late in the course.

Diagnosis

Mostly clinical; the clinical diagnosis of rabies is straightforward in developing countries when a nonimmunized patient presents after a bite by a known rabid animal.

Laboratory Investigation

To confirm clinically diagnosed rabies several investigation may be done:

- Detection of antirabies antibody
- Rabies-specific antibody can be detected in serum or cerebrospinal fluid (CSF) samples
- Isolation of virus
- Detection of viral protein or RNA

- Culture of rabies virus in cell culture media and after animal injection. Rabies virus can best be isolated for culture from saliva or from brain biopsy material.

Management

Neither rabies immune globulin (RIG) nor rabies vaccine alters the course of disease once symptoms have appeared.

Supportive

Treatment of symptomatic rabies in unvaccinated patients is usually supportive.

- Minimization of environmental stimuli that precipitate spasms
- Meticulous respiratory care and
- Control of pain and anxiety.

Vaccine

Pre-exposure Prophylaxis

Pre-exposure prophylaxis is recommended for those who are at risk of acquiring rabies or in close contact with reservoir or animal vector such as laboratory staff, veterinary surgeons, doctors.

WHO recommends the following vaccines:

- Human diploid cell vaccine (HDCV) [each dose = 1.0 mL]
- Purified chick embryo cell vaccine (PCECV) [each dose = 0.5 mL]
- Purified Vero-rabies vaccine (PVRV) [each dose = 1.0 mL].

Cell culture vaccines are highly immunogenic, free of serious reactions, and effective in post-exposure prophylaxis.

These are given intramuscularly (IM) on D0, D7 and D28 over deltoid. A booster dose given after 1–3 years.

Post-exposure Prophylaxis (Fig. 33)

Active immunization: Injection of HDCV, PVRV and PCEC are commonly used for active vaccination. The benefits of using these vaccines are risk free, well- tolerated and more antigenic.

Dosage schedule:

- Subject unvaccinated against rabies: Injection HDCV (1 mL) or PVRV (0.5 mL) or PCEC (1 mL) given IM over deltoid on day 0, 3, 7, 14, 30, ± 90.
- Individuals at continued risk of rabies exposure should have antibody titer every two years; if inadequate, should be given a booster dose.
- Subject fully vaccinated:
  - If bite within 1 year: One injection should be given
  - If bite within 5 years: Two injections on day 1 and day 3
  - If bite after 5 years: Revaccination should be considered.
- NTV-ARV: 14 injections at a dose of 0.25 mL (for children) subcutaneously on anterior abdominal wall around umbilicus with three booster doses on days 10, 20, and 90 after completion of 14 injections may be given.

Passive immunization: Human rabies immunoglobulin (HRIG; dose 20 IU/kg) infiltrated in the area around and into the wounds.

Prevention

Factors that determine the post-exposure prophylaxis are:

- The epidemiology of animal rabies in the region
- The type of exposure
- Whether the exposure was provoked or unprovoked
- The species and vaccination status of the animal.

WHO Definitions of Categories of Exposure for the Use of Rabies Biologicals

Category of Exposure

Category I: Touching or feeding animal licks on intact skin (that is no exposure)

Category II: Nibbling of uncovered skin minor scratches or abrasions without bleeding

Category III: Single or multiple transdermal bites or scratches contamination of mucous membrane with saliva from licks/ licks on broken skin; exposure to bats.

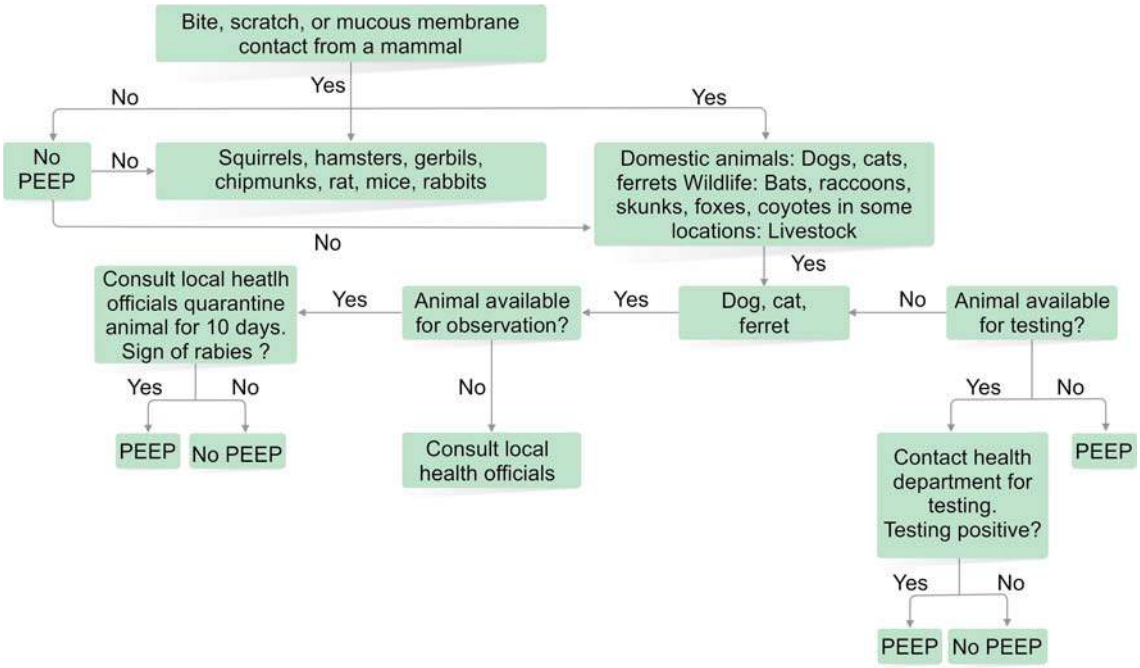


Fig. 33: Algorithm for evaluating a child for rabies post-exposure prophylaxis

Recommended Prophylaxis

For Category I exposure: No prophylaxis is required.
For Category II exposure: Immediate vaccination is recommended.
For Category III exposure: Immediate vaccination and administration of rabies immunoglobulin are recommended.

For categories II and III, thorough handwashing and flushing (for about 15 minutes, if possible) with soap or detergent and copious amount of water of all bite wounds and scratches should be done immediately or as early as possible.

ACQUIRED IMMUNODEFICIENCY SYNDROME IN CHILDREN

Approximately 90% of all HIV positive people in the world live in developing countries. Globally, the number of children younger than 15 years living with AIDS have been increased from 1.6 million in 2001 to 2.5 million in 2009. However, the number of newly infected children is being declining since 2003 due to increasing access to prevention and parent-to-child transmission (PPTCT) services.

Epidemiology of HIV and HIV Diagnosis

There are two primary types of HIV that cause AIDS (HIV-1 and HIV-2). HIV-1 is more contagious and cause pandemic. For this reason most laboratories focus on HIV-1. The subtype of HIV-1 also differs by content and regions. Although most new infections are subtype C, the geographical distribution of HIV-1 is complex. HIV diagnostic tests detect specific proteins/genetic material (HIV-DNA and RNA PCR) and many are designed and engineered for subtype of HIV in a particular population.

HIV is preventable infection. Early diagnosis and treatment of HIV can greatly affect child survival. The high mortality rates of infected infants underscore the importance of early diagnosis. Without intervention up to 30% of infants born to HIV positive mother are infected during pregnancy, delivery and breast feeding. Median infant survival time after HIV infection in infancy is just over a year.

HIV disease progresses very rapidly in very young children especially first few months of life often leading to death. HIV infected infants frequently presents with clinical symptoms in the first year of life. Without care and treatment about one-third of infants living with HIV will die in their first year of life and almost 50% of children in second year of life. Therefore early diagnosis and proper management of HIV infection is critical in children.

Diagnosis of HIV Infection in Children

Diagnostic testing for HIV infection by antibody test in particular in children younger than 18 months, differ from older children, adolescent and adult because of presence of maternal antibody. HIV specific immunoglobulins such as IgG HIV antibody are passively transferred across the placenta. The mean age for clearing of maternal antibody is just 10 months, but maternal antibody may persist in infant until 18 months of age.

Diagnostic tests fall in two main categories:
1. Antibody tests like:
   - HIV rapid test
   - HIV enzyme-linked immunosorbent assay (ELISA) also called enzyme immunoassay (EIA)
   - Western blot.
2. Virologic tests:
   - HIV DNA PCR assay
   - RNA assay
   - p24 antigen assay
   - Viral culture.

Antibody Tests

Because antibody tests are inexpensive and relatively easy to perform they are widely available. However, they can yield false-positive and false-negative result. False-negative result occur when HIV-infected individual do not produce detectable antibodies such as during early acute phase of infection (window period) and very late stage of infection when immune suppression is severe and antibodies are no longer been produced in response to HIV infection. World Health Organization (WHO) and Pediatric Technical Resource Group (NACO) recommends the using the antibody test 6 weeks after exposure to HIV case. As mentioned earlier one of the most important limitation of antibody test occur in infants younger than 18 months. During pregnancy, infected mother passively transfer IgG HIV antibody to the fetus through the placenta. The presence of these antibody means the infant is exposed and might be infected.

Rapid Antibody Tests

Being cheaper and simple, it increases access to HIV test especially in resource poor settings. It is also an ideal test for situation in which an immediate result is necessary like a pregnant woman in labor. They can also be done with a single heel, finger prick. Rapid tests are highly sensitive (93–100%) and specific (98–100%).

Other Antibody Tests (ELISA)

ELISA is like the rapid test is also specific and highly sensitive in identifying antibodies to HIV. False positive are syphilis, hematologic malignancy, pregnancy and recent blood transfusion. ELISA usually require serum sample for processing but that test with use of urine or oral fluid has also been developed. ELISA is usually a qualitative (positive or negative) test. A negative ELISA does not require confirmatory testing provided the patient was not tested during window period. A positive ELISA however should be confirmed by Western blot assay to further minimize the possibilities of a false result. However western blot is rarely used nowadays.

Western Blot

Western blot antibody test detects the antibody against specific HIV proteins. Western blots are typically used to confirm a reactive ELISA result. A negative western blot indicates that the positive ELISA was a false positive. The positive Western blot confirms the HIV-1 antibodies.

Virologic Tests

HIV-1 DNA PCR

HIV-1 DNA PCR test is the gold standard for the diagnosis of HIV. It was previously very expensive test. Fortunately, DNA

PCR is now becoming less expensive and becoming available in resource poor countries. The test has excellent sensitivity and specificity even in the first month of life. Because almost all prenatal and perinatal infection is detectable by DNA PCR at 4–6 weeks of age, this test is excellent for early infant diagnosis.

HIV RNA PCR

HIV RNA PCR, another important virologic test commonly used to monitor response to HIV treatment. Whereas DNA PCR is a qualitative test providing positive or negative results, RNA PCR tests are quantitative and indicate how much HIV is in the blood. For this reason, RNA PCR is also known as the viral load.

HIV RNA PCR tests are more expensive than DNA PCR tests. Simpler, faster and less expensive RNA PCR tests are in development.

Antigen (p24) Test—An Ultrasensitive Test

Another test can directly detect HIV in the bloodstream is the p24 antigen test. The antigen p24 is a major core protein of HIV that can be found either free in the blood stream of IV infected people or bound to anti-p24 antibody. An ultrasensitive p24 test has been developed that can be performed successfully using both serum and dried blood spot (DBS) collection techniques, with reported sensitivity and specificity of 98% and 100%, respectively. This ELISA based technology is less expensive than DNA and RNA tests and involves simpler laboratory techniques.

HIV Culture

HIV culture is a virologic test that requires incubating peripheral blood cells from a patient to determine the presence of HIV in the blood sample. The sensitivity of HIV culture is same as that of DNA PCR but takes long time (up to 6 weeks) to get the result. It is therefore used for research only.

Testing by Virology in Infants

During early infancy when maternal antibody can complicate the interpretation of antibody test, virologic tests can be used to determine whether the infant is HIV infected. Virologic testing is becoming available worldwide and has an increasing role guiding early clinical decisions related to feeding choices, co-trimoxazole prophylaxis, early HIV care and treatment. Infants of HIV positive mother are tested at 14–21 days, 1–2 months and 4–6 months.

Antibody Testing in Infants

Even an infant becomes infected and begins making his/her own antibodies; antibody test cannot differentiate from mother and those from infant. Therefore positive antibody test indicates that the infant has been exposed and may or may not be infected. Despite this factor HIV antibody testing is still useful screening tool in later infancy. Up to 93% of 9-month-old HIV uninfected infants and 95% 12-month-old uninfected infants will have lost their maternal antibodies. For this reason, a positive test in later infancy indicates a HIV infection.

Blood Collection and Testing

HIV Testing and Dried Blood Sample (DBS)

Until recently, HIV testing required phlebotomist, a centrifuge, and quick transport of the serum sample between the health clinics and the lab. The development of DBS collection method has eliminated many of these logistical barriers and has provided increase access to HIV testing.

DBS simplifies blood sample collection and owing to its high stability, allows for convenient sample handling and transport. Only a few drops of blood is required from a finger, toe, or heel stick which are collected on special filter paper.

DBS collection has been used successfully to perform virologic and antibody tests, including DNA PCR, RNA PCR, p24 antigen detection and ELISA. DBS has greatly facilitated the early infant diagnosis of HIV.

Steps for collection of DBS for HIV testing:

1. Fill out appropriate paperwork: DBS card, lab order form, clinic logbook.
2. Choose the puncture site (Fig. 34).
3. Warm the puncture site.
4. Wash hands, put on gloves.
5. Position baby with foot down.
6. Clean the site with an alcohol swab and allow drying for 30 seconds.

Site of puncture

Small child (<4 months, <5 kg)
- Puncture the heel
- Not fingers, since risk of hitting bone

Medium Infants (4–10 months, 5–10 kg)
- Puncture the toe
- If malnourished, still use heel

Larger Infants (>10 months, >10 kg)
- Puncture 4th finger
- Slightly lateral side

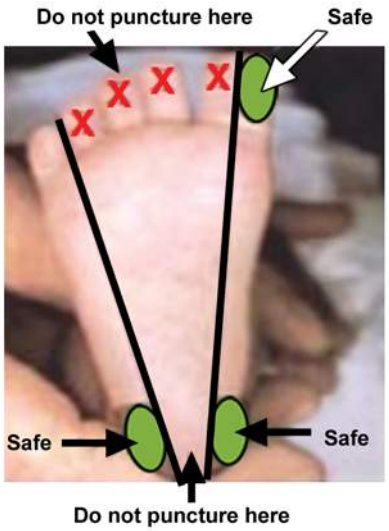


Fig. 34: Sites of puncture for collection of DBS for HIV testing

Fig. 35: Procedure of filling circle with drop

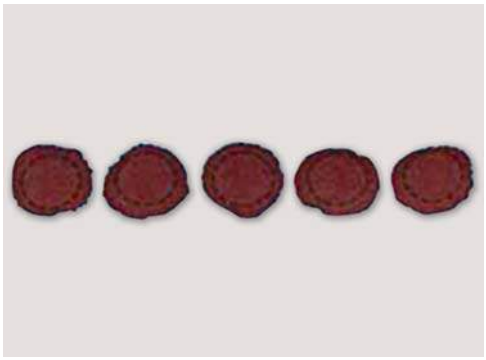


Fig. 36: Dry DBS sample

7. Press lancet on to site, prick skin.
8. Wipe away first drop.
9. Allow large drop to collect.
10. Touch blood drop to card (Fig. 35).
11. Fill entire circle with drop.
12. Fill all 5 circles (at least 3)
13. Apply mild pressure and clean the puncture site.
14. Dry and package the DBS samples for storage and transport to the laboratory (Fig. 36).

Algorithm for Diagnosis of HIV Infection in Children

The Paediatric Technical Resource Group at NACO has provided testing algorithms for infant up to six months of age (Fig. 37) and 6–18 months for confirmation of HIV infection in exposed infants (Fig. 38).

Algoithm for evaluation of breastfed and non-breastfed children is given in Figure 39.

Presumptive Diagnosis Where there is No Virologic Testing Available

Clinical criteria for presumptive diagnosis of severe HIV disease in infants and children less than 18 months of age requiring ART in situations where virological testing is not available.

A presumptive diagnosis of severe HIV disease should be made if:

- The infant is confirmed HIV antibody positive
- Diagnosis of any AIDS-indicator conditions can be made
- The infant is symptomatic with two or more of the following:
  - Oral thrush
  - Severe pneumonia
  - Severe sepsis.

Other factors that support the diagnosis of severe HIV disease in an HIV seropositive infant include:

IMCI Definitions

- Oral thrush:
  Creamy white to yellow soft small plaques on red or normally colored mucosa which can often be scrapped (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender
- Severe pneumonia
  Cough or difficult breathing in a child with chest indrawing, stridor or any of the IMCI general danger signs, i.e. lethargy or unconsciousness, not able to drink or breastfeed, vomiting and presence of history of convulsions during current illness; responding to antibiotics
- Severe sepsis
  Fever and low body temperature in a young infant with any severe sign such as fast breathing, chest indrawing, bulging fontanelle, lethargy, reduced movement, not feeding or sucking breast milk, convulsions, etc.

- Recent HIV-related maternal death; or
- Advanced HIV disease in mother
- CD4 <20%.

Confirmation of diagnosis of HIV infection should be sought, whenever available.

Clinical Staging of HIV Infection

Children infected with HIV often have severe disease when first evaluated, or they may develop AIDS over time, much like adults. Immunologic and clinical categories are used to evaluate the HIV disease status in children and to make treatment decision.

Primary Infection or Acute Retroviral Syndrome

- Primary infection refers to the time when HIV first enters the body. An acute retroviral syndrome is mainly encountered in adults and occasionally in older children and adolescents. Signs and symptoms of acute retroviral syndrome include fever, myalgia (muscle pain), headache, nausea, vomiting, diarrhea, night sweats, weight loss, and rash. These signs and symptoms usually occur 2–4 weeks after infection, subside after a few days, and often are misdiagnosed as influenza or infectious mononucleosis.
- During primary infection, the CD4+ count in the blood decreases remarkably but rarely drops to less than 200 cells/μL. The virus targets CD4+ cells in the lymphnodes and thymus during this time, making the HIV-infected person vulnerable to opportunistic infections and limiting the thymus's ability to produce T lymphocytes.
- HIV antibody testing using an enzyme-linked immunosorbent assay (ELISA) or enzyme immunoassay (EIA) may yield positive or negative results depending on the time of seroconversion. DNA PCR and RNA PCR will be positive in genuine infection.

Clinical Latency/Asymptomatic Disease (Clinical Stage 1)

- During latency, HIV-infected patients may or may not have signs or symptoms of HIV infection though persistent lymphadenopathy is common
- In HIV-infected adults, this phase may last 8–10 years
- The HIV enzyme-linked immunosorbent assay and Western blot or immunofluorescence assay will be positive

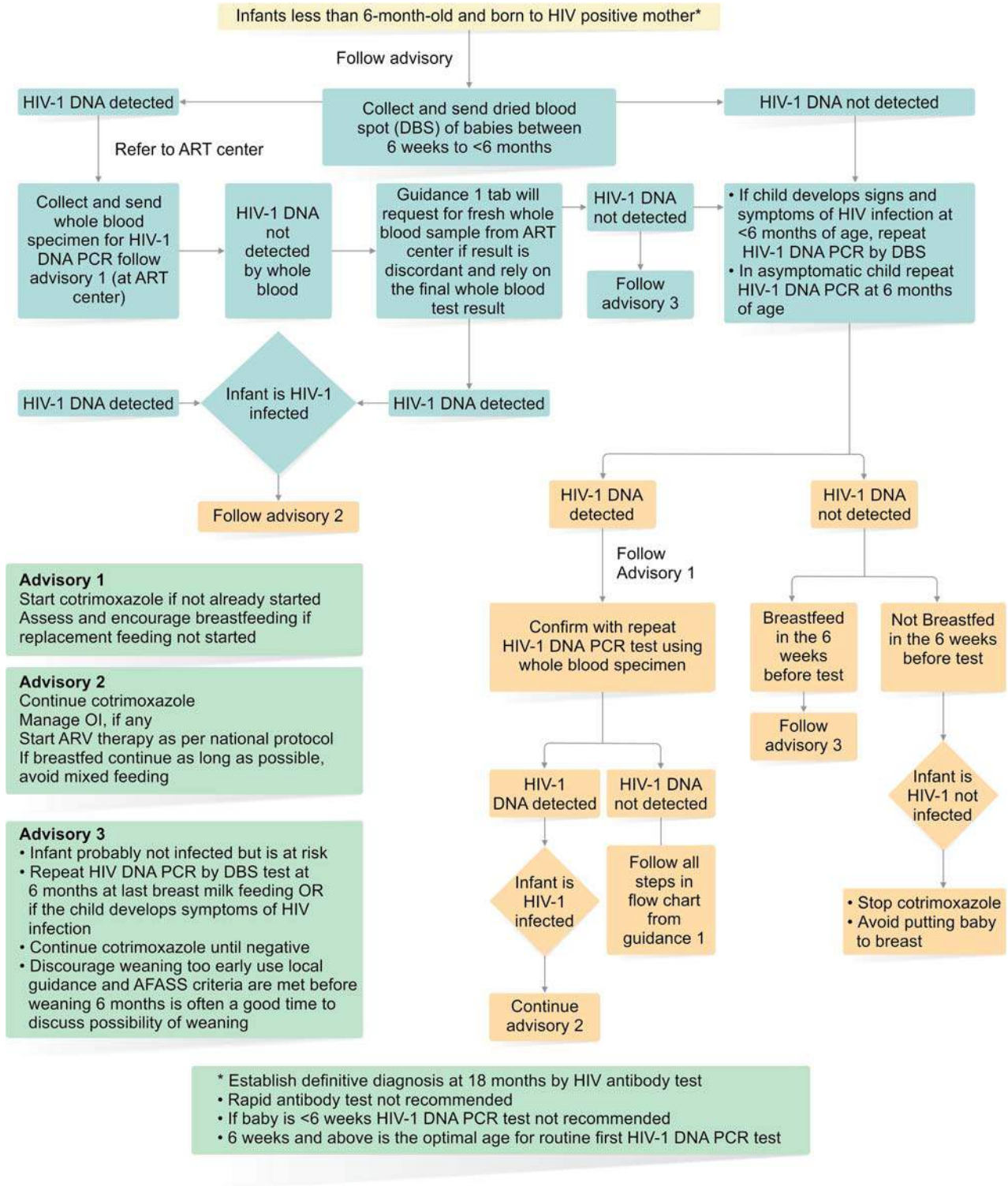


Fig. 37: Algorithm of management of a child <6 months born to HIV positive mother

Abbreniations: HIV human immunodeficiency virus: DNA; deoxy ribonucleic acid; PCR, polymerase chain reaction; DBS, dried blood spots, Art antiretro viral therapy; AFASS, accessible, feasible, affordable, sustainable and safe; OI, other infection

- The CD4+ count is greater than 500 cells/μL in children over 5 years of age.

Mild Signs and Symptoms of HIV (Clinical Stage 2)

- Candidiasis (Fig. 40), lymphadenopathy, molluscum contagiosum, angular stomatitis, persistent hepatosplenomegaly (Fig. 41), papular pruritic eruption, herpes zoster (Fig. 42), and/or peripheral neuropathy
- The viral load increases and the CD4+ count falls in between 350–499/L in children older than 5 years
- They can be reassigned stage 3 or 4 if a condition from one of those occurs, but they cannot be reassigned to clinical stage 1 or 2 if they become asymptomatic.

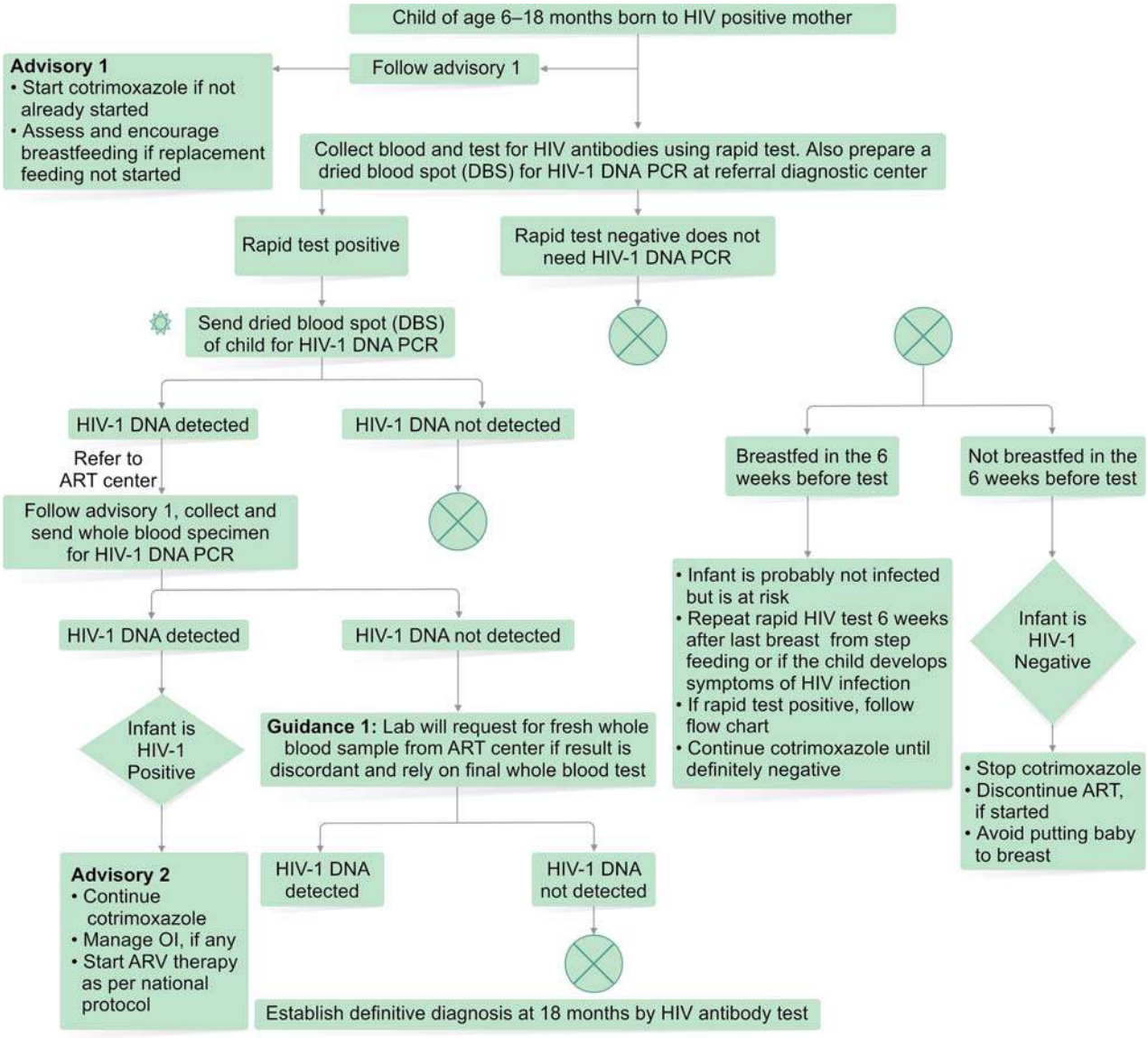


Fig. 38: Management of a child aged 6–18 months born to an HIV positive mother

Advanced Signs and Symptoms (Clinical Stage 3)

- This stage is characterized by development of cryptosporidiosis, pulmonary and lymph node tuberculosis (Fig. 43), wasting, persistent fever (longer than 1 month), persistent candidiasis, recurrent bacterial pneumonia and other opportunistic infection
- The viral load continually increases and the CD4+ count falls to less than 200–349 cells/L in children older than 5 years.

Clinical Stage 4

- Clinical stage 4 is manifested by advanced HIV disease, or AIDS. There may be continued developing new opportunistic infections, such as *Pneumocystis jirovecci* pneumonia (formerly *Pneumocystis carinii*), *Mycobacterium avium* complex, cryptococcal meningitis, progressive multifocal leukoencephalopathy, Kaposi sarcoma and other infections that commonly occur with a severely depressed immune system
- The viral load is very high, and the CD4+ count is less than 200 cells/μL in children older than 5 years
- Death may ensue in this stage.

WHO Clinical Staging of HIV in Children

Clinical Stage 1

- Asymptomatic
- Persistent generalized lymphadenopathy.

WHO HIV Clinical Stage 2: Selected Example

Clinical Stage 2

- Unexplained persistent hepatosplenomegaly
- Papular pruritic eruptions
- Fungal nail infections
- Angular cheilosis
- Linear gingival erythema
- Extensive molluscum contagiosum
- Recurrent oral ulceration (Fig. 44)
- Unexplained persistent parotid enlargement
- Herpes zoster
- Recurrent or chronic upper respiratory tract infections (otitis media, otorrhea, sinusitis, tonsillitis).

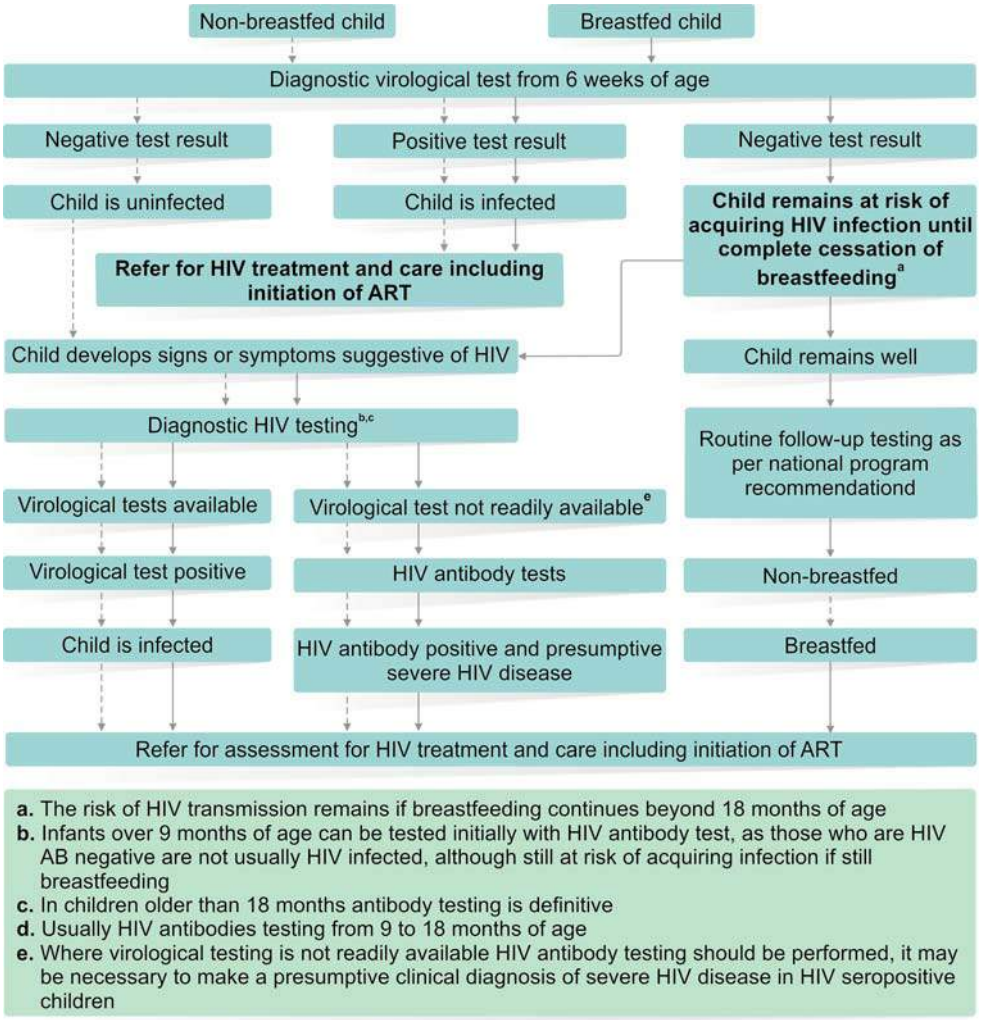


Fig. 39: Evaluation of breastfed and non-breastfed children

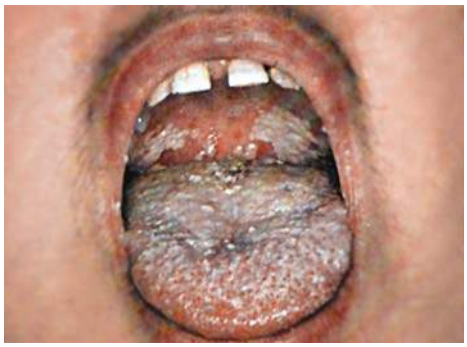


Fig. 40: Recurrent oral candidiasis

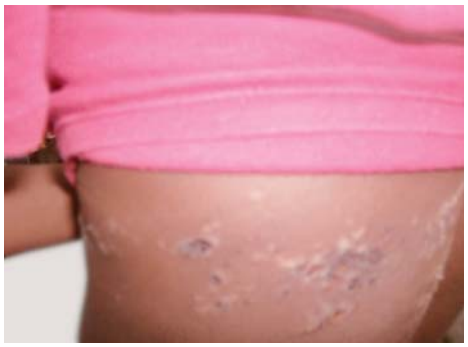


Fig. 42: Herpes zoster

Fig. 41: Unexplained persistent hepatomegaly

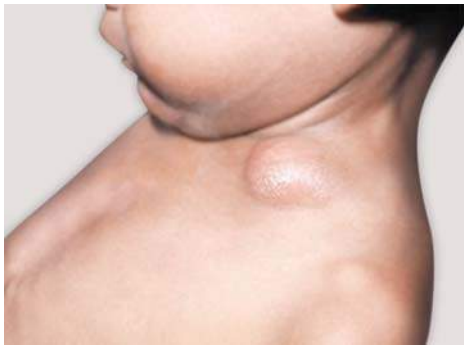


Fig. 43: Tubercular lymphadenitis

WHO HIV Clinical Stage 3 : Selected Example

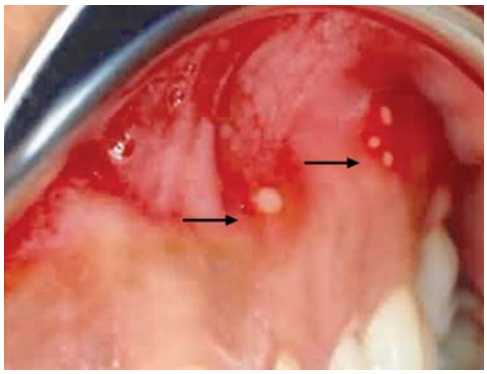


Fig. 44: Recurrent oral ulceration

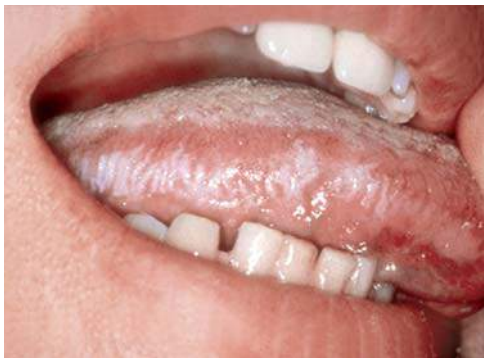


Fig. 45: Oral hairy leukoplakia

Clinical Stage 3

- Unexplained moderate malnutrition or wasting not adequately responding to standard therapy
- Unexplained persistent diarrhea (14 days or more)
- Unexplained persistent fever (above 37.50°C, intermittent or constant, for longer than one month)
- Persistent oral candidiasis (Fig. 44) (after first 6–8 weeks of life)
- Oral hairy leukoplakia (Fig. 45)
- Acute necrotizing ulcerative gingivitis or periodontitis
- Lymph node tuberculosis (Fig. 43)
- Pulmonary tuberculosis
- Severe recurrent bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis
- Chronic HIV associated lung disease including bronchiectasis
- Unexplained anemia (<8 g/dL), neutropenia (<0.5 × 10^9/L^3) and or chronic thrombocytopenia (< 50 × 10^9/L^3).

Clinical Stage 4

- Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
- *Pneumocystis carinii* pneumonia
- Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
- Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration, or visceral at any site)
- Extrapulmonary tuberculosis (Fig. 46)
- Kaposi sarcoma (Fig. 47)
- Esophageal candidiasis (or Candida of trachea, bronchi or lungs)

WHO HIV Clinical Stage 4: Selected Example

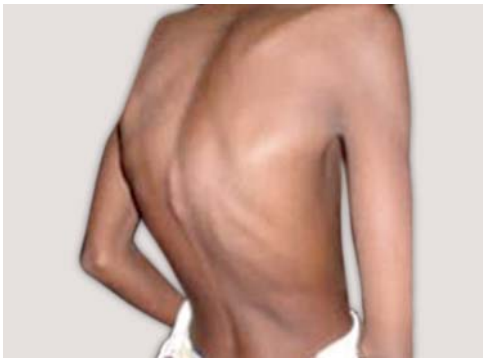


Fig. 46: Extrapulmonary TB (of spine)

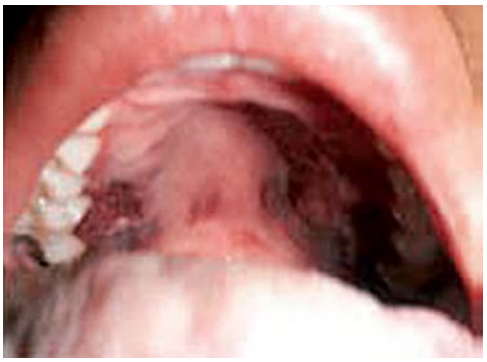


Fig. 47: Kaposi sarcoma

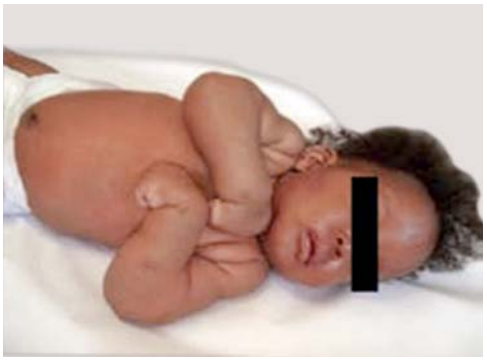


Fig. 48: HIV encephalopathy

- Cytomegalovirus infection; retinitis, or CMV infection affecting another organ, with onset at age over 1 month
- Central nervous system toxoplasmosis (after the neonatal period)
- Extrapulmonary cryptococcosis (including meningitis)
- HIV encephalopathy (Fig. 48)
- Disseminated endemic mycoses (extrapulmonary histoplasmosis, coccidiomycosis)
- Chronic cryptosporidiosis (with diarrhea)
- Chronic isoporiasis
- Disseminated nontuberculous mycobacteria infection
- Cerebral or B-cell non-Hodgkin's lymphoma
- Progressive multifocal leukoencephalopathy
- HIV-associated cardiomyopathy or nephropathy
  - Unexplained refers to where the condition is not explained by other cause
  - Some additional specific conditions can be included in regional classifications (e.g. disseminated penicilliosis

in Asia, HIV-associated rectovaginal fistula in Africa), and reactivation of American trympanosomiasis.

Immune Staging of HIV Infection According to CD4 Count

CD4 counts and percentage values in healthy infants without HIV infection are considerably higher than values than observed in adults and slowly decline to the adult values by 5 years. In children under 5 years, the absolute CD4 count tends to vary more with age than does CD4 percentage. Therefore, in HIV exposed infants and children younger than five years, CD4 percentage is preferred for clinical assessment of degree of immune suppression and monitoring immune recovery, whereas absolute CD4 count can be used in older children (Table 10).

Summary of Diagnosis of HIV Infection

- Clinical signs and symptoms as well as specific laboratory test are required for diagnosis of HIV infection
- Screening for HIV infection can be carried out by HIV rapid test and enzyme-linked immunosorbent assay (ELISA) by detecting antibodies. These tests determine HIV exposure in infants younger than 18 months and diagnose HIV infection in children older than 18 months and in adults
- As there is passive placental transfer of maternal HIV IgG antibody during pregnancy, antibody tests are unreliable to diagnose HIV in infants younger than 18 months
- In infants younger than 18 months, the definitive diagnosis can be made by virologic testing (e.g. DNA PCR)
- In infants younger than 18 months of age, presumptive diagnosis of HIV can be made by a positive antibody test along with certain signs and symptoms of HIV. This assessment can be carried out in absence of readily available virologic tests
- Dried blood spot (DBS) is convenient for sample handling and transport. It also provides increase access to DNA PCR due to its high stability
- Early diagnosis is very much important to ensure timely enrolment of HIV exposed infant into care, initiation of cotrimoxazole prophylaxis and appropriate infant feeding counseling. Early diagnosis depends upon the clinical signs and symptoms, rapid testing and virologic testing.

Prevention

Prevention of Parent to Child Transmission

Mother-to-child transmission (MTCT) is by far the most significant route of transmission of HIV infection in children below the age of 15 years. HIV can be transmitted during pregnancy, during child birth, or breastfeeding. Without intervention, the risk of transmission from an infected mother to her child ranges from 15% to 25% in developed countries and 25–45% in developing countries. This difference is largely attributed to breastfeeding practice.

The Prevention of Mother to Child Transmission (PMTCT) program aims to prevent the perinatal transmission of the HIV from an HIV infected pregnant mother to her newborn baby.

Significant progress is being made in the global scale- up of prevention of mother-to-child transmission of HIV (MTCT), including high burden in resource-limited settings.

For the first time, the elimination of mother-to-child transmission of HIV (MTCT) is now considered a realistic public health goal and an important part of the campaign to achieve the millennium development goals.

The program entails counseling and testing of pregnant women in the ICTCs. Pregnant women who are found to be HIV positive are given a single dose of nevirapine (NVP) at the time of labor; their newborn babies also get a single dose of nevirapine immediately after birth so as to prevent transmission of HIV from mother to child.

Table 10: Classification of HIV-associated immunodeficiency CD4 count

Class	Age (months) related CD4 values			
	≤11 (%)	12–35 (%)	36–59 (%)	≥60 (cells/cumm)
Not significant	>35	>30	>25	>500
Mild	30–35	25–30	20–25	350–499
Advanced	25–29	20–24	15–19	200–349
Severe	<25	<20	<15	<200 or <15%

The Four-Pronged Approach for Preventing Mother to Child Transmission of HIV

Prong 1 (Prevention of HIV in Women)

- Enhancing community engagement and mobilization, including male involvement in MCH
- Making reproductive health service adolescent friendly and integrating voluntary counseling and testing (VCT) information
- Screening and treatment for STIs
- Promoting condom use
- Providing preventive counseling for HIV negative women and their partners
- Encouraging disclosure of HIV status amongst couples
- Addressing traditional practices that promote the transmission of HIV/AIDS
- Empowering women and girls.

Prong 2 (Prevention of Unintended Pregnancy)

- Provision of VCT in ANC and family planning units
- Provision of family planning information and services to women and their partners in the context of HIV.

Prong 3 (Prevention of MTCT)

- Strengthening of MCH services including, malaria prevention (IPT and ITNs), and strategies to reach pregnant women not reached through ANC
- Integration of routine counselling and testing (100% counseling with opt out model) in MCH services
- Provision for ARVs for PMCT
- Ensuring safe delivery practices including practice of stringent infection control/universal precaution
- Counseling for optimal and safe infant feeding options as well as maternal nutrition
- Condom use
- Male involvement in pre- and postnatal services and community counseling.

Prong 4 (Care and Support)

- Screening and treatment of opportunistic infections among mothers and their families

- Postpartum maternal TB prophylaxis
- PCP cotrimoxazole prophylaxis in children from 6 weeks
- Establishment of referral linkage for palliative care and support for symptomatic mothers and their families
- Provision of nutrition, ongoing counseling and psychosocial support for both the mothers and their families
- Supporting the creation of peer-support groups for infected mothers and their families
- Development of linkage with IMCI, home-based care and orphan programs
- Empowering women and girls.

Care of the Mother

Pregnancy is a special situation which provides a unique opportunity for the prevention of vertical transmission of HIV using various interventions. The risk of transmission of HIV from an infected mother is 14–32 percent if the child is not breastfed, and 25–48 percent if the child is breastfed. More than two-thirds of such transmission occurs during labor, when the baby is exposed to maternal genital fluids, and a significant proportion occurs through breastfeeding.

The goals of management of HIV in pregnancy are dual: managing the mother's HIV status and prevention of mother-to-child transmission (PMTC).

The following points should be remembered in drug selection of ART:

- Efavirenz (EFV) should be avoided in the first trimester of pregnancy (because of risk of teratology)
- Zidovudine (AZT) should be included as one of the components of the regimen
- When NVP is used and the mother's CD4 count is >250/mm^3, close monitoring of liver function is required
- When women who are already on ART become pregnant, the benefits and risks of ART in the first trimester need to be considered. The benefits are a reduction in the risk of developing resistance and a decrease in the risk to the mother. The risk of continuing ART consists of the potential for ARV fetal toxicity, particularly in first trimester of pregnancy.

The criteria for initiating ART in pregnant women are the same as for other adults.

- WHO clinical stage 3 or 4
- WHO clinical stage 1 or 2 disease and CD4 <200 cells/mm^3
- WHO stage 3 disease and CD <350 cells/mm^3.

The initiation of ART helps prevent transmission of HIV to the newborn and also benefits the mother's own health. Once initiated, it should be continued postpartum.

The preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) is NVP, with which there has been extensive clinical experience globally. Its efficacy in reducing mother-to-child transmission has been proven. EFV may be considered after the first trimester.

The consistent use of condoms is recommended for male sex partners of all HIV infected women who are on ART. This is for the prevention of secondary transmission of HIV from/to the partner, as well as the prevention of unplanned pregnancy.

Antiretroviral treatment options recommended for HIV infected pregnant women who are eligible for treatment:

Maternal ART plus Infant ARV Prophylaxis

Mother: Maternal antepartum daily ART, starting as soon as possible irrespective of gestational age, and continued during pregnancy, delivery and thereafter. Recommended regimens include:

- AZT + Lamivudine (3TC) + NVP, or
- AZT + 3TC + EFV.

Infant: Daily NVP or twice daily AZT from birth until 4–6 weeks of age (irrespective of mode of infant feeding)

ARV prophylaxis is recommended for HIV infected pregnant women who do not need treatment for their own health (Fig. 38).

Care of the Infant at Birth

HIV infection is difficult to diagnose in infants as most infected babies appear healthy and exhibit no signs and symptoms at birth. Maternal predictors of infant disease progression include maternal viral load, maternal CD4 count (<200), rapidly progressing maternal disease, and maternal death.

Definition of HIV exposure: Infants and children born to mothers living with HIV, until HIV infection in the infant or child is reliably excluded and the infant or child is no longer exposed through breastfeeding. Care of the HIV-exposed infants should follow standard neonatal care according to safe motherhood guidelines including the following:

- Infant should be handled with gloves until all blood and maternal secretions have been washed off (early baby bathing)
- The baby's mouth and nostrils should be wiped as soon as the head is delivered
- The cord should be clamped soon after birth, but milking should be avoided. Cover the cord with gloved hand and gauze before cutting to avoid blood splattering.
- Initiate feeding within the first hour of birth according to the mother's preferred and informed choices.

Infant Feeding Choices

The mother who has chosen not to breastfeed must be able to prepare food hygienically should be advised to use cup and spoonfeeding not bottlefeeding. In case replacement feeding is not possible, exclusive breast feeding for the first six months of life with early cessation is recommended.

Breastfeeding provides the infant with all required nutrients and immunological factors that help to protect against common infections. This protection is reduced when the child is given water or any other substances during exclusive breastfeeding. Mixed feeding, i.e. breast milk and formula feeds combined, is the most hazardous form of infant feeding. Exclusive replacement feeding is the ideal option but it may not be affordable and feasible, where safe drinking water, fuel or clean utensils are scarce. In such scenario, HIV infected women should be counseled during the antenatal period about infant feeding choices and to make an informed decision. Where exclusive replacement feeding is acceptable, feasible, affordable, sustainable, and safe (AFASS), avoidance of all breastfeeding is recommended.

The risk of HIV transmission especially if combined with ART may be less than 0.5 percent, if exclusive breastfeeding is done. If family support is not present, exclusive breastfeeding may be difficult and the parents may need consistent psychosocial support.

When the child reaches the age of six months or earlier, breastfeeding should be stopped within two weeks while ensuring the comfort level of both mother and infant. At

the same time, good quality complementary foods should be introduced, ensuring adequate amounts of proteins and micronutrients.

Antiretroviral Therapy in Children

As the mortality rate is high in children living with HIV/AIDS (CLHA), hence their management is challenging.

Management of Children with HIV Infection

The management of CLHA involves a multidisciplinary approach with appropriate attention to growth, nutrition and immunization of child. It also includes treatment and prevention of opportunistic infections as well as antiretroviral therapy.

Antiretroviral Therapy

Antiretroviral therapy decreases the mortality in CLHA. Therefore, early effective ART is recommended by WHO and NACO. It is important to realize that ART is not a cure for HIV infection; however, it improves the long-term outcome of CLHA.

Pre-ART counseling: Once started ART has to be continued lifelong. Adequate counseling of caregiver regarding dose, duration, timing and side effects of drugs is mandatory before initiating ART.

Time of initiation of ART (Table 11)

- All children <18 months of age with presumptive clinical diagnosis of HIV
- All infected children <24 months of age
- In children of 24–59 months of age:
  - If WHO clinical stage 3 and 4 disease or
  - CD4 <25% or CD4 count <750 cells/m^3 whichever is lower
- For >60 months age
  - If WHO clinical stage 3 and 4 disease or
  - CD count <350/mm^3.

Presumptive Diagnosis of HIV

In HIV antibody positive cases <18 months age, where a confirmation of HIV infection is not possible because of nonavailability of virologic testing, presumptive diagnosis of severe HIV infection can be made if he/she has positive HIV antibody test and has two of the following: Severe pneumonia, severe sepsis or thrush. Other factors that support the diagnosis of severe HIV disease in an HIV seropositive infant include: Recent HIV-related maternal death; or advanced HIV disease in the mother or if the patient has CD4 <20%. Such cases should be started on ART with family being informed about possibility of HIV infection. However, the confirmation of HIV infection should be done as soon as possible using appropriate testing methods. ART should be stopped only when the diagnosis of HIV infection has been ruled out and the child is no longer exposed to infection via breastfeeding from an HIV infected mother. Presumptive diagnosis of HIV disease should not be used in children >18 months age as antibody testing establishes their HIV infection status.

Total leukocyte count (TLC) criteria for severe hiv immunodeficiency requiring initiation of art (Table 12); suggested for use in infants and children with clinical stage 2 and where cd4 measurement is not available.

ART Drugs

ART drugs belong to one of the following categories:

- Reverse transcriptase inhibitors (RTIs):
  - Nucleoside reverse transcriptase inhibitors (NsRTI/NRTI): Zidovudine (AZT), stavudine (d4T), lamivudine (3TC), Emtricitabine (FTC), didanosine (ddl), abacavir (ABC)
  - Nucleotide reverse transcriptase inhibitors (NtRTI): Tenofovir (TDF).
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs):
  - Nevirapine (NVP), efavirenz (EFV)
- Integrase inhibitors:
  - Raltegravir
- Protease inhibitors:
  - Atazanavir (ATV), ritonavir (RTV), lopinavir (LPV), saquinavir (SQV), indinavir (IDV), nelfinavir (NFV), amprenavir (APV), fosamprenavir (FPV), tipranavir, darunavir (DRV).

NRTI

Zidovudine: AZT, a thymidine analog is the prototype NRTI. It is effective against HIV1 and HIV2. After phosphorylation in the host cell, AZT selectively inhibits viral reverse transcriptase. Hence, it prevents infection of new cells by HIV.
Dose: 180–240 mg/m^2/dose twice daily with a maximum dose 300 mg twice daily.

Side-effects: It is well-tolerated by children. AZT can lead to anemia and neutropenia by causing bone marrow suppression.

Table 11: CD4 criteria for severe HIV immunodeficiency

Immunological marker[a]	Age-specific recommendation to initiate ART[b] (months)			
	<12	12–35	36–59	>60
%CD4+[c]	Treat all	<20%	<15%	<15%
CD count cells/mm^3		<750	<350	<200

a Immunological markers supplement clinical assessment and should therefore be used in combination with clinical staging. CD4 is preferably measured after stabilization of acute presenting conditions.
b ART should be initiated by these cut-off levels, regardless of clinical stage; a drop of CD4 below these levels significantly increases the risk of disease progression and mortality.
c %CD4+ is preferred for children aged <5 years.

Table 12: Total leukocyte count (TLC) criteria for severe HIV immunodeficiency

Immunological marker[a]	Age-specific recommendation to initiate ART[b]			
	<12	12–35	36–59	>60[c]
TLC (cells/mm^3)	Treat all	<3000	<2500	<2000

a Immunological markers supplement clinical assessment and should therefore be used in combination with clinical staging.
b A drop of TLC below these levels significantly increases the risk of disease progression and mortality.
c There are fewer data available on which to base recommendations on the use of TLC for decision making in children aged over 8 years.
TLC = Total lymphocytes count.

Hence, hematological monitoring and close follow-up for Hb is advised (for children on AZT based regimens—Hb test to be done at 15 days, 1 month, and 2 months).

Lamivudine (3TC): 3TC is a deoxycytidine analog and is a potent NRTI. It is effective against HIV-1, HIV-2 and Hepatitis B. Some 3TC resistant mutants also become slow growing. It is absorbed orally and is mostly excreted unchanged in urine.

Dose:

- For infants <30-days-old: 2 mg/kg/dose twice daily
- For infants >30-days-old: 4 mg/kg/dose twice daily
- For children with weight >50 kg: 150 mg twice daily.

Side effects: Nausea, vomiting, rash and rarely hepatotoxicity.

NNRTI

Nevirapine: Nevirapine (NVP) is the only NNRTI recommended for use in infants and is the component of all three drugs FDC currently available. It is well-absorbed orally and is extensively metabolized by the liver. NVP should never be used alone except when it is given for prophylaxis.

Dose: 160–200 mg/m^2 to a maximum dose of 200 mg twice daily.

Side-effects: Life-threatening side effects are hepatotoxicity and skin rash including Steven-Johnson syndrome.

Protease inhibitors (PIs): Protease inhibitors (PIs) inhibit viral replications by inhibiting the enzyme protease that helps in assembly of new viral particles.

The side effects of PIs are dyslipidemia, lipodystrophy, hepatotoxicity, hyperglycemia, coagulopathy, osteoporosis and vascular necrosis.

Lopinavir (LPV): Lopinavir is the most commonly used PI. It is effective against both HIV-1 and HIV-2. It should be given with food.

Side-effects: Abdomen pain, GI upset, and hepatotoxicity.

ART Regimen

Fixed drug combinations (FDCs) are used for ART to improve adherence.

Current ART Regimen for Use in Children under NACO

The standard first-line regimen used for ART is triple drug therapy (2NRTI + 1NNRTi).

The commonly used are:
NRTI: Zidovudine (AZT), stavudine (d4T), lamivudine (3TC), and abacavir (ABC).

NNRTI: Efavirenz (EFV) and nevirapine (NVP).

Pediatric HIV Care, Support and Treatment (CST) and Prevention of Mother-to-Child Transmission

Prevalence Rate and Trends

The burden of pediatric HIV disease is high, despite PMTCT 2.3 million children currently living with HIV. This represents 7.5% of the total number of people with HIV. 370,000 new pediatric infections were traced globally in 2009. This represents 15% of the total number of new infections each year. Mortality in untreated children is very high. 260,000 deaths in children occur with HIV annually. In absence of treatment, 50% of infected children will die before the age of 2 years. Treatment and PMTCT interventions can reduce MTCT rate to less than 5%. But in 2009 only 50% of HIV positive pregnant women had access to PMTCT. And 30% of those received suboptimal prophylaxis with sd-NVP. Overall, pregnant women have the poorest access to treatment with only 15% of those who are eligible on ART.

The Global Plan to Eliminate MTCT of HIV and Pediatric HIV

Early infant diagnosis (EID) is essential to identify infected infants. But despite significant scale-up only 15% of HIV-exposed infants have access to EID.

Treatment 2.0 is a global initiative to regalvanize efforts to achieve universal access for adults and children living with HIV and maximize the impact of HIV treatment on HIV prevention to avert 10 million deaths by 2025.

Treatment 2.0 comprises of the following five key pillars:

1. Radically simplified HIV treatment with optimized drug regimens in once daily combinations
2. Prioritize point-of-care and other simple-to-use diagnostics
3. Reduced costs of commodities
4. Improve and decentralize service delivery
5. Strengthen community mobilization

The global plan to eliminate mother-to-child transmission (eMTCT) of HIV and keep mothers and children alive is a new effort to reduce new HIV infections in children by 90% or to fewer than 40,000 new pediatric infections globally over the next 4 years. Both Treatment 2.0 and eMTCT provide an unprecedented opportunity to address the burden of pediatric HIV and AIDS.

High Prevalence in South Asia

The adult HIV prevalence at national level has continued its steady decline from estimated level of 0.41% in 2001 through 0.35% in 2006 to 0.27% in 2011. Similar consistent declines are noted among both men and women at national level in India. Declining trends in adult HIV prevalence are sustained in all the high prevalence states (Andhra Pradesh, Karnataka, Maharashtra, Manipur, Nagaland and Tamil Nadu) and other states such as Mizoram and Goa. However, some states in the North such as Odisha, Chhattisgarh, Jharkhand and Uttarakhand, some in the North West region including Punjab, Chandigarh and Delhi, and some low prevalence States of North East including Assam have shown rising trends in adult HIV prevalence.

It is important to prevent mother-to-child transmission of HIV and to provide CST to people infected or affected by HIV and AIDS.

The key risk factors are a large commercial sex industry, low levels of condom use, needle sharing among IDUs, a high number of migrants and a low level of knowledge about HIV and AIDS among MARPs, young people and the general population.

The most effective way to reach these MARPs, vulnerable women and their children is through programs that target MARPs. The linkage between the programs should be strengthened. The benefit of improving knowledge on PPTCT and pediatric HIV among young people and women of child-bearing age is of paramount importance.

BACTERIAL INFECTIONS

Enteric Fever

Epidemiology

Enteric fever is caused by *Salmonella typhi* and *S. paratyphi* which leads to severe life-threatening disease that affects communities in underserved nations. Transmission occurs through feco-oral route by contaminated foods and water. Poor sanitation and personal hygiene helps spread of the disease. Flies help in carrying the organism from infected materials like stool, urine to food materials. The disease is more common in summer and at the beginning of rainy season. The epidemiology of enteric fever is changing over the centuries and for the last few decades.

The typhoid probably existed more than 2500 years ago. The term typhoid fever derived from Greek word "typhos" which translates as putrid odor and proposed to be the leading cause of death among the inhabitants of Athens which has precipitated the golden age of Athens which existed between 448 BC and 429 BC. It is presumed that the death of Alexander the great was probably due to typhoid fever.

Although typhoid fever is currently more frequently found in developing countries due to poor public health and sanitation, it was initially was more frequently reported in western world. It was the leading cause of mortality in several important cities in west like New York, London during the end of ninetieth and beginning of twentieth century. The death rate was as high as 170 per 100,000. However, during the middle of twentieth century, improvement of sanitation and water supply in western world together with advent and use of chloramphenicol, the mortality and morbidity in western world began to decline.

Currently, it is estimated that there are 22,000,000 illnesses and 200,000 deaths per year mostly in developing and least developed countries. High incidence estimate which is more than 100/100,000 per year was found in South East Asia and South Central Asia, while low incidence which is considered as <10/100,000 was reported in Europe, North America, Australia, and New Zealand.

The burden of typhoid fever in developing countries is not scientifically understood because of poor epidemiological data due to lack of resources for diagnosis and surveillance tools. It is probably the most common acute febrile illness in middle-income and low-income countries.

Human are the only reservoir of both *S. typhi* and *S. paratyphi* and route of transmission are ingestion of contaminated food and water, patients and carrier feces. *S. paratyphi* is believed to be associated more with consumption of vendor's food. Previously *S. typhi* was the most common cause of enteric fever; however, there is an epidemiological shift over the few decades with increased incidence of *S. paratyphi* particularly in South East Asia and South Asia and currently almost 50% of enteric fever is attributable to *S. paratyphi.*

Although typhoid fever can affect all age groups but infants and children are most susceptible and vulnerable to enteric fever.

More than one-half of typhoid occurs in both hospital and community patients less than 5 years of age and more than one-fourth occurs in less than 2 years of age. Another important epidemiological shift is multidrug resistant *S. typhi* and *S. paratyphi*. The multidrug *S. typhi* (MDR typhoid) is defined as resistant to ampicillin, chloramphenicol and sulfamethoxazole. Antibiotic resistant was initially found with chloramphenicol and subsequently to beta-lactams, quinolones, and azithromycin. MDR typhoid is currently very high in Asian African countries with significant variation between regions. The high incidence of MDR typhoid ranging from 60% to 37% in Pakistan, India, Nepal, Bangladesh, Vietnam and low incidence in China, Laos and Indonesia. In USA, 13% isolates are multidrug resistant and they were more likely to have travel outside US especially to India, Pakistan and Bangladesh. In UK, most cases are imported from India and Africa.

Incubation Period

7–14 days with a range of 3–60 days.

Pathogenesis

After ingestion of *Salmonella typhi* from food and water, *S. typhi* invades the gut and multiplies in the mononuclear phagocytic cells of the reticuloendothelial system (RES). The infected macrophage travels through the mesenteric lymphnodes, into the thoracic dust to seat the liver spleen, bone marrow and lymphnodes. It then causes apoptosis of macrophages and escaped into the blood stream where the Vi antigen forms a capsule to protect the bacteria from phagocytosis.

Salmonella forms a vacuole in the host cell called salmonella containing vacuole. The bacteria actively remodel the vacuole (compartment) and establish a niche where they are capable of survival and replication. Bacteria re-enter the GI tract from the gall bladder via the bile and may invade the urinary tract and appear in the stool. About 10% patients excrete *S. typhi* for 3 months and 2–5% become long-term carriers.

Clinical Features

In the beginning of illness, patients have fever indistinguishable from fever due to other acute febrile illness like seasonal flu and dengue syndrome. In children, the classic step ladder pattern of temperature may not be present. Fever may be continuous or remittent, moderate to high grade with or without chills. Enteric fever should be suspected if fever persists beyond 7 days or earlier in endemic areas and if the patient is toxic or there are many more cases of enteric fever in the neighborhood. Patients with MDR typhoid usually appear more sick and toxic at presentation (Fig. 49). Abdomen pain, constipation, cough myalgia, anorexia, vomiting, headache may be present. A central coated tongue with clear tip is characteristic but not pathognomonic. The coated tongue of typhoid (typhoid

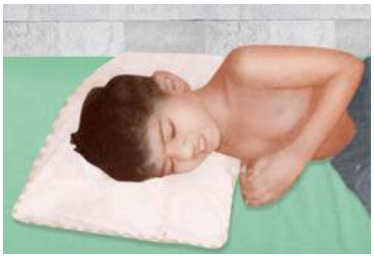


Fig. 49: Sick, anorexic child with typhoid

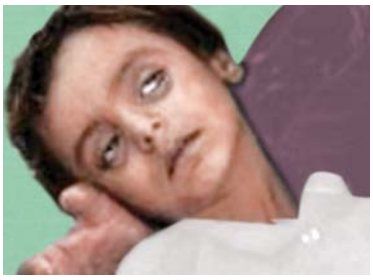


Fig. 50: Typhoid encephalopathy with impaired sensorium

tongue) usually clears when recovery takes place. The well-described rose spot (bacteremic emboli) which fades on pressure and lasts for few hours are not very commonly seen in children. Soft splenomegaly followed more commonly by hepatomegaly is noticeable from second week onward. A cecal gurgling (increased bowel sound in right iliac fossa around ileocecal junction) is frequently heard on auscultation. Coughs with rales and rhonchi may also be heard. Relative bradycardia characteristic of typhoid is not frequently found in children. Some patients may develop enteric encephalopathy, a condition characterized by altered sensorium, delirium (Fig. 50). In such conditions, patients are very toxic. Positive Kernig sign is associated with meningismus and not an indicator of meningitis in enteric fever. Even with proper antibiotic, fever may take as long as 5 days to subside by lysis, though patients feel better and toxemia might improve after 48–72 hours.

Complications

Following complications may be seen in enteric fever:

- GIT: Infrequent in children
  - Hemorrhage 1–2% in comparison to 10–15% in adult
  - Perforation: 0.5%
  - Peritonitis.

  Perforation occurs due to erosion of Peyer's patches of small intestine particularly near to ileocecal junction. Sudden drop of temperature, associated with pallor and shock herald peritonitis and perforation.
  - Hepatitis
  - Cholangitis
- CNS
  - Encephalopathy
- Respiratory
  - Bronchiolitis
  - Bronchopneumonia
- CVS
  - Myocarditis and hypotension
- Skeletal
  - Chronic osteomyelitis.

Relapse: Relapses may occur in 15% of treated cases and usually milder illness.

Diagnosis

The enteric fever should be suspected in any child when fever persisted beyond 5 days or more with hepatomegaly and splenomegaly in enteric fever endemic areas. An older child presented with toxemia and high fever for 5 days in summer or rainy season should be suspected to have typhoid fever. The best investigation for diagnosis depends on duration of fever and better remembered in Bengali surname BASU: Best result is obtained in first week by blood culture (B), in 2nd week by agglutination (A) test (Widal test), in 3rd week by stool (S) culture and in 4th week by urine (U) culture. The later two are poorly sensitive and not usually done in clinical practice.

Blood culture followed by conventional serology is the mainstay of salmonella infection diagnostic testing. Blood culture is 100% specific but has low sensitivity as only 40–60% are positive in enteric fever cases. In contrast, bone marrow aspirate culture is more than 80% sensitive and therefore is the gold standard for diagnosis of enteric fever. However, it is more invasive and may not be possible in resource poor countries due to limited expertise and expenses. Similarly stool (30–35%) and urine culture (7–10%) are also poorly sensitive. Positive culture in urine or stool may indicate either acute infection or chronic carriage.

Serologic tests have been done for more than 100 years. Positive O titer more than 1:80 and 1:160 (depending upon centers) dilution is significant in the Widal test. Rising antibody titer to O antigen is a better indicator. The Widal test has several limitations. Sensitivity is low in the first week of illness and in patients who received prior antibiotics. Specificity is low owing to anamnestic reaction, prior vaccination, cross reactivity with enterobacteriaeceae and subclinical infections in endemic areas. On the other hand, 10–15% Widal negative typhoid fever done even on the second week of illness show blood culture confirmed typhoid fever due to poor immunologic response to produce enough antibody for agglutination for Widal test. Therefore, patient showing negative Widal test after first week of febrile illness should not be ruled out of typhoid fever until blood culture report is available.

Other serological test: ELISA test for specific IgM is now available which is more sensitive and specific than Widal test.

Other Investigations

Full blood count: Nonspecific and may show leukopenia and thrombocytopenia, leukocytosis is less frequent finding.

Raised ESR and increased CRP are frequently found which is in contrast to acute viral fever which includes dengue, seasonal flu where ESR and CRP usually remain normal.

Abnormal liver function test with 2–3 folds increase of ALT and AST above normal limit may be found.

Treatment

Antibiotic treatment is started when enteric fever is clinically suspected while the result of confirmatory tests is pending. Selection of antibiotic depends on local patterns of antibiotic resistance and other factors such as severity of the disease, cost and availability of drugs. Treatment of enteric fever has become challenging in 21st century since the development of multidrug resistance (resistant to chloramphenicol, amoxicillin, sulfamethoxazole and trimethoprim) by the end of 1990s, as well as growing resistance against fluoroquinolones in last decade in some parts of Asia.

This is very relevant and carries significance as far as treatment of typhoid fever in Southeast Asia is concerned.

Fluoroquinolone (ciprofloxacin, ofloxacin, levofloxacin): Although fluoroquinolone like ciprofloxacin has the potential of joint toxicity in animal model, they are safely used in children in enteric fever. However, the use of quinolones are limited in many parts of Asia because of growing trend of high frequency typhoid with decreased susceptibility (DS) or full resistance (FS) to ciprofloxacin. During the past decades, there has been a progressive increase in the minimum inhibitory concentration (MIC) of ciprofloxacin to *S. typhi* and *S.paratyphi*. Local laboratories continue as before to report bacteria sensitive to fluoroquinolone in the face of the current MIC which are still below the susceptibility break point. Therefore, there is frequent clinical failure when drugs given do not reach desirable high MIC level to kill the bacteria. Resistance to nalidixic acid which can more easily be performed with less expertize has been suggested as a surrogate marker for high ciprofloxacin MICs that predict fluoroquinolone failure. Hence, resistance to nalidixic acid can be used to guide antibiotic therapy, especially where MIC testing is not available, i.e. if resistance to nalidixic acid is present, quinolones should not be used or if used, high-dose of ciprofloxacin and ofloxacin should be given irrespective of ciprofloxacin or ofloxacin sensitivity. If culture shows resistance to both nalidixic acid and ciprofloxacin, then it should not be used at all. The recommended dose for nalidixic acid sensitive typhoid fever is 20 mg/kg/day, while if used in nalidixic acid resistant or decreased susceptibility to ciprofloxacin (high MIC value), high-dose of ciprofloxacin (30–40 mg/kg/day) should be used, if ciprofloxacin has to be used. In decreased susceptibility or full resistance to fluoroquinolone, third-generation cephalosporin IV ceftriaxone or in uncomplicated typhoid oral cefixime are the drug of choice in the context of typhoid in countries, where fluoroquinolone resistant *S. typhi* are very high. Gatifloxacin is newer fluoroquinolone found effective in treatment of MDR typhoid. However its safety in pediatric practice is not well-established. CDC does not currently recommend its use in pediatric infectious disease. Further studies are required for its use in children with typhoid.

Cephalosporines

Ceftriaxone: Intravenous (IV) third-generation cephalosporine (ceftriaxone) is effective in treating severe/complicated MDR typhoid particularly in countries where MDR typhoid is associated with quinolone resistant or decreased quinolone sensitive typhoid. It more reliably attains optimum tissue concentration than oral cephalosporins. It is also useful in children who cannot take oral drugs. However, it is costlier than oral antibiotic and requires hospitalization and disliked by needle phobic children. Ceftriaxone is given as 80 mg/kg in single or two divided doses for 10–14 days. However, in patients showing defervescence, a switchover to oral cephalosporine (cefixime, cefpodoxime proxetil) can be used and thereby can be treated as an outpatient basis which suits many patients and caretakers. The oral drugs should be continued up to total 14 days as duration of therapy.

Cefixime: A third-generation oral cephalosporine can be used in nonsevere or noncomplicated typhoid fever and is the empirical drug of choice in the regions where frequency of both MDR and quinolone resistant typhoid is high. It can also be used in severe or complicated typhoid fever as switchover therapy after taking IV ceftriaxone for few days. Dose is higher than the conventional dose, i.e. 20 mg/kg/day in two divided doses for 2 weeks is recommended.

Currently, growing resistance to cefixime has been found in typhoid. Although found sensitive in culture sensitivity, cefixime has not been found effective in clinical cure in many children suffering from typhoid.

Cefpodoxime proxetil: This is another third-generation orally active antibiotic with similar pharmacological or antimicrobial activity like cefixime. This is also as effective as cefixime but cheaper than cefixime. The dose in typhoid fever is 16 mg/kg/day in two divided doses, double the conventional dose for 2 weeks.

Macrolide

Azithromycin: Azithromycin, a macrolide, is effective in treating typhoid and is one of the options of antibiotic in quinolone and cephalosporine resistant typhoid. However, there is also growing evidence of azithromycin resistant enteric fever in South Asia. Dose in typhoid is double the conventional dose, i.e. 20 mg/kg/day orally in single or two divided doses for 10–14 days.

Carbapenem

Due to much dependence on ceftriaxone for empirical treatment of typhoid, ceftriaxone-resistant typhoid is also encountered in clinical practice which is also resistant to ciprofloxacin. In such cases, IV carbapenem has been found effective in treating severe typhoid.

Duration of Treatment

Clinical cure and bacteriological cure do not always coincide. Clinical cure may be associated with only 20% bacteriological cure. Therefore antibiotic should be continued for 10–14 days, even there is clinical cure in order to eradicate bacteria from blood and as well as reticuloendothelial system, otherwise there will be more likelihood of relapse. On the other hand, even with bacteriological cure, there may be persistence of fever taking as long as 7 days or more to show defervescence, though patient may feel better and toxemia might improve. This is due to host immune response producing proinflammatory cytokines (IL-1, IL-2, IL-6, and IL-10) which may persist for a long-time in the circulation as well as in various organs.

Guidelines of antibiotics use in the regions where frequency of MDR and fluoroquinolone-resistant enteric fever is high

- In clinically nonsevere or uncomplicated enteric fever, third-generation oral antibiotic like cefixime is an empirical drug of choice. It is effective in both MDR and quinolone-resistant typhoid as well as multidrug sensitive and quinolone-sensitive typhoid.
- In clinically severe or complicated typhoid, IV ceftriaxone is the empirical drug of choice. Macrolides like azithromycin is the second choice as an empirical antibiotic for typhoid in such regions.
- In exceptional cases, ceftriaxone as well as quinolone-resistant typhoid, carbapenem is the drug of choice.

- Fluoroquinolone should not be used as starting drug for typhoid fever in such regions. However, if microbial culture subsequently shows *S. typhi* and *S. paratyphi* sensitive to nalidixic acid which is currently less frequently found in Indian subcontinent than quinolones like ciprofloxacin will be the better drug to switch. This is because quinolone has quick bactericidal activity, takes less time for bacteriological cure and frequency of carrier state is negligible with quinolone treatment.

In other part of the world where MDR (resistant to chloramphenicol, amoxicillin, and cotrimoxazole) typhoid and quinolone-resistant typhoid is not an issue:

In uncomplicated case, fluoroquinolone (ciprofloxacin, ofloxacin, and levofloxacin) is the drug of choice. Ciprofloxacin is given at dose of 20 mg/kg/day for 10–14 days. Alternative antibiotics are amoxicillin, chloramphenicol, and cotrimoxazole. Alongside the recent rise in resistance to quinolone, there has been return of sensitivity to first-line antibiotics such as chloramphenicol, amoxicillin, and cotrimoxazole. However, concerns of toxicity (chloramphenicol) and inconsistent report of sensitivity preclude their widespread use.

Chloramphenicol is still used in developing countries due to low cost, strain sensitivity and availability. Disadvantages are side effects including bone marrow depression, long course of treatment and development of carrier state.

In uncomplicated typhoid, in presence of MDR typhoid but sensitive to quinolone (South America, Central America, and Africa), high-dose of fluoroquinolone is the drug of choice. Other alternative drugs are cefixime and azithromycin.

In complicated or severe typhoid in presence of MDR typhoid but sensitive to quinolones (Central America, Africa and South America), high-dose of fluoroquinolones is the drug of choice. Alternative drugs are cefixime and azithromycin.

In severe or complicated typhoid secondary to sensitive strain (amoxicillin, chloramphenicol, cotrimoxazole and quinolone), treatment of choice is still fluoroquinolone. However, amoxicillin, chloramphenicol and cotrimoxazole can be used as alternatives.

It appears that both in severe and nonsevere typhoid in presence of MDR typhoid but not resistant to quinolone, quinolone is the drug of choice, where amoxicillin, chloramphenicol, co-trimoxazole, cannot be used. However, in both complicated and uncomplicated typhoid due to sensitive strain, quinolone is still the drug of choice, while other drugs like amoxicillin, chloramphenicol, and cotrimoxazole can also be used as alternative.

Uses of Steroid

Steroids are indicated if there is severe toxemia or encephalopathy. Blood transfusion is indicated if there is intestinal hemorrhage.

Prevention

Public health measures are the mainstay of prevention of typhoid fever. These are:
- Provision of safe water access
- Safe food handling practice
- Sanitation measures
- Public education
- Vaccination.

Vaccination

Partially effective typhoid vaccine is available:
- Vi polysaccharide vaccine (parenteral) and unconjugated polysaccharide vaccine: It is safe in immunocompromised host. Administered as single parenteral dose with a booster every 2/3 years. Its efficacy is about 61–80%. Indicated for children above 2 years. Protection starts 7 days after vaccination with maximum protection after 28 days.
- Ty21a (live attenuated oral vaccine): It is given orally in three to four doses every alternate day for optimal immunogenicity with an efficacy of 50–80%. It elicits protection from 10–14 days after third dose. Booster is required every 5 years. Since it should be swallowed, it is given orally. The vaccine acts by inducing local gut immunity. The vaccine is available as enteric coated capsule which should be swallowed intact and not chewed or opened. For this reason, it is suitable for children above 6 years of age. Antibiotics are contraindicated 3 days before and 7 days after vaccine administration.

Vaccine protection of typhoid in children: Typhoid is more serious condition in children than adults particularly in children below 2 years of age. The current vaccination policy with Vi polysaccharide vaccine do not cover this vulnerable age group leaving a significant number of children unprotected from typhoid. Aggressive efforts to develop typhoid fever vaccine (suitable conjugate vaccine) given to infants preferably with other childhood vaccines are urgently needed.

Non-typhoid Salmonella (NTS) Infection (Table 13)

Non-typhoid Salmonella (NTS) infection has a significant public health burden both in developing and industrialized countries even after improvement of sanitation and hygiene. According to the survey of WHO, the Salmonella species responsible for NTS are *S. enteritidis (65%), S. typhimurium (12%),* and *S. Newport (4%).* In Sub-Saharan Africa, invasive NTS is endemic and responsible for elevated morbidity and mortality in children less than 3 years of age and adults with HIV infection.

Incubation period: 6–12 hours.

Clinical features: Systemic manifestations are variable but severe in immunocompromised host. Risk factors that predispose to NTS infections are:

Table 13: Comparison between typhoid Salmonella and non-typhoid Salmonella infections

Features	Typhoid Salmonella	Non-typhoid Salmonella
Serotypes	*S. typhi* and *S. paratyphi*	Remainder strains
Reservoir	Human	Animals
Transmission	Predominantly water	Predominantly food
Location	Developing countries	Worldwide
Disease	Systemic	Local or systemic
HIV infection risk	No higher risk	Increased risk
Carrier state	1–4%	<1%

- Immunosuppression
- Decreased gastric acidity
- Recent use of antibiotic
- Changes in the intestinal flora
- Hemoglobinopathies
- Extremes of age.

Presentation

Intestinal:

Initially presents with nausea, vomiting and no bloody diarrhea. Other self-limiting symptoms are fever, chills, myalgias, arthralgia, and headache.

Extraintestinal:

- Meningitis
- Encephalopathy
- Endocarditis
- Pneumonia
- Empyema
- Abscess
- Urinary tract infection
- Osteomyelitis
- Cellulitis
- Arthritis.

DIPHTHERIA

Diphtheria is a disease caused by the organism *Corynebacterium diphtheriae*.

Microbiology

C. diphtheriae are Gram-positive rods that appear as club-shaped (wider at one end) and are arranged in V-or L-shaped manner. These rods have beaded appearance. The beads contain high energy phosphates and are seen as "metachromatic granules" under microscope.

Transmission

Humans are the only host. Both toxigenic and nontoxigenic *Corynebacterium* reside in upper respiratory tract. Infection of *Corynebacterium* spreads through airborne droplet. Another route of entry is the pre-existing skin lesion.

Pathogenesis

Diphtheria contains an exotoxin which is a single polypeptide with two functional domains. One domain mediates attachment to glycoprotein receptor of the cell membrane, while other domain shows enzymatic activity that inhibits protein synthesis by ADP ribosylation of elongation factor 2.

Clinical Features

C. diphtheriae causes diphtheria, while other *Corynebacterium spp*. (diphtheroids) are responsible for opportunistic infection.

According to site of involvement, diphtheria has several forms, i.e. faucial, laryngeal, nasal, cutaneous or conjunctival diphtheria. Among this, faucial and laryngeal diphtheria are the most dangerous forms and exert constitutional symptoms.

- Faucial diphtheria
  - Low-grade fever
  - Dysphagia
  - Drooling of saliva
  - Toxemia
  - Prostration
  - Pseudomembrane: It is a greyish-white or greyish-brown leather-like membrane which is seen on the tonsil or neighboring area, may extend to uvula, soft palate or hypopharynx (Fig. 51). It is firmly attached to underlying structure and bleeds on separation.
  - Bull neck appearance due to soft tissue edema and regional lymphadenitis (Fig. 52).
- Laryngeal Diphtheria
  - Hoarseness of voice
  - Croupy cough
  - Inspiratory stridor
  - Intercostal, subcostal and suprasternal recession during inspiration. This leads to hypoxemia.
- Nasal diphtheria: Nasal diphtheria is common in infant characterized by serosanguinous or purulent rhinitis may be associated with shallow ulcer on nose and upper lip.
- Cutaneous diphtheria: Cutaneous diphtheria is localized and toxic complications are few. It is characterized by indolent, nonhealing ulcer with grey-brown membrane.

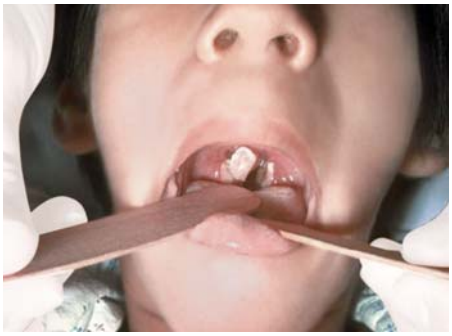


Fig. 51: Pseudomembrane in fauces

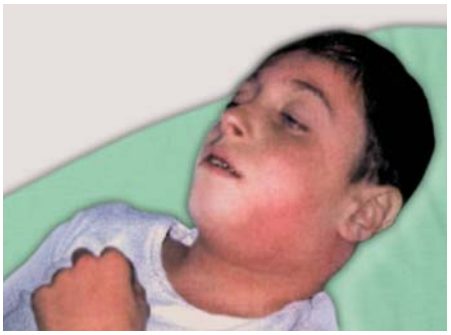


Fig. 52: Bull neck

Complications

Myocarditis

May occur any time but frequent from end of first week to 5–6 weeks. Signs of myocarditis are:

- Cardiac arrhythmia
- Cardiomegaly
- Muffled heart sound and
- Congestive cardiac failure.

Toxic Neuropathy

- May occur 10 days to 3 months after infection
- Generalized polyneuritis is mostly motor, symmetrical and more distal than proximal. Palatal palsy occurs around

second week. Characterized by nasal intonation of voice and regurgitation of food through nose. Ocular palsy occurs between third and fifth week, resulting in loss of accommodation reflex. Facial as well as laryngeal nerves may be paralyzed.

Diaphragmatic Paralysis

It may lead to difficulty in respiration.

Differential Diagnosis

Faucial Diphtheria

- Acute streptococcal pharyngitis
- Oral thrush
- Infectious mononucleosis
- Agranulocytosis
- Viral membranous tonsillitis.

Laryngeal Diphtheria

- Croup
- Laryngotracheobronchitis
- Peritonsillar abscess
- Retropharyngeal abscess
- Foreign body.

Nasal Diphtheria

- Foreign body
- Snuffle.

Diagnosis

There should be high index of suspicion. The diagnosis is suspected on the basis of clinical examination particularly the presence of a gray adherent membrane in the pharynx which bleeds on removal. The following investigation may be useful for diagnosis:

- Throat swab Klebs Loeffler bacilli (KLB)
- The diagnosis is confirmed by culture of bacilli from the swab from larynx or pharynx
- Rapid technique like the florescent antibody technique may be used to identify diphtheria bacilli quickly.

Management (Table 14)

The broad principles of management include:

- Neutralization of free circulating toxin by administration of antitoxin
- Antibiotics to eradicate bacteria
- Supportive and symptomatic treatment
- Management of complication.

Prevention and Control

The patient should be kept isolated until two successive cultures of throat and nose are negative for diphtheria bacillus. All contaminated articles should be disinfected.

Close contact should be given chemoprophylaxis with oral erythromycin 40–50/day for 7 days or injection benzathine penicillin 60,000–120,000 units IM once.

Immunization is discussed in immunization schedule.

WHOOPING COUGH (PERTUSSIS)

Pertussis is a significant cause of morbidity and mortality among the unimmunized or insufficiently immunized children. Wide introduction of pertussis vaccine has allowed a more than 90% reduction in the global incidence. However, many countries have experienced a resurgence of the disease over the past decades. Globally, pertussis is a disease that remains a public health problem in all age groups. Disease in infancy continues to be a significant problem with high-risk of serious morbidity and mortality in both developed and developing countries.

Pertussis is an acute, communicable infection of the respiratory tract caused by the Gram-negative bacterium, *Bordetella pertussis and B. parapertussis*.

Microbiology

B. pertussis is a small, Gram-negative, pleomorphic coccobacilli. They are fastidious, surviving only a few hours in respiratory secretions and requiring special media for culture.

Table 14: Management outline for diphtheria

Specific treatment	• Diphtheria antitoxin (DAT): Dose: Depends on site and severity: – Pharyngeal or laryngeal diphtheria of 48-hour duration: 20,000–40,000 unit – Nasopharyngeal lesion: 40,000–60,000 unit – Extensive disease of 3 days or more duration or patient with swelling of neck: 80,000–120,000 unit *Antibiotic* • Procaine penicillin: 300,000–600,000 unit IM 12 hourly until the patient can swallow followed by oral penicillin (125–250 mg) 6 hourly for 14 days Or • Erythromycin (if sensitive to penicillin: 25–30 mg/kg/day) for 14 days
Supportive care	• Bed rest for 2–3 weeks • Oxygen inhalation • Maintenance of nutrition • Close monitoring
Treatment of complications	• Respiratory obstruction • Humidified oxygen • Tracheotomy if severe obstruction • Myocarditis • Fluid and Salt restriction • Diuretics and digoxin may be used
Neurological complications	• Nasogastric feeding in palatal palsy • Generalized weakness due to polyneuritis is treated as GBS

Antigenic Determinant of Pertussis

B. pertussis contains a variety of components that are antigenic or biologically active.

Adhesins: Adhesion is done by the following adhesins:
- Fimbriae (FIM)
- Filamentous hemagglutinin (FHA)
- Pertactin (PRN)
- Vag8 95-kd
- BrkA 73-kd
- SphB1
- Tracheal colonization factor (TcfA).

Toxins: Toxins liberated by *B. pertussis* are:
- Pertussis toxin (PT)
- Adenylate cyclase toxin (ACT)
- Dermonecrotic toxin (DNT)
- Tracheal cytotoxin
- Lipopolysaccharide (LPS) (endotoxin).

Incubation Period

3–12 days.

Route of Transmission

Pertussis transmission occurs through respiratory droplet during coughing. Pertussis is highly contagious. Its attack rate is very high, 100% in susceptible individuals exposed to aerosol droplets at close range. In children and especially in those less than 1 year of age, pertussis causes significant morbidity and mortality.

Clinical Features

Classically, pertussis is divided into three clinical stages catarrhal, paroxysmal, and convalescent stages. Total duration of clinical features may last up to 12 weeks, also called the 100-day cough.

Catarrhal Stage (1–2 weeks)

Start with nondistinctive symptoms of congestion and rhinorrhea variably accompanied by low-grade fever, sneezing, lacrimation, and conjunctival suffusion.

Paroxysmal Stage (2–6 weeks)

- Cough: Dry, intermittent, irritative hack and evolves into the inexorable paroxysms that are the hallmark of pertussis (Fig. 53). A well-appearing, playful toddler with insignificant provocation suddenly expresses an anxious aura and may clutch a parent or comforting adult before beginning a machine-gun burst of uninterrupted cough on a single exhalation, chin and chest held forward, tongue protruding maximally, eyes bulging and watering, face purple, until coughing ceases and a loud whoop follows as inspired air traverses the still partially closed airway.
- Post-tussive emesis and exhaustion.

Convalescent Stage (≥2 weeks)

- The number, severity, and duration of episodes of cough diminish.
- *Infants <3 months of age* do not display the classic stages. Whoop infrequently occurs in infants <3 month of age. A well-appearing young infant with cough begins to choke, gasp, gag, and flail extremities, with face reddened.

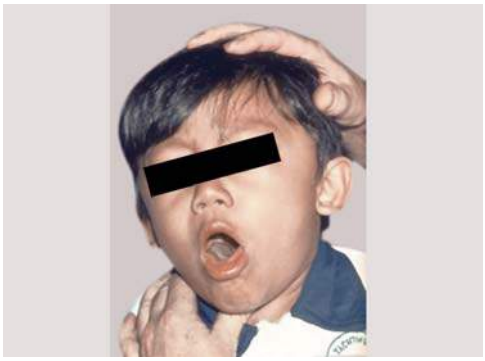


Fig. 53: Child in paroxysmal stage of whooping cough

- *Adolescents* and previously immunized children have foreshortening of all stages of pertussis.

Resurgence of Pertussis in Adolescents and Adults

As mentioned earlier, there is resurgence of pertussis in different parts of the world even with successful primary vaccination. This is due to progressive waning of both natural and vaccine-induced immunity and increased recognition of the disease at this age. Adults commonly have a persistent cough for up to 4 months often requiring medical treatment for associated morbidity. Pertussis is suspected in such conditions when other conditions causing chronic cough like pulmonary tuberculosis (TB) or hyper-responsive airway disease like bronchial asthma are excluded. Proper history, physical examination and if facilities are available relevant investigations help diagnosing pertussis in adults.

Physical Signs

Findings on physical examination generally are uninformative. Signs of lower respiratory tract disease are evident when complicated by secondary bacterial pneumonia. Conjunctival hemorrhages and petechiae may be found.

Diagnosis

Pertussis is suspected in any individual who has pure or predominant complaint of cough, especially with the absence of following features: Fever, malaise or myalgia, exanthem or enanthem, sore throat, hoarseness, tachypnea, wheezes, and rales.

Pertussis should be suspected:
- In infants <3 months of age with:
  - Gagging, gasping, apnea, cyanosis, or an apparent life-threatening event (ALTE)
- In older children with:
  - Cough illness is escalating at 7–10 days
  - Coughing episodes are not continuous
- In adolescent and adults with:
  - Persistent cough up to 4 months (new entity) particularly when alternate diagnosis like tuberculosis or bronchial asthma is excluded.

Differential Diagnosis

Differential diagnoses of paroxysmal cough are:
- Foreign body aspiration
- Endobronchial tuberculosis

- Lymphnodes pressing on trachea/bronchi
- Adenovirus infection (with serotype 1, 2, 3, and 5).

Laboratory Investigations

- Complete blood count
  - Leukocytosis (may be as high as 90%) with absolute lymphocytosis (>15 × 10^9/L)
  - Extremely low ESR
- Isolation of organism and culture
- Chest X-ray: Chest X-ray shows perihilar prominence in butterfly pattern. Parenchymal consolidation may be evident if there is secondary bacterial infection.
- Isolation of organism and culture: Organisms can be isolated in Bordet-Gengou medium by cough plate method or through nasopharyngeal aspiration
- Direct fluorescent antibody test
- Polymerase chain reaction.

Treatment

Supportive

- Infants with life-threatening episodes may require oxygen inhalation, intubation and ventilation
- Maintenance of nutrition either through nasogastric tube or parenteral.

Antibiotics

Erythromycin 40–50 mg/kg/24 hours in four divided dose for 14 days can eradicate carriage and reduce spread but does not alter the course of the disease.

Complications (Fig. 54)

- Respiratory
  - Apnea
  - Pneumonia
  - Bronchiectasis
  - Laryngospasm
  - Pneumothorax
  - Subcutaneous/interstitial emphysema
  - Otitis media
  - Secondary bacterial infection
  - Reactivation of pulmonary tuberculosis
- CNS
  - Seizure
  - Cerebral hypoxia, ischemia
  - Necrosis of brain
  - Cerebral parenchymal hemorrhage
- Others
  - Poor intake leading to malnutrition (Fig. 55)
  - Subconjunctival hemorrhage
  - Inguinal hernia
  - Rectal prolapse.

  Mortality is highest under six months of age.

Prevention

- Patient isolation for five days after starting of erythromycin therapy
- Prophylactic antibiotics (erythromycin) 40–50 mg/kg/24h in 4 divided doses for 14 days to household contacts.

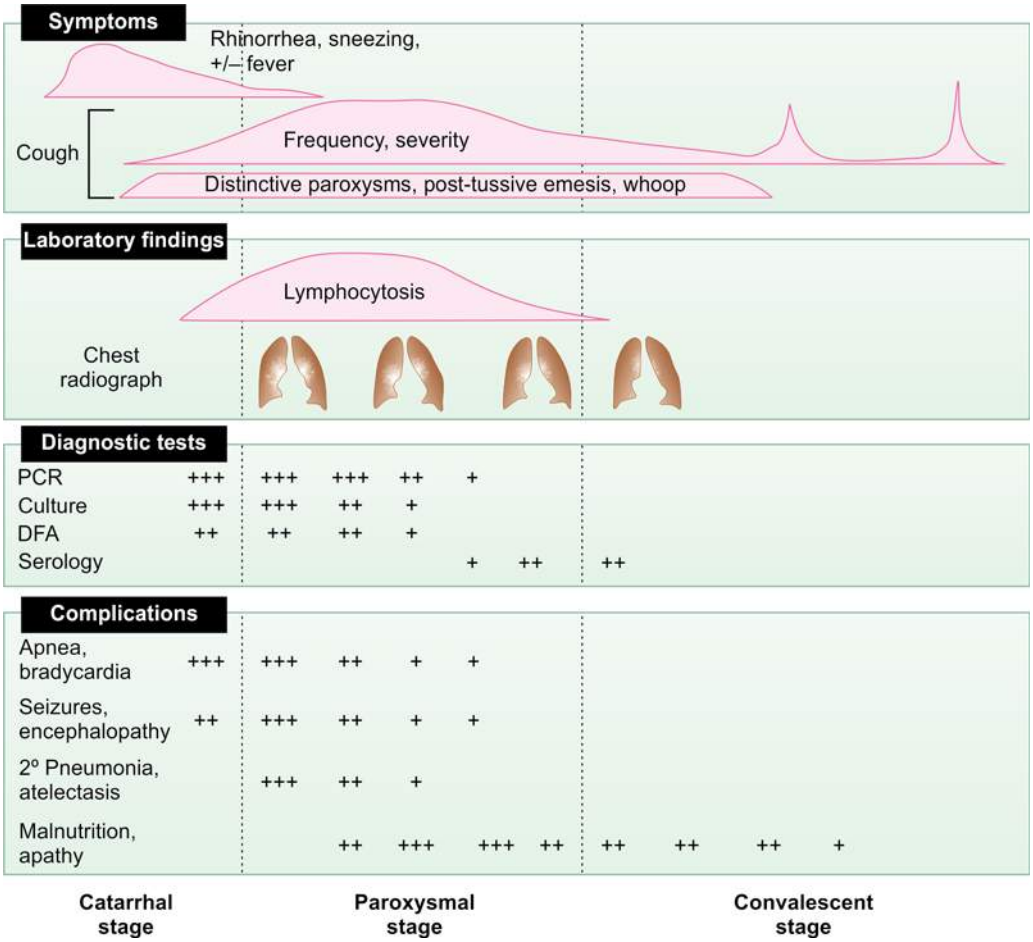


Fig. 54: Manifestation and complications of pertussis with sensitive laboratory investigations

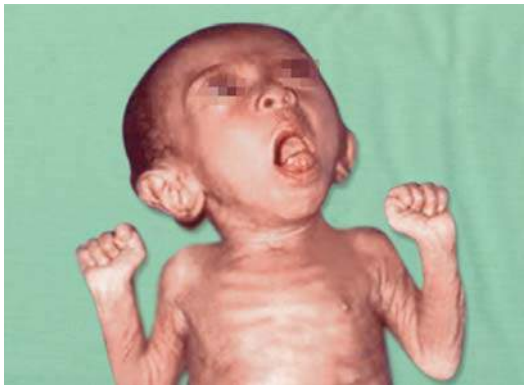


Fig. 55: A child with whooping cough with malnutrition due to poor intake and loss of energy through cough

- Vaccination with DPT in children <7 years of age who have received 3rd dose of DPT >6 months before contact or 4th dose >3 years before contact with pertussis patient should receive booster dose of pertussis vaccine.

Vaccination for Pertussis

Two types of vaccines are available:

- Whole cell pertussis vaccine in DPT (diphtheria, tetanus and whole cell pertussis) (DTPw)
- Acellular pertussis vaccine (DTPa).

In addition both whole cell (Pw) and acellular (Pa) vaccine are given in same vial (combination vaccine) with hepatitis B (HepB), *Haemophilus influenzae (Hib)* and inactivated polio vaccine (IPV). Five-component acellular pertussis vaccine is used in primary vaccination in UK and other industrialized countries. In addition, acellular pertussis vaccine is given in the same vial with diphtheria, tetanus, inactivated polio vaccine, H (DTPa-IPV-Hib, pentaxim) and as hexavalent vaccine with diphtheria, acellular pertussis, tetanus, IPV, Hepatitis B and Haemophilus influenzae (DTPa-IPV-Hib HepB, Infanrix). Both acellular and whole cell vaccines have similar efficacy, but acellular pertussis vaccine is less reactogenic, than whole cell vaccine causing less fever, less sterile inflammation at vaccination site. In fact, whole cell vaccine is replaced by acellular vaccine in Western countries like in the UK. Acellular pertussis vaccine is made from highly purified selected component of the organisms which are treated with formaldehyde and adsorbed in adjuvant. However, whole cell vaccine (DTPw/DTPw-HepB-Hib) is relatively cheaper than acellular vaccine (DTPa/DTPa-IPV Hib, DTPa-IPV-Hib-HepB) and suitable for mass vaccination in developing countries. As children grow older, they usually show more reactogenicity to DTPw vaccine and therefore booster dose at 5 years of age is preferably given by acellular pertussis containing combined vaccine. However, DTPw can also be used as booster dose in developing countries.

New Approach of Vaccine Prevention of Pertussis by Cocooning Strategy

As discussed earlier, despite well-conducted primary vaccination, containing pertussis vaccine, there is resurgence of disease over the past decades with increasing case burden observed in adolescents and adults. The major causes for this epidemiological shift are the waning of both natural and vaccine-induced immunity as well as increased recognition of disease in this group.

Studies have shown that adults are the predominant source of infection to infants. Therefore, strategies to protect infants now also emphasize vaccination of adolescents and adults particularly those with close contacts with infants like parents, all household contacts and healthcare workers, who are at high-risk of transmitting infections to infants.

A cocoon strategy in which all potential adolescents and adult contacts of infants are vaccinated with booster dose is probably most cost-effective solution. Antepartum vaccination of pregnant women and new mother are now given in the USA, and vaccination of contacts is strongly supported. Although adolescents and adults can suffer a lot from pertussis due to gradual waning of vaccine-induced or infection-induced immunity, it is the young infants who are vulnerable for catastrophic consequence of pertussis infection.

Key Points

- Globally, pertussis remains a major public health problem
- There is resurgence of pertussis in many countries.
- Pertussis continues to carry high-risk of mortality and morbidity in young infants
- Increased recognition of pertussis in adolescents and adults due to waning of immunity
- These affected adults and adolescents group carry high-risk of transmitting infection to infants
- Booster dose of vaccine of infants coming in close contact with infected adult is useful and cost-effective in decreasing incidence of whooping cough in infants—the cocooning strategy.

TETANUS

Tetanus is caused by the bacteria *Clostridium tetani*.

Epidemiology

Adequate immunization with tetanus toxoid and standard hygiene, childbirth practices, and wound care has lowered worldwide morbidity and mortality from tetanus. Having a seasonal trend, more cases of tetanus occur in summer or "wet" seasons.

Microbiology

Clostridium tetani is an anaerobic, Gram-positive, motile, spore-forming bacillus. It is usually present in soil and human and animal feces. Other clostridia present in soil and human feces are *Clostridium tetanomorphum*, *Clostridium tertium*, and *Clostridium tetanoides*. As it is a strict anaerobe that grows best at 33–37°C, it can be cultured in many different routine media used for anaerobic organisms, such as thioglycolate, casein hydrolysate, and cooked meat.

C. tetani produces two exotoxins named as tetanolysin and tetanospasmin. Tetanolysin induces hemolysis but plays no role in the disease. Tetanospasmin is responsible for all of the clinical features of the disease.

Pathophysiology

Tetanospasmin exerts its effects at the following four sites:

1. The motor end-plates in skeletal muscle: Tetanus toxin interferes with neuromuscular transmission → Inhibits

Release of acetylcholine from the nerve terminals in muscle → interferes with contraction coupling or with the mechanisms involved in contraction and relaxation → muscle contraction

2. The spinal cord: Profoundly alters the activity of the more complex polysynaptic reflexes involving interneurons → inhibition of antagonists hyperpolarization of the membranes of neurons supressed → the primary phenomena of tetanus → unchecked and uncoordinated excitatory impulses multiply and traverse reflex pathways to produce the characteristic tetanic spasms of muscle
3. The brain: Effects of tetanospasmin on the brain are the same as those on the spinal cord
4. The sympathetic nervous system (in some cases): Signs and symptoms include profuse sweating, peripheral vasoconstriction, labile hypertension, cardiac arrhythmias, tachycardia, increased output of carbon dioxide, elevated urinary concentration of catecholamines, and hypotension.

Incubation Period

3–18 days.

The distance of the site of invasion by *C. tetani* from the CNS and the length of the interval between injury and the onset of disease determines the incubation period.

Clinical Features

Tetanus occurs in two forms: Generalized and localized. Localized tetanus eventually progresses to generalized tetanus.

Localized Tetanus

Local tetanus is characterized by unyielding, persistent, painful rigidity of the group of muscles that are closer to *C. tetani* inoculation site. If there are injuries to the scalp, eye, face, ear, or neck; in conjunction with chronic otitis media; and rarely, after tonsillectomy, there may develop cephalic tetanus, a variant of localized tetanus characterized by III, IV, VII, IX, X, and XII cranial nerve palsy, either isolated or in group.

Generalized Tetanus

Lock jaw: Initially, there is masseteric spasm which leads to lock jaw (trismus) and dysphagia followed by stiffness, difficulty in chewing, drooling of saliva (due to pharyngospasm).

Risus sardonicus: Clenching of the jaws, laterally drawn lips and raised eyebrows occur due to intractable facial and buccal muscle spasm.

Opisthotonus (Fig. 56): Body assumes an arched posture (opisthotonus) due to sudden severe contraction of opposing muscle groups. This spasm persists for a few seconds to minutes with intervening repeating periods.

Fig. 56: Opisthotonus in child suffering from tetanus

- Airway obstruction due to laryngeal and respiratory muscle spasm
- Autonomic dysfunction
  - Tachycardia
  - Labile hypertension
  - Cardiac arrhythmia
  - Constipation
  - Urinary retention.

Neonatal tetanus

Usually begins 3–14 days after birth and is characterized by poor sucking and excessive crying. Other manifestations are trismus, difficulty in swallowing, other tetanic spasms, and frequently, marked opisthotonus. Causes of death from neonatal tetanus are bronchopneumonia or hemorrhage in the lungs (or both). Other nonpulmonary complications responsible for a fatal outcome are hepatitis, omphalitis, cerebral hemorrhage, thrombosis, and rupture of the renal vein.

Diagnosis

Tetanus is diagnosed clinically depending upon the spasm, opisthotonus and clear sensorium at the time of seizures.

Differential Diagnosis

- Cephalic tetanus
  - Bell palsy
  - Trigeminal neuritis, and
  - Encephalitis.
- Generalized tetanus
  - Rabies
  - Strychnine poisoning,
  - Phenothiazine reactions.
- Trismus
  - Tonsillitis
  - Peritonsillar abscess
  - Temporomandibular joint dysfunction
  - Parotitis.
- Tetany
  - Hypocalcemia
  - Hyperventilation.

Laboratory Investigations

- Complete blood count
  - Leukocytosis may or may not be present.
- Staining of wound swab and culture: Characteristic Gram-positive rods, some of which may contain subterminal spores. Anaerobic cultures of exudate or necrotic tissue may grow typical sporulated rods and vegetative forms.

Management

All cases of tetanus require hospitalization and strict isolation as the muscle spasm in a patient with tetanus can be triggered by touch, light or sound.

Goals for Management of Generalized Tetanus

- Neutralization of toxin still present in the blood before it comes in contact with the nervous system by the

administration of antitoxin as soon as the possibility of the disease is suspected or confirmed
- Surgical removal of the site of entry of the organism, when possible
  - Omphalectomy in children with neonatal tetanus
  - Hysterectomy in case of induced and often septic abortions
- Constant and meticulous nursing care
- Close monitoring of fluid, electrolyte, and caloric balance because they frequently are abnormal, especially in patients with high temperature and repeated seizures, as well as in those unable to take food or liquids because of severe trismus, dysphagia, or hydrophobia.

Treatment

Eradication of C. tetani

Penicillin G 100,000 units/kg/24h in 4–6 divided doses for 10–14 days. Alternative drugs are metronidazole, erythromycin, and tetracycline.

Neutralization of Accessible Toxin by Tetanus Immunoglobulin (TIG)

TIG neutralizes the circulatory toxin but not the already bound toxin. The dose is 500 IU intramuscular but higher dose up to 3,000–6,000 IU may be required in special situation. Alternatives are human intravenous immunoglobulin (IVIG) or tetanus antitoxin (TAT) which should be introduced after appropriate sensitivity test.

Control of Seizures

To control tetanic spasm:

Diazepam: 0.1–0.2 mg/kg every 3–6 hours IV; after achieving control dose is maintained for 2–6 weeks.

If seizure is not controlled and there is severe cough, neuromuscular blocking agents (D tubocurarine, pancuronium, vecuronium etc.) are used and patients are kept on mechanical ventilator for respiratory support.

Signs of poor prognosis

- Aspiration pneumonia
- Hypoxic brain injury
- Gap between injury and onset of trismus <1 week
- Gap between trismus and generalized spasm <3 days.

Prevention

Prevention of Maternal and Neonatal Tetanus

- Educating pregnant women concerning the danger of using contaminated materials for cutting the umbilical cord and covering the stump
- Training midwives in the application of modern techniques of obstetric asepsis
- Developing hospitals in which babies are born under strict asepsis and
- Immunizing all women of child-bearing age or, if such immunization is not possible, all who are pregnant.

To protect tetanus in women of child-bearing age and subsequently to prevent neonatal tetanus of their newborn babies, all women are given 5 doses of tetanus toxoid (TT) starting from 15 years and completed within 2 years and 7 months. The schedule is:
- First dose at 0 month
- Second dose 1 month after first dose
- Third dose 6 months after second dose
- Fourth dose 1 year after third dose
- Fifth dose 1 year after fourth dose.

In India, all pregnant women are given TT vaccine as per National immunization schedule of pregnant women in India as follows:
- TT1: Early in pregnancy
- TT2: 4 weeks after TT1
- TT booster: If received 2 TT doses in a pregnancy with last 3 years.

Immunization

Active immunization: Active immunization for tetanus is carried out in conjunction with immunization against diphtheria and pertussis in the form of diphtheria and tetanus toxoids (DTPw) and acellular pertussis vaccine adsorbed (DTPa).

Passive immunization:
- Tetanus immunoglobulin (TIG) is given to high-risk cases before onset of symptoms at a dose of 250–500 units intramuscularly.
- Tetanus toxoid (TT) is given after snake, dog or other animal bite. It should be given at a site different from TIG, if immunization status is not known.
- Tetanus prophylaxis in wound management
  - Cleaning of the wound
  - Debridement when indicated, and
  - Proper immunization.

STAPHYLOCOCCAL INFECTION

Staphylococcus (staph) are Gram-positive bacteria which are divided into coagulase positive *S. aureus* and coagulase negative *Staph. epidermidis*.

Epidemiology

S. aureus colonises in the mucous membrane of 30–50% of healthy children. The usual sites are throat, nose, rectum, axilla, vagina and perineum.

S. epidermidis is part of normal flora of skin and also found in mucosal areas.

Transmission

Staph. aureus most often transmitted by direct contact. Infection occurs when immune system is compromised and many infections are caused by endogenous organisms. Methicillin resistant *S. aureus* (MRSA) and Methicillin Resistant Coagulase negative Staphylococcus (CONS) are the important causes of nosocomial infection. CONS are the commonest cause of infection associated with implanted foreign materials like CSF shunts and IV lines.

Pathogenesis

Staphylococcus causes a variety of superficial infection and infection beyond the skin may be localized suppurative adenitis or bacteremia leading to septicemia or deep seated hematogenous infection like osteomyelitis, septic arthritis, pneumonia. Invasive disease is more common in immunocompromised individuals.

Staphylococcus produces three exotoxin-mediated syndromes:
1. Toxic shock syndrome (TSS)
2. Scalded skin syndrome (SSS)
3. Food poisoning.

CONS are the most common cause of neonatal sepsis and in immunocompromised individuals. CONS are relatively low pathogenicity species but cause indwelling infection of implanted foreign materials like central venous line and CSF shunts which can be cured by removal of the foreign body together with appropriate antibiotics.

Clinical Features

Superficial Infections

Staphylococcus is the most common cause of boils, impetigo (Fig. 57), paronychia, wound infections and styes. Atopic dermatitis complicated by secondary infection is mostly due to *Staph. aureus.* Cellulitis including periorbital cellulitis cervical lymphadenitis (Fig. 58) is also due to *Staph. aureus*.

Deep Infection

Staph aureus may cause septicemia or pneumonia, septic arthritis and osteomyelitis.

Staphylococcal Food Poisoning

Ingestion of food contaminated with preformed enterotoxin from *Staph aureus* may cause food poisoning associated with vomiting, abdominal pain with or without diarrhea which occurs usually within 6 hours of taking contaminated food.

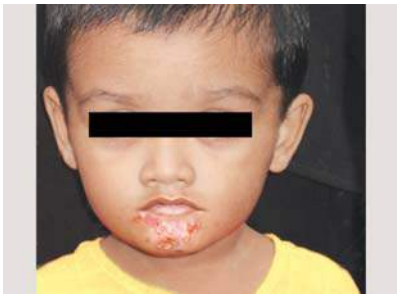


Fig. 57: Impetigo due to staphylococcal infection

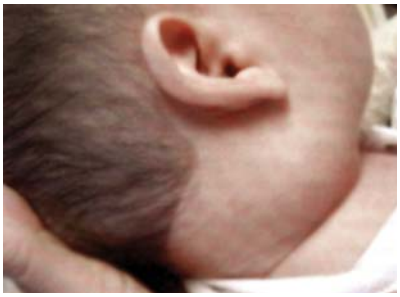


Fig. 58: Acute pyogenic cervical adenitis and abscess formation

Staphylococcal Scalded Skin Syndrome (SSSS)

This is caused by exfoliative Staph toxin, which causes separation of skin through stratum granulosum layer of the epidermis. It affects children, infants and neonates, and clinical features depend on age. In neonate, generalized exfoliation may occur (Fig. 59). Older children develop fever and malaise and scarlatiniform eruption and localized bulla in skin around eyes, nose, other part of the body with subsequent development of bullae areas of epidermis separate with gentle pressure (Nikolsky's sign) leaving denuded areas of skin which subsequently dry and heal without scarring. Treatment involves intravenous fluid management and IV antistaphylococcal antibiotics. No topical antibiotic is required.

TOXIC SHOCK SYNDROME

Toxic shock syndrome (TSS) is a febrile illness caused by Gram-positive bacteria which is characterized by sudden onset, acute, febrile illness typically rapidly progressing to shock and multiorgan failure.

Etiology

The causative agents are:
- *Staphylococcus aureus* and
- *Streptococcus pyogenes* [Lancefield group A beta-hemolytic streptococcus (GAS)]
- Non-group A streptococci may also cause TSS.

Pathogenesis

Exotoxin produced by *S. aureu*s and *S. pyogenes* mediates the development of TSS. These exotoxins are super antigen in nature. Super antigens are a family of immunomodulatory proteins. These stimulate a large number of T cells leading to massive cytokine release. Super antigen directly interact with the class II major histocompatibility complex (MHC) molecule and then with the T-cell receptor. Then activated T cells release interleukin-1 (IL-1), interleukin-2 (IL-2), tumor necrosis factor (TNF) alpha and beta and interferon (IFN) gamma in large amount. This massive amount of cytokines causes capillary leakage leading to clinical manifestation of TSS.

Risk Factors for Nonmenstrual Toxic Shock Syndrome

- Colonization with toxin producing *Staph. aureus*
- Absence of protective antitoxin antibody
- Infected site:
  - Primary *Staph. aureus* infection: Cellulitis, carbuncle, osteomyelitis, peritonsillar abscess, pneumonia

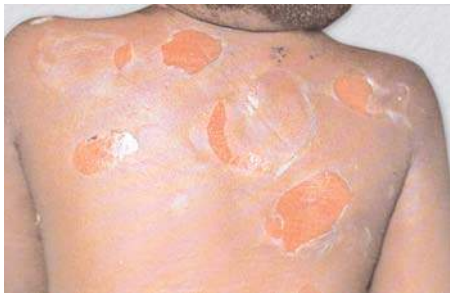


Fig. 59: Manifestation of staphylococcal scalded skin syndrome

- Wound infection after surgery: Abdominal, neurosurgery, genitourinary surgery
- Skin or mucous membrane disruption: Burns, dermatitis, varicella, superficial/penetrating trauma (insect bite, needle-stick injury)
- After surgical or nonsurgical foreign body placement: Surgical prosthesis, catheters, sponge
- No obvious focus of infection (vaginal or pharyngeal colonization).

Clinical Features

- In acute phase:
  - Abrupt onset of fever with chills, headache, myalgia, gastrointestinal symptoms like vomiting, diarrhea and abdominal pain
  - Diffuse erythroderma, flushing of body, conjunctival and pharyngeal hyperemia, hypotension and decreased urine output occurs in first 1–2 days.
- Toxin-mediated cerebral edema: Toxic encephalopathy may occur on 4–5 days if remains untreated.
- Adult respiratory distress syndrome: Occurs when there is aggressive fluid resuscitation causing pulmonary edema.
- Myocardial failure due to coronary vasculitis and arrhythmia
- Desquamation
  - Appears on trunk and extremities.
  - Starts from 10–12 days after onset of symptoms and it continues for a month.

Diagnosis

Clinical Findings

- Fever: Temperature 38.9°C
- Rash: Diffuse macular erythroderma
- Desquamation: 1–2 weeks after onset of illness, particularly on palms, soles, fingers and toes
- Hypotension:
  - Systolic blood pressure <90 mm of Hg in adults; <5th percentile by age for children <16-year-old
  - Orthostatic drop in blood pressure >15 mm of Hg from lying to sitting
  - Orthostatic syncope or orthostatic dizziness.

Organ Involvement

Organ systems involved in TSS are as follows:

- *Gastrointestinal*: Vomiting or diarrhea
- *Muscular:*
  - Severe myalgia
  - CPK greater than twice the upper limit of normal.
- *Mucous membrane:* Vaginal, oropharyngeal or conjunctival hyperemia
- *Renal:*
  - BUN/serum creatinine greater then twice the upper limit of normal or
  - >5 WBC per high power field (HPF) in urine microscopy in the absence of urinary tract infection.
- *Hepatic*: Total bilirubin, AST or ALT greater than twice the upper limit of normal.
- *Hematological***:** Platelet <100,000/mm^3.
- *CNS*: Disorientation or alteration of consciousness without focal neurological signs when fever and hypotension is absent.

Definition of TSS Given by Center for Disease Control

Probable: A case with five of the six clinical findings described above

Confirmed: A case with six of the clinical findings described above, including desquamation could occur.

The difference between staphylococcal and streptococcal TSS is mentioned in Table 15.

Differential Diagnosis

- Infection
  - Meningococcemia
  - Kawasaki disease
  - Staphylococcal scalded skin syndrome
  - Toxic epidermal necrolysis (TEN)
  - Septic shock
  - Leptospirosis
  - Rocky mountain spotted fever
- Drug reactions
  - Phenytoin
  - Pseudoephedrine
  - Quinidine
  - Sulfonamides
  - Beta-lactam antibiotics
  - Quinolone.

Laboratory Investigations

- Full blood count:
  - Neutrophilia with absolute lymphopenia
    - Decreased Hb
    - Decreased platelet count
- BUN and serum creatinine
  - Increased in renal involvement
- CPK
  - Increased in muscle involvement
- Serum calcium: Decreases (hypocalcemia)
- Blood culture: Blood culture is positive in 60–80% cases of streptococcal TSS.

Management

Supportive

Surgical therapy:

- Removal of foreign body
- Complete drainage of soft tissue or necrotizing fascitis.

Table 15: Clinical difference between streptococcal and staphylococcal TSS

	Streptococcal TSS	Staphylococcal TSS
Typical rash	Less common	Very common
Association	Soft tissue infection Varicella infection NSAID	Tampon use Surgical procedure NSAID Burns Influenza Infection
Mortality	30–60%	<3%
Positive blood culture	60–80%	Low

Specific

- Antibiotics: Total duration for antibiotic therapy is 10–14 days. Initial empiric therapy for:
  - Streptococcus: Penicillin + clindamycin
  - Staphylococcus: Cloxacillin + clindamycin

  In case of methicillin-resistant *Staph. aureus* (MRSA), the alternative choice is vancomycin. Linezolid is another drug for vancomycin alternative.
- Management of systemic complication of toxins:
  - Fluid replacement: To maintain adequate tissue perfusion, intravascular volume should be restored. Due to capillary leakage, pleural, pericardial or peritoneal effusion may occur. Monitoring for myocardial dysfunction, acute renal failure, encephalopathy, disseminated intravascular coagulation and ARDS.
  - Intravenous immunoglobulin (IVIG): If there is no significant clinical outcome, administration of IVIG may be tried as it contains neutralizing substances to streptococcus and staphylococcal super antigen.
    Dose: 400 mg/kg over several hours as single dose.
  - Corticosteroid: Not used routinely. A short course of dexamethasone or methyl prednisolone can be used in hypotensive patient who do not respond to fluid resuscitation, antibiotics and intravenous immunoglobulin.
  - Organism isolation: Isolation of organism should be carried out and susceptibility to antibiotics should be tested.

Prognosis

Death occurs in few days, if untreated, due to cardiomyopathy, arrhythmia, respiratory failure or bleeding caused by DIC. Few patients may develop fatigue, muscle weakness, chronic dermatitis, impaired memory and poorly sustained concentration. Gangrene, telogen effluvium and chronic renal failure may occur if hypotension is prolonged.

Prevention

It can be prevented by several measures:
- Proper care of surgical wound
- Postsurgical intense wound care
- Strict asepsis in operative surgery
- Use of high absorbency tampon
- Women having TSS should not use tampon.

STREPTOCOCCAL INFECTION

Streptococci are the most common organisms responsible for bacterial infection in children and infants.

Microbiology

Streptococci are Gram-positive cocci arranged in chains. Depending upon hemolysis property, they are divided into three groups, i.e. β-hemolytic (complete hemolysis), α (partial hemolysis) and γ (no hemolysis). Again on the basis of cell wall carbohydrate (c-carbohydrate), streptococci are classified into various groups: A through H and K through V.

Mode of Transmission

The organisms are transmitted through droplet infection during acute phase of illness, and also from person-to-person contact.

Pathophysiology

Antigenic Determinants

Group A streptococci:
- Inflammation-related enzymes
  - Hyaluronidase
  - Streptokinase
  - Deoxyribonuclease or DNase (streptodornase).
- Toxins
  - Erythrogenic toxin
  - Pyrogenic exotoxin A
  - Exotoxin B.
- Hemolysin
  - Streptolysin O (oxygen labile)
  - Streptolysin S (oxygen sensitive)

Group B streptococci:
- C-carbohydrate: Located at cell wall
- M protein:
  - It protrudes from outer surface of the cell and interferes with phagocytosis.
  - Depending upon production of certain M protein, Strains of *Streptococcus pyogenes* are of two groups namely rheumatogenic and nephritogenic which are responsible primarily for rheumatic fever and acute glomerulonephritis respectively.
- Polysaccharide capsule: Also prevents phagocytosis.

Streptococci produce both suppurative and nonsuppurative diseases.
- Nonsuppurative diseases are (poststreptococcal infection):
  - Acute rheumatic fever: Occurs following only sore throat after a latent period of 1–3 weeks
  - Acute glomerulonephritis (AGN): Can follow either a sore throat (latent period 1–2 weeks) or skin infection (latent period 2–3 weeks)
- Suppurative diseases are:
  - Impetigo
  - Wound infection
  - Cellulitis
  - Ecthyma
  - Otitis media
  - Bronchopneumonia
  - Septic arthritis
  - Septicemia
  - Osteomyelitis
  - Nonspecific upper respiratory tract infection
  - Acute pharyngotonsilitis
  - Retro/parapharyngeal abscess
  - Cervical adenitis
  - Meningitis
  - Vaginitis in prepubertal girls.

Laboratory Investigations

- Throat swab for Gram staining and culture
- Demonstration of rising titer of antistreptococcal antibodies
  - Antistreptolysin O (ASO)
  - Anti-DNase B.

Treatment

Penicillin is the drug of choice for streptococcal infection. Macrolides or cephalosporins are the alternative choice for patients hypersensitive to penicillin.

- Streptococcal pharyngitis/pyoderma
  Oral: Penicillin V 125–250 mg tid for 10 days.
- Sore throat
  - Less than 27 kg: 6 lacs (600,000) units of benzathine penicillin deep IM, single dose
  - More than 27 kg: 12 lacs (1,200,000) units of benzathine penicillin deep IM, single dose or
  - Oral: Amoxicillin 25–50 mg/kg/day in three divided doses or cephadroxyl 15 mg/kg/24h in two divided doses for 7–10 days.
- Severe infection
  - For pneumonia, osteomyelitis, septic arthritis
    - ◊ Benzyl or crystalline penicilline: 1–2 lacs (100,000–200,000) unit/kg/day in divided doses
  - For meningitis
    - ◊ 2–4 lacs (200,000-400,000) unit/kg/day in divided doses for 14–21 days.

In mixed infection with staphylococcus, a broad spectrum cover with co-amoxiclav is indicated.

Group B streptococcus is an important cause of perinatal infection in Western world.

SCARLET FEVER

Scarlet fever is a diffuse erythematous eruption that generally occurs in association with pharyngitis. Development of the scarlet fever rash requires prior exposure to *S. pyogenes* and occurs as a result of delayed-type skin reactivity to pyrogenic exotoxin (erythrogenic toxin, usually types A, B, or C) produced by the organism.

Organism

Group A Beta-hemolytic Streptococcus

- The rash is highly dependent upon toxin expression: pre-existing humoral immunity to the specific SPE toxin prevents the clinical manifestations of scarlet fever.
- The mode of transmission, age distribution and other epidemiologic features are similar to those for streptococcus pharyngitis.

Clinical Features

- Rash
  - One to two days after onset of sore throat, rash appears on face, sparing the area around the lips ("circumoral pallor"), and spreading to the neck, chest, back, trunk, and limbs
  - Rash is a diffuse blanching erythema with punctate elevations around hair follicles that give it a characteristic "sandpaper" feel to the touch (Fig. 60)
  - It is accentuated in skin folds by capillary hemorrhage (Pastia's lines)
  - Palms and soles are usually spared
  - Rash is followed by desquamation, which starts on the hands (Fig. 61).
- The tongue is red with prominent papillae called strawberry tongue (Fig. 62), and later becomes white called white strawberry tongue (Fig. 63).

Investigations

- Throat swab
- ASOT.

Differential Diagnosis

- Measles and other viral exanthemata
- Kawasaki's disease
- *Arcanobacterium haemolyticum* causes rash and pharyngitis.

Treatment

Oral penicillin V or parenteral benzyl penicillin.

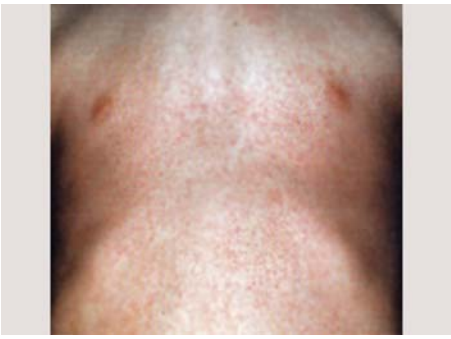


Fig. 60: Fine papular rash with sand paper or goose flesh-like appearance

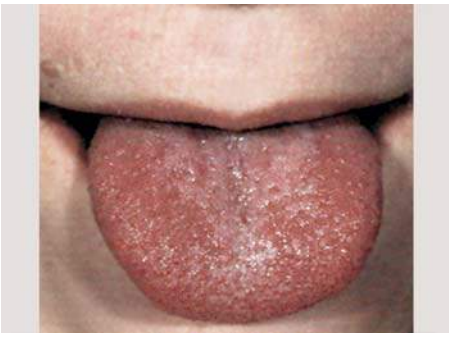


Fig. 62: Red strawberry tongue

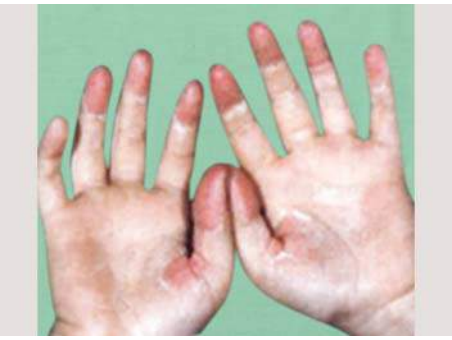


Fig. 61: Peeling of skin of fingers

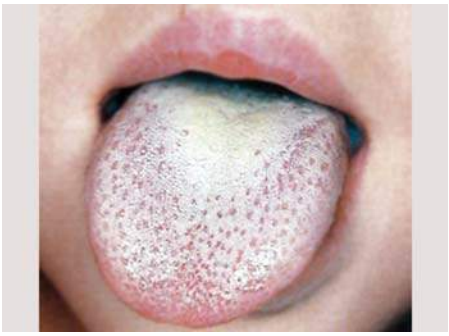


Fig. 63: White strawberry tongue

Complications

- Rheumatic fever
- Poststreptococcal glomerulonephritis
- Erythema nodosum.

STREPTOCOCCUS VIRIDANS

- Viridans Streptococci are a group of alpha-hemolytic streptococci or oral streptococci that reside on the oral mucosa of all human being.
- It is an important cause of infective endocarditis.

Microbiology

Strept. viridans are Gram-positive, catalase-negative, non-motile, nonspore-forming, facultative anaerobes.

Natural Habitat

These are predominantly upper respiratory tract normal flora; other than respiratory tract, they reside throughout the gastrointestinal tract, and in the female genital tract, occasionally in skin.

Clinical Manifestations

- Endocarditis: Viridans endocarditis is characterized by fever, malaise, anorexia, splenomegaly, altered cardiac examination, petechiae, Osler nodes, Roth spots, Janeway lesions, and splinter hemorrhages
- Bacteremia and septicemia
- Neonatal septicemia, meningitis
- Osteomyelitis and septic arthritis
- Pneumonia
- Dental caries.

Treatment

Viridans streptococci are sensitive to penicillin, though penicillin-resistant strains occur commonly in patients with long-term penicillin therapy.

Other alternatives are cephalosporines like ceftriaxone and cefotaxime.

Prevention

- Prevention of caries:
  - Fluoridation of water supplies,
  - Inclusion of fluoride in toothpaste, and
  - Modification of diet (e.g. use of sugar substitute)
- Prevention of endocarditis: Systemic antibiotic prophylaxis of patients with known endocardial defects who are undergoing dental procedures
- Prevention of sepsis in neutropenic patients with cancer:
  - Levofloxacin is used as prophylaxis but resistance is common
  - The Center for Disease Control does not recommend the routine use of penicillin prophylaxis in patients receiving bone marrow transplants.

PNEUMOCOCCAL INFECTION

Pneumococcal infection caused by *Streptococcus pneumoniae* is a capsulated organism which causes wide spectrum of infection starting from minor infection like otitis media to more severe infection like pneumonia, septicemia and meningitis.

Globally, pneumonia remains as one of the challenges to child health and survival, responsible for approximately 156 million new episodes in children under 5 years of age annually. Pneumococcal pneumonia accounts for approximately 741,000 global death annually with 28% occurring in Southeast Asia and western pacific region. In addition, pneumococcal disease is the leading cause of vaccine preventable death less than 5 years of age. India account for one out of four child death from pneumonia. About 30-40% all severe pneumonia in children likely to be pneumococcal origin. If this figure is applied to the UNICEF estimate of 410,000 childhood pneumonia death each year, than one can project that in India between 1,23,000 and 1,64,000 children aged less than 5 years die annually from pneumococcal pneumonia.

Transmission

- From person-to-person contact and by droplet
- Invasive disease occurs in association with upper respiratory tract infection.

Etiology and Pathogenesis

There are 99 serotypes of pneumococcus. The serotype distribution of pneumococcal pneumonia causing invasive pneumococcal disease (IPD) varies from country to country. Serotype 6 causes most invasive childhood infection in the USA. Data on the serotypes causing severe pneumococcal diseases in India is limited, but available data suggest that serotype 7 valent vaccine accounts for approximated 52% of severe disease under the age of 5 years. Serotype 1 causes more pneumonia than meningitis. In most common serotypes found in published study in India are included in new PCV including PCV 10 and PCV 13.

High-risk group includes: Nephrotic syndrome, asplenia (organic and functional), varicella infection, sickle-cell disease, immunodeficiency, childhood malignancies and children taking cytotoxic drugs for malignancies.

Clinical Features

The features of pneumococcal infection are:

- Upper respiratory tract infection
- Otitis media
- Conjunctivitis
- Mastoiditis
- Periorbital cellulitis
- Lobar pneumonia
- Bacteremia
- Invasive infections like septicemia, meningitis, septic arthritis, osteomyelitis, and endocarditis.

Diagnosis

- Demonstration of pneumococci on Gram stain or culture of blood, CSF, pleural or synovial fluid which are sterile normally
- Complete blood count may give the clue to bacterial infection.

Treatment

Penicillin (amoxicillin), cephalosporine (ceftriaxone, cefuroxime) and macrolides (erythromycin, clarithromycin) are used for the treatment of pneumococcal infection.

The first-line drug for pneumococcal infection in:
- Lobar pneumonia: IV cefuroxime, oral co-amoxiclav
- Bacterial meningitis: IV ceftriaxone
- Cervical lymphadenitis: IV or oral co-amoxiclav.

Prevention

Vaccination

There are two types of pneumococcal vaccines available:
1. Pneumococcal conjugate vaccine
2. Pneumococcal polysaccharide vaccine (PPV).

Seven-valent pneumococcal conjugate vaccine: Capsular polysaccharides, 7-valent, which is conjugated to protein CRM_{197}. It protects against pneumococcal meningitis, pneumonia, bacteremia and otitis media.

However, serotype distribution of *Strept. pneumoniae* causing invasive pneumonia differs in different parts of the world. Similarly, *S. pneumoniae* distribution in Southeast Asia differs from distribution in many parts of the world. Therefore, further new conjugate vaccines in addition and replacement by new valent vaccines have been discovered and now practiced in South East Asia and Western Pacific region.

New conjugate vaccines are PCV-10 and PCV-13. Both PCV-10 and PCV-13 vaccines can be given as a continuation of previously given PCV-7 conjugate vaccine.

PCV-10 conjugate vaccine: Pneumococcal, *Haemophilus influenzae* protein conjugate vaccine (PHi/DCV) which contains 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F is expected to cover 70–80% of pneumococcal strains. PCV-10 or PHiDCV is conjugated with nontypable *H. influenza (*NTHi) protein which also helps to prevent otitis media in children due to H. influenzae infection, a leading cause of chronic suppurative otitis media (CSOM) in children.

PCV-13 conjugate vaccine: It is another 13-valent conjugate vaccine which will cover more pneumococcal serotype with wide protection from invasive pneumococci.

Dose: 3 doses are given at interval of one month between doses starting from 1 and $^1/_2$ months (45 days) of age. Booster dose is recommended at 12–15 months' age.
- If the vaccine is given from 7 to 11 months of age, total number of vaccine is to be given is three. Two doses are given 4 weeks apart. Third after the 1 year of birth:
- If given between 12 and 23 months of age, two doses are given two months apart
- If given after 24 months through 5 years of age, one vaccine is given
- In addition to PCV, at risk children like nephrotic syndrome, sickle-cell disease, asplenia, children being treated with cytotoxic drugs for malignant disease including acute leukemia, a single dose of pneumococcal polysaccharide vaccine (PPV) is offered along with penicillin prophylaxis.

Pneumococcal polysaccharide vaccine (PPV): Capsular polysaccharide vaccine, not effective below 2 years of age.

Penicillin Prophylaxis

Penicillin prophylaxis is required for the patients suffering from:
- Nephrotic syndrome
- Sickle-cell disease
- Asplenia
- HIV
- Other congenital or acquired immunodeficiency.

MENINGOCOCCAL INFECTION

Neisseria meningitides is also known as meningococcus which is a commensal in the nasopharynx of humans.

Microbiology

N. meningitidis is a fastidious encapsulated, oxidase-positive, aerobic diplococcus, Gram-negative, kidney-shaped arranged in pairs. Five groups, namely A, B, C, W-135 and Y are responsible for human disease.

Mode of Transmission

Through contact with respiratory secretions or aerosol droplets.

Pathogenesis

Virulence factors of *N. meningitidis* are:
- *Polysaccharide capsule:* Prevent phagocytosis by polymorphonuclear leukocytes
- *Endotoxin (lipopolysaccharide):* Responsible for fever, shock and other pathophysiologic changes
- *Immunoglobin A (IgA) protease:* By cleaving secretary IgA, it helps in attachment of the bacterium to membrane of upper respiratory tract.

The most important diseases caused by *N. meningitidis* are meningococcemia and meningitis.

Clinical Features

The clinical outcome of meningococcal disease has a wide spectrum that range from occult bacteremia and fever to septicemia, shock and death.

The spectrum of meningococcal infections is:
- Bacteremia: Occult bacteremia presents like nonspecific viral febrile illness
- Meningococcemic sepsis without meningitis: Acute meningococcemia present with pharyngitis, fever with skin rash (Fig. 64), headache, myalgia, superficial bleeding leading to shock, DIC, acidosis, renal failure, myocardial failure, pneumonia and adrenal hemorrhage
- Meningitis with or without meningococcemia
- Meningoencephalitis.

Poor prognostic signs of meningococcal infection:
- Hyperpyrexia
- Hypotension, hypothermia, purpura fulminance, seizure or shock during presentation
- Leukopenia, thrombocytopenia, and petechiae within 12 hours of admission along with an absence of meningitis.

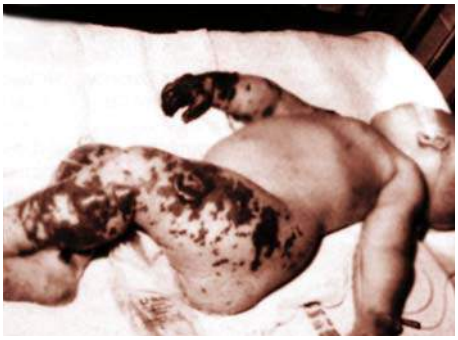


Fig. 64: Meningococcal septicemia with purpuric skin rash

Laboratory Diagnosis

- Gram staining of organisms obtained from CSF, aspirates from cutaneous lesion and other body fluids
- Isolation by culture of blood, CSF, other body fluids
- Complete blood count
- Detection of meningococcal capsular antigen in serum, CSF, joint fluid and urine by:
  - Counter immunoelectrophoresis
  - Latex agglutination test.

Treatment

If meningococcal disease is suspected, urgent antibiotic treatment is vital. In primary care, a single dose of benzylpenicillin IV or IM is recommended. In hospital, IV penicillin with a third-generation cephalosporine such as ceftriaxone is initiated after blood culture has been given. In resource poor countries, IV C penicillin can be continued in hospital is another option at a dose of 2.5–3 lac/kg/24h in 6 divided doses for 7 days.

Meningococcal septicemia is discussed in Paediatric Neurology Chapter.

Practically, meningitis is initially treated with ceftriaxone, concurrent with IV dexamethasone administration to prevent sensorineural hearing loss.

Additional management measure may include fluid restriction and other measures to reduce intracranial pressure. Treatment duration should be of 7–21 days depending upon age and clinical condition.

Mortality and Prognosis

Meningococcal disease has a higher mortality in septicemia (10%) than in meningitis (2%).

- Short-term sequelae include:
  - Shock
  - Hypothermia
  - Intractable seizure
  - SIADH
  - Subdural effusion
  - Development of purpura fulminance.
- Long-term sequelae include:
  - Sensorineural deafness
  - Epilepsy
  - Developmental disorder.

Long-term sequelae are more common in pneumococcal meningitis than meningococcal meningitis.

Prevention

Rifampicin is used as the drug for meningococcal prophylaxis of the close contacts who are suspected to be the nasopharyngeal carriers.

Dose

- Infants: 5 mg/kg/dose 12 hourly for 2 days
- Others: 10 mg/kg/dose 12 hourly for 2 days.

Vaccination

Vaccines available are:

- Meningococcus C conjugate vaccine (Men-C)
- Meningococcus AC conjugate vaccine
- Quadrivalent ACYW-135 conjugate.

The epidemiology of meningococcal disease is constantly changing with major fluctuation of disease incidence and serogroup distribution.

Meningococcal conjugate vaccine is available in many parts of Europe and given in immunization schedule. Effective vaccine against Group A and C conjugate vaccines are available but there is still no effective vaccine for group B meningococcus in Europe which accounts for the majority of isolated in the UK. There is rapid emergence of serogroup Y disease, in some countries like United States. The meningitis belt of sub-Saharan Africa continues to suffer from devastating serogroup A disease and more recently serogroup W-135 which has necessitated the quadrivalent conjugate meningococcal vaccine (ACYW-135).

HAEMOPHILUS INFLUENZAE

Haemophilus influenzae is a common cause of respiratory tract infection and meningitis in infants and young children.

Microbiology

H. influenzae is a Gram-negative, fastidious, coccobacilli. It requires special enrichment (factor X and V) for growth in culture media. The capsule of Haemophilus is of polysaccharide polyribosylribitol phosphate (PRP) in nature and antigenic. Based on capsular antigen *H. influenzae* is classified into a–f serotypes, among which b serotype is most virulent one.

Antigens of *H. influenzae* are the capsular antigen, noncapsular cell wall antigen (lipopolysaccharide) and IgA protease.

Resistance to Antibiotics

Resistance to *H. influenzae* infection depends on several host defences, like:

- Mucosal factors that prevent the organism from attaching and penetrating the respiratory epithelium
- Activation of the alternative and classical complement pathways that leads to killing of the organism and initiation of other inflammatory responses
- Induction of antibody formation
- Phagocytosis and killing by macrophages and polymorphonuclear cells in tissues, the circulation, and the reticuloendothelial system, and
- Cell-mediated immunity.

Epidemiology

Majority of children suffering from *H. influenzae* are up to 5 years of age, though the peak age ranges from 6 to 12 months. 95% of such infection is caused by b serotype. Nontypable, noncapsulated strains cause otitis media and sinusitis in newborn and children.

Transmission

Haemophilus is transmitted through direct contact and sometimes by respiratory droplet. Humans are the only natural host.

Clinical Features

Haemophilus influenzae Type b (HIb) Infection

Bacteremia: A focal infection such as meningitis, pneumonia, or cellulitis develops in approximately 30–50 percent of children with occult Hib bacteremia.

Meningitis: Most important and serious complication by invasive disease which is not distinguishable from other bacterial meningitis. Signs and symptoms are:

Particularly in young infants (nonspecific)	In older children
• Irritability • Fever • Lethargy • Poor feeding • Vomiting	• Headache, • Photophobia • Meningismus

With fulminant Hib meningitis, very rapid neurologic deterioration may occur with increased intracranial pressure, seizures, coma, and respiratory arrest.

Pneumonia: *Haemophilus influenzae* type b (Hib) pneumonia is clinically indistinguishable from other bacterial pneumonias and presents with preceding upper respiratory tract infection, fever, and cough accompanied by peripheral leukocytosis with a predominance of polymorphonuclear leukocytes.

Epiglottitis: Acute epiglottitis usually starts abruptly, with high fever, sore throat, dysphagia, and sepsis. Antecedent upper respiratory tract infection with cough occurs in approximately 50 percent of patients. There may be:

- Agitation
- Drooling due to inability of swallowing oropharyngeal secretions
- Progressive respiratory distress with tachypnea, and retractions
- Stridor
- Cyanosis
- The child may sit forward with the chin extended to maintain an open airway.

Joint infection: Septic arthritis involves a single large joint at the knee, ankle, elbow, or hip in more than 90 percent of cases. Contiguous osteomyelitis occurs in 10–20 percent.

Cellulitis: Though uncommon but when cellulitis occurs it involves the cheek (74%) (buccal cellulitis), the periorbital region, and the neck (85%) and rarely on the extremities.

Pericarditis: Hib pericarditis usually is a complication of adjacent pneumonia and is characterized by fever, an ill appearance, respiratory distress, and tachycardia.

Neonatal septicemia: *Haemophilus influenzae* is one of the causes of early onset neonatal sepsis.

Other invasive infections: Other invasive Hib infections include:

- Endophthalmitis
- CSF shunt infections
- Necrotizing fasciitis
- Pyomyositis
- Peritonitis
- Scrotal abscess
- Brain abscess
- Polyserositis
- Tenosynovitis
- Epididymitis
- Lung abscess
- Periappendiceal abscess
- Bacterial tracheitis.

Invasive disease also may be characterized by fever alone, fever with petechiae, or fever of unknown origin.

Infection due to Nontypable Haemophilus influenzae

Mucosal infections: Unencapsulated or non-Hib strains cause a variety of mucosal infections, including otitis media, sinusitis, conjunctivitis, and bronchitis. *H. influenzae* is the second leading cause of acute otitis media in adults and children.

Laboratory Investigations

- Complete blood count
- CSF study:
  - Pleocytosis (mean, 4,000–5,000 white blood cells/μL) with predominant polymorphonuclear leukocytes
  - Hypoglycorrhachia
  - Elevated CSF protein concentration.
- X-ray
  - Chest X-ray
    - May reveal Hib pneumonia: Segmental, lobar, interstitial, or diffuse.
    - Pleural or pericardial effusion may be present
    - Rarely, there may be cavitation or pneumatocoele
- Lateral neck radiograph (Fig. 65)
- Dilatation of the hypopharynx and the "thumbprint" sign (swollen epiglottis).
- Staining of specimen with methylene blue and demonstrating blue-black coccobacilli
- Isolation of organism by special culture method
- Detection of PRP in CSF/serum/urine/other relevant body fluids by:
  - Counter immunoelectrophoresis (CE)
  - Latex particle agglutination (most sensitive)
  - Enzyme-linked immunosorbent assay (ELISA).

Treatment

Haemophilus influenzae is sensitive to ampicillin, amoxicillin-clavulinic acid, chloramphenicol, third-generation cephalosporin like cefotaxim, ceftriaxone, and cefixime.

Duration of Therapy

- Pneumonia and cellulitis: 7–10 days
- Meningitis: 10–14 days
- Septic arthritis: 3 weeks.

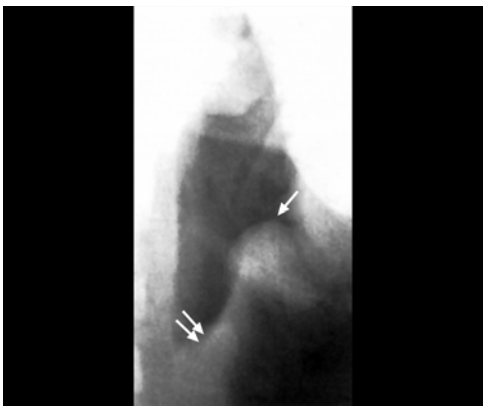


Fig. 65: Lateral neck radiograph in acute epiglottis showing swollen and thumb-shaped epiglottis (↓), the aryepiglottic folds are widened (↓↓) and the hypopharynx is distended

Complications

Hib meningitis:

- Seizures
- Cerebral edema
- Subdural effusions or empyema
- Inappropriate secretion of antidiuretic hormone (SIADH)
- Cortical infarction (often manifested by focal neurologic abnormalities)
- Cerebritis
- Intracerebral abscess
- Hydrocephalus
- Cerebral herniation rarely.

Prevention

Prophylactic Antibiotics

Rifampicin is used for chemoprophylaxis of *Haemophilus influenzae*.

Dose:

- 0–1 month: 10 mg/kg/day
- >1 month: 20 mg/kg/day (not exceeding 600 mg/day)
- Adults: 600 mg/day (pregnant women are excluded).

Vaccination

Conjugate vaccines are available as monovalent (Hib) or combined vaccine as pentavalent or hexavalent. It is available as pentavalent vaccine with diphtheria, tetanus, whole cell pertussis, Hib, hepatitis B (DTPw-Hib-HepB) and with diphtheria, tetanus, acellular pertussis, inactivated polio vaccine, Hib (DTPa-IPV-Hib) and as hexavalent vaccine with diphtheria, tetanus, acellular pertussis, inactivated polio vaccine and hepatitis B (DTPa-IPV-Hib-HepB).

Pneumococcal conjugate vaccine in prevention of Haemophilus influenzae: Some new pneumococcal conjugate vaccine like PHiDCV (tenvalent pneumococcal conjugate vaccine) is conjugated with *H. influenzae* protein D. In this process in the prevention of invasive pneumococcal disease, it also helps to prevent nontypable *H. influenzae* infection which is the leading cause of suppurative otitis media in children.

ANTHRAX

During World War I, *B. anthracis* was manufactured as an agent for biologic warfare. Anthrax is transmissible by the respiratory route, so inhalation anthrax usually is fatal. *B. anthracis* spores are stable in the environment. The accidental release of anthrax spores from a military research facility in Sverdlovsk in the former Soviet Union in 1979 resulted in at least 68 deaths from inhalational anthrax. In the United States in October and November 2001, there was an outbreak of anthrax. The spores of *B. anthracis* were disseminated by mail, resulting in 5 deaths from inhalation and 22 total cases of cutaneous and inhalational anthrax. The spores were "weaponized," or finely milled, and treated with chemicals to prevent clumping so that they dispersed when the envelopes were opened and leaked from sealed envelopes as they passed through mail sorting machines. A single anthrax strain was implicated in that outbreak.

Bacteriology

B. anthracis is a Gram-positive, spore-forming, nonmotile, aerobic bacilli. Optimal growth occurs at 36°C in nonselective media. Colonies are grey white, rough, and flat and may have comma-shaped projections caused by the outgrowth of chains of bacilli from the edges of the colony, giving it a "Medusa head" appearance.

Epidemiology

- Systemic anthrax is primarily a disease of herbivores. Humans become accidentally infected through contact with infected animals or their products
- About 20,000–100,000 human cases of anthrax occur
- Yearly worldwide. South and Central America, Southern Europe, Eastern Europe, Asia, Africa, the Caribbean and the Middle East are the highest endemic areas.

Incubation Period

- 2–5 days.

Pathogenesis (Fig. 66)

B. anthracis have two exotoxins and one antigen, edema factor (EF), lethal factor (LF) and protective antigen (PA), respectively. Neither EF nor LF is toxic alone; when they combine with protective antigen, the effect becomes devastating.

Clinical Manifestations

There are three distinct forms of anthrax. These are:

Cutaneous Anthrax

Cutaneous anthrax occurs by inoculation of anthrax spores through injured or abraded skin. The lesion occurs mainly on exposed areas like head and neck, trunk and extremities. A small, nontender, but frequently pruritic, papule develops at the site of inoculation. The lesion progresses to a serious or serosanguineous vesicle with surrounding non-pitting edema within 36 hours. Satellite vesicles, sometimes referred to as a "pearly wreath," may be seen occasionally. The lesion undergoes central necrosis, with a black eschar left behind which usually is 1–3 cm in diameter, with sharply-defined margins (Fig. 67).

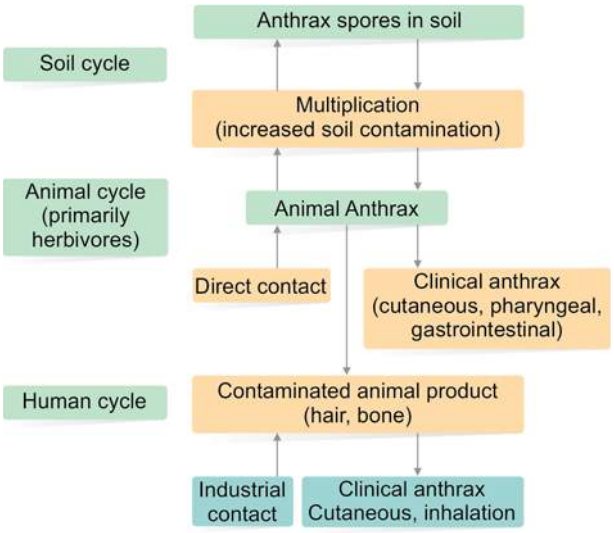


Fig. 66: Pathogenesis of anthrax

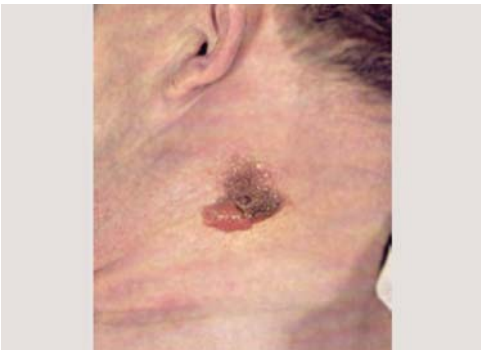


Fig. 67: Formation of black eschar over the hemorrhagic bullae

Inhalational Anthrax

- Incubation period
- Symptoms of inhalational anthrax in the initial stage are nonspecific and resemble the symptoms of a respiratory viral illness or bronchitis. These are malaise, low-grade fever, myalgia, and nonproductive cough
- After several days of illness, dyspnea and stridor initiate onset of the second stage, which usually terminates fatally within 24 hours
- Chest radiographs show a widened mediastinum with smooth borders and evidence of hemorrhagic mediastinitis and pleural effusions.

Gastrointestinal Anthrax

- Infection occurs through ingestion of contaminated meat
- Presents with oropharyngeal or intestinal manifestations
  - Oropharyngeal manifestations:
    - Fever
    - Severe sore throat
    - Neck swelling caused by edema and enlargement of cervical lymph nodes
    - Dysphagia and respiratory difficulty.
  - Intestinal manifestations:
    - Fever
    - Nausea, anorexia
    - Vomiting of blood-tinged or coffee ground-like material and melena are common symptoms and are secondary to ulceration of the intestinal mucosa
    - Diffuse abdominal pain.

Meningitis

- Anthrax meningitis is frequently associated with cutaneous disease
- Anthrax can disseminate to the meninges from any site of primary involvement. Anthrax meningitis is characterized by a sudden onset and fulminant course
- Initial symptoms include intense headache, nausea and vomiting, myalgia, chills, dizziness, and occasionally, a petechial rash
- Meningism is usually but not invariably, present because of the acuity of the course
- Progressive neurologic deterioration with delirium, convulsions and coma can occur in hours or over the course of 2–4 days.

Differential Diagnosis

- Ecthyma gangrenosum
- Rat-bite fever
- Ulceroglandular tularemia
- Plague
- Glanders
- Scrub typhus
- Rickettsialpox
- Cowpox
- Staphylococcal lymphangitis.

Laboratory Investigations

- Visualization of *B. anthracis* by smear and culture. Samples to be used are vesicular fluid or exudate from cutaneous lesions and from pleural fluid, blood and CSF in systemic infection
- Quick ELISA for screening
- Detection of antibodies against protective antigen (PA)
  - Immunofluorescent assay
  - Real-time polymerase chain reaction
  - ELISA: ELISA used to detect IgG to *B. anthracis* protective antigen is highly sensitive, has good specificity, and yields a positive result 10 days after the onset of symptoms.
- CSF study in anthrax meningitis
  Examination of cerebrospinal fluid reveals:
  - Gross or microscopic hemorrhage
  - Leukocytosis consisting predominantly of polymorphonuclear leukocytes
  - Elevated protein
  - Depressed glucose levels
  - Gram-positive rods can be seen easily on smears of cerebrospinal fluid.
- Complete blood count: Peripheral leukocytosis is a common finding, and the white blood cell count may be 60,000–80,000 cells/mm^3
- Culture
- Neuroimaging may reveal multiple hemorrhages in the ventricles, subarachnoid space, and deep grey matter.

Treatment

Supportive

- Maintenance of fluid and electrolyte balances
- Endotracheal intubation, if indicated, to maintain a patent airway, and
- Local care for cutaneous lesions
- Systemic steroids may reduce the severity of infections in patients with massive edema or meningitis.

Specific

Most of *B. anthracis* are susceptible to penicillin and tetracycline.

The initial regimen should be intravenous ciprofloxacin (400 mg every 8–12 hourly) or alternatively doxycycline (200 mg every 8–12 hourly) for treatment of inhalational anthrax, gastrointestinal anthrax, anthrax meningitis or cutaneous meningitis if there is presence of:

- Systemic signs
- Extensive edema and
- Lesions on the head and neck.

For penicillin susceptible organism, the dose is 300,000–400,000 U/kg/day intravenously or 50,000 U/kg/day orally for at least 60 days.

For bioterrorism-associated cutaneous anthrax

- Ciprofloxacin 10–15 mg/kg every 12 hours (not to exceed 1 g/day) orally until susceptibility data are available
- Doxycycline is an alternative antimicrobial for initial therapy. The dosage is 100 mg orally every 12 hours (children >8-year-old) or 5 mg/kg/day in divided doses given every 12 hours (children <8-year-old)
- Duration of treatment is 60 days
- Other antibiotics can be used are levofloxacin, gatifloxacin, penicillin, ampicillin, clindamycin, vancomycin, rifampin, imipenem, meropenem, clarithromycin, and chloramphenicol.

Prognosis

- Cutaneous anthrax of the eyelid may be complicated by ectropion of the upper lid and corneal scarring with blindness
- Immunity probably is lifelong in most patients. Second attacks of cutaneous anthrax are mild.
- Fatality rates are high for systemic anthrax and range from 50 to 100 percent for gastrointestinal anthrax to virtually 100 percent for inhalation anthrax, but children who have survived these infections have no apparent sequelae.

Prevention

- Livestock immunization programs
- Spread of anthrax in animals can be prevented by disposal of contaminated carcasses by burning and annual vaccination of livestock in known enzootic areas
- Reporting of all suspected or proven cases of anthrax to public health officials
- Isolation of hospitalized patients until the lesions are bacteriologically sterile
- Contaminated dressings and clothing must be burned or sterilized, and the patient's room must be disinfected to destroy spores.

Prevention of Inhalational Anthrax after Exposure to Spores

- *Ciprofloxacin*
  - 10–15 mg/kg orally every 12 hours (maximum of 500 mg orally 12 hourly) or
- *Doxycycline*
  - Children >8 years: 100 mg orally 12 hourly
  - Children <8 years: 5 mg/kg/day in divided orally 12 hourly
  - Along with a three-dose regimen of vaccine (given at 0, 2, and 4 weeks after exposure).

Vaccination:

Anthrax vaccine adsorbed is the only vaccine licenced. It is an aluminum hydroxide-precipitated preparation of protective antigen from an attenuated, nonencapsulated anthrax strain.

For primary immunization:

- Three subcutaneous injections at 0, 2, and 4 weeks and
- Three booster vaccinations at 6, 12, and 18 months
- Annual booster dose is given to maintain immunity.

LEPROSY

Leprosy is the disease that affects skin, mucous membrane and nerve leading to sensory and/or motor loss and deformities. Leprosy is caused by *Mycobacterium leprae*.

Microbiology

M. leprae is an acid fast, alcohol fast bacillus. It has following distinguish criteria:

- Does not grow on routine laboratory media
- Infects the footpads of mice in a characteristic manner
- Acid-fastness is extractable with pyridine
- Invades nerves of the host
- Suspensions of dead bacilli produce a characteristic pattern of reactions when injected into the skin of patients (lepromin reaction) with the various clinical forms of leprosy
- Produces the species-specific antigen phenolic glycolipid-1 (PGL-1)
- Exhibits species specific DNA sequences.

Transmission

M. leprae is transmitted through:

- Respiratory tract by inhalation of infected droplet
- Inoculation of leprosy bacilli through breach in skin by injury or tattoo.

Incubation Period

2–5 years.

Pathophysiology

After entry to human body, there occurs hematogenous spread of bacilli. The phenolic glycolipid present in its cell wall resists phagocytosis. They lodge intracellularly.

Certain human leukocyte antigens (HLA-DR) seem to be associated with specific forms of leprosy. HLA-DR2 and HLA-DR3 alleles are associated with tuberculoid disease, and HLA-DQ1 is associated with lepromatous disease.

Clinical Features

The cardinal signs of leprosy are:

- Hypoesthetic lesions of the skin
- Thickened peripheral nerve or nerves, and
- AFB in skin smears.

When other causes are excluded, presence of any one of the signs strongly supports leprosy.

Skin

- Hypopigmented patch: This may be hypopigmented or erythematous with or without change in hair, sweating
- Hypoaesthesia: In the order, temperature before pain/pressure before touch. It may be limited to skin patch (coterminous sensory loss) or symmetrical in distal extensor surfaces, not delimited to skin lesions—stocking type.

Thickened Peripheral Nerves

Peripheral nerve trunk becomes palpably thickened which may/may not be tender depending upon disease activity.

AFB in Skin Smears

AFB is demonstrable on skin-slit smear, fine needle aspiration cytology or skin/nerve biopsy.

Classification of Leprosy

Clinical Classification

- Tuberculoid leprosy (TL)
- Borderline tuberculoid (BT)
- Borderline (BB)
- Borderline lepromatous (BL)
- Lepromatous leprosy (LL)
- Indeterminate (I).

WHO classifies leprosy into two groups:

1. Paucibacillary (PB) Hansens'
   - <5 skin plus nerve lesion and/or
   - AFB not demonstrable in skin slit smear, FNAC and/or biopsy.
2. Multibacillary (MB) Hansens'
   - >5 skin + nerve lesion
   - AFB positive:

Even single AFB in any of the fields (at least 200 high-power fields are to be scanned) of skin slit smear, FNAC smear and/or histopathology whenever available.

Differential Diagnosis

- Superficial mycoses (in early leprosy)
- Leishmaniasis
- Lymphoma
- Granuloma annulare
- Granuloma multiforme (Mkar disease)
- Lupus erythematosus
- Psoriasis
- Pityriasis rosea
- Sarcoidosis
- Neurofibromatosis.

Treatment of Leprosy

WHO recommended multidrug therapy for leprosy.

- Paucibacillary disease (2 drugs) (Table 16)
  - 6 × 4 weekly cycles to be completed in maximum 9 months (otherwise inadequate)
  - No single gap to reach 4 weeks (otherwise irregular).
- Multibacillary disease (3 drugs) (Table 17)
  - 24 × 4 weekly cycles to be completed in maximum of 36 months (otherwise inadequate)
  - No single gap in treatment should extend to 4 weeks (otherwise irregular).

Treatment of Reactions

For Type I (Leprae) Reaction

- Continue multidrug therapy as per the disease type
- Add either NSAIDs, chloroquine or antioxidant

Table 16: Paucibacillary disease (2 drugs)

Drugs	Supervised by doctor/ nurse Monthly 1 dose 4 weekly	Self-administered by patients at home For the last 4 weeks
	(taken in empty stomach)	
Rifampicin	10–15 mg/kg	
Dapsone	1–2 mg/kg	<12 years 50 mg once daily or 1–2 mg/kg/day

Table 17: Multibacillary disease (3 drugs)

Drugs	Supervised by doctor/ nurse Monthly 1 dose 4 weekly	Self-administered by patients at home For the last 4 weeks
	(taken in empty stomach)	
Rifampicin	10–15 mg/kg	
Dapsone	1–2 mg/kg	<12 years 50 mg OD or 1–2 mg/kg/day
Clofazimine	<12 years: 150 mg <2 years: 50 mg	<12 years: 50 mg/ alternate day <2 years twice weekly

- Add corticosteroids if there is acute neuritis/motor loss (facial palsy) and systemic symptoms.

For Type 2 [Erythema Nodosum Leprosum (ENL)] Reaction

- Continue multidrug therapy as per the disease type
- Add either NSAIDs, chloroquine, clofazimine, or pentoxifylline.
- Add corticosteroids if there is necrotic lesions, severe systemic symptoms, neuritis specific organ/system involvement of eyes/liver/kidney/heart.

Complications

There are two types of reaction, namely type 1 and type 2 reaction.

1. **Type 1 reaction of leprosy:** It is cell-mediated delayed type of hypersensitivity reaction.
2. **Type 2 reaction or erythema nodosum leprosum (ENL) reaction:** In this type of reaction, immune complexes (antigen excess type) are precipitated or deposited in tissues, blood vessels and vascular endothelium of different organs.

Prognosis

Nearly in all patients with adequate and specific chemotherapy, prognosis is good. Due to nerve damage patients with borderline or advanced TT leprosy frequently become mutilated. Borderline patients can downgrade toward LL leprosy. In patients with LL leprosy, the disease is progressive and can cause death from laryngeal obstruction.

Tuberculosis in children is discussed in Pulmonology Chapter.

KAWASAKI DISEASE

Other name of Kawasaki Disease is acute febrile muco-cutaneous syndrome. It is a vasculitis of unknown etiology that is characterized by multisystem involvement and inflammation of small to medium-sized arteries with resulting aneurysm formation.

Epidemiology

Kawasaki disease occurs widely throughout the world, but the highest incidence is observed in Japan. Although Kawasaki Disease (KD) can affect children of all races, it is more common among children of Asian descent. KD most commonly occurs in children younger than age 5 years, with a peak between ages 2 and 3 years, and is rare in children older than age 7 years. A seasonal variability has been described with a peak between February and May, but the disease occurs throughout the year.

Clinical Features

Clinical manifestation of KD is described in three phases (Fig. 68). Aneurysmal involvement of the coronary arteries is the most important manifestation of KD.

The three phases are as follows:

1. Acute Phase
   Lasts 1 to 2 weeks.
   - Sudden onset of a high, hectic fever (≥40°C) without an apparent source
   - Conjunctival erythema
   - Conjunctivitis is bilateral and non-suppurative
   - Mucosal changes, including dry, cracked lips and a strawberry tongue (Figs 69 and 70)
   - Cervical lymphadenopathy (Fig. 69)
   - Cervical lymphadenopathy is found in 70% of children and should be greater than 1.5 cm in diameter for the purposes of diagnosis
   - Swelling of the hands and feet
   - Rash, which can vary in appearance, occurs in 80% of children with KD and may be particularly accentuated in the inguinal area and on the chest
   - Extreme irritability: Prominent, especially in infants
   - Abdominal pain and hydrops of the gallbladder
   - CSF pleocytosis, and
   - Arthritis: Particularly of medium-sized to large joints, can arise
   - Carditis: In the acute phase, may be manifested by tachycardia, shortness of breath, or overt congestive heart failure
   - Giant coronary artery aneurysms: Rare but occur most commonly in very young children, can appear during this phase.
2. Subacute Phase
   Lasts until about the fourth week.
   - Gradual resolution of fever (if untreated) and other symptoms
   - Desquamation of the skin: Particularly of the fingers and toes, appears at this point (Fig. 71)

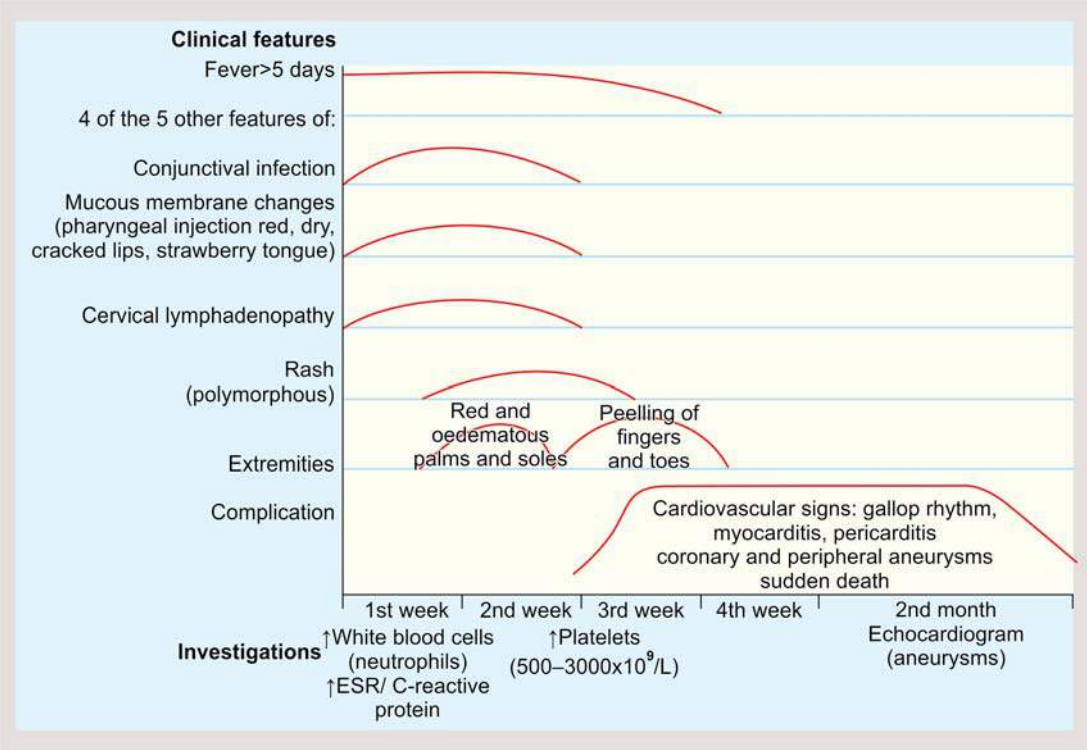


Fig. 68: Clinical features of kawasaki Disease

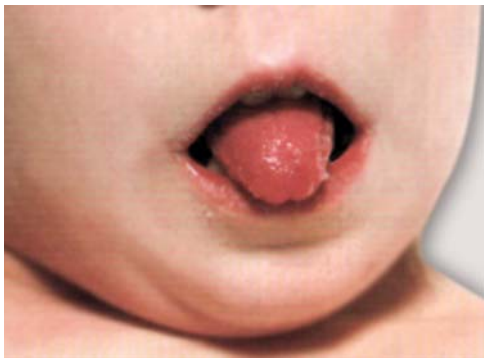


Fig. 69: Strawberry tongue and right cervical lymphadenopathy in Kawasaki disease

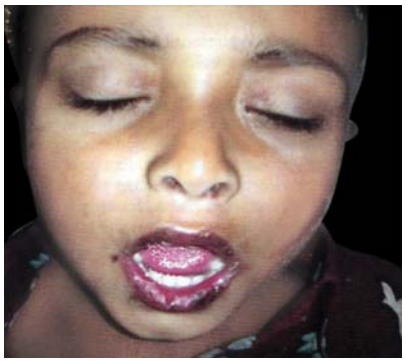


Fig. 70: Facial appearance in Kawasaki disease showing cracked lips and rash

- The platelet count, previously normal or slightly elevated, increases to a significant degree (often >1 million/mm^3)
- Onset of coronary artery aneurysms:
  - Usually appear in the subacute and convalescent phases, and pose the highest risk of sudden death
- Risk factors for development of coronary artery aneurysms include:
  - Age younger than one year and age older than nine years
  - Male sex
  - Fever ≥14 days
  - Serum sodium concentration <135 mEq/L
  - Hematocrit <35 percent
  - White cell count >12,000/mm^3.

3. **Convalescent phase**
   The convalescent phase begins with the disappearance of clinical symptoms and continues until the ESR returns to normal, usually 6 to 8 weeks after the onset of illness. Beau lines of the fingernails may appear during this phase (Fig. 72).

Differential Diagnosis

Infectious

- Scarlet fever
- Epstein-Barr virus
- Adenovirus
- Meningococcemia
- Measles
- Rubella
- Roseola infantum
- Staphylococcal toxic shock syndrome
- Scalded skin syndrome
- Toxoplasmosis
- Leptospirosis
- Rocky mountain spotted fever.

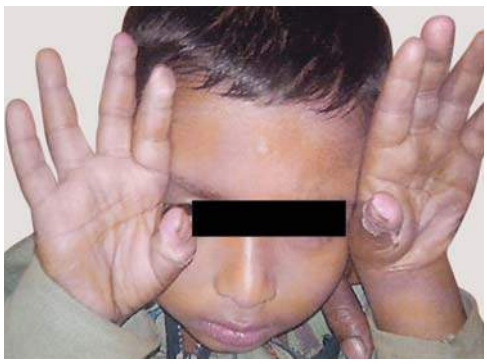


Fig. 71: Desquamation of the tips of the fingers in Kawasaki disease

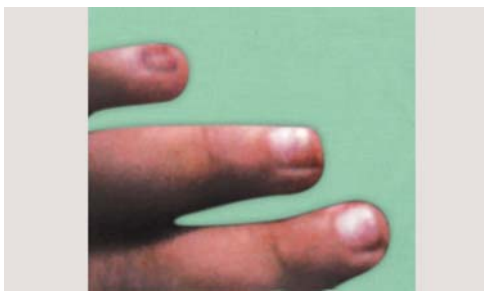


Fig. 72: Beau lines of the fingernails

Inflammatory

- Juvenile rheumatoid arthritis (systemic onset)
- Polyarteritis nodosa
- Behçet syndrome.

Hypersensitivity

- Drug reaction
- Stevens-Johnson syndrome (erythema multiforme).

Diagnosis

Criteria for Diagnosis of Kawasaki Disease

Fever of ≥5 days' duration associated with at least 4* of the following 5 changes:

1. Bilateral non-suppurative conjunctivitis
2. One of more changes of the mucous membranes of the upper respiratory tract, including pharyngeal injection, dry fissured lips, injected lips, and "strawberry" tongue
3. One or more changes of the extremities, including peripheral erythema, peripheral edema, periungual desquamation, and generalized desquamation
4. Polymorphous rash, primarily truncal
5. Cervical lymphadenopathy >1.5 cm in diameter.

Disease cannot be explained by some other known disease process.

*A diagnosis of Kawasaki disease can be made if fever and only 3 changes are present in conjunction with coronary artery disease documented by two-dimensional echocardiography or coronary angiography.

Laboratory Investigations

No laboratory studies are included among the diagnostic criteria for typical KD. However, certain findings may support the diagnosis of KD.

It is particularly important to exclude other causes of fever, notably infection.

- Blood and urine cultures
- Chest X-ray
- Complete blood count
  In the acute phase, inflammatory parameters are elevated, including WBC count, platelet count, and the ESR, which can be profoundly elevated (often >80 mm/hour)
  In the subacute phase, platelet count is markedly elevated
- CSF study: If performed to exclude infection, may show pleocytosis
- Liver function test: Hepatobiliary function may be abnormal
- Echocardiography: The development of coronary artery aneurysms is identified by performing two-dimensional echocardiograms, usually during the acute phase, at 2 to 3 weeks, and at 6 to 8 weeks. More frequent echocardiograms and, potentially, coronary angiography are indicated for patients who develop coronary artery abnormalities.

Treatment

Intravenous Immunoglobulin

A single dose of IVIG (2 g/kg over 12 hours) results in rapid defervescence and resolution of clinical illness in most patients and more importantly reduces the incidence of coronary artery aneurysms in patients with KD.

Aspirin

Aspirin is initially given in anti-inflammatory doses (80 to 100 mg/kg/day divided every 6 hours) in the acute phase.

When the fever has resolved for at least 48 hours, the dose of aspirin is decreased to antithrombotic doses (3 to 5 mg/kg/day as a single dose). This dose is continued through the subacute and convalescent phases, usually for 6 to 8 weeks, until follow-up echocardiography fails to show the presence of coronary artery aneurysms.

Complications

- Coronary artery thrombosis
- Peripheral artery aneurysm
- Coronary artery aneurysms
- Myocardial infarction
- Myopericarditis
- Congestive heart failure
- Hydrops of gallbladder
- Aseptic meningitis
- Irritability
- Arthritis
- Sterile pyuria (urethritis)
- Thombocytosis (late)
- Diarrhea
- Pancreatitis
- Peripheral gangrene.

RICKETTSIAL DISEASES

Rickettsial diseases are a group of specific communicable diseases caused by obligate intracellular gram-negative bacilli and transmitted to man by arthropod vectors (except Q fever) (Table 18).

Microbiology

Rickettsia is a group of motile, gram-negative, non-spore forming highly pleomorphic bacteria that present as cocci (0.1 micron), rods (1–4 micron) or thread-like (10 micron), obligate intracellular parasite.

Table 18: Classification of Rickettsial diseases

Disease	Rickettsial agent	Vector	Reservoir
Typhus group			
Epidemic typhus	*R. prowazekii*	Louse	Human
Murine typhus	*R. typhi*	Flea	Rodent
Scrub typhus	*R. tsutsugamushi*	Mite	Rodent
Spotted fever group			
Indian tick typhus	*R. conorii*	Tick	Dog/rodent
Rocky mountain spotted fever	*R. Rickettsii*	Tick	Dos/rodent
Rickettsial pox	*R. akari*	Mite	Mice
Other			
Q fever	*C. burnetti*	Nil	Cattle, sheep, goat
Trench fever	*Rochalimaea quintana*	Louse	Humans
Ehrlichiosis	*Ehrlicia*	Tick	Deer/dog
Anaplasmosis	*Anaplasma phagocytophilium*	Tick	Deer/dog

Mode of Transmission

Tick, mite, flea and louse are the natural hosts, reservoir and vectors of rickettsial organism (except Q fever). These maintain the infection naturally by transovarial transmission (passage of the organism from infected ticks to their progeny) and transstadial passage. Ticks transmit the infectious agent to mammalian hosts (including human) by regurgitation of saliva during feeding. Dogs and rodents serve as reservoir host for these vectors. These reservoir vectors can themselves develop the diseases and are important vehicles for bringing potentially infected vectors into the environment shared by humans.

No vector is involved in Q fever. Transmission is by inhalation of infected dust from soil previously contaminated by urine or feces of diseased animal.

Incubation Period

In children, the incubation period is 2–14 days, average 7 days.

Pathogenesis

Rickettsias invade the endothelial lining of the vasculature (microvasculitis) within various organs. The organisms either multiply within the host cell and accumulate in large numbers before lysing the cell (typhus group), or damage the host cell membrane and escape and cause influx of water (spotted fever group). Within the endothelium of small blood vessels, rickettsia proliferate, release cytokine which in turn damages the endothelial integrity followed by fluid leakage and platelet aggregation. Polymorphs and monocytes proliferation leads to focal occlusive end-arteritis. The result is microinfarction termed as "typhus nodules of Wolhbachia". This process especially affects the brain, cardiac and skeletal muscle, skin, liver, lungs and kidneys. This may also cause venous thrombosis and gangrene of the extremities.

Clinical Features of Rickettsial Diseases

Severity of manifestations varies from a mild self-limiting illness to a life-threatening disaster. There is often history of exposure to tick or close contact with an infected pet animal.

- Initially non-specific symptoms like headache, fever, anorexia, myalgia and restlessness. Headache is severe, unremitting and usually unresponsive to analgesics
- Calf muscle pain
- Gastrointestinal symptoms
  - Nausea, vomiting, diarrhea and abdominal pain
- Skin rash
  - Usually does not appear until 2–4 days of illness
  - Spotted fever: Rash is initially discrete. Pale rose and blanching macules or maculo-papules appear characteristically on the extremities including the ankles, wrist or lower limbs. Rash spreads rapidly to involve the entire body including palm and sole. After several days, rash becomes more petechial or hemorrhagic (Figs 73 and 74).
  - Scrub typhus: Scrub typhus, rash is seen initially on the trunk or may not be present at all. Painless eschar, the tachenoire, may be seen at the site of tick attachment and regional lymphadenopathy.

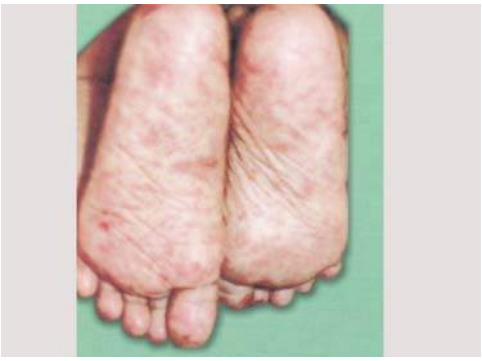


Fig. 73: Typical rickettsial rash in hands and feet (hands not shown)

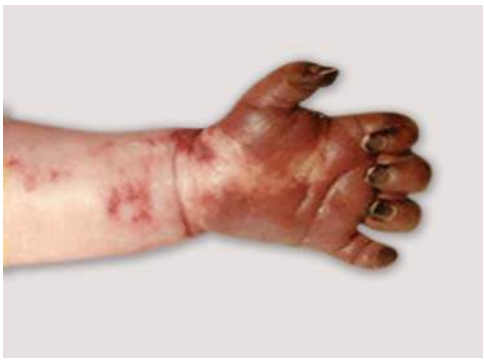


Fig. 74: Gangrenous hand in rickettsia

- CNS manifestation
  - Meningism, altered sensorium, seizures, ataxia, coma or auditory deficits.
- Pulmonary manifestations
  - Rales, infiltrates and non-cardiogenic edema.

In more severe cases, they may develop myocarditis, acute renal failure and vascular collapse.

Children with G6PD deficiency face an increased risk of developing a fulminant form of spotted fever disease.

Differential Diagnoses

- Meningococcemia
- Measles
- Entero-viral exanthem
- Others
  - Typhoid fever
  - Secondary syphilis
  - Leptospirosis
  - Toxic shock syndrome
  - Scarlet fever
  - Rubella
  - Kawasaki disease
  - Idiopathic thrombocytopenic purpura (ITP)
  - Thrombotic thrombocytopenic purpura (TTP)
  - Hemolytic uremic syndrome.
  - Henoch schonlein purpura
  - Aseptic meningitis
  - Dengue fever
  - Infectious mononucleosis
  - Anthrax.

Laboratory investigations

- Laboratory findings are nonspecific.
- Specific diagnosis of a rickettsial illness has most often been confirmed by serological testing.

Complete Blood Count

Total leukocytic count may be initially normal or low but leukocytosis develops with progression of disease.

There may be anemia, thrombocytopenia, and hypernatremia, elevated serum aminotransferase level.

CSF Study

Usually normal.

- Mononuclear pleocytosis (<10 to 300 cells) may occur.
- Elevated CSF protein (200 mg/dL) in 20% cases.

Immunofluorescence assay (IFA)

Expensive, not widely available

- IgM titer > 1:64 suggests an acute infection.
- IgG titer
  - >1:254 suggests an acute infection
  - >1:64 but >1:64 but <1:125 indicates previous infection.

Enzyme-linked immunosorbent assay

- Specific and sensitive
- It allows detection of IgG and IgM antibodies.

Weil-Felix test

This depends upon detection of antibodies to various *Proteus* species containing antigen with cross-reacting epitopes to antigens from members of genus rickettsia.

- *OX – 2*: Cross reacts with spotted fever group
- *OX – 19*: Cross reacts with typhus group
- *OX – K*: Cross reacts with scrub typhus.

Weil Felix test is an agglutination test. Significant titer is 1:80. Rising titer is more appropriate. Weil Felix test is a classical test widely available but unacceptable for accurate diagnosis because of very low specificity and sensitivity. The test can be used in developing countries where other tests are not available for diagnosis of rickettsial infection.The test should be interpreted in conjunction with history and clinical presentation.

Treatment

Doxycycline is the drug of choice. Chloramphenicol is reserved for patients with doxycycline allergy and for pregnant woman (Table 19).

Duration: at least 5–7 days and for at least 3 days until the patient is afebrile in order to avoid relapse.

Other Antibiotics

Mediterranean spotted fever

- Azithromycin (10 mg/kg/day once daily for 3 days)
- Clarithromycin (15 mg/kg/day bid for 7 days).

Prevention

No vaccine is available. Preventable measures are:

- Known ticks infested areas should be avoided
- Disinfection of dogs
- Health education of people about mode of transmission by ticks and means of personal protection is equally important.

Table 19: Drug and doses used in rickettsial diseases

Drug	Dose	Route	Freqency
Doxycycline	2.2 mg/kg/day Max mg/day	PO/IV	bid
Tetracycline	25–50 mg/kg/dose Max 2 gm/day	PO	6 hourly
Chloramphenicol	50–100 mg/kg/day Max 3 gm/day	PO	6 hourly

FUNGAL INFECTIONS

Fungal infections are one of the very important causes of the mortality and morbidity in the immunocompromised hosts. To discuss each and every fungal infection in detail is beyond the scope of this chapter, so the discussion will involve the epidemiological data and the diagnosis of invasive fungal infection. Therefore only candida infection will be discussed here. Historically, systemic Candida infections have been primarily responsible for invasive fungal infections (IFI) in the immunocompromised hosts but over the last decade mold infections have increased. The change may be secondary to either the introduction of more accurate diagnostic procedures for diagnosis of IFI or the widespread use of fluconazole prophylaxis. Fluconazole therapy targets many *Candida spp., but not Aspergillus spp.* (Table 20). Yeast infections are less common than mold infections, and Candida is still the predominant yeast pathogen.

Classification (Table 21)

Candida Species

About 12 out of 200 candida are associated with childhood fungal infection. *Candida albicans* is the most common fungi responsible for childhood mycoses.

Infection caused by candida albicans

- Superficial and mucosal infections
  - Oropharyngeal candidiasis or oral thrush
  - Diaper dermatitis characterized by confluent erythematous rash with satellite pustules

Table 20: Spectrum of activity of antifungal drugs

Amphotericin B	
	Blastomyces dermatitidis, Coccidioides immitis, Cryptococcus neoformans, Histoplasma capsulatum, Paracoccidioides brasiliensis, Sporothrix schenckii, most *Candida* species, *Aspergillus, Zygomycetes* (**not** *Candida lusitaniae, Scedosporium)*
5-Fluorocytosine	
	Only in combination therapy for *Candida, Cryptococcus neoformans*
Fluconazole	
	Most *Candida, C. neoformans, B. dermatitidis, H. capsulatum, C. immitis, Paracoccidioides brasiliensis* (**not** *Candida krusei, Candida glabrata, Aspergillus* species)
Itraconazole	
	Candida, Aspergillus, B. dermatitidis, Histoplasma capsulatum, C. immitis, P. brasiliensis (**not** *Zygomycetes)*
Voriconazole	
	Candida, Aspergillus, Fusarium, B. dermatitidis, H. capsulatum, C. immitis, Malassezia species, Scedosporium,
Caspofungin	
	Candida, Aspergillus species (***not*** *C. neoformans)*

Table 21: Classification of Human Infections Caused by the Medically Important Fungi

Clinical Category	Important fungi
Primary systemic mycoses	
Histoplasmosis	*Histoplasma capsulatum*
Coccidioidomycosis	*Coccidioides immitis*
Blastomycosis	*Blastomyces dermatitidis*
Para-coccidioidomycosis	*Paracoccidioides brasiliensis*
Opportunistic mycoses	
Invasive candidiasis	*Candida spp., Torulopsis spp.*
Invasive aspergillosis	*Aspergillus spp.*
Cryptococcosis	*Cryptococcus neoformans*
Inoculation/contamination mycoses	
Superficial mycoses	*Microsporum spp., Trichophyton spp., (dermatophytosis) a,g Epidermophyton spp.*
Pityriasis (tinea)	*Versicolor Malassezia furfur*
Sporotrichosis	*Sporothrix schenckii*

  - Oesophagitis: Occurs usually in immuno-compromised host, may or may not be associated with oral thrush
  - Chronic mucocutaneous candidiasis
  - Predisposing factors are HIV, inhaled corticosteroid use, autoimmune polyendocrinopathy–candidiasis ectodermal dystrophy, and Job syndrome
  - Vulvovaginitis—presents with pruritus, vaginal discharge, and dysuria
  - Congenital cutaneous candidiasis
    Uncommon. At birth there is a diffusely erythematous papular rash which gradually becomes pustular followed by development of vesicles and bullae.
- Invasive infection: Invasive candidiasis refers to all deep-seated *Candida* infections, including candidemia, as well as infections of single organs (liver, spleen, bone, and brain) occurring in immunocompromised conditions like hematologic malignancy, transplantation, or other primary or secondary immunodeficiency conditions.

Clinical Features

- Candidemia: Features are nonspecific and subtle and include temperature instability, lethargy, apnea, hypotension, respiratory distress, abdominal distension, hyperglycemia, and feeding intolerance.
- Meningoencephalitis: Complications arise from meningoencephalitis are granulomas, parenchymal abscesses, and vasculitis.
- Renal and urinary tract infections: Manifest as pyelonephritis, rising creatinine, hypertension, flank mass, or acute urinary obstruction from fungal mycetoma.
- Optic complications: Chorioretinal involvement or lens abscesses (rare).
- Hepatosplenic candidiasis: Hepatosplenic candidiasis (chronic disseminated candidiasis) occurs predominantly in leukemic patients but can occur in any patient at risk for candidemia. Nausea and vomiting, right upper-quadrant pain, and hepatomegaly or splenomegaly are the presenting features.
- Other disseminated infections: Endocarditis.

Table 22: Candida infections and their management strategies

Fungal infections	First-line options	Second-line options	Supportive management
Systemic Candidiasis	Fluconazole: 8–12 mg/kg daily PO/IV (some authors consider it as an 2nd line) Voriconazole (PO or IV): 4 mg/kg twice daily in children >12 years Caspofungin (IV): Day 1: 70 mg/m2 Day 2 onwards: 50 mg/m2/day	Amphotericin B lipid complex (IV): 5 mg/kg daily Liposomal amphotericin-B (IV): 3 mg/kg daily IV	Consider the use of G-CSF in neutropenic Steroids to be decreased if possible Remove CVC immediately if possible Do the fundoscopy before the treatment ends in every invasive candidiasis Treatment duration: Uncomplicated candidemia: 14 days once blood culture is sterile. Switch over to oral once blood is sterile. Complicated candidemia: duration of treat¬ment usually is 4–6 weeks depending upon the condition. Consider surgery if accessible in skin, sinus, lungs, CNS and soft tissue infections. Consider the use of G-CSF in neutropenic Steroids to be decreased if possible In a unit where we see more of zygomycosis, starting voriconazole might not be the first line. Duration is highly individual based on clinical and culture response. Once clinical response is achieved, IV can be switched over to oral voriconazole.

Laboratory Investigations

Complete blood count: Thrombocytopenia occurs in case of preterm very low birth weight babies with candidemia

- Culture
- Direct microscopic examination of specimens swabbed or scraped from surface lesions
- DNA PCR.

Antifungal Agents as an Empirical Therapy

Indication:

- Patient on antibiotics and day 5 of fever:
  - Start with liposomal amphotericin-B, dose 1–3 mg/kg daily IV or caspofungin IV, 70 mg/m^2/day on day 1 and then 50 mg/m^2/daily once (Table 22).

Antifungal Agents as Prophylaxis Therapy

Indication:

- Any patient who is undergoing hematopoietic stem cell transplant or high-dose chemotherapy:
  - Fluconazole @ dose of 8–12 mg/kg daily, is usually the first agent, or
  - Voriconazole @ dose of 1 mg/kg daily or
  - Micafungin @ dose of 1 mg/kg daily or
  - Posaconazole is recommended in patients with HSCT and graft versus host disease @ doses 200 mg three times a day and helps invasive fungal infections. Posaconazole has also shown the overall survival benefit in patients undergoing chemotherapy for AML or MDS.

Patient on azoles prophylaxis should be given polyene or echinocandin group drugs as these patients usually will be colonized with Glabrata or Krusei species.

PARASITIC INFECTIONS

Kala-azar

More than 90% visceral leishmaniasis (VL) occurs in 5 countries (Bangladesh, Brazil, India, Nepal and Sudan). In Southeast Asia region VL is reported from 96 contiguous districts bordering Bangladesh, India & Nepal. Approximately 147 million people are at risk in these three countries. Kala-azar is one of the most neglected tropical diseases affecting the poorest populations in the three endemic countries of this region, Bangladesh, India and Nepal. Approximately 200 million people in 109 districts of these countries are "at risk". Bangladesh, India and Nepal have committed themselves to collaborate in efforts to eliminate kala-azar from the Southeast Asia Region by 2015.

Epidemiology of Kala-azar

An estimated 200,000–400,000 new cases and 20,000–40,000 deaths from kala-azar occur each year. Among tropical diseases, it ranks second in mortality and fourth in loss of disability-adjusted life years. Kala-azar occurs in South Asia (India, Bangladesh and Nepal) and East Aftica (Sudan, Ethiopia, Kenya and Serratia).

Microbiology

Organism involved is *Leishmania*.

Leishmaniasis consists of a group of diseases that may affect the skin, mucous membranes and viscera caused by obligate intracellular hemoflagellates of the genus *Leishmania*. Infection is transmitted by several genera and species of blood-sucking sand flies (Fig. 75).

Three major clinical syndromes usually are recognized (Table 23):

1. Cutaneous (CL)
2. Mucocutaneous (MCL), and
3. Visceral leishmaniasis (VL).

Macrophages of the skin; mucous membranes; and spleen, liver, and bone marrow (reticuloendothelial system) are parasitized.

Life cycle of Leishmania: Leishmania organisms exist in the form of amastigotes in the mammalian host. These are

Fig. 75: Blood-sucking sandfly

Table 23: Diseases caused by various Leishmania species

Syndrome		Leishmania species
Visceral leishmaniasis		
	Old world	*L. donovani* and *L. infantum*
	New world	*L. chagasi* and *L. amazonensis*
Cutaneous leishmaniasis		
	Old world	*L. donovani, L. tropica, L. aethiopica, L. major* and *L. infantum*
	New world	*L. (L.) mexicana, L. (L.) amazonensis L. venezuelensis, L. braziliensis L. guyanensis, L. peruviana, L. panamensis* and *L. chagasi*
Mucocutaneous leishmaniasis		
	Old World	*L. aethiopica*
	New World	*L. braziliensis, L. guyanensis* and *L. panamensis*
Diffuse cutaneous leishmaniasis		
	Old world	*L. aethiopica*
	New world	*L. amazonensis and L. mexicana*
Viscerotropic leishmaniasis		
		L. (L.) tropica

obligate intracellular parasites of macrophages and the stage causing clinical manifestations of disease. The amastigote is a nonmotile, round or oval organism measuring 2–5 mm. The cytoplasm contains a central nucleus and a small rod-shaped kinetoplast associated with a flagellar rudiment. The amastigote multiplies by longitudinal binary fission and spreads to new host cells after destruction of earlier infected cells. Sandflies feeding on infected hosts ingest cells containing amastigotes, which rapidly transform into promastigotes, multiply extracellularly in the lumen of the sandfly gut, and progressively change to infective metacyclic promastigotes, which move forward to the pharynx, buccal cavity, and mouthparts. After inoculation into the host skin by an infected sandfly, metacyclic promastigotes rapidly attach to and enter cells of the mononuclear phagocyte system, where they transform into amastigotes that reside and multiply within phagolysosomes. The promastigote form is 15–20 mm in length and 1.5–3.5 mm in width, has a single anterior flagellum, contains a single central nucleus, and has a kinetoplast at the anterior end.

Clinical Manifestations

The onset generally is insidious.

- Intermittent low-grade fever, sweating: Fever can be continuous, intermittent, or remittent, often reaching 40°C. In some patients, the course of disease is more rapid (e.g. high fever, chills, malaise), and death can occur within a few weeks
- Anemia: Invariably present and often is severe, is secondary to multiple factors, including hypersplenism, autoimmune mechanisms, bone marrow infiltration, and coexistent iron deficiency
- Weakness
- Weight loss despite good appetite
- Progressive enlargement of the liver and spleen
- The primary lesion at the site of inoculation appears as a small papule or a cutaneous ulcer, but the lesion usually has resolved by the time the patient seeks medical attention
- The patient often is weak and emaciated, with marked abdominal distension secondary to enlargement of the spleen and liver
- Femoral and inguinal lymph nodes are moderately enlarged, but generalized lymphadenopathy is rare
- Darkening of the skin, especially on hands, feet, abdomen and forehead, commonly occurs in light-skinned patients giving rise to the name *kala-azar* (black fever) in India. In dark-skinned people, warty eruptions can develop. Jaundice, petechiae, ecchymoses, and purpura also can occur
- Oral and nasopharyngeal mucosal lesions occasionally occur in patients in India, East Africa, and Sudan appearing as nodules or ulcers of the gum, palate, tongue, or lip
- Lesions of the nasal mucosa can cause perforation of the septum.

The different forms of the disease are distinct in their causes, epidemiologic features, transmission, and geographic distribution.

Localized cutaneous leishmaniasis (LCL or oriental sore): It presents as one or a few papular, nodular, plaque like, or ulcerative lesions that are usually located on exposed skin, such as the face and extremities (Fig. 76).

Diffuse cutaneous leishmaniasis (DCL): It is a rare form of leishmaniasis caused by organisms of the *L. mexicana* complex in the New World, and *L. aethiopica* in the Old World.

DCL manifests as large nonulcerating macules, papules, nodules, or plaques that often involve large areas of skin and

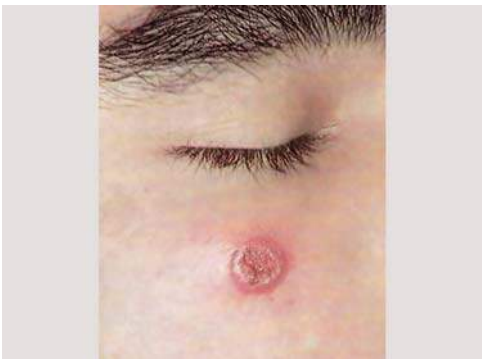


Fig. 76: Cutaneous leishmaniasis isolated, crateriform, ulcerating nodule on right cheek

may resemble lepromatous leprosy. The face and extremities are most commonly involved. Dissemination from the initial lesion usually takes place over several years. It is thought that an immunologic defect underlies this severe form of cutaneous leishmaniasis.

Mucosal leishmaniasis (ML) espundia: It is an uncommon but serious manifestation of leishmania infection resulting from hematogenous metastases to the nasal or oropharyngeal mucosa from a cutaneous infection. Patients with ML most commonly have nasal mucosal involvement and present with nasal congestion, discharge, and recurrent epistaxis.

Visceral leishmaniasis (VL kala-azar): It typically affects children of 5 years of age in the New World (*L. chagasi*) and Mediterranean region (*L. infantum*) and older children and young adults in Africa and Asia (*L. donovani*).

Oligosymptomatic children present with mild constitutional symptoms (malaise, intermittent diarrhea, poor activity tolerance) and intermittent fever; most will have a mildly enlarged liver.

Classic clinical features of kala-azar typically develop approximately 6 months after the onset of the illness. The features are high fever, marked splenomegaly, hepatomegaly, and severe cachexia.

At the terminal stage, there is:

- Massive hepatosplenomegaly (Fig. 77)
- Gross wasting
- Profound pancytopenia
- Anemia, severe enough to lead to heart failure
- Bleeding episodes, especially frequent epistaxis
- Jaundice
- Edema, and
- Ascites.

Post Kala-azar dermal leishmaniasis (PKDL): A small percentage of patients previously treated for VL develop diffuse skin lesions, a condition known as post-kala-azar dermal leishmaniasis (PKDL). These lesions may appear during or shortly after therapy (Africa) or up to several years later (India). The lesions of PKDL are hypopigmented, erythematous, or nodular and commonly involve the face and torso. They may persist for several months or for many years (Fig. 78).

Case Definition for Reporting

Kala-azar: An individual in an endemic area who has fever for more than two weeks, splenomegaly and "rK-39" test is positive should be diagnosed as a case of kala-azar.

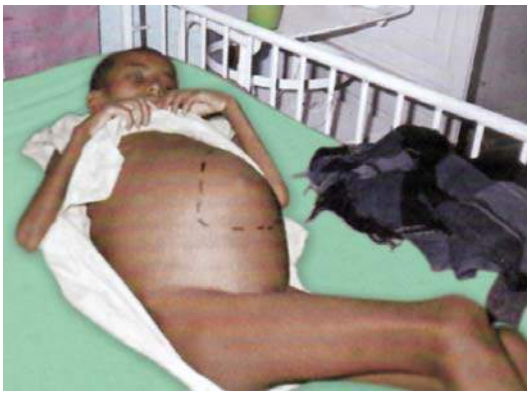


Fig. 77: Massive splenomegaly in visceral leishmaniasis

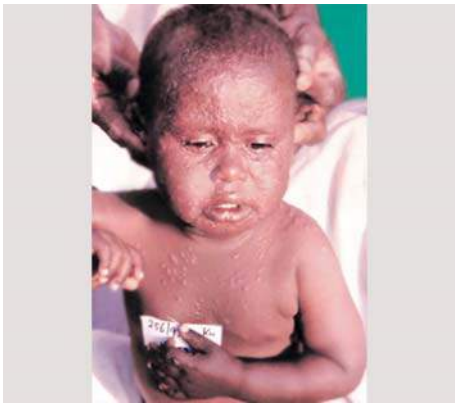


Fig. 78: Skin lesion of PKDL

Kala-Azar Treatment Failure (KATF): A case earlier diagnosed as kala-azar, took complete treatment within one year, reappearance of symptoms of Kala-azar and any positive lab evidence of parasite from bone marrow or splenic aspirate.

Post Kala-azar Dermal Leishmaniasis (PKDL): Multiple hypopigmented areas on skin without loss of sensation with any of one or combination of a) macule, b) papule, c) nodule, in a patient with history of kala-azar with high index of suspicion based on residing /traveling in endemic area and rK-39 test positive. Clinically suspected PKDL with rK-39 negatives needs tissue diagnosis.

Laboratory investigations

Definitive diagnosis of leishmaniasis is established by the demonstration of amastigotes in tissue specimens or isolation of the organism by culture. Amastigotes can be identified in Giemsa stained tissue sections, aspirates, or impression smears in about half of the cases of LCL but only rarely in the lesions of ML. Culture of a tissue biopsy or aspirate, best performed by using Novy-McNeal-Nicolle (NNN) biphasic blood agar medium.

In patients with VL, smears or cultures of material from splenic, bone marrow, or lymph node aspirations will show LD bodies (Fig. 79) which are usually diagnostic. Splenic aspiration has a higher diagnostic sensitivity.

Other investigations are:

- DAT
- rK-39 test or equivalent
- PCR.

Treatment of Kala-azar

Three drugs are recommended for the first-line treatment of kala-azar. These are:

- Drug of choice for first line: Miltefosine
- Alternate choice:
  - Paromomycin
  - Liposomal amphotericin B.
- Second-line drugs are:
  - Sodium stibogluconate (SSG)
  - Amphotericin B deoxycholate.

First-line Treatment of KA

Miltefosine:

Dose: 2.5 mg/kg body weight, twice daily by mouth in the morning and evening after meal for 28 days.

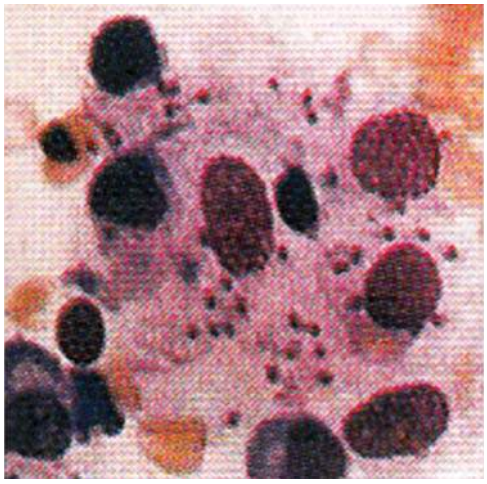


Fig. 79: Bone marrow examination showing LD bodies

In case of missed doses, the scheduled 28 doses may be taken within a period of 35 days. The daily dose should never exceed the recommended amount.

The doses should be calculated as follows:

- >12 years and weighing ≥25 kg: 100 mg (1 capsule of 50 mg in morning and evening)
- <12 years but weighing ≤25 kg: 50 mg (1 capsule of 50 mg in the morning after meal)
- 2–12 years: 2.5 mg/kg body weight (in two divided doses after meal).

If exact dose cannot be administered, the closest 10 mg increment will be chosen at the dose. Rounding will be done as follows:

- If calculation comes to <5 to round the dose down
- If calculation comes to >5 to round the dose up.

Paromomycin:

Dose: 11 mg/kg of paromomycin base (equivalent to 15 mg/kg/day paromomycin sulfate) for 21 days.

Route: Intramuscular (IM) at gluteal muscles.

Liposomal amphotericin B:

Dose: A total dose of 10–15 mg/kg divided into 3–5 doses given either daily or alternate days through intravenous infusion with 5% dextrose solution 500 mL. Initially, it should be started at 5 drop/min for half an hour, then 10 drop/min for half an hour and then rest within 4–6 hours.

Second-line of Treatment of Kala-azar

Amphotericin B deoxycholate:

Dose: 1 mg/kg body weight daily or alternate days IV (in 5% dextrose solution 500 mL) for 15 days.

Sodium stibogluconate:

Dose: 20 mg/kg body weight daily for 30 days IM.

Treatment for PKDL Cases

Duration: Six cycles with 10-day interval between cycles.

- Sodium stibogluconate (SSG): 20 mg/kg BW daily for 20 days IM
- Amphotericin B deoxycholate: 1 mg/kg BW daily or alternate days IV (in 5% dextrose solution 500 mL) for 15 doses per cycle
- Liposomal amphotericin B: Total doses of 10–15 mg/kg divided into 3–5 doses per cycle
- Miltefosine: 4 weeks, 8 weeks and 12 weeks.

In case of unavailability of miltefosine in kala-azar treatment failure (KATF):

- Paromomycin: 11 mg/kg of paromomycin base (equivalent to 15 mg/kg/day paromomycin sulfate) IM for 21 days
- Liposomal amphotericin: A total dose of 10–15 mg/kg divided into 3–5 doses given either daily or on alternate days through IV infusion with 5% dextrose solution.
- Second-line drugs:
  - Amphotericin B deoxycholate
  - SSG.

Prevention

Personal Protective Measures

- Sleeping in tents under fine-mesh netting
- Wearing long-sleeved clothing and using insect repellents.

Prevention of Sandfly Bites

- Elimination of sandflies (Phlebotomus and Lutzomyia) by residual spraying
- Permethrin-impregnated bed nets can be highly effective in preventing sandfly bites
- Animal reservoirs, such as infected dogs and rodents, should be destroyed.

MALARIA

Malaria is a major cause of mortality and morbidity in the tropical and subtropical regions of the world (Fig. 80). An estimated 300–500 million persons suffer from and more than 1 million die of malaria each year.

A majority of malaria deaths, particularly those in children under-five, occur in sub-Saharan Africa. The Southeast Asia region reports a high number of cases and deaths second only to Africa. Unlike some of the other acute diseases such as encephalitis, meningitis, and most of the chronic diseases, patients of severe malaria can recover completely without any long-term effects if treated promptly and correctly.

Malaria is caused by infection of red blood cells with protozoan parasites of the genus *Plasmodium*. The parasites are inoculated into the human host by a feeding female anopheline mosquito (Fig. 81). The four *Plasmodium* species that infect humans are *P. falciparum, P. vivax, P. ovale* and *P. malariae*. Increasingly, human infections with the monkey malaria parasite, *P. knowlesi*, have also been reported from the forested regions of Southeast Asia.

Life Cycle of Malaria Parasite (Fig. 82)

The life cycle of the malaria parasite is complex. The sporozoites are transmitted to humans by the bite of infected female mosquitoes of the genus *Anopheles*. The sporozoites circulate for a short time in the blood stream, and then invade liver cells, where they develop into exoerythrocytic schizonts during the next 5–15 days. *Plasmodium vivax* and *P. ovale* have a dormant stage, the hypnozoite that may remain in the liver for weeks or many years before the development of exoerythrocytic schizogony. This results in relapses of infection. *Plasmodium falciparum* and *P. malariae* have no persistent phase. An exoerythrocytic schizont contains 10,000–30,000 merozoites, which are released and invade the red blood cells. Erythrocyte invasion by merozoites is

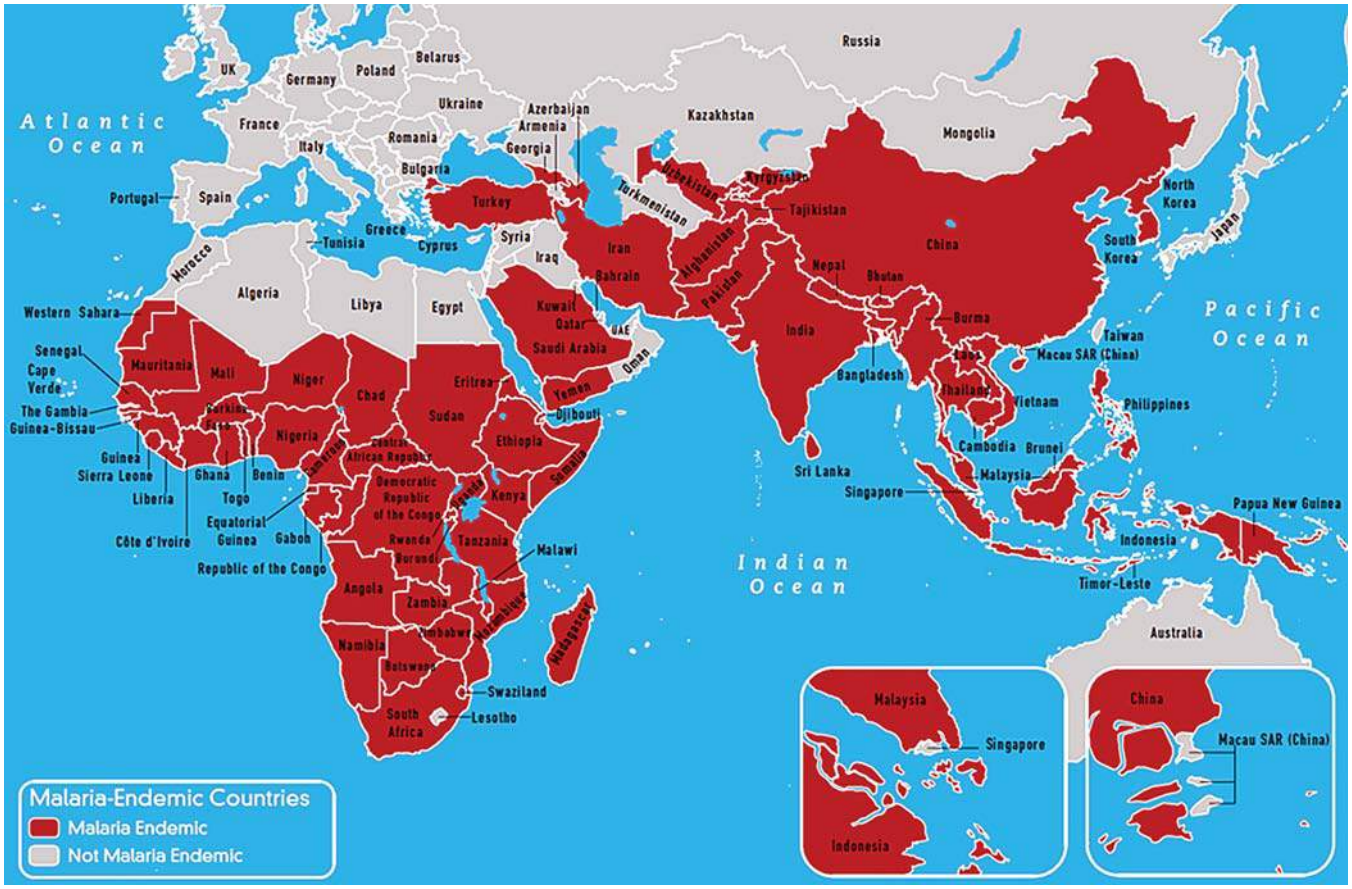


Fig. 80: Showing malaria endemic countries

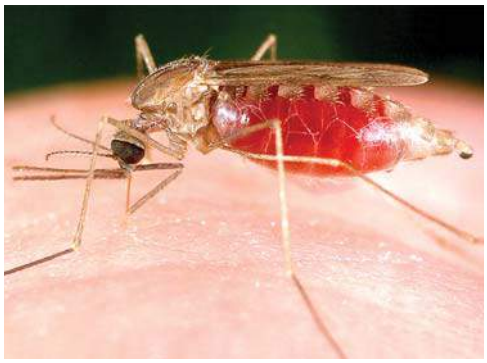


Fig. 81: Anopheline mosquito

dependent on the interactions of specific receptors on the erythrocyte membrane with ligands on the surface of the merozoite. The entire invasion process takes about 30 seconds. The merozoite develops within the erythrocyte through ring, trophozoite and schizont (erythrocytic schizogony). The parasite modifies its host cell in several ways to enhance its survival. The erythrocyte containing the segmented schizont eventually ruptures and releases the merozoites, which invade additional erythrocytes. In the course of these events, some merozoites invade erythrocytes, become differentiated into sexual forms, which are macrogametocytes (female) and microgametocytes (male). The duration of gametocytogony is assumed to be approximately 4–10 days depending on the *Plasmodium* species. Mature macrogametocytes taken into the midgut of the Anopheles mosquito escape from the erythrocyte to form macrogametes. Microgametocytes in the midgut exflagellate, each forms eight microgametes after a few minutes post-infection. The microgamete moves quickly to fertilize a macrogamete and forms a zygote. Within 18–24 hours, the zygote elongates into a slowly motile ookinete. The ookinete traverses the peritrophic membrane and the epithelial cell of the midgut, and then transforms into an oocyst beneath the basement membrane of the midgut epithelium. Between 7 and 15 days post-infection, depending on the *Plasmodium* species and ambient temperature, a single oocyst forms more than 10,000 sporozoites. The motile sporozoites migrate into the salivary glands and accumulate in the acinar cells of the salivary glands. When an infected mosquito bites a susceptible vertebrate host, the *Plasmodium* life cycle begins again.

Clinical Features

Nonsevere/Uncomplicated Malaria

Uncomplicated malaria is defined as symptomatic malaria without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction. The signs and symptoms of uncomplicated malaria are nonspecific. Malaria is, therefore, suspected clinically mostly on the basis of fever or a history of fever.

The most common clinical manifestation of malarial infection is a nonspecific febrile illness. The fever rarely follows classical descriptions of cyclical fevers with rigors and chills

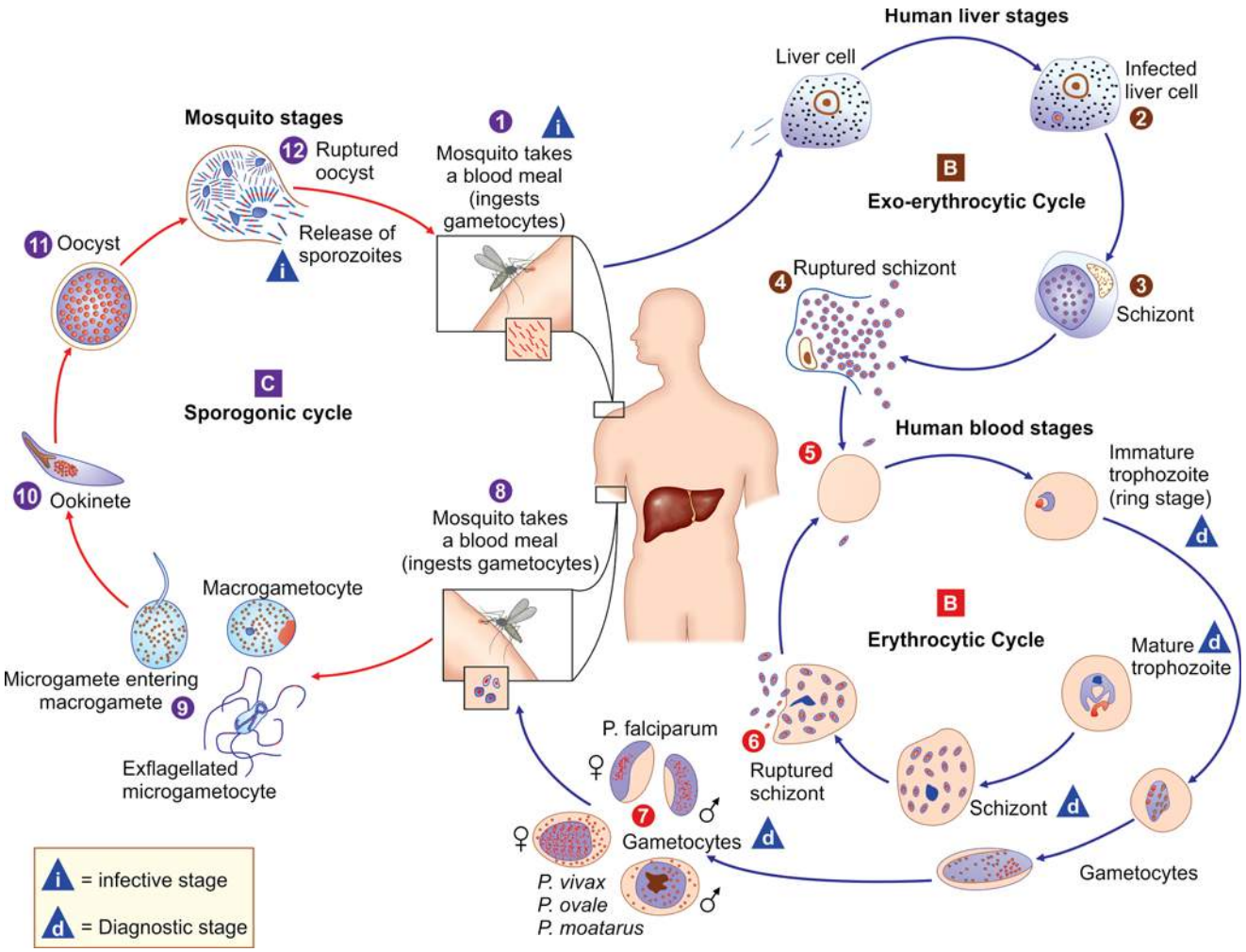


Fig. 82: Life cycle of malaria parasite

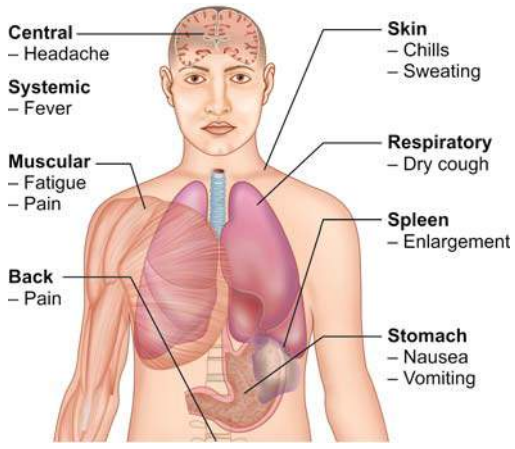


Fig. 83: Symptoms of malaria

and is essentially indistinguishable from many other common childhood infections.

Additional symptoms which are common include headache, cough, abdominal pain, vomiting and mild diarrhea. Older children, who are more vocal, may complain of headache and general body pains. Most frequent clinical examination finding is splenomegaly (Fig. 83).

Severe Malaria

Severe malaria occurs when there is/are cerebral malaria, severe anemia, renal failure, hypoglycemia, acidosis, etc. associated with malaria. If not treated promptly and effectively, severe malaria may lead to death. Severe malaria is mainly caused *by P. falciparum* but not all cases of *P. falciparum* are severe.

The treatment of this condition requires hospitalization and sometimes institution of intensive care. The signs of severe malaria may be nonspecific and can occur in other severe febrile diseases such as meningitis, encephalitis, septicemia, typhoid fever, leptospirosis and viral infections that are commonly seen in malarious areas.

Cerebral Malaria

Despite some heterogeneity in underlying pathology, cerebral malaria can usefully be described as a clinical entity.

Neurological signs:

- Coma: The clinical syndrome of cerebral malaria is deep coma (Fig. 84). This is defined by the inability to localize a painful stimulus in a patient with a *P. falciparum* parasitemia in whom other causes of encephalopathy have been excluded. Pupillary responses are usually well maintained and the development of sluggish responses

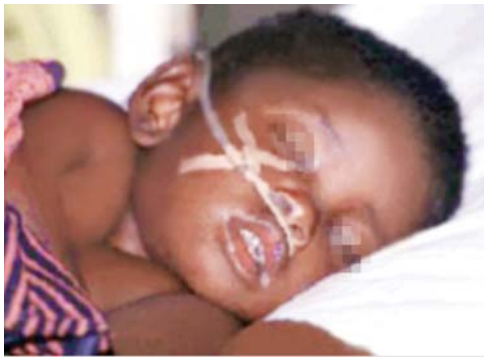


Fig. 84: Cerebral malaria in deep coma

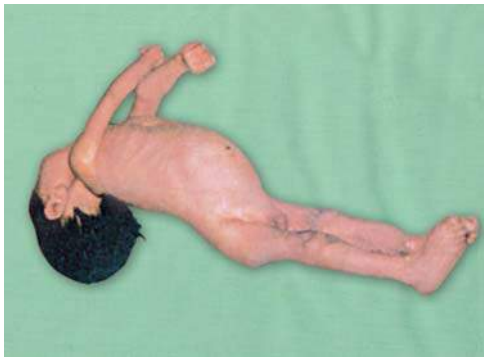


Fig. 85: Cerebral malaria in opisthotonic position

or unilateral abnormalities is a poor prognostic sign. Decorticate and decerebrate posturing are common, often posturing is extreme and the child adopts an opisthotonic position (Fig. 85) indistinguishable from that seen in severe meningitis. However, in contrast to meningitis, there is no sign of meningism like Kernig sign or neck rigidity. Unlike in cerebral malaria in adult, children with cerebral malaria usually keep their eyes open.

- Seizure: Physical signs are minimal and may be limited to nystagmoid eye movements, twitching of a single digit or hypoventilation with increased salivation.
- Abnormal respiratory patterns: Deep breathing is a sign of metabolic acidosis and needs urgent fluid resuscitation. Periodic respiration, often in association with abnormalities of papillary reflexes, is a grave sign and usually terminates in a respiratory arrest with continued cardiac output.
- Retinal abnormalities: Retinal abnormalities are not restricted to unconscious children, retinal hemorrhages and edema are detected in both prostrated children and children with cerebral malaria. Papilloedema associated with raised intracranial pressure is rare, but is associated with a poor prognosis.
- Raised intracranial pressure: Intracranial hypertension is an important pathogenic mechanism in many encephalopathies. Intracranial hypertension is common in children with cerebral malaria as determined by opening pressure at lumbar puncture.
- Prolonged postictal state: Children are susceptible to febrile seizures with prolonged postictal state.
- Covert status epilepticus: Hypoventilation, often with nystagmus and excessive salvation, is the commonest presentation of covert status epilepticus and is an indication for prompt antiepileptic medication. However, prophylactic antiepileptic drugs are not indicated.
- Metabolic acidosis and metabolic coma: Metabolic acidosis is a major feature in many children with severe malaria. Many children with severe malaria have low central venous pressures, children are also severely anemic and the combination of reduced red cell numbers with reduced circulating volume and potentially reduced tissue perfusion due to microvascular sequestration would seem to be a potent recipe for reduced tissue oxygen delivery. After fluid resuscitation, the hemoglobin concentration will fall and it may be necessary to review the question of whether blood transfusion is required. The more severe the acidosis or the clinical picture, the more urgent the requirement for volume resuscitation. Blood (or alternative fluids) should be given rapidly without diuretics.

Neurological sequelae of cerebral malaria:

- Major: Neurological sequelae which persist are in order of highest prevalence:
  - Hemiplegia
  - Speech disorders
  - Behavioral disorders and
  - Epilepsy.
- Less frequent permanent sequelae:
  - Blindness and
  - Generalized spasticity.

Other Clinical Features and Complications of Severe Malaria

Anemia

The pathogenesis of malarial anemia is complex; it clearly involves loss of uninfected as well as infected red cells.

Hypoglycemia

The commonest symptom is impaired consciousness, anywhere on the continuum from prostration to deep coma. However, hypoglycemia can develop suddenly in children without other obvious metabolic derangement.

Convulsions

The majority of convulsions occur in children without impaired consciousness (other than the temporary impairment due to the convulsion).

Renal Function and Fluid Balance

Acute tubular necrosis leading to established renal failure is rare in children with severe malaria. Serum creatinine and urea rise moderately.

Circulatory Collapse

It is an infrequent feature but has a very poor prognosis.

Hepatic Dysfunction

Liver enzymes are mildly elevated.

Pulmonary Edema

Pulmonary edema is rare in children, other than as a terminal event.

Bleeding Abnormalities

Its usual clinical manifestation is oozing around intravenous access sites. Variable degrees of thrombocytopenia are common, platelet counts often reaching very low values.

Hemoglobinuria

Hemoglobinuria is uncommon in children. Hemoglobinuria is probably more common in parts of Southeast Asia.

Gram-Negative Septicemia

Children may coexist with invasive bacterial disease which may contribute poor prognosis.

Diagnosis of Malaria

Prompt and accurate diagnosis of malaria is part of effective disease management. The diagnosis of malaria is based on clinical suspicion and on the detection of parasites in the blood (parasitological or confirmatory diagnosis).

Clinical Diagnosis

The signs and symptoms of malaria are nonspecific. Malaria is clinically suspected mostly on the basis of fever or a history of fever. Diagnosis based on clinical features alone has very low specificity and results in overtreatment. Other possible causes of fever and the need for alternative or additional treatment must always be carefully considered. The WHO recommendations for clinical diagnosis/suspicion of uncomplicated malaria in different epidemiological settings are as follows:

- *In settings where the risk of malaria is low*, clinical diagnosis of uncomplicated malaria should be based on the possibility of exposure to malaria and a history of fever in the previous three days with no features of other severe diseases.
- *In settings where the risk of malaria is high*, clinical diagnosis should be based on a history of fever in the previous 24 hours and/or the presence of anemia, for which pallor of the palms appears to be the most reliable sign in young children.

In all settings, clinical suspicion of malaria should be confirmed with a parasitological diagnosis. However, in settings where parasitological diagnosis is not possible, the decision to provide antimalarial treatment must be based on the prior probability of the illness being malaria. Other possible causes of fever and need for alternative treatment must always be carefully considered.

In children under 5 years of age, the WHO/United Nations Children's Fund (UNICEF) strategy for Integrated Management of Childhood Illness (IMCI) practical algorithms for management of the sick child should be used to ensure full assessment and appropriate case management of children at the first-level health facilities.

Parasitological Diagnosis

The changing epidemiology of malaria and the introduction of artemisinin-based combination therapy (ACT) have increased the urgency of improving the specificity of malaria diagnosis. Parasitological diagnosis has the following advantages:

- Improved patient care in parasite-positive patients
- Identification of parasite-negative patients in whom another diagnosis must be sought
- Prevention of unnecessary use of antimalarials, reducing frequency of adverse effects, especially in those who do not need the medicines, and drug pressure selecting for resistant parasites
- Improved malaria case detection and reporting
- Confirmation of treatment failures.

The two methods in routine use for parasitological diagnosis are light microscopy and rapid diagnostic tests (RDTs) (Figs 86 to 89). The latter detect parasite-specific antigens

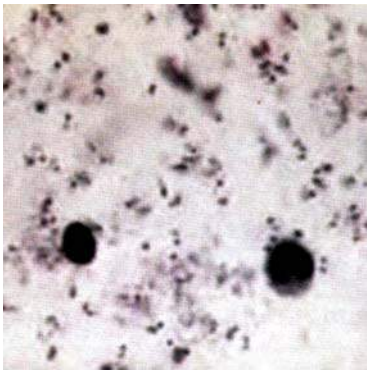


Fig. 86: Thick film showing numerous malaria parasites

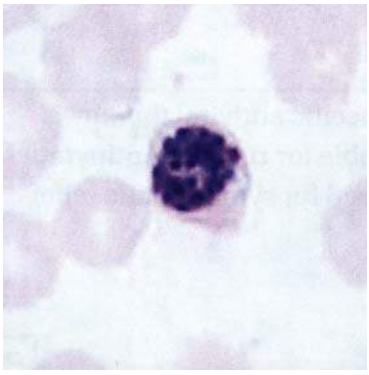


Fig. 87: Thin film showing Schizont

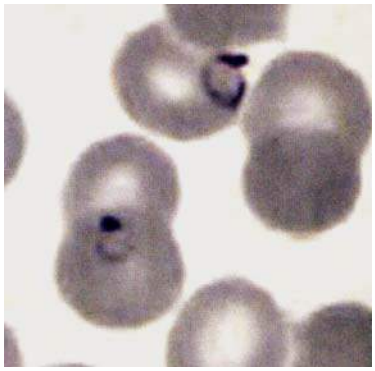


Fig. 88: Ring form of Falciparum malaria

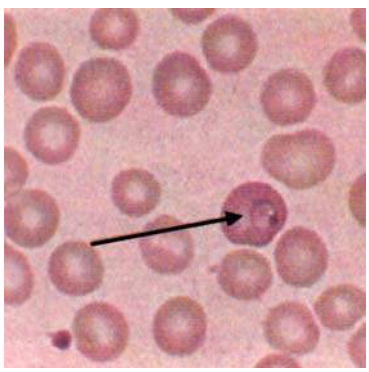


Fig. 89: *P. Vivax* in blood film with microcytic hypochromic RBC due to anemia

or enzymes and some have a certain ability to differentiate species.

The risk of false-negative microscopy is higher if the patient has received a recent dose of an artemisinin derivative.

The results of parasitological diagnosis should be available within a short time (less than 2 hours) of the patient presenting.

In the absence or delay of parasitological diagnosis, patients with suspected severe malaria, and other high-risk groups, should be treated immediately on clinical grounds.

Choice

The choice between RDTs and microscopy depends on local circumstances, including the skills available, patient case-load, epidemiology of malaria and the possible use of microscopy for the diagnosis of other diseases.

- Where malaria transmission is low-to-moderate and/or unstable: Parasitological confirmation of the diagnosis of malaria is strongly recommended.
- In stable high-transmission setting: Parasitological confirmation of the diagnosis of malaria provided by high-quality microscopy or, where this is not available, by rapid diagnostic tests (RDTs) is recommended for all suspected cases of malaria.
- In epidemics and complex emergencies: In epidemic and complex emergency situations, facilities for parasitological diagnosis may be unavailable or inadequate to cope with the case-load. In such circumstances, it may be impractical and unnecessary to demonstrate parasites before treatment in all cases of fever.

A parasitological confirmation of malaria in stable high-transmission settings is recommended; it improves the differential diagnosis of fever, improves fever case management, and reduces unnecessary use of antimalarial medicines. Antimalarial treatment on the basis of clinical suspicion of malaria should only be considered in situations where a parasitological diagnosis is not accessible.

Inborn Resistance to Malaria

Almost 60 years ago, Haldane formulated what has been known as "the malaria hypothesis" by suggesting a protective effect of thalassemia on *Plasmodium falciparum* infection (Haldane 1949). A number of genetic factors, most of which are associated with the red blood cells but also some of nonerythrocytic nature, have been suggested to be associated with protection against *P. falciparum* malaria and in particular with severe disease. Apart from sickle cell disease and the thalassemias, a number of inherited disorders/phenotypes such as hemoglobin C and E, glucose-6-phosphate dehydrogenase deficiency, ABO blood group O as well as certain human leukocyte antigens have been suggested to be associated with protection against the disease (Table 24).

Treatment of Uncomplicated Malaria (Drug Doses Given in Detail in Drug Therapy Chapter)

Antimalarial combination therapy is the simultaneous use of two or more blood schizontocidal medicines with independent modes of action and, thus, different biochemical targets in the parasite. The rationale is twofold: (1) The combination is often more effective; and (2) in the very rare event that a mutant parasite resistant to one of the medicines arises de novo during the course of the infection, this resistant parasite will be killed by the other antimalarial medicine.

Non-artemisinin-based Combination Therapy

Non-artemisinin-based combination treatments include sulfadoxine-pyrimethamine (SP) plus chloroquine (CQ) (SP+CQ) or amodiaquine (SP+AQ). The prevailing high

Table 24: Genetic factors associated with resistance to malaria

Genetic variants	Geographical distribution	Proposed mechanism
Hemoglobin defect		
α-thalassemia	All malaria endemic regions	Altered immune recognition, impaired rosetting
β-thalassemia	Southeast Asia, West Africa, Mediterranean	Altered immune recognition, impaired rosetting
HBS (Sickle cell disease/traits)	Indian subcontinent, sub-Saharan Africa	Impaired parasite growth, induced sickling, altered immune recognition, impaired rosetting
HbC	West Africa	Impairment of merozoite release, impaired rosetting
HbE	Southeast Asia	Impaired parasite growth, altered immune recognition, impaired rosetting
HbF	Worldwide	Sensitivity to oxidant stress
Red cell enzyme defect		
G-6-PD deficiency	Worldwide	Sensitivity to oxidant stress
Red cell membrane defect		
Southeast Asian (Melanesia) ovalocytosis	Melanesia	Reduced merozoite invasion (impaired cytoadhesion)
Lack of Duffy antigen	West Africa	Failure of merozoite invasion
ABO blood group O	Worldwide	Impaired rosetting
Glycophorin B deficiency	West Africa	Reduced merozoite invasion
Nonerythrocytic differences		
HLA-DRB1*1302- DQB1*0501	Worldwide	Not known
HLA-B53	Worldwide	Immune recognition of infected hepatocyte
TNF2 susceptible	Worldwide	Not known

levels of resistance to these medicines as monotherapy have compromised their efficacy even in combinations. There is no convincing evidence that chloroquine plus sulfadoxine-pyrimethamine provides any additional benefit over SP, so this combination is not recommended; amodiaquine plus sulfadoxine-pyrimethamine can be more effective than either drug alone; but it is usually inferior to ACTs, and it is no longer recommended for the treatment of malaria.

WHO recommends artemisinin-based combination therapies should be used in preference to amodiaquine plus sulfadoxine-pyrimethamine for the treatment of uncomplicated *P. falciparum* malaria.

Artemisinin-based Combination Therapy

These are combinations in which one of the components is artemisinin and its derivatives.

Artesunate, artemether, dihydroartemisinin: The artemisinins produce rapid clearance of parasitemia and rapid resolution of symptoms, by reducing parasite numbers 100- to 1000-folds per asexual cycle of the parasite (a factor of approximately 10,000 in each 48-hours asexual cycle), which is more than the other currently available antimalarials have achieved.

Because artemisinin and its derivatives are eliminated rapidly, when given alone or in combination with rapidly eliminated compounds (tetracyclines, clindamycin), a 7-day course of treatment with an artemisinin compound is required.

Shorter courses of 1–2 days of the artemisinin component of the ACTs would lead to a larger proportion of parasitemia for clearance by the partner medicine; this is not recommended for the following additional reasons:

- They are less efficacious (except when the partner drug is highly effective)
- They have less of an effect on gametocyte carriage
- They provide less protection of the slowly eliminated partner antimalarial

  In summary, the ACT options now recommended for treatment of uncomplicated falciparum malaria are:
- Artemether plus lumefantrine: This is currently available as a fixed-dose formulation with dispersible or standard tablets containing 20 mg of artemether and 120 mg of lumefantrine.

  Dose: The recommended treatment is a 6-dose regimen over a 3-day period.

  The dosing is based on the number of tablets per dose according to predefined weight bands given twice a day for 3 days.

Body Weight	Dose
5–14 kg	1 tablet
5–24 kg	2 tablets
25–34 kg	3 tablets
>34 kg	4 tablets

  This extrapolates to 1.7/12 mg/kg body weight of artemether and lumefantrine, respectively, per dose, given twice a day for 3 days, with a therapeutic dose range of 1.4–4 mg/kg of artemether and 10–16 mg/kg of lumefantrine.
- Artesunate plus amodiaquine: This is currently available as a fixed-dose formulation with tablets containing 25/67.5 mg, 50/135 mg or 100/270 mg of artesunate and amodiaquine. Blister packs of separate scored tablets containing 50 mg of artesunate and 153 mg base of amodiaquine, respectively, are also available.

  Dose: A target dose of 4 mg/kg/day artesunate and 10 mg/kg/day amodiaquine once a day for 3 days, with a therapeutic dose range between 2–10 mg/kg/day artesunate and 7.5–15 mg/kg/dose amodiaquine.
- Artesunate plus mefloquine: This is currently available as blister packs with separate scored tablets containing 50 mg of artesunate and 250 mg base of mefloquine, respectively. A fixed-dose formulation of artesunate and mefloquine is at an advanced stage of development.

  Dose: A target dose of 4 mg/kg/day artesunate given once a day for 3 days and 25 mg/kg of mefloquine either split over 2 days as 15 mg/kg and 10 mg/kg or over 3 days as 8.3 mg/kg/day once a day for 3 days. The therapeutic dose range is between 2 and10 mg/kg/dose/day of artesunate and 7–11 mg/kg/dose/day of mefloquine.

  Mefloquine is associated with an increased incidence of nausea, vomiting, dizziness, dysphoria and sleep disturbance.

  Treatment of uncomplicated *P. falciparum* malaria (usually on the second day) followed by 10 mg/kg one day later, or as a daily dose of 8.3 mg/kg for 3 days reduces acute vomiting and optimizes absorption, the 25 mg/kg dose is usually split and given either as 15 mg/kg.
- Artesunate plus sulfadoxine pyrimethamine: This is currently available as separate scored tablets containing 50 mg of artesunate and tablets containing 500 mg of sulfadoxine and 25 mg of pyrimethamine.

  Dose: A target dose of 4 mg/kg/day artesunate given once a day for 3 days and a single administration of 25/1.25 mg/kg sulfadoxine-pyrimethamine on day 1, with a therapeutic dose range between 2–10 mg/kg/day artesunate and 25–70/1.25–3.5 mg/kg sulfadoxine-pyrimethamine.
- Dihydroartemisinin plus piperaquine: This is currently available as a fixed-dose combination with tablets containing 40 mg of dihydroartemisinin and 320 mg of piperaquine.

  Dose: A target dose of 4 mg/kg/day dihydroartemisinin and 18 mg/kg/day piperaquine once a day for 3 days, with a therapeutic dose range between 2–10 mg/kg/day dihydroartemisinin and 16–26 mg/kg/dose piperaquine.
- Artesunate plus tetracycline or doxycycline or clindamycin: There are no blister co-packaged forms of any of these combination options. These are reserved for very rare occasions of treatment failures to the recommended ACTs and in some special groups, e.g. pregnant women failing ACT treatment. They are dosed separately and should only be used in a hospital setting.

  Dose: Artesunate (2 mg/kg once a day) plus tetracycline (4 mg/kg four times a day or doxycycline (3.5 mg/kg once a day) or clindamycin (10 mg/kg twice a day). Any of these combinations should be given for 7 days.

Additional Considerations for Clinical Management

Can the Patient Take Oral Medication?

Some patients cannot tolerate oral treatment, and they will require parenteral or rectal administration for 1–2 days until they can swallow and retain oral medication reliably. Although

such patients may never show other signs of severity, they should receive the same initial antimalarial dose regimens as for severe malaria. Initial parenteral treatment must always be followed by a full 3-day course of ACT.

Use of Antipyretics

Fever is a cardinal feature of malaria, and is associated with constitutional symptoms of lassitude, weakness, headache, anorexia and often nausea. In young children, high fevers are associated with vomiting, often regurgitating their medication, and seizures. Treatment is with antipyretics and, if necessary, fanning and tepid sponging. Antipyretics should be used if core temperatures >38.5°C. Paracetamol (acetaminophen) 15 mg/kg every 4 hours is widely used; it is safe and well tolerated, given orally or as a suppository. Ibuprofen (5 mg/kg) has been used successfully as an alternative in malaria and other childhood fevers. Acetylsalicylic acid (aspirin) should not be used in children because of the risks of Reye's syndrome.

Use of Antiemetics

Vomiting is common in acute malaria and may be severe. Antiemetics are widely used. Patients who vomit everything, including the medicines, should be managed as severe malaria.

Management of Seizures

Generalized seizures are more common in children with *P. falciparum* malaria than in those with the other malarias. This suggests an overlap between the cerebral pathology resulting from malaria and febrile convulsions. As seizures may be a prodrome of cerebral malaria, patients with repeated seizures (more than two seizures within a 24-hour period) should be treated as for severe malaria. If the seizure is ongoing, the airway should be maintained and anticonvulsants given (parenteral or rectal benzodiazepines or intramuscular paraldehyde). There is no evidence that prophylactic anticonvulsants are beneficial in otherwise uncomplicated malaria, and they are not recommended.

Coexisting Morbidities

HIV Infection

Worsening HIV-related immunosuppression may lead to more severe manifestations of malaria. Patients with HIV infection who develop malaria should receive prompt effective antimalarial treatment regimens. Treatment or intermittent preventive treatment with sulfadoxine pyrimethamine should not be given to HIV-infected patients receiving cotrimoxazole (trimethoprim plus sulfamethoxazole) prophylaxis.

In case of treatment of malaria in HIV-infected patients receiving zidovudine or efavirenz should, if possible, avoid amodiaquine-containing ACT regimens. Although HIV-infection and cotrimoxazole may also depress neutrophil counts, there is insufficient information on the interaction of amodiaquine containing ACT regimens with cotrimoxazole or HIV infection to make recommendations.

Severe Malnutrition

Malaria and malnutrition frequently coexist. Drug absorption may be reduced owing to diarrhea and vomiting, rapid gut transit and atrophy of the bowel mucosa. Absorption of intramuscular (IM) and possibly intrarectal drugs may be slower, and diminished muscle mass may make it difficult to administer repeated intramuscular injections. The volume of distribution of some drugs would be expected to be larger and plasma concentrations lower. Hypoalbuminemia, resulting from decreased synthesis as dietary deficiency occurs, could lead to an increase in the concentration of unbound drug; this may increase metabolic clearance, but hepatic dysfunction may reduce the metabolism of some drugs.

Management of Severe *P. falciparum* Malaria (Fig. 90)

Clinical Features

- Impaired consciousness or unrousable coma
- Prostration, i.e. generalized weakness so that the patient is unable to walk or sit up without assistance
- Failure to feed
- Multiple convulsions: more than two episodes in 24 hours
- Deep breathing, respiratory distress (acidotic breathing)
- Circulatory collapse or shock, systolic blood pressure <70 mm Hg in adults and <50 mm Hg in children
- Clinical jaundice plus evidence of other vital organ dysfunction
- Hemoglobinuria
- Abnormal spontaneous bleeding
- Pulmonary edema (radiological).

Laboratory Findings

- Hypoglycemia (blood glucose <2.2 mmol/L or <40 mg/dL)
- Metabolic acidosis (plasma bicarbonate <15 mmol/L)
- Severe normocytic anemia (Hb <5 g/dL, packed cell volume <15%)
- Hemoglobinuria
- Hyperparasitemia (>2%/100,000/μL in low intensity transmission areas or >5% or 250,000/μL in areas of high stable malaria transmission intensity)
- Hyperlactatemia (lactate >5 mmol/L)
- Renal impairment (serum creatinine >265 μmol/L).

Treatment Objectives

- The main objective is to prevent the patient from dying
- Secondary objectives are prevention of disabilities and prevention of recrudescence

Death from severe malaria often occurs within hours of admission to hospital or clinic, so it is essential that therapeutic concentrations of a highly effective antimalarial are achieved as soon as possible.

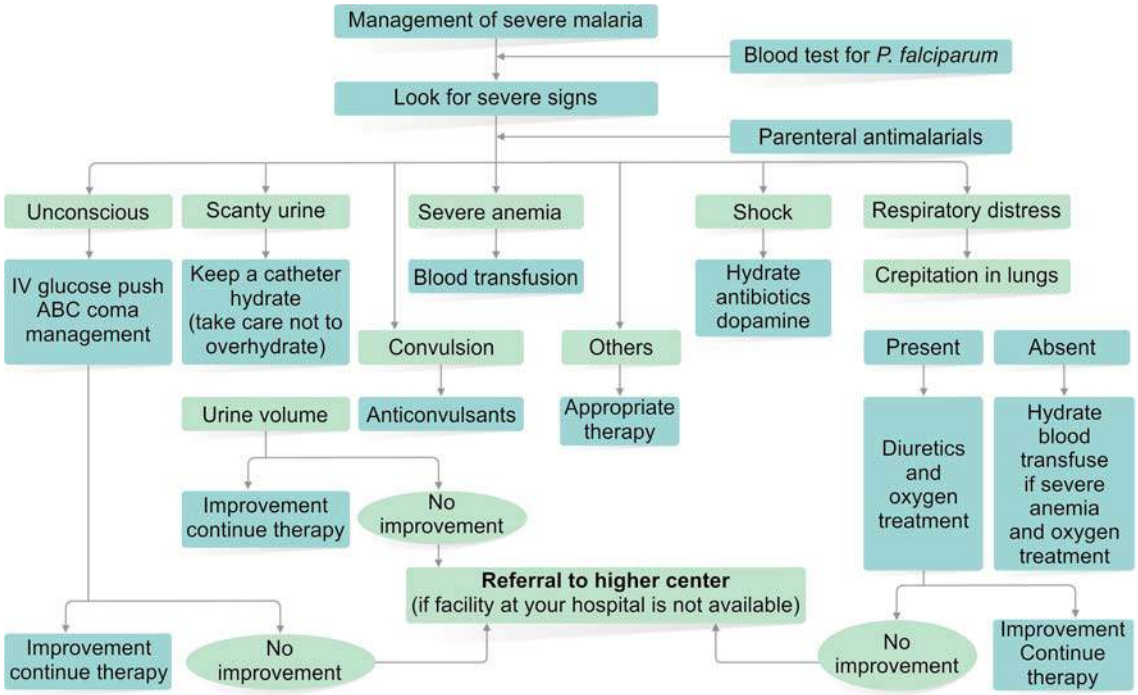
Management of severe malaria comprises four main areas:

1. Clinical assessment of the patient
2. Specific antimalarial treatment
3. Adjunctive therapy and
4. Supportive care.

Clinical Assessment

Severe malaria is a medical emergency.

- An open airway should be secured in unconscious patients and breathing and circulation assessed
- The patient should be weighed or body weight estimated, so that medicines, including antimalarials and fluids, can be given accordingly



Patient with ARF, ARDS, severe anaemia requiring multiple blood transfusions, and multiple complications (coma along with jaundice, oliguria, severe anaemia and breathing problem) and pregnant women with severe malaria should be referred to higher centres after starting a dose of parenteral antimalarial. Patient with single complication (excluding the above), convulsions, hyperpyrexia and other less severe type of complications can be treated in a small hospital.

Fig. 90: Chart on management of severe malaria in large hospitals/health facilities

- An intravenous cannula should be inserted and immediate measurements of blood glucose (stick test), hematocrit/hemoglobin, and parasitemia and, in adults, renal function should be taken
- A detailed clinical examination should be conducted, including a record of the coma score. Several coma scores have been advocated
- The Glasgow coma scale is suitable for adults, and the simple Blantyre modification or children's Glasgow coma scale are easily performed in children
- Unconscious patients should have a lumbar puncture for cerebrospinal fluid analysis to exclude bacterial meningitis
- The degree of acidosis is an important determinant of outcome; the plasma bicarbonate or venous lactate level should therefore be measured, if possible
- If facilities are available, arterial or capillary blood pH and gases should be measured in patients who are unconscious, hyperventilating or in shock
- Blood should be taken for cross-match, full blood count, platelet count, clotting studies, blood culture and full biochemistry (wherever possible).

The assessment of fluid balance is critical in severe malaria. Respiratory distress, in particular with acidotic breathing in severely anemic children, often indicates hypovolemia and requires prompt rehydration and, where indicated, blood transfusion.

Differential Diagnosis

The differential diagnosis of fever in a severely ill patient is broad.

- Coma and fever may result from meningoencephalitis or malaria
- Cerebral malaria is not associated with signs of meningeal irritation (neck stiffness, photophobia or Kernig sign), but the patient may be opisthotonic

As untreated bacterial meningitis is almost invariably fatal, a diagnostic lumbar puncture should be performed to exclude this condition. There is also considerable clinical overlap between septicemia, pneumonia and severe malaria, and these conditions may coexist.

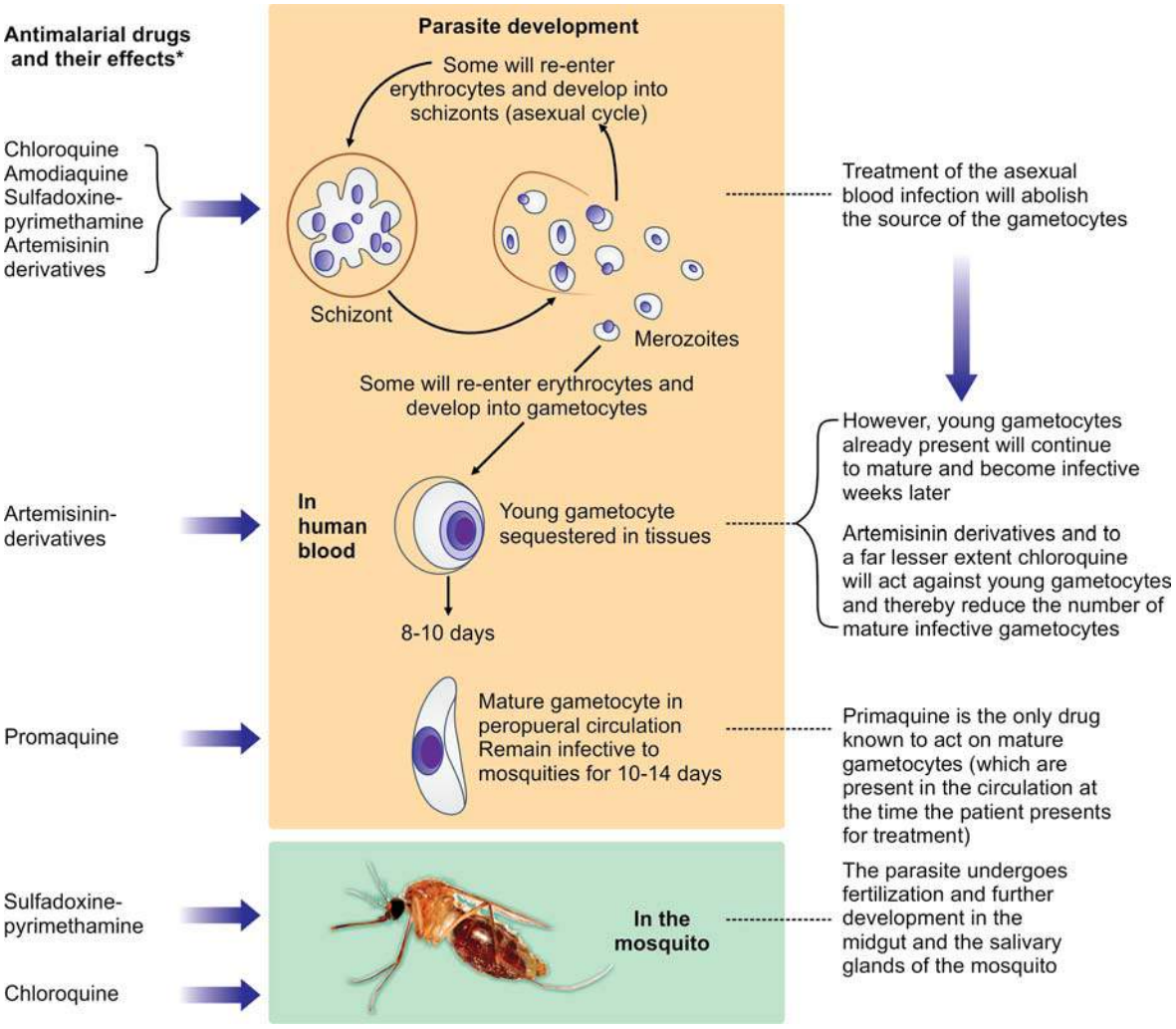
Specific Antimalarial Treatment

Transmission of *P. falciparum* and the effects of antimalarial drugs on malarial parasites at various stages of their life cycle are shown in Figure 91. It is essential that effective, parenteral (or rectal) antimalarial treatment in full doses is given promptly in severe malaria. Two classes of medicines are available for the parenteral treatment of severe malaria: The cinchona alkaloids (quinine and quinidine) and the artemisinin derivatives (artesunate, artemether and artemotil). Parenteral chloroquine is no longer recommended for the treatment of severe malaria, because of widespread resistance. Intramuscular sulfadoxine-pyrimethamine is also not recommended.

Artemisinin derivatives: Various artemisinin derivatives have been used in the treatment of severe malaria, including artemether, artemisinin (rectal), artemotil and artesunate.

For children (especially in the malaria endemic areas of Africa), the following antimalarial medicines are recommended, as there is insufficient evidence to recommend any of these antimalarial medicines over another:

- Artesunate 2.4 mg/kg body weight IV or IM given on admission (time = 0), then at 12 hours and 24 hours, then once a day



* When parasites are sensitive to the drug unless otherwise stated.

Fig. 91: Transmission of *P. falciparum* and the effects of antimalarial drugs on malarial parasites at various stage of their life cycle

- Quinine 20 mg salt/kg body weight on admission (IV infusion or divided IM injection), then 10 mg/kg body weight every 8 hours; infusion rate should not exceed 5 mg salt/kg body weight per hour
- Artemether 3.2 mg/kg body weight IM given on admission then 1.6 mg/kg body weight per day should only be used if none of the alternatives are available as its absorption may be erratic.

Give parenteral antimalarials in the treatment of severe malaria for a minimum of 24 hours, once started (irrespective of the patient's ability to tolerate oral medication earlier), and thereafter, complete treatment by giving a complete course of:

- Artemether plus lumefantrine
- Artesunate plus amodiaquine
- Dihydroartemisinin plus piperaquine
- Artesunate plus sulfadoxine-pyrimethamine
- Artesunate plus clindamycin or doxycycline
- Quinine plus clindamycin or doxycycline.

Quinine:

- Loading dose of quinine is, i.e. 20 mg quinine hydrochloride salt/kg body weight, twice the maintenance dose
- The maintenance dose of quinine is 10 mg quinine hydrochloride salt/kg body weight administered at 8-hour intervals, starting 8 hours after the first dose. Rapid administration of quinine is unsafe
- Each dose of parenteral quinine must be administered as a slow, rate-controlled infusion (usually diluted in 5% dextrose and infused over 4 hours). The infusion rate should not exceed 5 mg salt/kg body weight per hour.

Quinidine:

Quinidine commonly causes hypotension and concentration-dependent prolongation of ventricular repolarisation (QT prolongation). Quinidine is thus considered more toxic than quinine and should only be used if no other effective parenteral drugs are available.

Electrocardiographic monitoring and frequent assessment of vital signs are required if quinidine is used.

Adjunctive Treatment

Adjunctive treatment of severe mainfestations and complication of P. falciparum malaria is given in Table 25.

Table 25: Immediate adjuvant clinical management of severe manifestations and complications of *P. falciparum* malaria

Manifestation/ complication	Immediate management[a]
Coma (cerebral malaria)	Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycemia, bacterial meningitis); avoid harmful ancillary treatment, such as corticosteroids, heparin and adrenaline; intubate if necessary.
Hyperpyrexia	Administer tepid sponging, fanning, a cooling blanket and antipyretic drugs Paracetamol is preferred over more nephrotoxic drugs (e.g. NSAIDs[b])
Convulsions	Maintain airways; treat promptly with intravenous or rectal diazepam or intramuscular paraldehyde. Check blood glucose.
Hypoglycemia	Check blood glucose, correct hypoglycemia and maintain with glucose-containing infusion
Severe anemia	Transfuse with screened fresh whole blood
Acute pulmonary edema[c]	Prop patient up at an angle of 45°, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure/continuous positive airway pressure in life-threatening hypoxemia
Acute renal failure	Exclude prerenal causes, check fluid balance and urinary sodium; if in established renal failure, add hemofiltration or hemodialysis, or if unavailable, peritoneal dialysis
Spontaneous bleeding and coagulopathy	Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets, if available); give vitamin K injection
Metabolic acidosis	Exclude or treat hypoglycemia, hypovolemia and septicemia. If severe, add hemofiltration or hemodialysis
Shock	Suspect septicemia, take blood for cultures; give parenteral broad-spectrum antimicrobials, correct hemodynamic disturbances

[a] It is assumed that appropriate antimalarial treatment would have been started in all cases.
[b] Nonsteroidal anti-inflammatory drugs.
[c] Prevent by avoiding excess hydration.

At a Glance Treatment Guideline of Malaria

Treatment of Uncomplicated P. falciparum Malaria

- Artemisinin-based combination therapies (ACTs) are the recommended treatments for uncomplicated *P. falciparum* malaria
- The following ACTs are recommended:
  Artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, and artesunate plus sulfadoxine-pyrimethamine.
- The choice of ACT in a country or region will be based on the level of resistance of the partner medicine in the combination.
- Artemisinin and its derivatives should not be used as monotherapy.
- Second-line antimalarial treatment:
  - Alternative ACT known to be effective in the region
  - Artesunate plus tetracycline or doxycycline or clindamycin; any of these combinations to be given for 7 days
  - Quinine plus tetracycline or doxycycline or clindamycin; any of these combinations should be given for 7 days.

Treatment of Uncomplicated P. falciparum Malaria in Risk Group

- Malnourished patients: Although there are many reasons why antimalarial pharmacokinetics may be different in malnourished patients as compared with those who are well nourished, there is insufficient evidence to change current mg/kg body weight dosing recommendations.
- Infants and young children: ACTs for first-line treatment in infants and young children with attention to accurate dosing and ensuring the administered dose is retained.

Treatment of Severe Malaria

- Severe malaria is a medical emergency. After rapid clinical assessment and confirmation of the diagnosis, full doses of parenteral antimalarial treatment should be started without delay with whichever effective antimalarial is first available.
- For adults, artesunate IV or IM
  - Quinine is an acceptable alternative if parenteral artesunate is not available.
- For children (especially in the malaria endemic areas of Africa), the following antimalarial medicines are recommended as there is insufficient evidence to recommend any of these antimalarial medicines over another
  - Artesunate IV or IM
  - Quinine (IV infusion or divided IM injection)
  - Artemether IM (should only be used if none of the alternatives are available as its absorption may be erratic)
- Give parenteral antimalarials in the treatment of severe malaria for a minimum of 24 hours, once started (irrespective of the patient's ability to tolerate oral medication earlier) and, thereafter, complete treatment by giving a complete course of:
  - An ACT
  - Artesunate plus clindamycin or doxycycline
  - Quinine plus clindamycin or doxycycline.
- If complete treatment of severe malaria is not possible, patients should be given prereferral treatment and referred immediately to an appropriate facility for further treatment. The following are options for prereferral treatment: Rectal artesunate, quinine IM, artesunate IM, artemether IM.

Treatment of Uncomplicated P. vivax Malaria

- Chloroquine 25 mg base/kg body weight divided over 3 days, combined with primaquine 0.25 mg base/kg body weight, taken with food once daily for 14 days is the treatment of choice for chloroquine-sensitive infections

- In Oceania and Southeast Asia, the dose of primaquine should be 0.5 mg/kg body weight. Chloroquine combined with primaquine is the treatment of choice for chloroquine-sensitive infections
- ACTs combined with primaquine for chloroquine-resistant vivax malaria
- In mild-to-moderate G6PD deficiency, primaquine 0.75 mg base/kg body weight given once a week for 8 weeks. In severe G6PD deficiency, primaquine is contraindicated and should not be used
- Where ACT (exception AS + SP) has been adopted as the first-line treatment for *P. falciparum* malaria, it may also be used for *P. vivax* malaria in combination with primaquine for radical cure
- Artesunate plus sulfadoxine-pyrimethamine is not effective against *P. vivax* in many places.

Treatment of Uncomplicated Malaria in Epidemic Situation

- The following ACTs are recommended for antimalarial treatment in *P. falciparum* or mixed *P. falciparum/P. vivax* malaria epidemics:
  - Artemether plus lumefantrine
  - Artesunate plus amodiaquine
  - Artesunate plus mefloquine
  - Dihydroartemisinin plus piperaquine.
- The 14-day antirelapse therapy for vivax malaria patients (where applicable) should be postponed to the postepidemic period
- Treatment of severe malaria:
  - Artemether by the IM route is an acceptable and practical alternative for treatment of severe falciparum malaria during an epidemic. As soon as intensive case monitoring becomes possible, artesunate (IV or IM route) is the treatment of choice. Quinine can be used where artesunate is not available.

MANAGEMENT OF FEBRILE ILLNESS IN CHILDREN WITHOUT SOURCE

Fever in children without source can be defined as febrile illness when history and clinical examination do not reveal the source of fever. It is most probably the common illness for which medical advice is sought.

Nearly 50% of pediatric hospitalizations are attributable to febrile illness. Infectious disease remains the major cause of febrile illness and responsible for prime cause of childhood mortality and morbidity in children. Most acute febrile illnesses globally are due to viral cause like seasonal flu, and are less serious (except few like dengue fever). Although bacterial infection is less common but potentially serious and catastrophic if not diagnosed and treated by proper antibiotic timely. On the other hand, rationalization of antimicrobial therapy is necessary to avoid the possible side effects of antibiotics and increasing emergence of resistant bacterial strain. However, it is often difficult even by experienced healthcare provider to differentiate the viral and serious bacterial infection (SBI). It is important to recognize children at risk of serious illness due to SBI, so that appropriate decision can be taken whether they can be managed at home or referred to hospital.

Fever in children without any obvious source on clinical examination can be classified as:

- *Acute febrile illness* (Fig. 92) of less than 7–10 days' duration and
- *Prolonged febrile illness* lasting for more than 7–10 days' duration.

Assessment of Risk of Serious Illness in Children with Acute Febrile Illness (<7–10 Days' Duration) Without Source

It is important to assess severe illness in children with fever. Most severe illness occurs due to bacteremia with exception of few viral infections like dengue in dengue endemic areas. Untreated bacteremia can cause serious complications including death; therefore early, diagnosis of bacteremia in a febrile child is crucial in reducing childhood mortality. Various visual analog scales (VAS) are available with or without physical examination and with or without investigation. One of the useful validated VAS is Yale Observation Scale (YOS) consisting of six observational items which include: (i) Quality of cry, (ii) cry to stimulation, (iii) colour (total three C), (iv) wakefulness status ,(v) hydration and (vi) response to social overtures.

Points are given according to status in six items as shown in the Table 26. YOS scale more than 10 is suggestive of serious bacterial infection. A normal YOS score less than 10 rules out severe bacterial infection. YOS scale has good negative predictive value, i.e. a YOS scale <10 confidently rules out severe bacterial infection. However a positive YOS needs further investigation to confirm bacterial infection. This VAS (YOS) is cost-effective, since it does not contain any investigational items. It is therefore useful in rural-based hospitals particularly in resource-poor countries. YOS is more applicable in children below 36 months of age.

Sensitivity and specificity of YOS can be increased by further observing and examining physically for other clinical features

Figs 92A and B: (A) An infant with gangrenous bullous perioral skin lesion with acute febrile illness. Blood culture showed *Pseudomonas aeruginosa*; (B) The same child after successful management

which however require expertize, and therefore more applicable in secondary or tertiary hospital settings. These include counting respiratory rate and oxygen saturation for suspected pneumonia, counting capillary refilling time for hydration and circulatory status, observing for seizures, examining for signs of meningism for meningoencephalitis, presence of nonblanching rash (meningococcemia, dengue). The clinical features are divided into three groups according to severity so called "traffic light system." In this system, features in green zone fall in low-risk group, amber color indicates intermediate risk, and clinical feature of severe infection is indicated in red zone as shown in the Table 27.

In community setting, of rural area, febrile child with YOS >10 or in secondary and tertiary setting with 'traffic light system' in amber or red zone should be hospitalized for observation and management.

Investigation of Acute Febrile Illness without Source

Investigation and treatment of acute febrile illness not only depend on presenting clinical features but also age of the child.

Children <3 Months of age

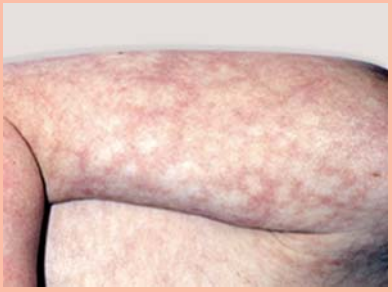
Fever in children <3 months of age carries more significance and likely to have underlying severe bacterial infection. It is better to admit the infant for observation and following investigation should be done:

- Full blood count
- Blood culture
- C-reactive protein

Table 26: Assessment of risk of serious illness (likelihood to be bacterial) in children with fever

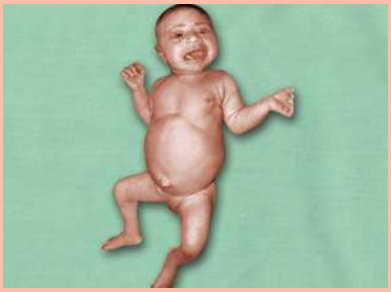
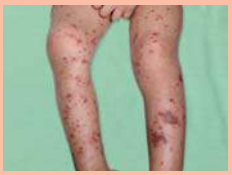
Observation item	Normal (Score 1)	Moderate impairment (Score 3)	Severe impairment (score 5)
1. *Quality of cry*	Strong with normal tone	Sobbing or whimpering	Weak, moaning or high pitch
2. *Cry to parent stimulation*	Cries briefly then stops	Cries off and on	Continued cry or no remission
3. *Response to social cues and overture (Smile, talk)*	Smile or alert (<2 months)	Brief smile or alert briefly (<2 months)	No smile, face anxious, dull, expressionless, no alert (<2 months)
4. *Color*	Pink or natural uniform skin color in dark skin	Pale extremities, acrocyanosis,	Pale, cyanotic, or ashen
5. *Hydration*	Skin and eyes normal , moist mucous membrane	Skin and eyes normal but mouth slightly dry	Skin doughy , eyes sunken, dry mucous membrane
6. *Wakefulness*	Awake. If asleep, waking quickly on stimulation	Eyes semiclosed, awakes with prolonged stimulation	Falls to sleep quickly, does not wake up on stimulation

Table 27: Traffic light system for assessing the risk of serious illness in children with fever

	Green: Low risk	Amber: Intermediate-risk	Red: High-risk
Color	Normal color of skin, lips and tongue	Pallor reported by the parents	Pale/ Mottled/ ashen/ blue  Mottled skin
Hydration	Normal skin and eyes Moist mucous membrane	Dry mucous membrane Poor feeding in infants CRT ≥ 3 sec Reduced urinary output	Reduced skin turgor, sunken eye  Sunken eye
Activity	Responds normally on social cues Content/Smiles Stays awake or awakens quickly Strong normal cry/ not crying	Not responding normally to social cues Wakes only with prolonged stimulation Decreased activity No smile	No response to social cues Appears ill to a healthcare professional Unable to rouse or if roused does not stay awake Weak/high-pitched/continuous cry

Contd...

Contd...

Respiratory	Normal respiration No tachypnea No chest indrawing Oxygen saturation >95% in air Crackles	Nasal flaring Tachypnea RR >50 breaths/min age 6 – 12 months RR >40 breaths/min age >12 month Oxygen saturation <95% in air Crackles	Grunting Tachypnea RR >60 breaths/min Moderate to severe chest indrawing  Chest indrawing	
Other	None of the amber red symptoms or signs	Swelling of a limb or joint Non-weight bearing/not using an extremity Fever for ≥5 days A new lump >2 cm  Swelling of right cervical lymph gland	Nonblanching rash Bulging fontanelle Neck stiffness Status epilepticus Focal neurological signs Focal seizures Age 0–3 months, temperature ≥38°C Age 3–6 months, temperature ≥39°C Bile stained vomiting	 Nonblanching rash  Stiff neck arched back

- Urine for routine and culture and sensitivity
- X-ray chest if respiratory signs are present
- Stool culture if diarrhea is present
- Lumbar puncture (LP) and CSF study should be done in all febrile babies below one month of age (unless contraindicated) and infants between 2 and 3 months of age if infant looks clinically unwell or WBC count is <5 or >15 × 10^9/L. LP should be done as early as possible before antibiotics are given.

Children above 3-month-old

Children with acute febrile illness without apparent source should be hospitalized for observation or if not possible to admit should be reviewed every day for assessment if below 6 months of age or every 2 days if more than 6 months of age. Following investigation should be done in febrile children >3 months of age without apparent source (Table 28).

YOS scale <10 or in children with green zone features of traffic light system are expected to have low or no risk of serious bacterial or viral infections. Only urine routine and culture should be done for UTI and no routine blood or chest X-ray is required.

Children with amber features should be tested with

- Full blood count
- Blood culture
- CRP
- Chest X-ray should be done if respiratory features (increased respiratory rate) are present in amber zone
- Lumbar puncture and CSF study should be considered in a child <1-year-old if intracranial infection is suspected (poor activity, poorly responsive, convulsion)
- Serological test (Widal) for enteric fever in endemic area. Dengue fever (NS1) in suspected dengue in dengue endemic area during febrile illness between 3 and 5 days.

These investigations are in addition to tests for UTI.

Children in high-risk features or red zone should be tested for UTI (urine routine and culture) and following additional tests should be done:

- Full blood count
- Blood culture and sensitivity
- CRP
- Chest X-ray
- Serological tests for enteric fever (widal) and dengue (dengue NS1) in endemic areas
- LP and CSF study if evidence of intracranial infection is present as shown in the Table 28.
- In addition, serum electrolytes and ABG should be done, if available.

The Role of Markers of Bacterial Infection in Children with Fever without a Source

(CRP, Procalcitonin, IL-6)

Although visual analog scale (VAS) like YOS or traffic light system assessment is useful in diagnosing SBI in resource poor community settings, it is not entirely reliable to exclude SBI in young children as it comprises subjective clinical evaluation.

Table 28: Suggested investigations in children aged 3 months to 5 years with fever without apparent source (according to traffic light system clinical features)

Green: Low-risk	Amber: Intermediate-risk	Red: High-risk
Test urine for UTI No routine blood or chest X-ray	Test urine for UTI And (unless deemed unnecessary by experienced pediatricians): Full blood count, Chest X-ray, CRP, blood culture, if fever >39°C and WBC >20 × 109/L. Dengue NS1 and Widal test in dengue and typhoid endemic area. Consider lumbar puncture if child <1-year-old.	Test urine for UTI Full blood count, blood culture, CRP, consider chest X-ray, lumbar puncture, serum electrolytes, blood gas if indicated

Various biochemical markers are used for diagnosis of severe bacterial infection without source.

WBC count and absolute neutrophil count (ANC) are used for diagnosis of SBI but frequently have disappointing diagnostic properties. Other surrogate markers of SBI have been evaluated and used in recent years. C-reactive protein (CRP) and recently procalcitonin (PCT) are shown to be better predictors.

CRP and procalcitonin have role in diagnosing bacterial infections in correlation with clinical condition. Published studies have demonstrated that CRP, PCT, WBC and ANC are superior to clinical evaluation in predicting SBI in children aged 1 month to 3 years. Blood culture specifically confirms the presence of bacteria, but generally not helpful due to its poor sensitivity. Only 5–20% of untreated pneumococcal occult bacteremia and 40–60% of untreated typhoid will yield positive bacteria on culture. Prior antibiotic can also negatively influence antimicrobial culture sensitivity. In such cases, CRP and PCT work as surrogate markers for bacterial infection.

There is no definite cutoff point of markers of bacterial infection in diagnosing SBI. A surrogate marker has to be interpreted depending on the values obtained on each patient. The higher the result (titer), the higher the probability of having SBI; it should not only be positive or negative, e.g. CRP >80 mg/L has higher probability of SBI than CRP >20 mg/L. Negative predictive value is more reliable than positive predictive value. If CRP <10 mg/L, it more reliably excludes SBI than CRP >60 mg/L which may not confirm SBI.

Procalcitonin (PCT)

Procalcitonin can indicate bacterial infection earlier than CRP and is probably more sensitive than CRP. This is more useful in neonatal sepsis, where raised CRP is preceded by raised PCT. However, superiority of PCT over CRP is yet to be established firmly.

Interleukin (IL)-6

IL-6 is also useful marker of SBI. It is one of the proinflammatory cytokine. Raised IL-6 in bacterial infection stimulates synthesis of CRP in liver. Therefore, IL–6 is an early indicator of SBI than CRP which follows earlier. Therefore, raised IL–6 can be used to detect early infection so that timely antibiotics can be initiated. IL–6 can also be used as a bacterial marker when CRP may not be elevated due to impairment of liver function, when infections are associated with significant liver involvement or in preterm neonates with impaired liver function. However, IL–6 estimation is not widely available in most hospital's diagnostic department.

Treatment

Immediate treatment by pediatrician in acute febrile illness of unknown source in children of all ages should be started with impaired level of consciousness, or looking toxic (lethargic, dehydrated, hypo/hyperventilated, cyanosed). Immediate treatment with parenteral antibiotics (3rd generation cephalosporine like ceftriaxone) should be administered until culture results are available. In neonate below 28 days, IV cefotaxime is given in place of ceftriaxone to avoid cholestasis. In children <3 months, amoxicillin may be added to cover *Listeria* where it is endemic.

Later management with antibiotic and its dose in SBI will depend on culture sensitivity report when available and pattern of involvement of bacterial infection (septicemia, meningitis).

Children with Fever and Shock (Bacteremic Shock)

- IV antibiotics should be given immediately
- Fluid resuscitation with immediate IV bolus dose of 20 ml/kg of isotonic saline (0.9% NaCl) is given
- Inotropic drugs like dopamine may have to be given if fluid resuscitation (up to 60 mL/kg) fails to maintain adequate blood pressure and tissue perfusion
- Oxygen should be given to children who have signs of shock or O_2 saturation <90%. IV acyclovir should be given if viral encephalitis is suspected. (For details, see management of septic shock)
- Shock can also occur in viral infection like dengue in dengue endemic areas. Fluid management of shock (normotensive and hypotensive shock in dengue) should be managed according to protocolized management in dengue
- IV acyclovir should be given if viral encephalitis is suspected.

Antipyretic Intervention

- Tepid sponging is not recommended for the treatment of fever
- The children with fever should not be undressed or overwrapped
- The use of antipyretic agent should be considered in children with fever who appear distressed or unwell due to fever. Not given on the basis of degree of fever alone
- Antipyretics should not be routinely used with sole aim of reducing body temperature in children with fever who are otherwise well
- Either paracetamol or ibuprofen can be used to reduce temperature in children with fever
- Alternate paracetamol with ibuprofen may be considered if the child does not respond to the first agent
- Antipyretic agents do not prevent febrile seizure and should not be used especially for this purpose.

Management of Children with Fever without Source: In Hospital or at Home?

In addition to clinical condition, the following factors should be considered while deciding upon the child to admit:

- Social and family circumstances
- Parental anxiety
- Other illness that affects the child (comorbidities)
- Contact with other people who have infectious disease
- Recent travel to tropical/subtropical areas with high risk of endemic infectious disease (dengue, malaria, typhoid) or travel to specific zones in same country
- When a febrile illness has no obvious cause but the child remains ill longer than expected for a self-limited illness.

What to Do if the Child Does Require Hospitalization but No Diagnosis has been Reached?

- In this case, a safety net should be provided for parents and caretakers
- If any red or amber features are present, patient should be provided with verbal or written information on warning symptoms and should be told how further healthcare can be obtained
- Arrangement for follow-up visit should be provided.

Children without risk (green zone) can be managed at home with appropriate advice as to when seek medical help.

MANAGEMENT OF SEPSIS AND SEPTIC SHOCK

It is very important cause of mortality in children, which is potentially preventable if managed timely and properly.

It is better to treat in pediatric intensive care unit (PICU). Immediate resuscitation should be done as early as possible to save life.

Resuscitation

Resuscitation should be undertaken in a structured manner with attention to the time elapsed and individual patient's response. Resuscitation should follow the standard algorithm of assessment of airway, breathing and circulation, though the priority is to support the circulation (Fig. 93). The resuscitation is aimed to maintain the adequacy of organ perfusion rather than simply BP as suggested by:

- Normal pulse (with no differential between peripheral and central pulses) and warm extremities
- Capillary refill time <2 seconds
- Normal mental status
- Adequate urine output (>1 mL/kg/h).

Fluid Therapy

There is a little evidence to support that the use of one form of IV fluid is superior to another form of IV fluid.

Crystalloid

Crystalloid solution is cheap and safe but may cause more tissue edema. Starting dose is 20 mL/kg.

Crystalloid solution used in children is:

- Normal saline (0.9% NaCl)
- Hartmann's or Ringer lactate solution.

Colloids

- Colloids contain larger molecules and are less prone to endothelial leak thus staying in the circulation for longer.
- Starting dose is 20 mL/kg.

Colloids used in children are:

- 4.5% human albumin (molecular weight 66,000)
- Gelatin solution such as gelofusine (succinylated gelatin with a molecular weight of 30,000) and haemaccel (polygeline, molecular weight 35,000).

Inotropic Agents

- Inotropic support should be considered early in the care of such cases if shock is not reversed with rapid fluid administration
- The choice for first-line inotrope is still a matter of debate; adrenaline seems to be the obvious candidate but dopamine or dobutamine can be used
- Noradrenaline is the obvious choice in the vasodilated patients, i.e. warm shock.

Induction of Anesthesia and Intubation in Septic Shock

Timing

- Semielective intubation and ventilation should be considered after 40–60 mL/kg IV fluid, particularly if signs of abnormal perfusion persist
- Multiple team members aid in the process
- Inotropes should be tried prior to intubation.

Induction Agents

- Ketamine (1–2 mg/kg IV) and fentanyl (2–5 mcg/kg IV) cause little cardiovascular depression and are probably the safest agents to use in septic shock
- Use of benzodiazepines, inhalational anesthetics, propofol, and thiopentone carries the risk of significant myocardial depression and systemic vasodilation. So these agents are not recommended in septic shock.

Treating the Cause of Sepsis

Likely cause of sepsis should be kept in utmost consideration during resuscitation and specific action should be taken when indicated. The causative organisms and appropriate antibiotics vary depending upon the age and country.

Supportive Care

Treatment of all patients with sepsis-induced multiorgan failure should be provided in PICU with an aim to maintain organ perfusion. One should bear in mind the following:

- Evaluate and re-evaluate antibiotic therapy, particularly in light of microbiological culture data
- Possibility of nosocomial superinfection (including fungal) at all times should be considered
- Possibility of surgical intervention should also be considered.

Management of Complications

- Respiratory
  - In sepsis, pulmonary edema occurs commonly due to myocardial failure capillary leak (ARDS).

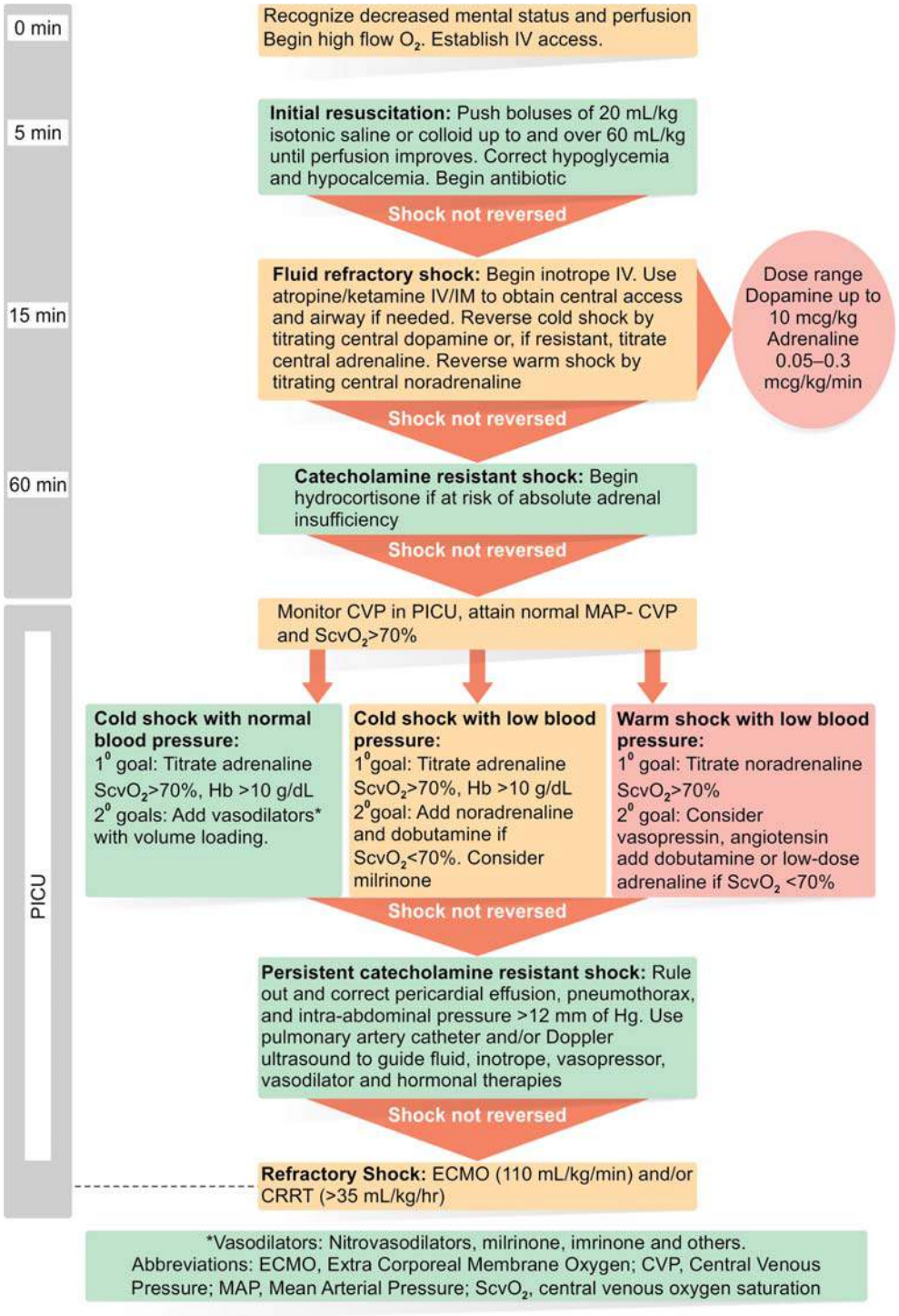


Fig. 93: Algorithm for stepwise management of hemodynamic support for infants and children with septic shock

- Use of PEEP (e.g. 8–12 cm H_2O) and relatively long inspiratory times (1.0–1.5 sec) are often effective in maintaining lung volumes without excessive PIP
- Minimize barotrauma and volutrauma by avoiding PIP >30 cm and tidal volumes of >7 mL/kg
- High-frequency oscillation is valuable if a PIP/plateau pressure >30 cm of H_2O or mean airway pressure >16 cm H_2O and FiO_2 >0.6 is required
- Arterial saturation (SaO_2) >90% usually ensures adequate oxygen delivery if cardiac output is maintained
- After shock has resolved, a conservative fluid therapy is associated with a shorter stay in ventilator.

- Cardiovascular
  - Beyond the early resuscitation phase, there are no clear recommendations for ongoing cardiovascular support
  - Patients may become less sensitive to catecholamines after a few days
  - Inotropes should be tapered slowly, not to be stopped suddenly.
- Renal
  - Prerenal failure leading to acute tubular necrosis (ATN) is common in septic shock (25%) but the risk can be much reduced by aggressive resuscitation.

- Coagulopathy
  - Coagulopathy is caused by consumption (DIC) and is a sign of severe sepsis
  - Effective resuscitation specifically reduces the risk of coagulopathy
  - Transfusion of FFP 20 mL/kg should be administered.
- Endocrine
  - Relative adrenal insufficiency does occur in septic shock
  - Administration of low-dose hydrocortisone improves shock but not survival in adults
  - Hydrocortisone at a dose of 2.5–5 mg/kg/day 6 hourly can be given to children with catecholamine refractory shock.
- Metabolic
  - Electrolyte abnormalities occur commonly in septic shock
  - Hypomagnesemia causes myocardial dysfunction and refractory hypokalemia
  - Hypokalemia can exacerbate myocardial function and precipitates arrhythmia
  - Hypocalcemia and hypophosphatemia can occur and affect myocardium and muscle function
  - Abnormalities should be corrected carefully in the acute setting via a central line, if possible.

ASSESSMENT OF A CHILD WITH PROLONGED FEVER (>7–10 DAYS' DURATION) OF UNKNOWN OR WELL-DEFINED SOURCE (NOT REVEALED FROM HISTORY AND PHYSICAL EXAMINATION)

Probable Source of Infection

The probable cause of prolonged fever depends on geographical position of the children. In Indian subcontinent, infection is the predominant cause of fever. In India, infection is attributed to 69% of all prolonged febrile children between 3 and 12-year-old.

Since viral infection is usually self-limiting, bacterial infections are more common agents of prolonged fever. Among bacterial infections, enteric fever (typhoid fever) is the most frequent cause of prolonged fever in children of Indian subcontinent. The other localized bacterial infections like abscess, sinusitis, septic arthritis, and osteomyelitis may also present as prolonged fever. But their source is clinically identified. However, some occult infections like perinephric abscess, subdiaphragmatic abscess, etc. may present as prolonged fever without apparent source.

Dengue fever usually does not last for more than 7 days and critical stages of dengue usually occur after 5 days with remission of fever, and therefore not a cause of prolonged fever in children. Mycobacteria, like *Mycobacterium tuberculosis* is an important cause of prolonged fever which may present as prolonged fever without obvious initial clue to source.

Among the parasites, malaria is a frequent cause of prolonged fever of unknown source. Visceral leishmaniasis (kala-azar) may present as prolonged fever in endemic areas, but usually have splenomegaly and other clinical features of kala-azar and therefore usually not a cause of prolonged fever of unknown origin where it is endemic.

Although most viral fever are self-limiting, few viral infections may cause prolonged fever apparently of unknown source. Hepatitis virus, particularly hepatitis B, non-A-E hepatitis and hepatitis due to infectious mononucleosis may cause prolonged fever without apparent source (anicteric hepatitis).

Cytomegalovirus infection and HIV infection are also associated with prolonged fever with initially undetectable etiology.

Other infections like rickettsial (typhus), chlamydial and fungal infection may be associated with prolonged fever without apparently showing their characteristic clinical features.

Malignancies

Children may present with prolonged fever as only clinical feature of underlying malignancy. Many malignant conditions in children presenting as fever are misdiagnosed as infectious diseases. A published study has found 70% of children who had acute leukemia presented with fever and initially misdiagnosed as infectious disease. However, infections are also frequently coexistent with malignancy.

Since majority of childhood malignancy are curable, it is desirable that they are identified earlier and treated timely. Clinicians should bear in mind that initial clinical features which include fever in malignancy may be misleading and can be misdiagnosed as infectious disease.

In children with prolonged fever, particular attention should be given to clinical features suggestive of malignancy like bone pain, bleeding manifestation, unusual pallor, nonblanching rash, lymphadenopathy and abdominal swelling (hepatosplenomegaly and intra-abdominal lump).

The common malignancies in children are acute lymphoblastic leukemia, CNS tumor and lymphoma.

Leukemia should be suspected if fever is associated with pallor, bone pain, lymphadenopathy and hepatosplenomegaly.

Lymphoma in children may present as painless masses in abdomen or neck accompanied by signs and symptoms due to local compression (breathing difficulty and features of venous obstruction if present in superior mediastinum). Systemic features like weight loss may be present.

Clinical features of CNS tumor include raised intracranial pressure, seizure and neurological deficit.

Collagen Diseases

Collagen disease is responsible for prolonged fever of unknown origin in 5–20% of cases. The most common collagen disease with fever is systemic onset juvenile idiopathic arthritis (JIA). Systemic onset JIA is characterized by once or twice daily spiking fever of >39°C which returns to baseline. Most of the spike occurs in afternoon or evening. In between fever, child appears normal. Each fever spike is associated with pink circular or linear macular rash. Other features include lymphadenopathy and splenomegaly.

Systemic Lupus Erythematosus (SLE)

Prolonged fever of clinically unknown origin, associated with multisystem involvement in a child particularly in girls of above 8 years of age is suggestive of SLE. Arthritis, malar rash (butterfly rash), seizures, nephritis, pericarditis, pleuritis, and weight loss occur in SLE. All above features may not occur in one patient.

Vascular Diseases (Vasculitis)

Kawasaki Disease

It is the most common vasculitis associated with prolonged fever. Although there are clinical characteristic features, some of the Kawasaki disease may present with only fever of 3–4 weeks duration, without its obvious characteristic clinical features. In addition to fever, these are four important features of Kawasaki disease; these are mucosal changes in lip and buccal mucosa, bilateral bulbar conjunctival infection, pleomorphic exanthema, cervical lymphadenopathy and changes in the extremity with rash or periungal peeling, which usually occurs in second or third week.

Other Causes of Prolonged Fever

Some drugs are associated with prolonged fever, which disappears with discontinuation of the offending drugs. The most common drugs involved are: Beta-lactam antibiotics, isoniazid, and diphenyl hydantoin.

Approach to Management of a Child with Prolonged Fever

Management consists of good history taking, thorough clinical examination and relevant laboratory investigation in order to come to a definite diagnosis, so that appropriate treatment can be provided.

History taking

A detailed and good history taking is very essential and integral part of diagnosis. First of all clinicians should be convinced that the prolonged fever is genuine and not fictitious. Although parent's conception of fever should not be disregarded by the clinician as untrue, in many unrecorded fever caretaker may wrongly perceive warm head and palm without raised temperature as fever. In infants particularly over bundling of the baby may show false increased temperature after removing clothes. Once clinician is convinced that he or she is dealing with genuine fever, next comes the issue whether it is prolonged one episode of fever or recurrent febrile illness due to back-to-back infection which is not uncommon in practice. Not uncommonly when a child suffers from typhoid fever for 10 days followed by another febrile illness in the following month, it may be narrated by parents as if the child is suffering from continued fever for 1 month.

History of immunization against vaccine preventable diseases should be taken, although all vaccines do not have high protective value and vaccine failure is not uncommon. Immunization history against *Haemophilus influenzae*, pneumococcus, typhoid fever, Hepatitis A and B should particularly be taken.

History of travel to endemic areas for some infectious disease should be sought. For example, if prolonged fever occurs after travel to endemic areas where malaria is endemic, one should suspect malaria as a probable differential diagnosis of prolonged fever of unknown source. Similarly if an Asian expatriate living in UK or USA develops prolonged fever of unknown source after returning from Indian subcontinent, clinician should consider typhoid, tuberculosis, etc. as differential diagnosis.

History of close contact with active tuberculosis is very important in developing countries in particular. It is also important to consider whether the child takes unpasteurized milk and dairy products, from which the child may develop bovine tuberculosis or brucellosis.

Drug history should also be asked. History of taking anti-TB drugs among close contact of child including mother sometimes provides clue to probable transmission of TB from close contact.

Physical Examination

A thorough physical examination should be done. Vitals should be recorded. Clinicians should look for pallor, jaundice (viral hepatitis), skin rash, lymphadenopathy, bony tenderness, and hepatosplenomegaly (leukemia). Physical examination may have to be done repeatedly to find new features like skin rash (SLE, Kawasaki), changing heart murmur, subacute infective endocarditis (SIE), etc.

Investigation

A battery of investigations should not be done initially; rather a rational approach should be taken to perform investigations relevant to likely diagnosis and close differential diagnoses. The investigations should be done to identify the probable causative organism or underlying cause responsible for fever on the basis of history and clinical examination of patient. The other features which can also help taking decision to do investigation are age of the child and local endemic disease like typhoid, malaria, etc. Before excluding less likely diagnosis, more common etiology should be tried to identify or ruled out through proper relevant investigation. Consideration should be given to availability and affordability of investigation. One has to compromise or prefer to do less specific but cheaper available investigation depending on affordability of parents or resource of medical institute.

Major difficulties in laboratory diagnosis of prolonged fever of clinically unknown source in resource poor developing countries are constraints, that include cost, availability and reliability of the laboratory test and injudicious use of antibiotics which hinders to yield true result particularly if fever is of infective origin. Diagnostic dilemmas are also frequently encountered both clinically and investigation wise in some common febrile illnesses in developing countries like malaria and typhoid. Final diagnosis is made by experienced clinicians by correlating investigation reports with clinical features. Other puzzling conditions for both parents and clinicians are immune-mediated fever which are not infrequently associated with typhoid fever, malaria and in simple viral fever where fever continues even after the underlying infective organisms have been eliminated.

It is desirable that initial investigation should be done to diagnose more commonly prevalent treatable diseases causing prolonged fever of unknown source. The investigation initially should be simple, less invasive and well-practiced unless otherwise indicated.

Since infection is a major cause of prolonged fever without source particularly in developing countries and majority of them are treatable, it makes more sense to exclude infectious disease, particularly common bacterial infection, unless otherwise indicated. After excluding infectious causes, other diseases responsible for prolonged fever of unknown source like childhood malignancies, collagen diseases, etc. should be looked for by performing relevant investigations.

Initial investigation of pyrexia of unknown source, particularly in developing countries therefore should include the following:

- FBC
- Peripheral blood film
- Platelet count
- ESR and CRP.

FBC >15,000/cumm (15×10^9/L) and absolute neutrophil count (ANC) >7500/cumm (7.5×10^9/L) is suggestive of bacterial infection. However in febrile neutropenia, absolute neutrophil count (ANC) of $<1 \times 10^9$/L is associated with severe bacterial infection (SBI).

FBC count <5,000/cumm ($<5 \times 10^9$/L) usually rules out bacterial infection except in typhoid and in neonate.

ESR: A normal ESR usually excludes rheumatological or malignant disorders.

Peripheral blood film (PBF): PBF can also provide clue as to the cause of fever. PBF showing significant lymphoblast is suggestive of acute leukemia. Polymorph showing toxic granules is suggestive of bacterial infection. Atypical lymphocytes may be seen in infectious mononucleosis and CMV infection. Malarial parasite may be detected in malaria.

Platelet count: Platelet count may be decreased in typhoid fever, ALL, aplastic anemia. Although it is decreased in dengue, it is not a cause of chronic fever. Platelet count is increased in Kawasaki disease.

CRP: CRP is increased in bacterial compared to viral infections. Discriminative value for bacterial infection is high in higher titer. It acts as a surrogate marker of bacterial infection particularly when blood culture is negative in presence of bacterial infection due to poor sensitivity of blood culture for many bacterial infections including typhoid. Other markers currently used are procalcitonin and IL-6.

Urine routine and culture: It is useful noninvasive test in young children and infants where clinical features of UTI, related to urinary symptoms (dysuria, polyuria) are frequently absent.

X-ray chest: A chest X-ray may be done in prolonged fever with unknown source, particularly if respiratory symptoms are present. It may help to diagnose *Mycoplasma pneumonia* where respiratory features (chest retraction and increased respiratory rate) may be absent. Evidence of pulmonary TB can also be obtained from X-ray chest.

MT: It is useful to diagnose TB in children.

Test to detect latent TB:

- New in vitro test: Quantiferon TB assay
- Measures interferon gamma (IFN-γ) produced by T-cells in whole blood after stimulation with PPD. First generation of γ-IFN assay is available in ELISA format in Quantiferon TB assay
- Other new ELISA to detect IFN–γ is ELIS POT.

Further investigations are done depending upon initial investigation in correlation with clinical findings. If the initial investigations are suggestive of bacterial infection (FBC, ANC, CRP), the attempts are taken to isolate the organisms.

Direct detection method for bacterial isolation from body fluid (blood, CSF, urine, gastric aspirate):

- Microscopy
- Culture technique
- Antigen detection
- Molecular assay (e.g. polymerase chain reaction).

Microscopy:

- Gram stain: To detect Gram-positive and Gram-negative bacteria
- Zeihl-Nelsen stain: To detect *M. tuberculosis* in gastric aspirate.

Bacterial Identification Using Specific Antisera (e.g. latex agglutination)

- Culture technique: Once bacteria are identified, it can be cultured in the presence of antibiotic to assess its susceptibility to antibiotics.
- Culture of various body fluids: Most widely used, often as part of initial infective screen is blood culture.
- Culture of other body fluids (CSF) is also done if clinically indicted. Culture techniques used are:
  - Using special media
  - Identification using specific antisera (latex agglutination)
  - Molecular method (e.g. DNA sequencing/PCR).

Serologic Tests

Serology test can be done to diagnose certain bacterial infection, e.g. Widal test for typhoid which is simple and cheap but not very much sensitive or specific. Currently, ELISA test for specific IgM for *S. typhi* are also available. Detection of IgM antibody by ELISA for scrub typhus is specific and sensitive. Immunofluorescence assay detecting IgM antibody (titer >1:64) is suggestive of rickettsial disease and considered as gold standard for diagnosis of rickettsial disease. However, Weil Felix test (which is included in the triple antigen test in the Indian subcontinent) can be used for diagnosing rickettsial disease in developing countries where above-mentioned tests are not available, although it is less accurate. The test depends on detection of antibodies to various *proteus* species. Significant titer is >1:180; a rising titer is more significant.

Virus Diagnosis

Though most viral infections causing fever are self-limiting, few viruses may cause prolonged febrile illness. Virology screen should be done if the clinical features and initial investigation (atypical lymphocytes in PBF and normal CRP) are suggestive of viral infection.

PCR is most sensitive and specific test for viral infection. It should be done in early part of infection before viral shedding is stopped. However, by the time the fever becomes prolonged, it may not be useful. Although PCR has revolutionized diagnostic pathology, its use is limited in developing countries due to its high cost.

Viral Serology

Viral serology studies are more appropriate in diagnosis of viral infection causing prolonged fever because once viral shedding is ceased, viral culture and PCR have no value. Diagnosis is made by either detecting antigen or antibody in blood or body fluid.

Methods include:

- Agglutination
- Immunofluorescence

- ELISA
- Complement fixation.

Antibody testing includes testing for hepatitis A-E, CMV, Epstein-Barr virus (EBV), HIV and other with potentiality to cause prolonged fever.

General principles:

- Rising IgM indicates new infection
- Rising IgG indicates new or previous infection or immunity as a result of vaccination
- Increasing IgG (rising titer), when two samples are taken within reasonable interval (paired sera) indicates new infection.

Rickettsial Infection

Diagnosis is made in suspected cases by either detecting antibody or antigen in blood or other body fluid. Methods include:

- Agglutination
- Immunofluorescence
- ELISA
- Complement fixation test.

Less expensive but less accurate test, Weil Felix test for diagnosis of rickettsial disease is useful in developing countries. A rising titer is more significant.

Fungal Infection

Direct microscopy is often used to diagnose fungal infection. Histopathological diagnosis can however be confirmed on culture.

Protozoal Infection

Malaria quite frequently may cause prolonged fever without obvious clinical features. PBF may show malarial parasite (MP); however, frequently it is not found in PBF causing diagnostic dilemma. New methods are available for identifying MP in PBF. They include Quantitative Buffy Coat (QBC) test. It involves staining of centrifuged and compressed red cell layers with acridine orange and examination under UV light source.

Rapid diagnostic tests detect malarial antigen (PfHRP2/PMA/PLDH) from asexual and sexual forms of parasite.

PCR: PCR has been found highly sensitive and specific for detecting all species of malaria.

Other investigations involving noninfective cause depend on probable diagnosis.

Bone marrow study (BMS): BMS should be done if laboratory findings of anemia, leukopenia or leukocytosis, thrombocytopenia are present to exclude ALL or aplastic anemia which may be associated with chronic febrile illness. Peripheral blood film showing significant blast cells is also suggestive of ALL and it should be confirmed by bone marrow study.

If history and clinical examination is suggestive of connective tissue disorder then tests for rheumatoid factor (RF), antinuclear antibody (ANA), anti-ds-DNA antibody, antiphospholipid antibody, etc. should be done. In majority of cases of juvenile chronic arthritis (JCA), the above tests are however negative. On the other hand, they are usually positive in SLE.

Imaging

Imaging which includes ultrasonogram of abdomen, CT/MRI of brain, mediastinum and abdomen, should be done in suspected solid tumor.

Echocardiogram

Echocardiogram should be done if subacute infective endocarditis is clinically suspected which affects heart valves. It is also useful in diagnosing and evaluating coronary artery abnormalities associated with Kawasaki disease.

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15 Endocrinology

HORMONES

Hormone is a chemical messenger made by tissues or ductless glands and secreted into blood.

Types of Hormones

Hormones are being classified in various ways:

- *According to mode of secretion*
  - *Autocrine*: Act on the same cell that synthesize the hormone
  - *Paracrine*: Act on neighboring cells in the same tissue
  - *Endocrine*: Act on cells distant to the site of origin carried via blood or lymph
  - *Pheromonal*: Volatile hormone released in the atmosphere where they can act on another individual.
- *According to chemical nature*
  - *Amines*: Catecholamines, thyroxine
  - *Peptides*: Oxytocin, insulin, luteinizing hormone (LH)
  - *Lipid and phospholipid derived hormone*:
    - Steroids: Cortisol, testosterone
    - Sterols: Calcitriol
    - Eicosanoid: Prostaglandin.

Biosynthesis, Transport and Metabolism

Biosynthesis

Classical hormones are synthesized in specialized cell types within particular endocrine glands. Biosynthesis and secretion are controlled by homeostatic negative feedback mechanisms that involve:

- Stimulating or releasing hormones
- Nervous system signals
- Plasma concentrations of nutrients or binding globulins
- Environmental effects such as light or temperature.

Secretion

Patterns of secretion are variable. The common patterns are:

- Continuous: T4
- Pulsatile: Follicle-stimulating hormone (FSH), LH, growth hormone (GH)
- Circadian: Cortisol
- Sleep-related: GH
- Stress-related: Adrenocorticotropic hormone.

Transport and Metabolism

Most hormones are transported in the blood, bind to carrier protein in the plasma. Some of the carrier proteins are specific with high affinity for particular hormones or nonspecific such as albumin.

Mechanism of Hormone Action

Hormones exert their effect by either stimulating or inhibiting biological processes. Most hormones act by binding with a receptor protein. The receptors are of two types:

1. Cell surface membrane receptor: Water-soluble amines and peptides hormones bind with cell surface membrane receptors.
2. Intracellular receptors: Steroids and thyroid hormones bind with intracellular receptors.

Cell surface membrane receptors: These are the integral membrane proteins of the target cells. Hormones combining with these receptors yield second messenger and complete signal transduction. There are two types of such receptors:

1. G-protein coupled receptors: Binding with hormones causes dissociation of intracellular trimeric G-protein and activates one of a variety of second messenger systems. Some examples of 2nd messenger are as follows:
   - Adenylate cyclase [produces cyclic adenosine monophosphate (cAMP)]: Epinephrine, norepinephrine, FSH, LH, thyroid-stimulating hormone (TSH), calcitonin, parathyroid hormone (PTH)
   - Inositol triphosphate system: Epinephrine and acetylcholine
   - Cyclic guanosine monophosphate (GMP): Peptide hormones like atrial natriuretic peptide (ANP).
2. Tyrosine kinase receptor: Ligand binding causes dimerizing the receptor and thus activates receptors. For example, insulin receptor. There may be self-phosphorylation of the tyrosine kinase or interaction of hormone with receptor leads to activation of cytoplasmic tyrosine kinase.

Intracellular receptors: The hormone-receptor complex binds to the promoter region of specific genes and modulates their expression. They are located in the cytoplasm and lipophilic in nature. They belong to nuclear receptor superfamily which has characteristic three domains. These receptors are of three classes:

1. Class I, thyroid receptor superfamily: Receptor for glucocorticoids, estrogen, androgen, mineralocorticoids belongs to this class. They are distributed in cytoplasm.
2. Class II, thyroid/retinoid family: They are located at nucleus. Receptors for thyroid hormone, vitamin D, retinoic acid belong to this class.
3. Class III, orphan receptor family: They share homology to known receptors but no ligand is yet identified.

Hypothalamus

Hypothalamus occupies most of the ventral region of the diencephalon. It is divided into three regions and has several nuclei (Fig. 1 and Table 1). Major nuclei are:

- Paraventricular nucleus (PVN)
- Supraoptic (SO)
- Arcuate nucleus (ARN)
- Ventromedial nucleus (VMN)
- Medial nucleus (MN)
- Optic chiasma (OC)
- Lateral hypothalamic area (LHA).

The hormones of the posterior lobe (PL) are released into the general circulation from the endings of SO and paraventricular neurons, whereas hypophysiotropic hormones are secreted into the portal hypophysial hormones circulation from the endings of arcuate and other hypothalamic neurons.

Pituitary

Pituitary gland is divided into two parts: (1) anterior pituitary (adenohyposphysis) and (2) posterior pituitary (neurohypophysis).

Anterior Pituitary

It is divided into three parts:

1. Pars distalis: Major part.
2. Pars tuberalis: A sheath wrapped around the pituitary stalk.
3. Pars intermedia: Often very small in human.

Anterior pituitary is functionally linked to the hypothalamus via the hypophyseal-portal vascular system in the pituitary stalk.

Hormones of anterior pituitary: Anterior pituitary produces six hormones under control of hypothalamus. They are as follows:

1. Growth hormone:
   - Stimulates the production of insulin-like growth factor 1 (IGF-1, the mediator of the indirect actions of GH)
   - Exerts direct actions on growth and metabolism
   - Modulates immune function and hemostasis.
2. Prolactin:
   - Stimulates milk production (protein and lactose synthesis, water excretion and sodium retention). Inhibits gonadotropin
   - Acts as immunomodulator.
3. Adrenocorticotropic hormone:
   - Stimulates glucocorticoids and sex steroids in the zona fasciculata and zona reticularis of the adrenal cortex
   - Induces hyperplasia and hypertrophy of the adrenal cortex.
4. Thyroid-stimulating hormone:
   - Stimulates all aspects of thyroid gland functions like hormone synthesis, secretion, hyperplasia, hypertrophy and vascularization.
5. Luteinizing hormone:
   Females:
   - Stimulates steroid hormone synthesis in theca interna cells, lutein cells and hilar cells
   - Promotes luteinization and maintains corpus luteum.

   Males:
   - Stimulates steroid hormone production in Leydig cells.
6. Follicle-stimulating hormone:
   Females:
   - Targets the granulosa cells to promote follicular development
   - Stimulates aromatase expression and inhibin secretion.

   Males:
   - Targets the Sertoli cells to promote spermatogenesis and to stimulate inhibin secretion.

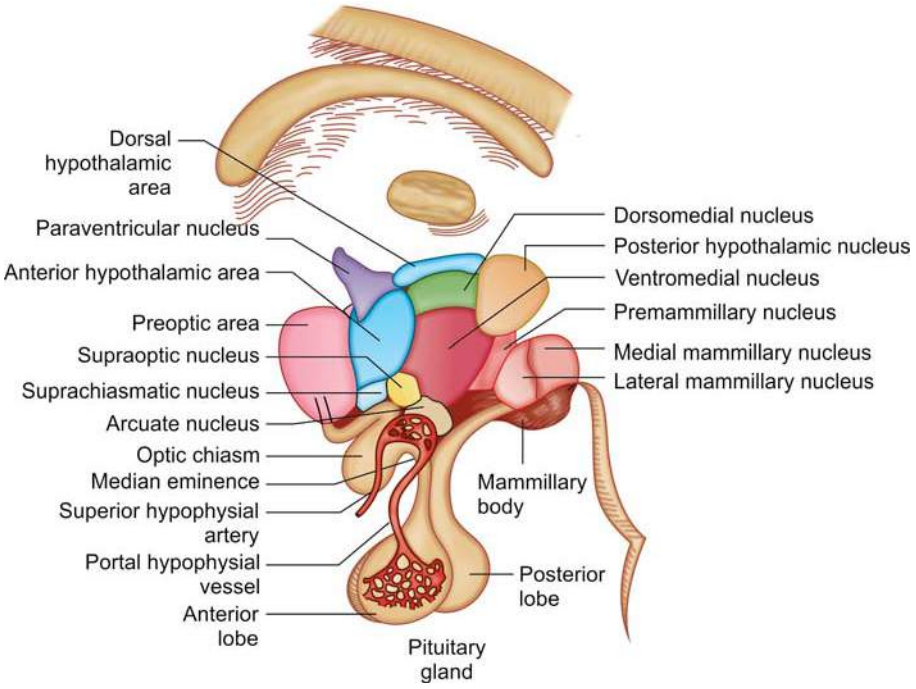


Fig. 1: Pituitary gland (anterior and posterior) and hypothalamus with nuclei present in hypothalamus

Table 1: Nucleus of the hypothalamus, their products and the effects of the hormones

Nucleus	Location	Major neurohormones or functions
Supraoptic	Anterolateral, above the optic tract	ADH: Osmoregulation, regulation of ECF volume Oxytocin: Regulation of uterine contractions and milk ejection
Paraventricular	Dorsal anterior periventricular	Magnocellular PVN: ADH, oxytocin: Same functions as above Parvocellular PVN TRH: Regulation of thyroid function CRH: Regulation of adrenocortical function, regulation of the sympathetic nervous system and adrenal medulla, regulation of appetite ADH: Coexpressed with CRH, regulation of adrenocortical function VIP: Prolactin-releasing factor (?)
Suprachiasmatic	Above the optic chiasm, anteroventral periventricular zone	Regulator of circadian rhythms and pineal function Zeitgeber (pacemaker): VIP, ADH neurons project mainly to the PVN
Arcuate	Medial basal hypothalamus close to the third ventricle	GHRH: Stimulation of GH GnRH: Regulation of pituitary gonadotropins (FSH and LH) Dopamine: Functions as PIH Somatostatin: Inhibition of GHRH release Regulation of appetite (neuropeptide Y, agouti-related transcript, -MSH, cocaine- and amphetamine-related transcript)
Periventricular	Anteroventral	Somatostatin: Inhibition of GH secretion by direct pituitary action: Most abundant SRIF location
Ventromedial	Ventromedial	GHRH (as above) Somatostatin: Inhibition of GHRH release Functions as a satiety center
Dorsomedial	Dorsomedial	Focal point of information processing: Receives input from VMN and lateral hypothalamus and projects to the PVN
Lateral hypothalamus	Lateral hypothalamus	Functions as a hunger center (melanin-concentrating hormone, anorexins)
Preoptic area	Preoptic area	Main regulator of ovulation in rodents. Only a few GnRH neurons in primates
Anterior hypothalamus	Anterior hypothalamus	Thermoregulation: “Cooling center” Anteroventral 3rd ventricular region: Regulation of thirst
Posterior hypothalamus	Posterior hypothalamus	Thermoregulation: “Heating center”

Abbreviations: ADH, antidiuretic hormone; ECF, extracellular fluid; PVN, paraventricular nucleus; TRH, thyrotropin-releasing hormone; CRH, corticotropin-releasing hormone; VIP, vasoactive intestinal polypeptide; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PIH, prolactin-inhibiting hormone; GH, growth hormone; GHRH, growth hormone-releasing hormone; SRIF, somatotropin release-inhibiting factor; VMN, ventromedial nucleus; GnRH, gonadotropin-releasing hormone

Posterior Pituitary

Posterior pituitary consists mainly of projections from the hypothalamus extending via the infundibulum to terminate behind the anterior pituitary gland. Hormones are synthesized in the cells of hypothalamic nuclei and secreted into the capillaries of the hypophyseal circulation.

Hormones of the posterior pituitary gland: The hormones secreted by posterior pituitary are oxytocin and arginine vasopressin (AVP) which are peptide in nature.

1. Oxytocin:
   Central action:
   - Sexual behavior and bonding: Having a role in arousal and is released during orgasm
   - Antistress function: Oxytocin encourage “Ten and befriend” activity
   - Fetal brain protection: By crossing the placenta, maternal placenta reduces the vulnerability of fetal cortical neurons to hypoxic damage.

   Peripheral action:
   - Acts on mammary gland causing milk to be “let down”
   - Uterine contraction during labor
   - Weak antidiuretic action.
2. Arginine vasopressin:
   Central actions:
   - Adrenocorticotropic hormone (ACTH) secretion: Acts on AVP receptor-IB (AVPRIB) receptors in the anterior pituitary to promote secretion of ACTH
   - Central nervous system (CNS) effects:
     - Regulation of blood pressure and temperature
     - Regulation of social behavior
     - Supports formation of pair bonds during sexual activity

   Peripheral actions:
   - Antidiuretic effects: Acts on AVPR2 receptor in the apical cells lining the collecting ducts of renal tubules to cause insertion of aquaporin-2 channel, allowing water to be reabsorbed down an osmotic gradient
   - Vasoconstriction: Acts on AVPRIA receptors on vascular smooth muscles causing vasoconstriction
   - Coagulation: AVPRIA receptors expressed on platelets and influences release of factor VIII and von Willebrand factor (vWF).

Hypopituitarism

Deficiency of one or multiple hormones of the anterior pituitary is termed as hypopituitarism.

Deficiency of all anterior pituitary hormones is termed as panhypopituitarism.

Etiology: Congenital hypopituitarism is caused by mutation in genes (e.g. PIT-1, HESX1, KAL1, etc.) encoding transcription factors important in pituitary development.

Cases of congenital hypopituitarism:

1. Hypothalamic:
   - Hypothalamic dysplasia
   - Hypothalamic hormone deficiency(s): corticotropin-releasing hormone (CRH), growth hormone-releasing hormone (GHRH), gonadotropin-releasing hormone (GnRH), thyrotropin-releasing hormone (TRH).
2. Anterior pituitary:
   - Dysplasia
   - Anterior pituitary hormone deficiency(s): GH, TSH, ACTH, FSH, LH.
3. Posterior pituitary:
   - Familial (X-linked or autosomal dominant)
   - Idiopathic
   - Secondary to: trauma/asphyxia, intraventricular hemorrhage, disseminated intravascular coagulation (DIC), inflammation (e.g. meningitis) and maternal drugs (e.g. lithium).
4. Associated with other congenital anomalies:
   - Anencephaly/holoprosencephaly
   - Agenesis of the corpus callosum
   - Persistent septum pellucidum
   - Familial pituitary hypoplasia
   - Septo-optic dysplasia
   - Central cleft lip and/or palate
   - Congenital rubella, congenital toxoplasmosis.

Causes of acquired hypopituitarism:

- Perinatal insult: Perinatal asphyxia
- Intracranial tumors: Craniopharyngioma
- Trauma
- Postsurgery
- Cranial irradiation.

Clinical features of hypopituitarism: Underlying causes and clinical presentation vary with age.

In the newborns:

1. Anterior hypopituitarism:
   - Symptoms and signs of hypoglycemia
   - Other symptoms and signs include micropenis, hypothermia and conjugated hyperbilirubinemia
   - Dysmorphic features such as midline defects and craniofacial anomalies
   - Optic nerve hypoplasia/dysplasia
   - Most have a birth length and weight below the mean (although usually within normal centiles)
   - Some have severe growth failure, even at birth
   - Although some children may grow normally in early childhood, in others growth failure is more immediate.
2. Posterior hypopituitarism:
   - May present with polyhydramnios
   - After birth, there may be signs of dehydration: excessive weight loss, irritability, fever, hypernatremia, convulsions or coma
   - Breastfed babies may present later with failure to thrive, anorexia, vomiting, fever, constipation, or developmental delay.

In older infants and children:

- Growth failure with delayed skeletal maturation due to GH deficiency or hypothyroidism secondary to TSH deficiency
- Absent or delayed puberty or infertility due to gonadotropin deficiency
- Weight gain with relative truncal obesity
- Hypoglycemia
- Visual and neurologic abnormalities
- Anosmia in Kallmann syndrome with delayed puberty.

Laboratory investigations:

Endocrine tests: By combination of random hormone level estimation and provocation test, hypothalamic-pituitary axis can be evaluated.

1. Random hormone levels:
   - For thyroid functions: Free thyroxine (FT_4), TSH
   - For adrenal cortical functions: Glucose, urea and electrolytes, morning serum cortisol
   - For gonads: In infants, random LH, FSH, estradiol and testosterone
   - Growth hormone.
2. Stimulation (provocation) tests:
   - Synacthen test for ACTH
   - Luteinizing hormone-releasing hormone (LHRH) stimulation test for FSH/LH response
   - Growth hormone stimulation test.

Imaging:

X-ray: In craniopharyngioma, a lateral skull X-ray may show an abnormal pituitary fossa and calcification.

MRI: MRI of brain is the modality to assess hypothalamic-pituitary function.

Management: Treatment depends on underlying cause. It is easier to replace target glands hormones like:

- GH replacement with synthetic somatotropin
- TSH replacement with T_4
- ACTH replacement by hydrocortisone
- LH, FSH replacement by testosterone or estrogen and progesterone.

Craniopharyngioma is treated by surgical resection in combination with radiotherapy if initial resection is incomplete.

GROWTH AND ITS DISORDERS

Growth consists of three phases superimposed upon each other, each of which is under different controls, nutritional and hormonal.

1. Infantile phase: Growth is predominantly under nutritional control. Children with congenital GH deficiency usually have normal birthweight and lengths.
2. Childhood phase: Childhood phase is under hormonal control, predominantly GH and thyroid hormone; also nutritional factors play a role. There is a steady and decelerating growth curve which starts at around 2–3 years of age and continues until puberty. By the 8th birthday, most children achieve three-quarter of their adult height.

   Malnutrition is associated with a GH resistant state with elevated serum GH, but abnormal pulsatility of IGF-1 and GH receptor (GHR). Growth hormone in infancy is

determined by nutrition. During the first year of life, infant grows more rapidly than any other period in extauterine life. By 2 years of age, a child is roughly half of adult height indicating that 50% of linear growth has already occurred.

3. Puberty phase: Puberty phase is under the control of GH and sex hormone acting synergistically. Height velocity may double during pubertal growth spurt, increasing trunk length is predominant. This lasts from adolescent onward and has different strength and timing in two sexes.

It is the phase of growth which accounts for the sex differences in the final height of around 14 cm between males and females. While girls enter their growth spurt earlier, the peak height velocity is not as great as in boys. The same sex steroids cause fusion of the epiphyseal growth plate and a cessation of growth, so final height is reduced if puberty is early.

Physiology of Growth

After initial infantile period, GH is the main factor involved in growth. The factors involved in GH secretion are shown in Figure 2.

At the hypothalamic region, GH is secreted under the influences of somatostatin (inhibitory) and GnRH (stimulatory). There are number of other factors acting at the hypothalamic region, including exercise, sleep and drugs, which are used diagnostically to secrete GH.

Growth hormone is secreted in a pulsatile fashion with pulses approximately every 180 minutes. The largest pulses are at the night time.

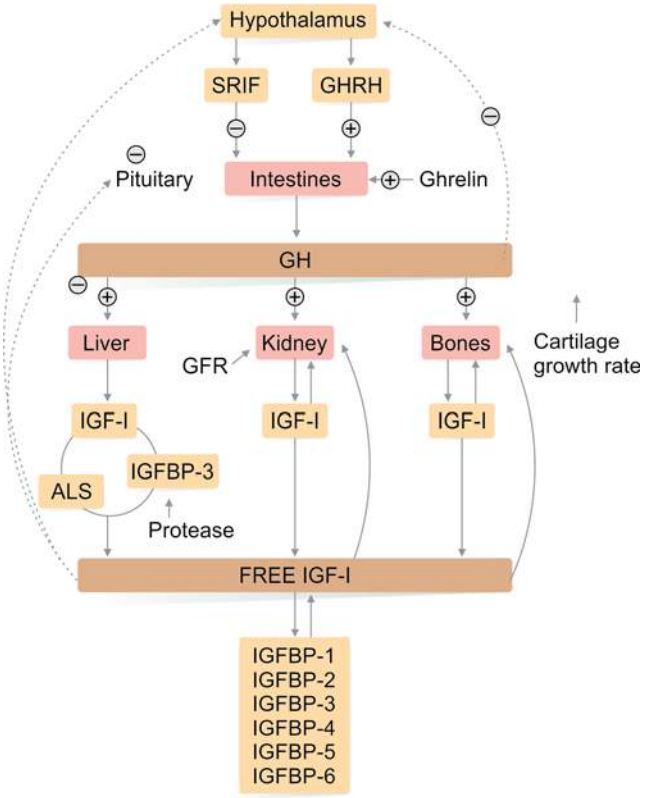


Fig. 2: Regulation of growth hormone secretion

Abbreviations: IGFBP, insulin-like growth factor-binding protein; IGF, insulin-like growth factor; GH, growth factor; SRIF, somatotropin release-inhibiting factor; GHRH, growth-hormone-releasing-hormone; ALS, amyotrophic lateral sclerosis

Growth hormone binds to transmembrane GHR which then causes dimerization and phosphorylation of GHR and JAK-2, a tyrosine kinase.

Human Growth Hormone

Growth hormone or somatotropin is produced in the anterior pituitary gland. Its production is modulated by a complex interplay of stimulatory and inhibitory factors. Growth hormone has its major effects on linear growth, but it also influences a variety of metabolic pathways, induces lipolysis, and stimulates anabolic activity. Growth hormone levels tend to be greatest during puberty and decline gradually in adulthood.

Regulation and Control of Secretion of GH

The pituitary gland contains large amounts of stored GH (5–10 mg). Growth hormone production is controlled by a complex interplay of hypothalamic stimulatory and inhibitory peptide, neurotransmitters, growth factors, sex steroids and nutritional conditions.

The most important regulators of GH are the hypothalamic hormones, GHRH, which is stimulatory and somatostatin which is inhibitory. GHRH and somatostatin, in turn, are regulated by feedback from blood GH and IGF-1 concentrations. The peptide ghrelin also stimulates GH release. GH acts directly on many organs to stimulate IGF-1 production. IGF-1 production in the liver provides the main source of blood IGF-1. Most of the IGF-1 in the circulation is bound to IGF-binding protein 3 (IGFBP-3) and a smaller fraction is bound to the five other IGF-binding proteins (IGFBPs). A small fraction of the total IGF-1 in blood is in a bioactive free form. In the kidney, IGF-1 increases the glomerular filtration rate (GFR). In bone, it acts on the epiphyseal plate, which leads to longitudinal bone growth. Growth hormone also has direct effects on many organs, which can be independent of IGF-1 action.

Large bursts of LH secretion characteristically occur at night in association with slow-wave sleep. The rate of GH secretion from the anterior pituitary is highest around puberty, and declines progressively thereafter. The amplitude of GH pulses is greater in women than in men.

Effects of Growth Hormone

Direct Effects

- Oppose insulin, being lipolytic in fat and causing gluconeogenesis in muscle
- Stimulates duration and multiplication of chondrocytes promoting long bone growth.

Indirect Effects

In the liver: Synthesis and secretion of peptide IGF-1 and other tissues stimulate bone growth, protein synthesis and muscle.

Other hormones involved in growth are:

- *Sex steroid*: Increasing level of sex steroid in puberty stimulates growth by increasing endogenous GH secretion and may also have a direct effect in IGF-1 production
- *Thyroxine*: Plays an important role in controlling growth in part by regulating GH secretion
- *Growth factors*:
  - Insulin-like growth factors: IGF-1, IGF-2 and IGF-3: Have a high sequence similarity to insulin and form part of a system referred to as GH-IGF axis.

- Fibroblast growth factors (FGF): Also called heparin binding growth factors promote angiogenesis and mitogenic action in several different cell types
- Transforming growth factor (TGF): TGF-alpha and beta cause the growth of fibroblast cells.

Auxology

Height is measured using a stadiometer: Supine height at less than 2 years of age and standing at above 2 years of age. The height is compared to the population based centile chart and compared to midparental height (MPH) to assess the child's genetic height potential. The height velocity in cm/year is determined by two measurements at least at 4–6 months apart.

Midparental Height

From 2 years of age, there is strong correlation between:

- A child's centile position for height and their final height centile
- A child's centile position and their parents' height centiles.

As adult males are on average 14 cm taller than adult females, MPH for a boy is calculated as follows:

$$\text{MPH for a boy} = \frac{\text{Father's height (cm)} + \text{Mother's height (cm)}}{2} + 7$$

For a girl, 7 cm is deducted rather than added.

$$\text{MPH for a girl} = \frac{\text{Father's height (cm)} + \text{Mother's height (cm)}}{2} - 7$$

The target centile ranges (TCRs) [±2 standard deviation (SD)] are 10 cm of MPH for a boy and ±8.5 cm of the MPH for a girl.

Height Velocity (Fig. 3)

Growth is not a continuous process but has a number of superimposed phases:

1. Weeks: Growth spurts with intervening growth arrest ("saltation and stasis").
2. Months: Seasonal variation in growth (usually faster in spring and summer compared with autumn and winter).
3. Years: Long-term variation over a number of years.

Mean Height Velocity

A mean height velocity on the 50th centile will cause a child to grow parallel to the 50th centile for height.

Weight Velocity

The term centile crossing rather than "weight velocity" usually used especially in infants. The phenomenon of regression to the mean means that children born larger for dates tend to catch down, whilst the small for dates catch up. Approximately 50% of children cross at least one centile line between 6 weeks and 12–18 months. Five percent cross two centile line. Pubertal assessment is also required for growth which is discussed later.

Bone Age

Although GH secretion continues throughout life, final height is achieved in the mid-to-late teens when bony epiphyses fuse under the influence of estrogen. As the hand and wrist contain numerous epiphyses, a radiograph of the non-dominant hand enables a "bone age" to be calculated, which is an estimate of the "biological" rather than the "chronological" age. By quantifying the years of remaining growth, it also enables an estimation of final height to be made.

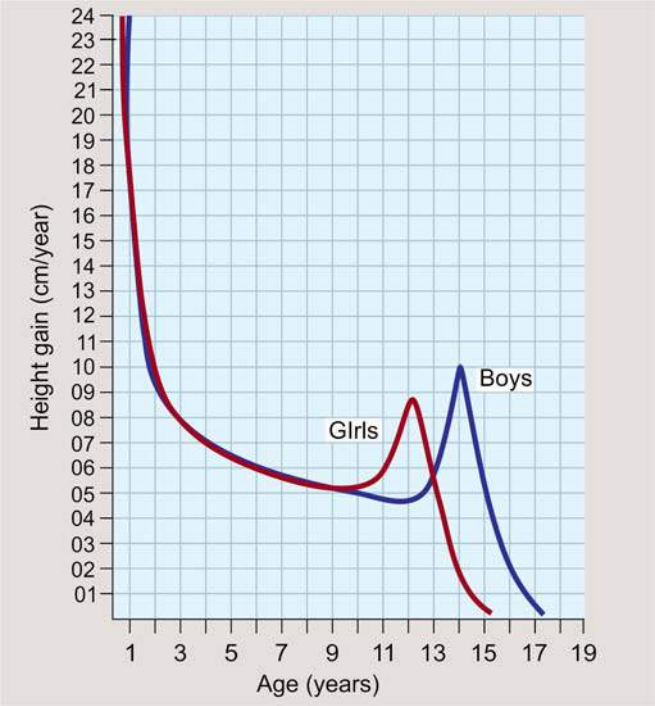


Fig. 3: Curves showing growth velocity of boys and girls. It shows that adult males are taller than females as they have a longer childhood growth phase, their peak height velocity is higher and their growth ceases later

Several different methods are used to estimate the bone age with Tanner and Whitehouse methods being most common. As tall and obese children mature faster than short children, it is usual for the bone age to be advanced in these children and delayed in short stature.

Growth Disorders

Different factors affect growth. These are as follows:

- *Environmental:*
  - Nutritional
  - Malnutrition
  - Socioeconomic
  - Poverty
- *Birth size*
  - Small for gestational age (SGA)
  - Intrauterine growth retardation (IUGR)
- *Chronic illness*
  - Cardiovascular: Chronic heart failure
  - Respiratory: Asthma, cystic fibrosis
  - Renal: Chronic renal failure (CRF)
  - Gastrointestinal: Celiac disease, inflammatory bowel disease
- *Familial:*
  - Familial height: Familial short stature
  - Familial growth pattern: Constitutional delay of growth and puberty
- *Endocrine:*
  - Thyroid hormone: Hypothyroidism
  - Growth hormone: GH deficiency

- Corticosteroid: Cushing's syndrome
- Sex steroids: Precocious puberty

- *Genetic:*
  - Turner syndrome (TS)
  - Noonan syndrome (NS)
  - Russell-Silver syndrome (RSS)
- *Psychological factors:*
  - Psychological deprivation.

Short Stature

Short stature is the commonest cause of referral to a pediatric endocrine unit. Although several conditions can lead to impaired growth, most children do not fit into any clearly defined category and are referred to as having idiopathic short stature.

Definition of short stature varies in relation to below which centiles of the height of a child will be. Short stature is usually defined as a height below the second (i.e. two standard deviations below the mean) or 0.4th centile (–2.6 SD) for age and/or linear growth velocity consistently less than –1 SD. It is important to use country-specific growth chart so that appropriate population standard are applied and overdiagnosis of short stature is avoided. While using growth chart, parents' height should be considered and MPH should be plotted.

Measuring height velocity is a sensitive indicator of linear growth failure. Two accurate measurements at least 6 months but preferably a year apart allow calculation of height velocity in cm/year. This is plotted at the midpoint in time on a height/velocity chart. A height velocity persistently below the 25th centile is abnormal and that child will eventually become short. The height centile of a child must be compared with the weight centile and an estimate of their genetic target centile and range calculated from the height of their parents.

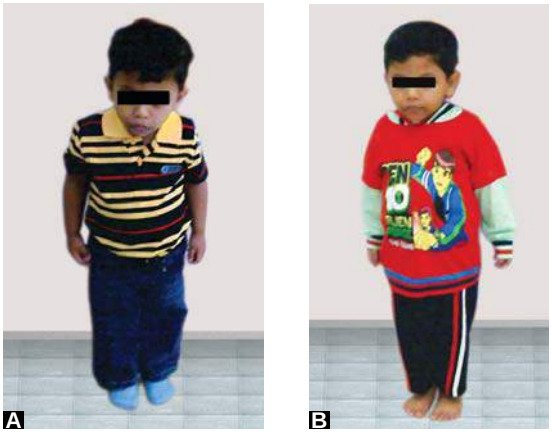
Causes of Short Stature

1. *Genetic*: Two major sets of genes determine child's height how tall he will be, other determines tempo of growth. These are assessed by MPH and bone age.
2. *Familial short stature and target height*:
   - Birthweight is normal
   - Other members of the family are usually short (Fig. 4)
   - Height is short but appropriate for parental height (as is final height)
   - Bone age is not substantially delayed
   - Height velocity is normal
   - Endocrine and other baseline testing is normal. Care needs to be taken though both the parents and the child not having an inherited growth disorder
   - There is absence of any other clinical features which might suggest an underlying disease.

     Parents' height should be taken in consideration, so that the height of the child can be properly interpreted for the family's genetic potential. The formula for calculating target height (TH) is: Father's height + mother's height divided by two plus 7 cm for boys and father's height + mother's height divided by two minus 7 cm for girls. This value is plotted then as adult height at 18 years and spread is 6 cm on the either side of the TH. This then is the target range, and if the child's height is within this percentile range, it is considered normal for that child
   - Treatment is explanation and reassurance.
3. *Idiopathic short stature (ISS)*: ISS is defined as a condition in which the height of an individual is more than 2 SD score (SDS) below the corresponding mean height for a given age and sex and population group without evidence of systemic, endocrine, nutritional or chromosomal abnormalities (Figs 5A and B). Specifically, children with ISS have normal birthweight and are GH sufficient. Idiopathic short stature is described as heterogenous group of children consisting of many presently unidentified causes of short stature. Many endocrinologists and authors include constitutional growth delay of growth and puberty (CDGP) and familial short stature underdefinition of ISS. In this process, it is estimated that approximately 60–80% of all short children at or below –2 SDS fits the definition of ISS. This definition of ISS includes short children labeled with CDGP and familial short stature.

   Idiopathic short stature is sometimes known as constitutional short stature and may be familial (as ISS above) or non-familial where the child's predicted height falls below the TH range. The criteria for ISS are as follow:
   - Height less than –2 SD (1.2%) for sex and age
   - Poor adult height prediction:
     - Less than 162.5 cm (5 ft 4 inch) for males
     - Less than 150 cm (4 ft 11 inch) in females

Fig. 4: Picture showing familial short stature. Mother 4'8", father 5'1", 10-year-old girl standing having height of age 6 years, 8-year-old boy having height of age 5 years



Figs 5A and B: (A) Idiopathic short stature in a 3-year-old child with height of 80 cm before treatment; (B) 9 months after GH treatment (somatotropin) the height reached to 88 cm

- No detectable cause for short stature. However, although idiopathic, some underlying genetic defects have been detected, e.g. HEX-1, SHOX gene haploinsufficiency
- Height velocity can be either normal or reduced.

4. *Constitutional delay of growth and puberty (CDGP)*: Relatively late in recognition of short stature at the secondary school when other peers are taller than the index child. It is one of the most common causes of (relative) short stature and is often a diagnosis of exclusion. It is more common in boys than girls (male:female ratio is 7:1).
   Features include:
   - Short stature during childhood when assessed by chronological age but not bone age
   - Poor growth from approx. 9–11 years of age onward, as peers enter the pubertal growth spurt
   - Delayed bone age (>2 SD but <3 SD)
   - Bone age is appropriate to height age
   - Often a history of CDGP in immediate relatives
   - Subnormal height velocity but spontaneous catch-up growth with the eventual onset of puberty
   - Family history of delayed puberty, e.g. menarche in child's mother after 15 years or father changing their shoes after entering in university
   - Delayed puberty (from 13 years onward in girls and 14 years onward in boys)
   - No evidence of any other underlying disorders which might produce delayed puberty.

Management: Explanation and reassurance that there will be eventually adequate catch-up growth which is usually sufficient. Rarely intervention, hormonal replacement may be required in child with considerable distress and behavioral changes.

Other Common Causes of Short Stature

1. Chronic malnutrition (nutritionally stunted): Frequently found in low-income and middle-income countries (Fig. 6).
2. Chronic systemic diseases:
   - Chronic infections such as tuberculosis
   - Chronic renal failure
   - Cardiac disease
   - Respiratory disease such as asthma
   - Collagen vascular disease, e.g. juvenile rheumatoid arthritis (JRA)
   - Inflammatory bowel disease.
3. Endocrine diseases:
   - Hypothyroidism
   - Growth hormone deficiency (GHD) and GH resistance syndrome
   - Cushing's syndrome
   - Delayed puberty
   - Precocious puberty.
4. Small for gestational age and IUGR:
   - Russell-Silver syndrome is associated with IUGR.
5. Chromosomal abnormalities and syndromes:
   - Turner syndrome
   - Noonan syndrome
   - Down syndrome.
6. Skeletal causes:
   - Mucopolysaccharidosis (MPS)
   - Achondroplasia
   - Hypochondroplasia.

Chronic malnutrition: It is an important cause of short stature. In chronic severe malnutrition, children become stunted as well as wasted. In chronic mild malnutrition, weight for age is decreased, height for age is significantly decreased, but weight for height is usually normal. The child may look small for his/her age but well-adapted with chronic nutritional stress, so-called "nutritional dwarfism".

Endocrine diseases: Only a minority of short stature have endocrine disorder. Hypothyroidism (Fig. 7) is confirmed on the basis of simple biochemical tests. The following increase the likelihood of GH or other hormone deficiency:

- Severe or progressive short stature
- Normal birthweight and length with subsequent growth failure
- Neonatal or late hypoglycemia
- Prolonged neonatal jaundice
- Micropenis and cryptorchidism
- Relative obesity and increased skin fold thickness
- Delayed dentition with bone age severely retarded and below height age
- A subnormal exercise provoked GH level usually less than 5 mU/L
- Previous cranial irradiation treatment or pituitary area surgery.

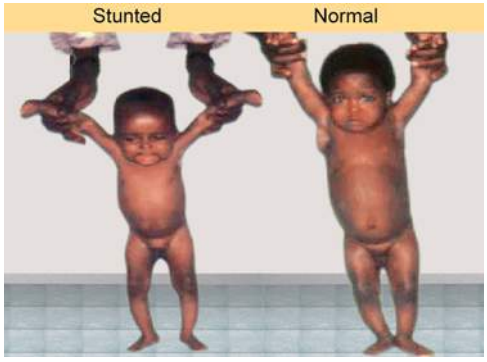


Fig. 6: Nutritionally stunted child in comparison to normal

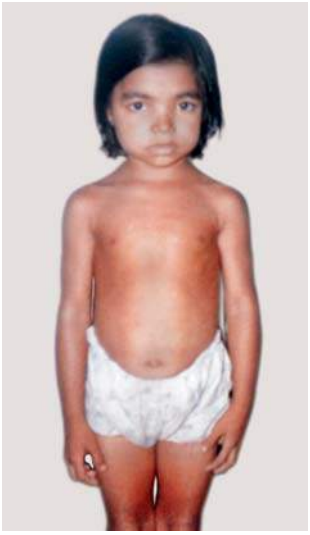


Fig. 7: A young girl with short stature due to hypothyroidism

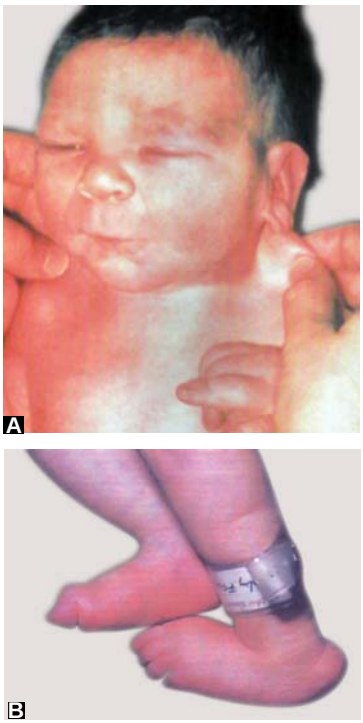
Small for gestational age and intrauterine growth restriction: Ex-IUGR children grow slowly than normal children and may be short for a long time. There is increased recognition that IUGR children develop diabetes mellitus (DM) and cardiac disease in adult life. Most children born SGA show postnatal catch-up growth with 90% achieving normal height (>–2 SD) about by 2 years of age. SGA born prematurely have different pattern of catch-up growth and take up to 4 years or more to achieve a height in the normal range.

Turner syndrome: It is the most common gonadal dysgenesis in female. Incidence is ~1 in 2500 live female births.

Genetics:
- Fifty percent have missing complete X chromosome (45,X)
- Fifty percent other abnormalities involving X chromosome which include deletion of short and long arm of X chromosome, duplication, ring chromosome or mosaicism.

Features regarding growth in TS:
- IUGR
- Poor growth in childhood
- Absent pubertal growth spurt
- Mild skeletal dysplasia.

Diagnosis:
- Clinical features:
  - Intrauterine period: On amniocentesis or following ultrasonographic finding of increased nuchal fold
  - Neonatal period: Non-pitting edema of hands and feet with webbed neck (Figs 8A and B) cardiac lesion like coarctation of aorta
  - Childhood: Dysmorphic features, short stature, educational problems.
  - Adolescence: Amenorrhea, arrested/delayed/absent puberty
  - At any age: By recognition of dysmorphic features



Figs 8A and B: (A) Turner syndrome presenting at birth with webbed neck; (B) Nonpitting pedal edema

  - Biochemical abnormality:
    - Abnormal GH secretion with other GH isoform.
    - Growth hormone insensitivity.
    - FSH, LH increased, estrogen decreased.
  - Ultrasonogram:
    - Streaky gonads.
    - Horseshoe shaped kidney.
  - Echocardiogram:
    - Coarctation of the aorta and other anomaly.
  - Karyotyping
  - Skeletal survey:
    - Evidence of cubitus valgus, absent 4th
    - metacarpal and metatarsal, scoliosis.

Noonan syndrome: Autosomal dominant condition. Incidence is about 1 in 1,000–2,500 children.

Clinical features: It shares phenotypic features with TS, hence called male Turner.

Facial: Low hairline and webbed neck (Fig. 9), wide epicanthic folds, low set and posteriorly rotated ears, hypertelorism, small upturned nose, deep philtrum, high arched palate.

Cardiac: Pulmonary stenosis, atrial septal defect (ASD) and ventricular septal defect (VSD), hypertrophic cardiomyopathy.

Gonadal: Delayed puberty, cryptorchidism.

Intellectual: Motor delay, poor IQ.

Other: Winged scapula, ophthalmological and hematological abnormalities, pectus carinatum, cubitus valgus.

Biochemical:
- GH: Low mean GH concentration, irregular wide pulses and high trough concentration
- IGF-1: Low.

Russell-Silver syndrome: It may be inherited as autosomal dominant, autosomal recessive and/or X-linked dominant fashion. Incidence is 1 in 75,000 births.
Diagnosis: For diagnosis of RSS, at least four of the following criteria should be present:
1. IUGR.
2. Poor postnatal growth with decrease height age.
3. Relatively normal head circumference.
4. Asymmetry, clinodactyly (Figs 10A and B).
5. Classical facial phenotype.

Clinical features:
- Growth failure in both prenatal and postnatal life

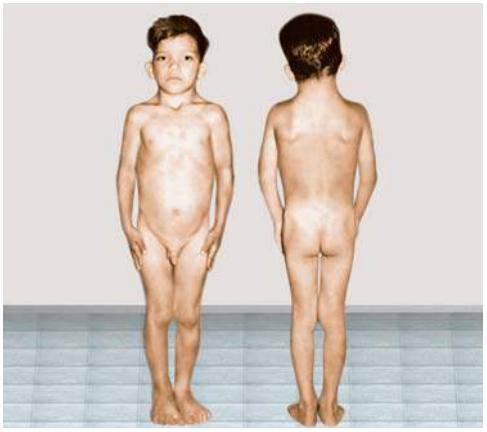


Fig. 9: A boy with Noonan syndrome having webbed neck, low hairline and winged scapula. The boy has pulmonary stenosis

Figs 10A and B: Russell-Silver syndrome. (A) A child with RSS at birth showing asymmetric lower limbs; (B) A 6-year-old child with height age of 2 years showing clinodactyly on 5th finger

- Dysmorphic features like triangular face, large head with prominent forehead, thin upper lip, clinodactyly, micrognathia
- Asymmetry of body or limbs (Fig. 10A)
- In males: Undescended testis and hypospadias
- Sweating, hypoglycemia
- Poor feeding.

Prader-Willi syndrome (PWS): Prader-Willi syndrome occurs due to deletion of 15q11–13. The condition is characterized by hypotonia, hyperphagia leading to gross obesity, short stature that is often due to GH deficiency, hypogonadism, and psychomotor retardation. They typically have small hand, feet, and almond-shaped eyes (Fig. 11).

Achondroplasia (Fig. 12A):

- Prevalence is about 1 in 25,000 births
- Autosomal dominant in inheritance, new mutation occurs in up to 85% cases
- It is due to two mutations (99% of cases) in the fibroblast receptor gene 3 (FGFR-3). Mutation in homozygous condition is lethal.

Clinical features:

- Short stature. Although autosomal dominant, parents may be of normal height as frequently it occurs due to new mutation (Fig. 12B)
- Large head with small foramen magnum
- Thick and short tubular bones with cupping of metaphysis
- Trident hands with short metacarpals and phalanges
- Short flattened vertebral bodies with increased intervertebral disc
- Squared and small iliac wings with a narrow sciatic notch
- Hydrops fetalis in homozygous achondroplasia.

Hypochondroplasia: It is due to mutation of FGFR-3 gene. Features are like that of achondroplasia but are of milder form and heterogenous (Fig. 13).

Clinical features:

- Long fibulae
- J-shaped sella turcica
- Failure of widening of lumbar interpedicular distances in the spine
- Anterior posterior shortening of lumbar pedicles and dorsal concavity of lumbar vertebral bodies.

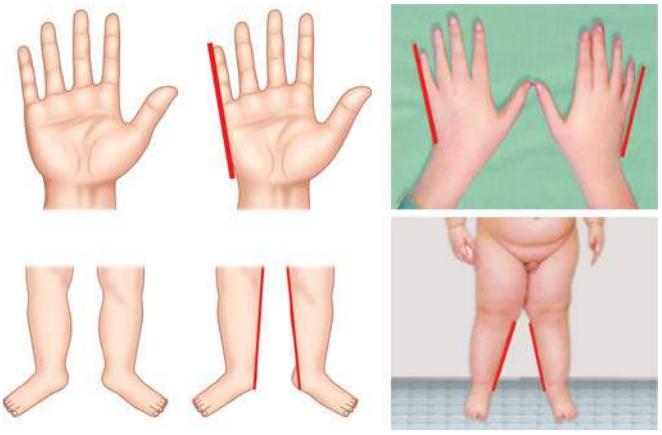


Fig. 11: Typical findings of hands and legs in child with Prader-Willi syndrome

Figs 12A and B: (A) A short statured child with achondroplasia; (B) Parents of same child with normal height with their short child due to new mutation

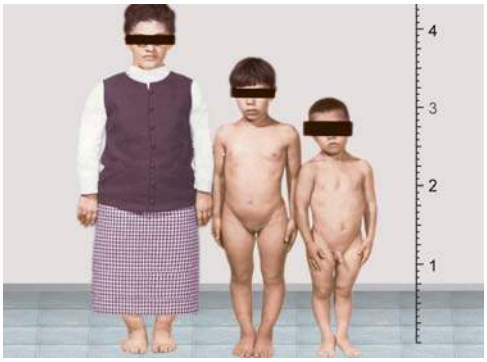


Fig. 13: Hypochondroplasia in mother and two children (autosomal dominant). Note the bowing of lower limbs but relative lack of craniofacial involvement and short stature of milder form than found in achondroplasia

Psychosocial deprivation/psychosocial short stature (PSS): Adverse social conditions, abuse, neglect/deprivation (both social and also psychosocial) contribute poor growth. This is a heterogeneous condition. Based on age and clinical/biochemical presentation, it is classified into three groups:

1. Type I PSS:
   - Onset in infancy
   - Weight faltering present
   - GH secretion is normal.

2. Type II PSS:
   - Onset at 3 years or more
   - Often depressed
   - Bizarre behavior of eating and drinking, hyperphagia, food hoarding and polydipsia
   - Decreased or absent GH secretion but reversible on hospitalization. Poor response to GH therapy.
3. Type III PSS:
   - Onset in infancy or older
   - Weight faltering and bizarre behavior usually not present
   - GH secretion is normal
   - Response to GH therapy is good.

Diagnosis of Short Stature

- Accurate measurement of growth parameters like height, weight, etc. Measurement of height of both parents and obtain any previous measurement if any.
- Careful history taking regarding:
  - Details of pregnancy, delivery, birthweight, perinatal history, any significant past medical history
  - Pattern of growth, systematic enquiry regarding any symptoms of underlying disorders or chronic disease
- Examination:
  - Dysmorphic features
  - Pubertal assessment
  - Evidence of disproportion
  - Signs of underlying diseases or chronic disorders
- Plotting appropriate data on growth chart
- Estimation of skeletal maturity using bone age
- Further investigations if appropriate.

Investigations for Short Stature

The purposes of investigations are:
- Presence or absence of primary growth disorder
- Identification of underlying chronic disorder which may require treatment.

Commonly done investigations are:
For chronic illness: Total blood count, erythrocyte sedimentation rate (ESR), urinalysis, liver function tests, celiac antibodies, bone profile.

For endocrine disorders:
- Thyroid function test
- GH stimulation test
- IGF-1, IGFBP-3
- Serum cortisol (at 8 am)
- Pituitary hormone assay: LH, FSH, testosterone, estradiol.

Karyotyping: When a chromosomal anomaly is evident it is mandatory to perform karyotyping both for boys and girls. Further genetic testing may be required if indicated.

Bone age: Determination of bone age by methods directed by Tanner and Whitehouse and Greulich and Pyle, is a cheap, very useful and reliable tool for assessment of short stature.

If bone age is delayed or advanced by 2 years or more, it is abnormal, suggesting underlying endocrine disorders (hypothyroidism, GH deficiency or Cushing's syndrome). Bone age is delayed in chronic illness but not as much as profound in endocrine disorder.

Neuroimaging:

X-ray skull: Provides some information about pituitary anatomy by presence of wide sella tercica and calcification (craniopharyngioma).

MRI: Best modality to diagnose pituitary gland and hypothalamic area pathology.

Growth hormone test: Intravenous insulin is given at a dose of 0.1 unit/kg to produce hypoglycemia up to less than 2.5 mmol/L and corresponding GH peak value is recorded. Sample is taken usually after 45 minutes when clinical symptoms of hypoglycemia like tachycardia, sweating and drowsiness but no loss of consciousness and corresponding blood glucose level falls below 2 mmol/L. However, it should be done under close supervision in hospital with backup emergency of pediatric team. Growth hormone peak value of less than 10 ng/mL indicates GH deficiency. This test measures GH response to induced hypoglycemia.

Other provocation tests include glucagon, arginine and dopamine provocation tests. Insulin provocation test is not suitable for children of less than 15 kg weight.

A diagnostic workup and management algorithm for short stature is mentioned in Figure 14.

Keys and summary of algorithm:
1. Short stature defined as absolute height less than –2 SD for age and/or linear growth velocity consistently less than –1 SD.
2. Children with height greater than –2 SD and/or height velocity greater than 0 SD are probably normal.
3. When a child is significantly short (height <–2.5 SD for age and height velocity <–1 SD) without any evidence of hypothyroidism, malnutrition or systemic disease, GH/IGF axis should be taken into account.
4. IGF-1 or IGFBP-3 less than –1 SD below the mean for age, GH/IGF axis evaluation is to be done exclusively.
5. Classic GH deficiency is made when GH peak is less than 10 μg/L. Workup for other pituitary deficiency and MRI of brain is to be considered to detect the cause and degree of hypothalamic/pituitary disease.
6. Diagnosis becomes unclear when GH peak is greater than 10 μg/L. So careful follow-up is indicated and GH treatment may be considered.
7. Children with Height –2 SD to –2.5 SD and/or Height velocity –1 to 0 SD for age should be carefully observed and may require further testing.
8. If IGF-1 or IGFBP-3 levels greater than –1 SD below the mean for age, non-hormonal causes are to be identified as the GH/IGF axis dysfunction is less likely.
9. If basal GH is elevated or growth hormone binding protein (GHBP) is less than 2 SD below the mean, the diagnosis goes in favor of GH insensitivity syndrome. Treatment is effective with IGF-1.

Management of Short Stature

Reassurance alone may be all that is required often. Depending upon the clinical aspect, various treatments are available. Treatment of underlying disorders often improves growth.

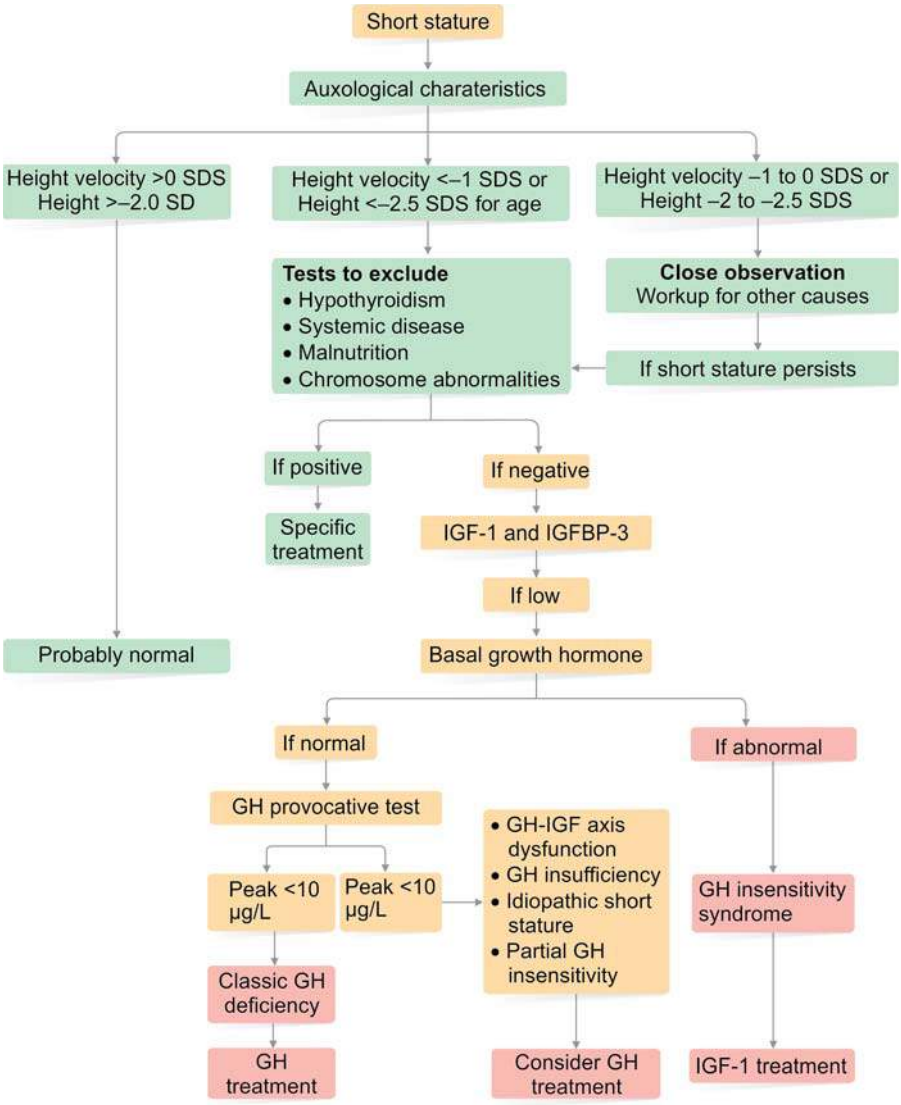


Fig. 14: Diagnostic workup and management algorithm for short stature

Abbreviations: SD, standard deviation; SDS, standard deviation score; IGF, insulin-like growth factor; IGFBP, IGF-binding protein; GH, growth hormone

Drug therapy:

- Sex steroid therapy: Estrogen in female and testosterone in male are used in the treatment of delayed puberty
- Growth hormone therapy (recombinant human GH or rhGH): Indications of GH are as follows:
  - GH deficiency: Both in adults and children
  - Turner syndrome
  - Chronic renal insufficiency (CRI)
  - Prader-Willi syndrome
  - Small for gestational age
  - Short stature homeobox (SHOX) deficiency.

  Recommended doses are shown on Table 2.
- IGF-1 therapy: Used in patients with GH insensitivity syndrome which is characterized by:
  - Height below –3 SD
  - IGFBP SDS less than 2.5 SD
  - GH "insufficiency" on provocative test.
- *Others: GnRH agonists and aromatase inhibitors*—inhibit production of estrogen and delay epiphyseal fusion.

Surgical: Surgical limb lengthening: In skeletal dysplasia, surgical limb lengthening with distraction of bones at ~1 mm/day can produce meaningful increase in height (up to 30 cm) and improve disproportion as well.

Table 2: Recommended doses for growth hormone

Diagnosis	Dose	
	µg/kg/day	mg/m^2/day
GH deficiency	23–39	0.7–1.0
TS	45–50	1.4
CRI	45–50	1.4
PWS	35	1.0
SGA	35–66	1.0–2.0
SHOX deficiency	45–50	1.4

Abbreviations: GH, growth hormone; TS, Turner syndrome; CRI, chronic renal insufficiency; PWS, Prader-Willi syndrome; SGA, small for gestational age; SHOX, short stature homeobox

Growth hormone therapy: Recombinant human GH replaces the human pituitary-derived GH, which had been withdrawn for safety concerns. Recombinant human GH treatment is not only indicated for GH deficient short statured children but also is useful in some clinical conditions of non-GHD associated with poor linear growth rate who may show improvement of linear growth. The common conditions of non-GHD short children who may be benefited by rhGH treatment are ISS, TS, CRI, SGA, PWS.

Children with short stature including ISS may be at risk for psychosocial problems. The etiology of short stature is not morally relevant in deciding who is entitled to treatment. These children share a central and seemingly valid concern of being short and "like to be taller" for physical need as well as to feel better if they get taller. Short stature is psychologically disabling and that taller stature as a result of rhGH therapy will lead to better psychosocial function.

Use of rhGH in ISS: Recombinant human GH therapy can induce increased adult height in children with ISS, but the degree and predictability of its effects remain uncertain. In 2003, the FDA of the United States have approved rhGH therapy for ISS defined as a height greater than 2.25 SDS below the mean, or less than 1.2 percentile for age and gender with height prediction below 5 ft 3 in (160 cm) in male and 4 ft 11 in (or 150 cm) in female and without evidence of underlying disease or GHD.

Use of rhGH in SGA: Adult height outcomes are improved by treatment initiated early and use of higher dose (0.47 μg/kg/week) in the peripubertal years. Recombinant human GH treatment in SGA children during puberty can also increase mean height 2.7 cm in boys and 2.5 cm in girls during puberty.

Use of rhGH in Turner syndrome: Newer studies demonstrate that rhGH with or without anabolic steroid can accelerate growth and lead to height predicted in girls with TS.

Growth hormone should be started with or without anabolic steroid (oxandrolone) at early age of life (3–4 years). More modest effects of total height gain can also be observed when initiation and addition of estrogen treatment occurs before 14 years of age.

Use of rhGH in CRF: Growth failure is often associated with chronic kidney disease (CKD). The genetic height potential is usually not attained in these children and the mean adult height is 2 SD below the mean. A poor growth is due to both endocrine and non-endocrine cause with decreased level of IGF-1 and increased level of IGFBP-1. Pharmacological doses of rhGH corrects height deficit in children with CKD/CRI before transplant. Recombinant human GH treatment at a dose of 28 IU/m^2/week in children with CRF can result in significant increase in height velocity (3.50 cm/year).

Prader-Willi syndrome: Most individuals have GH deficiency when formally tested. Use of GH for growth failure and genetically confirmed PDS was approved by the FDA and has been approved for use in most countries. The response of GH in PDS is greatest during the first 12 months of therapy. GH has additional positive metabolic effects in these children. It improves the muscle tone, decreases the fat mass, increases the lean body mass and bone mineral density.

Assessment of response to GH therapy: The response to GH therapy has traditionally been expressed in terms of height velocity (measured as cm/year), and is derived from data observed over a period of a full year. In general, average height velocity decreases as it approaches puberty.

Side effects of GH therapy: rhGH therapy is generally safe. However, the following clinically insignificant side effects may take place:

- Insulin insensitivity but overt DM is rare
- Benign intracranial hypertension
- Slipped capital femoral epiphysis
- Scoliosis
- Reduced testicular volume
- Gynecomastia.

Leukemia and other malignancies are not associated with GH therapy as previously thought.

Cost of GH therapy: Biosynthetic rhGH is expensive, and ethical consideration regarding its use is inextricably tight to this fact. Strategies to limit cost, including targeting the dose by weight in treatment earlier in childhood and cessation of treatment at normal rather than maximum height.

Like any medical intervention, the merits of rhGH therapy for patients with short stature are judged by weighing the morbidity of untreated condition and benefits arising from the treatment against cost, risk and potential alternatives.

THYROID GLAND AND ITS DYSFUNCTION

The thyroid gland is the body's largest single organ specialized for endocrine hormone production. Its function is to secrete an appropriate amount of thyroid hormones, primarily 3,5,3′,5′-L-tetraiodothyronine (thyroxine, T_4), and a lesser quantity of 3,5,3′-I-triiodothyronine (T_3), which arises mainly from the subsequent extrathyroidal deiodination of T_4. The thyroid also contains parafollicular or C cells that produce calcitonin, a 32-amino-acid polypeptide that inhibits bone resorption (Fig. 15).

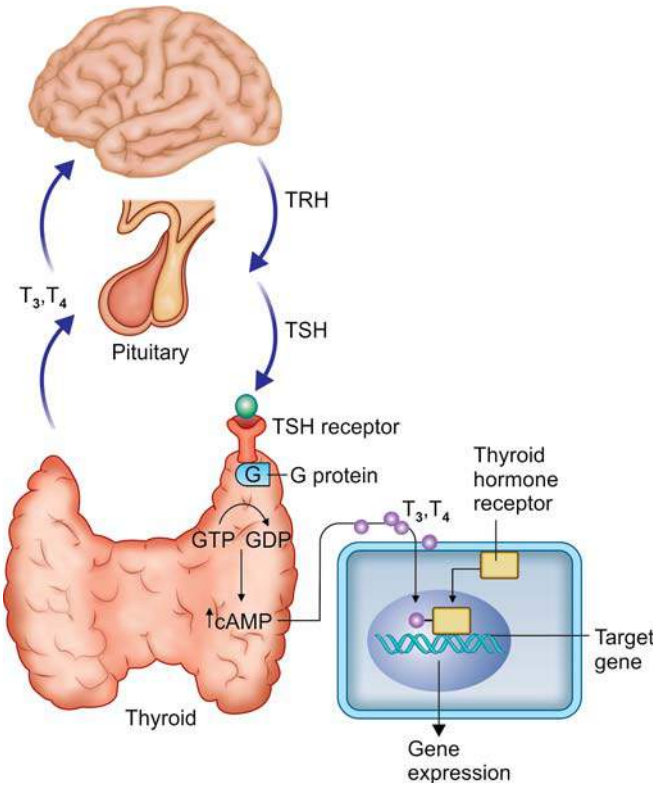


Fig. 15: Mechanism of action of thyroid hormones

Abbreviations: T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; TRH, thyrotropin-releasing hormone; G protein, guanosine nucleotide-binding protein

Biosynthesis of Thyroid Hormones

Thyroid hormones and analogs are tyrosine derivatives. The steps in the synthesis and release of thyroid hormones are as follows:

- Iodide trapping by the thyroid gland
- Synthesis of thyroglobulin (TG)
- Organification of trapped iodide as mono- and diiodotyrosine (MIT and DIT)
- Coupling of the iodotyrosines within TG to form the iodothyronines [T_4 and triiodothyronine (T_3)] and storage in follicular colloid
- Pinocytosis of colloid droplets and hydrolysis of TG within the cytoplasmic phagolysosomes to release MIT, DIT, T_4 and T_3
- Deiodination of MIT and DIT with intrathyroidal recycling of the iodine.

Regulation of Thyroid Hormone

Circulating TSH and iodide levels largely regulate thyroid function. TSH activates adenylate cyclase and stimulates the production and accumulation of cyclic adenosine monophosphate, which in turn appears to mediate most of the effects of TSH on thyroid metabolism (iodide trapping, iodotyrosine synthesis, TG synthesis, glucose oxidation, colloid pinocytosis, hormone release and thyroid growth). TSH secretion is modulated by TRH, a peptide synthesized in the hypothalamus and secreted into the pituitary portal vascular system for transport to the anterior pituitary thyrotroph cell. TRH production is modulated by environmental temperature via peripheral and central (hypothalamic) thermal sensors. The regulation of thyroid hormone is summarized in Figure 16.

Function of Thyroid Hormones

Central Nervous System Development

- Increases myelinogenesis.

Effects on Growth and Development

Fetal thyroid hormones are essential for development of the brain in utero. Postnatally, thyroid hormones are essential for both the production and the normal action of growth hormone.

- Stimulation of pituitary GH synthesis and secretion
- Potentiation of GH stimulation of IGF synthesis and action
- Stimulation of growth factor production:
  - Epidermal growth factor
  - Nerve growth factor
  - Erythropoietin
- Stimulation of bone metabolism/growth:
  - Cartilage response to IGF-1
  - Osteoblastic/osteoclastic bone remodeling.

Caloriegenic/Thermogenic Effects

- Stimulation of mitochondrial enzyme synthesis
- Stimulation of UCP-1 and UCP-3 in brown adipose tissue and muscle
- Stimulation of membrane Na^+/K^+ ATPase.

Thyroid Function Tests (Table 3)

Thyroid Hormones and TSH

Assay of thyroid hormones free T_3 (FT_3) and free T_4 (FT_4) are reliable as only 1% of thyroid hormones remain in free state and 99% are bound to transport proteins.

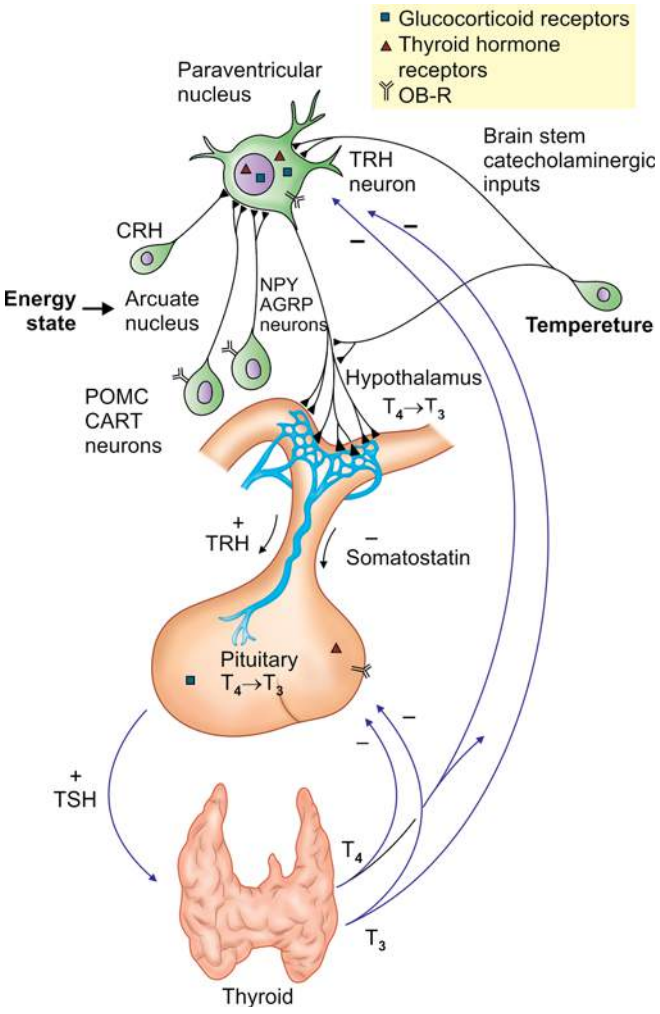


Fig. 16: Regulation of thyroid hormone

Abbreviations: T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; TRH, thyrotropin-releasing hormone; CRH; corticotropin-releasing hormone; NPY, neuropeptide Y; AGRP, agouti-related peptide; Pomc CART, pro-opiomelanocortin, and cocaine- and amphetamine-regulated transcript

Thyroid Imaging

Ultrasonography (USG): Thyroid USG provides information when there is cyst or nodules and provides scope for guided aspiration, biopsy or drainage.

Scintigraphy: Thyroid scintigraphy or radionuclide imaging using radioactive iodine or technetium is useful for functional imaging. Uptake is uniformly increased in thyrotoxicosis, reduced in thyroiditis and presence of "cold" nodule in case of malignancy.

Antithyroid Antibodies

Antithyroid antibodies (anti-TG and antimicrosomal antibodies) are important in case of autoimmune thyroiditis.

Interpretation of Thyroid Function Tests

- *Serum T_4*: In primary hypothyroidism, FT_4 and FT_3 are low and TSH raised, but in secondary hypothyroidism FT_3, FT_4 and TSH are low
- *Serum T_3*: Bound to thyroxine-binding globulin (TBG); therefore, serum T_3 levels are subject to the same protein-binding limitations as serum T_4

Table 3: Thyroid function tests in different thyroid conditions

Condition	T_4	FT_4I	T_3	FT_3I	TSH	TSI	TRH stimulation
Hypothyroidism							
Primary	↓	↓	↓	↓	↑	±	↑
Secondary	↓	↓	↓	↓	↓, N	–	↓
Tertiary	↓	↓	↓	↓	↓, N	–	N
Peripheral unresponsiveness	↑, N	↑, N	↑, N	↑	↑, N	–	N, ↑
Hyperthyroidism							
Graves' disease	↑	↑	↑	↑	↓	+	↓
Toxic nodular goiter	↑	↑	↑	↑	↓	–	↓
Pituitary TSH-secreting tumors	↑	↑	↑	↑	↑	–	↓
T3 thyrotoxicosis	N	N	↑	↑	↓	±	↓
T4 thyrotoxicosis	↑	↑	N	N	↓	±	↓

Abbreviations: ↑, increased; ↓, decreased; ±, variable; FT3I, free T3 index; FT4I, free T4 index; N, normal; T3, triiodothyronine; T4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating immunoglobulin.

- *T_3 hyperthyroidism (thyrotoxicosis)*: Increased T_3, normal free thyroxine index (FTI)
- *Toxic nodular goiter*: Increased T_3, normal or increased T_4
- *Iodine deficiency*: Normal T_3, possibly decreased T_4
- *Thyroid replacement therapy with liothyronine*: Normal T_4, increased T_3 if patient is symptomatically hyperthyroid
- *Serum TG*:
  - Elevated in thyroid cancer and thyrotoxicosis emanating from the thyroid gland
  - Normal in thyrotoxicosis secondary to iatrogenic ingestion of thyroid hormone
- *Radioactive iodine uptake (RAIU)*: It measures the thyroid's ability to concentrate iodine:
  - Normal 24 hours RAIU is 10–30%
  - An overactive thyroid shows an increased uptake, whereas an underactive thyroid (hypothyroidism, subacute thyroiditis) shows a decreased uptake
  - Increased homogeneous uptake: Graves' disease (GD), iodine deficiency
  - Increased heterogeneous uptake: Toxic multinodular goiter
  - Single focus of increased uptake: Hot nodule.
- *TRH stimulation*: TRH stimulation can be used to diagnose clinically suspected hyperthyroidism when the laboratory tests are inconclusive. Its use has been replaced by the sensitive TSH assay for most purposes.

Hypothyroidsm (Table 4)

Hypothyroidism results from congenital or acquired deficiency of thyroid hormones either from a defect in the gland itself (primary hypothyroidism) or from a result of reduced TSH stimulation (central or hypopituitary hypothyroidism).

When symptoms appear after a period of apparently normal thyroid function, the disorder may be truly acquired or might only appear so as a result of one of a variety of congenital defects in which the manifestation of the deficiency is delayed.

Depending on the hypothalamic-pituitary-thyroid axis location of hormone defect etiology may be central, primary or peripheral.

Central

- Malformation: Septo-optic dysplasia, holoprosencephaly
- Genetic defects

Table 4: Causes of hypothyroidism

Manifestation	Causes
Newborn	
No goiter	Thyroid gland digenesis or ectopic location
	Exposure to iodides
	TSH deficiency
	TRH deficiency
Goiter	Inborn defect in hormone synthesis or effect
	Maternal goitrogen ingestion, including propylthiouracil, methimazole, iodides
	Severe iodide deficiency (endemic)
Child	
No goiter	Thyroid gland dysgenesis
	Cystinosis
	Hypothalamic-pituitary insufficiency
	Surgical after thyrotoxicosis or other thyroid surgery
Goiter	Hashimoto thyroiditis: Chronic lymphocytic thyroiditis
	Inborn defect in hormone synthesis or effect
	Goitrogenic drugs
	Infiltrative (sarcoid, lymphoma)

Abbreviations: TSH, thyroid-stimulating hormone; TRH, thyrotropin-releasing hormone

- CNS insults: Trauma, surgery, radiation, infection
- CNS tumors: Craniopharyngioma, germinoma

Central is again divided into secondary and tertiary depending upon involvement of pituitary and hypothalamus.

Primary

Primary occurs in the thyroid gland due to:

- Dysgenesis: Aplasia, dysplasia, ectopic
- Enzyme defects: Trapping, organification, TG
- Iodine deficiency: Endemic goiter
- Autoimmunity: Hashimoto's thyroiditis
- Ablation of thyroid gland: Surgery, radiation, infection
- Goitrogens: Thiocyanates, thionamides, lithium
- Systemic diseases: Cystinosis, histiocytosis.

Peripheral

- Resistance to T_4.

Congenital Hypothyroidism

Most cases of congenital hypothyroidism are not hereditary and result from thyroid dysgenesis. Some cases are familial; these are usually caused by one of the inborn errors of thyroid hormone synthesis and may be associated with goiter.

Clinical features of congenital hypothyroidism: Where facilities are available, neonatal screening identifies most of the cases of neonatal hypothyroid before presenting with overt clinical presentation.

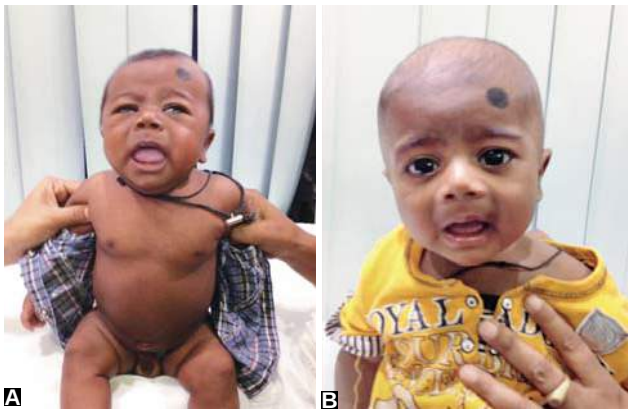
Clinical presentation of congenital hypothyroidism (Figs 17 and 18):

During neonatal period:

- Coarse facies
- Hoarse cry
- Large size
- Delayed passage of meconium
- Macroglossia
- Wide posterior fontanel
- Umbilical hernia
- Jaundice (conjugated or unconjugated)
- Thick skin
- Postmaturity
- Delayed bone age (identifiable on knee X-ray, but this is not usually performed. The lower femoral epiphysis appears at 36 weeks of gestation)
- Goiter
- Sleepy, placid and poor feeding, constipation
- Poor perfusion: Hypothermia, mottling and peripheral cyanosis
- Edema
- Bradycardia and cardiomegaly.

Late signs:

- Cretinous appearance
- Large tongue
- Hoarse cry
- Dry skin and hair
- Slow relaxation of tendon reflexes
- Developmental delay
- Linear growth failure
- Infantile proportions of upper and lower segment of body.



Figs 17A and B: Hypothyroidism before and after treatment. (A) A 5-month-old child previously undiagnosed and untreated hypothyroidism having coarse facies, thick lips and macroglossia; (B) Change of facies (disappearance of coarseness and appearance of brightness of face) 1 month after treatment with L-thyroxine

Other neurological signs:

- Spasticity with shifting gait
- In coordination with jerky movements
- Awkwardness
- Coarse tremor
- Increased deep tendon reflexes
- Cerebellar ataxia
- Strabismus and nystagmus
- Sensorineural hearing loss.

Myopathy:

- In rare cases of Kocher-Debré-Semelaigne syndrome, hypothyroidism is associated with generalized muscular pseudohypertrophy.

Laboratory Investigations

Newborn screening: TSH level is more specific and sensitive test and is used in different national programs. Cutoff levels are greater than 10–20 mU/L depending upon the methodology. Low TSH is detected in central hypothyroidism (rare).

1. *Thyroid function tests*: T_3, T_4 and TSH and TBG assay (Table 5)
   - Serum levels of T_4 or FT_4 are low
   - Serum levels of T_3 may be normal and are not helpful in the diagnosis
   - Levels of TSH are elevated, often to greater than 100 mU/L, if the defect is primarily in the thyroid
   - Serum levels of TG:
     - Usually low in infants with thyroid agenesis or defects of TG synthesis or secretion.

Table 5: Interpretation of thyroid function tests

	Total T_4	Free T_4	TSH	TBG
Primary hypothyroidism	↓	↓	↑	N
Hypothalamic (TRH) tertiary hypothyroidism	↓	↓	↓	N
Pituitary (TSH) secondary hypothyroidism	↓	↓	↓	N
TBG deficiency (thyroid agenesis)	↓	N	N	↓
TBG excess	↑	N	N	↑

Abbreviations: N, normal; ↓, decrease; ↑, increase; TRH, thyroid-releasing hormone; TSH, thyrotropin-releasing hormone; T4, thyroxine; TBG, thyroxine-binding globulin

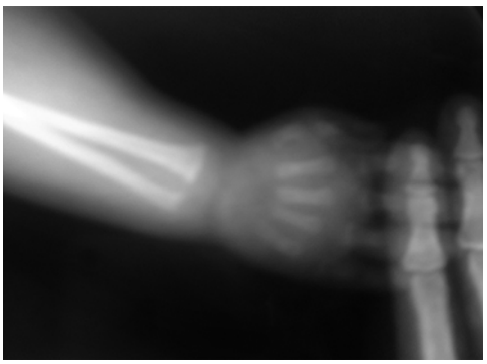


Fig. 18: X-ray of the above child shows no carpal bone on the wrist, delayed appearance of epiphyseal center. Biochemical tests confirmed hypothyroid

- Elevated with ectopic glands and other inborn errors of T4 synthesis, but there is a wide overlap of ranges.

2. *Thyroid autoantibodies*:
   - Thyroid peroxidase antibody (TPOAb)
   - Thyroglobulin antibody (TGAb)
   - Thyroxine receptor antibody (TrAb)
3. *X-ray*:
   - Delayed bone age (e.g. absence of distal femoral epiphysis) (Fig. 19)
   - Epiphyseal dysgenesis (the epiphyses often have multiple foci of ossification (Fig. 20)
   - Deformity (beaking) of the 12th thoracic or 1st or 2nd lumbar vertebra
   - Large fontanels and wide sutures with intersutural (Wormian) bones on skull X-ray
   - The sella turcica is often enlarged and round and rarely there may be erosion and thinning.
4. *Scintigraphy*: Helps to pinpoint the underlying cause in infants with congenital hypothyroidism. Radionuclide scan done with ^{123}radioiodine and ^{99}technitium.
5. *USG*: To detect thyroid nodule or cysts.

Differential Diagnosis

- Down syndrome
- Mucopolysaccharidosis

The differences between hypothyroidism, Down syndrome and mucopolysaccharidosis are shown in Table 6.

Treatment of Congenital Hypothyroidism

Levothyroxine (LT_4) is the drug of choice.

In neonates: The initial starting dose is 10–15 μg/kg/day (total 37.5–50 μg/day) but higher dose is necessary depending upon the severity of the disease.
In children: 4 μg/kg/day.

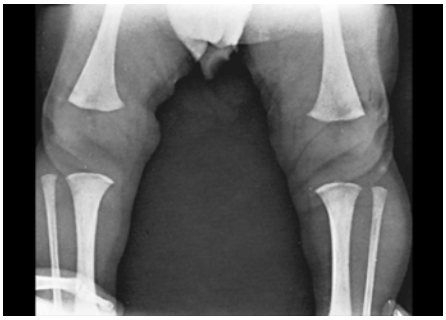


Fig. 19: Absence of distal femoral epiphysis

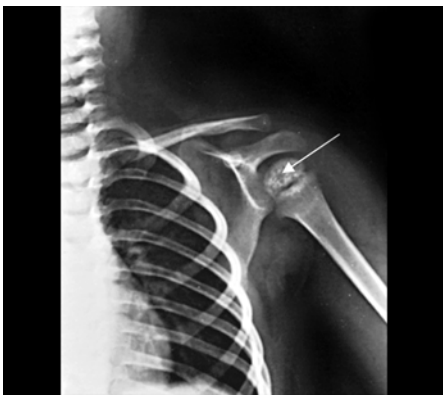


Fig. 20: X-ray humerus showing epiphyseal dysgenesis

Monitoring of serum T_4, FT_4 and TSH should be done.
- Monthly in the first 6 month of life
- Every 2–3 months between 6 months and 2 years.

Prognosis

Outcome is universally poor in children with congenital hypothyroid who had been diagnosed beyond neonatal period. Mental retardation and shot stature are the common sequale. Early diagnosis and treatment following neonatal screening has resulted in normal intellectual outcome.

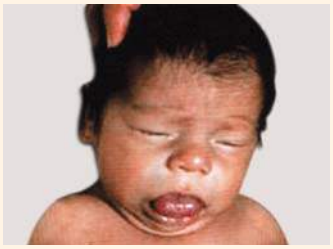
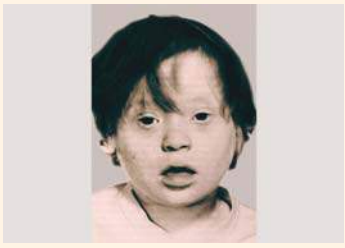
Algorithm for workup and management of congenital hypothyroidism (Fig. 24):
- Screening of newborn by dried blood spot by heel prick within 4 days of life preferably within 24 hours. Cord blood for T_4 and TSH alternatively can be done
- Maternal history, physical examination and clinical features suggestive of autoimmune thyroiditis
- Serum confirmation should be done whose validity has been documented in cord or neonatal serum specimen
- A thyroid ultrasound will confirm the three diseases
- If TSH is increased but FT_4 is decreased, thyroid ultrasound should be done to detect athyreosis or ectopic thyroid. Treat with lifelong T_4 in both the cases
- In familiar dyshormonogenesis, USG shows goitrous thyroid in case of iodine deficiency. Treat with T_4 therapy with iodine supplement. If TSH is increased but thyroid scan detects ectopic thyroid no further study is required, but lifelong treatment is required. If ectopic thyroid is detected baby should be evaluated at the age of 3 years for transient neonatal hypothyroidism
- Start LT_4 therapy
- If TSH is normal and FT_4 is decreased, detect TBG in both patient and parent. In TBG deficiency and in normal TBG, no therapy is required
- If TSH is unmeasurable and both T_3 and T_4 are decreased, MRI is done to exclude secondary causes of hypothyroidism. Treat with LT_4. Reevaluate with TRH at the age of 3 years
- Both iodine deficiency and iodine excess may cause congenital hypothyroidism as shown in the algorithm. In both cases LT_4 supplement should be given.

Acquired Hypothyroidism

- Subclinical hypothyroidism (TSH >4.5 mU/L, normal T_4 or FT_4) is more common
- Approximately 2% of adolescents are affected
- Most commonly results from autoimmune thyroiditis [chronic lymphocytic thyroiditis (CLT)]; 6% of children aged 12–19 years have evidence of autoimmune thyroid disease
- Female:male ratio is 2:1.

Classification of acquired hypothyroidism: Etiologic classification of acquired hypothyroidism is as follows:
- Autoimmune (acquired hypothyroidism):
  - Hashimoto thyroiditis
  - Polyglandular autoimmune syndrome, type I and II
- Iatrogenic:
  - Propylthiouracil, methimazole (MMI), iodides, lithium, amiodarone
  - Irradiation
  - Radioiodine
  - Thyroidectomy

Table 6: Comparison between hypothyroidism, Down syndrome and mucopolysaccharidosis

	Hypothyroidism	Down syndrome	Mucopolysaccharidosis
Appearance	Lethargic	Active	Poor activity
Face	Coarse facies with wrinkled forehead and depressed broad nose	Flat facies, small nose, choanal atresia/hypoplasia present	Gargoyle-like facies with thick nasal and supraorbital ridge and thick lips
Tongue	Protrudes out due to macroglossia (Fig. 21)	Protrudes out due to small oral cavity not due to macroglossia (Fig. 22), may be fissured so-called scrotal tongue	Tongue normal or large (macroglossia) which may protrude out (Fig. 23)
Eyes	Narrow palpebral fissure with normal slanting eyes	Upward and outward slanting eyes, Brushfield spot on iris may be present, cataract	Clouding of cornea may be present
Hand	Broad hands with short fingers	Short broad hand with clinodactyly of little finger, Simian crease may be present	Broad hands with characteristic limitation of extension of joints of finger
Skin	Dry, cold and coarse skin	Normal skin	Dry and coarse skin
Umbilical hernia	Present	Present	Absent
Hepatosplenomegaly	Absent	Absent	Present
Bone deformity	No significant bone deformity	Absent (rarely associated with atlantoaxial dislocation with quadriplegia)	Lumbosacral kyphosis, coxa vara genu valgum are common in particularly Morquio type
Investigation X-ray wrist and thoracolumbar spine	Markedly delayed Epiphyseal dysgenesis present	Bony age is not significantly delayed No significant bony change in radiology	Delayed bone age not marked but epiphyseal dysgenesis and tapering of proximal ends of metacarpal bones
	 **Fig. 21:** Hypothyroidism (coarse features with macroglossia) with protrusion of big tongue not accommodating in normal size oral cavity	 **Fig. 22:** Down syndrome with mild protrusion of normal size tongue. Protrusion occurs due to small oral cavity	 **Fig. 23:** Mucopolysaccharidosis with coarse features with flexion of hand (claw hand)

- Systemic disease:
  - Cystinosis
  - Langerhans cell histiocytosis
- Hemangiomas (large) of the liver (type 3 iodothyronine deiodinase): Type 3 iodothyronine deiodinase catalyses conversion of T_4 to reverse T_3 (rT_3) and T_3 to T_2. Thyroid secretion is increased, but it is not sufficient to compensate for the large increase in degradation of T_4 to rT_3
- Hypothalamic-pituitary disease:
  - Craniopharyngioma
  - Head trauma
  - Cells infiltrating pituitary gland (e.g. Langerhans cell histiocytosis)
  - Irradiation.

Clinical features of acquired hypothyroidism:

Linear growth: Short stature is one of the most important findings in hypothyroidism. This observation requires only a table or chart showing the mean heights of normal children of the community (Tanner and Whitehouse). The ratio of upper to lower skeletal segment is also abnormal (infantile) in hypothyroid children (Fig. 25). The lower segment is the distance from the top of the symphysis pubis to the ground; the upper segment is obtained by subtracting the lower segment from the total height. At birth the upper:lower ratio is 1.7:1; at 2 years it is 1.44:1; by 10–11 years the ratio is 1:1 (Fig. 26). Hypothyroid children have an unduly long upper segment because of their short legs.

Features of acquired hypothyroidism are as follows:

- Short stature/growth failure (Fig. 27)
- Cold intolerance
- Dry skin
- Cold peripheries
- Bradycardia
- Thin, dry hair
- Pale, puffy eyes with loss of eyebrows
- Goiter
- Slow-relaxing reflexes
- Constipation

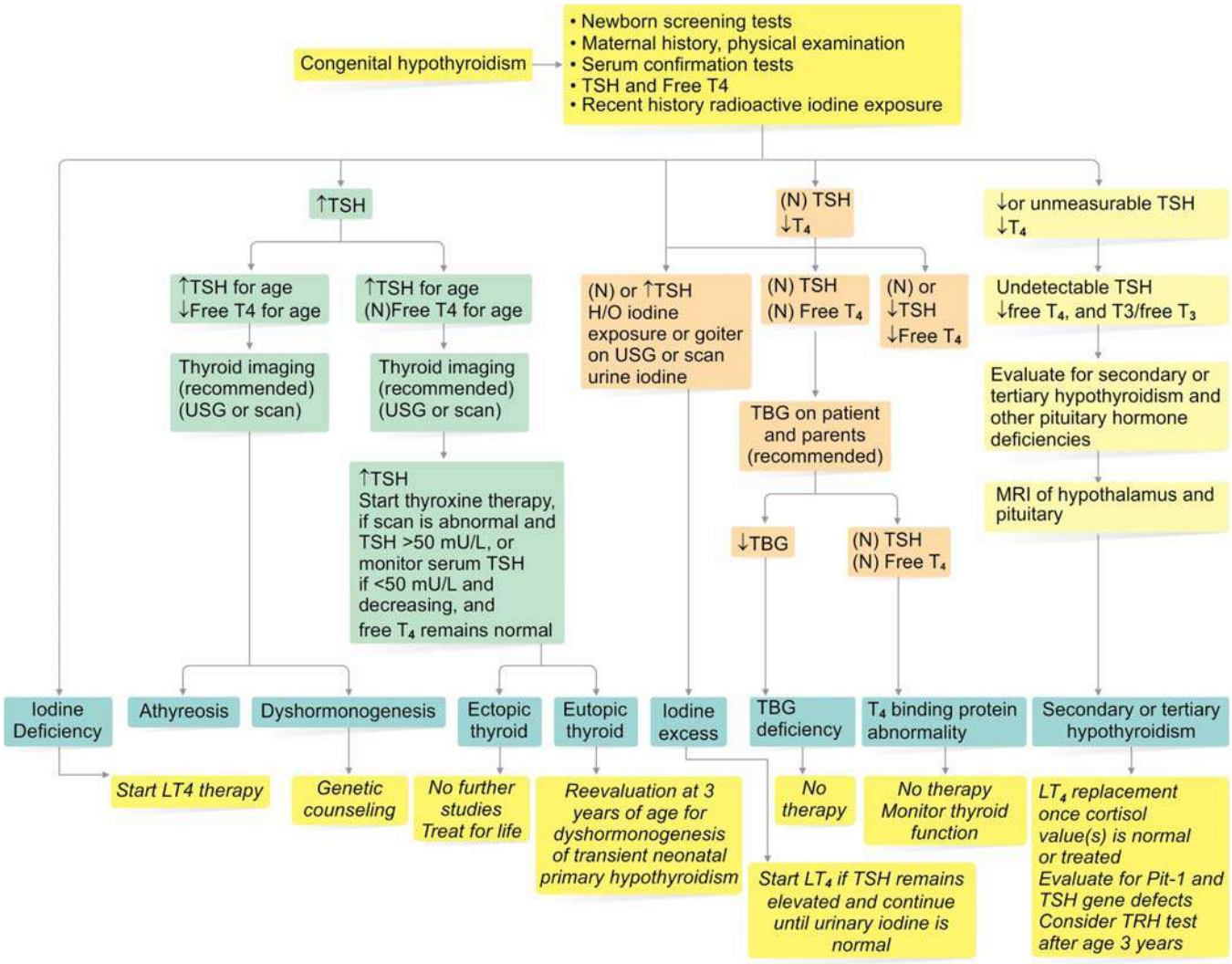


Fig. 24: Algorithm for diagnostic approach and management of congenital hypothyroidism

Abbreviations: TSH, thyroid-stimulating hormone; T_4, thyroxine; USG, ultrasonography; TBG, thyroxine-binding globulin; MRI, magnetic resonance imaging; LT_4, levothyroxine

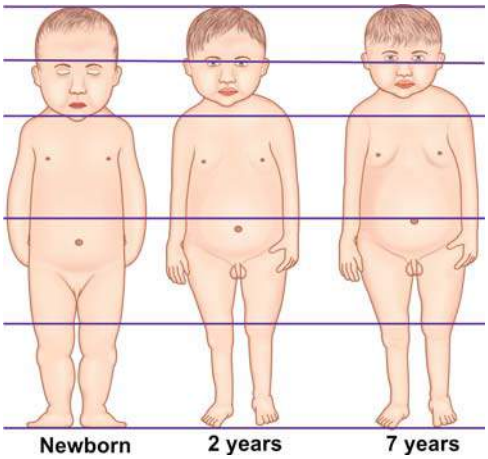


Fig. 25: Body proportion of untreated (neglected) hypothyroid, showing persistence of infantile body proportion at 2 and 7 years of age, with persistent increased ratio of upper and lower body segment

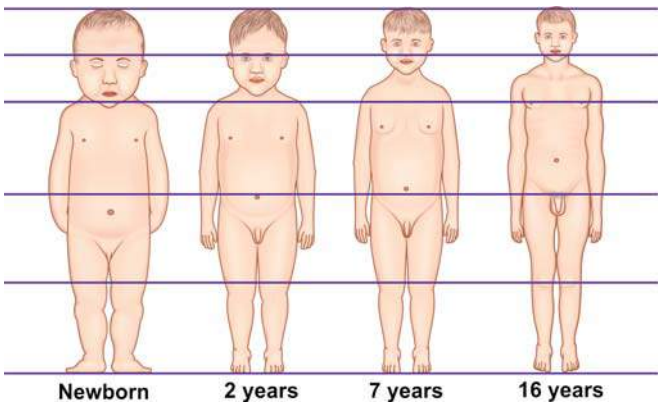


Fig. 26: Normal body proportion in boys from birth to adulthood

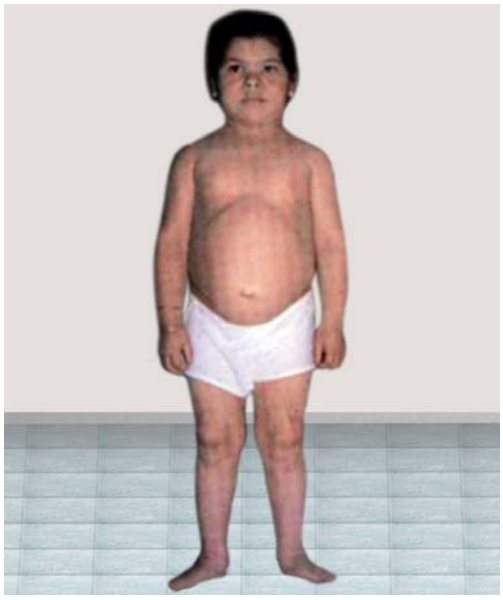


Fig. 27: A young boy with short stature due to hypothyroidism

- Delayed puberty
- Obesity
- Slipped upper femoral epiphysis
- Deterioration in school work
- Learning difficulties.

All children with unexplained mental retardation and short stature should be evaluated for hypothyroidism. A previously normal growing active child showing poor activity, laziness, fatigue and deterioration of school performance with or without linear growth retardation should be suspected for acquired hypothyroidism. In such cases, a firm nodular goiter indicates autoimmune thyroiditis. Family history of acquired thyroiditis is suggestive of autoimmune thyroiditis. Children with central hypothyroidism should be evaluated with pituitary function tests (TRH test) and MRI of the hypothalamic-pituitary regions. Thyroid antibodies (TAb) should be done in acquired primary hypothyroidism. Patients with no evidence of autoantibodies should be worked up for other causes of hypothyroidism by radionuclide scan, USG. Fine needle aspiration for biopsy may be required. The algorithm of diagnostic approach and management is mentioned in Fig. 28.

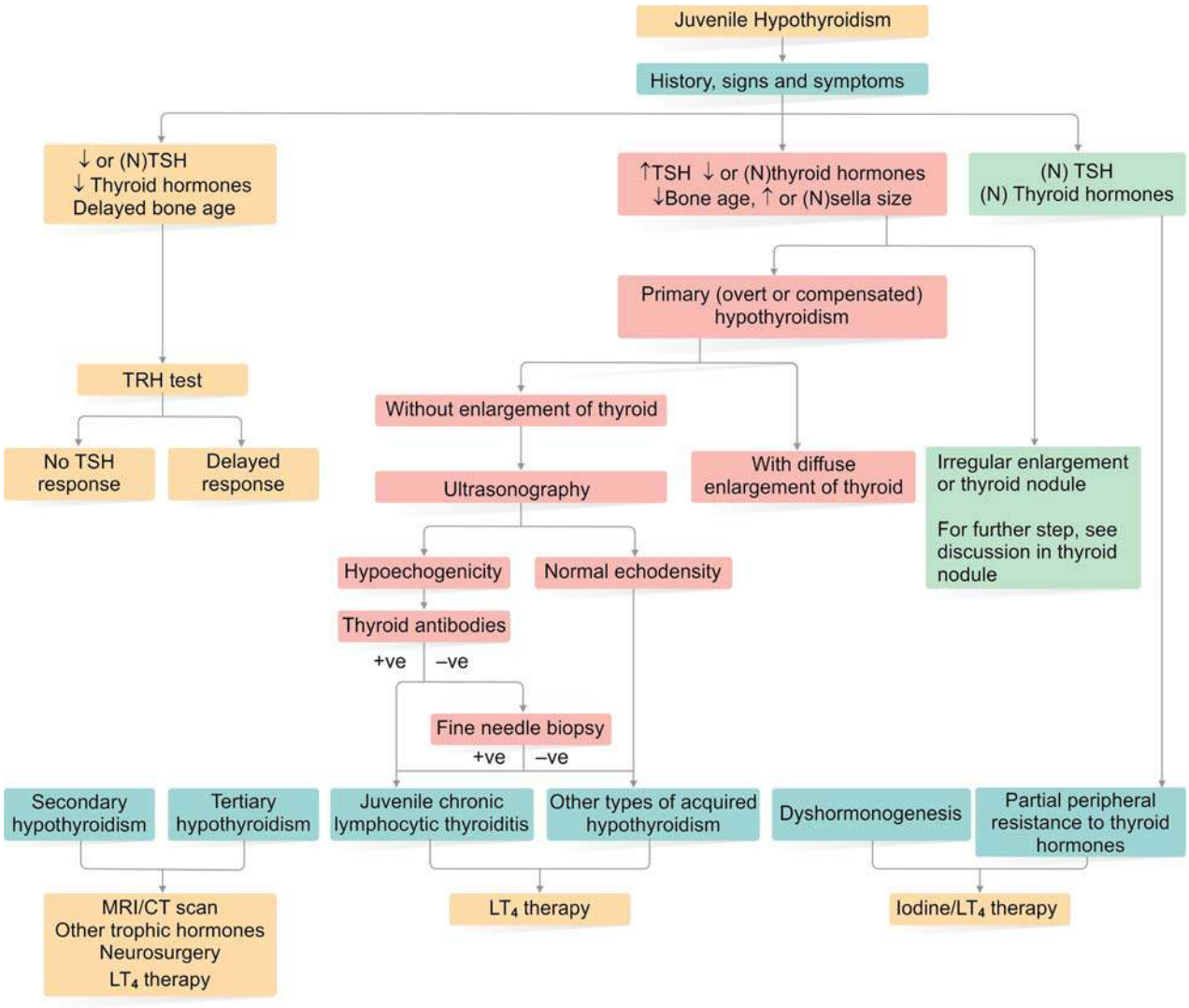


Fig. 28: Algorithm for diagnostic approach and management of acquired hypothyroidism

Abbreviations: TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; LT4, levothyroxine; MRI, magnetic resonance imaging; CT, computed tomography

Management: Management of acquired hypothyroidism should be gradual. Initial dose of T_4 is 4–5 µg/kg/day or 100 µg/m^2/day. Initial treatment should be started first at 25–50% of this dose with gradual increase every 3–4 weeks as required. The drug should be given in empty stomach at morning. Follow-up should be done in every 3 months during the first 2 years of therapy and then 6 monthly thereafter. TSH level should be estimated during routine visit and dose should be modified to maintain TSH level in the normal range. In every visit, growth, particularly height should be measured and should be asked about his activities and school performances.

A trial of discontinuation of thyroid hormones may be considered in goitrous hypothyroidism after regression of goiter. In such cases, serum TSH should be monitored, and if TSH found high, thyroxin should be restarted, T_4 may require lifelong replacement.

HYPERTHYROIDISM

Thyrotoxicosis is a hypermetabolic state caused by elevated circulating levels of FT_3 and T_4. As it is caused most commonly by hyperfunction of the thyroid gland, it is often referred to as hyperthyroidism. However, in certain conditions, the oversupply is related either to excessive release of preformed thyroid hormone (e.g. in thyroiditis) or to an extrathyroidal source (as mentioned below), rather than to hyperfunction of the gland. *Thus, in true sense, hyperthyroidism is only one (albeit the most common) category of thyrotoxicosis.* With this disclaimer, the terms *thyrotoxicosis* and *hyperthyroidism* are used interchangeably in common practice.

Causes of Thyrotoxicosis

- Associated with Hyperthyroidism
  - *Primary*:
    - Diffuse toxic hyperplasia (GD)
    - Hyperfunctioning (toxic) multinodular goiter
    - Hyperfunctioning (toxic) adenoma
  - *Secondary*:
    - TSH secreting pituitary adenoma
- Not Associated with Hyperthyroidism
  - Subacute granulomatous thyroiditis (painful)
  - Subacute lymphocytic thyroiditis (painless)
  - Struma ovarii (ovarian teratoma with thyroid)
  - Factitious thyrotoxicosis (exogenous T_4 intake).

Hyperthyroidism is uncommon in children. In young children with thyrotoxicosis about 95% are caused by GD.

Pathophysiology of Graves' Disease

Graves' disease is a multisystem autoimmune disorder involving the skin, eyes and the thyroid gland. It is caused by stimulatory antibodies to the TSH receptor. Like other autoimmune diseases, certain human leukocyte antigen (HLA) haplotypes, specifically HLA-B8 and -DR3 are genetically susceptible to GD. Allelic variants (polymorphisms) in genes encoding the inhibitory T-cell receptor CTLA-4 and the tyrosine phosphatase PTPN22 also play role in GD.

Autoantibodies that are formed in GD are directed to the TSH receptor, thyroid peroxisomes and TG. The autoantibodies to the TSH receptor are central to disease pathogenesis. TSH receptor directed antibodies are:

- *Thyroid-Stimulating Immunoglobulin*
  - An immunoglobulin G (IgG) antibody that binds to the TSH receptor and mimics the action of TSH, stimulating adenyl cyclase, with resultant increased release of thyroid hormones
  - This antibody is relatively specific for GD, in contrast to TG and thyroid peroxidase antibodies.
- *Thyroid Growth-Stimulating Immunoglobulins (TGIs)*
  - Directed against the TSH receptor
  - TGIs have been implicated in the proliferation of thyroid follicular epithelium.
- *TSH-Binding Inhibitor Immunoglobulins (TBII)*
  - These anti-TSH receptor antibodies prevent TSH from binding normally to its receptor on thyroid epithelial cells
  - Some forms of TBIIs mimic the action of TSH, resulting in the stimulation of thyroid epithelial cell activity, whereas other forms may actually inhibit thyroid cell function
  - It is not unusual to find the coexistence of stimulating and inhibiting immunoglobulins in the serum of the same patient, a finding that may explain why some patients with GD spontaneously develop episodes of hypothyroidism.

Clinical Features

Symptoms

- Palpitation
- Fatigue
- Insomnia
- Heat intolerance
- Secondary amenorrhea.

Signs

- Tachycardia
- Tremor
- Hyperactive precordium
- Exophthalmos (Fig. 29)
- Tall stature in prepubertal child
- Goiter.

Other signs of GD may include:

- Vitiligo
- Ophthalmopathy due to retro-orbital inflammation.

Laboratory Investigations

- *Thyroid function tests:*
  TSH, FT_3, FT_4, TGT, TBG

Fig. 29: Exophthalmos in hyperthyroidism

- *Thyroid autoantibodies:*
  These are TPOAb, TGAb, TrAb
  TrAb are positive in 95% of patients with GD
- *Imaging:* Imaging allows GD to differentiate from Hashimoto's appearances. Imaging modalities are:
  - Thyroid ultrasound scan
  - Radionucleotide (^{131}I or ^{99}Tc) scans.

Management

Short-term Management

- Beta-blockers (propranolol, atenolol)
- Beta-blockers are used in severe cases for symptomatic relief, control of tachycardia and hypertension.

Long-term Management

Antithyroid drug therapy:
Carbimazole:

- It acts for a peripheral substrate for thyroid peroxidase, inhibits organification of iodine and coupling iodotyrosine residues
- Duration of standard treatment is 2–4 years.

Surgery: Nowadays total thyroidectomy with long-term T_4 replacement is the better option to subtotal thyroidectomy.

Radioiodine: Radioiodine is given for ablation of thyroid gland and subsequent monitoring and replacement therapy undertaken.

GOITER

Goiter simply refers to enlargement of the thyroid gland. Goiter does not necessarily correlates the thyroid function, i.e. a person with goiter may have normal (euthyroid), over (hyperthyroid) or under function (hypothyroid) of thyroid gland.

Clinically goiter is defined as enlargement of lobes greater than the terminal phalanx of the patient's thumb (Fig. 30).

Classification

WHO classifies goiter as follows:

0	:	No goiter
1a	:	Palpable lobe
1b	:	Noticeable gland on neck hyperextension
2	:	Gland noticeable with neck in normal position
3	:	Visible gland at a distance of 10 meter

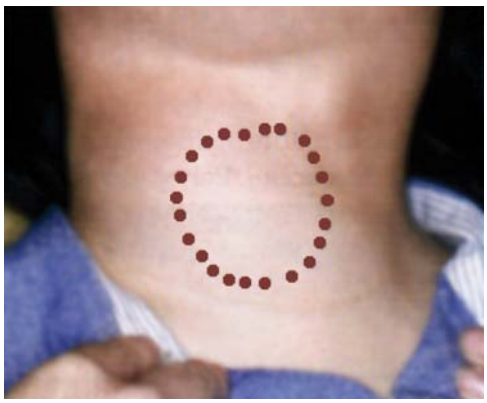


Fig. 30: Thyroid enlargement (goiter)

But the USG evaluation of thyroid volume is more accurate than palpation.

Differential Diagnosis of Goiter

False Goiter

- Physiological enlargement of the thyroid at puberty.
- Midline lesions associated with the thyroid, e.g. thyroglossal cyst.
- Midline lesions that are not thyroid associated, e.g. branchial cysts, histiocytosis of thymus.

True Goiter

- Colloid (simple) goiter:
  - Chronic lymphocytic thyroiditis
  - Iodine deficiency goiter
  - Graves' disease
- Autoimmune thyroid disease
- Goitrogen exposure like lithium
- Dyshormonogenesis
- Infectious
  - Subacute (viral) thyroiditis
  - Chronic suppurative thyroiditis
- Anatomical abnormalities
- Nodular goiter
  - Solitary
  - Adenoma, carcinoma, cyst
  - Multinodular: Secondary to autoimmune thyroid disease.

Molecular Basis of Enlargement of Thyroid Gland

Several genes are found to be associated with enlargement of thyroid gland. The mechanisms are listed in Table 7.

Clinical Evaluation of Enlarged Thyroid Gland

Clinical evaluation of goiter includes careful history and physical examination.

History should include:

- Family history of thyroid disease
- Geographical area of residence

Table 7: Genes associated with enlargement of thyroid gland

Gene	Role of gene in organogenesis/protein function
TITF1, PAX8, TITF2/FOXE1	During later stages; regulation of thyroid-specific gene expression
TPO	Thyroid differentiation; iodide organification
TG	Thyroid differentiation; structural prohormone
NIS	Iodide transport from the blood into thyroid cell (basal membrane)
PDS	Iodide transport from thyroid cell to follicular lumen (apical membrane)
DUOX1/THOX1 DUOX2/THOX2	Thyroidal hydrogen peroxide generation
DEHAL1	Deiodination for iodide recycling

Abbreviations: TPO, thyroid peroxidase; TG, thyroglobulin; NIS, sodium-iodide symporter; PDS, pendred syndrome; DEHAL1, iodotyrosine dehalogenase 1; TITF, thyroid transcription factor; PAX8, paired box gene 8; FOXE1, forkhead box protein E1

- Goitrogens
- Consanguinity
- Exposure to irradiance
- Medication history
- In newborns, history of maternal exposure to iodine or antithyroid drugs
- Symptoms suggestive of hyperthyroid or hypothyroid.

Physical examination should include general physical examination and features of hypo/hyperthyroidism. Examination of thyroid gland is of utmost important. Thyroid is examined for nodularity, consistency, surface and texture, signs of compression, lymphadenopathy and bruit. Any scar, erythema, asymmetry and any neck swelling should also be sought.

Laboratory Investigations

Initial investigations include measurement of TSH and TAb. T_4 level is required when TSH is increased and FT_4 is reliable indicator than total T_4. The following algorithm (Fig. 31) implies the evaluation of goiter depending upon the thyroid function status on the basis of TSH and TAb. For solitary nodule imaging study is required.

Hypothyroid Goiter

Chronic lymphocytic thyroiditis is the most common cause of acquired hypothyroidism. The incidence of CLT is associated with chromosomal abnormalities like TS, Klinefelter syndrome and Down syndrome and some autoimmune disease.

Chronic lymphocytic thyroiditis is common after the age of 4 years with a peak age of onset is in midpuberty. It is 2 times common in female than male.

Autoimmune thyroiditis is an important cause of hypothyroidism, though it also manifests as euthyroidism or hyperthyroidism.

Endemic goiter or iodine deficiency goiter is a cause of mental retardation in children in endemic areas that can be successfully prevented by addition of iodine to salt.

Clinical Features of Hypothyroidism

- Deceleration of growth
- Goiter
- Myxedematous changes of skin
- Constipation
- Cold intolerance
- Delayed skeletal maturation
- Somnolence
- Pseudoprecocious puberty
- Galactorrhea

In hypothyroid goiter, the thyroid gland is non-tender and firm, with a rubbery consistency and pebbly surface.

Treatment

Children with overt hypothyroidism are treated with LT_4 at a dose of 10 μg/kg/day for neonate and 4 μg/kg/day in children.

For compensated hypothyroidism monitoring of TSH level is important and timely follow-up and reassessment is essential.

Confirmed elevation of:

- TSH greater than 10 mIU/L: Treatment with T_4 is usually continued until growth is completed
- TSH greater than 20 mIU/L: The compensated status may progress to hypothyroidism and hence treatment with T_4 is required

In both of the cases thyroid status should be reassessed periodically.

Simple Goiter (Colloid Goiter)

Thyroid enlargement which is not of inflammatory, infectious or neoplastic origin is entitled as colloid goiter.

It is more common in girls with a high incidence near puberty.

The thyroid gland is usually firm, occasionally nodular or asymmetric. Size is variable. On histological appearance, thyroid follicles are filled with abundant colloid.

Investigations

- Biochemical markers show normal or low TSH. Scintiscan is normal.
- Thyroid autoantibodies are absent.

Treatment

It is usually reduced spontaneously with time and no drug is required.

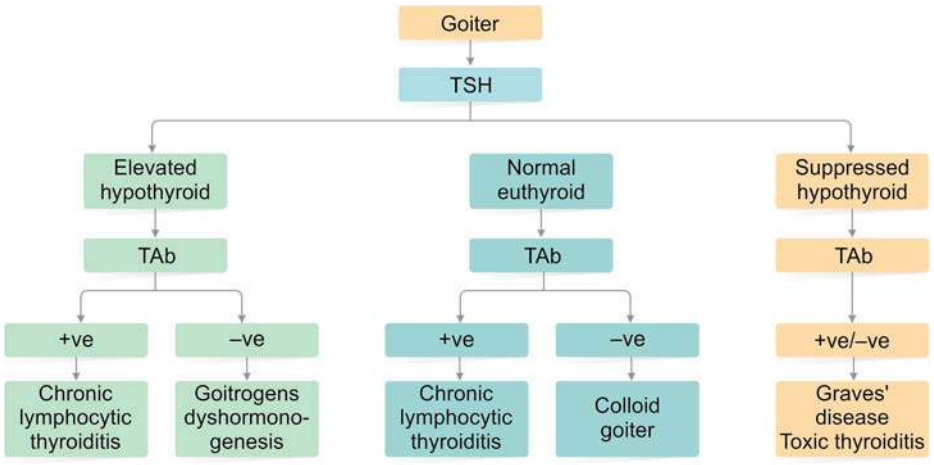


Fig. 31: Diagnosis of goiter dependence upon thyroid function test

Abbreviations: +ve, positive; -ve, negative; TAb, thyroid antibodies; TSH, thyroid-stimulating hormones

Hyperthyroid Goiter

Garves' disease is the main cause of hyperthyroidism in childhood and the disease results from excessive secretion of thyroid hormones. Prepubertal children, particularly children under 5 years of age, tend to have more severe disease, require longer medical therapy and achieve a lower rate of remission compared with pubertal children.

Other causes include:
- Toxic uninodular goiter (Plummer disease)
- Hyperfunctioning thyroid carcinoma
- Thyrotoxicosis factitia
- Subacute thyroiditis
- Acute suppurative thyroiditis.

Pathogenesis of Graves' Disease

Production of thyroid-stimulating immunoglobulin (TSI) cause diffuse enlargement of thyroid (diffuse toxic goiter).

Clinical Features

All but a few children with GD present with some degree of thyroid enlargement and most have symptoms and signs of excessive thyroid activity, such as tremors:
- Goiter
- Inability to fall asleep
- Weight loss despite an increased appetite, proximal muscle weakness
- Heat intolerance
- Headache
- Tachycardia
- Shortened attention span and emotional liability leading to severe behavioral and school difficulties
- Acceleration in linear growth, often accompanied by advance in bone age
- Delayed puberty
- Secondary amenorrhea.

Physical Examination

- Diffusely enlarged, soft thyroid gland
- Smooth skin and fine hair texture
- The hands are often warm and moist
- Excessive activity and a fine tremor of the tongue and fingers
- Thyroid bruit may be audible
- Presence of thyroid nodule suggests the possibility of a toxic adenoma
- Tachycardia, a wide pulse pressure and a hyperactive precordium are common
- Café-au-lait spots suggest a possible diagnosis of McCune-Albright syndrome, particularly in association with precocious puberty
- Severe ophthalmopathy is less common in children, although a stare, lid lag and mild proptosis may be present.

Laboratory Evaluation

- Thyroid hormones increased
- TSH decreased
- TSH receptor antibodies: Positive in GD
- Radioactive iodine (RAI) uptake and scan.

Treatment

- Medical treatment: Thionamides [propyl thiouracil (PTU), MMI and carbimazole (converted to MMI)] are the initial choice
- Radioactive iodine treatment
- Surgery

Algorithm of Diagnostic Workup and Management of Goiter in Children

Key to Algorithm of Diagnostic Workup and Management (Fig. 32)

The evaluation of diffuse goiter starts with the tests of thyroid hormones, TSH and TAb:
1. Classification of goiter size stage according to WHO. Thyroid volumetry by USG is more precise.
2. Neonatal goiter with euthyroidism or hypothyroidism is rare; in majority of cases are due to dyshormonogenesis and are usually self-limiting.
3. Family history; nutritive substances; iodine deficiency; goitrogens (e.g. natural thiocyanate, flavonoids, cassava through thiocyanate, etc.; synthetic: phenol, aliphatic hydrocarbon derivatives, etc.); iodine excess through drugs containing iodine (e.g. amiodarone); percholate, salicylate, diphenylhydantoins, phenothiazines, sulphonylurea, etc., antithyroid drugs blocking thyroid hormonogenesis.
4. The analysis of the thyroid volume and structure by USG is much more precise than the inspection and palpation.
5. Thyroid antibodies to thyroid peroxidase and TG are measured routinely.
6. Juvenile CLT does not need LT_4 therapy with euthyroidism and without significant enlargement of thyroid necessarily, but follow-up is essential to control the development of hypothyroidism or/and considerable goiter.
7. Simple (nontoxic, colloid) goiter or idiopathic goiter without positive immunological parameters and iodine deficiency is better to treat with LT_4 than to wait for possible spontaneous regression. In iodine deficiency without autoimmune phenomena, iodine treatment as well as combined LT_4 and iodine therapy is better to LT_4 therapy alone to reduce thyroid volume.
8. It is difficult to differentiate acute suppurative thyroiditis and abscess of the thyroglossal duct clinically. Fever, enlarged thyroid, mostly unilateral anterior cervical pain, later some erythema in the painful area and regional lymphadenopathy support the diagnosis. Treatment is antimicrobial therapy and surgical.

THE PARATHYROID GLAND AND ITS DISORDERS

Anatomy of Parathyroid Gland

Humans usually have four parathyroid (PT) glands: Two embedded in the superior poles of the thyroid and two in its inferior poles. Each PT gland is a richly vascularized disk containing two distinct types of cells. The abundant *chief cells*, which contain a prominent golgi apparatus plus endoplasmic reticulum and secretory granules, synthesize and secrete PTH. The less abundant and larger *oxyphil cells* contain oxyphil granules and large numbers of mitochondria in their cytoplasm. The PT glands are derived embryologically from the 3rd and 4th branchial arches.

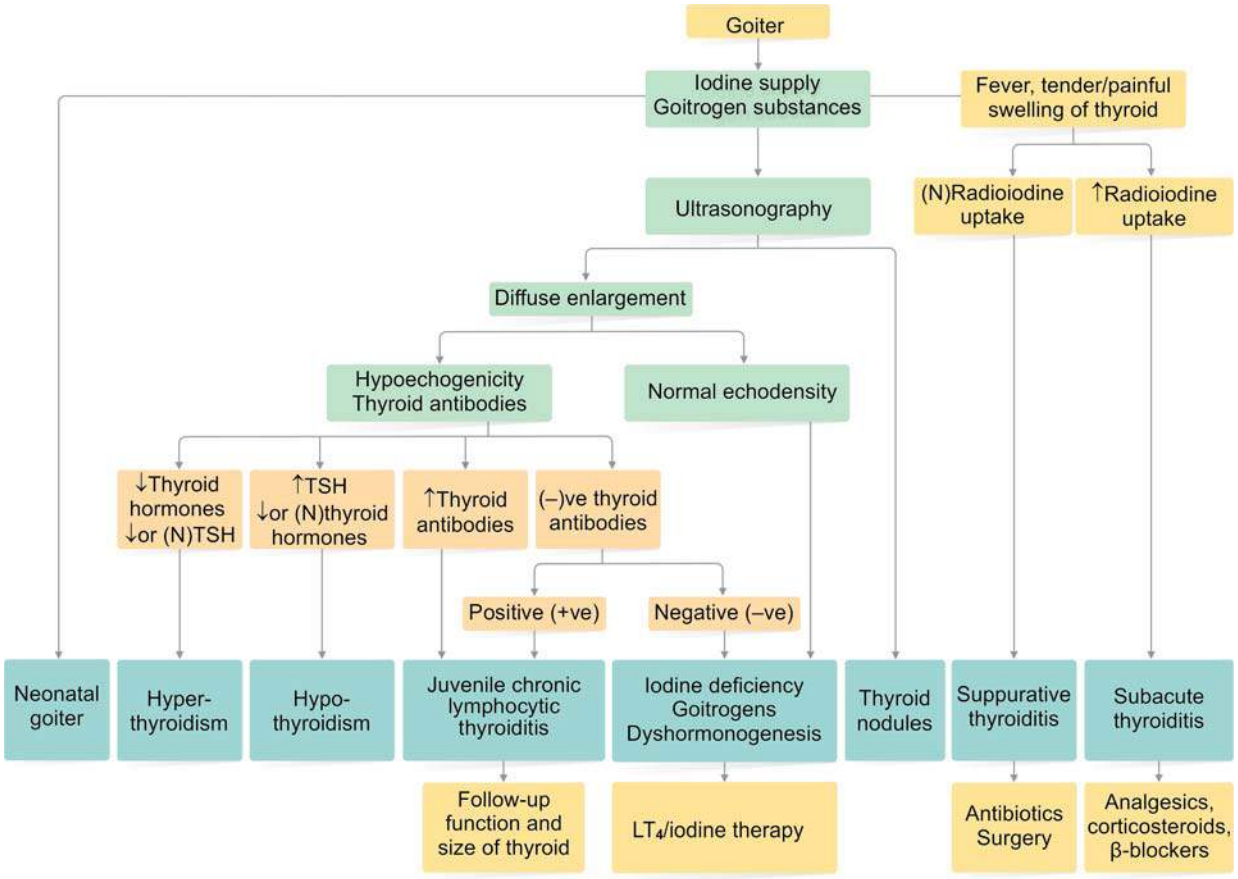


Fig. 32: Diagnostic workup and management algorithm of goiter in children

Abbreviations: +ve, positive; –ve, negative;↑, increase;↓, decrease; N, normal; LT4, levothyroxine; TSH, thyroid-stimulating hormone

Hormones of Parathyroid Gland

Chief cells secrete PTH whose main effect is to raise serum-calcium concentrations. A second hormone, parathyroid-related peptide (PTHrP) is also secreted, mainly during fetal life and probably has a role in maintaining the normal positive gradient of calcium across the placenta.

Actions of PTH

Parathyroid hormone has three main actions:

1. It stimulates osteoclasts to increase calcium (and phosphorus) resorption from bone thus increase bone turnover.
2. It promotes renal tubular phosphate excretion and, to a lesser extent, calcium reabsorption.
3. It increases 1-alpha hydroxylation of 25-hydroxyvitamin D [25(OH)D] in renal cells. This increases concentrations of circulating 1α, 25-dihydroxyvitamin D [1α,25$(OH)_2$D] which promotes calcium absorption in the gut, thereby increasing calcium levels.

Mechanism of Action of PTH

There are three different PTH receptors. One binds PTHrP (Fig. 33) and is known as the hPTH/PTHrP receptor. A 2nd receptor, PTH2R (hPTH2-R), does not bind PTHrP and is found in the brain, placenta, and pancreas. In addition, there is evidence for a 3rd receptor, carboxyl-terminal parathyroid hormone (CPTH), which reacts with the carboxyl terminal

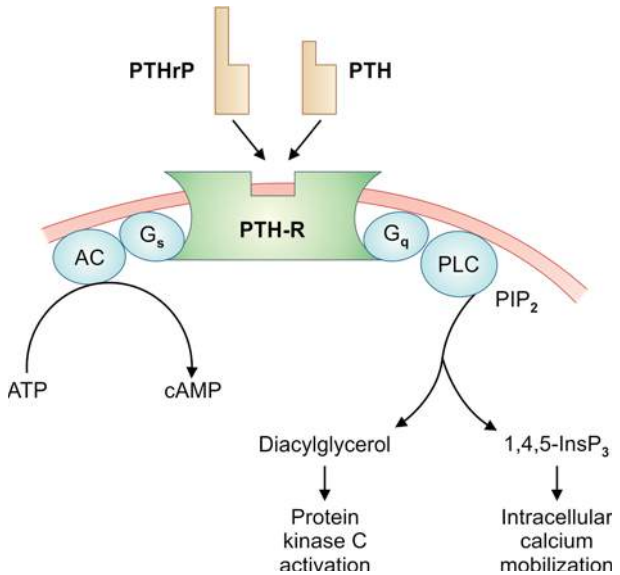


Fig. 33: Signal transduction pathways activated by PTH or PTHrP binding to the hPTH/hPTHrP receptor. Intracellular cAMP is increased via G_s and adenylyl cyclase. Diacylglycerol and IP_3 ($1,4,5\text{-}InsP_3$) are increased via G_q and PLC

Abbreviations: cAMP, cyclic adenosine monophosphate; ATP, adenosine triphosphate; PLC, phospholipase C; $InsP_3$, inositol trisphosphate; PTH, parathyroid hormone; PTHrP, parathyroid-related peptide

rather than the amino terminal of PTH. The first two receptors are coupled to G_s, and via this heterotrimeric G protein they activate adenylyl cyclase, increasing intracellular cAMP. The hPTH/PTHrP receptor also activates phospholipase C (PLC) via G_q, increasing intracellular Ca^{2+} and activating protein kinase C.

Regulation of PTH

Secretion of PTH is principally determined by the circulating concentration of ionized calcium. Calcium-sensing receptors (CaSR) on the gland mediate the secretion of hormone in response to hypocalcemia via a magnesium-dependent adenylate cyclase second messenger. Abnormalities of magnesium interfere with PTH secretion and genetic or acquired abnormalities of the calcium sensor result in persistent hyper- or hypocalcemia. Persistent hyperphosphatemia also stimulates PTH secretion and leads to PT gland hyperplasia. This is of particular importance in CRF. The following Figure 34 illustrates the role of PTH in calcium homeostasis.

Factors Affecting PTH Secretion

Several factors that affect the secretion of PTH are listed in Table 8.

Genetic Syndrome and Parathyroid Disorders

Several genetic diseases are associated with parathyroid disorder. They are listed in Table 9.

Disorders of Parathyroid Hormones

Diseases related to PTH disorders are:

- Hypoparathyroidism
- Hyperparathyroidism
- Pseudoparathyroidism.

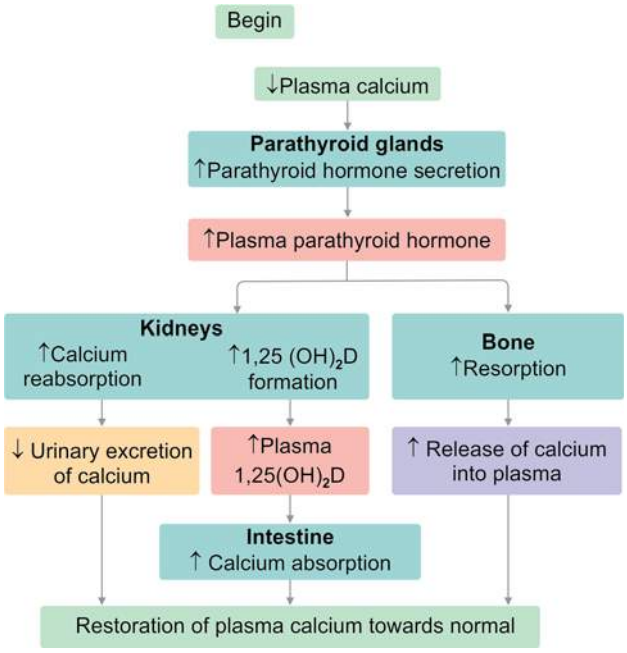


Fig. 34: Effects of PTH and 1,25-dihydroxycholecalciferol on whole body calcium homeostasis

Hypoparathyroidism

Parathyroid underactivity is extremely rare unless the cause is iatrogenic following thyroid/PT surgery. The causes of hypoparathyroidism are:

a. *Congenital parathyroid deficiency*
   - Isolated hypoparathyroidism
     - Familial:
       Autosomal dominant and recessive patterns are both caused by mutations in the signal peptide region of the PTH gene. This results in abnormal processing of pre-pro-PTH to PTH
       X-linked recessive disease causing PT aplasia is due to a deletion-insertion of a fragment from chromosome 2p25 into Xq27
   - DiGeorge syndrome
   - Other syndromic hypoparathyroidism:
     - The mitochondrial disorders Kearns-Sayre syndrome.
     - Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke (MELAS) syndrome

b. *Acquired parathyroid deficiency*
   - Surgical hypoparathyroidism
   - Autoimmune parathyroid disease
   - Infiltrative PT disease:
     - Hemochromatosis
     - Wilson's disease.

Manifestation of Hypoparathyroidism

Commonly children who show clinical hypoparathyroidism subsequently develop additional other endocrinological abnormality. The most common endocrine disorder is hypoadrenocorticism (Addison's disease). Other endocrine disorders include DM and diabetes insipidus, hypothyroidism that may be associated with autoimmune defect as manifested by chronic mucocutaneous candidiasis.

Transient Hypoparathyroidism in Neonatal Period

Present as symptomatic with evidence of hypocalcemia:

- Jitteriness

Table 8: Factors affecting PTH secretion

PTH secretion is stimulated by	PTH secretion is inhibited by
Hypocalcemia Hyperphosphatemia Reduced 1,25-dihydroxyvitamin D levels	Hypercalcemia FGF23 1,25-dihydroxyvitamin D

Abbreviations: PTH, parathyroid hormone; FGF23, fibroblast growth factor 23

Table 9: Genetic diseases associated with parathyroid disorders

Name of the condition	Chromosome	Inheritance	Calcium
CATCH 22 (DiGeorge)	22q11.2	Autosomal dominant	Low
Pseudohypopara-thyroidism	20q13	Autosomal dominant	Low
Familial hypoparathyroidism	1p	Autosomal dominant	High
Familial hypercalciuric-hypocalcemia	3q21-24	Autosomal dominant	Low
Primary hypomagnesemia	-	Autosomal recessive	Low

- Twitching of extremities, eyes and facial muscles, apneic spell
- Loose bowel motion
- Convulsion
- Rarely 1st sign of long standing PT gland hypofunction: DiGeorge syndrome, maternal hypoparatathyroidism, congenital isolated hypoparathyroidism.

Hypoparathyroidism with Onset after the Neonatal Period

The forms of hypoparathyroidism with onset after the neonatal period:

- Common presentation between 2 and 10 years
- Severe enamel hypoplasia in permanent teeth (Fig. 35)
- Carpal or pedals spasms (Fig. 36)
- Paresthesia of circumoral region
- Convulsion is the most prominent feature
- Increased intracranial pressure and papilledema (pseudotumor cerebri)
- Rarely calcification in the basal ganglia.

Diagnosis

The Trousseau test and Chvostek's sign are helpful in diagnosis. Tetany can be precipitated by hyperventilation.

Trousseau sign: A blood pressure cuff inflated above the systolic pressure on the upper arm causes development of carpopedal spasm with painful paresthesia.

Chvostek's sign: Tapping the facial nerve in front of the ear lightly with the index finger elicits twitching of the corner of the mouth.

Laboratory Investigations

- Low serum calcium
- Low PTH

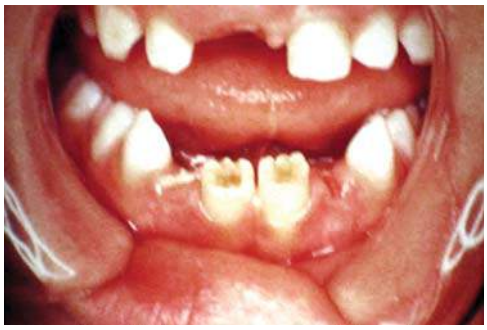


Fig. 35: Enamel hypoplasia in a girl with hypoparathyroidism

Fig. 36: A case of carpal spasm (part of carpopedal spasm) found in hypocalcemia due to hypoparathyroidism

- Low urinary calcium
- Low 1, 25 vitamin D
- High phosphate.

Special investigations are done for special variety of hypoparathyroidism, e.g.

- DiGeorge syndrome: Deletion of 22p
- Metabolic: Iron and copper overload
- Autoimmune
- Calcium sensing receptor.

Treatment of Hypoparathyroidism

Treatment of hypoparathyroidism is vitamin D or its metabolite.

Pseudohypoparathyroidism (PHP)

Other name is resistance to PTH action. In PHP, PTH production is adequate, but target organs (renal tubule, bone, or both) fail to respond because of receptor resistance. Resistance to PTH action is due to a heterozygous inactivating mutation in the stimulatory G protein subunit, associated with the PTH receptor, which leads to impaired signaling. Resistance to other G protein-dependent hormones, such as TSH, GHRH and FSH/LH, may also be present.

Types

There are several types of PHP with variable biochemical and phenotypic features. Biochemical abnormalities in PHP (hypocalcemia and hyperphosphatemia) are similar to those seen in hypoparathyroidism, but the PTH levels are elevated.

1. *Pseudohypoparathyroidism type I*:

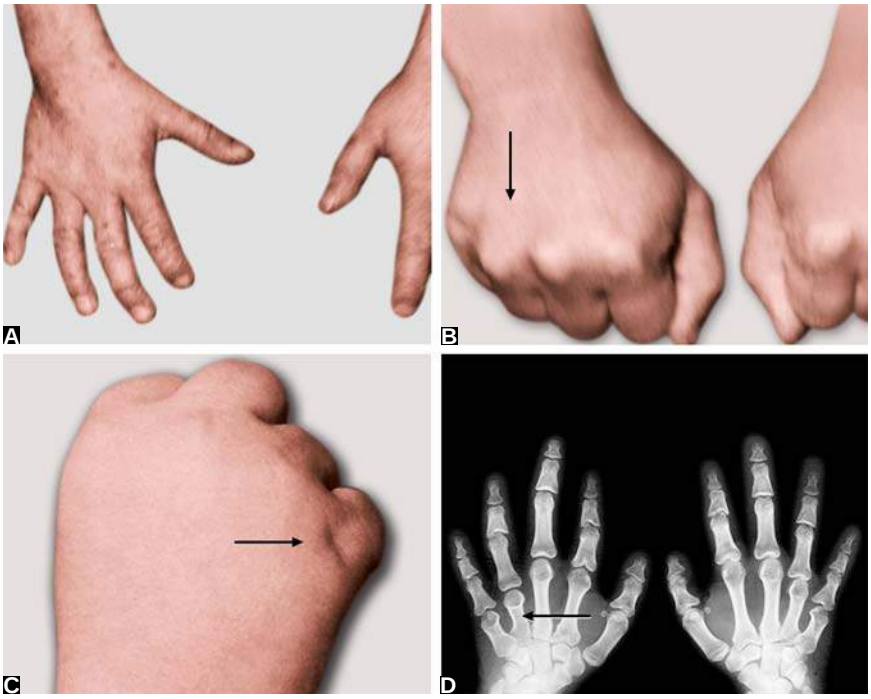
   Characteristic features:
   - Hypocalcemia
   - Hyperphosphatemia
   - Normal or increased PTH but refractoriness to endogenous PTH. Urinary excretion of cAMP fails to increase significantly when exogenous PTH is injected.

   Clinical features: Somatic and mental features of Albright's hereditary osteodystrophy (AHO) are present.
   - Shortening of 4th and 5th metacarpals clinically manifested as a dimple when a fist is made (Figs 37A to D)
   - Metatarsal are similarly affected (Fig. 38)
   - Short stature
   - Obesity
   - Round face
   - Cutaneous and subcutaneous plates of calcification may be present near joints
   - Calcification in the basal ganglia is very common.

   Pseudohypoparathyroidism is again subdivided into following subtypes:

   I. Pseudohypoparathyroidism type Ia (PHP-Ia): PHP-1a is an autosomal-dominant condition characterized by the biochemical features of hypoparathyroidism (hypocalcemia and hyperphosphatemia) with raised levels of PTH.

   Clinical features:
   - Albright' s hereditary osteodystrophy
   - Intracranial calcification (Fig. 39)
   - Sensorineural deafness
   - Poor sense of smell
   - Mild hypothyroidism
   - Menstrual irregularity.



Figs 37A to D: Clinical features. (A) Short 5th metacarpal; (B) Fisting of hand revealing absence of knuckle (bony prominence) of 5th metacarpal bone; (C) Dimple on fisting hand due to short 4th and 5th metacarpal bone; (D) X-ray of hand showing short 4th and 5th metacarpal bone

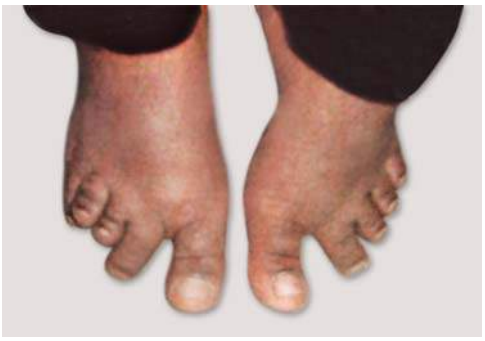


Fig. 38: Picture showing short 3rd and 4th toes bone in a girl with pesudohypoparathyroidism

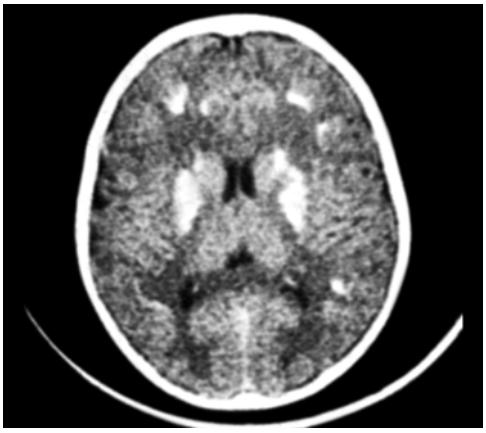


Fig. 39: CT scan of brain showing calcification of basal ganglia in a case of pseudohypoparathyroidism

II. Pseudohypoparathyroidism type Ib (PHP-Ib): Here the features of AHO are absent but PTH resistance is present.

III. Pseudohypoparathyroidism type Ic (PHP-Ic)**:** It is characterized by multiple hormone resistance, including PTH, together with features of AHO.

2. *Pseudohypoparathyroidism type II (PHP-II)*: Type II is a distinct or a rare form of PHP in which exogenous PTH elicits blunted phosphaturic and calcemic responses characteristics of PHP but there is prompt normal urinary excretion of cAMP. Features of AHO are absent in type II PHP.

Laboratory Investigations

- Hypocalcemia
- Hyperphosphatemia
- Hyperparathyroid hormone (↑PTH).
- High TSH, low FT4.
- Elevated FSH/LH.
- Neuroimaging (calcification of basal ganglia in CT scan).

Pseudopseudohypoparathyroidism (PPHP)

Pseudopseudohypoparathyroidism describes individuals with the AHO phenotype, but normal calcium homeostasis. PHP and PPHP can occur in the same cohort. Genomic imprinting is probably responsible for the different phenotypic expression of disease. Heterozygous loss of the maternal allele causes PHP and heterozygous loss of the paternal allele causes PPHP.

Differences between hypoparathyroidism, PHP type I and II, and PPHP are shown on the following Table 10.

Table 10: Difference between hypoparathyroidism, PHP type I and II and PPHP

	Hypoparathyroidism	PHP type 1	PHP type 2	PPHP
Age				
Hypocalcemia	Any age	Usually after 5 yrs	Usually after 5 yrs	Absent
Somatic signs	Absent	May be evident at birth	May be evident at birth	May be evident after birth
Somatic features (AHO)	Absent	Often present (1a), may be absent (1b)	Absent	Present
Mental retardation	Absent	Often present, may be absent	Absent	Usually present, may be absent
Intracranial calcification	Absent	Frequently present	Not known	Absent
Plasma chemistry				
Calcium	–	–	–	N
Phosphate				N
Alkaline phosphatase		N or	N	N
PTH	0 or low	N or		N
Skeletal X-ray				
Periosteal erosion	Absent	Absent or present	Absent	Absent
PTH response test				
Urinary Camp	Normal	0 or slight	N	N
Phosphaturia effect	Normal	Blunted	Blunted	N
Calcemic effect	Full normal	Blunted	Blunted	N

Abbreviations: PHP, pseudohypoparathyroidism; PPHP, pseudopseudohypoparathyroidism; AHO, Albright's hereditary osteodystrophy; PTH, parathyroid hormone

Treatment of Hypoparathyroidism and Pseudohypoparathyroidism

The treatment of PHP is with large dose of vitamin D or vitamin D metabolite.

Hypocalcemia and hyperphosphatemia are readily corrected and tetany and convulsion are controlled, but the somatic and mental abnormalities are unaltered. No vitamin D treatment is required for patients with PPHP since calcium homeostasis is normal with the condition.

The most immediate urgency is symptomatic hypocalcemia. Convulsions, tetany, laryngeal stridor and cardiac arrhythmia are emergencies that require treatment with intravenously administered calcium. In the neonate, symptomatic hypocalcemia is hazards due to cerebral hemorrhage and sudden cardiac death. A starting dose is 0.1 mmol (0.2 mEq, 4 mg), elemental calcium per kg body weight per hour should be given in continuous infusion. Injectable calcium gluconate is usually marketed as 10% solution of the salt which should be diluted to approximately 2% before administration. IV infusion should be continued as long as needed to prevent hypocalcemia. IV calcium therapy can be stopped after 4–5 days and oral calcium supplement afterward.

Treatment with vitamin D and its metabolites: Except in early infancy and in post-thyroidectomy patients, hypoparathyroidism is a permanent condition and require long-term management. The definitive treatment of permanent hypoparathyroidism and PHP is vitamin D or related compound. Vitamin D is given as 2,000 IU/kg/day in hypoparathyroidism and PHP. Synthetic 1α,25$(OH)_2$D and 1α(OH)D3 are both used in the treatment of hypoparathyroidism and PHP.

1,25$(OH)_2$D3 [Calcitriol (Roche)] is marketed as capsule in 0.25 μg and 0.5 μg and is given 0.025 μg and 0.05 μg/kg bodyweight per day. The vitamin D hormone has advantages over vitamin D in respect to its speed of action and rate of disappearance of its calcemic effects when discontinued. It is particularly advantageous in treating acute symptomatic hypocalcemia like neonatal hypocalcemia and post-thyroidectomy tetany.

Calcium Homeostasis

Ninety-eight percent of total calcium in the body are found in skeleton. Only 2% is available in blood of which 50% is bound to plasma protein named albumin. The rest 50% of the circulatory calcium is ionized or free calcium which exerts the physiological effects of calcium.

The plasma calcium level is maintained by the interplay of three dynamic processes:

1. Tubular reabsorption from the kidneys.
2. Absorption from the small intestine.
3. Bone remodeling.

These processes are influenced by:

- Two calciotropic hormones: PTH and 1,25$(OH)_2$D3
- Calcium-sensing receptor (CaSR): It is a critical regulator of plasma calcium levels. It exerts its effect by directly influencing PTH release in response to circulating calcium levels.

Hypocalcemia (also Discussed in Fluid and Electrolyte Balance Chapter)

- *Hypocalcemia in neonate*
  - *Transient hypocalcemia in newborn (tetany of the newborn)*:
    - Transient neonatal hypoparathyroidism due to maternal hyperparathyroidism.
    - Feeding with high phosphate containing milk (raw cow's milk contains high phosphate and sodium).
    - Severe maternal rickets
    - Congenital rickets.

  Permanent:
  - Permanent isolated hypoparathyroidism
  - Primary hypomagnesemia with secondary hypocalcemia

  - Rare inborn error of magnesium absorption
  - DiGeorge syndrome.
- *Beyond neonatal period*
  - Vitamin D deficiency is the most important cause.
- *Beyond infancy*
  - Vitmain D deficiency
  - Chronic renal insufficiency
  - Hypoparathyroidism
  - Pseudohypoparathyroidism.

Hyperventilation state: Decreasing serum ionized calcium hysteric hyperventilation.

Etiology of Hypocalcemia

The causes are mentioned below:

- Hypoparathyroidism
- Rickets due to:
  - Vitamin D deficiency
  - Long-term anticonvulsant therapy
  - Biliary cirrhosis and chronic obstructive jaundice
  - Vitamin D dependent rickets
  - Low dietary calcium intake
- Acute and CRI
- Hypomagnesemia:
  - Primary
  - Secondary to:
    - Steatorrhea
    - Leukemia.
- Acute gastroenteritis, especially with hypertonic dehydration
- Nephrotic syndrome
- Respiratory and metabolic alkalosis.

Clinical Features of Hypocalcemia

- Unexplained movement or seizure
- Maternal rickets or clinical rickets in the child.

Symptoms:

- Irritability
- Twitching
- Tingling fingers toes or lips
- Stridor
- Numbness of fingers, toes or lips
- Seizure.

Signs:

- Seizure
- Carpopedal spasm
- Chvostek's signs (mentioned earlier)
- Trousseau sign (mentioned earlier).

Investigations

- Serum calcium
- Serum phosphate
- Alkaline phosphatase
- 25(OH)D3
- PTH
- Serum magnesium.

Management

- *Urgent*:
  - IV bolus calcium gluconate 0.1 mL/kg
  - Dilute with 0.9% saline of 5% dextrose and infuse over 10 minutes in to central line or large cannula in large vein as there is risk of calcium burn from quick tissue leak. Also do not coadminister with sodium bicarbonate as it may precipitate calcium carbonate
- *Subsequent steps*:
  - Continue calcium infusion 1–2 mmol/kg/day via central vein until hypocalcemic clinical status settles
  - Magnesium infusion if low or if clinical features are refractive to adequate calcium infusion
- *Stabilization*:
  - Vitamin D analog is offered if hypoparathyroidism is associated
  - Oral calcium supplement.

Hypercalcemia (Also Discussed in Fluid and Electrolyte Balance Chapter)

Hypercalcemia is rare in childhood.

Etiology of Hypercalcemia

Causes of hypercalcemia include:

- Hypervitaminosis D
- Hyperparathyroidism:
  - Adenoma
  - Hyperplasia
  - Familial neonatal hyperparathyroidism
- Familial hypocalciuric hypercalcemia
- Chronic renal insufficiency and post-transplantation
- Infantile hypercalcemic syndrome
- Infantile idiopathic hypercalcemia: Pesent during first year of life and may also linked to vitamin D insensitivity
- Williams syndrome (Fig. 40)
- Maternal hypocalcemia may lead to hyperparathyroid response in fetus raising calcium levels
- Neonatal primary hyperparathyroidism: Rare. Inactivating homozygous mutation of CaSR gene results in hyperparathyroidism. Symptoms are anorexia, constipation, abdominal pain, polyuria and polydipsia
- Other hypercalcemic states:
  - Prolonged immobilization
  - Pre-existing bone disorder during chemotherapy.

Biochemistry

- Calcium level greater than 2.6 mmol/L.
- Suppressed plasma PTH.
- Inappropriate calcemic response.

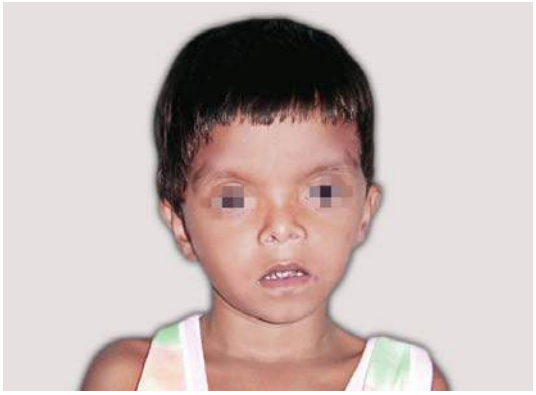


Fig. 40: A child with Williams syndrome with characteristic Elfin facies, small mandible, full cheek with broad nasal bridge. Supravalvular aortic stenosis is the main cardiac complication

Management

- *Immediate*:
  - Normal saline infusion and maintenance of plasma deficit if present
  - IV furosemide infusion 1–1.5 mg/kg/daily maximum 20 mg daily
  - If persistent hypercalcemia is present, IV pamindronate infusion 0.5 mg/kg daily for 2–3 days. Pamidronate may be repeated if required
- *Subsequent*:
  - Depends upon the cause of hypercalcemia.

Idiopathic hypercalcemia of infancy: May present in the first year of life and linked to vitamin D deficiency.

Williams Syndrome

Specific etiology is unknown. It is one of the causes of hypercalcemia. It occurs due to deletion of one elastin allele at chromosome 7 (7q 11.23). Exact frequency is not known. It may be associated with normocalcemia.

Clinical features:

- *Dysmorphic facies (Fig. 40)*: Elfin facies, small mandible, full cheeks with prominent maxilla, long philtrum, upturned nose, upper lip with cupid curve, small peg-like teeth with numerous caries, periorbital fullness, broad nasal bridge, open mouth, stellate pattern in iris and strabismus
- *Hypercalcemia*
- *Cognitive function and personality*: Patients are polite, sociable, well-developed, so called "cocktail party" personality
- *Cardiac defects:* Supravalvular aortic stenosis is most common. Peripheral pulmonary stenosis, hypoplasia of aorta, coronary artery stenosis and ASD or VSD may also occur
- *Miscellaneous*: Hypertension, renal artery stenosis, joint laxity, contracture, failure to thrive.

Investigation:

Initial investigation includes:

- Echocardiogram
- Renal uracil DNA glycosylase (UDG)
- Baseline serum calcium
- Renal biochemistry
- Routine karyotyping.

Diagnosis is confirmed by fluorescent in situ hybridization (FISH) analysis.

Treatment:

- Supportive treatment and treatment of associated condition
- Prednisolone or calcitonin to control hypercalcemia.

Prevention:

- Vitamin D containing food and preparation would be withdrawn. The infant should be fed with low calcium milk (Locason)
- Multisystemic managemengt involve management of hypertension and hypercalcemia
- Supravalvular aortic stenosis requires lifelong cardiac follow-up.

Hyperparathyroidism

Hyperparathyroidism is the commonest cause of chronic hypercalcemia in children. Hyperparathyroidism in children most commonly occurs as a secondary consequence of vitamin D deficiency. Chronic kidney disease may also be a factor.

Etiology

- *Primary hyperparathyroidism*: It is uncommon in children
  - Adenoma: Most common
  - Primary hyperplasia
  - Parathyroid carcinoma
- *Secondary hyperparathyroidism*: Secondary hyperparathyroidism is caused by any condition that gives rise to chronic hypocalcemia, which in turn leads to compensatory overactivity of the PT glands. Renal failure is by far the most common cause of secondary hyperparathyroidism.

Clinical Features

The signs and symptoms of hyperparathyroidism reflect the combined effects of increased PTH secretion and hypercalcemia.

Primary hyperparathyroidism: Primary hyperparathyroidism may be:

- Asymptomatic and identified after a routine chemistry profile
- Associated with the classic clinical manifestations of primary hyperparathyroidism.

Primary hyperparathyroidism is associated with "painful bones, renal stones, abdominal groans and psychic moans." The constellation of symptoms includes:

- Central nervous system alterations, including depression, lethargy and eventually seizures
- Neuromuscular abnormalities, including weakness and fatigue
- Cardiac manifestations, including aortic or mitral valve calcifications (or both)
- Gastrointestinal disturbances, including constipation, nausea, peptic ulcers, pancreatitis and gallstones
- Nephrolithiasis (renal stones).

Investigations

The diagnosis is made from the combination of:

- Hypercalcemia
- Raised PTH
- Hypercalciuria.

The enlarge parathyroid glands can sometimes be identified by USG or sestamibi scanning.

Neonatal Severe Primary Hyperparathyroidism

Neonatal severe primary hyperparathyroidism is caused by a homozygous inactivating mutation of CaSR and causes severe primary hyperparathyroidism. These infants develop crumbling bones, which may result in respiratory distress and early nephrocalcinosis. The appearances of the bones on radiography resemble those of severe rickets, and multiple fractures may be present. Treatment usually requires total parathyroidectomy, which renders patients' hypoparathyroid and needing replacement with 1α-hydroxycholecalciferol (1α-OHCC).

The *adrenal glands* are paired endocrine organs consisting of both cortex and medulla, which differ in their development, structure and function.

Adrenal Cortex (Fig. 41)

The *cortex* consists of three layers of distinct cell types. Beneath the capsule of the adrenal is the narrow layer of zona glomerulosa. An equally intervening is the broad zona fasciculata, which makes up about 75% of the total cortex. The adrenal cortex synthesizes three different types of steroids:

- G*lucocorticoids* (principally cortisol), which are synthesized primarily in the zona fasciculata with a small contribution from the zona reticularis.
- M*ineralocorticoids,* the most important being aldosterone, which is generated in the zona glomerulosa.
- S*ex steroids* (estrogens and androgens), which are produced largely in the zona reticularis.

Adrenal Medulla (Fig. 41)

The *adrenal medulla* is composed of chromaffin cells, which synthesize and secrete *catecholamines,* mainly epinephrine.

Biosynthesis of Adrenocortical Hormones

The major paths by which the naturally occurring adrenocortical hormones are synthesized in the body are summarized in Figures 42 and 43. The precursor of all steroids is cholesterol. Some of the cholesterol is synthesized from acetate, but most of it is taken up from low-density lipoprotein (LDL) in the circulation. LDL receptors are especially abundant in adrenocortical cells. The cholesterol is esterified and stored in lipid droplets. *Cholesterol ester hydrolase* catalyzes the formation of free cholesterol in the lipid droplets. The cholesterol is transported to mitochondria by a sterol carrier protein. In the mitochondria, it is converted to pregnenolone in a reaction catalyzed by an enzyme known as *cholesterol desmolase* or *side-chain cleavage (scc) enzyme*. This enzyme, like most of the enzymes involved in steroid biosynthesis, is a member of the cytochrome P450 superfamily and is also known as *P450scc* or *CYP11A1*.

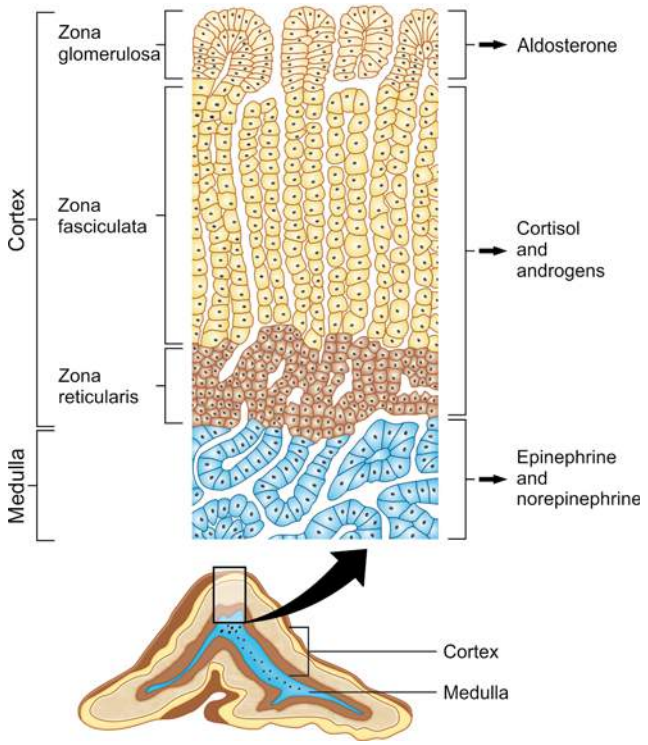


Fig. 41: Section through an adrenal gland showing both the medulla and the zones of the cortex, as well as the hormones they secrete

Regulation of Adrenal Hormone Secretion (Figs 44 and 45)

Steroidogenesis in the zona fasciculata and reticularis is under hypothalamic-pituitary control; secretion of aldosterone from the zona glomerulosa is under the control of the renin-angiotensin system.

A. Regulation of Cortisol Secretion

Cortisol secretion is closely regulated by ACTH, and plasma cortisol levels parallel those of ACTH (Fig. 46). There are three mechanisms of neuroendocrine control:

1. Episodic secretion and the circadian (diurnal) rhythm of ACTH.

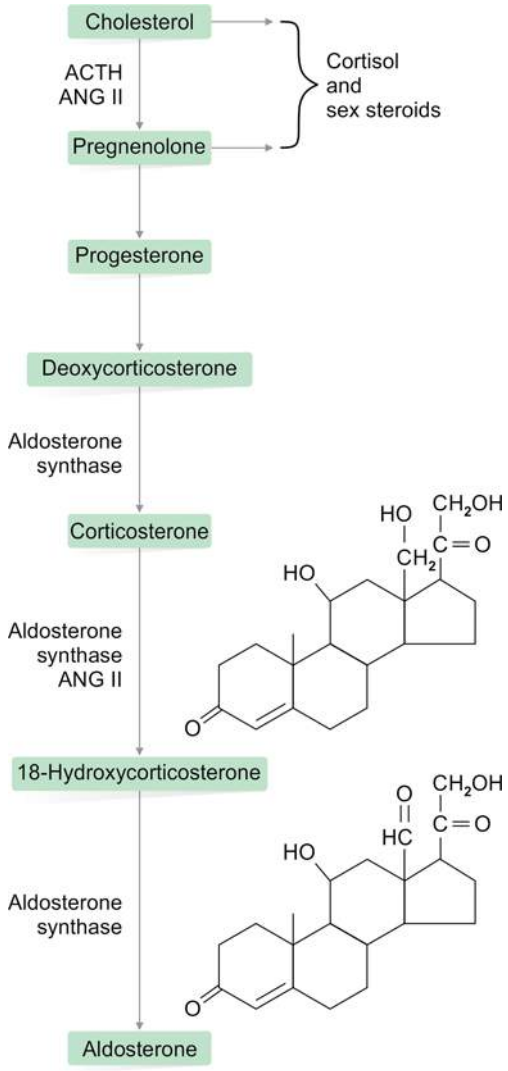


Fig. 42: Outline of synthesis of hormones in glomerulosa of adrenal gland

Abbreviations: ACTH, adrenocorticotropic hormone; ANG, angiotensin

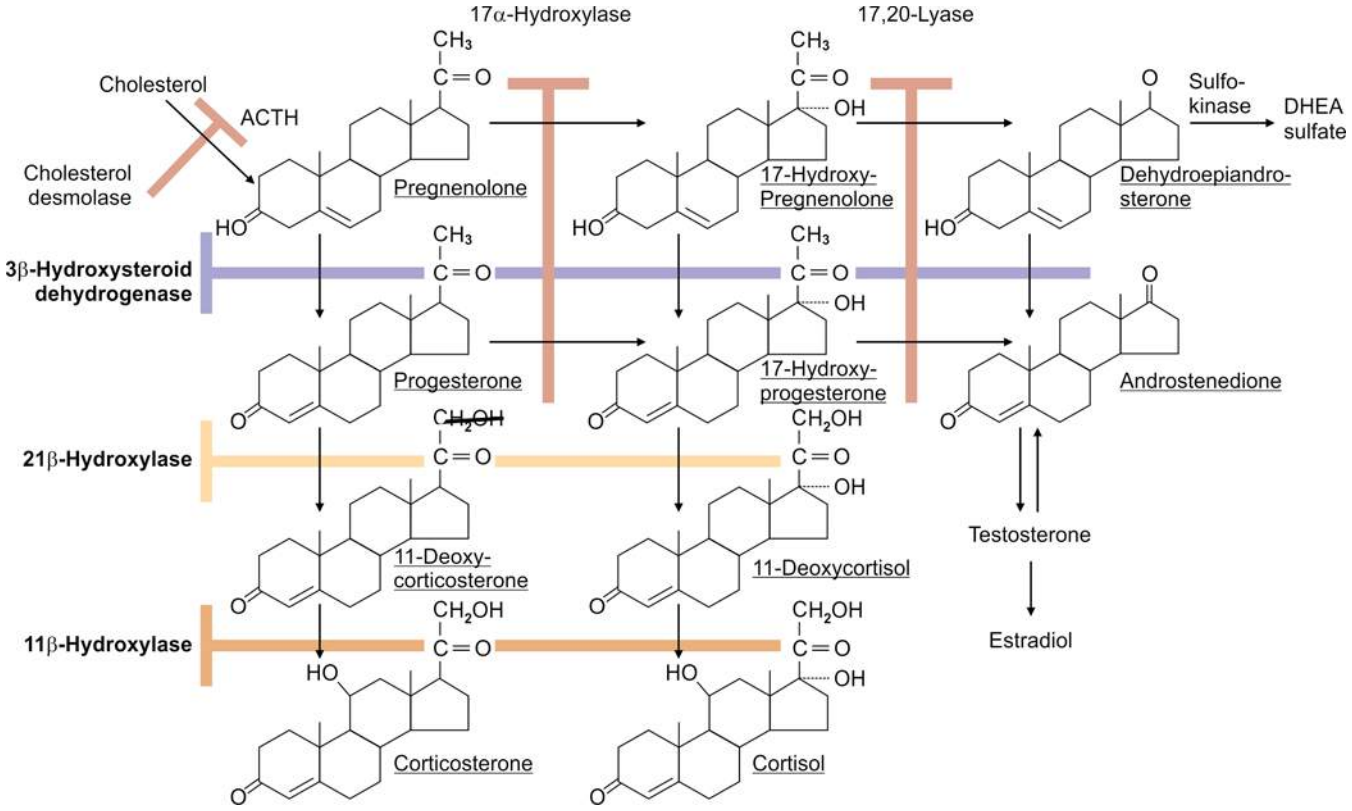


Fig. 43: Outline of synthesis of hormones in zona fasiculata and zona reticularis of adrenal gland and the enzymes involved. The enzymes for the reactions are numbered on the left and at the top of the chart, with the steps catalyzed shown by the shaded bars. (1) P450scc, cholesterol 20,22-hydroxylase:20,22-desmolase activity; (2) 3β-HSD/ISOM, 3-hydroxysteroid dehydrogenase; δ5-oxosteroid isomerase activity; (3) P450c21, 21α-hydroxylase activity; (4) P450c11, 11β -hydroxylase activity; (5) P450c17, 17β-hydroxylase activity; (6) P450c17, 17,20-lyase/ desmolase activity; (7) sulfokinase

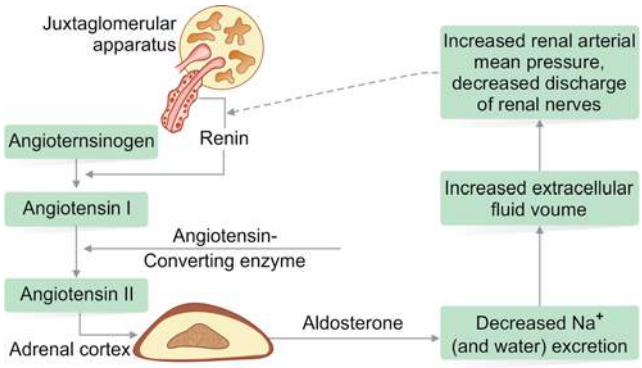


Fig. 44: Feedback mechanism of aldosterone secretion

2. Stress responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis.
3. Feedback inhibition by cortisol of ACTH secretion.

B. Regulation of Aldosterone Secretion (Fig. 46)

Renin is secreted from the juxtaglomerular cells in the kidney dependent on renal arterial blood pressure. Renin converts angiotensinogen to angiotensin I, which is converted in the lungs by angiotensin converting enzyme (ACE) into angiotensin II. Angiotensin stimulates adrenal aldosterone synthesis. Extracellular fraction (ECF) of potassium has an important direct inhibitory influence on aldosterone secretion.

DISORDERS OF ADRENOCORTICAL HORMONES

Disorders of adrenal hormones can be broadly classified under two headings: Insufficiency of adrenal hormone secretion and excess secretion of adrenal hormones.

Excess Secretion of Adrenal Hormones

Hyperfunction of the adrenal glands yields excessive secretion of its three hormones, i.e.

1. *Glucocorticoids*
   Excess secretion of glucocorticoid leads to a clinical syndrome named "Cushing's syndrome".
2. *Mineralocorticoids*
   Conn's syndrome is the effect of excess mineralocorticoid secretion.
3. *Androgen*
   Excess secretion of androgen results in:
   - Masculinization (adrenogenital syndrome)
   - Precocious pseudopuberty
   - Female pseudohermaphroditism.

Cushing's Syndrome

Cushing's syndrome comprises the symptoms and signs associated with prolonged exposure to inappropriately elevated levels of free plasma glucocorticoids. The use of the term glucocorticoidin covers excess from both

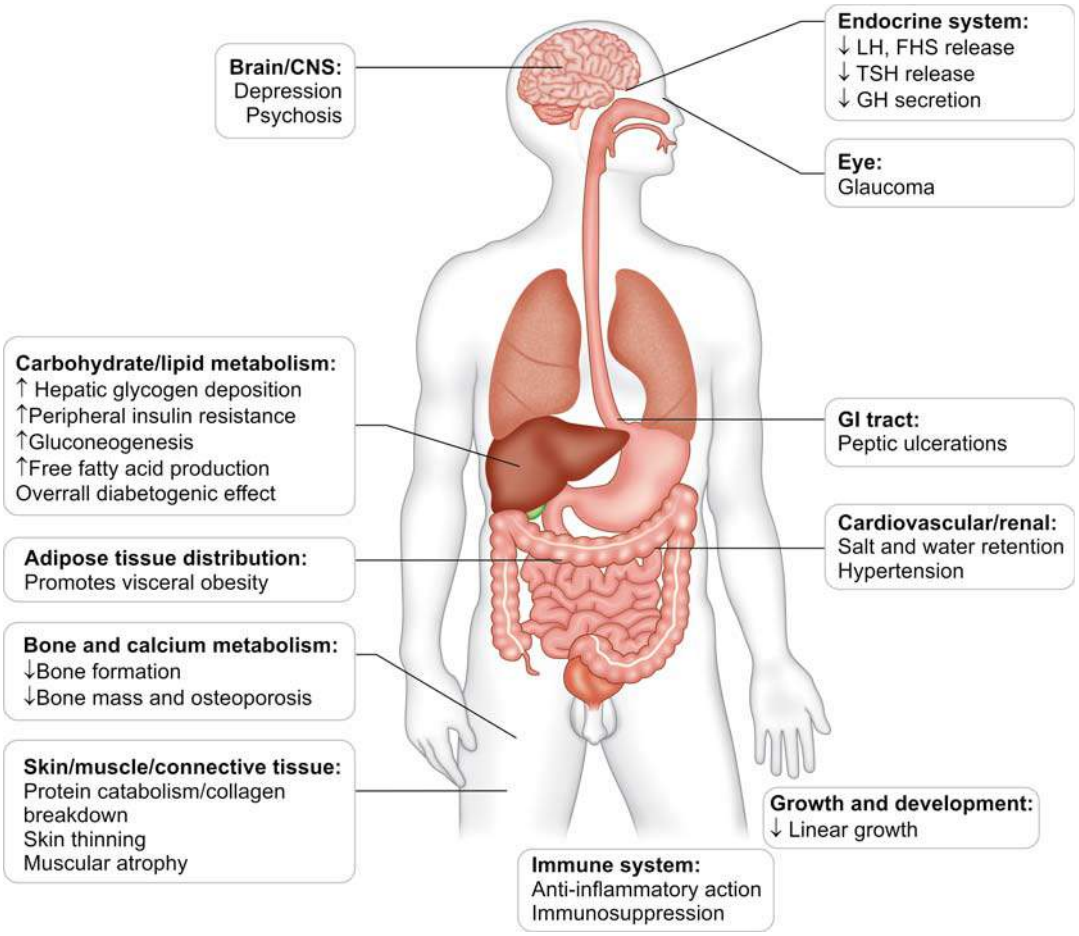


Fig. 45: Principal sites of action of adrenal hormones and the effects of excess secretion
Abbreviations: CNS, central nervous system; ↓, decrease; ↑, increase

endogenous (cortisol) and exogenous (e.g. prednisolone, dexamethasone) sources. Iatrogenic Cushing's syndrome is common. Endogenous causes of Cushing's syndrome are rare and result in loss of the normal feedback mechanism of the HPA axis and the normal circadian rhythm of cortisol secretion.

The related disorder caused by ACTH of non-pituitary origin is termed the ectopic ACTH syndrome.

Cushing's Disease

The term Cushing's syndrome is used to describe all causes, whereas Cushing's disease is reserved for cases of pituitary-dependent Cushing's syndrome.

Etiology of Cushing's Syndrome

- *ACTH-dependent causes*:
  - Cushing's disease (pituitary-dependent)
  - Ectopic ACTH syndrome
  - Ectopic CRH syndrome
  - Macronodular adrenal hyperplasia
  - Iatrogenic (treatment with 1-24 ACTH).
- *ACTH-independent causes*:
  - Adrenal adenoma and carcinoma
  - Primary pigmented nodular adrenal hyperplasia and Carney's syndrome
  - McCune-Albright syndrome
  - Aberrant receptor expression (gastric inhibitory polypeptide, interleukin-1β)
  - Iatrogenic (e.g. pharmacologic doses of prednisolone, dexamethasone).
- *Pseudo-Cushing's syndromes*:
  - Alcoholism
  - Depression
  - Obesity.

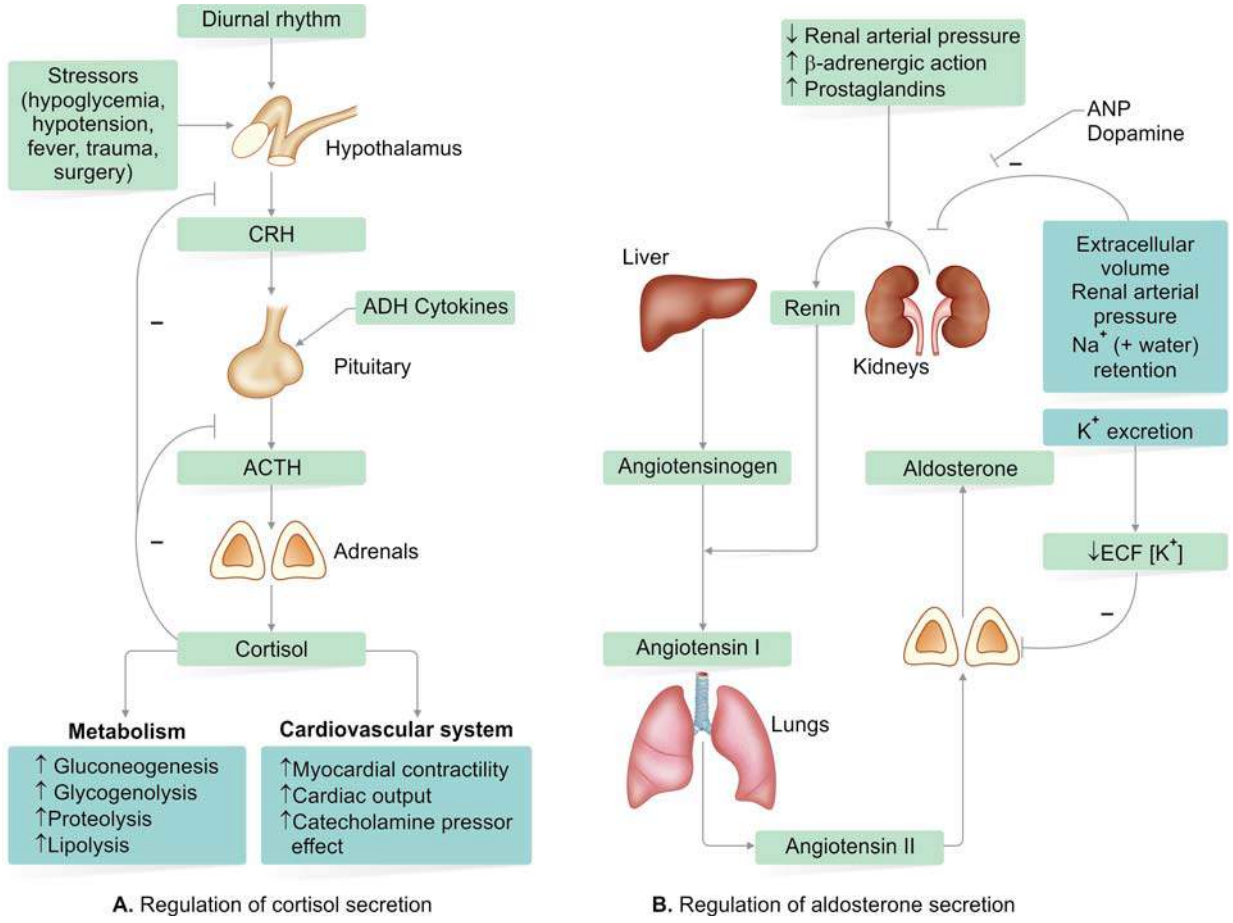
The most common causes of Cushing's syndrome in infancy are:

- Adrenal tumors: Carcinoma, adenoma
- Ectopic ACTH syndrome
- Nodular adrenal hyperplasia
- Undefined adrenal hyperplasia
- ACTH-producing tumor.

Clinical Features of Cushing's Syndrome (Figs 47 and 48)

Symptoms:

- Weight gain
- Menstrual abnormality
- Hirsutism
- Psychiatric dysfunction
- Backache
- Muscle weakness
- Fractures
- Loss of scalp hair.



Figs 46A and B: Normal negative feedback regulation of cortisol and aldosterone secretion (A) Hypothalamic-pituitary-adrenal axis. Adrenocorticotropic hormone is secreted from the anterior pituitary under the influence of two principle secretagogues, CRH and AVP; other factors, including cytokines, also play a role. CRH secretion is regulated by an inbuilt circadian rhythm and by additional stressors operating through the hypothalamus. Secretion of CRH and ACTH is inhibited by cortisol, highlighting the importance of negative feedback control; (B) Renin-angiotensin-aldosterone system (RAAS)

Abbreviations: ACTH, adrenocorticotropic hormone; ECF, extracellular fluid; CRH, corticotropin-releasing hormone; ADH, antidiuretic hormone; Na^+, sodium ions; K^+, potassium ions; ANP, atrial natriuretic peptide

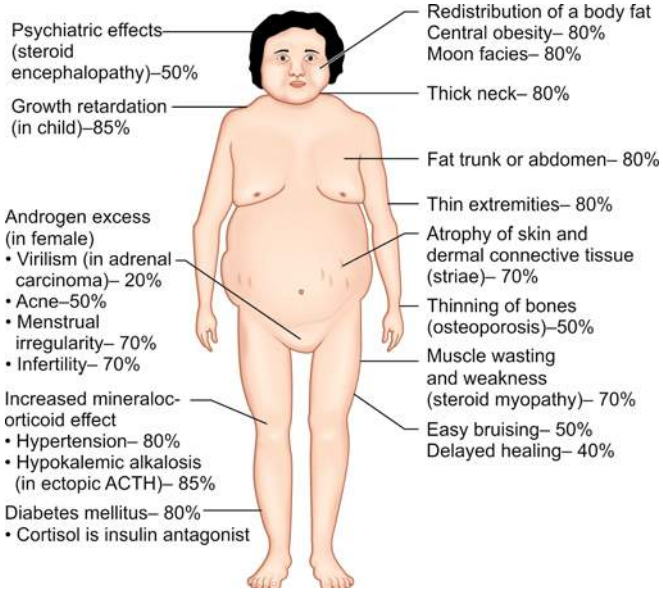


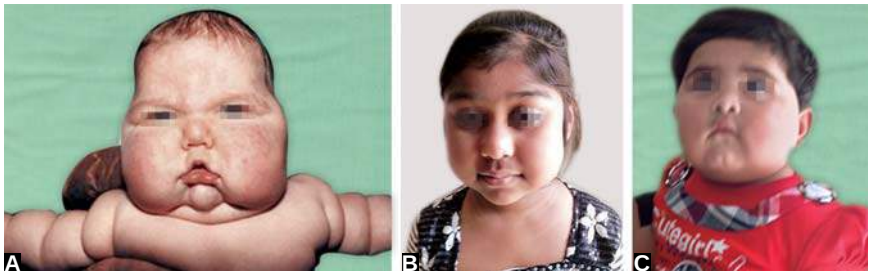
Fig. 47: Features of Cushing's syndrome

Signs:

- Obesity: Generalized obesity is common in younger children
- Plethora
- Moon face: The face is rounded, with prominent cheeks and a flushed appearance
- Hypertension
- Bruising
- Red-purple striae
- Muscle weakness
- Ankle edema
- Pigmentation
- Signs of abnormal masculinization: Occurs commonly in children with adrenal tumor. These are:
  - Hirsutism on the face and trunk
  - Pubic hair
  - Acne
  - Deepening of the voice
  - Enlargement of the clitoris in girls.

Others:

- Diabetes
- Osteoporosis
- Renal calculi.



Figs 48A to C: (A). An infant with characteristic facies of Cushing's syndrome; (B) Cushingoid face due to prolonged corticosteroid therapy (exogenous steroid); (C) Pseudo Cushing's syndrome showing rounded face with prominent flushed cheek due to obesity

Laboratory Investigations

Investigations are directed toward the confirmation of the diagnosis and finding of etiology.

- The commonly used screening test includes free cortisol and overnight dexamethasone suppression test. Abolition of circadian rhythm of plasma cortisol is the earliest marker of hypercortisolism
- Estimation of morning and evening cortisol has been used for screening of Cushing's syndrome. The estimation of midnight cortisol, the time of physiological lowest value of cortisol is useful screening test for Cushing's syndrome
- 10–20% of cortisol is excreted in urine as 17-oxosteroid (17-hydroxycorticosteroid). In Cushing's syndrome due to adenoma or hyperplasia, urinary 17-oxosteroid values may be normal or insignificantly increased. A high level indicates adrenocortical malignant tumor. A raised urinary cortisol greater than 90 nmol/24 hour is diagnostic of Cushing's syndrome
- In Cushing's syndrome due to adrenal carcinoma, urinary tetra-hydro-S (derived from 11- deoxycortisol) is markedly increased
- Overnight dexamethasone suppression test: It involves estimation of cortisol level after a single midnight dose of dexamethasone 0.3 mg/m^2. Lack of suppression of cortisol level to less than 5 µg/dL favors the diagnosis of Cushing's syndrome.

Dexamethasone suppression test (DMST):

Low dose dexamethasone suppression test: This includes administration of dexamethasone orally 0.5 mg 6 hourly for 8 doses. Plasma cortisol less than 50 nmol/L on day 4 excludes Cushing's syndrome, where as serum cortisol level greater than 5 µg/dL is diagnostic of Cushing's syndrome.

Indications: Diagnosis of Cushing's syndrome

Procedure:

Day 1:

- Admit patient
- Insert IV cannula for sampling
- Collect samples for ACTH and cortisol at 24.00 hour and following morning at 9.00 hour
- Sample must be taken when child is asleep.

Day 2:

Start dexamethasone 0.5 mg 6 hourly for 8 doses, i.e.

Day 2	12.00 h	18.00 h	24.00 h	
Day 3	06.00 h	12.00 h	18.00 h	24.00 h
Day 4	06.00 h			

Day 4: Repeat samples for ACTH and cortisol at 9.00 h.

Sample required:

- ACTH: To take lab immediately on ice.
- Cortisol.

It is important to distinguish Cushing's disease from Cushing's syndrome and to differentiate ACTH dependent causes from autonomous adrenal steroid production.

The most important feature is the ACTH level. ACTH dependent Cushing's syndrome has high ACTH level (>15 pg/mL) than ACTH independent Cushing's syndrome (ACTH <5 µg/mL). Ectopic ACTH production has very high ACTH level (>100 pg/mL).

High dose dexamethasone suppression test:

Indication: It is a differential diagnosis of Cushing's syndrome whereas low dose dexamethasone suppression test is used for screening purpose.

High dose dexamethasone suppression tests are used to differentiate various conditions associated with Cushing's syndrome. High dose dexamethasone suppression test is based on the principle that high doses of this agent suppress ACTH production in individual with pituitary lesions but not in those with ectopic ACTH production. In Cushing's syndrome due to adrenal tumors, dexamethasone suppression test is associated with unchanged high cortisol (serum and urine) and low ACTH.

Procedure: The high dose suppression test involves estimation of cortisol level after 8 doses of dexamethasone at a dose of 2 mg per dose or 3.7 mg/m^2/day. The procedure is same as that of low dose dexamethasone suppression test except the dose.

Sample required:

- ACTH: To take lab immediately on ice
- Cortisol.

Interpretation:

- Pituitary dependent hypercortisolemia (Cushing's disease): Plasma cortisol usually suppress to at least 50% of basal level
- Adrenal tumor and ectopic ACTH: Failure to suppress.

The following Table 11 illustrates the different biochemical parameters of common causes of Cushing's syndrome:

Table 11: Laboratory findings of common causes of Cushing's syndrome

Disorders	UFC	HDDST	ACTH
Pituitary lesion			
• Microadenoma	High	Suppressed	High
• Macroadenoma	High	Not suppressed	High
Ectopic ACTH	High	Not suppressed	High
Exogenous	Low	Not suppressed	Low
Adrenal lesion	High	Not suppressed	Low

Abbreviations: UFC, urinary free cortisol; HDDST, high dose dexamethasone suppression test; ACTH, adrenocorticotropic hormone

Other Investigations

Imaging:
USG scan: In children, adrenal glands are large and identifiable on ultrasound.

MRI: MRI of hypothalamic-pituitary region in children with ACTH dependent Cushing's syndrome.

Inferior petrosal sinus lesions should be targeted in neuroimaging as this is the most important identifiable source of ACTH production in children.

Treatment of Cushing's Syndrome

Medical management: Iatrogenic Cushing's syndrome is reversible on withdrawal of corticosteroid or corticotropin. Inhibitors of steroidogenesis (cyproheptadine, metyrapone, ketoconazole) have been tried with variable success rate.

Surgical: Surgical resection of adrenal lesions is recommended for adrenal adenoma and carcinoma, if identifiable surgical removal of ACTH secreting micro- or macroadenoma is required. Several attempts may be necessary with a follow-up with pituitary radiotherapy. Pituitary hormone replacement therapy may be required as well as hydrocortisone for lifelong after pituitary ablation or surgery.

Algorithm for Diagnostic Workup and Management for Cushing's Syndrome

An algorithm for diagnostic workup and management for Cushing's syndrome is mentioned in Figure 49.

Summary of algorithm for diagnostic workup and management of Cushing's syndrome is as follows:

1. Central obesity, growth failure, drug history, hirsutism, buffalo hump, striae.
2. Fat distribution is central, extremities may be normal or thin. Normal growth rate excludes Cushing's syndrome, other than in adrenal cortical carcinoma.
3. The low dose dexamethasone suppression test is not essential once hypercortisolism is proven.
4. Young children with adrenocortical carcinoma may have early excessive linear growth and evidence of excessive androgen (masculinizing) or estrogen (feminizing) secretion.
5. Transsphenoidal surgery is preferred and should be done at centers with expertise in pituitary neurosurgery.
6. Bilateral inferior petrosal sinus sampling (IPSS) is technically demanding, especially in children and adolescents.
7. Fluorine-18-fluorodeoxyglucose PET is experimental, but promising.

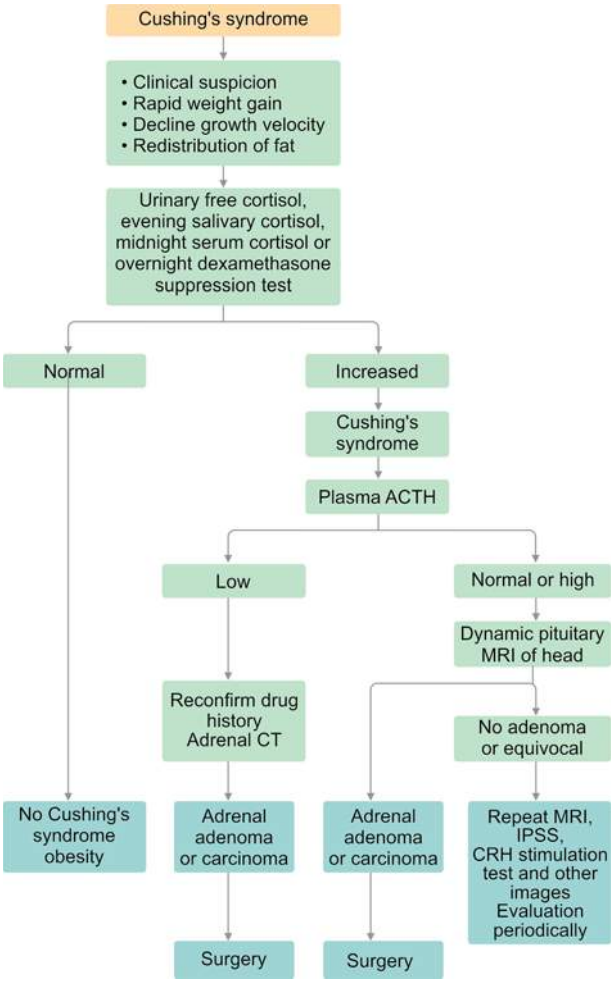


Fig. 49: Algorithm for diagnostic workup and management of Cushing's syndrome

Abbreviations: ACTH, adrenocorticotropic hormone; CT, computed tomography

HYPERALDOSTERONISM

Etiology of Hyperaldosteronism

The etiology of hyperaldosteronism is as follows:

- *Primary hyperaldosteronism*
  - Adenoma
  - Hyperplasia
  - Glucocorticoid remediable hyperaldosteronism (GRA)
- *Secondary hyperaldosteronism*
  - Renin secreting tumor
  - Renal artery stenosis
  - Cardiac failure
  - Liver disease
  - Nephrotic syndrome
- *Apparent mineralocorticoid excess*
  - Congenital adrenal hyperplasia (CAH)
  - Liddle syndrome
  - 11β-hydroxysteroid dehydrogenase.

Clinical Features

Most common clinical features are hypertension and hypokalemic alkalosis.

Laboratory Investigations

- *Serum aldosterone*
  High in primary hyperaldosteronism or GRA
- *Serum electrolytes*
  Hypokalemia
- *Blood gas analysis*
  Metabolic alkalosis
- *Dexamethasone suppression test (DMST)*
  In GRA:
  - Aldosterone level decreases
  - Clinical and laboratory features resolve after DMST

In primary hyperaldosteronism:
- No effect

- Adrenal imaging
  Confirms the presence of adrenal tumors.

Treatment

- Salt restriction
- Antialdosterone agents like spironolactone and eplerenone
- Physiological hydrocortisone replacement: Suppresses ACTH secretion in GRA
- Surgery for adrenal adenoma.

ADRENAL INSUFFICIENCY

Causes of adrenal insufficiency are listed in Table 12.

Clinical Features of Adrenal Insufficiency

Signs and Symptoms of Adrenal Insufficiency

Glucocorticoid deficiency:
- Fasting hypoglycemia
- Increased insulin sensitivity
- Decreased gastric acidity
- Gastrointestinal symptoms (nausea, vomiting)
- Fatigue.

Mineralocorticoid deficiency:
- Muscle weakness
- Weight loss
- Fatigue
- Nausea, vomiting, anorexia
- Salt craving
- Hypotension
- Hyperkalemia
- Hyponatremia
- Acidosis.

Adrenal androgen deficiency:
- Decreased pubic and axillary hair
- Decreased libido.

Increased β-lipotropin levels:
- Hyperpigmentation.

Table 12: Causes of adrenal insufficiency

Primary	
	Congenital
	• Dysplasia, e.g. congenital adrenal hyperplasia Enzyme blocks, e.g. 21-hydroxylase deficiency • Adrenoleukodystrophy
	Acquired (Addison's disease)
	• Tuberculosis • Autoimmune adrenalitis • Waterhouse-Friderichsen syndrome (occurs in meningococcal septicemia)
Secondary	
	• Panhypopituitarism • CRH receptor defect • Isolated ACTH deficiency
Tertiary	
	• High dose glucorticoid therapy • CNS malformation • Pituitary tumors

Laboratory Evaluation of Adrenal Insufficiency

• Serum sodium	Low
• Serum potassium	High
• Serum cortisol	Low or undetectable (at 8.00 am serum cortisol is normally >450 nmol/L)
• Serum ACTH	▪ Raised in primary adrenal insufficiency ▪ Low in secondary adrenal insufficiency
• Serum Dehydroepiandrosterone sulfate (DHEAS)	Low
• Synacthen test	Low or absent cortisol rise
• Other	Antiadrenal antibody for autoimmune adrenalitis
• Workup for TB – MT test – Imaging – Abdominal CT scan	Important cause in developing countries

Synacthen test

Synacthen test or ACTH stimulation test is the best test for adrenocortical reserve. Serum cortisol level is estimated after 0.25 mg of ACTH injection IM. Serum cortisol level less than 18 µg/dL is suggestive of adrenal insufficiency. The next stage is estimation of ACTH level. If ACTH is elevated then primary adrenal insufficiency is suspected.

Short dose synacthen test:

Indication: Investigating primary adrenal insufficiency including Addison's disease

ADDISON'S DISEASE

Addison's disease is due to primary adrenal insufficiency.

Etiology

- Autoimmune adrenalitis (80%)
  - HLA associated antibodies
  - Antibodies against 21-hydroxylase
- Tuberculosis, HIV, hemorrhage
- Genetic
  - X-linked adrenoleukodystrophy (ABCD1)
  - X-linked congenital adrenal hypoplasia (DAX1)
  - Familial glucocorticoids deficiency (MC2R)
  - Autoimmune polyendocrinopathy syndrome (AIRE).

Clinical Features

- Weakness
- Fatigue
- Anorexia
- Nausea/vomiting
- Weight loss
- Hyperpigmentation (Figs 50 and 51).

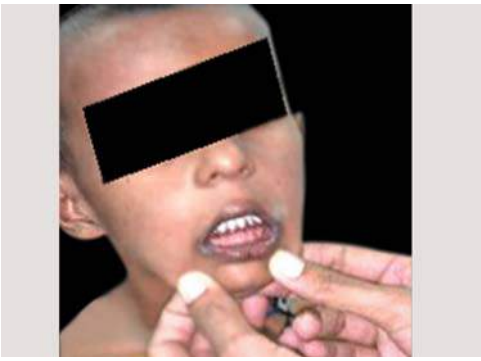


Fig. 50: Hyperpigmentation over the gums and lips in adrenal insufficiency

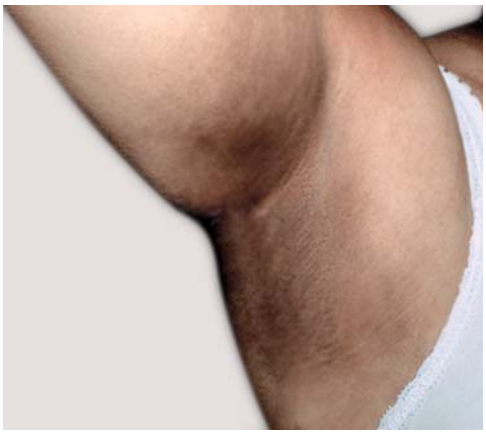


Fig. 51: Hyperpigmentation in axilla in adrenal insufficiency

Mechanism of Hyperpigmentation

When the primary organ fails, the trophic hormone is increased as much as 100 times normal or more. As ACTH has biological homology to melanocyte stimulating hormone, it stimulates melanin deposition in melanocytes.

- Hypotension
- Salt craving
- Depression.

Laboratory Features

- Hyperkalemia due to aldosterone deficiency
- Hyponatremia due to cortisol deficiency
- Anemia
- Hypoglycemia due to cortisol deficiency
- Elevated blood urea nitrogen (BUN) and creatinine due to dehydration
- Hypercalcemia due to dehydration and increased gastro-intestinal calcium absorption
- Calcification on X-ray or CT scan (tuberculosis may be found).

Diagnosis

ACTH is consistently elevated in Addison's disease and should be measured simultaneously with serum cortisol where plasma cortisol level may be low which is diagnostic of Addison's disease.

- Low morning cortisol with high ACTH
- Synacthen stimulation produces a minimal cortisol response.

ADRENAL CRISIS

Acute adrenal crisis occurs most commonly in the child with undiagnosed chronic adrenal insufficiency who is subjected to an additional severe stress such as major illness, trauma or surgery.

Clinical Features

Symptoms

- Dizziness
- Drowsiness following lethargy
- Vomiting (may be profuse).

Signs

- Pallor of shock but hyperpigmentation may be present (skin crease, scars, buccal cavity and in areas unexposed to sunlight)
- Tachycardia
- Tachypnea
- Dehydration
- Acute abdomen.

Laboratory Investigations

- Blood glucose
- Serum electrolytes
- Serum cortisol
- Adrenal steroids
- Serum ACTH
- Synacthen test.

Management of Adrenal Crisis

Immediate Management

- Treat shock with IV 0.9% sodium chloride saline boluses 10 mL/kg
- Treat hypoglycemia with IV 10% glucose boluses 2 mL/kg
- Continue infusion (0.9% saline with 5% glucose) at maintenance plus calculated deficit
- Treat hypokalemia if present
- IV bolus hydrocortisone @ 4 mg/kg or using following regimen:
  - Infant 25 mg
  - 2–5 years 50 mg
  - >5 years 100 mg

Further Steps

- Monitor and correct sodium and potassium disturbances
- Treat other underlying condition, e.g. infection even if only suspected
- Establish hydrocortisone infusion 2.0 mg/kg/day.

Stabilization

- Correction of dehydration and hypoglycemia
- Physiological replacement of steroid
  - Hydrocortisone: 10–12 mg/m^2/day in three divided doses (usually 50% on waking, 25% at lunch time and 25% in the evening)
  - Fludrocortisone: 150 µg/m^2/day once daily
  - Oral saline: May be offered 2–3 times in infants under 1–2 years
- Treatment of underlying precipitating illness.

Puberty

Puberty is a process, not an event, that results from a complex series of coordinated neuroendocrine changes leading to internal and external physical changes in primary and secondary sexual characteristics and eventual reproductive competence.

With a view to reproductive capability, the acquisition of secondary sexual characteristics is known as puberty. These secondary sexual characteristics are as follows:

Both Sexes

- Growth spurt
- Reproductive function attainment
- Pubic and axillary hair development.

Male

- Breaking of voice (also in girls to some extent)
- Enlargement of penis and scrotum
- Increase of testicular volume.

Female

- Achievement of menstruation (menarche)
- Enlargement of female internal organs
- Breast development (may also occur in male as gynecomastia).

Components of Puberty

There are two distinct yet overlapping components of puberty particularly relevant to its measurement: adrenarche and gonadarche. Each component represents a different endocrine axis as well as different external physical characteristics.

Adrenarche, or "awakening of the adrenal glands," includes maturation of the adrenal gland and the ensuing rise of adrenal androgens.

Gonadarche occurs with reactivation of GnRH neurons and secretion of estradiol and testosterone.

Physiology of Puberty

Normal puberty is governed by hypothalamo-pituitary-gonadal (HPG) axis. Onset of puberty is initiated by increase in pulsatile GnRH secretion from hypothalamus resulting in release of follicle-stimulating hormone (FSH) and pulsatile release of LH from pituitary. LH in turn causes release of sex hormones from the gonads.

LH:

- In males LH acts on Leydig cells of testis and produce androgens including testosterone. In female, LH triggers ovulation and formation of corpus luteum which secretes progesterone.

FSH:

- In male, it acts on Sertoli cells to promote spermatogenesis
- In female, initiates growth of ovarian follicles.

Sex hormones:

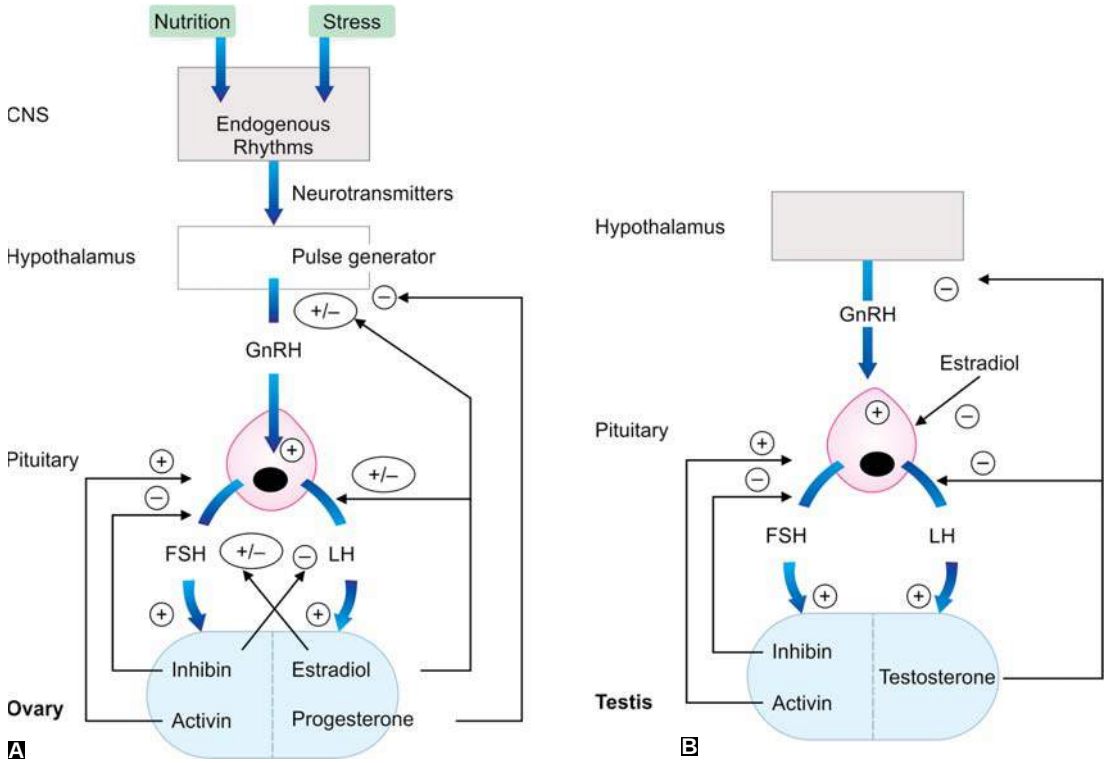
Androgens:

- Produced in gonads and adrenal glands
- Roles:
  - Virilization
  - Development of pubic and axillary hair, as well as body odor, greasiness of skin, hair and acne.

Estrogen:

- Responsible for breast development in girls and epiphyseal fusion in both sexes

A schematic diagram of HPG axis is shown in Figure 52.



Figs 52A and B: Hypothalamo-pituitary-gonadal axis. (A) Girls; (B) Boys

Abbreviations: CNS, central nervous system; GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone

Pubertal Staging

Usually assessment of puberty is done according to Tanner, which includes three parameters namely genital development of boys, breast development of girls and pubic hair in both sexes.

The staging is given in Table 13.

Disorders of Puberty

The commonly dealt disorders of puberty are precocious puberty and delayed puberty. Disorders of puberty are the results of different sensitivity of the HPG axis.

Delayed Puberty

Three terms are to be distinguished from each other during the discussion; they are late puberty, delayed puberty and arrested puberty.

Late puberty: The pubertal events are within normal limits (3rd–97th centiles) but occur within later centiles (lower).

Arrested puberty: Puberty begins but fails to progress adequately is known as arrested puberty.

Delayed puberty: Delayed puberty is said to occur when there is absence of secondary sexual characteristics by 13 years in a girl (or if the first period occurs after the age of 15 years) and by 14 years in a boy.

Etiology of delayed puberty

Central causes of delayed puberty in both sexes:

- *Intact HPG axis:*
  - Constitutional delay in growth and puberty (CDGP)
  - Hypothyroidism
  - Chronic disease
  - Poor nutrition
  - Steroid therapy
  - Psychosocial deprivation.
- Impaired hypothalamo-pituitary (HP) axis:
  - GnRH/LH/FSH deficiency:
  - Developmental anomalies of HP axis:
  - Tumors adjacent to HP axis:
  - Irradiation/trauma/surgery.

Peripheral causes of delayed puberty (hypergonadotropic hypogonadism):

- *Male:*
  - Gonadal dysgenesis
  - Syndromes associated with cryptorchidism:
  - Bilateral testicular damage:
    - Undescended testis
    - Torsion
    - Radiotherapy
    - Chemotherapy
    - Failed orchidopexy
- *Female:*
  - Disorders of sex development
  - Gonadal dysgenesis:
  - Polycystic ovarian syndrome (PCOS)
  - Ovarian damage by:
    - Radiotherapy
    - Chemotherapy
    - Autoimmune ovarian failure
- Specific conditions:
  - Constitutional delay in growth and puberty
  - Central pubertal delay with intact HP axis
  - Central pubertal delay with impairment of HP axis (hypogonadotropic hypogonadism)
  - Peripheral pubertal delay (hypergonadotropic hypogonadism)
    - Turner syndrome
    - Klienfelter syndrome.

Table 13: Puertal staging parameters

Genital development in boys (Fig. 54A)		
Stage 1	:	Prepubertal
Stage 2	:	Enlargement of scrotum and testes measured by orchidometer (Fig. 53)
Stage 3	:	Enlargement of penis, initially in length, further growth of scrotum and testes
Stage 4	:	Increase in size of penis with growth in breadth
Stage 5	:	Genitalia of adult size and shape
Pubic hair development in both sexes (Fig. 54B)		
Stage 1	:	Prepubertal
Stage 2	:	Sparse growth of long downy hair, chiefly along the base of penis or labia
Stage 3	:	Darker, coarser and curlier hair, spreading sparsely over the junction of the pubes
Stage 4	:	Hair is adult type, but covered area is still smaller than that of adult
Stage 5	:	Hair is in adult quality and quantity, spreads to medial aspect of thighs
Stage 6	:	Spread of hair to linea alba
Breast development in girls (Fig. 54C)		
Stage 1	:	Prepubertal
Stage 2	:	Breast bud stage, elevation of breast and papilla
Stage 3	:	Further enlargement of breast and areola, with no separation of their contour
Stage 4	:	Projection of areola and papilla to form a mound above the level of breast
Stage 5	:	Mature stage, projection of papilla only

Evaluation of delayed puberty

First-line evaluation:

Ruling out underlying disorders: The aim of initial evaluation is to rule out underlying disorders causing delayed puberty. Pubertal development is assessed clinically and biochemically for counseling and predicting further pubertal development. Absent or slow or cessation of development after onset is consistent with permanent hypogonadism.

Family history: A family history, including childhood growth patterns and age at pubertal onset of the parents, should be obtained. Delayed puberty in a parent or sibling

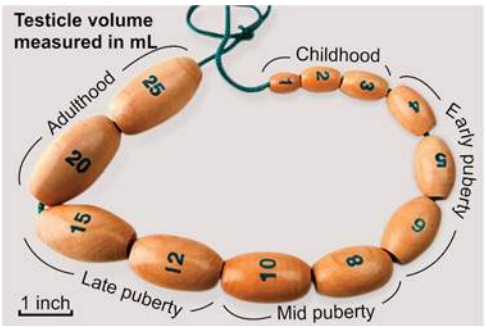
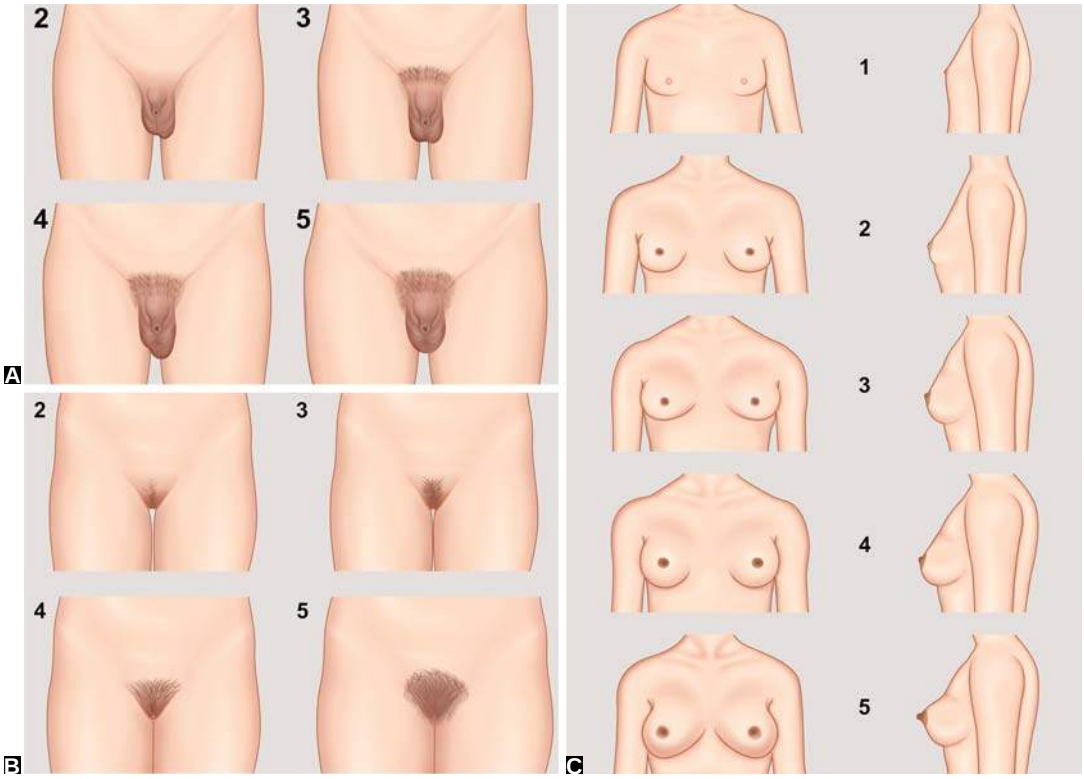


Fig. 53: Orchidometer for measuring testicular volume



Figs 54A to C: Pubertal staging: (A) Genital development in boys; (B) Pubic hair development in both sexes; (C) Breast development in girls

followed by spontaneous onset of puberty suggests CDGP. History or symptoms of chronic disease, with emphasis on specific disorders (e.g. celiac disease, thyroid disease, and anorexia) should be obtained. These disorders may cause temporary delay of puberty (functional hypogonadotropic hypogonadism). Other information regarding medication (steroid in particular) use, nutritional status, and psychosocial functioning should also be obtained.

Physical examination: Delayed puberty is often associated with short stature and slow growth for age although the height and growth rate are within the prepubertal normal range. For assessment of longitudinal growth previous height and weight measurements should be obtained and plotted.

A summary of primary evaluation and interpretation of tests are mentioned in Table 14.

Investigations for first-line evaluation:
Bone age radiography: A delay in bone age (usually delayed by at least 18 months) is characteristic but not diagnostic of CDGP. It may also occur in patients with chronic illness, hypogonadotropic hypogonadism or gonadal failure.

Hormone measurement: Baseline endocrine/hormone measurement of serum FSH, LH and estradiol (more useful in girls).

Pubertal onset is characterized by the accentuation of diurnal secretion of gonadotropin and testosterone (in boys) and estrogen (in girls) before apparent phenotypic changes. Basal levels of LH and FSH are low in patients with CDGP or hypogonadotropic hypogonadism, whereas such levels are usually elevated in those with gonadal failure.

Thyroid function tests (T_4 and TSH): Late puberty may be the only symptom in hypothyroidism.

Blood counts: CBC, ESR and other tests are as appropriate as renal function test, liver function tests and celiac antibodies.

Brain imaging: If signs or symptoms suggest a lesion in the CNS, MRI of brain is indicated.
Second-line evaluation: Most patients will not have any apparent alternative cause for delayed puberty on initial evaluation, suggesting CDGP as the likely diagnosis.

- No test can reliably distinguish CDGP from isolated hypogonadotropic hypogonadism. If basal gonadotropin levels are inconclusive; in such case stimulation by GnRH or a GnRH agonist may be helpful
- Stimulated levels of LH in the pubertal range indicate that the HPG axis has been reactivated and that secondary sexual development is likely to occur within 1 year
- Growth hormone secretion in the basal state, as well as after provocative testing, may be decreased in patients with CDGP.

Specific second-line investigations and their interpretations are mentioned in Table 15.

An algorithm for evaluation of delayed puberty and management is shown in Figure 55.

Management of delayed puberty (Fig. 55)

In case of physiological variant of delayed puberty, no treatment is required, but underlying disease is detected treat accordingly (e.g. T_4 therapy in hypothyroidism, management of CRI)

Only following points should be addressed:
Reassurance and support

- Understanding the difficulties from the parent's perspective
- Counseling in lifestyle skills
- Repeated assessment of progress for reassurance.

Few patients may require short-term therapy.

Table 14: Interpretation of first-line assessment for delayed puberty

Growth rate	• In early adolescence in both sexes, an annual growth rate of less than 3 cm is suggestive of a disease specifically inhibiting growth (e.g. hypothyroidism, GH deficiency and hypercortisolism), but such rates can also be seen in CDGP
Tanner staging	• In girls, Tanner stage two breast development is usually the first physical marker of puberty • In boys, a testicular volume of >3 mL is a more reliable indicator of the onset of puberty than Tanner stage two genital development
Testis volume in boys	• A testicular volume of >3 mL (≥2.5 cm in length) indicates central puberty. Most healthy boys with a testicular volume of 3 mL will have a further increase in testicular volume or pubic-hair stage, or both, at repeated examination 6 months later
Bone age	• A bone-age delay of >2 years has arbitrarily been used as a criterion for CDGP but is nonspecific • A bone-age delay of 4 years has been associated with a mean over prediction of adult height of 8 cm • In children with short stature who have no bone-age delay, adult height is usually underestimated by the Bayley-Pinneau tables
Biochemical analysis	• Common tests including complete blood count, ESR, creatinine, electrolytes, bicarbonate, alkaline phosphatase, albumin, thyrotropin and FT4 are done to rule out chronic disorders • Additional testing may be necessary on the basis of family history and symptoms and signs including screening for celiac disease and inflammatory bowel disease
Serum LH	• LH is a better marker of pubertal initiation than FSH • Values of <0.1 IU per liter are not specific for hypogonadotropic hypogonadism • Values of >0.2 IU per liter on ICMA or >0.6 IU per liter on IFMA are specific but not sensitive for the initiation of central puberty • Some adolescents in early puberty have lower values
Serum FSH	• In delayed puberty, a value above the upper limit of the normal range for the assay is a sensitive and specific marker of primary gonadal failure • Values of <0.2 IU per liter on ICMA or <1.0 IU per liter on IFMA suggest hypogonadotropic hypogonadism but are not diagnostic
Serum IGF-1	• It is used to screen for GH deficiency • An increase in the level during follow-up or during or after treatment with sex steroids makes the diagnosis of GH deficiency less likely • Growth hormone provocation tests are needed to diagnose GH deficiency
Serum testosterone in boys	• A morning value of 20 ng per deciliter (0.7 nmol/L) often predicts the appearance of pubertal signs within 12–15 months
Estradiol (specific for girls)	Prepubertal girls have estradiol levels of 1.6 +/–2.6 pg/mL. Pubertal onset is characterized by the accentuation of diurnal secretion of gonadotropin and estradiol in girls before apparent phenotypic changes

Abbreviations: GH, growth hormone; CDGP, constitutional growth delay of growth and puberty; ICMA, immune-chemiluminometric assay; IFMA, immunofluorometric

Male:
- Oxandrolone: 1.25–2.5 mg for 3–6 months.
- Testosterone esters: 50–100 mg IM monthly or 40 mg orally either on alternate day or daily for 3–6 months.

Female:
Ethinyl estradiol: 2 μg/day for 3 months.

PRECOCIOUS PUBERTY

Premature Sexual Maturation

Premature sexual maturation is the development of secondary sexual characteristics at an inappropriately young age: less than 8 years in a girl, less than 9 years in a boy. It is a general term that encompasses different causes of early sexual activation. Some of these are innocent and require no specific treatment, only adequate explanation. Correct diagnosis of the underlying cause of the symptoms and signs is vital as the management of each is very different. Most children presenting with signs of early sexual maturation do not have true central precocious puberty.

Causes of Premature Sexual Maturation

- Central precocious puberty
- Gonadotropin-independent precocious puberty
- Thelarche
- Thelarche variant
- Adrenarche
- Isolated menarche
- Hypothyroidism.

Typically, menarche occurs about 2 years after thelarche, with longer intervals in girls who have early breast development and shorter intervals in girls whose breast development is later.

Precocious Puberty

Precocious puberty is defined by the onset of secondary sexual characters before the age of 8 years in girls and 9 years in boys.

Epidemiology

It is 4–10 times more frequent in females than in males and more common among African-American than among Caucasian children. The age of adrenarche in females is race-dependent.

Etiology of Precocious Puberty (Fig. 56)

1. *Central precociuos puberty (CPP, gonadotropin-dependent)*: The majority causes of CPP in girls are defined as idiopathic, since no organic lesion is found whereas intracranial

Table 15: Second-line evaluations and their interpretations for delayed puberty

Gonadotropin-releasing hormone/gonadorelin stimulation test[*]
A predominant response of LH after stimulation or peak LH levels of 5–8 IU per liter (depending on the assay) suggests the onset of central puberty GnRH test can be performed after hCG test or if the child is primed with sex steroid for GH provocation test. However, patients with CDGP or hypogonadotropic hypogonadism may have a prepubertal response Procedure of GnRH stimulation test: • Collect baseline blood sample for LH and FSH • Give GnRH IV 25 μg/m^2 or 2.5 μg/kg (max. 100 μg/kg) • Collect the blood sample to measure FSH, LH and testosterone (in boys) after 20–60 minutes
Human chorionic gonadotropin (hCG) stimulation test[*]
Peak testosterone levels are lower in patients with hypogonadotropic hypogonadism than in those with CDGP Indications: • To investigate testicular response to gonadotropin in case of hypo- and hypergonadotropic hypogonadism Dose: On day 1 baseline investigation for testosterone 1000 hCG IM daily for 3 days (infant) 1500 hCG IM daily for 3 days (for older children) On day 4 DHT and testosterone Interpretation: • A rise of testosterone 5 nmol/L indicates good testicular (Leydig cell) function • hCG interferes with FSH, LH estimation and these measurements should be completed before carrying out the FSH, LH test
Growth factors and growth hormone provocation tests
Growth factors and GH secretion in the basal state as well as after provocative test (exercise-induced, insulin-induced hypoglycemia, arginine levodopa) are to be done Interpretation: • May be decreased in CDGP and GHD associated with delayed puberty • If low gonadotropin/sex hormones or mismatch between growth and puberty consider a central disorder; MRI scan is indicated
Serum prolactin
Elevated levels may indicate hypothalamic-pituitary tumors causing hypogonadotropic hypogonadism
Pelvic ultrasound
Direct visualization of Müllerian tube structures (cervix, vagina, uterus, Fallopian tube) and ovaries
Karyotype
Karyotype is indicated to exclude Turner syndrome or mosaic (45, XO)
Serum inhibin B[*]
Prepubertal boys with a baseline inhibin B level of >35 pg per milliliter have a higher likelihood of CDGP. In boys, unmeasurable inhibin B indicates primary germinal failure
MRI of brain
It is done to exclude intracranial lesions if indicated. Imaging in patients with the Kallmann syndrome commonly shows olfactory-bulb and sulcus aplasia or hypoplasia and thus may help differentiate the Kallmann syndrome from hypogonadotropic hypogonadism in patients with an apparently normal or difficult-to-evaluate sense of smell
[*]These tests are used to try to differentiate CDGP from isolated hypogonadotropic hypogonadism *Abbreviations*: LH, luteinizing hormone; hCG, human chorionic gonadotropin; CDGP, constitutional growth delay of growth and puberty; GH, growth hormone; GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; DHT, dihydrotestosterone; GHD, growth hormone deficiency; MRI, magnetic resonance imaging

lesions are common in boys with CPP. MRI now allows the identification of previously unseen intracranial lesions for CPP. Thus reducing the number of cases previously allowed as idiopathic.

- Idiopathic: Most frequent cause
- Adoption from underdeveloped to developed part of the world
- Tumor: Astrocytoma, glioma, germinoma, hypothalamic hamartoma
- Congenital anomaly: Hydrocephalus
- Infection/postinfection: Encephalitis, meningitis
- Radiation
- Trauma: Neurosurgical, nonsurgical
- Ischemia.

2. *Gonadal steroid-dependent (gonadotropin-independent)*:
   - McCune-Albright syndrome: Females predominate
   - Familial male-limited precocious puberty
   - Gonadal neoplasia (benign, malignant)
   - Ovarian follicular cyst
   - Leydig cell nodular hyperplasia
   - Aromatase excess
   - Human chorionic gonadotropin (hCG) secreting tumor
   - Primary hypothyroidism
   - Exogenous steroids (oral contraceptive pills, skin creams, testosterone).
3. *Adrenal steroid-dependent (gonadotropin-independent)*:
   - Congenital adrenal hyperplasia:
   - 21-hydroxylase deficiency (21-OHD)

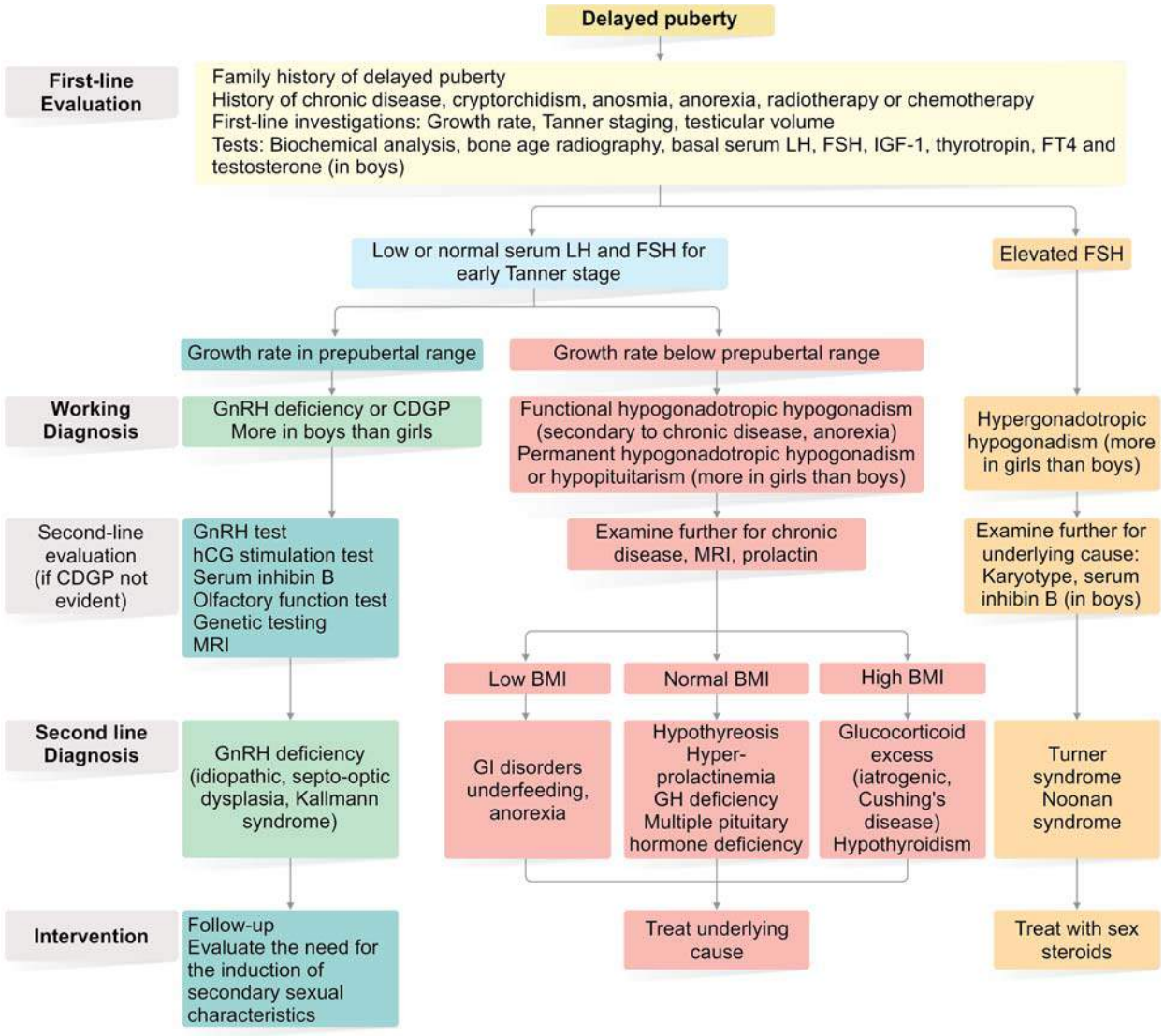


Fig. 55: Algorithmic approach for diagnosis and management of delayed puberty
Abbreviations: LH, luteinizing hormone; FSH, follicle-stimulating hormone; IGF, insulin-like growth factor; CDGP, constitutional growth delay of growth and puberty; BMI, body mass index; GnRH, gonadotropin-releasing hormone; MRI, magnetic resonance imaging

- 11 hydroxylase deficiency
- 11 hydroxysteroid dehydrogenase deficiency
- Glucocorticoid resistance
- Adrenal tumor (benign, malignant)
- Adrenal rest tumors
- Exogenous steroids [e.g. dehydroepiandrosterone (DHEA)]

4. *Incomplete precocious puberty (gonadotropin-independent)*:
   - Premature thelarche
   - Premature adrenarche
   - Premature menarche: Look for gynecological causes.

Pathophysiology of Precocious Puberty

Normal onset of puberty is determined by multiple incompletely understood intracerebral processes. In a simplified model, gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter that inhibits GnRH secretion. In contrast, glutamatergic neurotransmission stimulates GnRH production. Changes in the balance of these signals trigger puberty. Disturbances of the hypothalamus

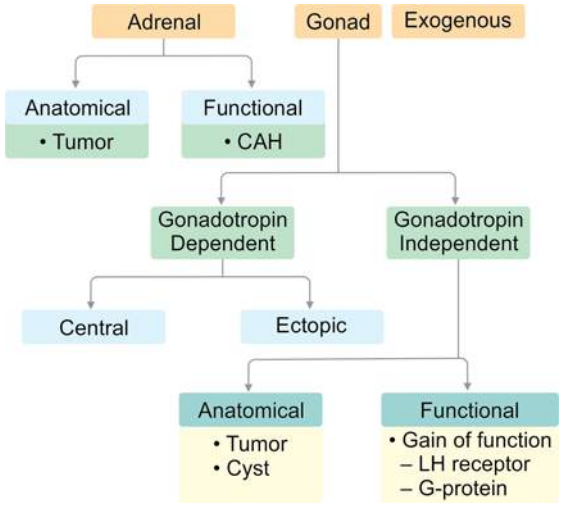


Fig. 56: Schematic approach to principle etiology of precocious puberty

or higher neurologic centers can result in abnormal GnRH release. During prepubertal period, gonadotropin secretion is minimal. As puberty begins, gonadotropins are released from the pituitary gland in apulsatile fashion, particularly at night. With increased gonadotropin release, the ability of GnRH to stimulate release of FSH and later both LH and FSH comes. Gonadotropin-independent sexual precocity can arise from a variety of anatomic or functional lesions, like benign or malignant tumors of the adrenal cortex or gonad that can produce sex steroids autonomously. Exogenous sex steroids, like oral contraceptives, skin creams, meat, from hormone treated animals, plant phytoestrogens and anabolic steroid may also contribute to precocious puberty.

Prolonged hypothyroidism is a curious cause of precocious puberty that may result from gonadotropin-like action of TSH or activation of gonadotropin receptors by TSH.

A number of genetic lesions in hormone synthetic enzymes, receptors and postreceptor signals cause abnormal sex steroid production.

- Excess aromatase activity, converting androgens to estrogens, causes premature thelarche in girls and gynecomastia in boys
- Mutations of the LH receptor can result in unbridled Leydig cell activity and the syndrome of familial male-limited precocious puberty (testotoxicosis)
- Postreceptor signals from mutated stimulatory G-protein complexes cause the McCune-Albright syndrome (precocious puberty, café-au-lait macules, polyostotic fibrous dysplasia).

Central Precocious Puberty (Gonadotropin-dependent Precocious Puberty)

- CPP is due to early or premature activation of HP axis, either idiopathic or due to secondary to an underlying disorders
- CPP is more common in girls with a ratio of 10:1
- Growth acceleration may occur relatively early in boys and may result in tall stature
- Psychological problems may arise due to pubertal levels of sex steroids, resulting in "adolescent behavior"
- Physical finding:
  Boys: Rapid growth, testicular enlargement, deepening of voice, development of pubic hair (Fig. 57)
  Girls: Breast development is followed by other features of normal puberty including growth spurt, development of axillary hair, pubic hair and vaginal discharge
- Bone age is advanced, often by more than 2 years.

Laboratory Evaluation

- *Thyroid function test*: To exclude hypothyroidism
- *Baseline testosterone or estradiol*: Elevated above prepubertal level
- *GnRH test*: Pubertal gonadotropin response with LH predominance over FSH and peak responses greater than 5 IU/L
- *Pelvic ultrasound*: To evaluate ovarian follicular activity, uterine growth and maturation
- *MRI of brain (CT scan of brain if MRI unavailable)*: Cranial MRI scan is indicated in all girls and boys with CPP. Occult intracranial lesions are found in 4.8–13.3% of girls and 20% of boys (Fig. 58).

Treatment

When appropriate, therapy is considered in intracranial or gonadal pathology. Not all the large idiopathic group will be thought to warrant drug therapy, but counseling is required for the family and the child as anxiety might arise because sexual maturation is not necessarily age matched and associated with abnormal behavioral and psychological development. Young girls are at risk of sexual interference and unwanted pregnancies.

Aims of treatment include:

- To arrest clinical signs of puberty
- To retard skeletal maturation thereby achieving TH potential
- Improvement of psychosocial stress associated with precocious puberty.

GnRH analogs are the mainstay of treatment.

- Leuprorelin leuprolide 60 µg/kg or leuprolide 300 µg/kg IM injection every 4 weeks. The treatment is discontinued at the chronological age of 11 years and bone age is of 5 years
- Goserelin (Zoladex) can also be used similarly
- Intranasal buserelin is rarely used as it requires frequent administration a day
- Cyproterone acetate is useful in suppressing gonadotropin with an antiandrogenic effect. It is given in a dose of 75–100 mg/m^2/day. However, use of cyproterone acetate is replaced by GnRH analogs which have better efficacy.

Monitoring response to treatment: Monitoring should be done in every 3 months. Following parameters are monitored:

- Halting testicular or breast development with regression in some cases

Fig. 57: A 6-year-old boy with pubic hair growth and enlargement of testis (volume 12 mL). The child also developed adult body odor; characteristic features of precocious puberty

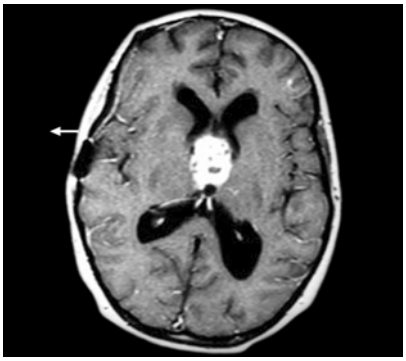


Fig. 58: MRI showing hypothalamic pilocytic astrocytoma: A cause of central precocious puberty

- Regression of pelvic ultrasound changes (pubertal uterus and ovary)
- Reduction of mood swings
- Bone age and height velocity are slow to show changes
- Patients with satisfactory therapeutic response baseline testosterone and estradiol and GnRH stimulation will show a prepubertal response.

If there is failure of response following steps can be taken:

- Gradually increase the GnRH analog (GnRHa) to half the recommended dosage interval
- Cyproterone acetate at low dose may be added (25 mg bid).

Gonadotropin-independent Precocious Puberty (GIPP)

Rarely occurs, though more commonly in boys than girls. Almost always it occurs as McCune–Albright syndrome (MAS) which is characterized by abnormal bone cysts (polyostotic fibrous dysplasia) and skin pigmentation (*café-au-lait* patches in "coast of Maine" distribution).

ABNORMAL PATTERN OF GONADOTROPIN SECRETION

Premature Thelarche

- May be present at birth or develop within first few months of life
- Usually self-limiting
- It occurs due to episodic formation of ovarian cysts and/or increased sensitivity of breast tissue to normal levels of circulating estrogen
- Breast development is not associated with axillary or pubic hair growth and no menarche (Fig. 59)
- Growth velocity is normal, bone age is not advanced
- Unilateral or bilateral thelarche in girls occur
- Breast development is usually cyclical and is generally burnt out by 4 years of age
- Puberty occurs at usual time, final height is normal and normal fertility.

Management

- No investigation for mild cases
- Ovarian cyst may become evident on pelvic ultrasound

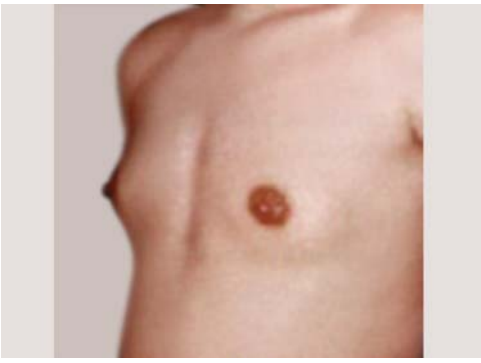


Fig. 59: A girl with isolated premature development of breast (thelarche) without development of axillary hair (left axilla devoid of hair) shown in the picture. Also no pubic hair (not shown in the picture) and menarche occur. Pelvic USG showed prepubertal uterus and small volume ovaries

- Characteristic patterns of pulsatile FSH secretion unlike the normal puberty where pulsatile release of GnRH and LH takes place
- Regular follow-up
- Reassurance.

Thelarche Variant

In thelarche variant, the clinical picture is in between thelarche and central precocious puberty. Here, a partial activation of the HPG axis may occur.

Features

- Slow clinical progress in puberty (usually in girls) and no rapid growth acceleration
- Final height not affected
- Bone age not advanced greater than 2 years.

Investigations

- Low estradiol secretion
- GnRH testing shows peak LH/FSH responses less than 5 IU/L or FSH predominance.

Isolated Premature Menarche

It is cyclical vaginal bleeding in girls with no or few signs of pubertal development. Other causes of vaginal bleeding are exogenous estrogen administration, vulvovaginitis, foreign body and sexual abuse.

- Usually rare
- Occurs between 4 and 8 years of age
- Normal pubertal development, including menarche, occurs at the same time as in other girls
- Bone age not advanced
- Pelvic ultrasound may detect a prepubertal uterus
- In doubtful cases GnRH test may be required.

Management

No treatment is required but follow-up is essential.

Hypothyroidism

Elevated TRH stimulates both TSH and FSH. The resulting premature sexual development is non-constant and pubic hair does not develop. Girls develop isolated breast development and in boys genital changes occur with testicular enlargement.

Investigation

Thyroid function tests should be performed as part of the assessment of early sexual maturation.

Management

Follicle-stimulating hormone falls with T_4 treatment but it may "prime" the hypothalamus and precocious puberty may subsequently develop which may affect final height.

Depending on the primary source of the hormonal production, precocious puberty may be classified as central (also known as gonadotropin dependent or true) or peripheral (also known as gonadotropin independent or precocious pseudopuberty)

Precocious Pubarche

Pubarche refers to the presence of pubic or axillary hair on clinical examination. If this occurs before the age of 8 years in girls and 9 years in boys, it is referred to as premature pubarche (also known as exaggerated adrenarche or premature adrenarche).

It can be a part of true precocious puberty (with gonadarche) or it can occur isolatedly without gonadarche (no menarche or thelarche). In precocious pubarche, axillary hair may be associated with pubic hair or may be isolated with only pubic hair or axillary hair.

There may be evidence of virilization which involves one or more of the following:

- Clitomegaly in female
- Changes in scrotal size and pigmentation and increased penile size in boys
- There may be adult body odor in both sexes.

The features can be differentiated from true precocious puberty by the fact that it is conspicuous by its absence of gonadarche that is there is no corresponding pubertal breast development (Fig. 60) or menarche, which is found in true precocious puberty.

Other characteristic features are:

- Bone age in upper normal range (<2 years advance)
- Final height is normal despite advanced bone age
- There is no evidence that continuous androgen secretion is abnormal, they are sensitive to normal level of androgens
- More associated with children born with SGA [low birthweight (LBW) associated with IUGR].

Investigations

Bone age: It should not be more than 2 years. It is assessed by using X-ray film of hand and wrist, radial and cubital epiphysis, metacarpal and phalanges with reference to standard.

Biochemical:

- Serum DHEAS
- Serum 17-hydroxyprogesterone (17-OHP)
- Androstenedione (Δ4)
- ACTH stimulation test
- Dexamethasone suppression test.

Fig. 60: Precocious puberache. Picture showing a girl who developed axillary and pubic hair before 8 years of age without gonadarche (without breast development and no menarche)

Treatment

Isolated precocious puberache is a benign condition not requiring any treatment. Reassurance and follow-up is necessary. Precocious pubarche associated with well-defined underlying disease/clinical condition should be treated accordingly as shown in the algorithm for diagnostic workup and management of precocious puberty.

Low Birthweight and Precocious Pubarche

The phenotype of premature adrenarche varies considerably between populations but has been found to be associated with LBW babies particularly associated IUGR. However, there is ethnic variation of vulnerability. It has been found increasingly in Caribbean-Hispanic and African-American girls in the USA. They were found to have increased insulin resistance, adverse cardiometabolic risk and later development to PCOS.

In the majority of cases, no specific treatment is recommended, but where there is a history of LBW, with associated insulin resistance, intervention with the insulin sensitizing agent metformin either as monotherapy or in combination with the antiandrogen flutamide at low doses can be considered.

Precocious puberache associated with LBW and IUGR: This is a benign condition not requiring any treatment. However, they should be followed up as they may develop early puberty and PCOS.

Algorithm for Diagnostic Workup and Management of Precocious Pubarche

An algorithm for diagnostic workup and management plan for precocious pubarche is mentioned in Figure 61.

Key points to algorithm:

1. Precocious pubarche is defined as the occurrence of pubic hair before the chronological age of 8 years in a girl and 9 years in a boy.
2. Virilization involves the following signs: Clitoral hypertrophy in girl, changes in scrotal size, texture and pigmentation and increased penile length in boy.
3. Growth curve should be drawn using retrospective or prospective data from school or medical record. Height velocity calculated in cm/year.
4. Bone age is determined by X-ray of left hand and wrist. The reading should primarily be based on radial and cubital epiphysis, metacarpals and phalanges. Significantly advanced bone age means 2 years ahead of chronological age.
5. The circulating value of DHEAS is low (30 μg/dL) between 0.5 and 6 years. Then due to adrenarche, it starts increasing gradually till the age of 16 years at which it is greater than 80 μg/dL (average 120; upper limit is 250 μg/dL in girls and 400 μg/dL in boys). This increase is consistent with adrenarche.
6. Androgen originates from both adrenal gland and gonads. It is mainly produced by the adrenal glands (during adrearche) until puberty (gonadarche) after which the gonads account for 2/3rd of the production. The circulating level of serum androsterone is low between 0.5 and 6 years. Between age of 6 and 9 years normal level is below 75 ng/mL in both sexes.

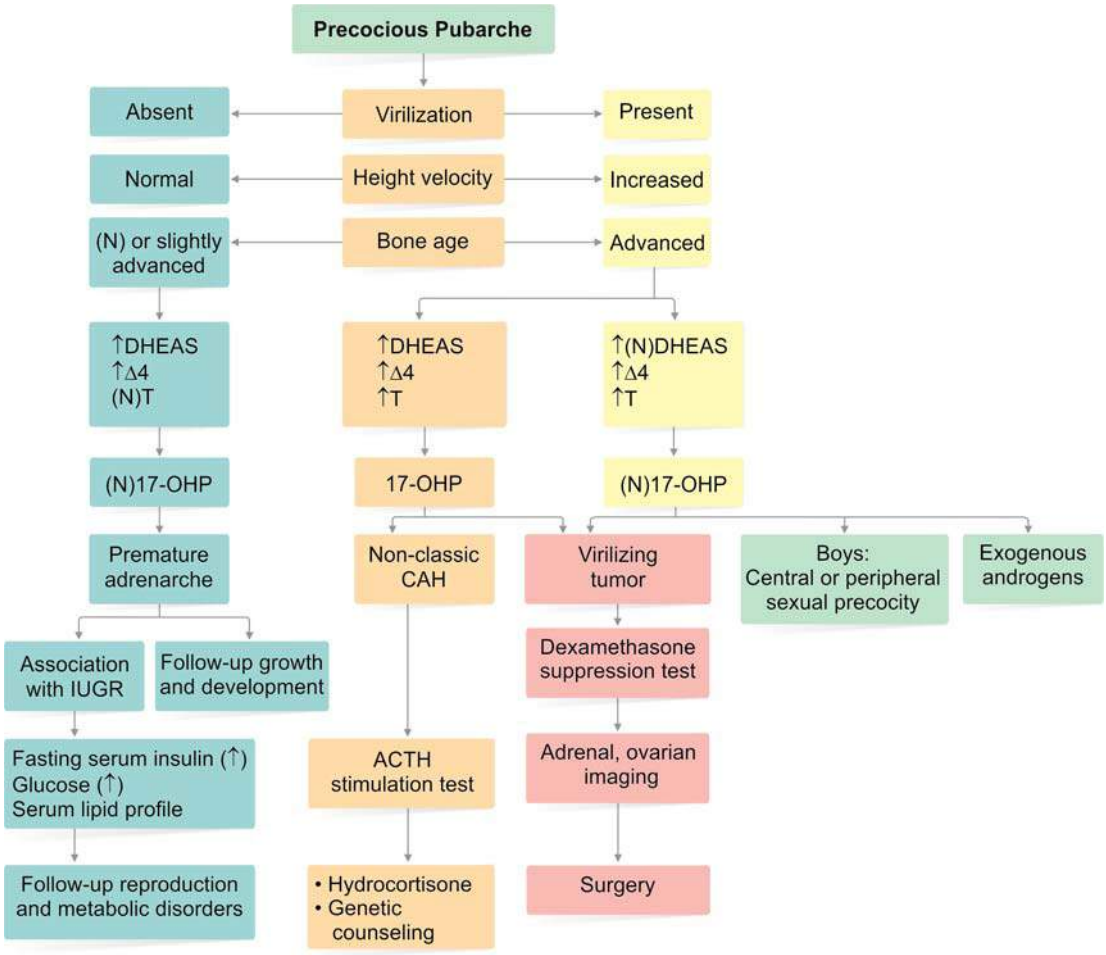


Fig. 61: Algorithm for diagnostic workup and management of precocious pubarche

Abbreviations: DHEAS, dihydroepiandrosterone sulfate; Δ4, androstenedione; OHP, hydroxylprogesterone; IUGR, intrauterine growth retardation; T, testosterone; CAH, congenital adrenal hyperplasia; N, normal; ↑increase

7. Testosterone is also derived from adrenal and gonadal origin. It is mainly produced by adrenal gland (during adrenarche) until gonadarche. After gonadarche 50% comes from ovaries in girls and 95% from testis in boys. The circulating level is less than 30 ng/dL between 0.5 and 9 years of age in both sexes.
8. 17-OHP shows normal circadian variation with peak levels obtained around 8.00 am. In prepubertal subjects, the serum levels of 17-OHP should be less than 120 ng/mL.
9. Premature adrenarche is characterized by increased levels of DHEAS and to a lesser extent, androstenedione (Δ4) in the early pubertal range with normal testosterone and 17-OHP levels. This is a benign condition not requiring any treatment. It requires follow-up because few of these patients, particularly those with DHEAS over 140 µg/dL or androstenedione over 75 ng/dL, will later develop PCOS. If associated IUGR, investigate for fasting insulin and glucose for insulin resistance.
10. Nonclassic CAH is a late expression of a mild deficit in adrenal enzymes involved in steroid biosynthesis. The most frequently affected enzyme is 21-OHD (classical CAH). After premature adrenarche, nonclassic CAH is the most common diagnosis in a patient with precocious pubarche.
11. The ACTH stimulation test consists of IV injection of 0.1 mg of short-acting tetracosactide (8:00 am, fasting state) and blood collection before injection and after 60 minutes for measurement of cortisol and 17-OHP. In normal subjects, the peak level of 17-OHP should not exceed 650 ng/dL. Levels higher than 1,200 ng/dL are required for diagnosis of nonclassic CAH.
12. Hydrocortisone replacement therapy should be given in a daily dosage of 10–20 mg/m^2 divided into 3–4 daily doses using the least effective dose to normalize 17-OHP serum levels and the rates of growth and bone maturation.
13. Genetic counseling is warranted in nonclassic CAH which is an autosomal-recessive disorder. When available, molecular biology studies of 21-OHD gene are helpful.
14. Typically, adrenal tumors result in elevated DHEAS levels while ovarian tumors cause elevated serum levels of Δ4 to a greater extent than 17-OHP.
15. The dexamethasone suppression test consists of administration of 20 µg/kg of dexamethasone every 6 hour for 3–6 days and study of serum cortisol and androgen levels. Nonsuppressibility of serum androgen levels indicates a nonadrenal origin or an autonomous tumor.

16. Adrenal-ovarian imaging can be easily obtained through USG. This technique has, however, a limited sensitivity, particularly for adrenal tumors, and a CT or MRI scan may be required in the absence of any echographic anomaly if the suspicion of virilization is high.
17. Exogenous androgens are a rare cause of virilization. The use of anabolic steroids may also cause premature development of pubic hair.

CONGENITAL ADRENAL HYPERPLASIA (FIG. 62)

Congenital adrenal hyperplasia (CAH) refers to a family of inherited disorders of adrenal steroidogenesis. The common functional defect in each disorder is impaired cortisol secretion, resulting in hypersecretion of CRH and ACTH and consequent hyperplasia of the adrenal glands. Greater than 90% of CAH are caused by the defect in the enzyme 21-hydroxylase (21-OHD).

Genetic Basis of CAH

It is an autosomal recessive disorder. The 21-hydroxylase gene is located on chromosome 6p21.3 within the HLA histocompatibility complex.

There are two highly homologous 21-hydroxylase genes resulting from ancestral duplication: an active gene, CYP21A2 (CYP21B) and an inactive pseudogene CYP21A1P (CYP21A, CYP21P). Spontaneous recombination between CYP21A2 and CYP21A1P are detected in one in 10^3–10^5 sperm cells. The high rate of intergenic recombination that occurs could be indirectly due to the position of the gene within the MHC. Most patients are compound heterozygotes (i.e. they have different mutations on the two alleles), and the clinical phenotype is generally related to the less severely mutated allele and, consequently to the residual 21-hydroxylase activity.

Types

More than 90% of cases of CAH are caused by a defect in the enzyme 21-hydroxylase (21-OHD). Four other enzyme deficiencies in the steroid biosynthesis pathway, along with one cholesterol transport protein defect, account for the remaining cases. Depending on the severity of the enzyme deficiency, 21-OHD is defined as classic (severe form) or nonclassic (mild form). Approximately 75% of patients who have the classic form also have salt-wasting due to inadequate aldosterone production, further subdividing the classification into classic simple virilizing (CSV) and classic salt-wasting (CSW) forms.

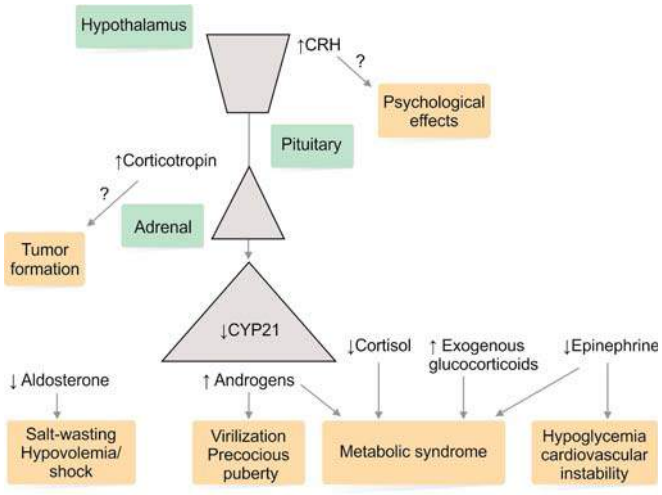


Fig. 62: Biochemical pathway of CAH with its clinical conditions

Abbreviations: ↑, increase; ↓, decrease.

Depending upon the enzyme involved CAH is classified as follows:

1. 21-OHD
   a. Classic form:
      i. Classic salt-wasting greater than 75%.
      ii. Classic simple virilizing
   b. Nonclassic form (21-OHD)
2. 11β-hydroxylase deficiency.
3. 3β-hydroxysteroid dehydrogenase deficiency, classical form.
4. 17α-hydroxylase/17,20-lyase deficiency.
5. Lipoid congenital adrenal hyperplasia.
6. P450 oxidoreductase (POR) deficiency.

Clinical Features

The clinical presentation of the various forms of CAH depends on the following:

- The affected enzyme
- The residual enzymatic activity
- The consequences of deficiencies of the end products
- The hormonal effects of the elevated precursors.

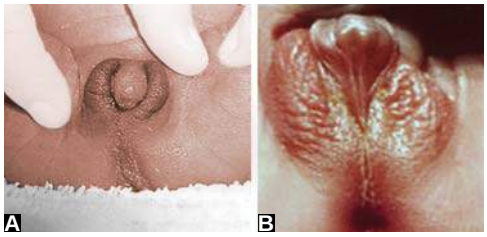
The severity of CAH depends on the degree of 21-OHD caused by CYP21A2 mutations. The classic forms present in childhood and are characterized by striking overproduction of cortisol precursors and adrenal androgens. In the most severe form, concomitant aldosterone deficiency leads to loss of salt. In the mildest form, there is sufficient cortisol production but at the expense of excess androgens.

Classic CAH

Approximately 75% of patients who have classic CAH due to 21-OHD have a deficiency of aldosterone (CSW form). Unlike those who have the simple virilizing form, who present with only virilization, these patients present with salt-wasting features. The early signs of CSW, include vomiting, anorexia and sometimes diarrhea, which if untreated, may develop in to adrenal crisis with vascular collapse and shock. Hypoglycemia, hyponatremia, hyperkalemia and metabolic acidosis may be present. They will present within the first few weeks after birth, the median age of presentation is around 12 days. Hyperpigmentation of skin creases and genitalia may be early signs of adrenal insufficiency. Of note, affected infants initially demand frequent feedings, possibly due to dehydration or salt craving.

Female infants with classic CAH present at birth with typical features of:

- Ambiguous genitalia due to exposure to high concentrations of androgens in utero, and CAH due to 21-OHD is the most common cause of ambiguous genitalia in 46,XX infants. Characteristic findings include an:
  - Enlarged clitoris (Fig. 63A).
  - Partly fused (Fig. 63B).
  - Rugose labia majora.
  - A common urogenital sinus in place of a separate urethra and vagina.
- The internal female organs, the uterus, Fallopian tubes and ovaries are normal; Wolffian duct structures are not present.



Figs 63A and B: Female infant with CAH with ambiguous genitalia. (A) Clitoromegaly; (B) Fusion of labioscrotal fold

Boys with classic CAH have no gonadal sign of CAH at birth, except subtle hyperpigmentation and possible penile enlargement. The clinical features of CSW occur at 7–10 days of life.

Classic Salt-Wasting Variety

Clinical features of CSW in both boys and girls present with following features:

- Vomiting
- Weight loss
- Lethargy
- Dehydration
- Hyponatremia
- Hyperkalemia
- Shock.

Both boys and girls with the salt-wasting form, if not treated soon after birth, will also experience a salt-losing adrenal crisis in the neonatal period. However, in girls, the ambiguous genitalia typically lead to early diagnosis and may help clinician in preparing management of subsequent adrenal crisis. However, in male children, it is difficult to apprehend and predict adrenal crisis in early neonatal period as there is no ambiguous genitalia at birth. There may be only subtle hyperpigmentation around genitalia at birth which can be easily missed out.

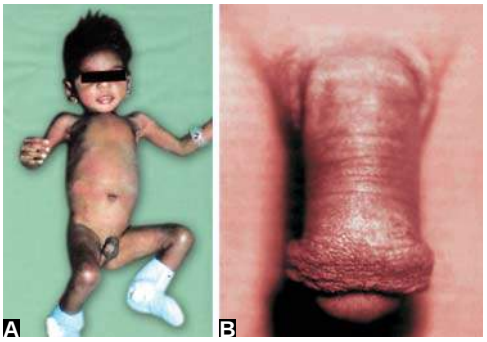
Poor feeding is a late sign of CAH and severe adrenal crisis and warrants emergency management.

The signs of adrenal crises are as follows (all features may not be present in one patient):

- Decreased activity/fatigue
- Altered sensorium/unresponsiveness
- Poor feeding/weak suck
- Dry mucous membranes
- Hyperpigmentation
- Abdominal pain
- Vomiting
- Hyponatremia
- Hyperkalemia
- Hypoglycemia
- Metabolic acidosis
- Hypothermia
- Hypotension
- Dehydration
- Lack of weight gain.

Classic Simple Virilizing CAH (Figs 64A and B)

In the simple virilizing form, the steroidogenic effect is not profound as in salt-wasting form. The residual enzyme activity can generate sufficient cortisol and aldosterone to survive, but not enough to prevent excess androgen release.



Figs 64A and B: (A) A male infant with CAH with virilization; (B) 5-year-old boy suffering from CAH showing increased penile length and appearance of pubic hair

Presentation at Birth

Male at Birth

- May remain undetected at birth
- Increases scrotal pigmentation without anatomic abnormality
- If not treated, presentation beyond 2 years of age includes:
  - Virilization
  - Rapid growth.

Female

At birth: Evidence of virilization of genitalia:

- Clitoromegaly
- Fusion of labioscrotal fold
- May resemble cryptorchid male.

Beyond 2 years of age:

- Virlization
- Rapid growth.

Nonclassic

Nonclassic 21-OHD is one of the most common autosomal recessive disorders in humans. Its prevalence rate is approximately 3.7% (1 in 27) in Ashkenazi Jews and 0.1% (1 in 1,000) in white populations. In this disorder, partial deficiency of 21-hydroxylation, results in milder symptoms of the disease. Patients with nonclassic CAH do not have cortisol deficiency, but instead have manifestations of hyperandrogenism, generally later in childhood or in early adulthood. Genital ambiguity is not present at birth and androgen excess manifests later in life for both males and females. In the early ages, presentations include premature adrenarche and an advanced bone age. These patients can present with early pubarche or as young women with hirsutism (60%), oligomenorrhea or amenorrhea (54%) with polycystic ovaries and acne (33%), 5–10% of children with precocious pubarche. Conversely, some women with nonclassic CAH have no apparent clinical symptoms, and many men with nonclassic CAH remain free of symptoms.

Laboratory Investigations

CAH

Initial laboratory investigation includes:

- Serum electrolytes (hyponatremia and hyperkalemia)
- 17-OHP $\rightarrow$ increased
- Serum ACTH

- Serum cortisol
- Glucose/dextrose stick at bedside
- Arterial blood gas/serum pH
- Liver function tests
- Pelvic USG to detect internal genitalia
- Karyotype (more relevant in ambiguous genitalia).

Classic 21-OHD

Investigations more relevant to classic 21-OHD:

- 17-OHP concentrations: A very high concentration of 17-OHP (more than 242 nmol/L; normal less than 3 nmol/L at 3 days in full-term infant) in a randomly timed blood sample is diagnostic of classic 21-OHD
- 17-OHP in salt-losing patients has typically higher value than non-salt-losers
- Corticotropin stimulation test or short synacthen test can be used to assess borderline cases. This test is also useful for nonclassic variety of CAH
- Genetic analysis can be helpful to confirm the diagnosis
- Salt-wasting is diagnosed by low (↓) plasma sodium, high (↑) plasma potassium, and increased urinary sodium excretion.

Nonclassic

The gold standard for diagnosis of the nonclassic form is a corticotropin stimulation test (short synacthen test), with measurement of 17-OHP at 60 min. A dose of 0.25 mg ACTH injection is given through intravenous route and estimation of 17-OHP is done after 60 min. This test can be done at any time of day. A stimulated concentration of 17-OHP higher than 45 nmol/L is diagnostic of 21-OHD. Higher rises are seen in more severe (classical form) cases.

Drawbacks of laboratory evaluation:

- 17-OHP levels often are falsely negative before postnatal day 3 due to interference by fetal adrenal metabolites
- Due to high ACTH drive in preterm infant sick/stressed neonates of all gestational age, the levels of 17-OHP are higher
- Phenotypic male with undescended testis may be fully virilized genetic females with CAH. This should be formally excluded to prevent an adrenal crisis.

Short Synacthen Test

Can be done anytime and fasting is not required.

Indication: Investigation for possible CAH

Dose:

0–6 months	62.5 µg
6 months–2 years	125 µg
>2 years	250 µg

Procedure:

- Collect baseline blood
- Give IV synacthen (ACTH) at time 00 hour
- Collect two urine samples if possible.
- Collect all urine.

Management of CAH (CSW)

Initial Management

Rehydration with normal saline and correction of hypoglycemia are required urgently. A bolus dose of hydrocortisone should be given and an infusion established.

When stable, regular maintenance treatment can be started:

- Hydrocortisone 10–15 mg/m^2/day.
- Fludrocortisone 150 µg/m^2/day.
- Sodium supplements for the first year pending maturation of renal tubular sodium resorption: 5 mmol/kg/day in divided doses.

Monitoring

- 4–6 monthly
  Clinic review:
  - Check weight, height, height velocity and blood pressure
  - Observation of pubertal staging
- 6–12 monthly
  - 17-OHP hormone profile
- Annually
  - Bone age estimation
  - Plasma renin activity

Follow-Up

- Careful follow-up to ensure balanced steroid replacement
- Girls with virilization require sensitive consideration of the need for surgical correction and psychological support.

Prenatal Therapy

Prenatal treatment is controversial, since the risk of having an affected female fetus is only one in eight when both parents are known carriers. When only one embryo will be affected, the remaining seven embryos will be exposed to high dose of glucocorticoid unnecessarily as prenatal therapy.

In pregnancies in which the fetus is at risk of classic CAH, maternal dexamethasone treatment has successfully suppressed the fetal HPA axis and reduced the genital ambiguity of affected female infants. As the masculinization of the external genitalia begins by 8 weeks of gestation, treatment should be started as soon as the pregnancy is confirmed.

For an affected female fetus, treatment is continued throughout pregnancy. About 85% of prenatally treated female infants are born with normal or slightly virilized genitalia.

Potential maternal side-effects include the signs and symptoms of Cushing's syndrome.

Management of CAH in Neonatal Period

Management of patients with classic CAH during the neonatal period is challenging. Two-third of these patients is salt-losers. Neonates are particularly vulnerable to hypovolemia and electrolyte disturbances, as well as hypoglycemia. The hydrocortisone dose in neonates should not exceed 25 mg/m^2 daily, and monitoring of weight and length supplemented by serial measurement of adrenal steroid concentrations, plasma renin activity and electrolyte concentrations should guide management.

Complications of CAH

- *Hyperandrogenism*: It is associated with poor compliance and results in:
  - Clitoromegaly
  - Penile growth
  - Pubic hair development
  - Central gonadotropin-dependent precocious puberty due to hypothalamic activation

- *Poor compliance with treatment*: Poor compliance with treatment results in initial overgrowth, rapid bone age acceleration and therefore premature cessation of growth.
- *Obesity*: Obesity is due to higher physiological dose of glucocorticoids to suppress androgen secretion.
- *Testicular tumors*: Tumors of adrenal rests in poorly compliant boys [testicular adrenal tumors (TARTs)] may cause disordered testicular architecture and results in infertility.

Algorithms for Diagnostic Workup and Management of CAH

Algorithm for diagnostic workup and management of CAH in the neonatal period and beyond neonatal period are mentioned in Figures 65 and 66.

Elaboration and keys of algorithm for diagnostic workup and management in the newborn period (Fig. 65):

1. Neonatal screening for elevated 17-OHP may reveal 21-OHD in a boy that has not yet developed any clinical symptoms. Even after confirmation of high 17-OHP in blood, it is advisable to perform mutation analysis in order to subclassify into severe forms (these children will, however, have developed symptoms of failure to thrive, dehydration and salt loss before the DNA analysis is finished), moderately severe forms.
2. By far the most common form of CAH is due to deficiency in 21-hydroxylase (21-OHD). Most girls with severe forms of CAH will present at 5–15 days of age with virilization at birth, vomiting, failure to thrive and dehydration. Boys easily escape early diagnosis and may be misinterpreted as gastroenteritis. CAH must be ruled out in "bilateral cryptorchidism".
3. Hyponatremia may also occur in moderately severe forms of 21-OHD (simple virilizing forms) if the child is under stress
4. There is no sharp limit between severe (salt losing) and moderate (simple virilizing) forms. Mild (nonclassical) forms are generally not detected until after the neonatal period
5. If available, mutation analysis of the 21-hydroxylase gene should be done in all cases. Generally there is good correlation between genotype and phenotype in this disorder
6. Without stress, dose of hydrocortisone is to be started at 15 mg/m^2. The dose is 3–4 times higher if the child is in stress, which is to be tapered to a maintenance dose. The doses should be lowest in the first year of life. If renin level is high fludrocortisone (initially 25–50 µg/day) is given. Addition of salt (0.5 g x 2–3) to the diet often stabilizes the situation during the first 1 or 2 years of life.
7. Lower urinary tract obstruction in a neonate may cause salt loss and imitate CAH. Ultrasound of pelvis.
8. A steroid pattern resembling both 21 and 17-hydroxylase deficiency (moderately elevated 17-OHP and subnormal androgen levels) may be caused by a partial deficiency of POR.

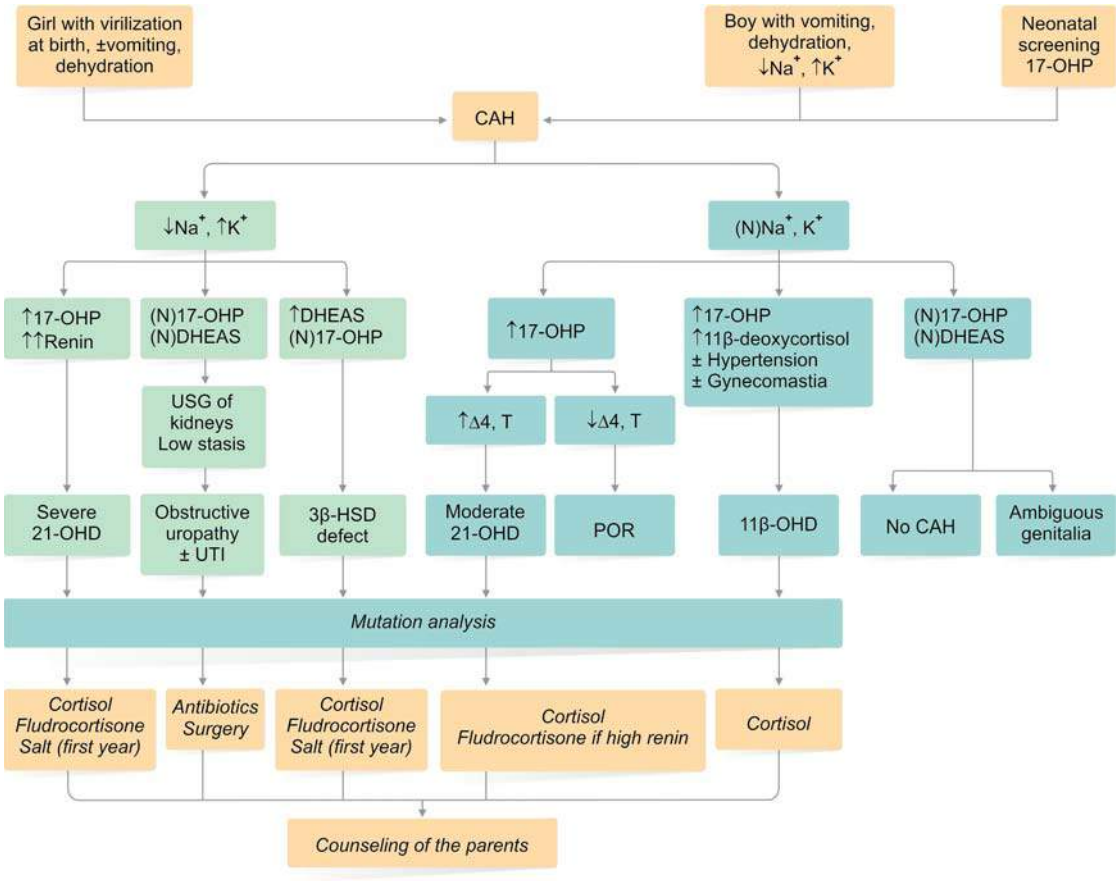


Fig. 65: Algorithm for diagnostic workup of congenital adrenal hyperplasia presenting during newborn period

Abbreviations: CAH, congenital adrenal hyperplasia; OHP, hydroxyprogesterone; HSD, hydroxysteroid dehydrogenase; UTI, urinary tract infection; DHEAS, dehydroepiandrosterone sulfate; Na+, sodium ions; K+, potassium ions; USG, ultrasonography; POR; P450 oxidoreductase; ↑, increase; ↓, decrease.

If genitalia are ambiguous, it should be considered as a medical emergency and the parents should bring their child to a competent team of experienced endocrinologist, surgeon, psychiatrist and geneticist within the first day after birth. Prolonged or hesitant management during the first day might hamper future acceptance of the child by the family.

Key to algorithm for diagnostic workup and management after newborn period (Fig. 66):

1. The clinical picture is that of a child with signs of androgen excess. Girl shows pubic hair, oily skin, acne, apocrine sweat odor and some clitoromegaly. Boys will have early "skin puberty", rapid growth and advanced genital maturation for age, but not testicular growth.
2. If baseline 17-OHP level in blood is borderline normal, a bolus injection of ACTH, measuring 17-OHP before and after 1 hour can yield more information.
3. Premature adrenarche is here used as the biochemical finding of elevated "adrenal androgens" mostly DHEA and its sulfate. The clinical correlate is premature skin puberty (pubic hair, oily skin, apocrine sweat odor, acne) without signs of gonadal puberty (breast enlargement in girls and testicular growth in boys).
4. Adrenal tumor is rare in childhood, but important differential diagnosis in isolated skin puberty.
5. Severe forms will have been diagnosed earlier due to salt loss and dehydration. Females with moderately severe forms can have a variable degree of virilization at birth. Males will often be diagnosed due to increased penile length and linear growth.
6. Nonclassical (mild) forms of 21-OHD may not have any symptoms during childhood. Borderline early signs of androgen excess may have passed unnoticed, until workup in adulthood for infertility and hirsutism (females) or partial adrenal insufficiency during stress (males and females).
7. 11β-OHD is rare in northern Europe, but constitutes about one-third of all CAH in the Middle East.
8. Mutation analysis has become a very useful tool in the diagnosis of both 21-hydroxylase and 11β-OHD and might be used instead of extensive hormone analysis. The genotype/phenotype correlation is generally good in 21-OHD.
9. In moderately severe 21-OHD salt loss may not be clinically evident. However, elevated renin level in blood indicates that the capacity to produce mineralocorticoids is subnormal, and less glucocorticoids are needed if a small dose (0.05–0.1 mg/m^2) of fludrocortisone is added.
10. Conventionally hydrocortisone treatment is begun when 21-OHD is diagnosed. However, some adult men with mild forms of 21-OHD are diagnosed, only because of family workup without having presented other symptoms than a somewhat early puberty and shorter stature than expected for family.
11. Some patients with 11β-OHD remain hypertensive even during adequate glucocorticoid treatment. Spironolactone may then be added to counteract excess mineralocorticoids.

DIABETES MELLITUS IN CHILDREN

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action or both. Type 1 diabetes mellitus

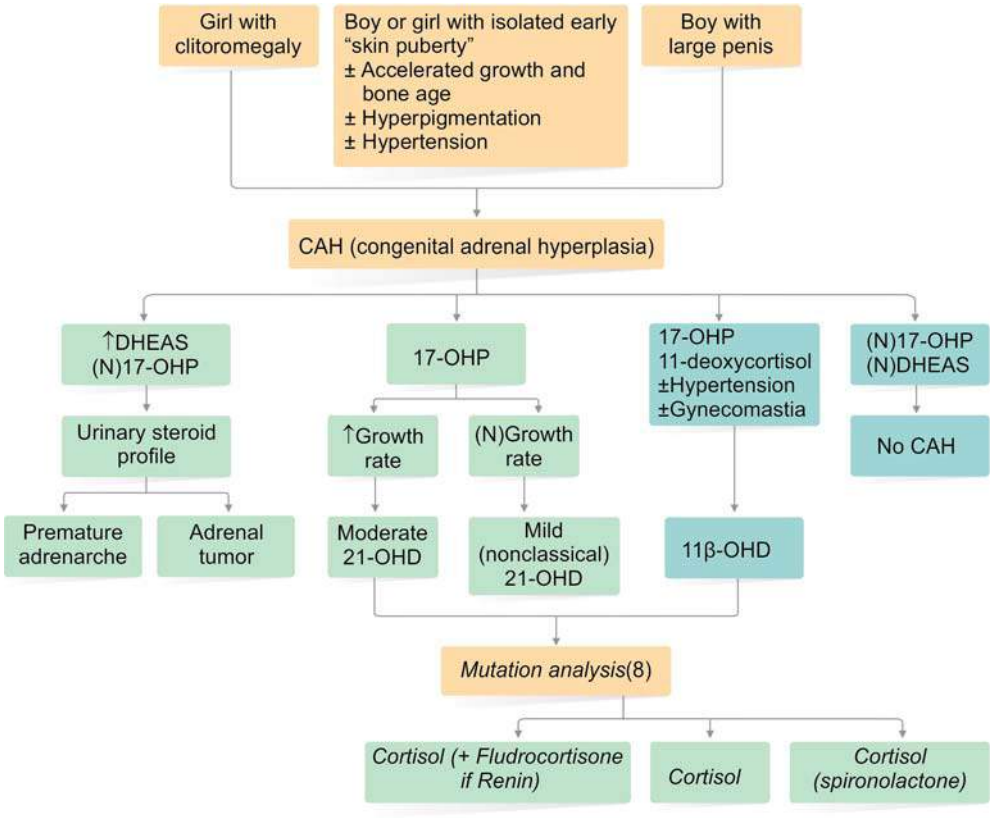


Fig. 66: Algorithm for diagnostic workup of CAH presenting after newborn period

Abbreviations: ↑, increase; DHEAS, dihydroepiandrosterone sulphate; OHP, hydroxyprogesterone; OHD, 21-hydroxylase deficiency; POR, P450 oxidoreductase; Δ4, androstenedione

(T1DM) represents more than 90% of childhood diabetes. Children may also have Type 2 diabetes mellitus (T2DM) and other specific types of diabetes, e.g. fibrocalculous pancreatic diabetes (FCPD).

Etiological Classification of Diabetes Mellitus

- *Type 1*
  β-cell destruction, usually leading to absolute insulin deficiency
  - Immune-mediated
  - Idiopathic
- *Type 2*
  It may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance.
- *Other specific types*
  - *Genetic defects of β-cell function*:
    - Chromosome 12, hepatocyte nuclear factor-1α [HNF-1α; maturity-onset diabetes of the young 3 (MODY3)]
    - Chromosome 7, glucokinase (MODY2)
    - Chromosome 20, HNF-4α (MODY1)
    - Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
    - Chromosome 17, HNF-1β (MODY5)
    - Chromosome 2, neurogenic differentiation (NeuroD1; MODY6)
    - Mitochondrial DNA
    - Others.
  - *Genetic defects in insulin action*:
    - Type A insulin resistance
    - Leprechaunism
    - Others.
  - *Diseases of the exocrine pancreas*:
    - Pancreatitis
    - Trauma/pancreatectomy
    - Fibrocalculous pancreatopathy
    - Others.
  - *Endocrinopathies*:
    - Acromegaly
    - Cushing's syndrome
    - Hyperthyroidism
    - Glucagonoma
    - Others.
  - *Drug or chemical induced*:
    - Glucocorticoids
    - Thyroid hormone
    - β-adrenergic agonists
    - Thiazides
    - Others.
  - *Infections*:
    - Congenital rubella
    - Cytomegalovirus
    - Others.
  - *Uncommon forms of immune-mediated diabetes*:
    - "Stiff-man" syndrome
    - Anti-insulin receptor antibodies
    - Autoimmune polyendocrine syndrome (APS) I and II
    - Others.
  - *Other genetic syndromes sometimes associated with diabetes*:
    - Down syndrome
    - Klinefelter syndrome
    - Turner syndrome
    - Others.
  - *Gestational diabetes*

Diagnostic Criteria for Diabetes Mellitus in Children and Adolescents

Children with T1DM usually present with characteristic symptoms, such as polyuria, polydipsia, weight loss, in association with glycosuria and often ketonuria. In its most severe form, diabetes ketoacidosis (DKA) may develop leading to stupor, coma and if not timely diagnosed and treated to death. The diagnosis is usually confirmed quickly by measurement of a marked elevation of blood glucose level and oral glucose tolerance test (OGTT) should not be performed if diabetes can be diagnosed using fasting, random or postprandial criteria as excessive hyperglycemia can result. Criteria for the diagnosis of DM are given in Table 16.

In the absence of symptoms or presence of mild symptoms of diabetes, hyperglycemia detected incidentally or under conditions of acute infective, traumatic, circulatory or other stress may be transitory and should not in itself be regarded as diagnostic of diabetes. In such circumstances instead of relying on single plasma glucose concentration, diagnosis may require continued observation with fasting and/or 2 hours postprandial blood glucose levels and/or an OGTT.

Impaired Glucose Tolerance (IGT) and Impaired Fasting Glycemia (IFG)

Individuals with IFG and/or IGT have been referred to as having prediabetes, indicating the relatively high risk for the future development of diabetes.

IFG is defined as fasting blood glucose (FBG) more than normal range of 5.6–6.9 mmol/L (100–125 mg/dL) according to American Diabetes Association (ADA) criteria and more than range of 6.1–6.9 mmol/L (110–125 mg/dL) according to WHO criteria.

IGT is defined as 2 hour values in the OGTT of more than normal range of 7.8–11.0 mmol/L (140–199 mg/dL).

Type 1 Diabetes Mellitus

It represents a state of absolute/near absolute insulinopenia with short period of classical symptoms. Children and adolescents are prone to ketoacidosis and exogenous insulin is essential for life.

Table 16: Criteria for diagnosis of diabetes mellitus

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no calorie intake for at least 8 hours
OR 2 hours plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing 75 g anhydrous glucose dissolved in water or 1.75 g/kg bodyweight to a maximum of 75 g
OR In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmo/L)
Abbreviations: FPG, fasting plasma glucose; WHO, World Health Organization; OGTT, oral glucose tolerance test

Type 2 Diabetes Mellitus

It is increasingly recognized in children with global rise of obesity. It is characterized by insulin resistance and relative insulin deficiency and commonly associated with other features of the insulin resistance syndrome (hyperlipidemia, hypertension, acanthosis nigricans, ovarian hyperandrogenism, nonalcoholic fatty liver disease). In youth most often occurs during the second decade of life, with a mean age of diagnosis of 13.5 years. Development of ketoacidosis is less common. T2DM in childhood is more common in African-Americans, Hispanic Americans and Asians than in those of European ancestry. Among Japanese children, T2DM is more common than T1DM and accounts for 80% of childhood diabetes.

Maturity-Onset Diabetes of Young

Several forms of diabetes are associated with monogenic defects in β-cell function. Before these genetic defects were identified, this subset of diabetes was diagnosed on clinical grounds and described by the term MODY. This subtype of DM consists of a group of heterogeneous clinical entities characterized by onset between the ages 9 and 25 years, autosomal dominant inheritance and a primary defect in insulin secretion. Patients are non-insulin dependent or require only a small insulin dose to achieve good glycemic control.

Fibrocalculous Pancreatic Diabetes

It is a disease of exocrine pancreas under the category of "other specific types of diabetes". It is prevalent in tropical regions with cardinal triad of abdominal pain, pancreatic calculi and diabetes, in the absence of other causes of chronic pancreatitis. The age of onset is usually 10–30 years, majority of patients are lean, have very high plasma glucose, requiring insulin for control and are ketosis resistant. Pancreatic calculi are detected by plain X-ray/USG.

Neonatal Diabetes Mellitus (NDM)

It is insulin requiring diabetes diagnosed in the first 6 months of life. It is a rare condition with an incidence of 215,000–500,000 live births. About 50% have permanent neonatal diabetes mellitus (PNDM) and the rest transient neonatal diabetes mellitus (TNDM) which can recur in 50% of cases during the pediatric age range. For most patients with NDM the molecular etiology can now be defined which has important implications for the treatment, prognosis and genetic counseling. Patients with neonatal diabetes due to defect in adenosine triphosphate (ATP)-sensitive potassium channel of β-cell of pancreas (patients with KCNJ11 and ABCC8 mutation) can be successfully treated with oral sulfonylurea and achieve better glycemic control and quality of life. Apart from mutation in ATP-sensitive potassium channel, other causes of NDM need to be treated with insulin.

TYPE 1 DIABETES MELLITUS

Incidence

Globally, the number of people with T1DM is unknown, although it is estimated that 80,000 children develop the disease every year. In the US, the number of persons with T1DM is estimated to be 1 to 3 million. The incidence of T1DM varies worldwide. As the distance from the equator increases, the risk appears to rise.

Clinical Manifestations

Classical symptoms are polyuria polydipsia, polyphagia, general weakness, weight loss, etc. There may be atypical presentation like abdominal pain, pruritus vulvae, visual problem, infection, mood changes, irritable behavior, etc.

Pathogenesis of T1DM

Individuals have an absolute deficiency of insulin secretion and are prone to ketoacidosis. It may be:

A. *Immune-mediated*
   Here T-cell mediated autoimmune pancreatic islet β-cell destruction occurs. Susceptibility to autoimmune T1DM is determined by multiple genes. The environmental triggers (chemical and/or virus) that initiate pancreatic ß-cell destruction remain largely unknown. The serological markers of an autoimmune pathological process are islet cells, glutamic acid decarboxylase (GAD), insulinoma antigen-2 (IA-2), IA-2β or insulin autoantibodies.
B. *Idiopathic form*
   Here antibodies are absent. Most are of African and Asian ancestry.

Phases of Diabetes

T1DM has following phases:

- Preclinical diabetes: Months or years preceding the clinical presentation of T1DM when antibodies can be detected as markers of β cell autoimmunity
- Presentation of T1DM
- Partial remission or honeymoon phase: In approximately 80% of children and adolescents, insulin requirements decrease transiently following initiation of insulin treatment
- Chronic phase of lifelong dependency on administered insulin.

Management

The goals of management of childhood diabetes are:

- Setting of realistic goals for each child and family
- Near normalization of blood glucose level and glycated hemoglobin (HbA1c)
- Prevention of DKA
- Avoidance of severe hypoglycemia
- Assuring as near quality of life as possible
- Maintaining normal growth, development and maturation
- Providing readily available multidisciplinary support
- Maintaining close surveillance and prevention of micro- and macrovascular complications.

Important components of management of childhood diabetes are insulin therapy, education, nutrition, exercise, glucose monitoring, etc.

Insulin Therapy in T1DM

Various insulin preparations are available for children and adolescents, these are:

- Regular insulin (short acting) has to be taken 20–30 minutes before meals, is combined with intermediate acting insulin in twice daily regimen and also used as premeal bolus injection in basal-bolus regimen
- Intermediate acting insulin
- Rapid acting insulin analogs
  - Aspart
  - Lispro
  - Glulisine

The rapid acting analogs are most often used as prandial (meal related) boluses in combination with basal insulin in basal-bolus regimen and in insulin pumps. They can be given immediately before meal and after meal when needed (infants and toddlers) but are more expensive compared to regular insulin.

- Basal insulin analogs:
  - Glargine
  - Detemir

The long acting basal analogs are usually used once a day, may need twice daily.

- Premixed insulin preparations
  - Fixed ratio mixture of regular (or rapid acting) and intermediate acting insulin in different ratio (e.g. 30:70, 50:50)

Types of insulin preparation with suggested action profile is shown in Table 17.

Insulin regimens: Frequently used regiments are:

- Twice daily injection: Mixture of short and intermediate acting insulin (before breakfast and the main evening meal/dinner), the conventional therapy. Children often require more (two-third) of their total daily dose in the morning and the rest in evening with approximately one-third of the insulin dose short acting and approximately two-third intermediate acting. Later dose is adjusted according to blood glucose monitoring.
- Thrice injection daily: Mixture of short/rapid and intermediate acting insulin is given before breakfast, short/rapid acting insulin before afternoon snack/main evening meal and intermediate acting insulin before bed.
- Basal bolus regimen (intensive therapy):
  - Multiple dose insulin injection (MDI): A long acting (basal) analog and preprandial rapid acting analog/short acting insulin: Of the total daily requirement, 40–60% should be basal insulin, usually at bed time (can be given at other times), rest rapid acting/regular insulin before each main meal (breakfast, lunch and main evening meal/ dinner)
  - Continuous subcutaneous insulin infusion (CSII/pump therapy) with a fixed or a variable basal doses and bolus doses with meals with a rapid acting analog.

Table 17: Types of insulin and their action profiles

Insulin type	Onset of action	Peak of action	Duration
Regular/soluble (short acting)	30–60 minutes	2–4 hours	5–8 hours
Intermediate acting (NPH)	1–2 hours	4–8 hours	12–18 hours
Rapid-acting analog	10–20 minutes	1–3 hours	3–5 hours
Long acting analog	1–2 hours	None	20–24 hours

Abbreviations: NPH, Neutral potamine Hagedorn

American Diabetes Association for type 1 diabetes recommends use of MDI (3–4 injections per day of basal and prandial insulin) or CSII therapy and for many patients (especially if hypoglycemia is a problem), use of insulin analogs. In our present context where majority of children with diabetes are from very poor socioeconomic background, the conventional therapy is more suitable. Therefore, choice of insulin and insulin regimens should be individualized.

Insulin dose: Initial insulin is started at a dose of 0.5–1 U/kg/day and then adjusted according to blood glucose profile. Daily insulin dose depends on various factors such as age, weight, pubertal stage, diet, exercise pattern, undercurrent illness, etc. During the partial remission phase, the total daily insulin dose is often less than 0.5 U/kg/day. Prepubertal children usually require 0.7–1 U/kg/day. During puberty, requirement may rise substantially above 1 and even up to 2 U/kg/day.

Target range of blood glucose: The optimal ranges according to International Society of Pediatric and Adolescent Diabetes (ISPAD) are:

- Preprandial fasting plasma glucose (FPG) between 5 and 8 mmol/L
- Postprandial plasma glucose between 5 and 10 mmol/L
- Bedtime plasma glucose between 6.7 and 10 mmol/L
- Nocturnal plasma glucose between 4.5 and 9 mmol/L
- HbA1c less than 7.5%.

American Diabetes Association recommends HbA1c targets of less than 8.5% in children under 6 years of age, less than 8% for children aged 6–12 years and less than 7.5 % for adolescents/young adult aged 13–19 years.

Education

Education of the patient and family is the cornerstone of diabetes care and should include simple explanation about the disease, insulin injection technique, explanation and management of hypoglycemia, dietary advice, exercise, monitoring, sick day management including ketosis and prevention of ketoacidosis, micro- and macrovascular complication and their prevention, foot care, dental care, travel, etc.

Nutrition

Nutrition plays an essential role in the management of patients with T1DM. Appropriate energy is required to meet the needs for energy expenditure, growth and development. Dietary recommendations for children with diabetes are based on healthy eating recommendations, suitable for all children and adults and therefore the whole family. The child's age, sex, weight, activity, food preference, insulin regimen, social, cultural and ethnic background should be considered while planning a meal with the help of a dietician. A rough calculation is provided by the formula of 1,000 calories at 1 year of age and additional 100 calories per year of age after that up to adolescence. Since many children present with significant weight loss, their calorie need may be quite high initially. Later care may be needed in some children to avoid obesity. The day's meal plan should be divided into three main meals (breakfast, lunch, dinner) and 2–3 snacks (mid-morning, evening and bedtime). Total daily energy intake should be distributed as follows: carbohydrate 50–55%, fat 30–35% and protein 10–15%. Approximately 70% of carbohydrate content

should be derived from complex carbohydrate such as starch. Intake of sucrose and highly refined sugar should be limited. Nonnutritive sweeteners, such as aspartame, are used in a variety of products. Sorbitol and xylitol should not be used as artificial sweeteners. Diets with high-fiber content should be encouraged such as wholegrain breads and cereals, legumes (lentils, peas, beans), fruits and vegetables. Dietary fat derived from animal sources should be reduced and replaced by polyunsaturated fat from vegetable sources. Less than 10% of calories should be derived from saturated fats, up to 10% from polyunsaturated fats and the remaining fat-derived calories from monounsaturated fats. Protein intake should be 2.0 g/kg/day for infants to 0.9 g/kg/day for teenagers. Sources of vegetable protein, such as legumes as well as animal protein, including fish, lean cuts of meat and low fat dairy products are recommended.

Carbohydrate counting: It has become a mainstay in the nutrition education and management of patients with DM. One carbohydrate serving equals to 15 g carbohydrate. Carbohydrate counting helps to determine the amount of carbohydrate in different foods, so that the foods can be interchanged accordingly. It also guides to adjust the insulin dose, e.g. one unit of short/rapid acting insulin are required for 10–20 g of carbohydrate.

Glycemic index (GI): The concept of glycemic index may be helpful in educating patients about choices within a food group. Glycemic index is a measure of the rate of rise of blood sugar after a particular type of food is eaten, in comparison with glucose, which is taken as 100. Within a major food groups, index food, e.g. vegetables, whole meal bread, whole meal rice, fruits, such as apple, grape fruit, orange, nuts, beans, are considered at low GI foods. Medium GI foods include mango (ripe), papaya, pineapple, banana, pulse, maize, etc. Examples of high GI foods include watermelon, dates, sweets, potato, white bread, white rice, etc. (Fig.67).

Exercise

Physical activity and exercise should be encouraged, e.g. walking, running, playing football, skipping and bicycle exercise. Provision should be made for extra calories before vigorous exercise to prevent hypoglycemia. In case of vigorous or prolonged exercise, usual insulin dose may need to be reduced for the scheduled day. Exercise should be avoided during periods of hypoglycemia and ketosis.

Monitoring

Monitoring of glycemic control includes daily monitoring of glucose at home as well as periodic monitoring of overall glycemia. Self monitoring of blood glucose (SMBG) should be done ideally 4–6 times at different times of the day. SMBG helps to monitor immediate and daily level of control, helps to determine immediate and daily insulin requirements and insulin adjustments, detects hypoglycemia and assists in its management, also assists in safe management of hyperglycemia. In resource poor countries, all children should be encouraged to monitor blood glucose at least once daily at different times of the day to make a profile for a week and it can be combined with urine testing. Urine/blood ketone should be monitored when hyperglycemia, illness/vomiting is present to prevent impending DKA.

An HbA1c measurement reflects the average blood glucose concentration during the preceding 2–3 months. ISPAD recommends 4–6 measurements/year in younger children and 3–4 measurements/year in older children but every child should have a minimum of one measurement per year.

Acute and chronic complications: Hypoglycemia and DKA are important acute complications of diabetes in children.

HYPOGLYCEMIA

Hypoglycemia is low blood glucose levels (blood glucose ≤3.9 mmol/L or 70 mg/dL). It can occur as a result of too much insulin, no food/too little food/delayed meal, increased activity, illness (diarrhea, vomiting, etc.).

Signs and Symptoms

Irritability, inconsolable crying, headache, hunger, tiredness, trembling, tachycardia, cold sweatiness, pallor, blurred vision, slurred speech, dizziness, confusion, convulsion and loss of consciousness.

Treatment

It is important for the child and people (teachers, the extended family) around to recognize and treat hypoglycemia. If a blood

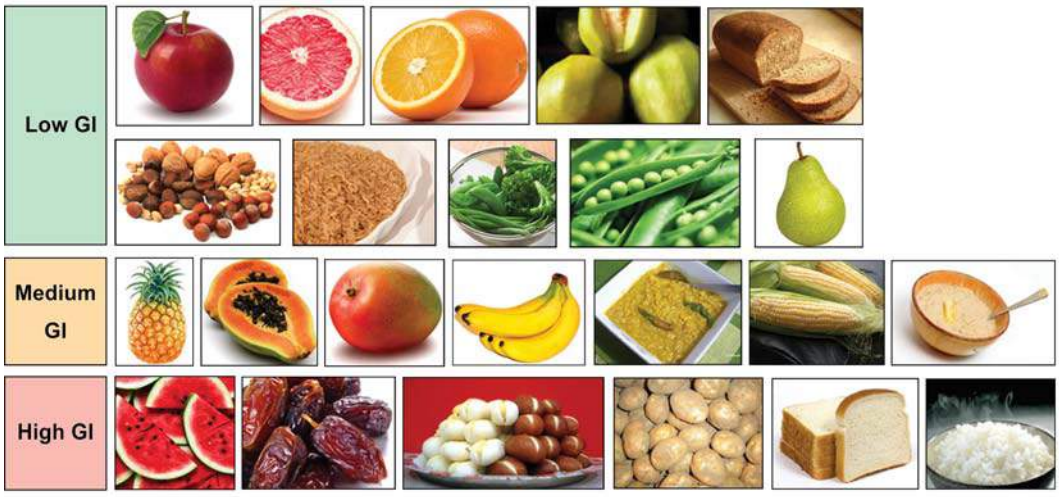


Fig. 67: Examples of foods of low GI, medium GI and high GI values

glucose meter is available, documentation of a suspected episode of hypoglycemia with blood glucose values is advisable without any delay in treatment. If the child is conscious and can take food orally then feeding with rapid-acting carbohydrate food such as 10–15 g of carbohydrate in the form of sugar (2–3 teaspoonful), sweetened drinks like glucose water, canned or bottled drinks, fruit juices (100–200 mL) must be taken. If the child is having severe symptoms (is not able to eat), is unconscious, having a convulsion then urgent treatment should be given with injection glucagon 0.5 mg for age less than 12 years, 1 mg for ages greater than 12 years, or 10–30 µg/kg bodyweight subcutaneously or intramuscularly. In a hospital setting IV glucagon may be given. If glucagon is not available the child should receive IV dextrose slowly over several minutes. Once recovered a snack (fruit, bread, cereal and milk) should be given to prevent recurrence of hypoglycemia.

Prevention of Hypoglycemia

It is important to remind the child and parents often about the symptoms and causes of hypoglycemia. Repeated episode of hypoglycemia needs review of the management of the child, including insulin doses, eating plan, exercise, etc. The child should carry a small snack such as a fruit or a packet of biscuit, powdered sugar or glucose and a diabetes identification card. Ideally glucagon vial should be available in the house.

DIABETIC KETOACIDOSIS

It is the commonest cause of diabetes-related deaths in children.

Pathophysiology

Diabetic ketoacidosis (DKA) results from absolute or relative deficiency of circulating insulin and the combined effects of increased levels of counter regulatory hormones: catecholamines, glucagon, cortisol and growth hormone. Absolute deficiency occurs in previously undiagnosed T1DM and when patients on treatment do not take insulin. Relative deficiency occurs in response to stress (e.g. sepsis, trauma). The combination of low serum insulin and high counter regulatory hormone results in an accelerated catabolic state with increased glucose production via glycogenolysis and gluconeogenesis, impaired peripheral glucose utilization resulting in hyperglycemia and hyperosmolality, and increased lipolysis and ketogenesis, causing ketonemia and metabolic acidosis. Hyperglycemia exceeding renal threshold and hyperketonemia cause osmotic diuresis, loss of fluid and electrolyte and dehydration.

Biochemichal Criteria

- Hyperglycemia [blood glucose >11 mmol/L (200 mg/dL)]
- Venous pH less than 7.3 or bicarbonate less than 15 mmol/L
- Ketonemia and ketonuria.

Severity of DKA

- *Mild*: Venous pH less than 7.3 or bicarbonate less than 15 mmol/L
- *Moderate*: pH less than 7.2, bicarbonate less than 10 mmo/L
- *Severe*: pH less than 7.1, bicarbonate less than 5 mmol/L.

Clinical Manifestations (Fig. 68)

Dehydration, rapid, deep, sighing (Kussmaul) respiration, fruity breath, nausea, vomiting, abdominal pain, progressive obtundation and loss of consciousness.

Management of DKA

Effective treatment of DKA involves the following stages:

Assessment

- Clinical assessment including history and examination. Evidence of infection should be looked for
- Assessment of severity of dehydration:
  5% Dry mucous membranes, reduced skin turgor
  10% Capillary return 3 seconds or more, sunken eyes
  10% + Shock, poor peripheral pulses

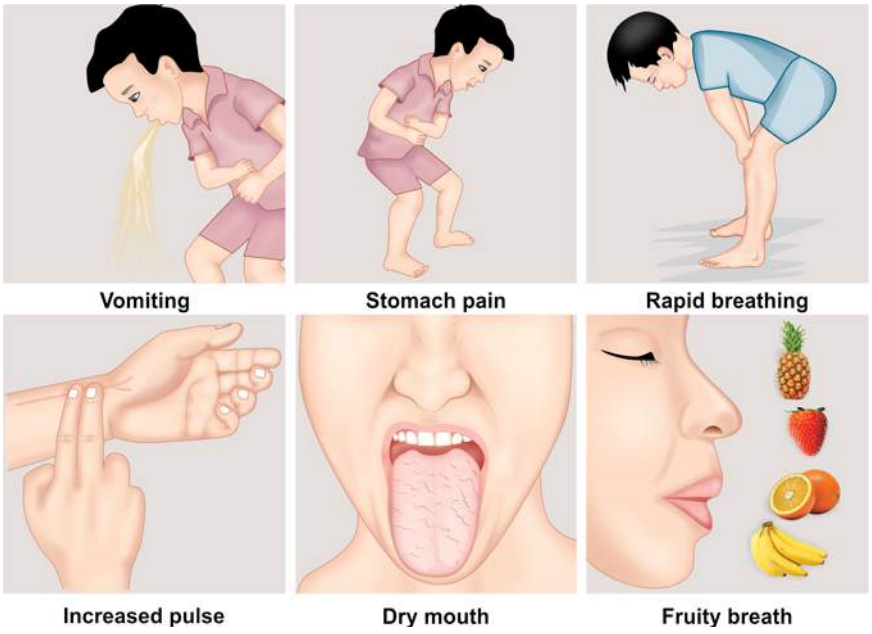


Fig. 68: Some important clinical features of diabetic ketoacidosis

Clinical assessment of dehydration can be difficult, in moderate DKA 5–7% and in severe DKA 7–10% dehydration may be used

- Assessment of level of consciousness
- Determination of weight
- Biochemical assessment: Blood glucose, blood gas, urine for ketone, complete blood count, electrolyte, urea, creatinine, others as indicated. If laboratory measurement of serum potassium is delayed, an electrocardiography (ECG) should be performed for baseline evaluation of potassium status.

Resuscitation

- Secure the airway
- Oxygen should be given with impaired circulation and/or shock
- Set up an IV channel
- Treatment of shock (decreased perfusion) with normal saline 0.9%, 10–20 mL/kg over 1–2 hours and may be repeated until circulation is restored (maximum 30 mL/kg).
- Placement of catheter and nasogastric tube if required.

Fluid Replacement

Requirement = Deficit + Maintenance

- Calculate deficit = Estimated % dehydration × bodyweight (kg and equivalent in mL)
- Calculate maintenance (Table 18).
- Then add deficit to 48 hours maintenance and replace this volume evenly over 48 hours initially with 0.9% normal saline
- When blood glucose falls to 14–17 mmol/L or blood glucose falls greater than 5 mmol/L/hr, change to 0.45% saline with 5% glucose
- It may be necessary to use 10% or even 12.5% dextrose to prevent hypoglycemia while continuing insulin infusion.

Insulin Therapy

Insulin should be started only after circulation has been restored and 1–2 hours after starting fluid replacement therapy. Recommended initial insulin dose is 0.1 U/kg/hr, ideally by continuous low dose IV infusion (e.g. one method is to dilute 50 units regular/soluble insulin in 50 mL normal saline, 1 unit = 1 mL). In younger children, insulin may be started at lower dose (0.05 U/kg/h). The dose of insulin should usually remain at 0.1 U/kg/h at least until resolution of DKA (Ph >7.3, bicarbonate >15 mmol/L). Aim to keep blood glucose around 11 mmol/L until resolution of DKA.

In circumstances where continuous IV infusion of insulin is not possible, hourly IM/SC administration of short acting insulin or rapid acting insulin analog 0.1 U/kg has been shown to be effective, but should not be used in subjects whose peripheral circulation is impaired.

Table 18: Calculation of maintenance fluid

Approximate age (years)	Weight (kg)	Maintenance fluid (mL/kg/24 hours)
<1	3–9	80
1–5	10–19	70
6–9	20–29	60
10–14	30–50	50
>15	>50	35

Potassium Replacement

Potassium replacement should be started after initial volume expansion concurrent with starting insulin therapy. If patient is hyperkalemic, potassium replacement therapy should be deferred until urine output is documented. In case of unavailability of immediate potassium measurement, an ECG should be done to detect hyper- or hypokalemia. The starting potassium concentration should be 40 mmol/L in the saline.

Subsequent potassium replacement therapy should be based on serum potassium measurements.

Monitoring

- Hourly monitoring of vital signs, level of consciousness, capillary blood glucose
- Monitoring of urine ketone in every sample of urine passed
- Recording of intake output, insulin therapy
- Laboratory test: Serum electrolyte, blood gas every 2–4 hours, others as indicated (e.g. creatinine, urea, etc).

Introduction to Oral Fluids and Transition to SC Insulin Injections

Oral fluids should be introduced after substantial clinical improvements have occurred. Oral fluid volume should be subtracted from the IV calculations. Insulin by SC injection may be started when oral intake is tolerated. To prevent rebound hyperglycemia, the first SC insulin should be given15–30 minutes (with rapid acting insulin) or 1–2 hours (with regular insulin) before stopping the insulin infusion to allow sufficient time for the insulin to be absorbed.

Correction of Acidosis

Severe acidosis is reversible by fluid and insulin replacement. Bicarbonate therapy may cause paradoxical CNS acidosis, hypokalemia and increasing osmolality. Bicarbonate therapy may be considered for the treatment of patients with severe academia (arterial Ph <6.9) in whom decreased cardiac contractility and peripheral vasodilatation can further impair tissue perfusion and patients with life-threatening hyperklemia. It should be given cautiously 1–2 mmol/kg over 60 minutes.

Treatment of Infection

The infection should be treated**.**

Morbidity and Mortality in DKA

- Cerebral edema
- Hypoglycemia
- Hypokalemia
- Hyperkalemia
- Acute renal failure
- Aspiration pneumonia
- Pulmonary edema
- Thrombosis
- Sepsis
- Others.

Cerebral Edema

Cerebral edema is a fatal complication of DKA. Most deaths in DKA occur as a result of cerebral edema.

Factors associated with increased risk of cerebral edema include:

- Younger age
- New onset diabetes
- Longer duration of symptoms
- Greater hypocapnea at presentation after adjusting for degree of acidosis
- Increased serum urea nitrogen at presentation
- More severe acidosis at presentation
- Bicarbonate treatment for correction of acidosis
- An attenuated rise of measured serum sodium concentration during therapy
- Greater volumes of fluid given in the first 4 hours
- Administration of insulin in the first hour of fluid treatment.

Warning signs and symptoms of cerebral edema:

- Headache and slowing of heart rate
- Change in neurological status (restlessness, increased drowsiness)
- Specific neurological signs (e.g. cranial nerve palsies)
- Rising blood pressure
- Decreased oxygen saturation.

Treatment of cerebral edema:

- Reduction of rate of fluid administration by one-third
- Mannitol 0.5–1 g/kg IV over 20 minutes and repeat if there is no response in 30 minutes to 2 hours
- Hypertonic saline (3%), 5–10 mL/kg over 30 minutes, may be an alternative to mannitol or a second line of therapy
- Elevation of the head of the bed
- Intubation may be necessary for the patient with impending respiratory failure
- After treatment for cerebral edema has been started, it is advisable to do a cranial CT scan, to rule out other possible intracerebral causes of neurological deterioration, specially thrombosis or hemorrhage, which may benefit from specific therapy.

Chronic Complications

The long-term vascular complications of diabetes include microvascular (retinopathy, nephropathy, neuropathy) and macrovascular disease. Clinically evident microvascular complication may be less common in childhood and adolescence, but subclinical changes can be detected on screening tests and it may be possible to reverse or arrest them with early intervention. Intensive diabetes treatment and improved glycemic control confer a significant risk reduction for microvascular complication. Annual screening, avoidance of smoking, control of blood pressure, dislipidemia and obesity are advisable.

Comorbid Conditions

T1DM can be associated with thyroid disease, celiac disease, vitiligo and adrenal insufficiency. They reflect common genetic predisposition shared by these autoimmune diseases and the autoimmune nature of T1DM.

Prevention

Many trials are being undertaken for prevention of T1DM such as nutritional intervention, primary oral/intranasal insulin trial, European nicotinamide diabetes intervention trial, AntiCD3 treatment, stem cell therapy and so on and we can hope for prevention and cure of T1DM in future. But at present we must emphasize on diagnosis and treatment of T1DM without any delay to prevent DKA and death. It is a lifelong disease and imparts significant effects to the patients, their family and society. With the help of a dedicated, comprehensive, multidisciplinary support, these children can lead a healthy life. Complications can be reduced by intensive diabetes management as shown by diabetes control and complication trial (DCCT). Risk factors for complications, such as hyperglycemia, high blood pressure, lipid abnormalities, smoking, high body mass index (BMI), needs to be addressed.

With rapid urbanization, sedentary lifestyle, unhealthy eating with excess calorie, there is a global rise of obesity which parallels the rise of T2DM in children and adolescents. With change in lifestyle, T2DM can be prevented or delayed. It is high time, we address this health problem as well.

DEVELOPMENT OF GENITALIA AND SEX DIFFERENTIATION

Most individuals fall into one of two categories, clearly male or clearly female with complete consistency of genetic, gonadal, anatomic and psychological aspects of sex within any one individual; however there clearly is a complex gradient that runs from male to female occupied by many different varieties of people who do not fall neatly into one of the two standard sexual definitions.

The milestones of development stage of test in the embryo are as follows:

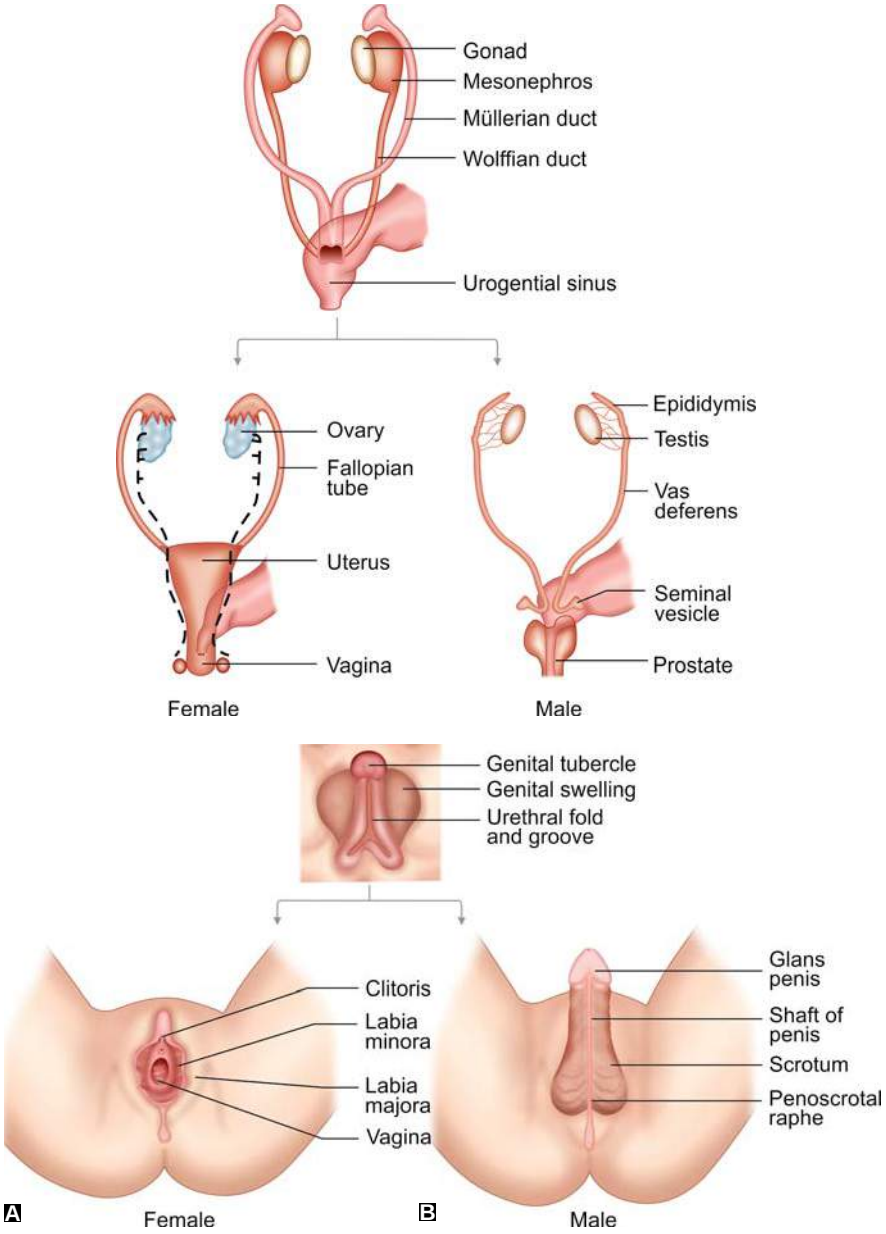
- 7th week: Testis (Sertoli cells) secrets anti-Müllerian hormone (AMH, also known as Müllerian inhibiting substances, MIS) to cause regression of Müllerian structures
- 8th week: Wolffian duct develops with testosterone secreted by testicular Leydig cells under stimulation from placental hCG
- 8th–13th week: Testosterone is converted to dihydrotestosterone (DHT) in genital tissue acting via the androgen receptor and allowing masculinization of external genitalia
- 13th week onward: Sex differentiation is complete, but growth of phallus continues with testosterone secretion now under control of LH secreted from the fetal pituitary gland.

Following Figure 69 illustrates the development of male and female external genitalia.

Genes and Sex Determination

The gonad remains bipotential until 6 weeks after the last menstrual period. Several genes have roles in differentiation of male and female sex differentiation. Sex-determining region of the Y chromosome (SRY), Wilms tumor 1 (WT-1), steroidogenic factor 1 (SF-1), SOX-9 are the common genes that direct the development of testis. The SRY gene is necessary but not sufficient for testicular differentiation. SRY causes the medullary region of the gonad to develop into Sertoli cells and later into testis cords and seminiferous tubules.

On the other hand, WNT_4 and DAX1 protect or enhance ovarian development. The gene WNT_4 is critical for normal ovarian and female sexual development.



Figs 69A and B: Primary sex differentiation. (A) In the absence of a testis, the Wolffian system atrophies, the Müllerian system develops and the common anlage differentiates into female external genitalia; (B) In the presence of a testis, internal genitalia develop from the Wolffian system, with atrophy of the Müllerian system, while the common anlage differentiates into male external genitalia

A mutation in WNT_4 leads to Müllerian duct regression and virilization in a 46,XX female, whereas duplication of the locus containing WNT_4 leads to 46, XY sex reversal.

Sexual Differentiation

The process of sexual differentiation follows a complicated pathway that requires knowledge of embryology and early endocrinology. Sexual differentiation can be subdivided into four main steps: Genetic, gonadal, ductal and genital differentiation.

Genetic

Chromosomal sex is typically XX for a female or XY for a male. Genetic sex determination occurs at the time of fertilization.

Gonadal Sex

At approximately the 5th week following fertilization, the urogenital ridge (ridge in the embryo lateral to the mesentery) thickens, which creates the gonadal ridge. The gonadal ridge remains undifferentiated for 2 weeks, at which point the first signs of either an ovary or a testis appears (week 7/8).

In a male, the Y chromosome contains SRY gene that is responsible for the activation of the testis determining factor (TDF). The Sertoli cells are responsible for secreting the MIS which plays an important role in ductal differentiation. Soon after the formation of the testicular cords, stromal mesenchymal cells differentiate into Leydig cells, which begin producing testosterone at week 10.

In females, the absence of the SRY gene ultimately results in the formation of an ovary. By the 9th or 10th week, the formation

of an ovary can be recognized by the absence of testicular features and the meiotic activity of the germ cells (formation of oogonia).

Ductal Differentiation (Fig. 70)

Both the Wolffian ducts and the Müllerian duct systems are present early on differentiation.

In males, the production of MIS causes the degeneration of the Müllerian duct system in an ipsilateral manner. The Wolffian duct is believed to be maintained exclusively by the production of testosterone. By the 7th week, the Wolffian system develops into the epididymis, vas deferens, seminal vesicles and ejaculatory ducts.

In females, the absence of MIS allows for the preservation of the Müllerian duct system. Müllerian duct matures into the Fallopian tubes, uterus and the upper vagina by the 8th week.

External Genitalia

The differentiation of the external genitalia begins at week 8, which results in recognizably female or male genitalia by 3 months.

In males, androgen stimulation during 9th week through 12 results in masculinization of the external genitalia.

- The genital tubercle elongates to form the phallus, while the urogenital folds elongate and fuse, resulting in the formation of the penile urethra
- The corpus spongiosum is a result of the differentiation of the mesenchymal masses around the penile urethra
- At the end of the 3rd month, a fold of skin from the base of the glans penis will have grown distally and created the prepuce
- The scrotum is the result of genital swelling with fusion and rogation.

Feminization of the external genitalia (which in fact reflects a lack of masculinization), begins during 8th week due to the absence of androgen production (or its bioavailability).

- The genital tubercle matures into the clitoris, and the labia majora develop from the genital swellings
- The caudal urogenital sinus shortens and widens to become the vaginal vestibule and the urogenital folds develop into the labia minora.

DISORDERS OF SEX DEVELOPMENT (DSDs)

Disorders of sex development are defined as a congenital condition associated with atypical chromosomal, gonadal or anatomical sex. According to *Intersex Society of North America* DSDs are defined as conditions involving the following elements:

- Congenital development of ambiguous genitalia (e.g. 46,XX virilizing CAH; clitoromegaly; micropenis)
- Congenital disjunction of internal and external sex anatomy (e.g. complete androgen insensitivity syndrome; 5α-reductase deficiency)
- Incomplete development of sex anatomy (e.g. vaginal agenesis; gonadal agenesis)
- Sex chromosome anomalies (e.g. TS; Klinefelter syndrome; sex chromosome mosaicism)
- Disorders of gonadal development (e.g. ovotestes).

Nomenclature (Table 19)

In previous literature, the commonly used terms were "ambiguous genitalia," "intersex" or "hermaphroditism", etc. These are unhelpful, and perceived to be derogatory by some affected families. In its place, a consensus statement recommends the term "*disorder of sex development*", a generic definition encompassing any problem noted at birth where the genitalia are atypical in relation to the chromosomes or gonads. The karyotype is used as a prefix to define the category of DSDs, replacing the mysterious terminology of male or female pseudohermaphroditism (now known as XY DSDs or XX DSDs, respectively). The new nomenclature has provided a simple and logical classification of the causes of DSDs.

Based on the underlying etiopathogenesis in the process of fetal sex differentiation, DSDs may be endocrine-related or not.

Non-endocrine disorders derive from the abnormal morphogenesis of the urogenital primordia, i.e. malformative DSDs. Endocrine causes include disorders resulting in

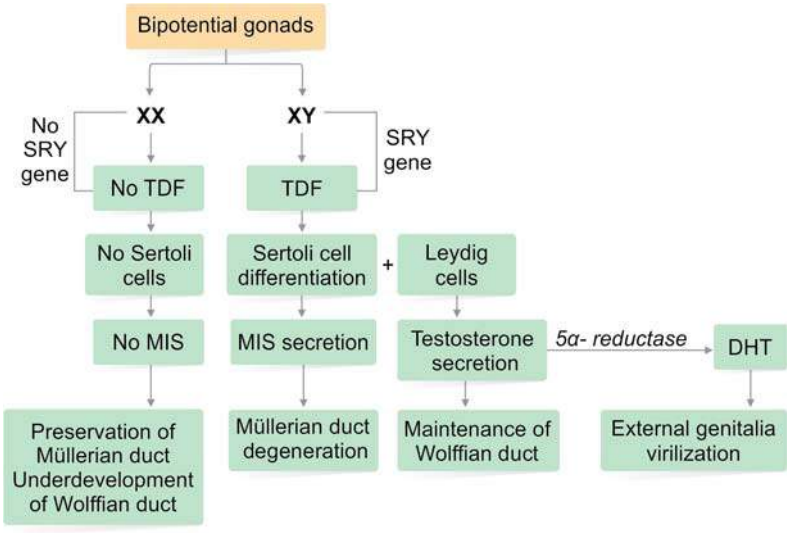


Fig. 70: Ductal differentiation

Abbreviations: SRY, sex-determining region Y chromosome; TDF, testis determining factor; MIS, Müllerian inhibiting substance; DHT, di-hydrotestosterone (potent androgen)

insufficient production or action of testicular hormones. DSDs due to impaired production of fetal male hormones reflect an early-onset hypogonadism, whereas end-organ defects explain impaired virilization of the genitalia in the presence of normal male hormone levels.

Table 19: Nomenclature relating to disorders of sex development

Previous nomenclature	Proposed terms
Intersex	DSDs
• Male pseudohermaphrodite • Undervirilization of an XY male • Undermasculinization of an XY male	46,XY DSDs
• Female pseudohermaphrodite • Overvirilization of an XX female • Masculinization of an XX female	46,XX DSDs
True hermaphrodite	Ovotesticular DSDs
XX male or XX sex reversal	46,XX testicular DSDs
XY sex reversal	46,XY complete gonadal dysgenesis

Abbreviations: DSDs, disorders of sex development

When abnormal gonadal ridge differentiation and testis development occur, early-onset fetal hypogonadism involves all testicular cell populations and the condition is known as dysgenetic DSDs.

Classification of DSDs

The etiological classification of DSDs is shown in the Table 20.

Pathophysiology of DSDs

Three major categories of developmental aberrations are responsible for the most common forms of DSDs in newborns:

1. In the first category, genetic females are masculinized by an overabundance of androgenic steroid production, causing a genital abnormality that requires highly specialized medical or surgical management (or both).
2. In the second category, DSDs occur because of deficient androgen production or action in genetic males.
3. The third category of abnormalities results from mutations leading to absent, incomplete or asymmetric gonadal differentiation.

Table 20: Etiological classification of disorders of sex development

Sex chromosome DSDs	46,XY DSDs	46,XX DSDs
45,X (Turner syndrome and variants)	Disorders of gonadal (testicular) development: • Complete or partial gonadal dysgenesis (SRY, SOX9, SF-1, WT1, DHH, TSPYL1, DAX1 dupl, WNT_4 dupl, 9p24 del) • Gonadal/testis regression • Ovotesticular DSDs • Ovarian DSDs (CBX2)	Disorders of gonadal (ovarian) development: • Gonadal dysgenesis (FSHR, BMP15, SF-1) • Testicular DSDs (SRY^+, SOX9 dup, RSPO1) • Ovotesticular DSDs
47,XXY (Klinefelter syndrome and variants)	Disorders of androgen synthesis and action: 1. Disorders in androgen synthesis • Leydig cell hypoplasia, aplasia (LHCGR, LH/choriogonadotropin receptor) • Congenital lipoid adrenal hyperplasia (STAR) • Cholesterol side-chain cleavage deficiency (CYP11A1) • 17α-hydroxylase/17,20-lyase deficiency (CYP17A1) • 3β-hydroxysteroid dehydrogenase 2 • 17β-hydroxysteroid dehydrogenase deficiency • 5α-reductase 2 deficiency (SRD5A2) • P450 oxidoreductase deficiency • Smith-Lemli-Opitz syndrome (DHCR7) 2. Disorders of androgen action • Androgen insensitivity syndrome (AR, androgen receptor) • Drugs and environmental modulators	Androgen excess: 1. Fetal • 21-hydroxylase deficiency (CYP21A2) • 3β-hydroxysteroid dehydrogenase 2 (HSD3β2) • 11β-hydroxylase deficiency (CYP11β1) • P450 oxidoreductase deficiency • Glucocorticoid receptor mutations (GR) 2. Fetoplacental • Aromatase deficiency (CYP19) • P450 oxidoreductase deficiency 3. Maternal • Maternal virilizing tumors (e.g. luteomas) • Androgenic drugs
45,X/46,XY (mixed gonadal dysgenesis, ovotesticular DSDs)	Others: • Persistent Müllerian duct syndrome (AMH and AMHR) • Vanishing testis syndrome • Congenital hypogonadotropic hypogonadism (DAX1) • Cryptorchidism (INSL3, GREAT) • Isolated hypospadias (MAMLD1) • Syndromic associations of male genital development (e.g. cloacal anomalies, Robinow, Aarskog, hand-foot-genital (HOXA13), popliteal pterygium) • Environmental influences	Others: • Müllerian agenesis/hypoplasia (e.g. MURCS) (WNT_4) • Vaginal atresia (e.g. McKusick-Kaufman) • Uterine abnormalities [e.g. MODY5 (TCF2)] • Labial adhesions • Syndromic associations (e.g. cloacal anomalies)
46,XX/46,XY (chimeric or ovotesticular DSDs)		

Abbreviations: DSDs, disorders of sex development, LH, luteinizing hormone; AMH, anti-Müllerian hormone; AMHR, anti-Müllerian hormone receptor; MURCS, Müllerian duct aplasia, renal aplasia and cervicothoracic somite dysplasia; MODY, maturity-onset diabetes of the young; FSHR, follicle-stimulating hormone receptor; TCF, transcription factor

46,XX DSDs (Over Androgenization of 46, XX Genetic Females)

The most common cause of over androgenization or virilization is a defect in the P450 (heme pigment 450 oxidases, which metabolize multiple substrates) adrenal enzymes responsible for the conversion of progesterones to glucocorticoids and mineralocorticoids, resulting in the syndrome of CAH or adrenogenital syndrome, which is now known as 46,XX DSDs (over androgenization). This syndrome affects both males and females but causes ambiguous genitalia only in females.

The molecular defect in these 46,XX genetic females with adrenogenital syndrome resides in the adrenal glands. The condition presents in a wide clinical spectrum (Fig. 71).

- The ovaries, uterus and Fallopian tubes are normal
- Vagina, however, is foreshortened as a result of having failed to migrate to the perineum. It joins the urethra either at the position of the prostate, if masculinization is severe, or at a more distal position, if masculinization is less severe
- The external genitalia are characterized by variable clitoral enlargement, ranging from trivial to severe; some patients form an almost normal phallus

The labia can be masculinized to form either labioscrotal folds or in the most severe cases, complete scrotal fusion.

46,XY Disorders of Sex Development (Fig. 72)

Under Virilization of the Male (46,XY)

Insufficient masculinization of a 46,XY genetic male can occur due to insufficient testosterone production, an androgen receptor deficiency (previously known as testicular feminizing syndrome), or an inability to convert testosterone to DHT resulting in 46,XY DSDs. Deficiency of androgen production occurs because of genetic enzymatic defects including steroid acute regulatory protein (StAR), resulting in lipoid adrenal hyperplasia (formerly thought to represent defects in cholesterol desmolase, P450scc or CYP11A1), CYP11A1 (20,22 desmolase), CYP17 (17-hydroxylase or lyase), 3β-hydroxysteroid dehydrogenase (3β-HSD), and 17β-hydroxysteroid dehydrogenase (17β-HSD), together and sequentially are responsible for the cascade of metabolism from cholesterol to testosterone.

In these patients, stimulation by chorionic gonadotropin produces little or no testosterone; in contrast, MIS levels are normal or high for age. The testes may be undescended, small or both. Under the influence of normal MIS, there should be non-Müllerian structures. Because of testosterone deficiency, the penis may be small and hypospadiac. Male child may present with female external genitalia with impacted testis in the inguinal canal as inguinal hernia (Fig. 73).

Serum levels of testosterone may be high; MIS may be normal or in some cases, considerably elevated and Müllerian structures are normally regressed. The gonads are symmetric and may be intra-abdominal or descended. However, not all patients are with the 46,XY karyotype.

Abnormalities of Gonadal Development and Differentiation (Fig. 74)

Abnormalities of the sex chromosomes usually manifest as failed, incomplete or asymmetric gonadal differentiation. Patients with these disorders have either bilateral streak gonads, as in 46,XY pure gonadal dysgenesis or asymmetric gonadal development, as in mixed gonadal dysgenesis (MGD) or ovotesticular DSDs.

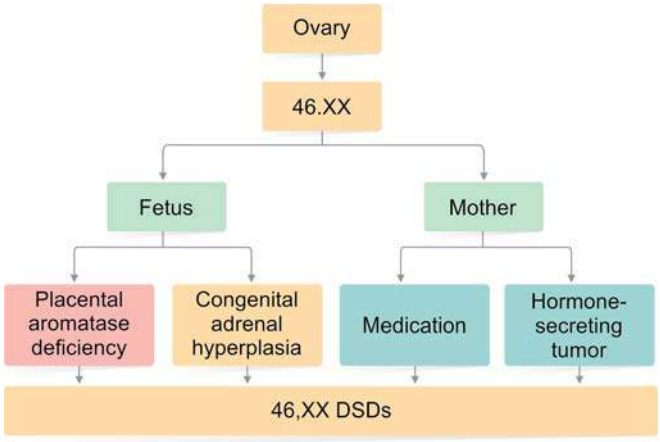


Fig. 71: Disorders of female sex development
Abbreviation: DSDs, disorders of sex development

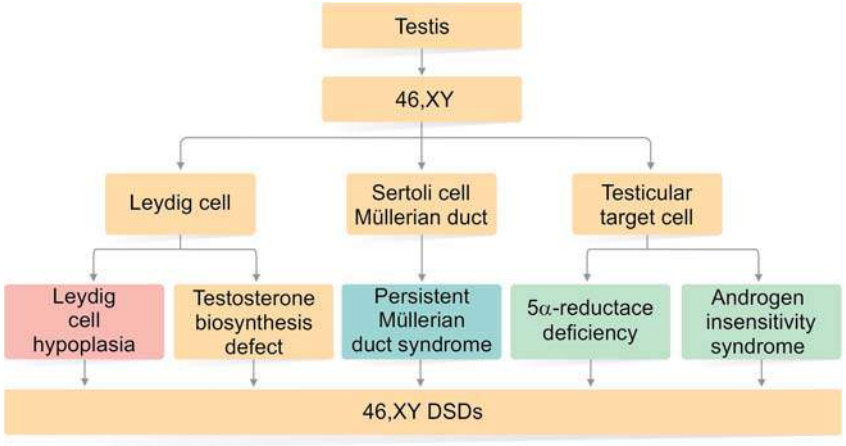


Fig. 72: Disorders of male sex development
Abbreviation: DSDs, disorders of sex development

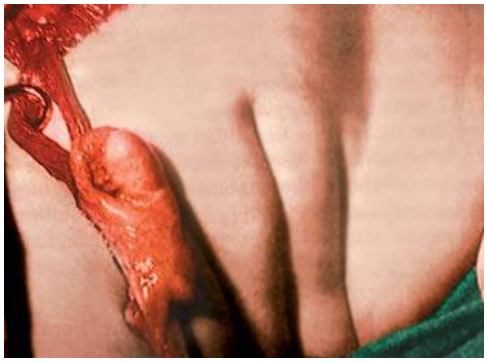


Fig. 73: Female genitalia with testis present as right sided inguinal hernia in androgen receptor deficiency

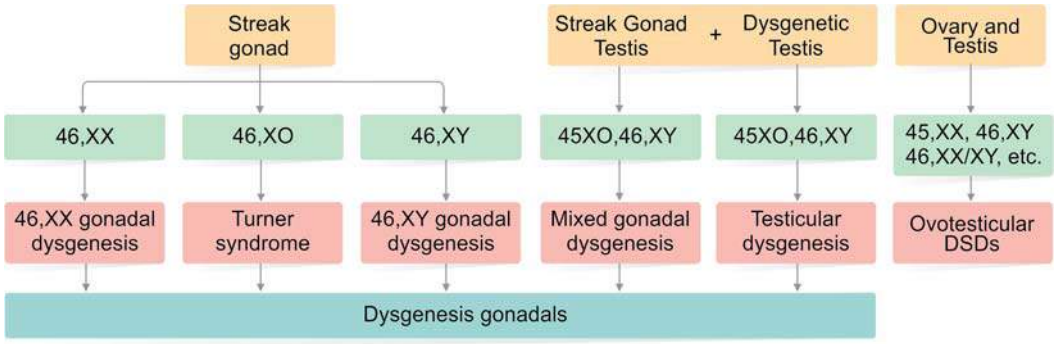


Fig. 74: Abnormalities due to gonadal dysgenesis and differentiation

Abbreviation: DSDs, disorders of sex development

There are two different categories of gonadal dysgenesis—pure and partial.

In Pure (Complete) Gonadal Dysgenesis

The genotype can be either 46,XX, 46,XY, or a TS karyotype (45,XO, or for mosaic Turner 45,XO/46,XX).

In Partial Gonadal Dysgenesis

There is partial testicular development. Partial dysgenesis includes MGD and testicular or ovarian regression. The genotype is often 45,XO/46,XY, although it can be 46,XY.

In *MGD (also known as asymmetric gonadal dysgenesis),* the gonads are asymmetric, most often with a small dysgenetic testis on one side and a streak gonad on the other. Most patients with this defect have retained Müllerian ducts. The small testis can produce enough testosterone to cause masculinization and hypertrophy of the clitoris.

Ovotesticular DSDs

True ovotesticular DSDs (true hermaphrodites) are rare. More than 90% of these patients have a 46,XX karyotype. Asymmetry characterizes many of these patients, who have simultaneous ovarian and testicular differentiation without the dysgenesis characteristic of MGD.

- The testicular and ovarian tissue can be separated on both sides or combined in one or both gonads as an ovotestis
- When ovarian tissue and testicular tissue coexist in the same gonad, the testis is always central and the ovarian tissue is polar
- The Müllerian structures are regressed on the side of the testicular tissue but retained on the side of the ovarian tissue and in the midline as well, with the vagina entering the distal urethra as a urogenital sinus defect.

Diagnosis of DSDs

In the newborn period, in particular, when an infant is born with ambiguous genitalia reflecting a possible diagnosis of DSDs, there is felt a sense of urgency to provide the family with not only the specific diagnosis but in conjunction a gender assignment. This urgency arises from the cultural pressures that necessitate the usual announcement of "It's a boy" or "It's a girl" to friends, family and colleagues.

History

- Family history
  - Consanguinity
  - Infertility
  - Gonadal/urogenital malformations
- Maternal history
  - Past pregnancy history
  - Antenatal drug use
- Maternal symptoms suggestive of androgen excess.

Physical Examination

- General health
- Extragenital:
  - Hydration status
  - BP
  - Jaundice
  - Hyperpigmentation of areola

- Genital:
  - Testicular tissue
  - External genitalia using prader staging
  - Length of clitoris/phallus
  - Fusion/rugosity of scrotal folds
  - Vaginal opening/common urogenital sinus
  - Patency of rectum
  - Hyperpigmentation
  - Digital rectal examination for uterus.

Criteria that Suggest DSDs

- Overt genital ambiguity (e.g. cloacal exstrophy)
- Apparent female genitalia with an enlarged clitoris, posterior labial fusion or an inguinal/labial mass (Fig. 75A)
- Apparent male genitalia with bilateral undescended testes, micropenis, isolated perineal hypospadias or mild hypospadias with undescended testis (Fig. 75B)
- A family history of DSDs such as complete androgen insensitivity syndrome (CAIS)
- Discordance between genital appearance and a prenatal karyotype

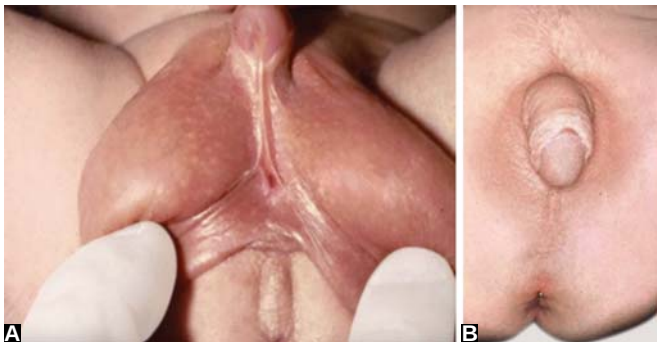
Most causes of DSDs are recognized in the neonatal period; later presentations in older children and young adults include:

- Previously unrecognized genital ambiguity, inguinal hernia in a female
- Delayed or incomplete puberty
- Virilization in a female
- Primary amenorrhea
- Breast development in a male
- Gross and occasionally cyclic hematuria in a male.

Investigations

First-line testing in newborns includes:

- Karyotyping with X- and Y-specific probe detection (even when prenatal karyotype is available)
- Imaging (abdominopelvic ultrasound)
- Measurement of 17-OHP
- Testosterone
- Gonadotropins
- Anti-Müllerian hormone
- Serum electrolytes
- Urinalysis.



Figs 75A and B: (A) Severe clitoral hypertrophy caused by masculinization of the external genitalia of a 46,XX patient with female pseudohermaphroditism caused by CAH; (B) Incomplete masculinization of the external genitalia of a 46,XY patient with male pseudohermaphroditism. There is a microphallus with perineoscrotal hypospadias and bifid and prepenile scrota

The results of these investigations are generally available within hours and will be sufficient for making a working diagnosis. Decision-making algorithms are available to guide additional investigation (Fig. 76).

Gender Assignment in Newborn Infants

Gender identity refers to the intrinsic sense of oneself as female or male.

Gender role refers to the set of behaviors typical of one gender or another, these will vary with context such as the surrounding culture.

Sexual orientation refers to an individual's erotic responsiveness, that is the gender or genders to whom one is attracted (homosexual, heterosexual, bisexual).

Gender identity, gender role and sexual orientation each are components and yet may be distinct.

Initial gender uncertainty is unsettling and stressful for families. Factors that influence gender assignment include:

- The diagnosis, karyotype, gonadal function
- Genital appearance:
  - Phenotype (body habitus, Prader staging of external genitalia)
  - Internal genitalia (i.e. presence of uterus)
- Surgical options
- Risk of future malignancy and prenatal androgen influences on target tissue (including the brain)
- Need for lifelong replacement therapy
- The potential for fertility and sexuality
- Views of the family
- Sometimes the circumstances relating to cultural practices.

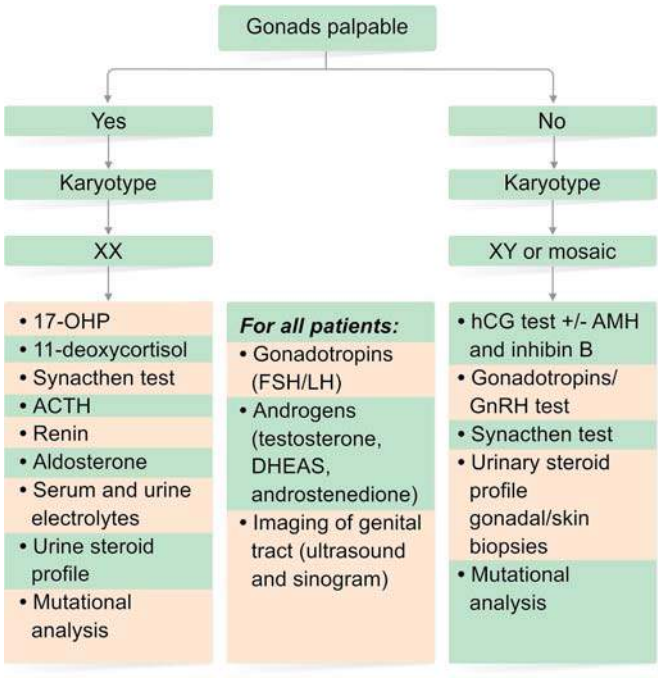


Fig. 76: Algorithm to guide investigation for disorders of sex development

Abbreviations: OHP, hydroxyprogesterone; ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; DHEAS, dehydroepiandrosterone sulfate; GnRH, gonadotropin-releasing hormone; AMH, anti-Müllerian hormone

More than 90% of 46,XX CAH patients and all 46,XY CAIS assigned females in infancy identify as females. Evidence supports the current recommendation to raise markedly virilized 46,XX infants with CAH as female.

Medical Management of DSDs

Recommendations on the optimal management of newborns and individuals with DSDs suggest a multidisciplinary team involvement. These interprofessional teams consist of care providers from pediatric endocrinology, urology, gynecology, genetics, psychology, psychiatry, social work and nursing. Each team may function differently in consultation processes, but it is advisable to have one individual function as a coordinator, assisting families to move through the process with the team, providing consistency of care and information.

For new DSDs patients, the team should develop a plan for clinical management with respect to diagnosis, gender assignment and treatment options before making any recommendations. Ideally, discussions with the family are conducted by one professional with appropriate communication skills.

Support groups have an important role in the delivery of care to DSDs patients and their families.

46,XX DSDs

CAH:

Hydrocortisone: 8–10 mg/m^2/day, with lower-range dosages in toddlers and higher in adolescents.

Fludrocortisone (9α-fluorocortisol): 0.05–0.2 mg/day is started in severely virilized infants and in those less virilized with a family history of salt-wasting as part of 46,XX DSDs (CAH).

46,XY DSDs

Those with 5α-reductase or 17β-hydroxysteroid reductase deficiency, it may not be appropriate to assign a gender at birth.

- Patients assigned to the female gender should receive early surgical correction of the external genitalia and gonadectomy but do not receive hormone therapy until puberty, at which time they will require estrogen and progesterone treatment. Vaginal replacement should be planned for late puberty
- If it is elected to assign these infants to the male gender, 25 mg of testosterone enanthate or cypionate is given once every 3 or 4 weeks for about three doses to confirm that the penis responds to androgens or to improve the size of the penis before surgery.

Chromosomal abnormalities

- Patients with MGD or ovotesticular disease assigned to the:
  - Female gender: No steroidal replacement is required in childhood
  - Male gender: Presurgical testosterone stimulation of the penis may be required before hypospadias repair

  Treatment does not recommence until adolescence. If the patient is assigned to the female gender, replacement of estrogen and progesterone is started at adolescence
- Patients with 46,XY pure gonadal dysgenesis: Require neither surgical nor medical therapy as newborns, and estrogen and progesterone replacement begins at adolescence
- Adrenal replacement therapy may be complex in patients with SF-1 mutations characteristic of the adrenal hypoplasia congenita syndrome
- Vaginal replacement should be planned for late puberty.

Surgical Treatment of Disorders of Sexual Differentiation

Patients with DSDs who have anatomic problems, such as clitoral enlargement and labial fusion, are a source of great concern and challenges for parents, patients and the medical team involved in their treatment.

Preoperative Evaluation

- Imaging studies: Retrograde genitogram
- Laparoscopy: It is helpful for identification or removal of Müllerian structures.

Surgical Reconstruction

Panendoscopy: Each reconstructive procedure is preceded by a panendoscopy using a pediatric cystoscope.

- Patients with 46,XX DSDs, MGD, and ovotesticular DSDs have a cervix at the most proximal part of the vagina
- Patients with 46,XY DSDs have either a small prostatic utricle or a deeper, more generous cavity that has no proximal cervix.

Reconstruction for female gender assignment: All 46,XX DSDs newborns should be assigned to the female gender, regardless of the extent of masculinization, and undergo surgical reconstruction consistent with the female gender assignment.

Reconstruction for male gender assignment: The treatment strategy is similar for all patients assigned to the male gender. Most of these patients have a small penis with a penoscrotal, scrotal or perineal hypospadias; a severe ventral curvature; and a partial or complete prepenile scrotum. The dorsal foreskin is redundant and the glans is often split, lacking its normal conical configuration.

Müllerian duct remnants: Surgical treatment of Müllerian duct remnants is required in patients with severe hypospadias, ovotesticular disease or MGD who have been assigned the male gender. The retained Müllerian ducts can become quite enlarged, leading to recurrent urinary tract infections, epididymo-orchitis, urinary retention, secondary incontinence due to urine trapping and infertility.

Gonadectomy: Gonadectomy would be recommended when the gonads are inconsistent with the sex of rearing.

Psychosocial Management

Psychosocial care provided by mental health staff with expertise in DSDs should be an integral part of management to promote positive adaptation.

The process of disclosure concerning facts about karyotype, gonadal status and prospects for future fertility is a collaborative. It should be planned with the parents from the time of diagnosis.

Outcome of DSDs

Long-term outcome in DSDs should include external and internal genital phenotype, physical health including fertility, sexual function and social and psychosexual adjustment,

mental health, quality of life and social participation. There are additional health problems in individuals with DSDs, including the consequences of associated problems such as other malformations, developmental delay and intellectual impairment, delayed growth and development and unwanted effects of hormones on libido and body image.

Surgical Outcome

- Outcomes from clitoroplasty identify problems related to decreased sexual sensitivity, loss of clitoral tissue and cosmetic issues
- Techniques for vaginoplasty carry the potential for scarring at the introitus necessitating repeated modification before sexual function can be reliable
- The outcome in undermasculinized males with a phallus depends on the degree of hypospadias and the amount of erectile tissue
- Feminizing genitoplasty as opposed to masculinizing genitoplasty requires less surgery to achieve an acceptable outcome and results in fewer urologic difficulties.

Psychosexual Outcomes/Quality of Life Measures

Quality of life for women includes aspects of intimacy with partners, arousal and sexual function, as well as self-esteem, social functioning and mental health. Women with DSDs may show fewer partnerships and delayed sexual milestones.

Overall quality of life is lower than in population control with higher anxiety and lower self-esteem. Mental health and social functioning may also be adversely affected.

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16 Nephrology

RENAL SYSTEM

The kidneys are bean-shaped organs that lie against the back of the abdominal wall beneath the peritoneum, the membranous connective tissue sheet that lines the abdominal cavity and reflects back over all of the intestines.

Development of Human Kidney

Human kidney development begins at the fifth week of gestation. The first functioning nephrons are formed by week 9. Nephrogenesis is completed by 32–34 weeks.

Anatomy of Kidney (Fig. 1)

All functions of the kidney occur in miniature small functional units called nephrons.

The blood supply is provided by the renal artery that comes directly off the abdominal aorta and is drained by the renal vein that drains into the inferior vena cava. These large vessels divert about 20% of the cardiac output, or about 1 L/min to the kidneys.

Structure of Kidney

A longitudinal cross-section of the kidney shows two easily distinguished parts (Fig. 2):

- *Cortex*
  - Lies beneath the tough renal capsule
  - Has a reddish-brown and granular appearance
  - Contains many glomeruli, which are little balls of capillaries and crammed together and surrounded by a thin epithelial capsule, called Bowman's capsule.
- *Medulla*

The medulla consists of an outer part and an inner part. The outer part of medulla has a striated appearance due to tubules running from the cortex down into the medulla. The tubules collect into structures called renal pyramids. Each kidney typically has 8–10 of these renal pyramids.

The tubules coalesce into progressively larger tubules, the collecting ducts, which in turn, fuse to form ducts of Bellini, which pierce through the apex of the renal pyramids in a series of 18–24 tiny holes in each pyramid. This flattened area of the renal pyramid that is pierced by the ducts of Bellini is called the cribriform area.

Urine in its final stages passes through the tiny orifices in the cribriform area to reach a minor calix (from the Greek "kalyx," meaning "cup").

Two or more minor calices fuse to form a major calix. The urine eventually is collected into the ureters, which drain into the urinary bladder.

The ureter is a tube that contains smooth muscle. The ureters can actively propel the urine into the bladder by peristalsis, a wave of muscular contraction that begins in the kidney and continues to the urinary bladder, which also has a layer of smooth muscle.

The urine is stored in the bladder and voided to the outside of the body through the urethra.

Urination requires the active contraction of the bladder and relaxation of the urinary sphincters.

Renal Physiology

Intact glomerular filtration and tubular function (proximal tubule, loop of Henle and distal tubule) regulate normal renal function (Fig. 3). Urine formation results from

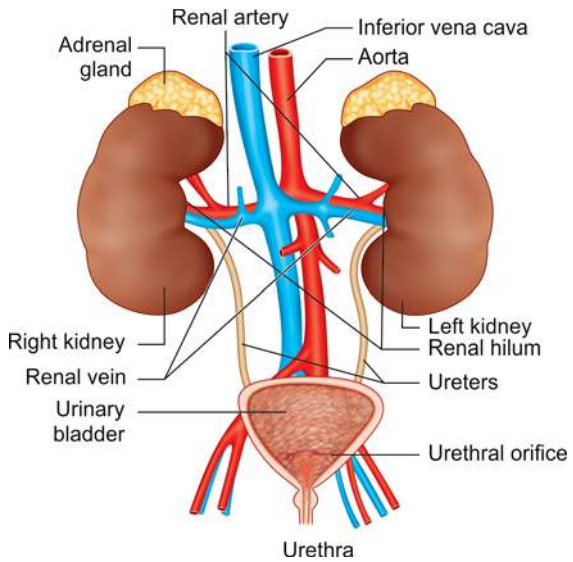


Fig. 1: Anatomical representation of kidneys with surrounding structures

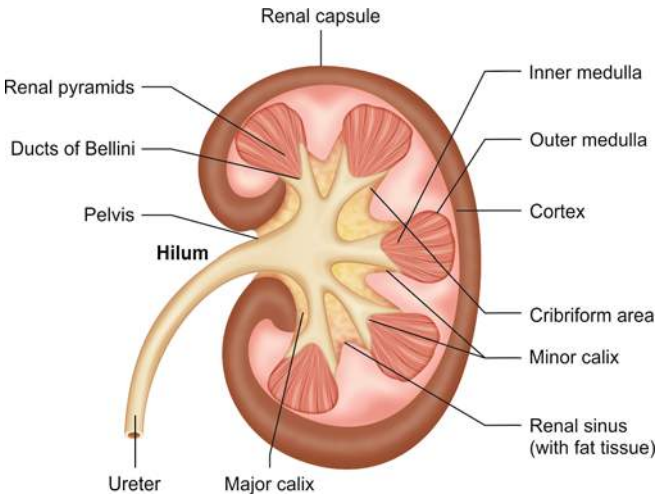


Fig. 2: Longitudinal section of a kidney showing gross structure

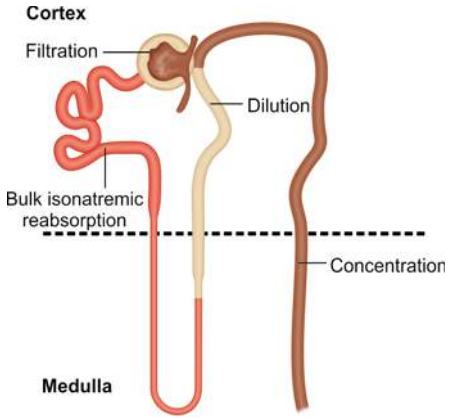


Fig. 3: Schematic diagram of a nephron showing its major parts and principal functions

glomerular filtration and "fine-tuning" of filtrate along the tubules. Glomerular filtration results from a net pressure in the glomerulus that favors movement of fluid out of the capillaries. Tone of the afferent arteriole and efferent arterioles, particularly the latter, regulates the intraglomerular pressure.

Proximal Tubule

- Site for isosmotic reabsorption of the glomerular filtrate
- Approximately two-third of the filtered volume is reabsorbed in the proximal tubule
- Substances reabsorbed from proximal tubule are:
  - Completely: Glucose and amino acids
  - Near complete: Potassium
  - Mostly: Phosphate and bicarbonate
- Secretion of following substances occur:
  - Organic acids and penicillin.

Loop of Henle

- Twenty-five percent of sodium chloride is reabsorbed here.
- Active chloride transport is the principal mechanism that "fuels" the countercurrent multiplier and consequently the medullary interstitial hypertonic gradient required for urinary concentration.

Distal Tubule

1. *Distal convoluted tubule:*
   - It is water impermeable.
   - It contributes to the dilution of urine by active sodium chloride absorption, driven by a different mechanism than at the loop of Henle.
2. *Collecting ducts:*
   - It is the primary site of antidiuretic hormone activity, which produces concentrated urine.
   - It is also the site of active hydrogen ion secretion, which is responsible for the final acidification of the urine.

Major Function of Kidneys

The three major functions of the kidneys comprise:

1. Maintenance of a constant extracellular environment for optimum cell functioning or homeostasis.
2. Hormone secretion (including erythropoietin for red blood cell (RBC) production; renin and angiotensin II affecting renal and systemic hemodynamics; and hydroxylated vitamin D affecting calcium, phosphate and bone metabolism)
   - Erythropoietin is secreted in response to hypoxia
   - Vitamin D is activated by hydroxylation which is again stimulated by parathyroid hormone (PTH) and by low plasma inorganic phosphate.
3. Miscellaneous functions include gluconeogenesis and peptide hormone catabolism.

- Gluconeogenesis: Produces glucose during fasting by converting amino acids into glucose.
- Degradation of several polypeptide hormones including angiotensin II, parathyroid hormone, insulin and glucagon.

Overview of Investigations for Renal Function

- *Urinalysis*
  It is easy and useful method of screening for several renal abnormalities.
  - *Macroscopic urinalysis*:
    1. Dipstick tests: It detects the presence of protein, blood and glucose
    2. Nitrate test: Detects bacteriuria if the bacterium reduces nitrate to nitrite
    3. Leukocyte esterase test: Detects the presence of white blood cells
  - *Microscopic urinalysis*: To detect pyuria and verify hematuria (presence of RBCs), casts and crystals
  - *Specific gravity (SG)*: It reflects the concentrating and diluting ability of the kidney. In normal conditions, it reflects a person's hydration status
  - *Urinary pH*: Usually ranges from 5–8 depending on the acid-base balance of the body and can be estimated using the reagent test strip
- *Plasma creatinine concentration*
  - Rises progressively throughout childhood according to height and muscle bulk
  - Plasma creatinine may not rise above normal for age until renal function has fallen to less than half normal
- *Glomerular filtration rate (GFR)*
  A rough estimate of GFR can be obtained using the formula:

$$\frac{\text{Height (in cm)} \times 40}{\text{Plasma creatinine}\left(\mu\frac{\text{mol}}{\text{L}}\right)}$$

More accurate measurement of GFR is by measuring the clearance from the plasma of a substance that is freely filtered at the glomerulus and is not secreted or reabsorbed by the tubules (e.g. inulin, EDTA). The need for repeated blood tests limits its use in children (Table 1).

- *Creatinine clearance*
  Rarely measured in children because of the difficulties in collecting a complete, timed urine sample
- *Radiological investigation of the kidneys and urinary tract*
  - *Plain X-ray of abdomen involving kidney, ureter and bladder (KUB) region*: Useful for detection in calculi, abdominal mass, sacral agenesis and spina bifida.
  - *Ultrasonography (USG)*:
    - Noninvasive procedure for anatomical assessment of the whole urinary tract

Table 1: Normal GFR in neonates, children and adolescents

Age	Mean GFR ± SD (mL/min/1.73 m^2)
29–34 weeks gestational age (GA) 1 week postnatal age	15.3 ± 5.6
29–34 weeks GA 2–8 weeks postnatal age	28.7 ± 13.8
29–34 weeks GA >8 weeks postnatal age	51.4
1 week term males and females	41 ± 15
2–8 weeks term males and females	66 ± 25
>8 weeks term males and females	96 ± 22
2–12 years (males and females)	133 ± 27
13–21 years (males)	140 ± 30
13–21 years (females)	126 ± 22

  - Information about kidney function cannot be obtained
  - Accuracy is operator-dependent.
- *Pulsed Doppler studies*:
  - Arterial and venous blood flow can be assessed
  - Can be used to calculate a resistive index within the kidneys.
- *Functional scanning*:
  - Radioisotopes give a lower radiation dose than conventional X-rays
  - Comparison of individual kidney function can be noted
  - Good images are difficult to obtain in the first month of life.
- *Intravenous urography (IVU)*:
  - Detailed anatomy of the calyces or ureter can be obtained
  - Currently used infrequently, replaced by radioisotope imaging and magnetic resonance imaging (MRI).
- *Micturating cystourethrography (MCUG) or voiding cystourethrography (VCUG)* (Fig. 4):
  - It is a gold standard investigation to detect vesicoureteric reflux (VUR), also detects posterior urethral valve (PUV) and delineates bladder outline
  - Requires catheterization of bladder which can be distressing
  - Elevates risk for urinary tract infection (UTI) and radiation hazards

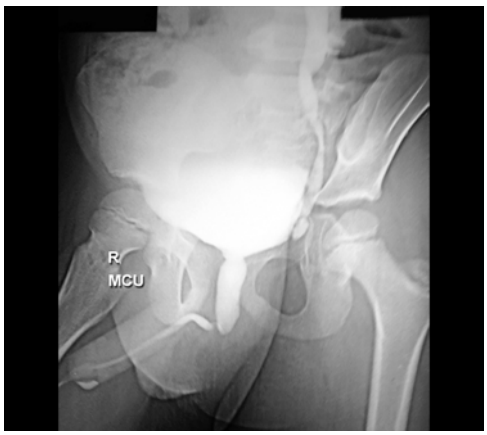


Fig. 4: Micturating cystourethrography showing posterior urethral valve with VUR better seen on left side. The bladder catheter is also visible

- *Radio nuclear imaging*:
  - Radio nuclear imaging of kidney and urinary tract has been simplified. Radionuclide studies have replaced conventional radiological studies like IVU.
  - They are highly sensitive, noninvasive and exposes patients to less radiation compared to radio contrast studies
  - The compounds used include, dimercaptosuccinic acid (DMSA), diethylenetriaminepentaacetic acid (DTPA) and mercapto-acetyltriglycine (MAG3), are labeled with radioactive material ^{99M}Technitium
- *Static nuclear medicine scanning*:
  - Isotope-labeled substance (e.g. DMSA) is incorporated into the functioning renal tissue (Fig. 5)
  - It is particularly good for the detection of renal scars.
- *DMSA*
  - It is helpful for identifying ectopic kidney and confirming non-functional kidney
  - Duplex kidney can also be identified
  - Sensitive to identify scar due to UTI (reflux nephropathy). However, controversy exists over the optimum timing of DMSA scanning following UTI. Early scar may be detected by DMSA scan within first week of UTI. Acute changes may persist for up to 6 months and may advocate delay in scan until 6 months post UTI.
- *DTPA scan*

  A DTPA renogram is useful for evaluating perfusion and function of each kidney. Obstruction to urine flow can be diagnosed by challenging the flow of urine by IV frusemide or captopril. Normally there is a prompt washout of the radionucleotide but these clearing may not occur in subjects with upper urinary tract obstruction (UTO).
- *MAG3*
  - Provides highly satisfactory information of renal structures and function
  - Indirect cystography can be performed using IV MAG3 (as a part of dynamic investigation) to detect VUR, with minimal radiation exposure than radiocontrast MCUG and also avoiding the need for catheterization (Fig. 6).

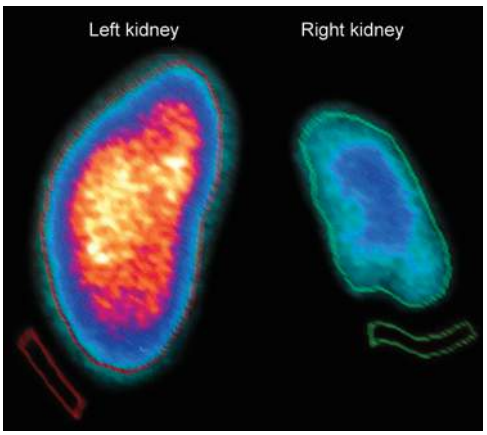


Fig. 5: Dimercaptosuccinic acid showing loss of volume of right kidney. Left kidney is normal

Fig. 6: A view of indirect radioisotope (MAG-3) cystogram

- However, following are the drawbacks of MAG3:
  - ◊ Child need to be fully continent
  - ◊ Lower grade of VUR may be missed out, therefore, cannot be used for grading of VUR
  - ◊ The investigation does not generate information about posterior urethral anatomy

– *Cross-sec tional imaging*

– *Computed tomography (CT) scan*
- Excellent modality for imaging renal parenchyma
- Method of choice for assessment of renal mass and renal trauma
- Renal calculi can be clearly identified which can be missed out in ultrasonographic examination
- There is significant radiation hazard.

– Magnetic resonance imaging
- It can be used for the assessment of renal parenchyma and function through MR renography or drainage system MR urography.
- It is not associated with radiation hazards.

DISORDERS OF RENAL SYSTEM

The disorders of the renal system can be broadly classified under following headings:

- Disorders of renal development
- Disorders of glomerular function
- Renal tubular disorders
- Tubulointerstitial disorders
- Disorders of urinary tract

DISORDERS OF RENAL DEVELOPMENT

Developmental abnormalities of the renal tract account for 30–50% of end-stage renal disease in children. Depending upon gross and microscopic anatomical features, a generally accepted classification scheme consists of:

- Renal agenesis
- Simple renal hypoplasia
- Renal dysplasia
- Renal dysplasia/hypoplasia (hypodysplasia)

Epidemiology

The incidence of renal and urinary tract malformations is 0.3–1.6 per 1,000 live-born and stillborn infants. Lower urinary tract abnormalities are found in about 50% of affected patients and include VUR (25%), ureteropelvic junction obstruction (11%) and ureterovesical junction obstruction (11%).

Renal Agenesis

I. Bilateral Renal Agenesis

During fetal life, bilateral failure of primary nephrogenesis causes a characteristic pattern of facial compression and pulmonary hypoplasia (Potter syndrome) due to the absence of amniotic fluid (Fig. 7).

Presentation:

- Severe oligohydramnios, evident in the second trimester
- Pneumothorax at neonatal period (due to pulmonary hypoplasia resulting from renal agenesis).

Antenatal diagnosis:

- USG: Severe oligohydramnios can be evident at the second trimester (21–23 weeks)
- High-resolution color Doppler USG: To detect the fetal renal arteries, distinguishing severe renal hypoplasia from renal agenesis
- Antenatal MRI: To detect the full range of renal malformations.

II. Unilateral Renal Agenesis (URA)

It is associated with developmental abnormalities of other tissues, particularly the inner ear, genital tract and axial skeleton. Few of them have an ipsilateral mild-moderate sensorineural hearing deficit and Müllerian ducts anomalies.

Diagnosis

- Nuclear DMSA or MAG3 scanning may identify residual hypoplastic/dysplastic tissue instead of complete URA on the affected side.
- USG or renal scans: Evidence of patchy dysplasia can be detected

III. Multicystic/Dysplastic Kidney (MCDK)

MCDKs are recognized as clusters of multiloculated thin-walled cysts, which do not appear to connect, distinguish them from hydronephrotic kidneys.

Failure of union of ureteric bud gives rise to MCDK. The ureteric bud with the renal mesenchyme results in a nonfunctioning kidney that is replaced by large

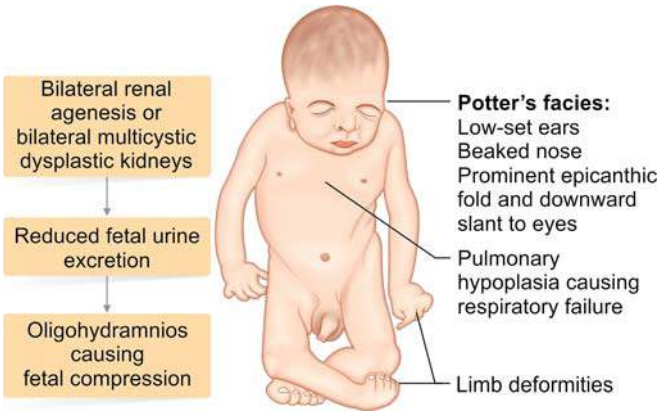


Fig. 7: Bilateral renal agenesis in Potter sequence

communicating cysts of varying sizes with no renal cortex and an atretic ureter (Fig. 8).

It is twice more common in male than female.

Presentation: It appears as a unilateral mass on routine neonatal examination.

Investigation:

USG: Large non-communicating cysts of varying size with no renal parenchyma.

DMSA scan: Absence of renal function on the affected site. If function is present the diagnosis may be severe pelviureteric junction obstruction (PUJO) with "cysts" being dilated calyx.

Micturating cystourethrogram: Indicated prenatally or postnatally if there is suspicion of dilatation of ureter.

Management:

Medical:

- Kidney less than 5 cm usually involute or cause no problem
- Management of hypertension, if any

Review and follow-up annually (BP, urine dipstic test for protein and USG).

Surgical: Surgical option is nephrectomy by laparoscopy at around 12 months of age.

Indications for surgery:

- No involution beyond 2 years
- Appearance of complications like infection and hypertension.

Prognosis: Involution of MCDK may occur in utero or postnatally, usually by 2 years of age. Depending upon size:

- MCDKs less than 5 cm involutes usually
- MCDKs 5–7 cm may involute
- MCDKs greater than 7 cm rarely involutes.

Complications:

- Contralateral VUR in 25% cases
- Malignant transformation
- Transformation into Wilms tumor, adenocarcinoma and embryonal carcinoma
- Hypertension
- Larger cyst may cause bleeding or rupture.

Renal Hypoplasia

These may be primary or associated with other renal diseases.

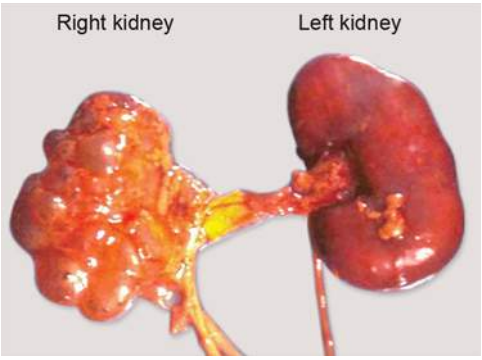


Fig. 8: Nonfunctional multicystic/dysplastic right kidney and grossly normal-appearing left kidney from an infant

I. Primary Renal Hypoplasia

a. Renal coloboma syndrome: There is dysplasia and glomerular hypertrophy is presumably the compensatory response to the deficit in nephron number.

b. Branchiootorenal syndrome:

- Autosomal recessive disorder
- Characterized by variable degrees of renal hypoplasia with branchial arch defects (lateral cervical fistulas or cysts) and a hearing disorder associated with malformed auricle, atresia of the ear canal, anomalies of the middle ear and hypoplasia of the cochlea or semicircular canals
- Renal hypoplasia may be very subtle or may cause end-stage renal failure between 12 and 36 years of age.

c. Renal tubular dysgenesis (RTD): RTD is restricted to specific nephron segment.

Pathology: Autosomal recessive mutation of genes in the renin-angiotensin pathway

Features:

- Severe hypotension
- Potter sequence
- Fetal oliguria is accompanied by cranial hypoplasia (cranial suture diastasis).

Management: Fresh frozen plasma transfusion and peritoneal dialysis (PD).

II. Renal Hypoplasia/Dysplasia due to Fetal Urinary Tract Obstruction

It is seen most commonly in male babies with posterior urethral valves. Other causes of UTO are:

- Prune belly syndrome
- Urethral atresia

III. Syndromic Renal Hypoplasia/Dysplasia

Renal hypoplasia may be associated with several syndromes like:

- VATER syndrome (vertebral defects, anal atresia, tracheoesophageal fistula and renal dysplasia)
- VACTERL syndrome (with additional limb and cardiac defects)
- HDR syndrome (hypoparathyroidism, deafness and renal anomalies)
- Townes-Brocks syndrome
- Nail-patella syndrome
- Perlman syndrome (renal dysplasia and Wilms tumor are associated with fetal gigantism and multiple congenital anomalies).

STRUCTURAL ANOMALIES OF THE URINARY TRACT

Horseshoe Kidney

In this type of abnormality the lower ends of both the kidneys are fused with a narrow isthmus over the midline and thus placed caudally. It may be associated with Turner syndrome.

Presentation

- May be asymptomatic and remains undetected
- Symptomatic cases are usually associated with other congenital anomalies

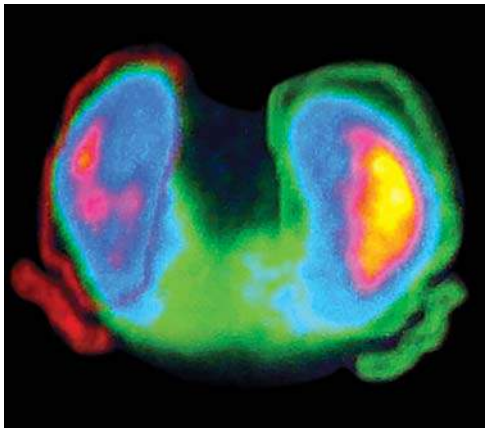


Fig. 9: Isotope scan showing an horseshoe kidney

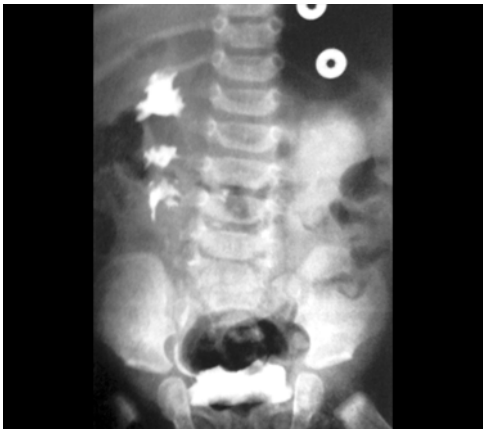


Fig. 10: Intravenous urography showing crossed fused renal ectopia with both collecting system visualized on the right side

- Common presenting features are hematuria, abdominal pain and UTI.

Diagnosis

- Radiological investigations like isotope scan (Fig. 9), IVU, DMSA, CT scan or MRI
- Ultrasonography is not helpful.

Complications

- Pelviureteric junction obstruction leading to obstructive uropathy
- Renal calculi and UTI secondary to obstructive uropathy
- Hypertension increase risk of developing Wilms tumor.

Ectopic Kidney

Away from their normal site, pelvis is the common site for ectopic kidney, hence also termed as pelvic kidney. They result from failure of ascent of the kidney during the period of embryogenesis. These kidneys are not reniform and may be associated with ureteric abnormalities. Children having ectopic kidney are usually asymptomatic.

Crossed Fused Renal Ectopia

It is commonly associated with cloacal and anorectal abnormalities, often with ureteric lesion.

One kidney crosses the midline and lies in an abnormally rotated position, below and medial to the normally sited one with its upper pole fused to the normal kidney's lower pole (Fig. 10). The insertion of ureter from ectopic kidney is normal.

Duplex Kidney

Duplication of ureteric bud gives rise to duplex kidney and collecting systems which may be partial or complex (Fig. 11). In both cases the kidneys are enlarged. In complete, variety two separate pelvicalyceal system with ureters enter the bladder separately (upper pole ureter entering below that of lower pole) and lower pole at risk from reflux and scarring. Dribbling may occur when upper pole ureter terminates ectopically into urethra or vagina. Incomplete duplication results in "uncomplicated" duplex kidney, with either simply a divided pelvis or two ureters that join before entering the bladder.

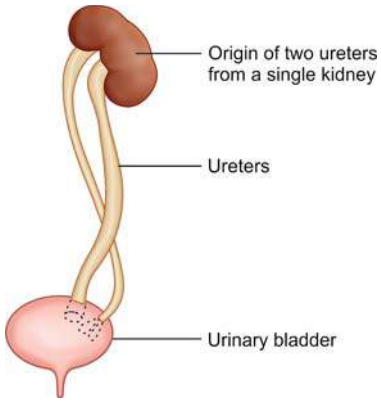


Fig. 11: Kidney with duplex ureter

DISORDERS OF PELVIS, URETERS

Pelviureteric Junction Obstruction

- Commonest cause of obstruction of upper urinary tract. Affects the lower pole PUJ in a duplex kidney
- More common in boys
- Incidence is 1:1000
- May be intermittent, often associated with other renal anomalies like ectopic kidneys, duplex kidneys
- It may be bilateral in 40% of cases.

Presentation

- Antenatally PUJO is the most likely cause of hydronephrosis (Fig. 12).
- Older children
  - Hematuria
  - Acute loin or abdominal pain
  - Palpable flank mass
  - Infection: pyonephrosis
  - Nausea, vomiting

Investigations

USG: Dilated renal pelvis with no dilatation of ureter

MAG3 scan: Confirms the diagnosis

With the presence of obstruction, isotope accumulates within the kidney, and the drainage curve continues to rise even after change of posture or diuretic to encourage drainage.

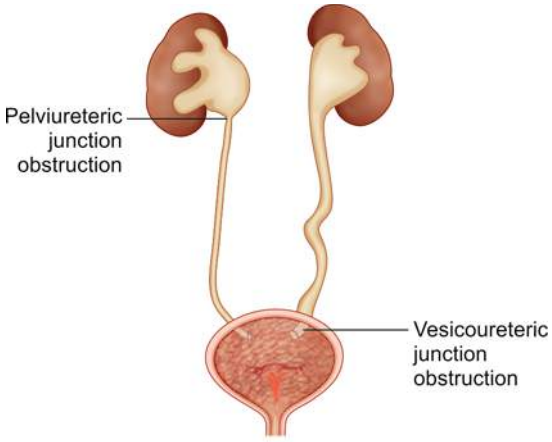


Fig. 12: Pelviureteric junction obstruction causing hydronephrosis

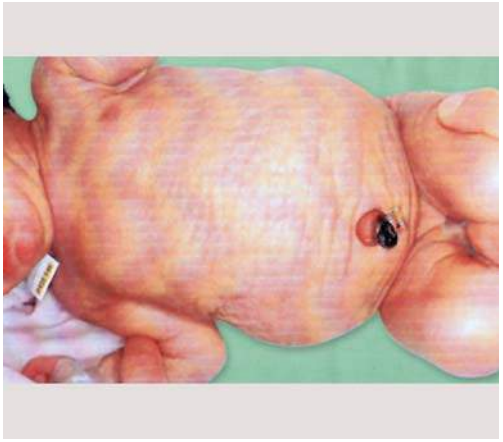


Fig. 13: A baby with prune belly syndrome with absence of abdominal wall muscles

IVU: IVU was the traditional investigation of choice for PUJO, which now has been replaced by radioisotope scanning. Good anatomical and some functional information can be obtained.

Management

Surgery is the treatment of choice. The aim of surgery is to improve the function or to prevent further deterioration of the affected kidney.
The options are:
- Open pyeloplasty (Anderson Hynes)
- Laparoscopic pyeloplasty.

Indications for surgery:

Presence of clinical symptoms
- Fall of differential function of kidney to less than 40%
- Fall of differential function greater than 10% during follow-up
- Increasing dilation of kidney during follow-up.

Megaureter

Megaureter refers to abnormally wide ureter.

Classification

Megaureter is classified into two groups:
- Primary megaureter (PM)
  - Nonobstructed primary megaureter (refluxing)
  - Obstructed or refluxing
- Secondary megaureter due to obstructive lesions like urethral obstruction, bladder outlet obstruction.

Primary megaureter:

- Common in boys
- Commonly involves left ureter
- Bilateral in 25% cases
- Diagnosed antenatlly in routine USG
- Commonly associated with prune belly syndrome with absence of abdominal wall muscles, hypospadias and dilated bladder with VUR (Fig. 13).

Nonobstructive primary megaureter:
- Majority of primary megaureter
- No evidence of VUR
- Treatment: Conservative.

Obstructive primary megaureter:
- Distal ureter is aperistaltic
- Treatment: Surgical correction.

Investigations

- Antenatally: Routine USG
- Postnatally:
  - USG: Hydroureter and hydronephrosis is evident and quantifies the extent
  - MCUG: Vesicoureteric reflex is detected or excluded. Secondary causes, like PUVs, bladder dysfunction, are ruled out.
  - MAG3 scan: To distinguish between obstructed and nonobstructed megaureter
  - IVU: To detect PUJO in obstructed primary megaureter.

Management

- Patients presenting with pyonephrosis and/or pyelonephrosis are treated with systemic antibiotics and drainage of obstructed system by percutaneous nephrostomy. Nephrectomy is considered if the renal function is severely impaired.
- Nonobstructed PM: Conservatively treated as the dilatation will resolve with time.
- Obstructed PM: Surgical treatment is required if there is:
  - Severe urinary sepsis
  - Worsening obstruction with increasing hydronephrosis and deteriorating relative renal function
  - Any symptoms of infection, calculi formation and pain.

Ureterocele

It is a congenital condition in which the terminal part of the ureter distends within the bladder to form a sac, due to an abnormality in the submucosal part of the ureter and stenosis of the ureteric orifice (Fig. 14).

Ureteroceles are more common in girls occurring usually in association with a duplex system.

Posterior Urethral Valves

The incidence is 1/5,000–8,000 male births. Mucosal folds or a membrane obstruct urine flow from the bladder with bilateral hydronephrosis and hydroureter and a thickened bladder wall.

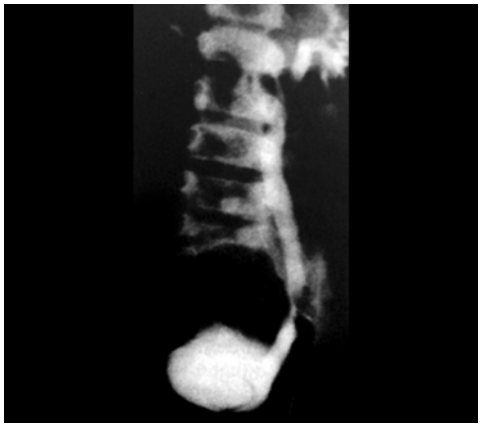


Fig. 14: IVU showing a single moiety in the left kidney with "cobra head" appearance of the ureterovesical junction

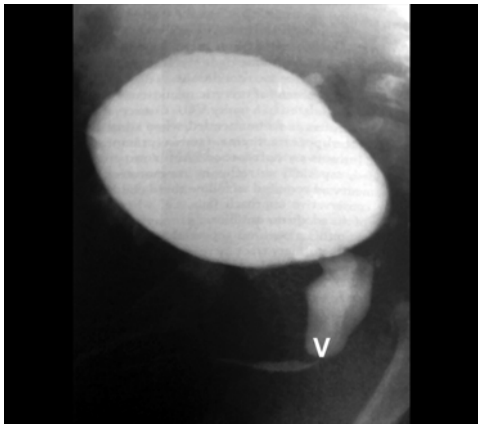


Fig. 15: Posterior urethral valve: MCUG showing dilated posterior urethral valve. The bladder is also hypertrophied and enlarged

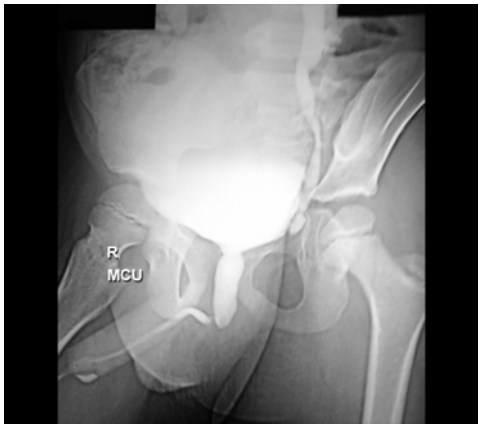


Fig. 16: Micturating cystourethrography showing dilated posterior urethral valve and VUR due to obstruction at posterior urethra

Most are diagnosed on antenatal ultrasound in which case antenatal interventions are an option including vesicoamniotic shunt placement, bladder aspiration and drainage of severe hydronephrosis. Postnatally diagnosed by MCUG (Figs 15 and 16) and treated by catheterization and later valve ablation.

INGUINOSCROTAL DISORDERS

Bladder Exstrophy and Epispadias

- More common in boys than girls
- Incidence is one in 10,000–50,000

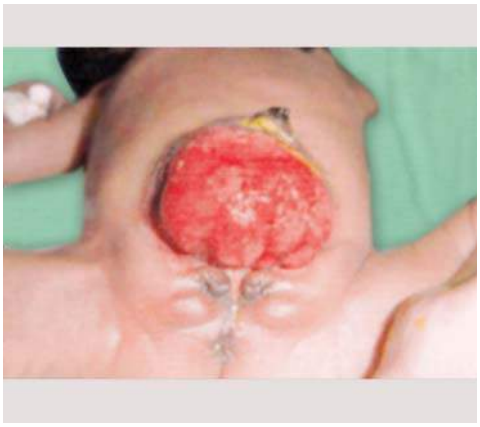


Fig. 17: Bladder exstrophy

- It results from disordered development of the cloacal membrane which is associated with:
  - Defect of lower abdominal wall and anterior bladder wall with outward herniation of posterior bladder wall mucosa (Fig. 17)
  - Anteriorly displaced anus and separation of pubic symphysis
  - Genital anomalies
    Male: Epispadias with dorsal chordee, often bilateral undescended testis
    Female: Epispadias with bifid clitoris.

Treatment

Surgical repair is the treatment. The bladder is repaired in neonatal period followed by multiple operations to enable urinary continence and to reconstruct the genital tract.

Cryptorchidism

Cryptorchidism refers to absence of one or both testes from the scrotum.

- It is a common abnormality affecting boys 7% at birth and 25% in preterm infants.
- Right-sided cryptorchidism is common.
- Unilateral cryptorchidism is four times common than bilateral.

Causes

Causes of cryptorchidism include:
Maldescent of testis: It may be:

- Undescended due to arrest in the normal path near the pubic tubercle, inguinal canal or in the abdomen
- Ectopic, usually in the superficial perineal pouch.

Retractile: Due to an exaggerated cremasteric reflex.

Ascending testis: Due to short spermatic cord pulls up the retractile to previously normal testis.

Anorchidism: Rare condition. Other names are testicular agenesis, anorchia. It occurs due to ischemic necrosis during descent.

Syndromal: Several syndromes are associated with usual bilateral cryptorchidism. They are:

- Prader-Willi syndrome
- Kallmann syndrome
- Bardet-Biedl syndrome
- Prune belly syndrome.

Diagnosis

It is usually noted during physical examination of the newborn and at 6 weeks of life. Penile, femoral and perineal regions are examined carefully to detect ectopic, undescended or retractile testis.

Management

As spontaneous descent is rare after age of 1 year, the treatment should be completed by the age of 12–18 months to preserve fertility.

Medical management: Treatment with human chorionic gonadotropin (hCG) or gonadotropin-releasing hormone (GnRH).

Surgical treatment:

- For palpable testis: Orchidopexy via inguinal route
- For nonpalpabe testis: Examination under anesthesia followed by inguinal exploration ± laparoscopy to find the testis. Modes of surgery are orchidopexy, orchidolysis or removal.

Children above 10 years of age: When a normal testis is present, the intraabdominal testis is to be removed as there is risk of malignancy, torsion and trauma.

Children above 10 years of age with bilateral intraabdominal testis: An attempt is made to move them into the scrotum.

Cloacal Exstrophy

Cloacal exstrophy consists of rudimentary midgut with imperforate anus and lumbosacral defects.

URINARY TRACT INFECTION

Urinary tract infection is an important cause of childhood morbidity affecting 3–10% girls and 1–3% boys. The diagnosis of UTI can easily be missed, which may result in later renal parenchymal damage with scarring, hypertension and other complications. Pediatrician therefore should be aware about the clinical features of UTI and well equipped with knowledge and skill to evaluate UTI.

Over the past 10 years various expert groups have proposed guidelines for evaluation and management of UTI. Significant changes in practice occurred since the guideline was published. Many previous concepts of management and evaluation of UTI have been replaced by new high quality evidence-based findings of management of UTI.

A standard evidence-based clinical practice guideline is essential for optimal management of UTI. However, a clinical practice guideline cannot replace clinical judgement rather it helps in clinical decision making. Therefore a protocolized clinical practice guideline cannot be an absolute guideline for clinical management. Clinical practice is also very much geographical. Evidence-based clinical practice may require to be compromised to some extent depending on the limitation of infrastructure and scarcity of resources particularly in developing countries.

Definitions

- *Urinary tract infection*
  UTI is defined as growth of significant number of uropathogenic organisms of a single species in an appropriately collected urine specimen in the presence of symptoms. Among symptoms, fever is the most common particularly in infants and hence also called febrile UTI. Fever is defined as temperature of at least 38°C (>100.4°F).
- *Recurrent UTI*
  Recurrent UTI is defined as significant growth of bacteria in properly collected urine with symptoms occurring after initial symptomatic UTI.
- *Asymptomatic UTI*
  Asymptomatic UTI or asymptomatic bacteriuria (ABU) is defined as significant bacteriuria in absence of symptoms. Asymptomatic bacteriuria is not considered as true UTI.
- *Complicated UTI*
  Presence of high fever (>39°C), toxicity, vomiting, diarrhea, dehydration, pain in renal angle, raised C-reactive protein (CRP), raised creatinine associated with UTI is considered to be complicated UTI.
- *Simple UTI*
  Patient with low-grade fever, dysuria and urgency of micturition and absence of clinical features of complicated UTI is considered to have simple UTI.

Clinical Features

Clinical features are usually not related to urinary tract in infant and young children.

- Fever; particularly fever without source or focus
- Recurrent abdominal pain
- Vomiting
- Diarrhea
- Poor appetite
- Poor weight gain.

In Neonates and Infants under 3 Months

- Clinical features of sepsis with fever, jaundice, lethargy and feeding problem.

In Older Children

Classical symptoms more related to urinary tract

- Dysuria, urgency, flank pain
- Dysuria without fever is often due to vulvitis in girls or balanitis in uncircumcised boys rather than UTI.

Diagnosis

A febrile infant or a symptomatic young child should be suspected of having UTI when there is no apparent source of infection. The presence of another clinically obvious source of infection like tonsillitis reduces the likelihood of UTI significantly.

Infants below 2 months may present with sepsis, while older children and adolescents usually present with classical features of dysuria, urgency, abdominal and flank pain.

Predictors and Risk Factors of Symptomatic UTI

- Temperature of at least 39°C for at least 2 days
- Absence of another source of infection
- Age less than 12 months, high-risk group if age less than 3 months
- Uncircumcised male child
- Vulval synechiae in girls
- Non-black race.

Confirmation of Presumptive Clinical Diagnosis

The diagnosis of UTI should be confirmed with clinical symptoms with positive culture of properly collected urine specimen. Presence of pyuria increases the sensitivity of culture positivity and differentiates true UTI from asymptomatic bacteriuria.

Criteria for Positive Laboratory Evidence of UTI

The definition of positive and negative culture results are operational and are not absolute. The time the urine resides in bladder is an important factor for the magnitude of colony count.

In Older Children (>2 Years)

Colony count in a specimen 100,000 (10^5) colony-forming unit (CFU)/mm of a single uropathogen obtained by midstream clean-catch method is considered to be significant bacteriuria for the diagnosis of UTI.

In Younger Infant and Newborn

- Urine collected by urethral catheterization which should be done in infant under 2 years of age, appropriate threshold for significant bacteriuria is greater than 50,000 CFU/mm ($>5 \times 10^4$ CFU/mm).
- Any growth in urine culture is considered significant if urine is collected by suprapubic aspiration (SPA).

Is Significant Bacteriuria Enough for UTI Requiring Intervention?

Positive urine culture in absence of clinical symptoms and/or absence of laboratory evidence of inflammation (pyuria) currently considered as asymptomatic UTI rather than true UTI and does not require intervention.

Laboratory evidence of inflammation/infection includes pyuria, positive nitrite test, increased blood CRP, etc.

Essentials of Urinalysis—Some Fallacies and Paradox

Urinalysis is a not substitute of urine culture for the diagnosis of UTI. On the other hand, significant bacteriuria is the diagnostic test for UTI, but it needs to be interpreted in conjunction with urinalysis for evidence of inflammation and to increase the sensitivity of positive culture results. Positive urine culture in absence of pyuria is called ABU not requiring treatment particularly if there is no clinical symptom. Urinalysis is important when clinicians think to start antibiotics promptly in desperate condition in risk UTI, when delay of treatment is potentially risky for significant kidney damage. Depending upon the evidence of UTI in urinalysis, clinician may compel to start antibiotics as culture results are not available for at least 24 hours.

Urinalysis

- Urinalysis is not a substitute of urine culture for the diagnosis of UTI
- The presence or absence of urinary white cells alone is not a reliable feature of UTI, as they may be present in febrile children without UTI and in male children with balanitis or female children with vulvovaginitis without genuine UTI.
- Absence of pyuria does not preclude urine culture. False-negative pyuria in true UTI can occur due to lysis of leukocytes during storage when repeat urinalysis may be required.
- Genuine absence of pyuria with significant bacteriuria in culture particularly without symptom (fever) is suggestive of asymptomatic bacteriuria.
- Asymptomatic bacteriuria is a benign condition and does not require treatment. Current evidence suggests significant bacteriuria in absence of pyuria is not true UTI. On the other hand, febrile children may have pyuria without significant bacteriuria which is also not true UTI.
- Both urinalysis and culture is required to establish the diagnosis of UTI.
- If urinalysis suggests infection (pyuria/bacteriuria) and culture suggests significant bacteriuria from properly collected urine specimen then true UTI is established.

Collection of Urine Specimen for Urinalysis

Unlike for culture, urinalysis can be performed on any urine specimen, including urine collected from a bag applied to perineum (Fig. 18). However, specimen should be fresh (<1 hour after voiding in room temperature or <4 hours after voiding with refrigeration).

Advantages of Urinalysis

- It is a rapid screening test for detecting UTI. It does not require special technique or special procedure to collect urine for analysis. It can be tested in infants in urine collected from an adhesive plastic bag applied to perineum (Fig. 18).
- If there is a high index of suspicion of complicated UTI in a toxic child which warrants immediate antibiotics administration then positive urinalysis helps to take decision as the culture result takes at least 24 hours for availability whereas urinalysis result is available within an hour.
- In febrile infants with low risk of UTI group, a negative urinalysis allows to defer urine culture when collection of urine for culture requires more invasive, uncomfortable procedure like SPA or bladder catheterization. In such cases it also allows clinicians to monitor clinical course without initiating antimicrobial therapy, recognizing that negative urinalysis do not rule out UTI with certainty.

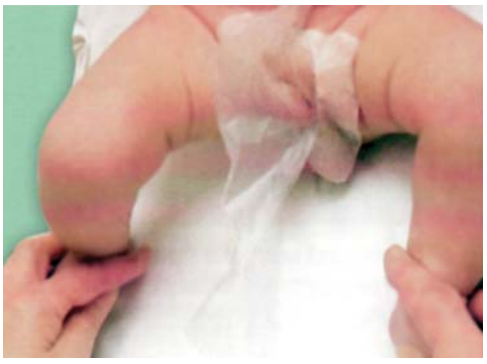


Fig. 18: Urine specimen from sterile bag suitable for urinalysis. Chance of contamination is high giving high false-positive predictive value. However, it has excellent negative predictive value

Components of Urinalysis Relevant to UTI

- *Significant pyuria*: Defined as more than 10 leukocytes/mm^3 in a fresh uncentrifuged sample or greater than 5 leukocyte/high power field (HPF) in a centrifuged sample (Fig. 19).
- *Rapid screening*:

Dipstick test

Nitrite test

Good positive predictive value (specificity 98%). Negative results do not rule out UTI, as it takes one hour for urine to stay in bladder to convert nitrite to nitrate to be positive and infants void urine frequently so do not allow this. Therefore, it is not a sensitive test (53% sensitivity).

Leukocyte esterase test

It has higher sensitivity (83%) but lower specificity (78%) than nitrite test. It is more sensitive (94%) in symptomatic UTI. Asymptomatic bacteriuria can be distinguished from true UTI by absence of leukocyte esterase in urine.

- *Microscopic analysis of bacteriuria*:

The presence of bacteria in a fresh Gram-stained specimen of uncentrifuged urine correlates with 10^5 CFU/mm in urine culture (Fig. 20).

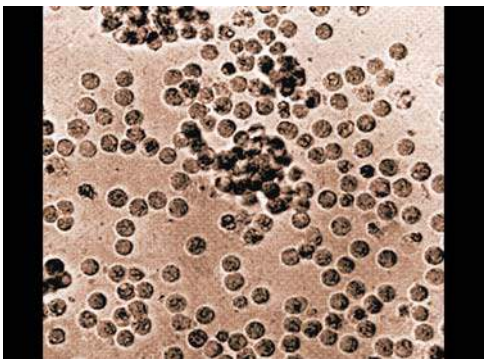


Fig. 19: Gross pyuria: Many WBCs aggregated in clumps

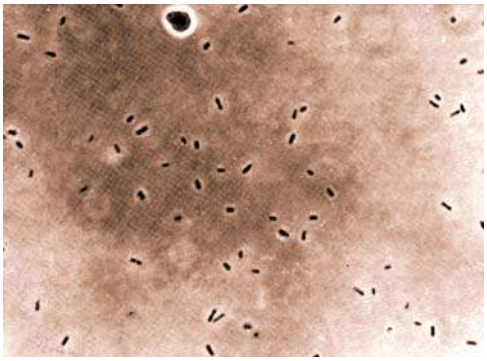


Fig. 20: Bacteriuria: Infected urine viewed under high power; showing many organisms

Establishment for Diagnosis of UTI

A clinician should require both urinalysis result that suggests infection (pyuria and/or bacteriuria), and the presence of significant bacteriuria (10^5 CFU/mm in midstream clean-catch urine, 5×10^4 CFU/mm in urethral catheterization or any number of pathogen in SPA) of an uropathogen from an appropriately collected urine specimen.

Appropriately collected urine specimen can be obtained by following procedures:

Proper Collection of Urine

How to collect and when to collect:

Depends on the age of the child

- Clean-catch midstream urine
- Suprapubic aspiration
- Transurethral catheterization (TUC).

Clean-catch midstream urine:

Clean-catch midstream urine is used for bladder controlled older child to minimize contamination by periurethral flora (Fig. 21). Simple washing of genitalia with soap and water is sufficient to minimize contamination.

Although SPA and TUC are the standard methods for collection of urine in a newborn and young infants, currently a new technique of fast noninvasive and safe collection by clean-catch method have been found successful even in young infant and newborn. It consists of repeated tapping of suprapubic area, stimulation of the lower back which finally results in micturition (Figs 22A and B). Midstream urine sample can then be caught in sterile collector (Fig. 22C). Two persons are required to perform the procedure.

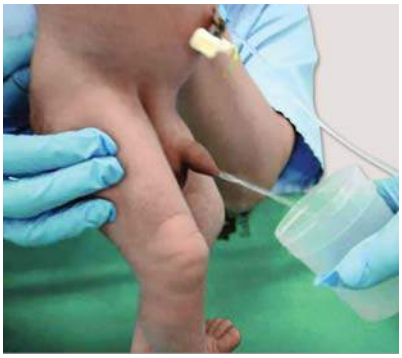
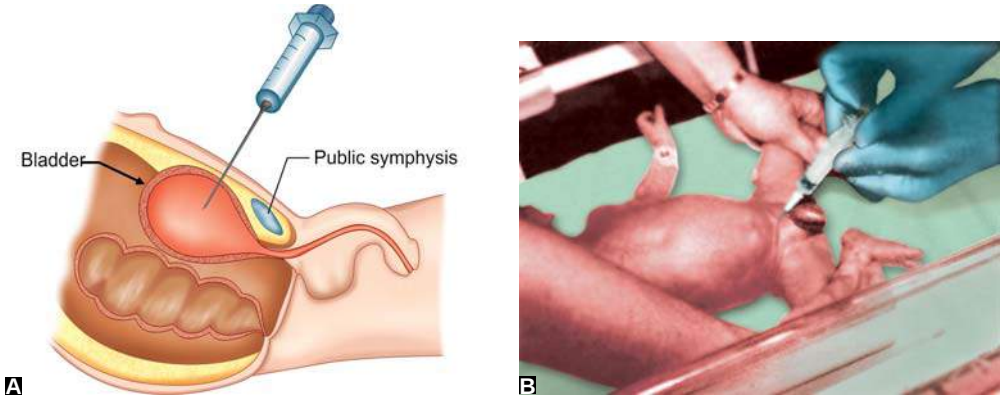


Fig. 21: Midstream urine sample collection in a sterile container

Figs 22A to C: Midstream urine collection of a newborn by clean-catch method. (A) Tapping in the suprapubic area; (B) Stimulation of the lower back; (C) Midstream urine sample collection in a sterile container

Source: Reproduced from Herreros Fernández ML, González Merino N, Tagarro García A, et al. A new technique for fast and safe collection of urine in newborns. Arch Dis Child. 2013;98(1):27-9.



Figs 23A and B: The procedure of suprapubic aspiration of urine in a baby

Suprapubic aspiration and transurethral bladder catheterization:

Suprapubic aspiration and TUC are the standard methods of urine collection for newborn, infant and young children particularly below 2 years (Fig. 23). Both techniques are safe and easy to perform. However, parents perceive SPA to be more invasive and painful than transurethral catheter collection of urine. In such circumstance TUC is preferable. However, there may be no alternative to SPA for boys with significant phimosis or girls with tight labial adhesions.

Culture from Bag Specimen

Specimen obtained from a bag is likely to be contaminated and is not recommended. However, a negative culture in such method is always negative and therefore valid only if yield negative (high negative predictive value). It is useful for urinalysis without urine culture in bladder uncontrolled child.

Urine Collection and Preservation for Investigation

The urine specimen should be promptly plated within 1 hour of collection. In case of delay it can be stored in a refrigerator at 4°C for up to 10–24 hours.

Usual Uropathogens Causing UTI

- *Escherichia coli* (*E. coli*, most common)
- *Klebsiella*
- *Enterobacter*
- *Proteus*
- *Pseudomonas*
- *Enterococcus* and *Candida*

Escherichia coli having fimbria on their surface are more relevant in causing UTI. *E. coli* strains having specific hemolysin and toxins are more pathogenic.

Treatment of UTI

Goal of Treatment of UTI

Goal of treatment of acute UTI is to eliminate the acute infection to prevent complication and to reduce the likelihood of renal damage. A misdiagnosis of UTI can lead to renal scarring if left untreated. Overdiagnosis of UTI, on the other hand, can lead to overtreatment and unnecessary urinary imaging.

Initial Treatment

When to initiate treatment, what is the route of administration of antimicrobial therapy and what initial investigations should be done?

An assessment and initial evaluation should be done to take appropriate steps of management. The following conditions may have to be encountered in pediatric practice and should be managed accordingly:

1. Subjective assessment of degree of illness and toxicity should be done. A febrile, sick and toxic child suspected of UTI should be hospitalized, and immediate antimicrobial treatment should be started. However, before initiating antibiotics, urine specimen should be obtained through catheterization or SPA in infants (<2 years) and by midstream clean-catch urine in bladder controlled older children.
2. Initial treatment of febrile (symptomatic) but non-toxic look, not so sick with no apparent source of other infection but in high-risk group of UTI (children <3 months, fever >39°C for >24 hours, uncircumcised male child, non-black race), immediate antibiotic treatment should not be given without evidence of infection in urine tests. In such cases one of the following two strategies can be taken:
   a. Perform urinalysis: If urinalysis reveals UTI (pyuria, positive leukocyte esterase and positive nitrite test), then properly collected urine specimen should be sent for culture. Antibiotic should be started only if urine culture is positive. However, antibiotic may be given in high-risk group for UTI by an experienced physician pending urine culture if urine culture cannot be done due to resource constraint or if patient is unreliable for follow-up.
   b. If urinalysis of fresh urine is negative (no pyuria, negative leukocyte esterase, negative nitrite test), it is reasonable to monitor the clinical course without sending urine for culture and without initiating antimicrobial therapy, recognizing that negative urinalysis results do not rule out UTI with certainty.
3. Initial treatment of low-risk group: If the clinician determines that the febrile infant is in low risk of having UTI then clinical follow-up and monitoring without testing is sufficient.

The aforementioned approach is based on current high quality evidence-based guideline. In clinical practice, the

Table 2: Dosages of antimicrobial therapy

Drugs	Dose (mg/kg//day)
Parenteral	
Cefotaxime	100–150, 2–3 divided doses, IV
Ceftriaxone	75–100, 1–2 divided doses, IV
Amoxicillin	30–50, 2–3 divided doses, IV
Amikacin	10–15, single dose, IV or IM
Gentamicin	5–6, single dose, IV or IM
Oral	
Cefixime	8–10, 2 divided dose
Cefalexin	50–70, 2–3 divided doses
Ciprofloxacin	10–20, 2 divided doses
Co-amoxiclav	30–40 amoxicillin, 2 divided doses
Ofloxacin	15–20, 2 divided doses
Cotrimoxazole	6–10, of trimethoprim in 2 divided doses

guideline is modifiable depending upon the clinical judgment by an experienced clinician, geographical locations, medical-health infrastructure and resource availability.

Route of Administration of Antimicrobial Therapy

Both oral and parenteral routes are equally effective. However, parenteral route is preferred if a patient is:

a. Toxic
b. Unable to retain oral intake including medication
c. When compliance with oral medication is uncertain.

Parenteral antibiotic under such conditions should be continued until clinical improvement occurs generally within 24–48 hours, when the child can retain orally administered fluid and antibiotics.

Choice of Antibiotics

It should be guided by local susceptibility pattern (Table 2). A third-generation cephalosporin is preferred. Therapy with a single daily dose of an aminoglycoside can be used in children with normal renal function.

Nitrofurantoin used as prophylaxis is not suitable for treatment as it does not achieve therapeutic concentration. Once the results of antimicrobial susceptibility are revealed, treatment is modified accordingly. Total duration is of 10–14 days.

Supportive therapy: During an episode of acute UTI, it is important to maintain adequate hydration. A sick febrile child with inadequate oral intake or dehydration may require parenteral fluid. Paracetamol is used to relieve pain.

A repeat urine culture is not necessary unless there is persistence of fever and toxicity despite 72 hours of adequate antibiotic therapy.

Recurrent UTI

Second or more episodes of symptomatic UTI is called recurrent UTI. Recurrent UTI are observed in 30–50% children, more commonly in infants. Most commonly occurs within 3 months of initial episodes. Recurrent ABU is not considered as true recurrent UTI. Patients with recurrent UTI at any age require detail imaging with ultrasonogram, DMSA scan and MCUG.

Asymptomatic Bacteriuria

Asymptomatic bacteriuria refers to significant bacteriuria in a child who has no symptoms of UTI which includes fever. It is also evidenced by absence of significant pyuria in urinalysis in presence of significant bacteriuria. It is present in 1–2% of girls and 0.05–0.2% in boys. It is a benign condition and does not require treatment rather antibiotic treatment of ABU may be followed by symptomatic organism with more virulent strain.

The presence of ABU in previously treated UTI is also not considered as true recurrent UTI.

UTI with Vesicoureteric Reflux

Vesicoureteric reflux which refers to retrograde flow of urine from bladder to upper urinary tract at rest or particularly during micturition is present in up to 30–35% of children with febrile UTI. It is a major risk factor for acute pyelonephritis and reflux nephropathy.

Antimicrobial Prophylaxis in Recurrent UTI and in UTI with Reflux

Long-term low dose antibiotic prophylaxis is administered conventionally to patient with:

- Recurrent febrile UTI even without VUR
- Urinary tract infection below 1 year of age while awaiting imaging studies
- Urinary tract infection associated with VUR (currently debatable).

Current Evidence-based Guideline of UTI Prophylaxis

Current evidences, however, do not support the use of antimicrobial prophylaxis to prevent febrile recurrent UTI in infants without VUR or with reflux of grades I-IV as antibiotic prophylaxis found unable to alter the clinical outcome in such conditions. Antibiotic should be given therapeutically only if the evidence of infection in urine is present but not to prevent infection.

Clinical management of UTI with reflux on the basis of this current evidence is currently not practiced in many pediatric centers of developing countries including in Indian subcontinents, considering the limitation of infrastructure and scarcity of resources.

Drug Used in Prophylaxis

Effective nontoxic with few side-effects, not causing alteration of gut flora, relatively narrow spectrum drug, less likely to cause drug resistance are preferred. Nitrofurantione is an ideal drug in such conditions. Other drugs which can be used are cortimoxazole and cefalexin. The medication is given as single bedtime dose. Drug doses and their possible side effects are given in the Table 3.

Nonpharmacological Prevention of UTI

Simple physical measures can prevent or decrease the incidence of UTI. These include the following:

- Adequate fluid intake
- Frequent voiding
- Complete voiding of urine before going to bed with double micturition

Table 3: Antimicrobials for prophylaxis of urinary tract infections

Medication	Dose (mg/kg/day)	Side effects and remarks
Nitrofurantoin	1–2	May cause vomiting and nausea; avoid in infants less than 3-month-old, glucose-6-phosphate dehydrogenase (G6PD) deficiency and renal insufficiency
Cotrimoxazole	1–2 of trimethoprim	Avoid in infants less than 3-month-old, G6PD deficiency
Cefalexin	10	Drug of choice in first 3–6 months of life

- Avoidance of constipation by taking enough fiber containing diet
- Avoidance of holding of urine for long time
- Treatment of bladder and bowel voiding dysfunction
- Circumcision of male child particularly with phimosis who suffered from UTI
- Daily bath and avoidance of bubble bath.

Evaluation after First Episode of UTI

The concepts of radiological imaging are changing according to new high-quality evidences. New evidence suggests that intense imaging and subsequent management do not significantly alter the long-term outcome in children with reflux nephropathy diagnosed following UTI. Moreover, in resource-rich countries most of the remediable congenital anomalies of renal tract are diagnosed antenatally and managed accordingly after birth, reducing the need for further invasive radiological evaluation after UTI to detect underlying congenital renal anomalies.

However, due to limitation of health infrastructure in resource-poor developing countries, the diagnosis of UTI is often missed or delayed and underlying congenital renal anomalies which include VUR in particular are not usually diagnosed antenatally. Therefore, recommendation for radiological evaluation following first UTI in developing countries which include Indian subcontinent is different than western countries. Protocolized standard imaging suitable in Indian subcontinent are given in Table 4.

Table 4: Imaging for first episode of UTI

Age	Modalities
<1 year	Ultrasound MCUG DMSA renal scan
1–5 years	Ultrasound DMSA scan MCU if ultrasound or DMSA scan is abnormal
After 5 years	Ultrasound If USG is abnormal MCUG and DMSA
Any age with recurrent UTI	Ultrasound, DMSA scan and MCUG

Renal and Bladder Ultrasonography (RBUS)

- It is a noninvasive and relatively cheap
- Can assess renal size
- Can evaluate renal parenchyma
- Can detect pelvicalyceal (PC) dilatation which helps to undertake further radiological evaluation
- Can detect gross previously undiagnosed renal anatomic abnormalities
- Can monitor renal growth.

Drawbacks of RBUS

- The yield of actionable findings is relatively low
- Prenatal RBUS has reduced the prevalence of previously unsuspected obstructive uropathy in western countries
- Normal RBUS does not reliably rule out structural abnormality.

Timing of performing RBUS

- Depends on clinical conditions
- Usually after initial clinical condition subsides as early inflammatory edema prevents baseline study
- Within 2 days of initial acute condition if serious complications, like perinephric abscess or pyonephrosis, is suspected.

Dimercaptosuccinic Acid Scan

- More sensitive in detecting acute pyonephrosis and later scarring (Fig. 24) which is more important.
- Early detection of acute pyelonephritis by DMSA scan is, however, not essential as it is generally accepted that both upper and lower part of renal tract are affected in UTI and detection of acute condition does not alter clinical management. Therefore, the procedure is done at least 3 months after symptomatic UTI in children below 5 years of age.

Micturating Cystourethrogram

Radionuclide labeled MCUG is the standard for diagnosing and grading the severity of VUR and defining urethral and bladder anatomy (Fig. 25). MCUG can be carried out within 2–3 weeks of treatment of UTI. MCUG can be done in below 1 year of age after initial symptomatic UTI and age 1–5 years if ultrasound and DMSA scan is abnormal. MCUG is also done if there is recurrence of febrile UTI at any age.

Other Radionuclide Studies Used in UTI

Direct radionuclide cystography (DRCG):

- It is associated with lower radiation dose than MCUG, which carries importance for girls

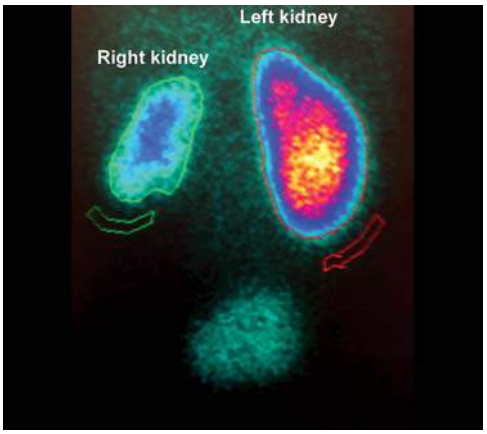


Fig. 24: DMSA scan showing smaller right kidney with multiple scars due to reflux nephropathy. Left kidney is normal

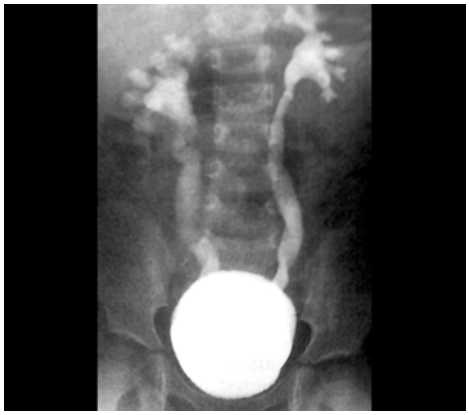


Fig. 25: MCUG showing bilateral VUR with dilatation of ureter and clubbing of calyces (grade IV/V reflux) associated with UTI

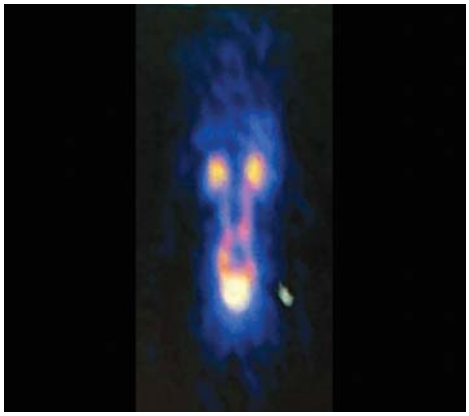


Fig. 26: Indirect cystography using intravenous MAG3, a less invasive procedure to monitor VUR with or without UTI

- It is usually used for follow-up studies
- However, it requires catheterization.

Indirect cystography using intravenous MAG3:

- Avoid the need for catheterization
- Can be used to monitor VUR with or without UTI, however, the child needs to be fully continent (Fig. 26).
- Drawbacks: Lower grade of VUR and posterior urethral valve anatomy cannot be obtained.

VESICOURETERIC REFLUX

Vesicoureteric reflex refers to the retrograde flow of urine from bladder to ureter and pelvis at rest or during micturition. Vesicoureteric reflux is considered a significant factor for the development of progressive renal damage in the presence of UTI.

Vesicoureteric reflex may be primary (isolated anomaly) or secondary (associated with other anomalies of the urinary tract).

To date, MCUG or VCUG is the preferred method for the initial diagnosis of VUR in children with UTI or in the workup of an antenatal diagnosis of fetal uropathy.

Classification or Grading of VUR

Grading of reflux is based on the work of International Reflux Study Group and includes VUR from grades I–V, which is listed in Table 5 and Figure 27.

Etiology of VUR

Genetic defect causing congenital anomalies of the vesicoureteric junction is the cause of primary VUR. Secondary VUR results from a number of disorders, which affect the structure or function of urinary tract like bladder outlet obstruction.

Primary VUR

Primary VUR is an autosomal dominant (AD) with reduced penetrance and variable expression.

A flap valve at the junction of ureter and bladder regulates anterograde flow of urine and thus prevent retrograde flow during voiding. Defect in this valve affecting either active or passive mechanism or both gives rise to VUR. Figures 28A and B are showing flow of urine in a normal child (Fig. 28A) and in a child with VUR (Fig. 28B) where urine flows retrogradely from bladder to ureter during micturition.

Secondary VUR

Secondary VUR arises from high intravesical pressure caused by a number of conditions like:

- *Neurogenic bladder*
  - Myelomeningocele
  - Spinal cord injury

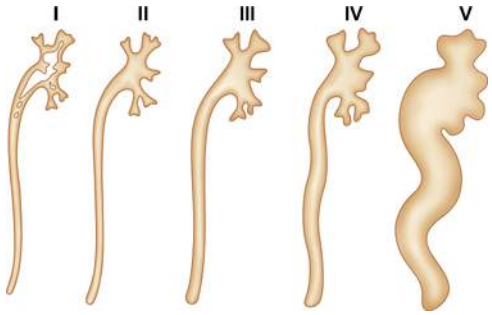
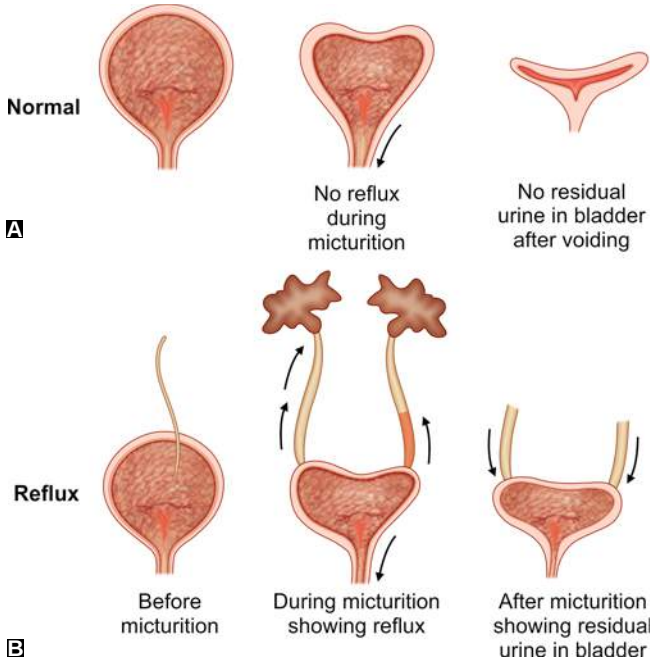


Fig. 27: Schematic diagram of different stages of VUR

Table 5: Grading and radiological correlates of VUR

Grade	Findings	Radiologic findings
Grade I	VUR limited to the ureter, does not reach the renal pelvis	Contrast filling of an undilated ureter
Grade II	VUR up the renal cavities without dilatation of pelvis or calyceal fornices	Contrast filling of ureter and pelvis without dilatation
Grade III	VUR extending up to the kidney with mild dilatation or tortuosity of the ureter and renal pelvis with no or minor blunting of the calyceal fornices	Contrast filling of ureter, pelvic and calyceal system with mild dilatation
Grade IV	Moderate to marked dilatation or tortuosity of the ureter, renal pelvis and fornices	Contrast filling of ureter, pelvic and calyceal system with dilatation and atrophy of the renal parenchyma
Grade V	Marked tortuosity and dilatation of the ureter and pyelocalyceal system with loss of papillary impressions on calyces	Massive hydronephrosis with tortuosity of the ureters occasionally intrarenal reflux



Figs 28A and B: Vesicoureteric reflux. (A) Normal voiding without VUR and no urine in bladder after voiding; (B) Retrograde flow of urine from bladder to ureter during micturition in VUR. Reflux in right urinary system (during micturition) up to kidney (grade IV/V) and in left, reflux up to ureter (grade I). There is also residual urine in bladder after voiding

- *Bladder outlet obstruction*
  - Posterior urethral valve
- *Bladder dysfunction*
  - Dysfunctional voiding

Clinical Conditions Associated with VUR

1. Reflux nephropathy
2. VUR and UTI
3. VUR and renal dysplasia

Reflux Nephropathy

Reflux nephropathy is known to represent both:

- Acquired kidney damage (chronic pyelonephritis)—more common in girls
- Congenital kidney malformation (renal dysplasia)—more common in boys.

UTI and VUR

Symptomatic UTI is significantly (40–50%) associated with VUR. Renal lesions (pyelonephritis, renal parenchymal damage) are associated with higher grade of reflux.

VUR and Renal Dysplasia

VUR and reflux nephropathy are both developmental aberrations. Renal abnormalities in patients with VUR may be present before birth more in boys. The kidneys become small and dysplastic.

Clinical Features

VUR may be symptomatic or asymptomatic.

Asymptomatic

Asymptomatic VUR is diagnosed either during prenatal USG or screening of relative of affected individuals.

Symptomatic

Symptomatic children may present with UTI.

Investigations

1. Urinalysis to detect UTI
2. Renal ultrasound: Shape and size of kidney, urinary tract dilatation and presence or absence of calculi can be detected.
3. Intravenous urography
4. MCUG: It is the definitive investigation for the detection and grading of VUR (Figs 29 to 33).

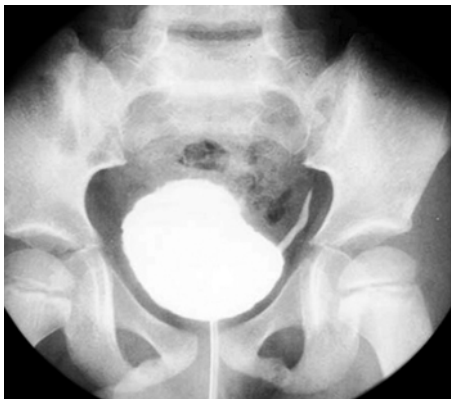


Fig. 29: MCUG showing unilateral grade I cystourethrogram

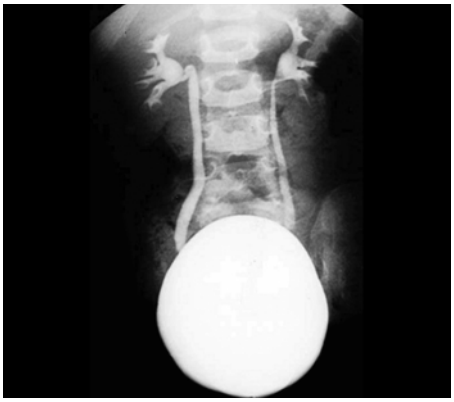


Fig. 30: Cystourethrogram showing bilateral grade II VUR

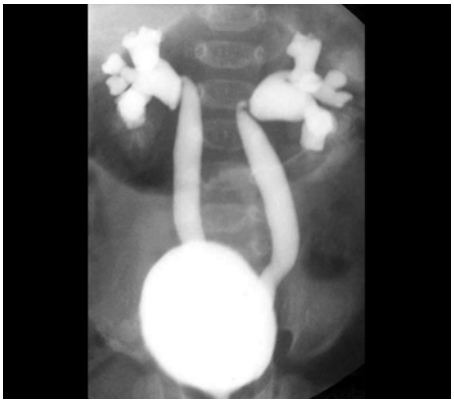


Fig. 31: MCUG showing bilateral grade III VUR

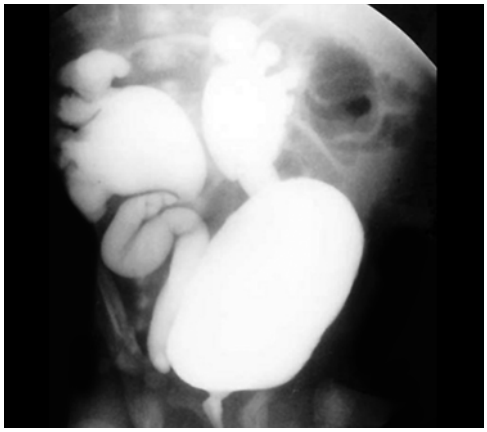


Fig. 32: MCUG showing bilateral grade IV VUR

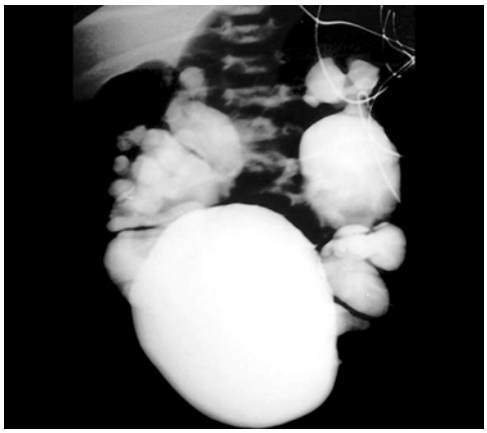


Fig. 33: MCUG showing bilateral grade V VUR

Management

The management depends on the grade of VUR, age and sex of the child, occurrence of UTI, presence or absence of reflux nephropathy or renal impairment.

The aim of treatment of VUR is to treat UTI to prevent renal damage.

Conventional Medical Treatment of Primary VUR with UTI

It is conventionally recommended that patients should receive initial antibiotic prophylaxis while awaiting spontaneous resolution of VUR. Grade I and II reflux require antibiotic prophylaxis until 1 year of age, if recurrence of UTI occurs after 1 year, antibiotic prophylaxis is restarted. In grade III-V antibiotic prophylaxis is required up to 5 years of age. Antibiotic prophylaxis should be prolonged above 5 years of age, if bladder bowel dysfunction (BBD) is present and surgery not done. Antireflux surgery is required if grade IV/V does not resolve by 5 years of age or breakthrough febrile UTI occurs during this time. Algorithm approach of management of VUR is given in Figure 34.

However, current high-quality evidences in western countries do not support the use of antibiotic prophylaxis in UTI with VUR of grades I-IV, as statistically significant benefit in preventing recurrent UTI/pyelonephritis or renal damage in infants with grades I-IV reflux or without reflux associated with UTI was not detected. For the same reason, currently American Academy of Pediatrics (AAP) does not recommend MCUG routinely, even in first febrile UTI below 1 year of age as it does not help in taking antimicrobial prophylaxis strategy.

Surgical Treatment

Bilateral grade IV or V reflux resolves spontaneously in less than 20% of patients after 5 years. Modes of surgical treatment are:

- Circumcision
- Trigonal reimplantation

Indications for surgical measures:

- Severe reflux
- Frequent breakthrough febrile infection
- Deteriorating DMSA appearance

Algorithm of Management of VUR

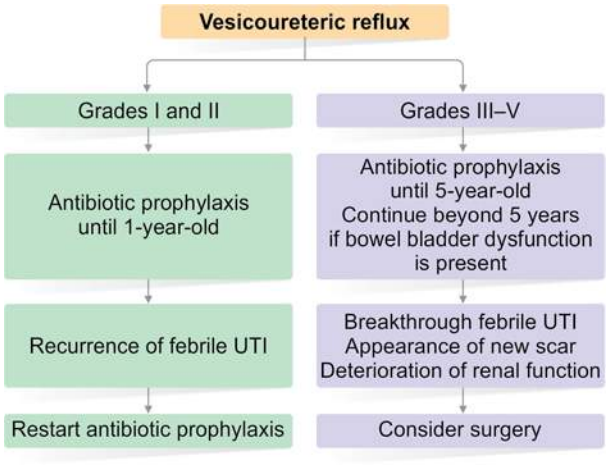


Fig. 34: Algorithm of management of VUR

DISORDERS OF GLOMERULAR FUNCTION

Glomerular filtration barrier is composed of three layers in series:

1. The fenestrated endothelium (Fig. 35A)
2. The glomerular basement membrane (GBM, Fig. 35A)
3. The visceral glomerular epithelium, comprised of podocytes and their slit diaphragms (Fig. 35B)

Podocytes affect the structure and function of the GBM and to regulate the integrity and survival of glomerular endothelial cells.

Nephrotic Syndrome (NS)

Nephrotic syndrome describes abnormal condition with triad of:

- Heavy proteinuria (>1 g/m^2/day)
- Hypoalbuminemia(<2.5 g/dL)
- Generalized edema

The vast majority (90%) is primary (idiopathic). Rarely, it is due to secondary causes like systemic lupus, anaphylactoid purpura, amyloidosis, etc.

Etiology and Pathogenesis

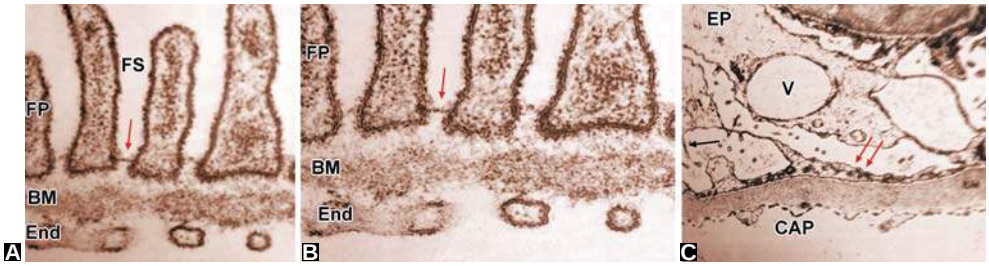
Primary (idiopathic) and secondary.

Etiology of primary NS:

- Minimal change nephrotic syndrome (MCNS)

Less common, other primary glomerular diseases causing NS are:

- Focal segmental glomerulosclerosis (FSGS): Second most common subtype



Figs 35A to C: Showing eletron microscope of minimal change disease. (A) Glomerular filter consisting of fenestrated endothelium, basement membrane and FP; (B) Arrow showing slit diaphragm; (C) Arrow showing effacement of podocyte FP in minimal change disease

Abbreviations: BM, Basement membrane; CAP, Capillary; End, Endothelium; EP, Epithelial; FP, Foot process; FS, Filtration slit

- Membranoproliferative glomerulonephritis (MPGN): Less common (<1%)
- Immunoglobulin M (IgM) mesangial nephropathy: Congenital NS

Minimal change nephrotic syndrome: Most frequent cause of primary NS. In MCNS there is no significant abnormality on light microscope in histopathology of kidney, hence called MCNS. However, electron microscope shows fusion of podocyte foot process (FP, Fig. 35A) and that is why also called FP disease. Most cases are sensitive to steroid.

Pathogenesis:

- Altered permeability of glomerular filtration barrier (GFB) leading to heavy proteinuria.
- Glomerular filtration barrier is formed by a GBM and podocyte slit diaphragm (PSD).
- Glomerular filtration barrier is a negatively charged membrane which repels negatively charged protein.
- Podocyte slit diaphragm lies the other side of GBM and consists of interconnecting network of FP.
- Glomerular filtration barrier and PSD will constitute the GFB which provides permeability selectivity, allowing small ions to pass freely but prevents large proteins like albumin or hemoglobin (Hb) to pass freely across.

In NS due to MCNS there is effacement or fusion of podocyte FP, which affects structure and function of GBM with altered permeability of glomerular filtration barrier leading to proteinuria (Fig. 35C).

In NS due to MCNS there is selective proteinuria which allows relatively low molecular weight particles, like albumin (66,000), transferrin (76,000), IgG, etc. to pass but high molecular weight protein like globulin cannot pass freely across.

The loss of protein in the urine (heavy proteinuria) brings about the following pathophysiological changes:

- Decreased serum albumin due to loss in urine in NS reduces plasma colloid oncotic pressure, leading to fluid shift from intravascular space to interstitial space causing intravascular hypovolemia. Edema occurs due to collection of fluid in extravascular space and hypovolemia occurs due to intravascular fluid shift from intravascular space.
- Renin-angiotensin mechanism is then stimulated following hypovolemia with increased secretion of antidiuretic hormone (ADH).

These changes lead to sodium and further water retention aggravating edema due to fluid shift.

Hypotension and hypertension: Usually NS due to MCNS is normotensive. Intravascular fluid depletion may cause hypotension. However, in spite of hypovolemia there may be paradoxical increase in blood pressure due to renin-angiotensin mechanism.

Infection

Pneumonococcal infection: Children suffering from NS are vulnerable to infection particularly to pneumococcal infection. Loss of Ig in urine, impaired antibody generation and defective opsonization of pneumococcal capsule (required for phagocytosis of *Pneumococcus*) by complement C3b (derived from alternate complement pathway) is the basis of increased vulnerability of pneumococcal sepsis in NS. Loss of protein in urine and prolong intake of oral steroid in high dose are also associated with acquired immunodeficiency and increased susceptibility to infection.

Clinical problems associated with invasive *Pneumococcus* in NS include 3Ps which include peritonitis, pneumonia and pyelonephritis (3Ps). Other frequent association is cellulites.

Thrombosis: Hemoconcentration, decreased level of antithrombin III due to urinary loss and raised fibrinogen concentration are associated with increased risk of thrombosis particularly venous thrombosis in NS.

Important Characteristics of MCNS

- Commonest glomerular disorder of childhood
- More common in boys (M:F is 2:1)
- More common in Asian children than Caucasian
- Median age of presentation is 4 years
- Over 90% respond to corticosteroid therapy but over 70% of these develop a relapse
- Long-term remission finally occurs in 80% of children
- Prognosis depends on steroid responsiveness. Since most of the children with NS are steroid responsive, there is low risk of developing chronic kidney disease (CKD)
- Secondary steroid resistance may develop lately as a very rare outcome.

Children with FSGS and mesangiocapillary glomerulonephritis (MCGN) have a poorer prognosis. Fortunately only few children suffer from such glomerular disorder. The likelihood of non-minimal change glomerular disorder with poorer outcome increases with late age of onset of nephrotic syndrome.

Atypical Presentation of Nephrotic Syndrome

- Age less than 12 months and greater than 12 years
- Persistent hypertension
- Impaired renal function
- Gross hematuria
- Low plasma C3
- Hepatitis B and C positive.

Clinical Presentation

- *Edema*: Most of the children (90%) will present with features of edema. Edema usually collects in the areas of low-tissue resistance (i.e. periorbital, scrotal and labial regions). Swelling of the face is usually the first clinical presentation particularly in the morning. As the edema increases, the evidence of pleural effusion and ascites may be found.
- *Abdominal pain and dizziness*: The child may present with acute abdominal pain due to hypovolemia or peritonitis. Hypovolemia can also be present with dizziness and postural hypotension.
- *Respiratory distress*: Pneumonia and pleural effusion associated with NS may present with respiratory distress. Abdominal distension due to ascites may also present as respiratory distress.
- There may be history of recent upper respiratory tract infection (viral URTI), generalized malaise, irritability and foamy urine.
- Initial presentation of periorbital edema may be misdiagnosed as allergic pleats.
- Once generalized edema is present, particularly when scrotal edema is present the diagnosis becomes easier.

Examination

Physical examination: Examination should be focused for diagnostic feature of NS, atypical presentation and evidence of complications of NS.

General examination: These include puffy face, periorbital edema (Fig. 36A) and dependent edema or pitting edema like pedal, sacral, abdominal wall and scrotal (Fig. 36B) edema.

Look to exclude secondary causes of NS like:

- Vasculitic lesion of Henoch-Schönlein purpura (HSP), skin lesion of systemic lupus erythematosus (SLE), skin evidence of lipoatrophy, etc.
- Hepatomegaly, jaundice (hepatitis B)
- Temperature.

Fever may indicate sepsis or peritonitis. A difference between core and toe temperature of more than 2°C is suggestive of poor peripheral perfusion and hypovolemia.

CVS examination:

Pulse: Low volume pulse, increased pulse rate (tachycardia)
BP: Normotensive, hypotensive or hypertensive

Evidence of hypovolemia is clinically assessed by low volume pulse, tachycardia, initial hypertension than hypotension, abdominal pain and tenderness and poor peripheral perfusion (cold clammy periphery).

Investigations

Investigation at first presentation:

Urinalysis:

- Urine dipstick analysis for protein and blood
- Early morning urine for protein creatinine ratio
- Urine microscopy and culture (UTI is significantly associated)
- Urine sodium particularly if there is signs and symptoms of hypovolemia.

Massive proteinuria in nephrotic syndrome: Massive or heavy proteinuria is one of the characteristic features of NS.

- A proteinuria may be considered normal if there is proteinuria of less than 4 mg/m^2/h or less than 100 mg/m^2/day.
- Abnormal but not nephrotic range is 4–40 mg/m^2/h or 100 mg to less than 1 g/m^2/day.
- Nephrotic range of proteinuria is greater than 40 mg/m^2/h or greater than 1 gm/m^2/day.

Dipstick testing provides the semiquantitative measure of urine protein concentration as follows:

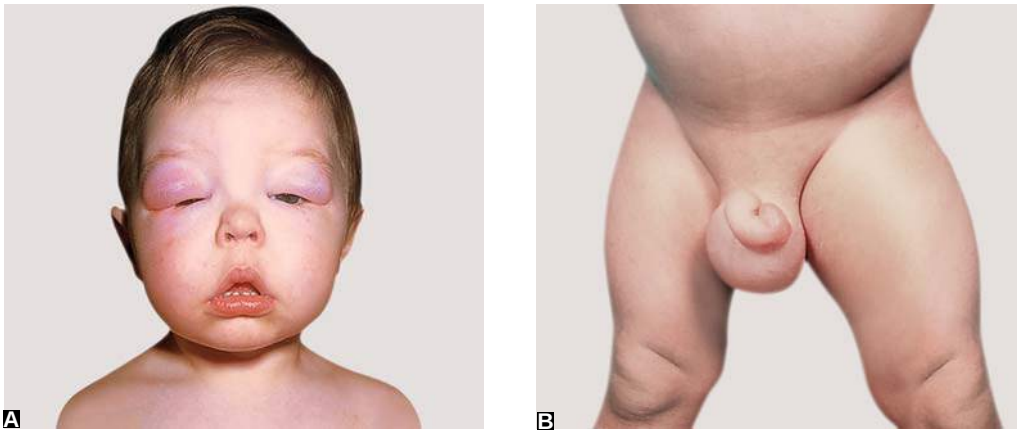
+	30 mg/dL
++ (2+)	100 mg/dL
+++ (3+)	300 mg/dL
++++ (4+)	2,000 mg/dL

Heavy or nephrotic range proteinuria defined as more than 3+ to 4+ (300–2,000 mg/dL) urine protein by dipstick or positive boiling test (heat coagulation test) in early morning urine for 3 consecutive days. A relapse is defined as detection of urine dipstick of 2+ or more protein in urine for 3 consecutive days.

The simplest test is the urinary protein:creatinine ratio on the spot sample. Usually in early morning, sample protein excretion should not exceed 20 mg/mmol of creatinine.

Hematuria:

- Hematuria of 1+ in dipstick is not uncommon
- Microscopic hematuria is present at onset in 20–30% of MCNS but macroscopic hematuria is uncommon.



Figs 36A and B: Edema. (A) A child showing puffy face; (B) Scrotal edema in a child

Blood test:

- Plasma albumin: Plasma albumin is less than 25 g/L (2.5 g/dL) in NS
- Full blood count with erythrocyte sedimentation rate (ESR):
  - High Hb and packed cell volume indicate hypovolemia
  - High ESR (usually >80) is also characteristics of MCNS
- Serum electrolytes: Serum electrolytes are normal in NS. Although retention of sodium occurs in NS, there may be hyponatremia due to hyperlipidemia.
- Urea and creatinine: Plasma urea and creatinine are usually normal in most cases of minimal change NS. Reversible acute renal failure (prerenal azotemia with moderate rise in urea and creatinine) can accompany in 30% cases due to hypovolemia in MCNS, but persisting high creatinine is an atypical feature.
- Serum lipid profile: Serum cholesterol and triglyceride are high
- X-ray chest and ultrasound of abdomen and chest to find pneumonia, pleural effusion and ascites, respectively
- Complement C3 and C4 level: Complement levels are normal in MCNS
- Hepatitis B and C serology.

Second-line investigation:

Second line investigation may include:

- Antistreptolysin O (ASO) titer and anti-DNase (ADNase) antibody and lupus serology including anti-double stranded DNA (anti-dsDNA) antibody for older children and with atypical presentation
- Varicella zoster serology to determine immune status.

Clinical evaluation and first line investigation will help to diagnose likely MCNS and steroid sensitive NS. Atypical cases require referral and possible renal biopsy.

Up to 25% of children with MCNS may have microscopic hematuria and may have transient hypertension due to hypovolemia at presentation. These conditions do not preclude empirical steroid therapy start. Initial hypertension is usually due to hypovolemia which should be corrected promptly.

Management

Acute management: Most patients with presenting features of NS should be hospitalized to ensure monitoring of clinical status and to provide education program to parents about the disease, its treatment, prognosis and for home urine monitoring.

Observation and general measure:

- Monitoring of temperature, heart rate, pulse BP, urine output (UO)
- Daily weight should be taken
- A salt restricted diet is recommended and no added salt. Salt containing food, like snacks and food containing salts, like salted biscuits, potato chips and salted-puffed rice, should be avoided. However, undue restriction that makes food unpalatable is not recommended.
- In the absence of hypovolemia, fluid intake may be modestly restricted.
- Oral penicillin can be given until edema is resolved.

Steroids: Steroids are the corner stone of management of all chronic inflammatory disease and other condition such as NS. Despite development of many new and effective drugs (anti-inflammatory and immunosuppressive), steroids hold the place as first line therapy for NS.

Among steroids only prednisolone and prednisone are found to be most effective in the treatment of proteinuria in NS. Adequacy of treatment of initial episode, both in terms of dose and duration of prednisolone is an important determinant of long-term outcome as more than 90% of children with MCNS and an additional 20% of FSGS are steroid responsive. The vast majority of children are given an empirical course of steroid without a renal biopsy.

Definition depending upon NS course and steroid sensitivity pattern:

a. Remission: Urinary albumin (Albustix test) nil or trace (or proteinuria <4 mg/m^2/h) for three consecutive early morning specimen.
b. Relapse: Urinary albumin 2+ to 4+ or proteinuria greater than 40 mg/m^2/h for three consecutive early morning specimen of those who were under remission previously.
c. Frequent relapse: Two or more relapse in initial 6 months or four or more relapse in any 12 months period.
d. Steroid dependence: Two consecutive relapse while on alternate day steroids for within 14 days of discontinuation of steroid therapy. These children almost invariably also have frequently relapsing NS.
e. Steroid resistant: Absent of remission (failure of proteinuria to resolve) despite therapy with daily prednisolone at a dose of 60 mg/m^2/day or 2 mg/kg/day for 4 weeks.

The terms MCNS and steroid sensitive/responsive NS are often used interchangeably. However, this is not strictly correct as a small proportion of cases of MCNS will not exhibit steroid sensitivity and about 20% FSGS will respond to steroid.

Dose and duration of initial steroid therapy: It is now increasingly recognized that increasing the duration of steroid therapy at first presentation, produces less relapse and more long-term remission during childhood. The previous International Study of Kidney Disease in Children (ISKDC) regimen was relatively a short course of steroid therapy. ISKDC regimen consists of once daily 60 mg/m^2 prednisolone for 28 days followed by 40 mg/m^2 given on alternate days for another 28 days (total almost 2 months). Currently a more prolonged initial prednisolone therapy is practiced in many centers with the hope of reduced rate of relapse. There is now good evidence that extended initial course of steroid to about 4–6 months (or more), by gradually tapering the alternate day part of the course, leads to a mark reduction of the proportion of the children who develop a frequently relapsing steroid dependent course and this scheme is increasingly replacing the previous standard protocol.

One of the current standard dose regimens of prednisolone in typical steroid sensitive NS is as follows:

Oral prednisolone: 60 mg/m^2/day (2 mg/kg/day) for 4 weeks. If weight is falsely high due to severe edema use ideal weight for height.

Prednisolone is then given in a tapering dose on alternate day for 12 weeks, i.e. total 16 weeks (almost 4 months) from initial dose.

Prednisolone is tapered every 2 weeks of 12 weeks in six steps from 60 mg/m^2 on alternate day to discontinuation as follows:

1. 60 mg/m^2 on alternate day for 2 weeks
2. 50 mg/m^2 on alternate day for 2 weeks
3. 40 mg/m^2 on alternate day for 2 weeks
4. 30 mg/m^2 on alternate day for 2 weeks
5. 20 mg/m^2 on alternate day for 2 weeks

6. 10 mg/m^2 on alternate day for 2 weeks

Another regimen consists of total 12 weeks treatment. It is given as follows:

1. 2 mg/kg/day (maximum 60 mg/kg) for 6 weeks followed by.
2. 1.5 mg/kg (maximum 40 mg) as a single morning dose for another 6 weeks.

Prednisolone is given as a single or divided dose, administered after meal to reduce gastrointestinal (GI) side effects. Concomitant antacids or H_2 blocker is not required until there is GI intolerance.

Management of edema:

- Mild to moderate edema will resolve spontaneously, when steroid induced remission and diuresis occur.
- Daily administration of oral corticosteroid induces diuresis within 2–4 days.
- Children with only mild peripheral edema do not require fluid restriction. However, when severe edema is present, mild fluid restriction (70% of maintenance) will prevent further edema formation.
- A low salt diet will control thirst.
- If patient's edema fails to improve with above measures or patient presents with significant edema and weight gain then treatment with diuretics should be considered. Oral diuretic is preferred to parenteral diuretic initially.
- Diuretic may be used cautiously to control edema in the initial phase provided that there is no hypovolemia, renal impairment and hypotension.
- It should be remembered that edematous nephrotic children are at risk of developing hypovolemia and children with NS who is being mildly fluid restricted with additional diuretic therapy will be kept under very close review to ensure that hypovolemia is avoided.
- A step up treatment with diuretic should be followed. Initial oral loop diuretics (frusemide at low dose 1–3 mg/kg/day is used), if no improvement (no diuresis, no weight loss or weight gain in 48 hours) then spironolactone (2–4 mg/kg/dose) is added. If no response the dose of frusemide is increased (4–6 mg/kg/day), if not improved then IV frusemide bolus (1–3 mg/kg/dose).
- If no response then 20% albumin 1 g/kg with frusemide is given. Albumin infusion may cause circulatory volume expansion with heart failure; therefore, should be given with caution along with frusemide.
- Albumin infusion is also given as 1st step of management of NS if significant edema is associated with significant hypovolemia (Fig. 37). Albumin should be infused slowly over 4 hours with frusemide 1–2 mg/kg IV given during 2nd half of the infusion. There are number of reports of intravascular volume overload with development of edema, therefore, the dose of albumin should not exceed 1 g/kg. Strict monitoring of vital signs should be done. Albumin should be used to correct refractory edema or significant edema associated with hypovolemia. There is no indication to use 20% albumin to correct hypoalbuminemia alone.

An algorithm may be followed (Fig. 37) while treating edema in NS.

Management of hypertension: There may be transient paradoxical hypertension in presence of hypovolemia due to stimulated renin-angiotensin mechanism. It does not require antihypertensive drug but should prompt the clinician

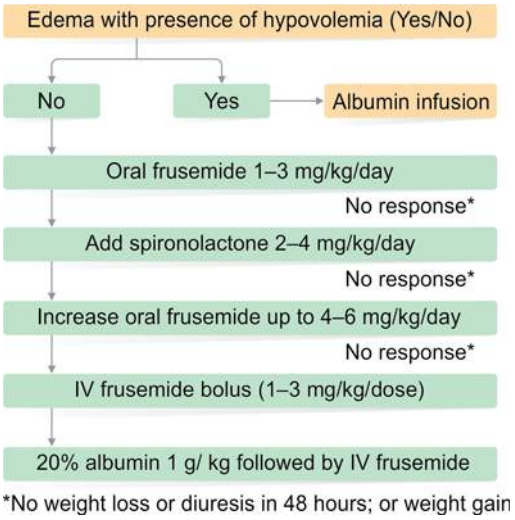


Fig. 37: Algorithm of management of edema in patients with NS. Hypovolemia is suggested by the presence of tachycardia, feeble pulses, cold extremities or hypotension

to consider intravascular fluid replacement. It is also not a contraindication to start initial empirical corticosteroid therapy. However, persistent hypertension in spite of decrease of edema and decline of corticosteroid dose merits antihypertensive treatment and angiotensin-converting enzyme (ACE) inhibitor such as enalapril (0.3–0.6 mg/kg/day) in two divided doses or ramipril is the drug of choice. Calcium channel blocker like amlodipine (0.1–0.6 mg/kg/day) may be required additionally for persisted hypertension.

Management of infection: As mentioned earlier children with NS are vulnerable to infection particularly with capsulated bacteria due to loss of complement (C3a) which is required for opsonization of encapsulated *Pneumococcus* for phagocytosis by macrophage. The common clinical manifestations are pneumonia, peritonitis, pyelonephritis (3Ps) and cellulitis which are associated with significant mortality and morbidity.

Fever or evidence of sepsis is an emergency, requiring broad spectrum antibiotics.

Fungal infection may occur during the course of therapy. Fungal skin rash or oral thrush should be treated with oral fluconazole. Fungal sepsis should be treated with IV amphotericin for 12–21 days. Varicella may be catastrophic in NS and should be treated with 7–10 days course of oral acyclovir in 80 mg/kg in three divided doses. In severe cases, IV acyclovir (10 mg/kg three times daily) can be given in three doses.

Immunization

Children with NS should receive pneumococcal conjugate vaccine (PCV) and influenza vaccine.

- Children starting vaccine at under 2 months of age should receive (primary vaccine) 0.5 mL IM PCV three doses if below 6 months, 4–8 weeks apart and booster at 15–18th months
- Children of age between 6–12 months: two doses, 4–6 weeks apart and booster at 15–18th month
- Children of age 12–23 months: two doses, 8 weeks apart and no booster
- Above 2 years: a single dose of PCV, followed by 8 weeks, later a pneumococcal polysaccharide vaccine (PPV-23).
- Children who continued to have relapse of NS may receive a repeat dose of PPV-23 5 years after the primary vaccination.

Varicella immunization: Nonimmune immunosuppressed patient exposed to infectious varicella should receive varicella immunoglobulin and acyclovir if chickenpox develops.

For prevention of varicella, varicella vaccine should be administered 4 weeks apart while the child is in remission and off immunosuppressive medication.

Polio vaccine: It is better to offer injectable inactivated polio vaccine (IPV) in children with NS and to their siblings to avoid oral live polio vaccine. If the child has already received oral polio vaccine in his/her primary immunization then two doses of parenteral vaccines are given at 2 months interval followed by a third dose 6 months after the first dose and a booster at 5 years.

Management of thrombosis:

- Thrombosis should be suspected if the patients with oliguria have flank pain, hematuria (renal vein thrombosis), altered sensorium or seizure (intracranial thrombosis). Diagnosis requires confirmation with Doppler ultrasound and cranial MRI if required (if intracranial thrombosis is suspected).
- There is no role of prophylactic anticoagulant in NS. However, if thrombosis occurs, therapy includes low dose of IV heparin followed by low molecular weight heparin subcutaneously followed by oral anticoagulant for a long time. Supportive care includes correction of dehydration.

Hyperlipidemia: Hyperlipidemia associated with NS does not require any treatment.

Nutritional management: No evidence exists to support any alteration of dietary protein content. Children should eat a balanced diet without restriction. A no added salt diet is a sensible measure in view of generalized edema. Snacks containing high salt should be avoided.

Calcium carbonate (250–500 mg) and vitamin D (125–250 IU) should be offered with prolonged therapy with prednisolone.

Mobility: No evidence exists to support the use of bed rest which may increase the risk of venous thrombosis, therefore, this practice is not desirable.

Stress dose of steroid: Children receiving high dose of steroid for more than 2 weeks are at increased risk of suppression of the hypothalamo-pituitary-adrenal axis. Such children will require steroid supplement in stressful conditions like during serious infections, undergoing surgery, anesthesia, etc. Initially IV hydrocortisone 4 mg/kg/day followed by oral prednisolone 0.5 mg/kg/day is given during stress and then rapidly tapered.

Prognosis of Steroid Sensitive Nephrotic Syndrome

Most children have a decrease in relapse rate and enter long-term remission. Up to 20% continue to relapse in adolescence. A minority develops secondary steroid resistance and a small subset of this develops CKD.

Therapy for Relapse of Steroid Sensitive Nephrotic Syndrome (SSNS)

Over 70% of SSNS will develop disease relapse in the first 6 months. An upper respiratory infection often precipitates relapse and in other no obvious causes are found. Mild proteinuria (between 1+ and 2+) may also sometime occur for few days during such infection and spontaneously disappear. It is desirable to wait for few days before starting new treatment. If there is a 2+ to 3+ or more proteinuria on Dipstick test for 3–4 days and significant edema appears treatment should be started. A relatively shorter duration compared to initial dose regimen is usually followed in relapse. Prednisolone is given in full high dose of 60 mg/m^2/day (2 mg/kg/day) single or divided dose until urine protein is nil or trace for 3 consecutive days and subsequently a single morning dose of 40 mg/m^2/day (1.5 mg/kg) on alternate days for 4 weeks and then discontinued. Treatment of relapse usually last for 5–6 weeks.

Therapy for Infrequent Relapse

Patients suffering from three or fewer relapse a year should receive treatment for relapse as described above.

Frequent Relapse Nephrotic Syndrome (FRNS) and Steroid Dependent Nephrotic Syndrome (SDNS)

Up to 50% patient develop frequently relapsing or steroid dependent course.

More than two relapses in the first 6 months after initial steroid response predict for high risk for SDNS or FRNS. These patients should be managed by or in consultation with a pediatric nephrologist.

Long-term alternate day steroid: Long-term treatment with steroid is required to treat FRNS and SDNS. A high daily dose of steroid for prolonged period is associated with significant adverse effects, like growth failure, hypertension and cataract, while undertreatment with steroid may cause heightened disease activity with frequent relapse with its complications. A safe low level of steroid therapy which will prevent complications but at the same time which will suppress disease activity is desirable.

Following treatment of relapse when remission occurs, prednisolone is gradually tapered to maintain patient in remission on alternate day dose of 0.25–0.75 mg/kg which is given for 9–18 months. This is usually effective in maintaining remission in subsets of patients. Relapses may occur following infection or without obvious cause and may require daily prednisolone therapy.

Essential features of treatment of FRNS and SDNS:

- The principle of drug treatment of FRNS and SDNS consists of long-term alternate morning dose steroid at a minimum dose which minimizes the side effects of prednisolone and at the same time prevent disease relapse.
- Prednisolone dose is gradually tapered aiming for dose in the range 0.25–0.75 mg/kg. After around 6 months of therapy, the dose should be tapered so that remission can occur with minimal prednisolone dose.
- Whenever relapses occur, the subsequent maintenance dose of prednisolone should be given just above the dose at which relapse occurred. Close monitoring of the child for early detection of adverse side effects of steroid should be done at regular interval. Normal monitoring of growth, assessment of pubertal growth and bone mineral density should be done whenever indicated.
- Troublesome relapse require frequent follow-up visit which will allow careful weaning of the steroid or introduction of steroid sparing agents.
- Patients with SDNS will require higher maintenance dose of steroid. An alternate or step up immunosuppressant

agents are used in case of failure of remission with one immunosuppressant with adequate dose and duration.

Long-term Steroid Treatment and Growth

Growth particularly height can be impaired in NS either due to heightened disease activity because of undertreatment with steroid or prolonged treatment with high dose of steroid. A safe level of steroid therapy which will suppress disease activity but will allow child to grow is desirable.

Long-term treatment with steroid in a dose of 0.25 mg/kg/day (0.5 mg/kg/alternate day) usually does not negatively affect growth. Catch-up growth is possible during reduced dose when some children are on steroid holiday with or without taking levamisole, cyclophosphamide or cyclosporine as a steroid sparing drug, replacing steroid.

Dose between 0.25 and 0.75 mg/kg/day have little effect on growth. Dose greater than 0.75 mg/kg/day is usually associated with slowing of growth velocity. However, it is essential to consider each patient individually and note growth velocity on different dose for the particular child.

Steroid Sparing Agents and Steroid Holidays

Patients with frequent relapse or steroid dependent NS require prolonged treatment with steroid in an order to maintain disease remission. Although long-term steroid with significant high dose or even normal therapeutic dose can cause disease remission, but it may cause significant side effects of steroids including growth failure and steroid toxicity (hypertension, Cushing syndrome, etc.). It is expected that once these groups of children become sensitive to steroid, they will also be sensitive to other immunosuppressive drugs. Therefore, attempts are taken to use following immunosuppressive drugs which if introduced along with steroid may help to reduce the dose of steroid (steroid sparing effects) or even in some circumstances it may be possible to stop steroid at least for some period (steroid holiday) during which steroid side effects can be minimized and child may show compensatory growth particularly linear growth.

In children with SDNS, the use of steroid sparing drugs, like levamisole, cyclosporine, allows significant catch-up growth reflected by significant overall increase in height when not taking prednisolone. Cumulative steroid dose is important in final height which may be one component of the positive effect on growth of a steroid holiday.

The addition of an alternative agent is recommended if the child cannot be maintained in stable remission on an acceptable low dose 0.25–0.75 mg/kg on alternate day or if features of toxicity, like growth failure, hypertension, cataract, etc. appear.

The immunosuppressive drugs used are following:

- Levamisole and cyclophosphamide
- Tacrolim 0.1–0.2 mg/m^2/day for 12–18 months can also be used.

If relapses occur then other immunosuppressive agents, like mycophenolate mofetil, calcinurin inhibitors and rituximab, are used in successive order as shown in the Figure 38.

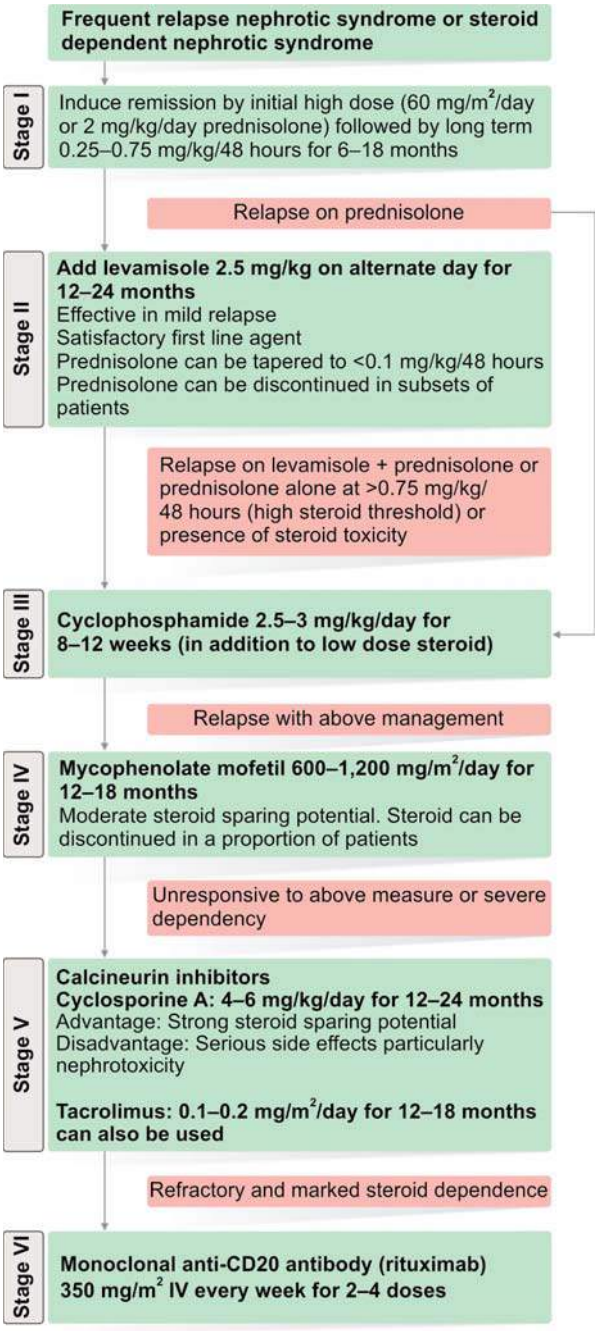


Fig. 38: Algorithm of management of FRNS and SDNS

Side Effects and Toxicity of Drugs Used in the Management of NS

I. Corticosteroids

- Cushingoid features like moon facies (Fig. 39), hirsutism, shoulder hump, massive obesity, striae, reduction of muscle mass and thinning of skin
- Hypertension
- Behavior disorders
- Osteoporosis
- Growth retardation
- Glucose intolerance
- Posterior subcapsular cataracts
- Myopathy
- Pseudotumor cerebri

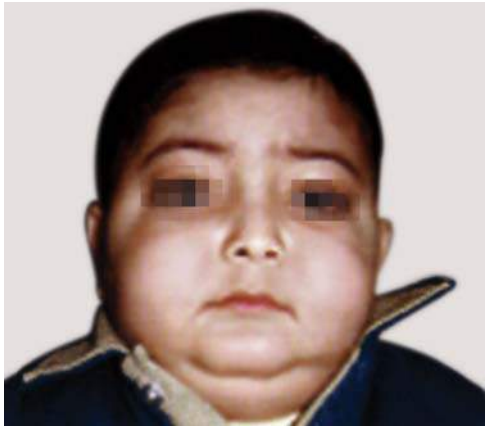


Fig. 39: Cushinoid face due to prolonged corticosteroid treatment in NS

II. Cyclophosphamide:
- Alopecia
- Hemorrhagic cystitis
- Bone marrow suppression
- Neutropenia
- Gonadal toxicity (azoospermia, ovarian fibrosis).

III. Levamisole:
- Neutropenia
- Vasculitis.

IV. Mycophenolate:
- Bone marrow suppression.

V. Cyclosporine:
- Hirsutism
- Gingival hypertrophy
- Hypertension
- Nephrotoxicity.

VI. Tacrolimus:
- Diabetes
- Nephrotoxicity.

Congenital and Infantile Nephrotic Syndrome

Congenital and infantile NS are two distinct presentations of NS presenting before 3 months age (congenital NS) and between 4 and 12 months of age (infantile NS).

Syndromal Association of Congenital NS

Following syndromes are associated with congenital NS:
- Denys-Drash syndrome
- Nail-patella syndrome (dysplastic nails and patella)
- Lowe syndrome (oculocerebrorenal syndrome)
- Galloway-Mowat syndrome (microcephaly and hiatus hernia)
- Frasier syndrome
- Pierson syndrome.

Etiology

The etiology of congenital and infantile NS may be primary or secondary.
The causes are as follows:

Primary:
- Finnish type congenital NS
- Diffuse mesangial sclerosis
- Focal segmental glomerulosclerosis
- Minimal change disease
- Membranous nephropathy.

Secondary:
- Infectious:
  - Congenital cytomegalovirus (CMV) infection
  - Hepatitis B and C
  - Congenital syphilis
  - Congenital toxoplasmosis
  - Congenital rubella
  - Malaria.
- Other:
  - SLE
  - Hemolytic uremic syndrome (HUS)
  - Nephroblastoma
  - Drug reaction
  - Mercury toxicity.

Finnish Type Congenital NS

Presentation:
- Autosomal recessive in inheritance
- Occurs due to mutation in the nephrin coding NPHS1 gene
- Almost in all cases end-stage renal failure (ESRF) develops.

Clinical features:
- Low birthweight
- Widely spaced fontanelles and cranial sutures
- Postural elbow and knee deformity
- Large placenta (>25% mass of newborn)
- Edema.

Investigations:
- Alpha feto-protein (AFP) is raised in maternal blood and amniotic fluid during pregnancy secondary to proteinuria
- Heavy proteinuria with rapid development of hypo-albuminemia
- Renal biopsy
  - Normal under light microscope in early life
  - Tubular dilatation resulting in diffuse microcystic change is the cardinal feature.

Management:
Aims of treatment:
- To maximize growth
- Reduce ineffective and thrombotic complications
- Maintain plasma albumin close to normal range by reduction of urinary protein loss and albumin infusion.

Treatment:
- Reduction of urinary protein loss:
  - Nephrectomy
  - Use of angiotensin-converting enzyme (ACE) inhibitors and prostaglandin inhibitor to reduce GFR thereby proteiuria
    ACE inhibitor: Captopril at a dose of 5 mg/kg in three divided doses
    Prostaglandin inhibitor like indomethacin at a dose of 4 mg/kg in three divided doses
- Replacement of albumin: Infusion of 20% albumin until bilateral nephrectomy is performed
- Diuretics:
  - Use frusemide to control edema
  - Close monitoring of growth and nutrition

- Administration of childhood vaccine: Use of thyroxine from birth.

Prognosis: By the age of 6–12 months, progressive glomerular sclerosis and interstitial fibrosis develop.

Diffuse Mesangial Sclerosis

- May be isolated renal disease or in association with Dennys-Drash syndrome
- Hypertension and CKD develop early in life.

Investigation:

Renal biopsy:

Light microscopy:

- Thickened glioblastoma multiforme (GBM) and increase mesangial matrix without hypercellularity
- Collapse capillary loops
- Dilated Bowman's space

Chromosomal analysis: For all pheotypical female to ensure that they are not male with pseudohermaphroditism.

Treatment:

- Renal transplantation
- Prophylactic nephrectomy for those with WT1 mutation.

Prognosis: Does not recur after transplantation.

Frasier's Syndrome

- Associated with male pseudohermaphroditism (46 XY DSD)
- Presents with:
  - Proteinuria between 2 and 6 years of age, also in infancy
  - Slow declination of renal function leading to ESRF.

Investigation: Characteristic histological features similar to those of FSGS.

Prognosis: High risk of development of gonadoblastoma.

Minimal Change Disease

- Rarely presents in infancy
- May be steroid responsive.

Focal Segmental Glomerulosclerosis

- May present in infancy
- Associated with NPHS2 mutation.

GLOMERULONEPHRITIS (GN)

It is the term used for a group of primary or secondary immune mediated renal disease characterized by inflammation of the glomeruli or small blood vessels in the kidney.

Etiology

The etiology includes noninfectious and postinfectious causes. These are as follows:

Postinfectious GN

Streptococcal:

- Nephritogenic strain of group A β-hemolytic streptococci.

Nonstreptococcal:

- Bacterial:
  - *Staphylococci*
  - *Pneumococci*
  - *Meningococci*
  - *Salmonella*
- Viral:
  - Hepatitis B and C
  - Cytomegalovirus
  - Epstein-Barr virus (EBV)
  - Echovirus
  - Varicella
  - Coxsackievirus
- Parasite:
  - *Plasmodium malariae*
  - *Plasmodium falciparum*
  - *Toxoplasma*
  - *Filaria.*

Noninfectious

- *Primary glomerular disease:*
  - Membranoproliferative GN
  - IgA nephropathy (Berger disease)
  - Mesangial proliferative GN
  - Focal and segmental glomerulosclerosis
- *Secondary to other systemic disorders:*
  - Henoch-Schönlein purpura
  - Systemic lupus erythematosus
  - Goodpasture syndrome
  - Hereditary nephropathy
  - Wegener's granulomatosis
- *Drugs:*
  - Penicillamine.

Pathogenesis

Glomerulonephritis leads to the following consequences: decreased GFR, proteinuria, hematuria, salt and water retention.

- *Reduction in GFR*
  Reduced GFR is associated either with acute kidney injury (AKI) or rapidly progressive renal failure.
- *Hematuria*
  It may be macroscopic or microscopic.
- *Proteinuria*
  Protein if massive may lead to hypoalbuminemia and the patient may present NS.
- *Salt and Water Retention*
  Retention of salt in GN leads to development of edema, intravascular volume expansion and systemic hypertension. These features constitute the hallmark of acute nephritis.

Clinical Features

Glomerulonephritis may present as asymptomatic hematuria or proteinuria, acute nephritis, rapidly progressive glomerulonephritis (RPGN) or mixed nephritic/nephrotic syndrome.

Acute Glomerulonephritis (AGN)

Acute glomerulonephritis is characterized by relatively abrupt onset of hematuria, oliguria, edema and hypertension. The clinical spectrum and histological severity are variable and are not always correlated. Milder presentation may be undetected, while in severe cases the child may present with complications

like anuria, hypertensive encephalopathy and heart failure. AGN following streptococcal infection is the commonest type.

Acute Poststreptococcal Glomerulonephritis (PSGN)

Etiology and epidemiology: AGN occurring after β-hemolytic streptococcal infection is the most common type in children which accounts about 80% of cases. Poststreptococcal glomerulonephritis occurs following pharyngitis, impetigo or skin lesion caused by group A β-hemolytic streptococci.

Poststreptococcal glomerulonephritis is decreasing in developed countries but in the developing countries it continues to be a significant cause of morbidity and mortality. Nephritis following pharyngitis is the most frequent cause of AGN in western countries, while in developing countries, skin infection (pyoderma) and impetigo are perhaps the most common cause of acute PSGN.

In North America, Saudi Arabia and Iran pharyngitis related nephritis is far more frequent than skin related nephritis. On the other hand, pyoderma associated nephritis predominates in developing countries, Southern USA and Chile. Skin infection particularly scabies with secondary bacterial infection by *Streptococcus* has been found to be a major association of acute nephritis in children. Secondary bacterial infection is one of the common complications of scabies which may be due to streptococcal or staphylococcal or both. Infected scabies and impetigo are perennial problems in tropical countries and epidemics of PSGN following infected scabies and impetigo are prevalent in different parts of the world.

Pathogenesis: The risk of developing AGN after infection with β-hemolytic streptococcus type 4 is 25%, while the overall risk with nephritogenic strains is 15%. Subclinical episodes occur 4–10 times more frequently than overt disease.

PSGN is a typical example of immune complex disease. The streptococcal antigen-antibody complexes are trapped in the glomerular capillaries as humps where they activate complement and initiate inflammatory changes (Fig. 40).

Pathology

- *Under light microscopy*: The glomeruli are enlarged and ischemic, and the capillary loops narrowed. There is proliferation of mesangial cells and infiltration with neutrophils.
- *Electron microscopy*: Deposits on subepithelial side of the glomerular basement membrane.
- *Immunofluorescence*: Granular deposits of IgG and complement (C3) along the capillary walls.

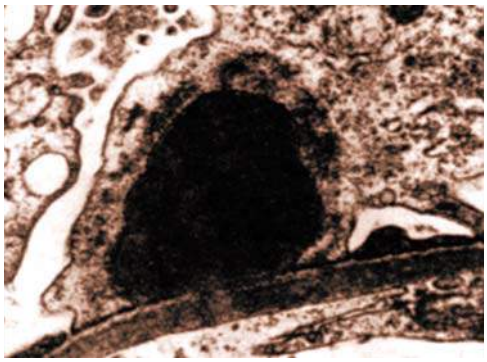


Fig. 40: Electron microscopy showing electron-dense subepithelial deposists or "humps"

Clinical Features

Onset of AGN is usually preceded by a history of sore throat (latent period is 7–14 days) or pyoderma or infected scabies (latent period is 2–4 weeks). The presenting features are:

- Milder cases present with microscopic hematuria and mild proteinuria
- Gross hematuria (Fig. 41E)
  - Lasts for few hours
  - Resolve within 1–2 weeks
- Edema
  - Usually on face (Fig. 41D)
  - Extends to hands and legs
- Oliguria
- Hypertension and hypertensive encephalopathy
  - Blood pressure is usually elevated
  - Hypertension persisting for more than 2–3 weeks is suggestive of chronic GN or RPGN
- Unconsciousness or altered level of consciousness
- Evidence of healed or active skin manifestation (infected scabies or impetigo) may be present (Figs 41A to C)
- Evidence of active pharyngitis, however, usually not present at the time of presentation of nephritis
- Atypical presentation
  - Mild edema without gross hematuria and any history of sore throat
  - May present with complications of AGN which include:
    - Acute pulmonary edema
    - Hypertensive encephalopathy
    - Acute kidney injury
    - Nephrotic syndrome
    - Systemic manifestation like fever, abdominal pain, rash, arthritis and hepatosplenomegaly.

Hypertensive Encephalopathy

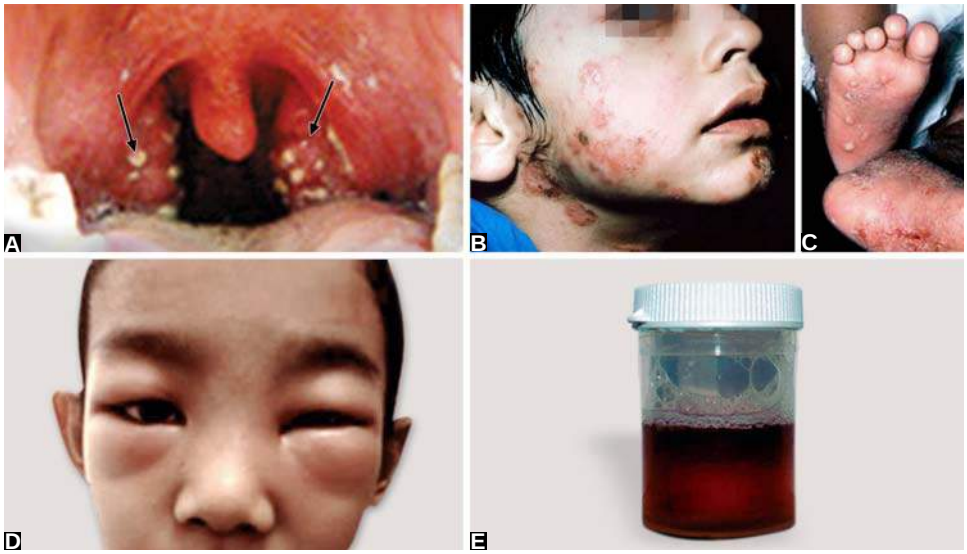
Hypertensive encephalopathy is occasionally present/manifest as convulsion, unconsciousness and neurological deficit. It is usually found in 10% of patients with PSGN. Hypertension alone is not responsible for encephalopathy or EEG change, but concomitant presence of azotemia may render the child more susceptible to cerebral autoregulatory dysfunction resulting in hypertensive encephalopathy. Although hypertensive encephalopathy improves rapidly with proper management of AGN, there are few reports of case fatality associated with hypertensive encephalopathy are reported.

Skin Infection and AGN

Considering possible serious consequences of skin infection in developing countries particularly in infected scabies, skin infection in children should be treated appropriately and optimally and should not be left untreated. Emphasis should be given on personal hygiene and cleanliness. Physician should be aware that the skin infection particularly pyoderma and infected scabies is not as benign as popularly believed and should manage the dermatosis appropriately and should prepare themselves accordingly to manage possible consequence of AGN.

Nephritic/Nephrotic Syndrome

Usually gross proteinuria does not occur in PSGN. However, in few cases (up to 4% of cases) there may be heavy proteinuria



Figs 41A to E: (A) Showing acute follicular tonsillitis; (B) Impetigo; (C) Infected scabies associated with acute PSGN; (D) Showing edema of face and eyelids; (E) Showing gross hematuria in acute PSGN

and hypoproteinemia which present as clinical features of nephritic/nephrotic syndrome.

Investigations

- *Urinalysis*:
  - Gross hematuria in majority of cases
  - Mild proteinuria
  - Microscopy
    - Dysmorphic RBC and RBC cast
- *Renal function tests*:
  - Blood urea: Elevated
  - Serum creatinine: Elevated
- *Serum electrolytes*:
  - Hyponatremia, hyperkalemia and acidosis
- *Evidence of streptococcal infection*: Evidence of streptococcal infection is suggested by elevated titer of ASO.
  - In poststreptococcal sore throat ASO titer begin to rise 1–3 weeks after the streptococcal infection, peaks at in 3–5 weeks and then falls
  - In pyoderma, anti-hyaluronidase and ADNase B rise
  - Culture from throat swab may reveal *Streptococci.*

Evidence of Streptococcal Infection in AGN following Sore Throat and Pyoderma

Antibodies include:

- ASO
- Streptokinase
- Anti-hyaluronidase
- ADNase B
- ANADase

After streptococcal pharyngitis 80% of children will have raised ASO titer whereas in pyoderma even when associated with AGN, ASO response is frequently slight or absent. Poor ASO response in skin infection is due to the fact that skin cholesterol is a potent and specific inhibitor of some of the biological activities of streptolysin O. Binding with cholesterol modifies both its hemolytic capacity and cardiotoxic effect and also prevents it from interaction with immunocompetent cells and thus prevents immune response. In contrast, immune response to DNase is greater in patients with pyoderma associated AGN than in patients with pharyngitis group. ADNase B titer also persists at elevated level for longer period of time than in comparable ASO titer. ADNase B titer appears to be most reliable for documenting serological evidence of streptococcal infection in patients with AGN particularly associated with streptococcal skin infection.

- Serum complement level
  - C3 level is low in about 90% cases of AGN
  - C3 regains normal value by 6–8 weeks
  - C4 level is normal
- Viral markers for hepatitis
  - Hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (anti-HCV)
- Echocardiogram (ECG)
- Chest X-ray
- Ultrasonography of KUB region
- Renal biopsy.

Indications for Renal Biopsy in Acute Glomerulonephritis

- Systemic features like fever, rash, heart disease, joint pain
- Delayed resolution of:
  - Oliguria, hypertension and/or azotemia persisting beyond 7–10 days
  - Gross hematuria persisting more than 3–4 weeks
  - Persistent microscopic hematuria beyond 12–18 months
  - Nephrotic range proteinuria more than 2 weeks
  - Persistent proteinuria more than 6 months
  - Low levels of C3 beyond 12 weeks
- High blood levels of urea or presence of anuria requiring dialysis (RPGN)
- Absence of serologic markers of streptococcal infection, normal levels of C3 in acute illness
- Mixed presentation of GN and NS

The biopsy findings of different GN are given in Table 6.

Management

Treatment is symptomatic. Patients with moderate to severe hypertension and oliguria should be hospitalized.

Table 6: Biopsy findings of different glomerulonephritis

A. Nonproliferative glomerulonephritis
• Minimal change glomerulonephritis – Light microscopy: No visible change – Electron microscopy: Fusion of FP of podocytes • Focal and segmental glomerulosclerosis – Segmental sclerosis (fibrosis) of foci of glomeruli – Feeding arteries are hyalinized • Membranous glomerulonephritis – GBM is thickened – "Spike and dome" pattern is seen due to diffuse glomerular uptake of IgG
B. Proliferative glomerulonephritis
• Postinfectious glomerulonephritis – Deposition of IgG and C3 within glomeruli • IgA nephropathy – Messangial proliferation and IgA deposit within the matrix • Membranoproliferative glomerulonephritis – Proliferation of cells and matrix within the mesangium • Crescentic glomerulonephritis – Passage of fibrin into Bowman's capsule and an influx of monocytes

General management:

- Strict bed rest is not essential.
- Fluid restriction (allowed amount of fluid is restricted to UO plus insensible loss)
- Diet
  - Dietary sodium restriction for fluid restriction
  - If AKI is present diet rich in carbohydrate should be offered.
  - Dietary intake of protein should be restricted until blood levels of urea reduced and UO increases.
- Weight: Weight should be monitored daily. Fluid intake is to be reduced if weight gain is evident.
- Diuretic
  - Loop diuretics like oral frusemide (1–3 mg/kg) can be used to control edema and volume related hypertension.
  - Intravenous frusemide (2–4 mg/kg) may be required in presence of pulmonary edema
- Hypertension
  - Restriction of salt and water intake control mild hypertension
  - Antihypertensive agent, like nifedipine, amlodipine and atenolol, can be used to control hypertension
  - Hypertensive emergencies need prompt treatment with IV nitropruside or labetalol
- Left ventricular failure
  - Control of hypertension
  - Intravenous frusemide to induce diuresis
  - Urgent dialysis if no immediate diuresis after IV frusemide administration

II. *Specific management*:

- Antibiotics can help eradicate the offending organism where appropriate.
- Penicillin may be administered for 7 days if active pyoderma and residual pharyngitis are present.
- Antibiotic therapy prevents spread of streptococcal infection among the contacts but do not help nephritis.

Prognosis and Outcome

The long-term outcome of PSGN is excellent. The symptoms begin to resolve in the 1st week with decreasing edema and blood pressure.

- Gross hematuria and significant proteinuria usually require about 2 weeks to resolve, whereas microscopic hematuria and mild proteinuria may persist for several months
- Hypertension subsides within 2–3 weeks
- Careful long-term follow-up is essential for children with AGN other than poststreptococcal infection. Follow-up includes periodic urine examination and measurement of blood pressure. Acute glomerulonephritis of non-streptococcal etiology have variable and unpredictable outcome.

RENAL INVOLVEMENT IN HENOCH-SCHÖNLEIN PURPURA

Henoch-Schönlein purpura in a generalized vasculitis characterized by various combination of skin, GI and renal involvement (Fig. 42).

Henoch-Schönlein purpura can occur at any age but is most common in childhood. It is usually a self-limited disease. The extra renal symptoms typically resolve rapidly without complication, and the long-term prognosis is mainly dependent on the severity of renal involvement.

Renal disease affects approximately one-third of patients varying from intermittent hematuria and proteinuria to severe nephrotic/nephritic syndrome (Table 7). Hypertension may be found in the presence of renal involvement. Although renal involvement is in most cases mild and self-limited, it has been claimed that about 1% of patients progress to ESRF. Henoch-Schönlein purpura nephritis occurs mostly in the early course of HSP.

Risk Factors for Developing HSP Nephritis

- Nephrotic syndrome
- Decreased Factor VIII activation
- Hypertension
- Renal failure at onset
- Abdominal pain
- Persisting purpura
- Older age.

Investigations

Investigations for HSP nephritis are same as for the diagnosis of HSP which include:

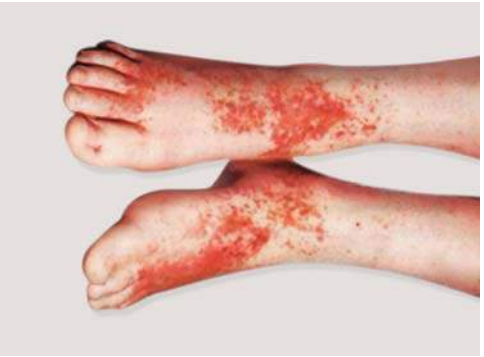


Fig. 42: Typical vasculitic rash of HSP

Table 7: Criteria for renal involvement of Henoch-Schönlein purpura

Renal symptoms	Criteria
Hematuria	>5 red cell/field/HPF for positive dipstick test
Proteinuria	Urine protein >200 mg/L, urine albumin >30 mg/L or positive dipstick test
Hematuria and proteinuria	See above
Nephrotic range proteinuria	24 hours urine protein >40 mg/m^2/h
Nephritic/nephrotic syndrome	>200 RBC/HPF and 24 hours urine protein >40 mg/m^2/hand at least two of the following findings: • Oliguria • Hypertension • Renal dysfunction

- Complete blood count
- Blood urea and serum creatinine
- Urinalysis for proteinuria and hematuria
- Serology
  - Antinuclear antibody (ANA)
  - Rheumatoid factor
  - Complement level (C3 and C4)
  - Serum IgA
- Skin biopsy
- Renal biopsy.

Renal Biopsy

A renal biopsy is indicated only in children with persistent or significant renal manifestations.

Indications for diagnostic renal biopsy in children with HSP are:

- Nephritic/nephrotic presentation
- Raised creatinine, hypertension, or oliguria
- Heavy proteinuria (U_a:U_{cr} persistently >100 mg/mmol) on an early morning urine sample at 4 weeks
- Serum albumin not necessarily in the nephrotic range
- Persistent proteinuria (not declining) after 4 weeks
- Impaired renal function (GFR <80 mL/min/1.7m^2).

Histological Classification of HSP Nephritis

Based on renal biopsy features HSP nephritis is classified under six grades. These grades are mentioned in Table 8.

Treatment

Rapidly Progressive Glomerulonephritis

Immunosuppressive agents can be used but do not have favorable response. Aggressive treatment with corticosteroid, cyclophosphamide and possibly plasma exchange may be helpful.

Treatment of HSP Nephritis which is not Rapidly Progressive

Daily three doses of 600 mg/m^2 methyl prednisolone followed by 2 mg/kg oral prednisolone for 4 weeks should be given. During 4 weeks' assessment, if there is no improvement stop prednisolone, if improvement then continue oral prednisolone up to 6 months in total.

Table 8: Histological grading of HSP nephritis

Grade I		
	Minor glomerular abnormality	
Grade II		
	Pure mesangial proliferation	
	IIa.	Focal
	IIb.	Diffuse
Grade III		
	Minor glomerular abnormalities or mesangial proliferation with crescent in less than 50% of glomeruli	
	IIIa.	Focal
	IIIb.	Diffuse mesangial proliferation
Grade IV		
	Similar to grade III but with crescents/segmental lesions in 50–75% of glomeruli	
	IVa.	Focal
	IVb.	Diffuse mesangial proliferation
Grade V		
	Similar to grade IV but with crescents/segmental lesions in >75% of glomeruli	
	Va.	Focal
	Vb.	Diffuse mesangial proliferation
Grade VI		
	Lesions resembling mebranoproliferative glomerulonephritis	

Role of Corticosteroid in HSPNephritis

Corticosteroids alleviate the extrarenal symptoms of HSP effectively but do not prevent the development of nephritis.

LUPUS NEPHRITIS

Lupus nephritis (LN) is the heterogeneous renal manifestation of SLE and is characterized by a high variability of clinical and histological presentations with an unpredictable course of renal disorders and extra- renal comorbidity. A significant number of children with SLE are associated with nephritis which usually becomes evident 2–3 years of onset of SLE.

Clinical Features

The initial clinical manifestation of LN is characterized mostly by glomerular dysfunction of varying range. Common presentations are:

- Macroscopic or microscopic hematuria
- Proteinuria including NS
- Hypertension
- Decreased GFR.

One-third of lupus patients may develop the antiphospholipid syndrome (APS) nephropathy that is characterized by arterial hypertension, proteinuria, hematuria and renal insufficiency.

Classification of Lupus Nephritis

International Society of Nephrology/Renal Pathology Society classifies LN into six categories which are given in Table 9.

Table 9: Classification of lupus nephritis

WHO Class	ISN/RPS classification
Class I	Minimal mesangial lupus nephritis LM: Normal glomeruli IF or ISN/RPS classification M: Mesangial immune deposits
Class II	Mesangial proliferative lupus nephritis LM: Pure mesangial hypercellularity of any degree of mesangial matrix expansion EM/IF: Mesangial immune deposits with none or few isolated subepithelial or subendothelial deposits
Class III	Focal lupus nephritis Involves <50% glomeruli: III(A); III(A/C); III (C)
Class IV	Diffuse lupus nephritis segmental (IV-S) or global (IV-G) (Fig. 43) Involving >50% glomeruli: IV-S (A); IV-S (A/C); IV-S (C); IV-G (A); IV-G (A/C); IV-G(C)
Class V	Membranous lupus nephritis (Fig. 44) Pure membranous, V+III; V+IV depending upon degree of proliferation
Class VI	Advanced sclerosing lupus nephritis >90% glomeruli show global sclerosis with no evidence of ongoing active glomerular disease

Abbreviation: A, Active; C, Chronic; G, Global; LM, Light microscopy; EM, Electron microscopy; IF, Immunofluorescence.

Laboratory Investigations

A number of investigations are required for the diagnosis of SLE and LN. Among these ANA is positive in 95% by enzyme-linked immunosorbent assay (ELISA). Anti-dsDNA is specific for SLE. Smith (Sm) antibody is specific to SLE as well as a marker for central nervous system (CNS) disease.

The investigations to be done at onset of SLE are as follows:

- *Blood*
  - Complete blood count
  - C-reactive perotein
  - Urea, creatinine
  - Serum electrolytes
  - Alkaline phosphatase
  - Transaminase
  - Total protein
  - Serum albumin
- *Serology*
  - Antinuclear antibody
  - Anti-dsDNA
  - AntiSm
  - Antiphospholipid antibody
  - Complement C3, C4 (low C3 and low C4)
- *Urinalysis*
- *Others*
  - Lipid profile
  - Thyroid function test
  - Chest X-ray
  - Tuberculin test
  - Coagulation screening
  - Pulmonary function testing
  - Screening for hepatitis B, C and HIV
- *Renal Biopsy*

  Indications for renal biopsy are:
  - Raised serum creatinine
  - Proteinuria
  - Active urinary sediment

Diagnosis of Lupus Nephritis

Diagnosis of LN can be made by using the following lupus criteria:

Lupus Criteria

I. Clinical criteria:

- Acute or subacute cutaneous lupus (Fig. 45)
- Chronic cutaneous lupus
- Oral/nasal ulcers
- Nonscarring alopecia
- Inflammatory synovitis with physician-observed swelling of two or more joints or tender joints with morning stiffness
- Serositis
- Renal: Urine protein/creatinine (or 24 hours urine protein) representing at least 500 mg of protein/24 hours or RBC casts

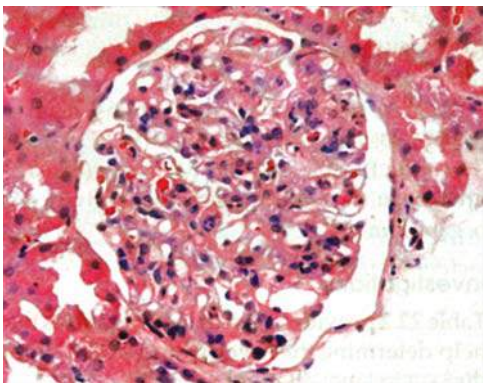


Fig. 43: Class IV LN: Light microscopy showing endocapillary and mesangial proliferation with luminal occlusion, suggestive of diffuse proliferative LN

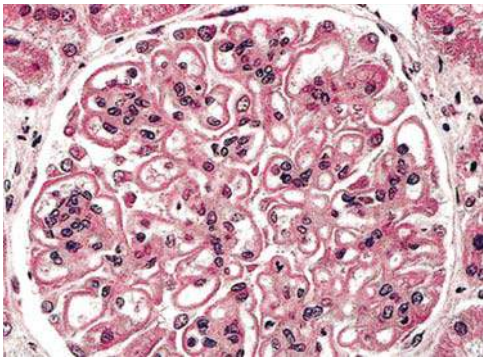


Fig. 44: Class V LN: Light microscopy showing glomerulus with stiff and diffusely thickened capillary walls, patent capillary lumina and lack of proliferation, suggestive of membranous LN

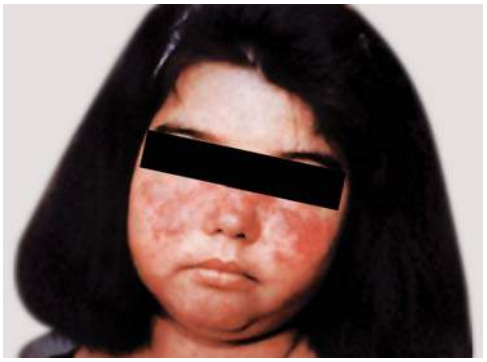


Fig. 45: Typical skin rash (butterfly distribution) of SLE

- Neurologic: Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, cerebritis (acute confusional state), hemolytic anemia
- Leukopenia (<4,000/mm^3 at least once) or lymphopenia (<1,000/mm^3 at least once)
- Thrombocytopenia (<100,000/mm^3) at least once

II. Immunologic criteria:

- Antinuclear antibody above laboratory reference range
- Anti-dsDNA above laboratory reference range (except ELISA: twice above laboratory reference range)
- AntiSm
- Antiphospholipid antibody
  - Lupus anticoagulant
  - False-positive test for syphilis
  - Anticardiolipin—at least twice normal or medium-high titer
  - Anti-beta 2-glycoprotein 1
- Low complement
  - Low C3
  - Low C4
  - Low CH50
- Direct Coombs test in absence of hemolytic anemia.

Treatment of Lupus Nephritis

General Treatment

- Use of sunscreen [sun protection factor (SPF) >15]
- Hydroxychloroquine sulfate (HCQ) for children with arthritis and skin disease
- Angiotensin-converting-enzyme inhibitors to control hypertension
- Calcium and vitamin D supplementation in children with prolonged steroid therapy
- Immunization
  - Avoid live vaccine
  - Pneumococcal vaccination for patients on long-term steroid.

Specific Treatment

Class II lupus nephritis:

Prednisolone (1 mg/kg/day) with tapering on maintenance + Azathioprine (2–2.5 mg/kg/day) for 12–24 months.

Class III/IV/ III+V/ IV + V lupus nephritis:

Prolonged immunosuppressive therapy is required which consists of induction treatment for 5–6 months followed by a maintenance therapy for 3–5 years.

Induction therapy: Methyl prednisolone (500 mg/m^2 for 3–5 days), high dose prednisolone (1–2 mg/kg/day for 6–8 weeks) are the choice for induction therapy.

Intravenous rituximab and IV immunoglobulin can be used in several specific settings.

Maintenance therapy: Class III and IV LN require prolonged period of maintenance therapy. The choices are:

- Prednisolone + Mycophenolate mofetil (MMF)
- Prednisolone + Azathioprine.

Class V lupus nephritis:

- The induction therapy for class V LN comprises prednisolone plus either of MMF or cyclophosphamide or azathioprine.
- Maintenance therapy is to be continued for 5 years after remission.

Prognosis

Prognosis of LN depends on the pathological types as well as treatment regimen.

- One-fifth of all Caucasian children with LN have class I and II LN and a good prognosis
- Prognosis of LN class III representing one-fifth of all LN patients in childhood depends on the percentage of affected glomeruli
- Class V LN has a good prognosis
- Prognosis of class VI is poor and immunosuppressive therapy may not be beneficial.

Features that suggest poor prognoses are:

- Persistent proteinuria
- Hypertension
- Increase in serum creatinine.

IMMUNOGLOBULIN A NEPHROPATHY

Immunoglobulin A nephropathy (IgAN) is a glomerular disease characterized by renal IgA deposits mostly in the mesangial area.

Epidemiology

- Immunoglobulin A nephropathy is common in children and adolescents.
- Primary IgAN is more frequently found in males than in females.

Etiology

Mucosal infection has been found to be associated with development of IgAN. Upper respiratory tract pathogen, like *Hemophilus para influenzae*, Coxsackie B4, *Staphylococcus aureus*, CMV, EBV, *Enterovirus*, have been found to cause IgAN.

Pathogenesis

An overview of pathogenesis of IgAN (Fig. 46):

1. Mucosal infection primes naïve B cells to class switch to become IgA$^+$ antibody-secreting cells (ASCs) through both T-cell-dependent (cytokine mediated) and T-cell-independent [Toll-like receptor (TLR) ligation] pathways.
2. Some IgA$^+$ASCs mishome to the systemic compartment during lymphocyte trafficking.
3. Displaced IgA$^+$ASCs take up residence in systemic sites and secrete normal "mucosal-type" (poorly galactosylated and polymeric) IgA1 into the systemic circulation.
4. IgA1 secretion by displaced mucosal ASC is augmented by TLR ligation from mucosal-derived pathogen-associated molecular patterns, which have entered the systemic compartment.

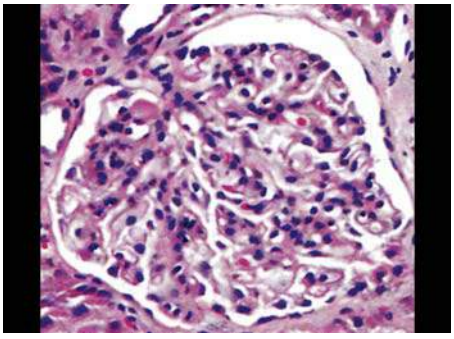


Fig 46: Mesangial proliferation in light microscopy

5. IgA1 immune complexes form in the systemic circulation. Poorly galactosylated polymeric IgA1 molecules are the substrate for immune complex formation and combine with:
   - IgG and IgA autoantibodies reactive to exposed neoepitopes in the poorly galactosylated IgA1 hinge region
   - Antimicrobial antibodies specific for carbohydrate components of the microbial cell wall, which are cross-reactive with the poorly galactosylated IgA1 hinge region
   - Soluble CD89 that is shed from myeloid cells in response to polymeric IgA1 binding.
6. IgA1 immune complexes deposit in the mesangium through a combination of mesangial trapping and increased affinity of poorly galactosylated IgA1 for extracellular matrix components. Immune complex deposition triggers a series of downstream pathways leading to glomerular injury and tubulointerstitial scarring.

Clinical Features

The features of IgAN vary. IgAN typically presents with macroscopic hematuria concomitant with upper respiratory tract infection.

- Hematuria
  There may be persistent hematuria or recurrent episodes of gross hematuria (occurs in 30–40% children).
  - Macroscopic hematuria
    - Urine is red or dark brown (coke colored)
  - Microscopic hematuria
- Proteinuria
- Flank or loin pain
- Fever may be present
- May also present as NS with hematuria.

Differential Diagnosis

Besides histological types on renal biopsy the differential diagnoses are:

- Postinfectious GN
- Systemic lupus erythematosus
- Henoch-Schönlein purpura
- Cryoglobulinemia.

Investigations

Urinalysis
- Urinalysis shows proteinuria and presence of RBCs with or without red cell casts
- 24 hours urinary protein excretion
- Urinary protein/creatinine ratio

- Renal function tests
  - Blood urea and serum creatinine may be high reflecting the degree of renal impairment
- Serum complement C3 and C4
  - Usually normal
- Serum IgA level
  - Usually high in 30–50% cases
- Renal biopsy
  - Immunofluorescence or immunocytochemistry study shows glomerular deposition of IgA which is the hallmark of IgAN (Fig. 47).

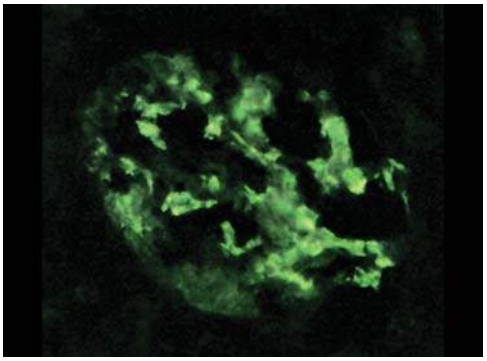


Fig 47: Immunofluorescence showing positive staining of IgA deposition in mesangium

Classification of IgAN

Classification based on renal histology and severity of renal damage is as follows:

1. Minimal or no mesangial hypercellularity without glomerular sclerosis
2. Focal and segmental glomerulosclerosis without active cellular proliferation
3. Focal proliferative GN
4. Diffuse proliferative GN
5. Biopsy showing ≥40% globally sclerotic glomeruli and/or ≥40% cortical tubular atrophy.

Diagnosis

The diagnosis of primary IgAN is confirmed by the presence of predominant IgA deposits in the glomeruli with the absence of systemic diseases (HSP, SLE), cutaneous or liver disease, and malabsorption syndrome.

Treatment

Treatment depends on clinical presentation. Outline of treatment is given in Table 10.

Table 10: IgA nephropathy treatment outline

Isolated microscopic or gross hematuria with normal renal function, no proteinuria	
	No specific treatment is required, only monitor urinary protein 3–6 monthly
Microscopic or gross hematuria with non-nephrotic proteinuria	
	• No specific treatment if urinary protein excretion is <0.5 g/1.73 m^2/day • ACE inhibitor or angiotensin receptor blockers (ARB) if proteinuria 0.5–1.0 g/m^2/day
Nephrotic range proteinuria or onset with NS	
	Prednisolone with cyclophosphamide followed by azathioprine and ACE inhibitor/ARB
Acute nephritic syndrome with no crescent on biopsy	
	Prednisolone and azathioprine
Rapidly progressive glomerulonephritis with crescents involving >30% glomeruli	
	Induction therapy with methylprednisolone followed by prednisolone and cyclophosphamide Maintenance therapy with prednisolone and azathioprine
Advanced disease where GFR <30 mL/min/1.73 m^2; high chronicity	
	Supportive therapy as immunosuppression is not beneficial

Prognosis

Children with IgAN and high levels of proteinuria are at risk for progressive disease.
Factors determining poor prognosis are:
- Presence of heavy proteinuria
- Persistent hypertension
- Impaired renal function at onset
- Renal biopsy showing sclerosis in >20% of glomeruli, crescents, tubulointerstitial disease.

MEMBRANOUS NEPHROPATHY

Membranous nephropathy, though uncommon in childhood is responsible for NS in few cases. Most of the patient present in late adolescence and late childhood.

Etiology

Idiopathic

Idiopathic MPGN is defined by exclusion of any other identifiable cause, most typically when the ultrastructural pattern is type I MPGN.

Secondary

Secondary to:
- Viral infection (hepatitis B or C, EBV)
- Systemic lupus erythematosus
- Sickle cell hemoglobinopathy
- Drugs (penicillamine, gold salts).

Clinical Features

Children with membranous nephropathy present with NS, asymptomatic proteinuria with or without hematuria.

Investigation

- Complete blood count
- Blood urea
- Serum creatinine
- Serum albumin
- Serum cholesterol
- Complement C3 level
- Urinalysis for proteinuria and microscopic hematuria
- Serological markers of hepatitis B and C, HIV
- Antinuclear antibody
- Renal biopsy
  - *Light microscopy:* Thickening of glomerular capillary wall
  - *Electron microscopy:* Multiple, finely granular, electron dense deposits along the subepithelial surface
  - *Immunofluorescence:* Granular staining for IgG and complement C3 found along the subepithelial surface. In case of SLE, "full house" pattern of immunoglobulin and C1q staining and mesangial or endocapillary proliferation are seen.

Treatment

Presumed idiopathic MPGN accompanied by NS and progressive decline of kidney function receive oral cyclophosphamide or MMF plus low-dose alternate day or daily corticosteroids with initial therapy limited to less than 6 months.

A. Asymptomatic, non-nephrotic proteinuria
- No immunosuppression in case of normal renal function and no edema
- Angiotensin receptor blocker and ACE inhibitor for proteinuria

B. Nephrotic syndrome
- Prednisolone 1.5 mg/kg on alternative day for 4 weeks followed by 1 mg/kg for 12–24 months and tapered plus
- Oral cyclophosphamide (2 mg/kg/day for 12 weeks)
- Other alternatives are:
  - Mycophenolate mofetil (600–1,000 mg/m^2)
  - Rituximab (375 mg/m^2 once weekly for 4 weeks).

Prognosis

- Prognosis is better if the onset is in early childhood, non-nephrotic proteinuria, and normal renal function at onset.
- Prognosis is poor if renal histology shows:
  - Tubulointestinal damage
  - Segmental and glomerular sclerosis
  - Intramembranous deposits with thickening and dissolution of the basement membrane.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

Other name is mesangiocapillary glomerulonephritis. This type of GN is characterized by mesangial cell proliferation and thickening of capillary wall due to subendothelial extension of the mesangium.

Classification

Membranoproliferative glomerulonephritis is classified as primary and secondary MPGN. Majority of causes are grouped under primary MPGN. Secondary is due to infection with several organisms.
- Primary MPGN
  - Idiopathic
- Secondary MPGN
  - Secondary due to infection with:
    - *Streptococci* and *Staphylococci*
    - Hepatitis B and C
    - Systemic lupus erythromatosus
    - Human immunodeficiency virus
  - Cryoglobulinemia type II

Pathological Classification

Membranoproliferative glomerulonephritis is classified into three categories based on immunofluorescence and electron microscopy findings.

Type I MPGN (classical or subendothelial MPGN):
- Most common type
- Subendothelial immune complex deposition secondary to activation of classic complement pathway
- Capillary wall thickening
- Double contouring of basement membrane.

Type II MPGN (dense deposit disease):
- Immune complex is absent
- Dense deposit within the glomerular basement membrane
- Results from activation of alternative complement pathway
- May be associated with partial lipodystrophy.

Type III MPGN:
- Variant of type I having subendothelial and subepithelial deposit.

Investigations

- Urinalysis for proteinuria, hematuria, RBC cast, dysmorphic red cell
- Blood: Urea, creatinine, lipid profile, transaminase
- 24 hours or spot urinary protein-creatinine ratio
- Serological markers of infection with HBV, HCV, HIV
- Others: Chest X-ray, USG of abdomen, ECG
- Complement abnormalities
  - C3 is low in greater than 50–60%, more commonly in type II MPGN
  - C1q and C4 is low in some cases
  - C2 or C3 are low in some children due to inherited abnormalities of the complement system.

Clinical Features

MPGN is the underlying cause of NS accounting for 5–7% cases. The presenting features are:
- Asymptomatic proteinuria and hematuria
- Nephrotic syndrome
- Acute nephritic syndrome
- Hypertension
- Recurrent gross hematuria
- Impaired renal function.

Treatment

- There is no specific treatment for MPGN. After exclusion of secondary causes, nephrotic range proteinuria is treated with oral prednisolone. ACE inhibitors can be used to treat proteinuria.
- For patients with RPGN: Initial IV methyl prednisolone (20–30 mg/kg/day IV for 3–6 pulses) followed by oral prednisolone
- Plasmapheresis is the choice of treatment for patients with Factor H deficiency MPGN type II with circulating C3 nephritic factor (C3NeF) and post-transplantation recurrence.

Prognosis

- End-stage renal disease may ensue in 50% cases if left untreated
- Spontaneous resolution rates are high in MPGN following treatment of bacterial infection
- Transplantation has no benefit as the rate of recurrence is high.

Factors that Causes Poor Outcome

- Type II MPGN
- Nephrotic syndrome at presentation
- Persistent low GFR beyond 12 months after diagnosis
- Significant amount of chronic damage (like interstitial fibrosis, tubular atrophy or glomerular sclerosis) on initial biopsy.

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Rapidly progressive glomerulonephritis consists of clinical features of GN with rapid loss of renal function. It is a medical emergency as it results in irreversible loss of renal function if left untreated.

Etiology

The etiology of RPGN is as follows:

I. Immune Complex GN

- Post-infectious
  - Poststreptococcal glomerulonephritis
  - Infective endocarditis
  - HIV
  - Hepatitis B and C
  - *S. aureus* sepsis
- Systemic disease
  - Systemic lupus nephritis
  - Henoch-Schönlein purpura
  - Rheumatoid arthritis
- Primary glomerulonephritis
  - IgA nephropathy
  - Membranoproliferative glomerulonephritis.

II. Pauci-immune Crescentic GN

- Idiopathic crescentic GN
- Microscopic polyangiitis
- Wegener's granulomatosis
- Drugs: Penicillamine, hydralazine, propylthiouracil.

III. Anti-glomerular Basement Membrane (Anti-GBM) GN

- Anti-GBM nephritis
- Goodpasture syndrome
- Post-renal transplant in Alport syndrome.

Clinical Features

The features are similar to those of post-infectious GN. The course of disease extends over several days. The presenting features are:
- Oliguria
- Macroscopic hematuria
- Hypertension
- Edema.

This condition may be complicated with hypertensive emergencies, pulmonary edema and cardiac failure.

Pauci-immune crescentic GN presents with some systemic features like:
- Respiratory tract: Cough, sinusitis
- Skin: Vasculitic rash
- Musculoskeletal: Joint pain and swelling
- Nervous system: Seizures, altered sensorium.

Investigations

- Complete blood count with peripheral blood film
- Urinalysis for proteinuria, hematuria
- Renal function tests: Urea, creatinine, electrolytes, calcium, phosphate
- Serology
  - ASO titer
  - Antinuclear antibody
  - Anti-dsDNA antibodies
  - Antineutrophil cytoplasmic antibodies (ANCA)
  - Immunofluorescence
  - ELISA
- Renal biopsy.

For Specific Diagnosis

- Anti-GBM antibodies
- Radiograph, CT scan of chest (for Goodpasture syndrome and vaculitides)
- Radiograph and CT scan of sinuses (for suspected Wegener's granuolmatosis).

Treatment

Supportive

- Maintenance of fluid and electrolyte balance
- Maintenance of adequate nutrition
- Control of infection
- Control of hypertension.

Specific

- *Induction of remission*: Initially high dose of corticosteroid and cyclophosphamide with pulse of IV methyl prednisolone (15–20 mg/kg for 3–6 days) followed by high dose of oral prednisolone (1.5–2 mg/kg/day daily for 4 weeks, with tapering to 0.5 mg/kg/day daily for 3 months and alternate day prednisolone for 122–24 months).
- Plasmapheresis:
  - During induction phase, double volume plasmapheresis is recommended for Pauci-immune, ANCA-positive crescentic GN and renal failure (serum creatinine >2.5–3 mg/dL)
  - Anti-GBM disease with anuria and severe azotemia
- *Maintenance*: Azathioprine 1.5–2 mg/kg/day or MMF (1,000–1,200 mg/m^2/day) and prednisolone 0.5–1 mg/kg on alternate days with tapering.

Prognosis

Better prognosis with spontaneous improvement ensues in patients with poststreptococcal crescentic GN. Prognosis is poor with Pauci-immune crescentic GN and MPGN.

DISORDERS OF RENAL TUBULES

Disorders of renal tubules consist of following diseases in three main categories. These are:

I. Proximal tubulopathies
- Cystinuria
- Cystinosis
- X-linked hypophosphatemic rickets
- Proximal (type 2) renal tubular acidosis (RTA)
- Fanconi syndrome.

II. Disorders of loop of Henle and distal tubules
- Bartter syndrome
- Gitelman syndrome
- Distal (type 1) RTA.

III. Disorders of collecting duct
- Nephrogenic diabetes insipidus
- Pseudohypoaldosteronism type I
- Liddle syndrome.

Cystinuria

It is an autosomal recessive disorder of cysteine and dibasic amino acids. Other amino acids involved are lysine, ornithine, arginine (LOA).

Pathology

Defect in the renal dibasic amino acid transporter causes excessive excretion of cysteine and dibasic amino acids. Cysteine is poorly soluble in normal urine pH and recurrent radiopaque urinary stones are formed.

Treatment

- High fluid and sodium (2–6 mmol/kg/day) intake
- Alkalinization of urine (bicarbonate 2–15 mmol/kg/day) with oral potassium citrate (2–6 mmol/kg/day)
- Phosphate salt supplementation
- D-penicillamine: If above measures fail.

Renal Tubular Acidosis

Renal tubular acidosis is a condition in which there is a defect in renal excretion of hydrogen ion, or reabsorption of bicarbonate, or both, which occurs in the absence of or out of proportion to an impairment in the GFR.

Pathophysiology and Types of RTA

Based on pathophysiology RTA is classified into three groups:
1. Type 1 (distal) RTA
2. Type 2 (proximal) RTA
3. Type 4.

Etiology of RTA

The causes of acquired renal tubular acidosis are listed here:

Type 1 (Distal) RTA:
- Systematic lupus erythematosus
- Sickle cell anemia
- Sjögren syndrome
- Reflux nephropathy
- Obstructive uropathy
- Drugs: Amphotericin B toxicity.

Type 2 (proximal) RTA:
- Isolated Type 2 RTA
- Fanconi syndrome
- Primary hyperparathyroidism
- Sjögren syndrome
- Paroxysmal nocturnal hemoglobinuria
- Acute tubulointerstitial nephritis.

Type 4 RTA:
- Aldosterone deficiency
  - Addison's disease
  - Adrenal TB, necrosis
- Aldosterone resistance
  - Post-transplantation
  - Drugs: Amiloride, ACE inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), calcineurin inhibitors
- Aldosterone deficiency in renal insufficiency
  - Interstitial nephritis
  - Obstructive uropathy
  - Nephrocalcinosis.

Type 1 RTA

The hallmark of distal RTA is the inability to lower the urine pH maximally in the face of moderate to severe systemic acidosis. Congenital forms of distal RTA are divided into:

- Autosomal dominant (type 1a)
- Autosomal recessive with (type 1b) hearing loss
- Autosomal recessive without (type 1c) hearing loss.

Clinical features:
- Hypokalemic acidosis
- Hypercalciuria
- Nephrocalcinosis.

Treatment:
- Sodium bicarbonate supplementation to correct acidosis. The required dose is 2–3 mEq/kg/day.
- Monitoring of urinary calcium excretion. Thiazide diuretics are required if hypercalciuria is present.

Type 2 (Proximal) RTA

The hallmark of proximal RTA is a reduced threshold for the reabsorption of bicarbonate and thus, these patients will have a low serum bicarbonate concentration. When the serum bicarbonate concentration increases and approaches the normal range, patients with proximal RTA will develop bicarbonaturia.

Clinical features:
- Vomiting
- Failure to thrive
- Urine pH may be less than 5.3
- Ammonium chloride leading to acidification of urine.

Treatment:
- Restriction of dietary sodium
- To correct acidosis, a combination of sodium and potassium citrate supplementation at a dose of 5–20 mEq/kg/day.

Cystinosis

It is a rare, autosomal recessive lysosomal storage disorder affecting lysosomal cysteine transport. Massive intralysosomal accumulation of cystine generates damage in renal tubules, particularly proximal tubules initially, manifested by Fanconi syndrome. Later accumulation of cystine (Fig. 48) crystal in other organ affects cornea (Fig. 49), thyroid, liver, spleen in particular.

Clinical features:
- Failure to thrive in previously normal infant
- Growth retardation
- Hypophosphatemic rickets at 6–12 months of age
- Normal anion gap metabolic acidosis

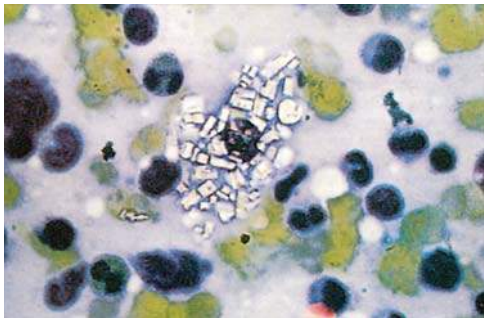


Fig. 48: Intracellular cystine crystals in cystinosis

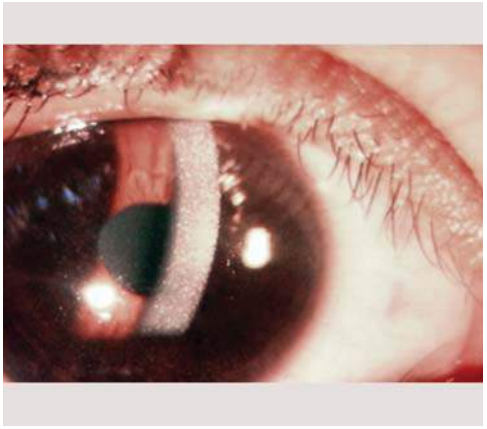


Fig. 49: Diffuse crystal is noted in the eyes of a girl with cystinosis

- Volume depletion
- Electrolyte imbalance
- Photophobia.

Diagnosis:
- Elevated leukocyte cystine level
- Corneal crystal on slit lamp examination (Fig. 49).

Treatment:
- Supportive
- High fluid intake
- Supplement of phosphate, sodium chloride, potassium and sodium bicarbonate
- Specific
- Mercaptomine reduces cysteine accumulation.

Prognosis and complications of cystinosis:
If remain untreated ESRF develops by 10 years of age. The following extrarenal complications also develop:
- Distal vacuolar myopathy
- Swallowing abnormalities
- Retinal blindness
- Hepatosplenomegaly, sometimes with hypersplenism
- Hypothyroidism
- Diabetes mellitus
- Hypogonadism, with pubertal delay
- Decreased pulmonary function
- Neurological deterioration
- Pancreatic exocrine insufficiency.

Fanconi Syndrome

Fanconi syndrome consists of skeletal findings secondary to hypophosphatemia (i.e. rickets), generalized aminoaciduria and glucosuria.

Etiology:
I. Inherited metabolic disorders:
- Cystinosis
- Tyrosinemia type I
- Lowe syndrome
- Galactosemia
- Glycogen storage disease
- Wilson disease.

II. Acquired:
- Heavy metal toxicity
- Drugs (expired tetracyclines).

Clinical features:
- Failure to thrive
- Polyuria
- Polydipsia
- Dehydration
- Rickets (hypophosphatemia)
- Acidosis (proximal type 2)
- Hypokalemia.

Treatment:
- Treatment is same as the treatment of proximal RTA with supplementation of phosphate
- For the healing of rickets small dose of vitamin D should be administered.

Bartter Syndrome

Autosomal recessive in inheritance.

Clinical features:
- Hypokalemic alkalosis with elevated renin and aldosterone levels and normal to low blood pressure
- Polyuria, polydipsia
- Salt craving
- Hypernatremic dehydration.

Antenatal presentation:
- Polyhydramnios
- Premature delivery
- Severe life-threatening dehydration.

Neonatal presentation:
- Failure to thrive.

Investigations:
- Urine:
  - Electrolytes (Na^+, K^+ and Cl^- all are high)
  - Calcium may be high
- Plasma electrolytes:
  - Sodium (variable), potassium and chloride (both are low)
  - Low magnesium
  - Normal calcium
- High plasma bicarbonate
- Renal function test
- Renal ultrasonogram for nephrocalcinosis
- Genetic analysis.

Treatment:
- Replacement of fluid and electrolyte losses
- Administration of indomethacin which reduces renal salt, water and potassium loss. The dose of indomethacin is 0.5–1 mg/kg/day, divided into 4 doses, with stepwise increase to a maximum of 2–4 mg/kg/day.

Gitelman Syndrome

- Autosomal recessive in inheritance
- Usually present in adolescence or later.

Clinical features:
- Neurological symptoms like seizure, tetany, muscle weakness, cramp
- Hypotension and dizziness
- Joint pains
- Nocturnal enuresis.

Investigations:
- Urine:
  - Electrolytes (Na^+, K^+ and Cl^- all are high)
  - Low calcium
  - High magnesium
- Plasma electrolytes:
  - Sodium, potassium and chloride all are low
  - Low magnesium
  - Normal calcium
- High plasma bicarbonate
- Renal function test
- Renal ultrasonogram for nephrocalcinosis
- Genetic analysis.

Treatment:
- Potassium and magnesium chloride supplementation to control electrolyte and acid-base balance.
- Severe hypokalemia can be managed with cautious use of spironolactone and amiloride as they precipitate hypotension.

Type 4 RTA

The primary effect of aldosterone on the collecting duct is to stimulate sodium reabsorption and potassium secretion in the principle cells. Patients that are aldosterone deficient or resistant to the actions of aldosterone have increased excretion of sodium which leads to volume depletion and potentially a decrease in the GFR. The acidosis in most patients with type 4 RTA is not as severe as in other forms of RTA.

HEMOLYTIC UREMIC SYNDROME

Hemolytic uremic syndrome is the commonest cause of acute renal failure (ARF) in children. It is categorized by a triad of clinical features, hemolytic anemia, thrombocytopenia and ARF.

Epidemiology

The incidence of HUS is greatest in children under 5 years of age and then peaks again in the elderly. Risk of developing HUS is greatest in areas with high density of cattle. Majority of cases occur in the summer months.

Etiology and Types

Hemolytic uremic syndrome is subdivided into two broad categories, typical, usually diarrhea-positive D+ HUS (more than 90% of cases) most commonly caused by Shiga toxin (Stx)-producing *E. coli* (STEC; also called verotoxin, VTEC), atypical, usually diarrhea-negative D- sHUS or aHUS (approximately 5% of cases).

I. *Typical HUS*

Infectious causes:
- *Escherichia coli*
- *Shigella dysenteriae*
- *Citrobacter freundii.*

II. *Atypical HUS*

- *Infectious causes*:
  - *Streptococcus pneumoniae.*

- *Inherited*:
  - Complement abnormalities
  - von Willebrand factor-cleaving protease constitutional deficiency
  - Cobalamin metabolism defect
- *Autoimmune*:
  - Systemic lupus erythematosus
  - Scleroderma
- *Drugs*:
  - Cyclosporine A, tacrolimus
  - Cytotoxic drugs
  - Quinine
- *Other*:
  - Autosomal dominant and recessive types
  - Cancer associated
  - Post-renal transplant
  - HIV associated.

Pathogenesis

Endothelial injury is the primary insult that initiates formation of platelet-fibrin hyaline microthrombi within the microvasculature of the kidney, which in turn, occludes arteriole and capillaries resulting in microangiopathic hemolytic anemia and consumptive thrombocytopenia (Fig. 50).

Clinical Features

Clinical features of HUS are preceded by an acute diarrheal illness with gross bloody stool. Atypical D- HUS develops insidiously and there may be no history of preceding infection. In typical D+ HUS, children develop pallor, petechiae or bleeding and reduced UO within 2–14 days of onset of intestinal symptoms.

The features of HUS according to system involvement are listed below:

Gastrointestinal

- Bloody or watery diarrhea
- Abdominal cramps
- Nausea and/or vomiting
- Rectal prolapse
- Intussusception
- Toxic dilatation of colon
- Bowel perforation.

Hematological

- Petechiae
- Mucosal bleeding
- Jaundice.

Renal

- Oligouria or anuria
- Hypo- or hypervolemia
- Hypovolemic shock
- Hypertension
- Edema.

Central Nervous System

- Lethargy
- Irritability
- Seizures
- Cranial nerve palsy
- Cerebral edema
- Encephalopathy
- Abnormal posturing
- Coma.

Cardiac

- Cardiomyopathy
- Arrhythmias secondary to electrolyte disturbances
- Myocarditis and tamponade.

Pancreas

- Diabetes mellitus
- Pancreatitis.

Differential Diagnosis

- Thrombotic thrombocytopenic purpura (TTP)
- Disseminated intravascular coagulation (DIC) sepsis
- Systemic lupus erythematosus
- Vasculitis.

Investigations

For typical HUS following investigations are advised:

Blood Tests

- *CBC:*
  - Anemia: Hb less than 8 g/dL
  - Leukocytosis
  - Thrombocytopenia (<60 × 109/L)
  - Film: Fragmented RBCs (Fig. 51)
- *Coagulation screening:*
  - Usually normal

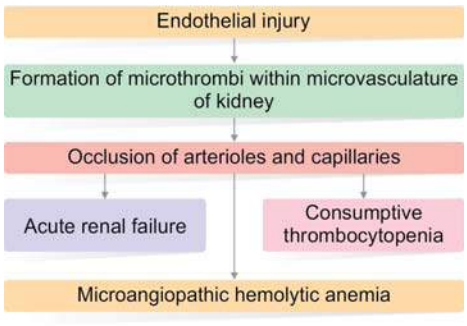


Fig. 50: Pathogenesis of HUS

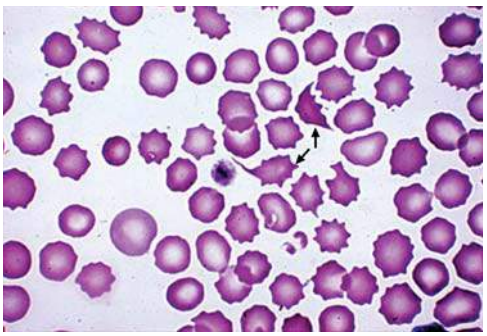


Fig. 51: Blood film showing fragmented RBCs and absence of platelet in HUS

- *Liver function tests*:
  - Low albumin
  - Raised bilirubin
  - Raised lactate dehydrogenase (LDH).
- *Renal function test:*
  - Serum creatinine: Raised
  - Blood urea: Raised
- *Serum electrolytes:*
  - Hyponatremia
  - Hyperkalemia
  - Hyperglycemia.

Urine Tests

- Dipstick test for proteinuria, hematuria
- Microscopy for red cells, white cells and casts.

Stool

Stool microscopy and culture for *E.coli.*

Serology

STEC/VTEC serology.

Culture

Stool and blood culture for identification of *E. coli.*

Imaging

- Plain X-ray abdomen showing typical thumb print sign (Fig. 52)
- Renal ultrasound scan.

For atypical HUS more specialized investigations are required. These are as follows:

- Complement levels/activity
- Factor H concentrations
- Plasma vWF protease activity
- Metabolic disease investigations
- Autoimmune antibody screen.

Management of HUS

Supportive

I. Fluid balance:

- Fluid resuscitation if the child is dehydrated and subsequent maintenance of balance insensible loss and UO

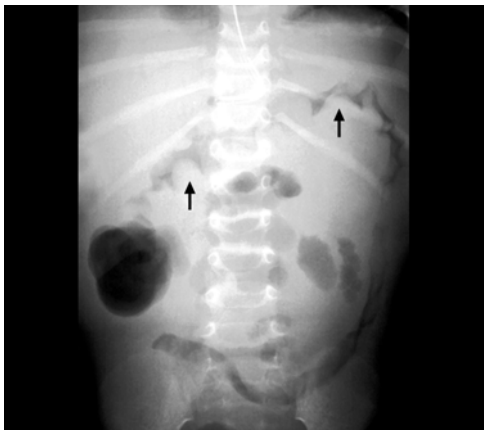


Fig. 52: X-ray showing colonic thumbprinting (arrows), consistent with marked submucosal edema characteristics of hemolytic uremic syndrome

- Diuretics may be used if there is fluid overload or oliguria/anuria.

II. Management of acute kidney injury:

- Management of electrolytes derangement
- Control of hypertension
- Blood transfusion to maintain Hb greater than 7.0 g/dL
- Maintenance of adequate nutrition with provision for high calorie.

Specific

III. Typical HUS: There is no specific treatment for typical HUS.

IV. Atypical HUS:

- Administration of fresh frozen plasma to replace vWF-cleaving protease
- Plasmapheresis to remove antibodies to this protein.

Complications of HUS

A. Intestinal

- Hemorrhagic colitis
- Colonic gangrene or perforation
- Pallor and jaundice develop secondary to hemolysis within 2 weeks of the intestinal symptoms.

B. Renal

Renal involvement is typically seen between days 4 and 7 after the onset of diarrhea. These are:

- Oligouria/anuria
- Persistent proteinuria
- Hypertension (20–30% of cases)
- Edema
- Chronic kidney disease.

C. Neurological

Central nervous involvement can occur in up to 20% of children.

- Complete recovery (50% cases)
- Neurological complications leading to death (17%)
- Severe neurological sequelae (23%).

D. Endocrine

- Diabetes mellitus.

Prognosis

Prognosis is generally good for D+ HUS. Acute mortality is as low as 5–10% in D+ HUS. Long-term complication may occur in 25% of cases with ESRF in 1.8% cases.

Features of poor prognosis are:

- Leukocytosis: 20×10^9/L with neutrophilia
- Shock during acute illness
- Anuria for more than 2 weeks
- Dialysis for more than 4 weeks is unlikely to lead to full renal recovery
- Hypertension
- Persistent proteinuria
- Central nervous involvement
- Severe colitis and/or rectal prolapse
- Cortical necrosis and thrombotic microangiopathy (more than 50% glomeruli involved) on renal biopsy
- Atypical HUS.

Prevention of HUS

Hygienic measures can effectively prevent the disease. Such measures are:

- Avoiding ingestion of contaminated food by:
  - Thorough cooking of meat products
  - Correct pasteurization of dairy products
  - Washing of vegetables/fruit thoroughly
- Avoid consumption of unpasteurized food products
- Encourage handwashing.

ENURESIS

Most children achieve night-time dryness by 5 years of age, when bladder volume exceeds nocturnal urine production. Nocturnal enuresis is common in the childhood population and many parents take it in their stride as a natural part of their child's development and maturation, putting practical strategies in place whilst awaiting spontaneous resolution.

The International Children's Continence Society defines enuresis as any type of wetting episode or urinary incontinence that occurs in discrete amounts during sleep in a child who is at least 5 years of age. Nocturnal enuresis is defined as the involuntary loss of urine at night, in the absence of physical disease, at any age when the child could reasonably be expected to be dry.

Epidemiology

Nocturnal enuresis affects 15–20% of 5-year-old, 5% of 10-year-old and 1–2% of 15-year-old children.

Types

Nocturnal enuresis may be of two types; primary and secondary respectively.

I. Primary Nocturnal Enuresis
The child has never been dry.

II. Secondary Nocturnal Enuresis
The child has previously been dry at night for 6 months or more after the age of 5 years.

Depending Upon Symptoms

1. *Monosymptomatic or uncomplicated nocturnal enuresis*: Nocturnal enuresis is not associated with other symptoms referable to urinary or GI tract (e.g. bladder bowel voiding disorder).
2. *Polysymptomatic or complicated nocturnal enuresis*: Bed wetting is associated with symptoms suggestive of lower urinary tract dysfunction.

Etiology

- Etiology is poorly understood.
- It has been proposed that delay in bladder control results in nocturnal enuresis.
- Loss of normal nocturnal rise in ADH production results in nocturnal urine production.

Pathophysiology

Three main components have been proposed in the pathogenesis of nocturnal enuresis:

- *Inability to wake during sleep in response to need to void*
  - Fundamental problem for all children with enuresis
  - Disorder of brainstem arousal that allows us to wake in response to stimuli
  - The mismatch between bladder capacity and urine production at night is also a manifestation.
- *Nocturnal polyuria*
  Nocturnal polyuria is defined as nocturnal urine production more than expected bladder capacity (EBC) for age (which is normally equal to or less than 130% of EBC for age). The causes of nocturnal polyuria are:
  - Excessive water intake prior to bed
  - Lack of nocturnal increase in arginine vasopressin (AVP) production from the posterior pituitary gland.
- *Reduced bladder capacity*
  Reduced bladder capacity is considered when it is found to be less than 65% of EBC. An overactive bladder (OAB) is the cause of small nocturnal bladder capacity. OAB is spontaneous, involuntary detrusor contractions during the filling/storage phase when the detrusor muscle is supposedly quiescent.

Assessment

History

Assessment of nocturnal enuresis requires a careful and directed history-taking which should include the following:
Enuresis profile: It is given in Table 11.

- *Neurodevelopmental issues*: Presence of any neurodevelopmental issues like motor disorder, learning difficulties, attention deficit hyperactivity disorder, autistic spectrum disorder, etc.
- *Complications*:
  - Known renal tract abnormality
  - Recurrent UTIs

Table 11: Enuresis profile

Severity	
	Mild (1–2/week); moderate (3–6/week); severe (7/week)
Monosymptomatic	
	Features associated with poor wake ability
	Spontaneously waking at night in response to internal stimuli (e.g. needing to void, feeling unwell, feeling excited (going on holiday or prior to religious holidays like Eid, Puja, Christmas), worry or anxiety or external stimuli (loud noise, attempts to waken by parents, strange or new environs, sleeping away from home), alarm clock or mobile phone
	Features associated with nocturnal polyuria
	• Copious or large quantities of urine passed at night • Early wetting within one-third of the night (usually by midnight) • Wet more than once per night
	Features associated with constitutionally small bladder
	• Single void in last half of night or in early morning • Shortened sleeping period
Polysymptomatic	
	Features associated with poor wake ability
	• Daytime symptoms of frequency and urgency with small voided volumes • Urinary incontinence by day both presently and at some time in the past • Often wet more than once at night with variable amounts • Wake at night after wetting or in response to voiding

  - Symptoms of bladder dysfunction: Difficulty with initiating void, stop-start stream, dribbling stream, abdominal straining during voiding, needing to sit to void in boys, and feeling of incomplete emptying, post-void residual, and episodes of retention, non-specific discomfort during or after a void
  - Constipation with or without soiling
  - Significant snoring at night with evidence of obstructive sleep apnea
  - Sickle cell disease
- *Useful charted parameters to determine significance*:
  - Enuresis episodes 14 days (enuresis severity) voiding diary 48 hours (frequency, urinary output)
  - Drinking diary 48 hours (fluid intake pattern)
  - Enuresis volumes 7 nights (presence of nocturnal polyuria)
  - Bowel movements 14 days (defecation frequency, stool type)
- *Child and family factors*:
  - Family history
  - Child's motivation
  - Child's drinking/voiding patterns
  - Bedtime routines
  - Sleeping arrangements
  - Parents' tolerance.

Examination

General physical examination with special attention to palpable bladder and spine is required.

- Signs of spinal dysraphism: Lumbar sacral spine (asymmetric natal cleft, dimples, sinus, lipoma, hairy patch, nevus)
- Ankle: Deep tendon reflexes
- Perineal sensation around sacrum
- Genitals
  - Urethral meatus
  - Urinary leakage
  - Excoriation.

Investigations

- Urinalysis and culture
- Urinary tract ultrasound
- Post-void residual uroflowmetry
- Bladder capacity by nuclear medicine imaging.

Management

Explanation and Education

- Child-friendly explanation of the causes and treatment of enuresis is essential before commencing treatment.
- Charts and diagrams are available now to help demystifying the condition and provide the understanding and basis on which further work is taken forward.

General Measures

- Primary nocturnal enuresis undergoes spontaneous remission which does not require any treatment.
- Treatment should be attempted if condition persists beyond 7 years of age.
- Daytime wetting should be investigated and treated prior to addressing nocturnal enuresis.
- Complications should also be appropriately treated first.

Specific Measures

The enuresis alarm:

- Enuresis alarm consists of a sensor attached via a cord to a bell. When the child wets the presence of urine on the sensor triggers the alarm to ring (Figs 53 and 54).
- Alarm systems are superior to behavioral techniques and drug therapy.
- Immediate alarm system is more effective than delayed alarm system.
- This system has high rates of drop out.

Behavioral measures:

May be used as first line measure. The measures are:

- Lifting: Taking the child to the toilet in the night without necessarily waking them which may discourage wetting during sleep
- Scheduled waking to pass urine
- Effective treatment of associated constipation
- Increasing daytime fluid intake to develop bladder capacity and reduce evening fluid intake.

Drug therapy:

- Desmopression
  Desmopressin is a chemical analog of AVP. It is indicated in the treatment of monosymptomatic nocturnal enuresis with symptoms of nocturnal polyuria.
  Dose: 20–40 μg intranasally or 200–400 μg orally at bed time
- Anticholinergics
  Anticholinergic medication, such as oxybutynin or tolterodine, acts as smooth muscle relaxants by blocking M2/M3 muscarinic receptors in the detrusor, thereby diminishing detrusor over activity and improving bladder storage function.

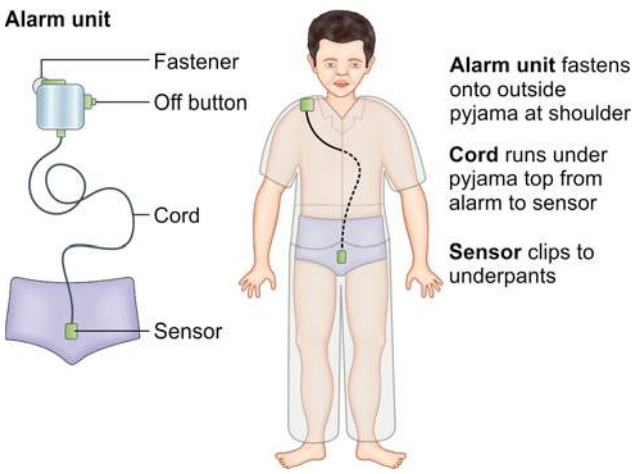


Fig. 53: Components of enuresis alarm

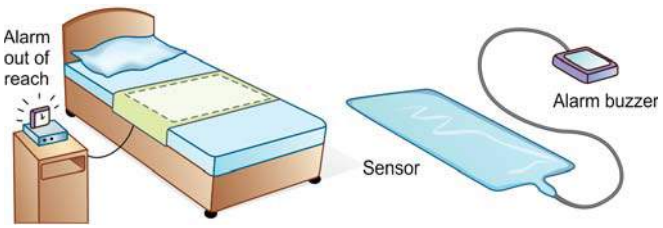


Fig. 54: Graphical representation of enuresis alarm

- Tricyclic antidepressant (TCA)
  TCA like imipramine is thought to work via a number of effects including anticholinergic effect, effects on arousal, sphincter and urine production. Relapse rate is high on discontinuation.

Therapy should be continued for 3–6 months of dry nights and weaned over 3–4 weeks.

DISORDERS OF ELECTROLYTES RELEVENT TO RENAL DISORDER

(Also discussed in Fluid and Electrolyte Balance Chapter)
Disorders of electrolytes mainly encompass the disorders of balance of sodium, potassium, calcium and magnesium. The disorders of calcium homeostasis are discussed in "Fluid and Electrolyte Balance" Chapter.

Disorders of Sodium Balance

Serum sodium along with urea and glucose determines the serum osmolality. Normal serum level of sodium is 135–145 mEq/L. Sodium homeostasis is closely related to water homeostasis. Two systems maintain water balance:

i. Regulation of ECF tonicity by hypothalamic osmoreceptor.
ii. Regulation of intravascular volume by volume receptors in great veins and right side of the heart.

In different clinical situations, water is retained or lost to maintain normal serum sodium level.

Hyponatremia

Hyponatremia is defined as serum sodium concentration less than 130 mEq/L. Hyponatremia more often reflects gain or retention of water than Na^+ depletion.

Etiology of hyponatremia: Etiology of hyponatremia is as follows:

I. Excess water:
- Water overload:
  - Iatrogenic excess hypotonic oral or IV fluid
  - Habitual drinkers
- Water retention
  - Syndrome of inappropriate ADH secretion
  - Acute kidney injury.

II. Sodium depletion:
- Renal loss: Inappropriate high urine volume and Na^+ concentration (>20 mmol/L):
  - Loop diuretics
  - Hypoaldosteronism (e.g. congenital adrenal hyperplasia)
  - Recovery phase of acute tubular necrosis
  - Tubulopathies
- Extrarenal loss: Appropriate oliguria and low urine Na^+ concentration (<10 mmol/L)
  - Gastroenteritis
  - Skin losses: Severe sweating, cystic fibrosis.

Clinical features: Mild hyponatremia is usually asymptomatic. Symptomatic manifestation occurs when serum sodium level falls below 125 mEq/L. When this occurs in less than 48 hours, it is known as acute hyponatremia.
The features are given in Table 12.

Table 12: Clinical features of various forms of hyponatremia

Acute hyponatremia	Chronic hyponatremia	Extreme low sodium
• Apathy • Restlessness • Altered sensorium • Seizures	• Anorexia • Nausea • Emesis • Muscle weakness and cramps • Irritability • Change in personality	*Initially* • Mutism • Dysarthria • Lethargy *Later* • Gait disturbance • Stupor • Tremor • Spastic quadriparesis • Pseudobulbar palsy

Management:

A. Asymptomatic hyponatremia:
- Normal saline for initial resuscitation
- Maintenance and replacement therapy with half normal saline in 5% dextrose
- Management of underlying disorders like malnutrition, liver disease, diuretic therapy, renal salt wasting, etc.

B. Symptomatic hyponatremia:
- Edematous state
  - With hypovolemia
    - With shock
      IV crystalloid (0.9% saline) 20 mL/kg
    - Without shock
      IV 20% human albumin 0.25–0.5 g/kg (1.25–2.5 mL/kg of 20% human albumin solution)
  - Without hypovolemia (cardiac failure, renal failure)
    - Salt and water restriction
    - Diuretics
  - Intractable hyponatremia with acidosis
    - Dialysis
- Hypovolemia without edema
  Replacement therapy
  - Estimation of deficit by following formula: Most reliable is acute change in weight (weight loss in kg = water deficit in liter)
  - Oral rehydration therapy
  - Replacement of Na deficit over 24 hours by using following formula
    Na deficit = [140 - (plasma Na)] × body weight in kg × 0.6)
    Maintenance of daily sodium requirement [(3 × body weight in kg) mmol] should also be provided over 24 hours.
- Management of syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Syndrome of Inappropriate ADH Secretion

Causes of SIADH:

- CNS disorders:
  - Hypoxic-ischemic encephalopathy
  - Infection
  - Trauma
  - Malignancy, primary or secondary
  - Capsular accident
  - Cerebral malformation
- Pulmonary disorders:
  - Acute or chronic infection
  - Cystic fibrosis
  - Malignancy
  - Positive pressure ventilation

- Post-surgery:
  - Abdominal, cardiothoracic and neurosurgery
  - Anesthetic or premedication
  - Pain may contribute to SIADH
- Miscellaneous:
  - Acute intermittent porphyria
  - Leukemia
  - Lymphoma.

Diagnosis of true SIADH includes following criteria:

- Absence of signs and symptoms of dehydration/hypovolemia
- Absence of other conditions that cause retention of free water, e.g. renal, hepatic, or cardiac failure, adrenal, pituitary or thyroid dysfunction
- Laboratory
  - Inappropriately elevated urinary osmolality
  - Hyponatremia (<135 mEq/L) and hypoosmolality (<270 mosm/kg)
  - Urine sodium concentration greater than 20 mmol/L
  - Decrease in hematocrit, plasma albumin, plasma urea and creatinine.

Treatment:

- Fluid restriction to 25% of maintenance fluid requirement
- If there is severe neurological symptoms and very low serum sodium, correction of sodium back to normal 125 mEq/L:
  3% NaCl (523 mmol/L, i.e. 0.5 mmol/mL of 3% NaCl) at 4–6 mL/kg/h.

As the osmolality of normal saline is 310 mosm/kg which is below the urine osmolality, it should be avoided.

Hypernatremia

Hypernatremia is defined as serum sodium over 150 mmol/L. It is caused commonly due to deficiency of water and rarely an excess of salt. Increased sodium concentration increases tonicity, stimulates both ADH secretion and thirst.

Etiology: The causes of hypernatremia are as follows:

I. Loss of water in excess of sodium:

Extrarenal water loss (U_{osm} >800 mosm/kg); U_{Na} <20 mmol/L

- Diarrhea
- Vomiting
- Gastrointestinal fistula
- Burns injury
- Hyperventilation
- Pyrexia
- Phototherapy.

II. Inadequate water intake:

Renal water loss (U_{osm} >800 mosm/kg and U_{Na} variable)

- Central and nephrogenic diabetes insipidus
- Hyperglycemia
- Osmotic/loop diuretic therapy
- Intrinsic renal disease.

III. Gain of sodium in excess of water:

(U_{osm} variable and U_{Na} 75–100 mmol/L)

- Excessive oral administration of salt (including salt poisoning)
- Deliberate reconstruction of nasogastric feed with salt water
- Improperly diluted baby milk formula
- Excessive IV administration of drugs rich in sodium like sodium bicarbonate, hypertonic saline, sodium citrate, saline enemas
- Mineralocorticoid excess
  - Cushing syndrome
  - Conn syndrome
- Hypertonic dialysis
- Sea water drowning.

Clinical features: As the ECF volume is relatively well-preserved, clinical evaluation of degree of dehydration may be difficult or underestimated.

CNS: Lethargy, irritability, nuchal rigidity, seizures, drowsiness, coma. A rapid increase in plasma osmolality causes shift of water from cerebral interstitial fluid with cellular dehydration. Subdural, subarachnoid and intraventricular hemorrhage and thrombosis of the venous sinuses may be seen in acute, severe hypernatremia.

In salt overload, features of volume overload may be seen:

- Edema
- Pulmonary venous congestion
- Hepatomegaly.

Treatment:

I. Management of hypernatremic dehydration:

- Plasma sodium should not be reduced by 15 mmol/day. If IV fluids are used then this is usually 0.45% saline/2.5% dextrose or 0.9% saline.
- Normal hydration should be achieved over 36–48 hours. If initial serum Na is greater than 170 mmol/L it should be corrected over 72 hours.
- Oral rehydration therapy in diarrheal-induced hypernatremic dehydration is safe in children who are not in shock.
- Correction of shock by 0.9% saline solution 20 mL/Kg over 30 minutes and repeated if necessary.
- If there is significant metabolic acidosis, bicarbonate should be added to the infusion.
- Persistent oliguria when circulatory impairment has been corrected indicates ARF (due to acute tubular necrosis).

II. Management of hypernatremia due to salt excess:

- If renal function is normal it is usually corrected spontaneously.
- Dialysis is indicated if renal failure is present.

Disorders of Potassium Balance

Hypokalemia

Hypokalemia is defined as serum potassium less than 3.5 mEq/L.

Etiology of hypokalemia:

- Potassium depletion:
  - Malnutrition
  - Gastrointestinal loss: Vomiting, diarrhea, intestinal fistulas, laxative abuse, chloridorrhea
  - Skin loss: Burns, excessive sweating
- Renal loss:
  - Recovery from AKI
  - Renal tubular acidosis (distal or type 1 RTA)
  - Bartter and Gitelman syndrome
  - Fanconi syndrome
  - Interstitial nephritis

- Diabetic ketoacidosis
- Mineralocorticoid excess
- Use of loop diuretics

- Redistribution:
  - Shift from ECF to ICF compartment during correction of metabolic acidosis, insulin treatment, prolonged/high dose of salbutamol nebulization during treatment of bronchial asthma
  - Hypokalemic periodic paralysis
  - Increased mineralocorticoid activity
  - Activation of β-adrenergic receptors
    - Catecholamine excess
    - Adrenergic agonists.

Clinical features:

- Muscle weakness, paralysis
- Smooth muscle involvement
  - Intestinal ileus
  - Ureteric dilatation
- Cardiac myocardial cell necrosis
- Arrhythmia, ECG changes
- Rhabdomyolysis and myoglobinuria
- Lethargy, confusion, tetany
- Autonomic insufficiency
- Renal consequences
  - Decrease concentrating capacity: Polyuria, polydipsia
  - Decreased GFR
  - Sodium retention—edema
  - Increased renal ammonia production with hepatic coma
  - Increased proton secretion in distal tubule (to allow sodium reabsorption) → maintenance of metabolic alkalosis
  - Renal cystic changes in long-standing hypokalemia.

ECG changes associated with hypokalemia (Fig. 55):

- Prolonged QT and QU interval
- Increased U wave amplitude
- Prolonged QRS
- ST depression
- Decreased T wave amplitude
- Increased P wave amplitude
- Increased PR interval.

Treatment of hypokalemia:

I. Acute severe hypokalemia:

- Infusion KCl should be used at 0.5 mmol/kg in 20 mL of 5% dextrose over 30 minutes.
- The concentration should not exceed 80 mmol/L except in the controlled environment of pediatric intensive care, or in other appropriate high dependency area with ECG monitoring.
- Chronic hypokalemia: Oral supplementation of potassium.

Hyperkalemia

Hyperkalemia is defined as serum potassium level exceeding 5.5 mEq/L.

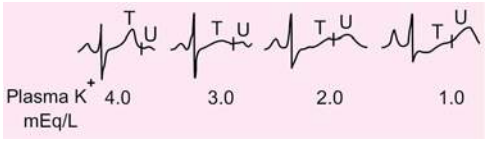


Fig. 55: ECG changes in hypokalemia

Etiology of hyperkalemia:

I. True hyperkalemia:

- GFR <15 mL/min/1.73 m^2
  - Decreased renal excretion
    - Acute kidney injury
    - End-stage renal failure
    - Potassium sparing diuretics
  - Increased potassium load
    - Oral or IV potassium supplementation
    - Blood transfusion, endogenous cell breakdown (e.g. tumor lysis syndrome)
- GFR >15 mL/min/1.73 m^2
  - Low plasma aldosterone, low plasma renin
    - Obstructive uropathy
    - Interstitial nephritis
    - Drugs: Cyclosporine, tacrolimus, NSAIDs
  - Low plasma aldosterone with normal/high plasma renin
    - Congenital adrenal hyperplasia
    - Addison's disease/congenital adrenal hypoplasia
    - Primary hypoaldosteronism
    - Drugs: ACE inhibitors
  - Normal/high plasma aldosterone
    - Type 1 RTA
    - Obstructive uropathy
    - Sickle cell disease
    - Post-renal transplantation
    - Pseudo-hypoaldosteronism
- Redistribution hyperkalemia:
  - Metabolic/respiratory acidosis
  - Hyperkalemic periodic paralysis
  - Mineralocorticoid deficiency
  - Insulin deficiency.

Clinical features:

- Muscle weakness
- Cardiac arrhythmia
- ECG changes.

ECG changes associated with hyperkalemia (Fig. 56):

- Peaked T waves (tenting)
- Loss of P wave
- Widened QRS
- ST depression
- Bradycardia, heart block, ventricular arrhythmia, cardiac arrest (K 10 mmol/L or higher).

Treatment of hyperkalemia:

- Hyperkalemia should be treated in emergency
- Seek for underlying pathology.

Principle of management:

- Antagonism of membrane actions:
  - Calcium
  - Hypertonic Na^+ solution (if hyponatremic)
- Increased K^+ entry into the cells:
  - Glucose and insulin

Fig. 56: ECG changes in hyperkalemia

  - $NaHCO_3$
  - β-Adrenergic agonists
  - Hypertonic Na^+ solution (if hyponatremic)
- Removal of the excess K^+:
  - Diuretics
  - Cation-exchange resin (Kayexalate)
  - Hemodialysis or PD

The management includes:

- Monitoring of cardiovascular status with the help of cardiac monitor
- Calcium gluconate 10%: 0.5 mL/kg IV over minutes
- Salbutamol nebulization: 2.5–5 mg; repeat three times if necessary, or may be given continuously
- Salbutamol IV: 4 µg/kg in 5 mL water given over 10–20 minutes
- Correction of acidosis: Sodium bicarbonate 1–2 mmol/kg IV over 30 minutes
- Calcium resonium: Initially 1 g/kg, then 0.25–1 g/kg qds PO/PR. If given orally, should be given with lactulose 5–10 mLqds
- Glucose: 0.5–1 g/kg and insulin 0.1–0.2 units/kg as a bolus, or continuous infusion of 10% dextrose at 5 mL/kg/h (0.5 g/kg/h) with insulin 0.1 unit/kg/h. Monitor glucose at least hourly.
- Dialysis.

Disorders of Magnesium

Hypomagnesemia

A decrease in plasma magnesium below 0.70 mmol/L is described as hypomagnesemia.It is often evident in critical care settings.

Etiology:

Etiology of hypomagnesemia is as follows:

Gastrointestinal causes:

- Decrease intake
- Decreased intestinal absorption
  - Prolonged diarrhea and laxative use
  - Malabsorption syndrome
  - Ileostomy
  - Short bowel syndrome
  - Primary intestinal hypomagnesemia.

Renal causes:

- Acquire
  - Tubular defect
    - Diuretic phase of acute tubular necrosis
    - Obstructive diuresis
  - Drugs
    - Diuretics: Loop and thiazide
    - Aminoglycoside
    - Amphotericin B
    - Foscarnet
    - Pentamidine
- Congenital
  - Gitelman syndrome
  - Hypomagnesemia with hypercalciuria and nephrocalcinosis.

Endocrine causes:

- Hypoparathyroidism
- Hyperthyroidism
- Infant of diabetic mother
- Hyperaldosteronism.

Miscellaneous:

- Hypercalcemia
- Intrauterine growth retardation
- Phosphate depletion
- Hungry bone syndrome.

Clinical features:

- Weakness tremor
- Tetany and seizures
- Positive Chvostek's and Trousseau signs.

Investigations:

- Serum electrolytes:
  - Hypocalcemia
  - Hypokalemia
- ECG:
  - Ventricular arrhythmia
  - Prolonged QT interval.

Treatment:

- Acute severe hypomagnesemia: 0.2 mL/kg of 50% magnesium sulfate IV over 30 minutes, dose may be repeated if necessary
- Chronic hypomagnesemia: Oral magnesium 0.2 mmol/kg three times per day.

Hypermagnesemia

- Hypermagnesemia is common in chronic renal failure (CRF) due to decreased excretion
- Levels of AKI parallel potassium and are derived from intracellular pool.

ACUTE KIDNEY INJURY

Acute kidney injury is a sudden, potentially reversible inability of the kidneys to maintain body chemistry and fluid balance that may clinically range from mild elevation in serum creatinine to anuria.

Causes of Acute Kidney Injury

Causes of AKI may be classified into three groups: Prerenal, renal, postrenal.

A. *Prerenal*

- *Hypovolemia*:
  - Gastrointestinal loss:
    - Dehydration, bleeding
  - Third space loss:
    - Nephrotic syndrome
  - Peripheral vasodilatation:
    - Sepsis
- *Circulatory failure*:
  - Congestive cardiac failure
  - Pericarditis
  - Cardiac tamponade
- Perinatal asphyxia
- Hepatorenal syndrome
- *Drugs*:
  - ACE inhibitors
  - Diuretics.

B. *Renal*

- *Glomerular*:
  - Acute glomerulonephritis

- Post-infectious GN
- Systemic disorders: SLE, HSP
- Membranoproliferative glomerulonephritis

- *Tubular*:
  - Established acute tubular necrosis due to:
    - Prolonged prerenal AKI
    - Ischemia
    - Toxin or drugs: Diethylene glycol
    - Obstructive: Crystal
- *Interstitial*:
  - Pyelonephritis
  - Interstitial nephritis
- *Vascular*:
  - Arterial:
    - Hemolytic uremic syndrome (HUS)
    - Occlusion by embolism
  - Venous:
    - Renal vein thrombosis
- *Acute on chronic*:
  - Decompensated CKD due to intercurrent infections.

C. Post-renal

- *Urethral obstruction*:
  - Posterior urethral valve
  - Urethral stricture
- Bilateral PUJO
- *Ureteral obstruction*:
  - Stenosis
  - Stone
  - Ureterocoele
- Neurogenic bladder.

Pathophysiology of AKI (Fig. 57)

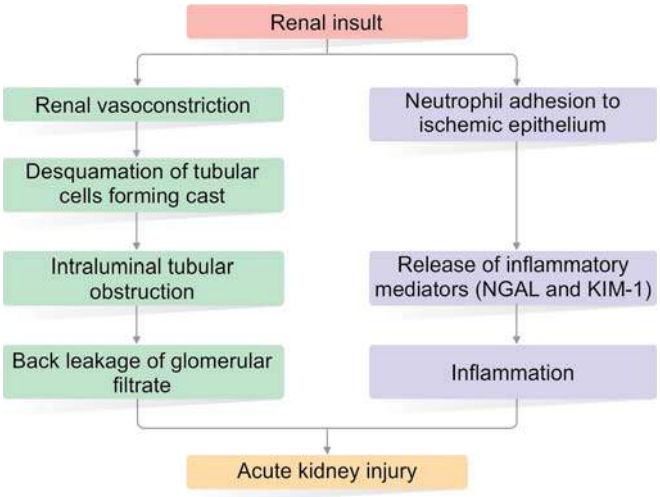


Fig. 57: Pathogenesis of AKI

Clinical Features

General

- Dehydration due to hypovolemia or fluid loss (GN)
- Anemia, jaundice, petechie in hemolytic uremic syndrome.

CVS

- *Shock*: Tachycardia, hypotension, prolonged capillary refill time
- *Fluid overload*: Hypertension, gallop rhythm.

Respiratory

- Crackels in pulmonary edema.

Abdomen

- Palpable urinary bladder or kidneys.

Diagnosis

Examination must include, assessment of circulatory status and fluid balance, to identify circulatory failure or hypovolemia which is consistent with prerenal failure or fluid overload.

The following features, history and examination provide clue to etiology of AKI:

I. *Prerenal*

- Diarrhea and vomiting
- Cardiac impairment
- Perinatal asphyxia
- Acute weight loss

II. *Renal*

- Bloody diarrhea (HUS)
- History of consumption of drugs
- Recent throat or skin infection
- Prolonged convulsion

III. *Postrenal*

- Previous UTI
- Antenatally diagnosed renal anomalies
- Poor urinary stream
- Renal calculi
- Palpable bladder or kidney
- Spinal abnormality

IV. *Acute or Chronic*

- Previous history of UTI
- Polydipsia and polyuria
- Poor urinary stream
- Family history of AKI
- Long-standing malaise
- Renal osteodystrophy.

Staging of AKI

The AKI network (AKIN) defines AKI stages as stage 1, 2 and 3 based on serum creatinine and UO criteria (Fig. 58). On the other hand, another staging system RIFLE is modified for pediatric use as pRIFLE. Both of these staging systems are mentioned Tables 13 and 14.

Only one criteria eitherserum creatinine or UO criteria should be fulfilled to assign a stage in case of AKIN staging.

Investigations

1. Ultrasonogram of urinary tract (Fig. 59)

To detect:

- Exclude obstruction
- Signs of CKD
- Vascular flow

2. Urinalysis
3. Urine biochemistry: To differentiate prerenal AKI and acute tubular necrosis. Urine osmolality and Na^+ concentration are the powerful indicators. The fractional excretion of Na^+ (FENa) is a useful index of tubular function which can be calculated using following formula:

$$FENa = [(\text{urine } Na^+ \times \text{serum creatinine})/(\text{serum } Na^+ \times \text{urine creatinine})] \times 100\%$$

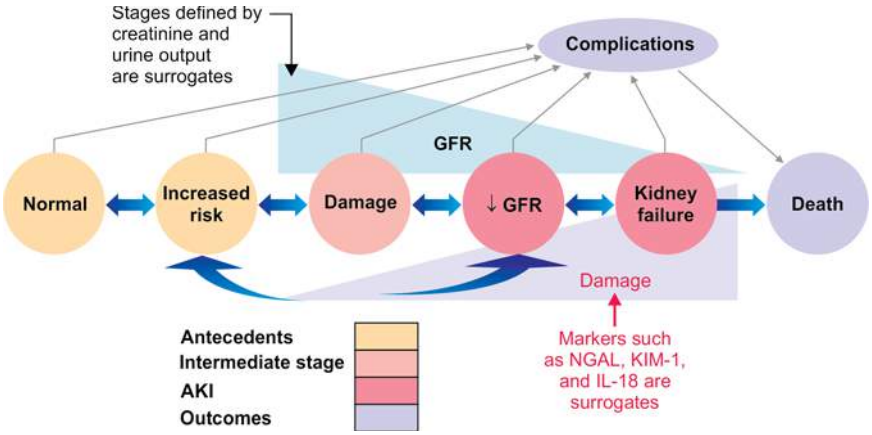


Fig. 58: Conceptual model for AKI. Red circles represent stages of AKI. Yellow circles represent potential antecedents of AKI, and the pink circle represents an intermediate stage (not yet defined). Thick arrows between the circles represent risk factors associated with the initiation and progression of disease that can be affected or detected by interventions. Purple circles represent outcomes of AKI. 'Complications' refers to all complications of AKI, including efforts at prevention and treatment, and complications in other organ systems

Table 13: AKIN staging of AKI

AKIN stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of >0.3 mg/dL or >150–200% form baseline	Less than 0.5 mL/kg/h for >6 hours
2	Increase in serum creatinine >200–300% form baseline	Less than 0.5 mL/kg/h for >12 hours
3	Increase in serum creatinine to more than 300% from baseline	Less than 0.3 mL/kg/h for 24 hours or anuria for 12 hours

Table 14: pRIFLE class of AKI

		GFR criteria	Urine output criteria
R	Risk	1·5-fold increase in serum creatinine or GFR decrease >25%	UO <0.5 mL/kg/h for 6 hours
I	Injury	Two-fold increase in serum creatinine or GFR decrease >50%	UO <0.5 mL/kg/h for 12 hours
F	Failure	Three-fold increase in serum creatinine or GFR decrease >75%, serum creatinine ≥4 mg/dL, or acute rise in serum creatinine ≥0·5 mg/Dl	UO <0.3 mL/kg/h for 24 hours or anuria for 12 hours
L	Loss	Complete loss of kidney function >4 weeks	
E	ESKD	End-stage kidney disease (>3 months)	

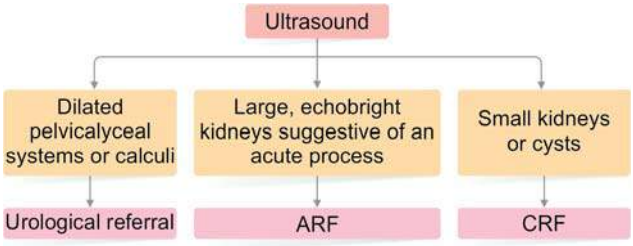


Fig. 59: Diagnosis of the cause of ARF by USG

a. Prerenal failure
   - Urine osmolality greater than 500 mOsm/kg
   - Urine sodium less than 10 mmol/L
   - Fractional excretion of Na^+ less than 1%

b. Acute tubular necrosis
   - Urine osmolality less than 300 mOsm/kg
   - Urine sodium greater than 40 mmol/L
   - FENa greater than 1%.

Urine NGAL Assay

Urine neutrophil gelatinase-associated lipocalin (NGAL) is an early predictive biomarker of AKI. Importantly, NGAL in the urine was found to be an early predictive biomarker of AKI in a variety of acute clinical settings. It is currently available in few hospitals in Bangladesh.

Table 15: Investigations to distinguish prerenal from renal failure

Measurement	Prerenal	Renal
Urinary volume	<0.5 mL/kg/h	Variable
Urine osmolality (mosmol/ kg) H_2O	>500	~300
Urine:plasma osmolality ratio	>1.3	<1.1
Urinary Na (mmol/L)*	<10	>20
Urinary urea (mmol/L)	>250 (>1,500 mg/100 mL)	<100 (<600 mg/100 mL)
Urinary NGAL assay	<0.3 ng/mL	Markedly increased

* If loop diuretics have not been used.

The biochemical differences between prerenal and renal failure are mentioned in Table 15.

4. Serum creatinine: Indicator for GFR. A doubling of serum creatinine indicates 50% reduction in GFR.
5. Complete blood count:
   - Leukopenia and thrombocytopenia suggests SLE
   - Microangiopathic anemia suggests HUS
6. Serum electrolytes, calcium, phosphate, magnesium

7. Renal imaging: Renal ultrasound detects obstructive uropathy, intrinsic renal disease, stones, renal vein thrombosis
8. Blood culture and CRP
9. Chest X-ray if cardiac or cardiac signs are present
10. Renal function test
11. Liver function test
12. Renal biopsy.

Indications of renal biopsy in AKI

- Deteriorating renal function
- Etiology unknown
- Associated with systemic diseases like HSP, SLE, etc.
- Nephritic/nephrotic presentation
  - Rapidly progressive glomerulonephritis or non-resolving GN.

To detect underlying etiology

I. For hemolytic uremic syndrome:
- Blood film for fragmented cells
- Stool culture
- VTEC serology
- Haptoglobins
- Lactate dehydrogenase.

II. Acute nephritis:
- Infected skin or throat swab
- ASO titer, ADNase B
- Immunoglobulin
- ANA, dsDNA, anti-GBM serology, ANCA, anticardiolipin antibody.

III. For acute or chronic kidney disease:
- Parathyroid hormone
- Bone X-ray for renal osteodystrophy.

Management of AKI

Supportive

Management of AKI encompasses treatment of life- threatening complications, maintenance of fluid, electrolyte and nutrition.

Fluid Management

- Assessment of hypovolemia and dehydration and correction accordingly
- In intrinsic renal disease, fluid intake is restricted to insensible losses and urinary output
- In fluid overloaded, oliguric patients, use loop diuretics to prevent pulmonary edema
- Recording of daily weight, intake-output, serum sodium is mandatory.

Electrolytes Management

- Correction of electrolyte abnormality
- Monitoring of potassium level and treatment of hyperkalemia
- Treatment of hypocalcemia
- Fluid restriction to treat hyponatremia.

Dietary Management

- Patients with AKI remain in a catabolic state and requires maximum calorie
- Offer protein 1.2–2 g/kg for infants and 0.8–1.2 g/kg in older children
- Amount of dietary protein, fluid and electrolyte should be increased when dialysis is started.

Control of Infection

- Maintaining strict asepsis during invasive procedure, care of IV lines
- Avoidance of long-term catheter
- Use of appropriate antibiotics.

Cautious Use of Drugs

- Dose of certain drugs should be adjusted
- Drugs increasing renal damage, impairing renal function or reduce renal perfusion should be avoided (aminoglycosides, radio-contrast media NSAIDs, amphotericin B, ACE inhibitors)
- Diuretics do not improve renal function or prognosis of intrinsic renal failure. They may be required to prevent intratubular precipitation (intravascular hemolysis, myoglobinuria, hyperuricemia) by means of high urine flow.

Specific

Specific management of underlying disorders are:
- Renal replacement therapy:
  - Intermittent peritoneal dialysis (IPD)
  - Hemodialysis
  - Continuous renal replacement therapy:
    - Continuous arteriovenous hemofiltration (CAVH)
    - Continuous venovenous hemofiltration (CVVH)
    - Continuous venovenous hemodiafiltration (CVVHD)
    - Slow continuous ultrafiltration (SCUF)
- Definitive surgery of UTO after treatment of AKI.

CHRONIC KIDNEY DISEASE

Chronic kidney disease is defined as kidney damage lasting for at least 3 months characterized by structural or functional abnormalities of the kidney with or without decreased GFR.

Etiology

Causes of CKD vary with the age of a child.

1. *Infants under 2 years of age*
   Structural abnormalities responsible in about 50% of cases. These are:
   - Renal dysplasia
   - Obstructive uropathy.
2. Children of 2–5 years of age
   - Renal dysplasia
   - Obstructive uropathy
   - Neonatal vascular accidents
   - Hemolytic uremic syndrome.
3. *Older Children and Adolescents*
   - Glomerular diseases:
     - Focal segmental glomerulonephritis
     - Crescentic GN
     - Lupus nephritis
   - Reflux nephropathy
   - Genetic disorders:
     - Alport syndrome.

Other less common causes are:
- Cystic kidney disease

Table 16: Staging of CKD

Stages of CKD	Description	GFR mL/min/1.73m^2
0	Risk factors: Diabetes, hypertension	>90
1	Renal damage (proteiuria), normal or ↑ GFR	>90
2	Mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	ESRF	<15

- Congenital nephrotic syndrome
- Cystinosis
- Hyperoxalouria
- Drug induced nephrotoxicity
- Malignancy
- Tubular and interstitial disorders.

Stages of CKD

Stages of CKD are based on the level of kidney function assessed by estimation of GFR. These CKD stages are applicable in children above 2 years of age as the renal maturation increases from infancy to reach adult values at the age of 2 years (Table 16).

Investigations

1. Urinalysis
2. Renal function test
3. To identify etiology
   a. Structural causes:
      - Ultrasonography of KUB
      - MCUG
      - Contrast CT scan
      - MR urography
      - Radionuclide DTPA
      - MAG3 scintigraphy
   b. Tubulointestinal causes:
      - DMSA renal scan
      - MR urography
      - Renal biopsy in selected cases
   c. Glomerular diseases:
      - Complement C3
      - ANA
      - Anti-dsDNA antibody
      - ANCA
      - HBsAg
      - HCV antibody
      - HIV antibody
      - Renal biopsy.

Management of CKD

Aims of management of CKD are as follows:
- Retardation of progression of disease
- To correct potentially reversible etiology.

The management includes:
1. Preservation of renal function
2. Treatment of complications
3. Renal replacement therapy.

Preservation of Renal Function

The aim is to delay progress to ESRF which can be achieved by:
- Relief of obstruction
- Control of hypertension: ACE inhibitors, like enalapril and ramipril, are the drugs of choice to control hypertension
- Control of proteinuria
- Prevention of upper respiratory tract infection.

Treatment of Complications

- *Nutrition and growth*: Protein restriction retards the growth of children with CKD but does not retard progression of disease process. So, protein restriction is not recommended in children with CKD. A balanced diet is to be offered with adequate calorie and protein. 10–12% calorie should be obtained from protein of high biological values.
- *Fluid, electrolytes and acid-base balance*:
  - There may be polyuria due to Na^+ and bicarbonate loss.
  - Na^+ supplementation should be provided in such a way that it should not produce hypertension, edema, hypernatremia.
- *Anemia*:
  - Erythropoietin administration
  - Iron and folic acid supplementation prior to erythropoietin therapy
- *Renal osteodystrophy*:
  - Control of plasma phosphate
    - Limit dietary intake
    - Use phosphate binder
  - Secondary hyperparathyroidism
    - 1-alfacalcidiol supplementation
- *Hypertension*:
  - If proteinuria is present ACE inhibitor should be advised.
  - Dihydropyridine (e.g. nifedipine, amlodipine, etc.) and beta blockers should be avoided
- *Psychosocial*: For better adherence to medication and diet and to prevent needle phobia, support from clinical psychologist is required.

Renal Replacement Therapy

- *Renal transplantation*:
  - It is the best modality but at least 7.5 kg weight is required for transplantation.
  - Ideal therapy is preemptive live-related renal transplant.
  - The side effects of renal transplantation are surgical complications, rejection and side effects that arise from immunosuppressive drugs.
- *Dialysis*:
  - Overnight or ambulatory PD is an alternative choice for renal transplant where transplantation is not feasible.
  - Hemodialysis may be another choice.

A schematic algorithm for evaluation and management of CKD is shown in Figure 60.

PERITONEAL DIALYSIS

Peritoneal dialysis is a mode of renal replacement therapy that can be used for a long time (Figs 61 and 62).

Types of Peritoneal Dialysis Regimen

Peritoneal dialysis regimen can be of continuous (with dialysis solution present in the peritoneal cavity evenly

through 24 hours) or intermittent (with empty abdomen for part of the day, usually during day time). These are:

A. Continuous ambulatory peritoneal dialysis (CAPD)
B. Automated peritoneal dialysis (APD)
   - Continuous cycling peritoneal dialysis (CCPD)
   - Nightly intermittent peritoneal dialysis (NIPD)

Continuous Ambulatory Peritoneal Dialysis (CAPD)

- Fluid is instilled manually into the peritoneal cavity, drained and replaced usually four times a day
- Better for adolescents
- The rate of developing peritonitis, hernia and leakage is high.

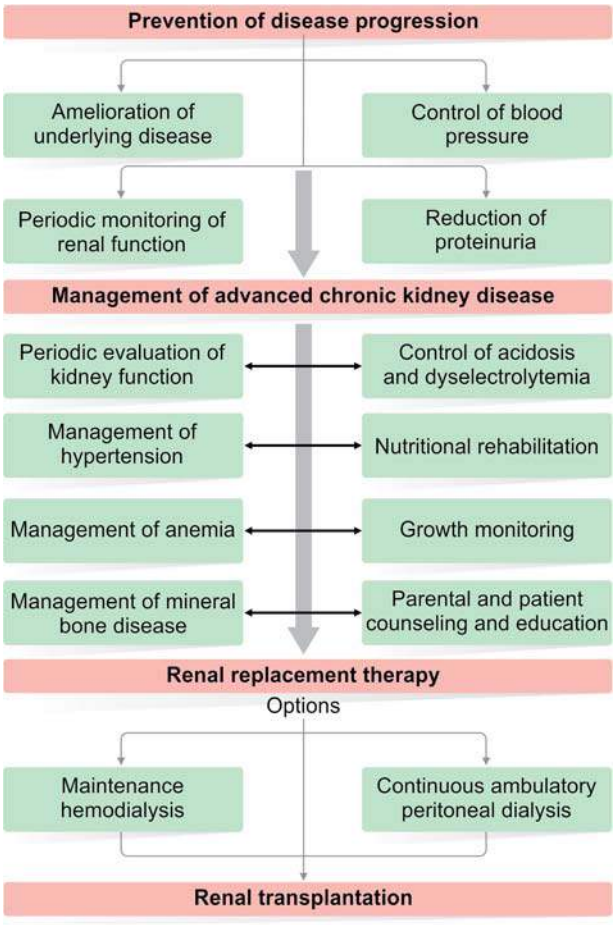


Fig. 60: Schematic algorithm of evaluation and management of CKD

Automated Peritoneal Dialysis (APD)

APD is usually administered as continuous cycling overnight. The benefits of APD over CAPD are as follows:

- Non-interruption of life by dialysis procedure in the day
- Continuous cycling peritoneal dialysis offers better ultrafiltration, clearance of middle molecules
- Nightly intermittent peritoneal dialysis offers reduced clearance of both small and large molecules
- Optimum dialysis may be obtained by assessment of membrane transport.

Fill	Drain
Peritoneal dialysis works inside the body. Dialysis solution flows through a tube into the abdominal cavity where it collects waste products from the blood.	Periodically, the used dialysis solution is drained from the abdominal cavity, carrying away waste products and excess water from the blood.

Complications of Peritoneal Dialysis

- Peritonitis:
  - Sclerosing peritonitis
- Scrotal fluid accumulation due to patent processus vaginalis
- Hernia
- Pleuroperitoneal fistula
- Intra-abdominal adhesion
- Parental/care stress and burn out
- Insulin resistance and dyslipidemia due to high intake of glucose.

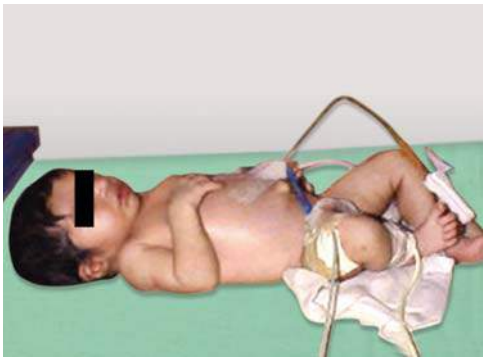


Fig. 62: A neonate undergoing peritoneal dialysis

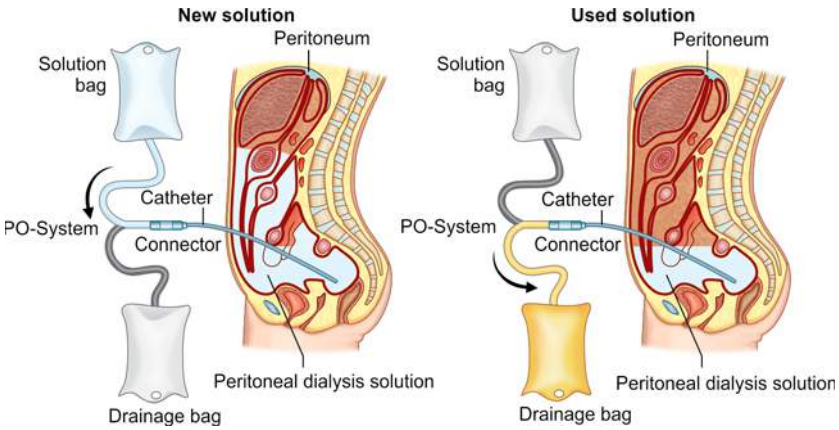


Fig. 61: Diagramatic representation of procedure of peritoneal dialysis

Hemodialysis

Principles

- Blood is drawn through a vascular access at a rate of 3–10 mL/kg/min (maximum 400 mL/min) then across as blood pump which generates positive pressure and forces it into the dialyzer.
- Counter current dialysis occurs across the semipermeable membrane of the dialyzer.
- Blood is purified by filtration and solute removal is returned to the patient circulation.
- Excess fluid is removed by ultrafiltration and solutes are removed by diffusion, convection and solvent drugs. Amount of ultrafiltration depends on the transmembrane pressure, the pressure difference between the blood and dialysate compartment.

An arteriovenous fistula is to be created prior to prescription of hemodialysis.

Continuous Renal Replacement Therapy

Continuous renal replacement therapy (CRRT) is a technique used in intensive care facility for the management of acute renal failure.

Types of CRRT

- *Continuous venovenous hemofiltration (CVVH)*: In this type blood is pumped from a vein, through the filter and back to a vein.
- *Continuous arteriovenous hemofiltration (CAVH)*: In this type blood is pumped from an artery, through the filter and back to a vein.

To add diffusive solute clearance, a counter current is used to hemodialyse (i.e. continuous venovenous hemodialysis; CVVHD and continuous arteriovenous hemodialysis; CAVHD).

Advantages

- Suitable for patients having cardiovascular instability as fluid removal is slow which allows no major fluid shift.
- Development of hypotension is less which decrease the risk of further ischemic insult to kidneys
- Therapeutic drug levels are more easily maintained.

Disadvantages

- Clearance is less than hemodialysis.
- Potassium and phosphate loss may be excessive.
- Not suitable for patients with inborn errors of metabolism because of very high ammonia level.

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17 Hemato-oncologic Disorder

PHYSIOLOGICAL BASIS OF HEMATOLOGICAL DISORDERS

HEMOPOIESIS

Hemopoiesis, also called hematopoiesis, is the process which maintains lifelong production of hemopoietic blood cells. The main site of hemopoiesis in fetal life is the liver, whereas throughout postnatal life, it is the bone marrow.

Location of Hemopoiesis

In Developing Embryo

The most important difference between hemopoiesis in the fetus compared to postnatal life is the changing pattern of hemoglobin (Hb) production at each stage of development. In developing embryo, the blood cell formation occurs in blood islands in the yolk sac from the end of the 3rd week of gestation and declines to an insignificant level by the end of the first trimester.

Bone Marrow

Around 5th month of gestation, bone marrow becomes the main site. Bone marrow is mesenchyme-derived tissue. Hemopoietic component is supported by a microenvironment of stromal cells, extracellular matrix and vascular structure. Some lymphoid cells are produced in the spleen, thymus and lymph nodes, and extramedullary hemopoiesis may occur in liver, thymus and spleen.

Pluripotent Hematopoietic Stem Cell

All hemopoietic tissues are derived from pluripotent stem cells which are crucial for normal blood production; deficiency causes bone marrow failure because stem cells are required for the ongoing replacement of dying cells. The next stage of committed progenitor cells or colony-forming cells accounts for the massive cell proliferation which maintains blood cell production. Hemopoietic stem cells from healthy donor can be used in children with bone marrow failure (stem cell transplantation).

Common lymphoid progenitors develop into lymphoblast and dendritic cells, the former going on to form natural killer cells and T and B lymphocytes. Myeloid progenitors develop into megakaryocytes, proerythroblasts and myeloblasts. Hemopoiesis is regulated and sustained by a network of cytokine growth factors including interleukins (ILs) and colony-stimulating factors (CSFs).

RED BLOOD CELLS

Erythropoiesis is regulated by the hormone erythropoietin and synthesized by the kidney, liver and elsewhere. Immature red cells or reticulocytes comprise 1% of circulating red cells and mature in 7 days. The normal lifespan of red blood cell (RBC) is 120 days.

Hemoglobin

Hemoglobin is the iron-containing oxygen (O_2) transport metalloprotein in the erythrocytes. In human, the Hb molecule consists of four globin protein subunits with a pocket containing heme group. Each heme group contains iron atom in flat porphyrin ring and is the site of O_2 binding.

The first globin chain produced is ε-globin followed almost immediately by α- and γ-globin, which are expressed from 4 weeks to 5 weeks of gestation. Fetal Hb (HbF) is made up of two α- and two γ-chains (α2γ2) and is the main Hb during fetal life. It has a higher affinity for O_2 than adult Hb, which allows it to extract and hold on to O_2, an advantage in the relatively hypoxic environment of the fetus. At birth, the types of Hb in the term infant are: HbF, hemoglobin A (HbA) and hemoglobin A2 (HbA2). Fetal Hb is gradually replaced by adult Hb during the first year of life. These fetal and embryonic Hbs are not normally detectable after infancy but they are produced in children with inherited disorders of Hb production (hemoglobinopathies) and their detection helps in the diagnosis of these disorders (Table 1).

Functions of Hb

Main function is O_2 delivery to tissues. As O_2 binds to iron atom causing a conformational change in the molecule which increases the affinity of the remaining heme group for O_2. This makes O_2 dissociation curve (Fig. 1) sigmoid in shape.

Several factors alter the O_2 affinity of Hb:

Left shift:

- Increased O_2 affinity with increased uptake from the lungs
- Increased pH

Table 1: Gene cluster of different Hb types

Hemoglobin type	α-gene cluster	β-gene cluster
Embryonic		
Hb Gower 1	ξ2	ξ2
Hb Gower 2	α2	ξ2
Hb portland	ξ2	γ2
Fetal		
HbF	α2	γ2
Proportion of hemoglobin types		
Birth	HbF 70–80%, HbA 25–30%, HbA2 1–3%	
Adult	HbA 97%, HbA2 2%	

Abbreviations: Hb, hemoglobin; HbF, fetal Hb; HbA, hemoglobin A; HbA2, hemoglobin A2.

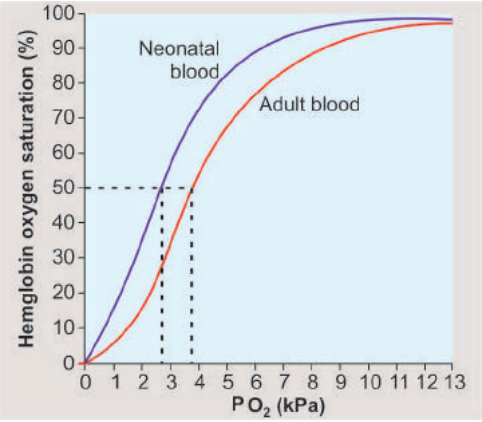


Fig. 1: Oxyhemoglobin dissociation curve

- Decreased PCO_2
- Decreased 2,3-diphosphoglycerate (2,3-DPG)
- Decreased temperature
- Hb variants (e.g. HbF).

Right shift:

- Decreased O_2 affinity with increased release to tissues
- Decreased pH
- Increased PCO_2
- Increased 2,3-DPG
- Increased temperature
- Hb variants (e.g. HbS).

WHITE BLOOD CELLS

White blood cells (WBCs) or leukocytes are classified into lymphocytes (T and B) and phagocytes: Monocytes and granulocytes (neutrophils, basophils, eosinophils).

Production is controlled by growth factors from stromal cells (endothelial cells, macrophage and fibroblasts) and T-cells. Granulocyte-monocyte CSF (GM-CSF) increases differentiation of stem cells into phagocytes. A large reservoir of granulocyte is present in the marrow up to 15 times the number in the circulation. Two pools of bloodstream granulocytes exist: (1) Circulating pool, included in blood count and (2) Marginating pool, which adheres to endothelium and is not included in blood count.

The circulating lifespan of neutrophils is 6–10 hours.

The lymphocyte lineage includes T and B lymphocytes, produced in the bone marrow and thymus and modified in secondary lymphoid tissue, spleen, lymph nodes, respiratory and gastrointestinal tracts (GITs).

PLATELETS

Platelets originate from megakaryocytes in the bone marrow and play an important role in primary hemostasis. Platelet production is controlled by thrombopoietin and IL-6. Lifespan of platelet is 7–10 days. Platelets have no nucleus but they do have microfilaments which hold the inactivated platelet in a discoid shape. They have two types of granules, the content of which differs:

1. *Alpha granule*: Fibrinogen, factor V, von Willebrand's factor (vWF) and platelet-derived growth factor (PDGF).
2. *Dense granules*: Adenosine diphosphate (ADP), adenosine triphosphate (ATP), bioactive amine, Ca^{2+}, Mg^{2+}.

Hemoglobin values at birth and onward and normal leukocyte count are shown in Tables 2 and 3 respectively.

ANEMIA

Anemia is defined as a decreased Hb level below the normal range. The normal range varies with age, so anemia can be defined as:

- Neonate: Hb <14 g/dL
- 1–12 months: Hb <10 g/dL
- 1–12 years: Hb <11 g/dL.

Common causes of anemia in children are given in Figure 2.

Approach to a Child with Anemia

Etiology of anemia varies with age of a child. Multifactorial etiology may also be responsible for development of anemia. So history gives important clues to anemia. Family history of anemia and requirement of blood transfusion point toward

Table 2: Red blood cell (RBC) values at various stages: mean and lower limit of normal (−2SD)

Age	Hb (g/dL)		Hematocrit (%)		RBC count (× 10^{12}/L)		MCV (fL)		MCH (pg)		MCHC (g/dL)	
	Mean	−2SD	Mean	−2SD	Mean	−2SD	Mean	−2SD	Mean	−2SD	Mean	−2SD
Birth	16.5	13.5	51	42	4.7	3.9	108	98	34	31	33	30
1 month	14	10	43	31	4.2	3.0	104	85	34	28	33	29
1 year	12	10.5	26	33	4.5	3.7	78	70	27	23	33	30
8 years	13.5	11.5	40	40	4.6	4.0	86	77	29	25	34	31

Abbreviations: SD, standard deviation; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration.

Table 3: Normal leukocyte count at different age

Age	Total leukocytes (× 10^9/L)		Neutrophils (× 10^9/L)			Lymphocytes (× 10^9/L)			Monocytes (× 10^9/L)		Eosinophils (× 10^9/L)	
	Mean	(Range)	Mean	(Range)	%	Mean	(Range)	%	Mean	%	Mean	%
Birth	18.1	(9.0–30.0)	11.0	(6.0–26.0)	61	5.5	(2.0–11.0)	31	1.1	6	0.4	2
1 month	10.8	(5.0–19.5)	3.8	(1.0–9.0)	35	6.0	(2.5–16.5)	56	0.7	7	0.3	3
1 year	11.4	(6.0–17.5)	3.5	(1.5–8.5)	31	7.0	(4.0–10.5)	61	0.6	5	0.3	3
8 years	8.3	(4.5–13.5)	4.4	(1.5–8.0)	53	3.3	1.5–6	39	0.4	4	0.2	2

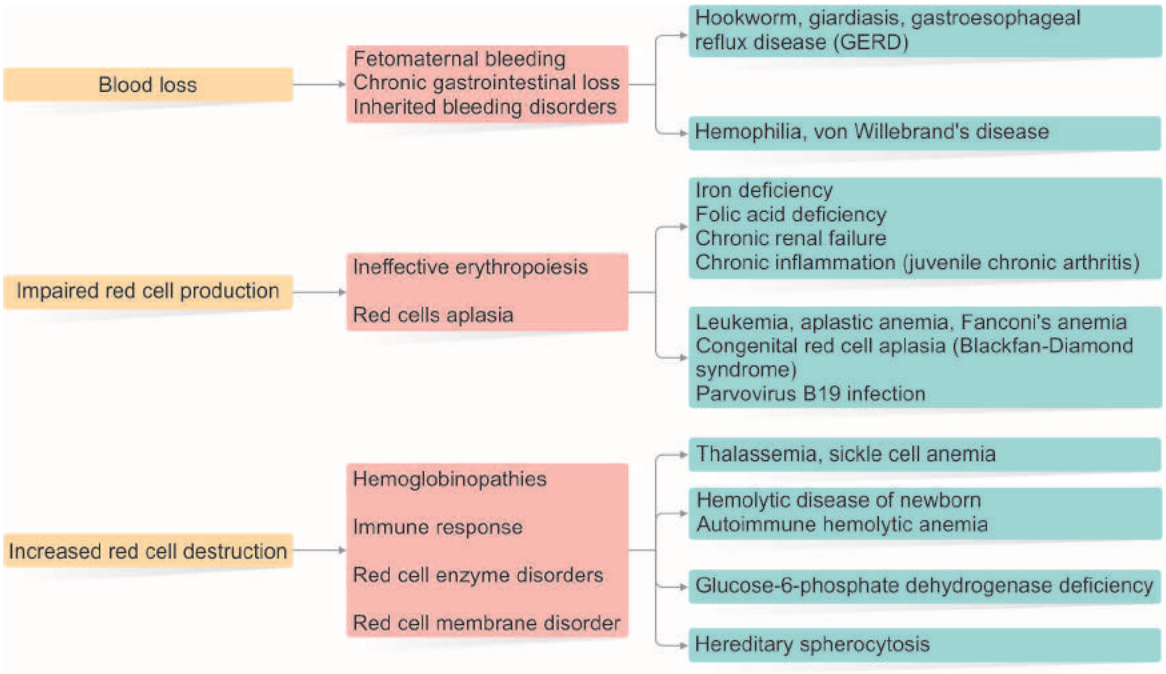


Fig. 2: Common causes of anemia in infants and children

thalassemia, whereas history of gallstone and recurrent episodes of jaundice give the clue to hereditary hemolytic anemia like hereditary spherocytosis (HS) and in such cases if the male child is affected then the most probable cause is glucose-6-phosphate dehydrogenase (G6PD) deficiency. Iron deficiency anemia can be suspected from dietary history like predominantly milk-based diet that is poor in iron content, early initiation of cow's milk (a usual practice in rural areas), in older infant inadequate weaning, chronic diarrhea. Pubertal growth spurt, menstruating and pregnant teens may also suffer from iron deficiency.

Physical Examination

Symptoms of anemia depend upon the cardiovascular status of the individual and rate of development of anemia. Though lassitude, tiredness, generalized muscular weakness and easy fatigability are the common symptoms, the presentation in children is different. Anemia in children is evidenced by irritability, poor feeding and inadequate school performance. Tachycardia, dyspnea on exertion and palpitation are other symptoms. Some central nervous system (CNS) manifestations of severe anemia is dizziness, headache, drowsiness, humming in the ears, fainting, tinnitus, lack of concentration, signs of anemia include pallor, which is seen on palm, sole, face, nail beds, oral mucosa and lower palpebral conjunctiva. There may be edema and hemic murmur in anemic heart failure.

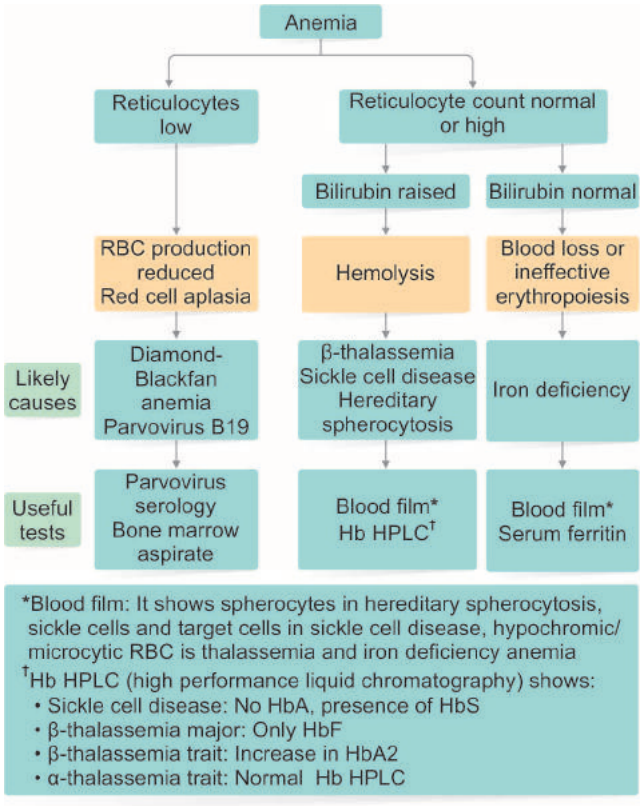


Fig. 3: Diagnostic approach of anemia in children

Laboratory Evaluation of Anemia

A complete hemogram is the clue to anemia. Essentially Hb is low along with other red cell like mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) indices guide the type of anemia. Depending upon MCV, anemia is divided into normocytic, microcytic and macrocytic anemia. The red cell distribution width (RDW) refers to variation of size of RBC; low RDW means uniform RBC while variation of size of RBC accounts for high RDW. Reticulocyte count reflects the degree of red cell production in response to hemolysis. Examination of peripheral smear shows the cellular morphology. Laboratory diagnostic approach of anemia in children is given in Figure 3.

Hemolytic anemia is defined as anemia due to reduced red cell lifespan due to increased red cell destruction in the circulation (intravascular hemolysis) or liver and spleen (extravascular hemolysis). The lifespan of a normal red cell is 120 days and the bone marrow produces 173,000 million red cells per day. In hemolysis, red cell survival may be reduced to a few days but bone marrow production can increase about eightfold, so hemolysis only leads to anemia when the bone marrow is no longer able to compensate for the premature destruction of red cells.

Under maximum stimulation, the normal marrow is capable of increasing its production rate about six to eight times its basal level. The reticulocyte count is useful in determining the erythroid regeneration in response to red cell destruction. The normal reticulocyte count value in newborn is 3.2 ± 1.4% and in children 1.2 ± 0.7%.

Clinical Approach to Diagnose Hemolytic Anemia

In rapidly occurring hemolysis, the symptoms are more pronounced and numerous. Evidence of anemia is seen by weakness, pallor and fatigue. In some hemolytic anemia, jaundice is a prominent finding, red or dark urine occurs in intravascular hemolysis. Hemolytic anemia is an important cause of neonatal jaundice. Splenomegaly is seen in much autoimmune and congenital hemolytic anemia. Some hemolytic anemias are associated with gallstone formation like congenital spherocytosis. Hemolysis due to hemoglobinopathies like thalassemia major makes of characteristic hemolytic facies, whereas leg ulcer may be found in hemolytic anemia due to sickle cell disease (SCD).

The causes of hemolytic anemia in childhood are shown in Table 4. Most acquired forms are immune-mediated; inherited forms are caused by abnormalities of red cell membrane or red cell enzyme defect. The hemoglobinopathies cause anemia due to combination of abnormal Hb molecule, ineffective erythropoiesis and reduced red cell lifespan.

Table 4: Causes of hemolytic anemia

Inherited disorders	
Hemoglobinopathies	Thalassemias Sickle cell disease
Red cell enzyme defect	Glucose-6-phosphate dehydrogenase (G6PD) deficiency Pyruvate kinase deficiency
Red cell membrane defect	Hereditary spherocytosis
Acquired	
Immune mediated:	
Alloimmune	Hemolytic disease of the newborn (HDN) Transfusion mismatch
Autoimmune	Evans syndrome Infections: EBV, mycoplasma Drugs: penicillin, sulfonamide
Nonimmune mediated	Microangiopathic hemolytic anemia: HUS, TTP Malaria, septicemia Drug toxicity: penicillin, sulfonamide, dapsone, sulfasalazine Burns Animal venoms

Abbreviations: EBV, Epstein-Barr virus; HUS, hemolytic-uremic syndrome; TTP, thrombotic thrombocytopenic purpura.

Investigations

- Complete blood count (CBC): The hallmark of hemolytic anemia includes reticulocytosis, elevated count above 1% after newborn associated with macrocytosis (young red cells are larger) except in HS where microspherocytes are prominent.
- Blood film: Polychromasia. Specific features related to etiology may be seen such as spherocytes or red cell fragments in microangiopathy.
- Bilirubin: Unconjugated hyperbilirubinemia.
- Haptoglobin: Decreased in intravascular hemolysis.
- Lactate dehydrogenase (LDH): Raised.

Management

- During acute attack of hemolysis, it is important to maintain fluid balance and urine output
- Management of shock by usual appropriate measures
- Blood transfusion in acute anemia must be used with caution in acquired hemolytic anemia as destruction of transfused blood may cause increased burden in kidney sometime causing thrombosis
- Acute autoimmune hemolytic anemia is treated with steroid like prednisolone 1–2 mg/kg which should be tapered over several months.

HEREDITARY SPHEROCYTOSIS

Hereditary spherocytosis is an autosomal dominant disorder caused by defect in RBC cytoskeleton spectrin and ankyrin. This abnormality contributes to early destruction of RBC in about 28 days. Family history of HS may be present.

Clinical Features

- Anemia—mild anemia (Hb 9–11 g/dL) in childhood
- Intercurrent infection may precipitate hemolysis
- Jaundice—usually develops during childhood but may be intermittent; may cause severe hemolytic jaundice in the first few days of life requiring exchange transfusion
- Mild to moderate splenomegaly—depending on the rate of hemolysis; in the first year of life, it may be the early presentation (Fig. 4)
- Aplastic crisis—uncommon, associated with parvovirus B19 infection
- Gallstones—due to increased bilirubin excretion.

Laboratory Investigations

- Blood film—spherocytes, microspherocytes are found and distributed uniformly (Fig. 5)
- Mean corpuscular hemoglobin concentration—increased
- Reticulocyte count—high in hemolytic crisis
- Increased LDH
- Decreased haptoglobin
- Eosin-5-maleimide (EMA) test: It is a fluorescent dye. Reduced binding with dye indicates 93% sensitivity and 99% specificity for HS.

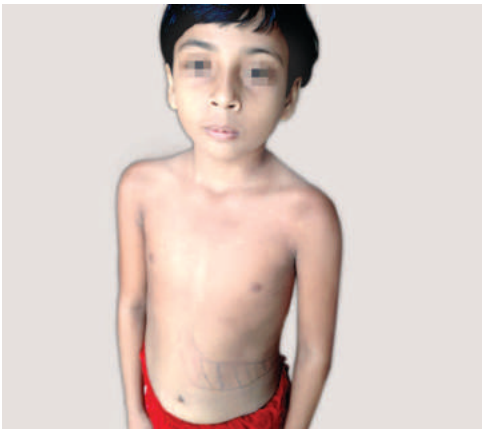


Fig. 4: A child with hereditary spherocytosis (HS) with splenomegaly (shown by drawn line)

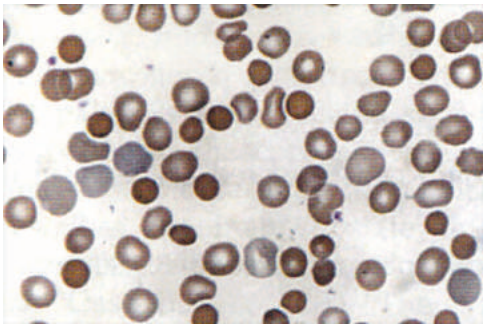


Fig. 5: Blood film showing spherocytes in hereditary spherocytosis (HS)

Management

- Children with mild to moderate anemia treated with folic acid
- Blood transfusion is required in severe hemolysis
- Splenectomy: Though it corrects anemia by preventing hemolysis but it is offered after age of 7 years and prior vaccination against capsulated organisms is offered. Postsplenectomy—lifelong oral penicillin—is also mandatory
- Cholecystectomy in case of symptomatic gallstone.

G6PD DEFICIENCY

Glucose-6-phosphate dehydrogenase deficiency is an X-linked recessive red cell enzyme defect. It is highly prevalent in central Africa, the Mediterranean, the Middle East and the Far East.

Glucose-6-phosphate dehydrogenase is required in Embden-Meyerhof pathway to generate nicotinamide adenine dinucleotide (NADH) and ATP and in hexose monophosphate shunt to generate nicotinamide adenine dinucleotide phosphate (NADPH). NADPH has the role of reduction of glutathione which protects Hb from oxidative damage.

Usually male are affected. G6PD gene is located at Xq28. Female can be affected when there occurs incomplete lyonization.

Types

Depending upon severity of enzyme deficiency, G6PD deficiency is classified into four classes. Approximately 13% of male Afro-Americans have mutant gene (G6PDA) causing less than 5–15% of G6PD enzyme activity. In Mediterranean, Middle East, African and Asian, incidence varies 5–40% with G6PD enzyme activity of less than 5% of normal.

Hemolysis is precipitated by:

- Infection
- Fava beans (broad beans)
- Naphthalene in mothballs
- Certain drugs:
  - Antimalarial: Primaquine, quinine, chloroquine
  - Antibiotics: Sulfonamides, quinolones
  - Analgesic: Aspirin.

Clinical Features

- Jaundice—onset is usually in the first 3 days of life. Worldwide it is the most common cause of severe neonatal jaundice requiring exchange transfusion
- Anemia.

Laboratory Investigations

- Full blood count (FBC):
  - Peripheral blood film shows Heinz body and bite cell during acute hemolysis (Figs 6A and B).
  - In between hemolysis, all patients show normal blood picture.
- Glucose-6-phosphate dehydrogenase enzyme assay
- DNA analysis: It is useful for heterogeneous females.

Management

Avoid oxidant drugs/foods, etc.; maintain good urine output with fluids; transfuse if required; folate supplements in chronic hemolysis; treat hyper–bilirubinemia in newborn.

PYRUVATE KINASE DEFICIENCY

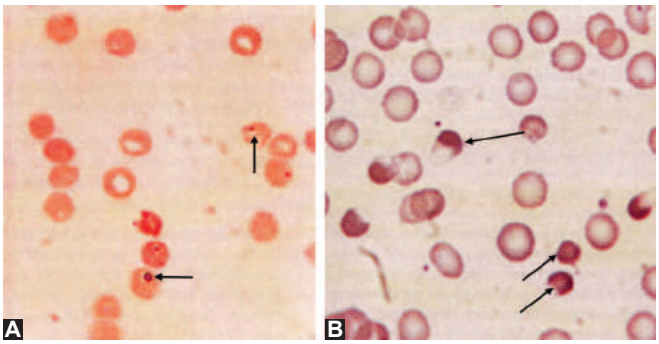
Autosomal recessive disorder caused by deficiency of pyruvate kinase (PK) enzyme (involved in glycolytic pathway) leading to unstable enzyme with reduction in ATP generation in RBCs. Oxygen curve is shifted to the right due to increased 2,3-DPG production.

Epidemiology

Affected persons are homozygous or double hetero–zygotes.

Clinical Features

- Variable, with chronic hemolytic syndrome
- May be apparent in neonate (if severe) or may present in later life
- Jaundice may be present.



Figs 6A and B: (A) Heinz body (arrows) and (B) bite cell (arrows) in G6PD deficiency

Diagnosis

- Complete blood count:
  - Variable degree of anemia
  - Reticulocytosis
- Direct antiglobulin test (DAT) negative
- Lactate dehydrogenase increased
- Serum haptoglobin decreased
- Assay of PK level yields definitive diagnosis.

Complication

- Aplastic crisis may be seen in viral infection (e.g. parvovirus B19).

Treatment

- Dependent on severity
- General supportive measures include:
  - Daily folic acid (5 mg/day)
- Transfusion may be required
- Splenectomy:
  - If high transfusion is required
- In aplastic crisis (e.g. viral infection):
  - Supportive measures should be used.

THALASSEMIA

The thalassemia term came from Greek word "thalassa" related to Mediterranean Sea and "emia" related to blood. Thalassemia is the most common childhood blood disorder in the world. It is a hereditary disorder where patients suffer from severe anemia and need regular blood transfusion. Regular transfusion leads to accumulation of iron which is toxic and this iron needs to be removed by drugs. The thalassemias are the commonest monogenic diseases due to globin gene defect. The molecular biology and genetics of the thalassemia syndrome have revealed 200 mutations. These diseases are commonly found in population of Southeast Asia and Africa.

Thalassemia can be classified as alpha-thalassemia (α-thalassemia) defect in the synthesis of α-chain, and beta-thalassemia (β-thalassemia) defect in the β-globin chains.

The major Hb found in children after 1 year of age is HbA which constitutes approximately 95% and minor component HbA2 accounts for 2–3%. The main Hb in fetal life is HbF; only traces remain after 1 year of life. HbS is ocassionally seen in Bangladesh but commonly seen in Africa. HbC is more seen in Ghana, Africa and HbD seen in Punjab, India.

Pathophysiology

The thalassemias are inherited disorders of globin chain synthesis which results from alteration of globin chain production. A decrease in the rate of production of globin chain (α, β, γ and δ) impedes Hb synthesis and creates an imbalance with normally produced globin chains. To form a normal Hb, two types of chains pair with each other at a ratio close to 1:1 is required. If an excess of one type of pair is present, it usually accumulates in the cell as unstable product which leads to red cell destruction prematurely. The reduction of chains may vary according to severity. When β-chains are produced at a lower rate then it is called β^+-thalassemia, but when β-chains are not at all produced it is called β^0-thalassemia.

Clinical Features

Thalassemia should be suspected in a child when microcytic hypochromic anemia does not respond with iron supplementation. Thalassemia major does not present at birth. They may not present until 6 months of age when β-chains are needed to pair with α-chain to form HbA after γ-chain production is turned off. Severe pallor and hepatosplenomegaly are almost always present. Clinical features of anemia like easy fatigability, irritability and palpitation may develop. Jaundice may be present. Characteristic hemolytic facies with malar prominence, frontal bossing and dental malocclusion may be present due to bony abnormalities from extramedullary erythropoiesis. Chest auscultation may reveal hemic heart murmur due to hyperdynamic circulation. Heart failure may develop in severe anemia.

Spectrum of Thalassemia

Beta-thalassemia is caused by mutation that results in reduced or nonproduction of β-globin chains. Around 200 mutations have been identified. Depending on the type of mutation, there may be intermedia or severe form of β-thalassemia. The beta form of thalassemia is particularly prevalent among Mediterranean people. Globally in 2010, it resulted in about 18,000 deaths. In Europe, the highest concentrations of the disease are found in Greece, Coastal regions in Turkey, in parts of Italy. Other Mediterranean people also have the high rate of thalassemia including people from West Asia and North Africa. South Asians are also affected with the world's highest concentration of carriers being in the Maldives.

Severe forms are known as thalassemia major as most homozygotes suffer from severe type and require transfusion to survive.

Thalassemias are divided into α- and β-thalassemia. Spectrum of thalassemia syndrome depends on degree of abnormal Hb causing β-thalassemia and abnormality due to combination with other Hb like HbE (HbE β-thalassemia).

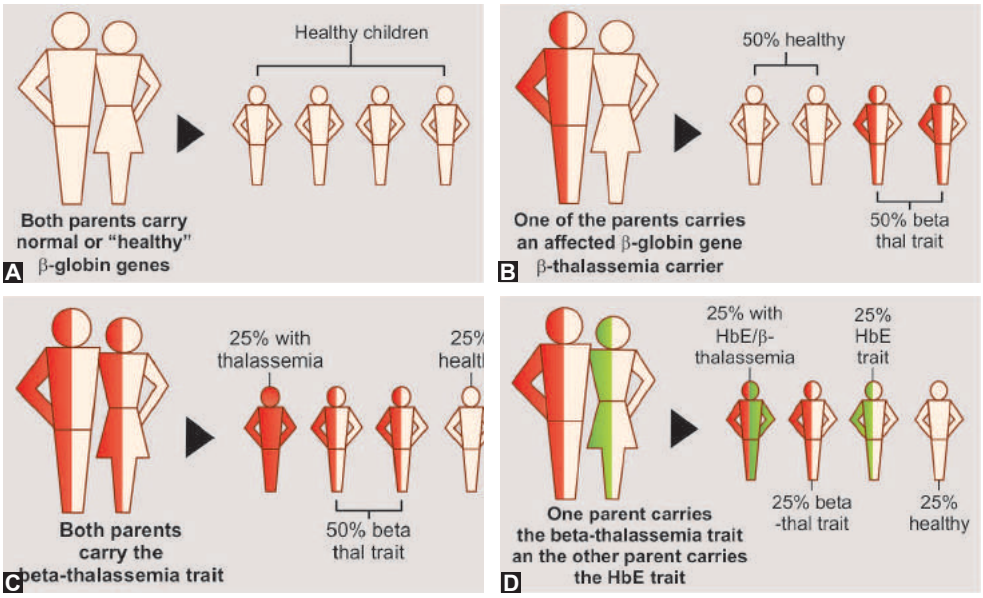
Spectrum of thalassemia consists of:

- β-thalassemia trait
- β-thalassemia intermedia
- β-thalassemia major
- Thalassemia with β-chain structural variants (E β-thalassemia).

Normally carrying β-thalassemia (thalassemia trait) individual is healthy; however, some may experience mild anemia which may be misdiagnosed as iron deficiency anemia. The peripheral blood film examination reveals marked hypochromia, microcytosis and presence of target cells. It differs from iron deficiency blood film that it does not have significant anisocytosis which is usually found in iron deficiency anemia. On the other hand, target cells are less frequently found in iron deficiency anemia. Hb electrophoresis may show elevated HbA2 (> 3.5%) and mild increase of HbF.

Can β-thalassemia carriers develop iron deficiency anemia?

It is not uncommon to have iron deficiency anemia coexistent with thalassemia minor in developing countries. HbA2 may not be increased in thalassemia minor when iron deficiency is associated with thalassemia trait. HbA2 is increased when iron deficiency is corrected in such cases. Carriers of β-thalassemia should be tested for serum iron and ferritin to diagnose iron deficiency. Hb electrophoresis by high



Figs 7A to D: Pattern of inheritance of offspring of different parents with thalassemia

performance liquid chromatography (HPLC) is more sensitive to detect raised HbA2 of thalassemia minor in presence of iron deficiency.

Should β-thalassemia carriers receive iron supplement?

Iron deficient thalassemia carrier should get iron supplement and iron fortified diet if they are iron deficient until iron deficiency is corrected. Serum iron, total iron-binding capacity (TIBC) and ferritin should be estimated if iron deficiency is suspected to be coexistent with β-thalassemia trait.

Beta-thalassemia carries no problem for normal life and longevity; moreover, they can provide protection against malaria. However, they carry significance for their next generation to develop thalassemia disease. When both the parents are carriers, there is one in four chances that the child will be affected with thalassemia major.

Is there any medical problem associated with carrier of β-thalassemia?

There is no physical problem for β-thalassemia trait and they are expected to have normal life expectancy.

How carriers of β-thalassemia affect their children?

When both the parents are carriers, there is one in four (25%) chances that the child will be affected by thalassemia major. Other possibilities are summarized in Figures 7A to D and Table 5.

Hemoglobin E Carriers

HbE carrier is 6% more than carriers of thalassemia (4%).

- Hemoglobin:
  - Normal or occasionally low and may be confused with iron deficiency
- Blood film:
  - Microcytosis with some target cells
- Hemoglobin E carriers are normal and lead normal life
- If HbE carriers marry β-thalassemia carriers then they have 25% chance of having HbE β-thalassemic children.

Table 5: Probability of inheriting thalassemia syndrome including HbE β-thalassemia from parents carrying genes of β-thalassemia and HbE (carrier and disease)

Situation	Inheritance pattern (for each pregnancy)
Both the parents are β-thalassemia trait/ carrier	• Normal baby (25%) • β-thalassemia trait/carrier (50%) • β-thalassemia major (25%)
One parent HbE disease + Partner β-thalassemia trait/carrier	• HbE trait/carrier (50%) • HbE β-thalassemia (50%)
One normal parent + Partner β-thalassemia carrier	• Normal baby (50%) • β-thalassemia carrier (50%)
One parent β-thalassemia trait/ carrier + Partner HbE carrier	• Normal child (25%) • β-thalassemia trait/carrier (25%) • HbE carrier (25%) • HbE β-thalassemia (25%)
One parent normal + Partner HbE carrier	• Normal child (50%) • HbE carrier (50%)
Both are HbE carrier	• Normal child (25%) • HbE carrier (50%) • HbE disease (25%)

Abbreviation: HbE, hemoglobin E.

Hemoglobin E Disease

- Mildly anemic but lead normal life
- Blood film:
  - Microcytosis, hypochromia with many target cells
- If patients with HbE disease marry β-thalassemia carriers then they have 50% chance of having HbE β-thalassemic children (pseudodominance).

Significance of Hemoglobin E

Neither HbE carrier nor HbE disease is dreadful disease. However, combination of β-thalassemia minor and HbE which constitutes HbE β-thalassemia has potential to be dreadful.

As the clinical manifestation is heterogeneous, they are classified into three categories:

1. Mild HbE β-thalassemia.
2. Moderately severe HbE β-thalassemia (like thalassemia intermedia).
3. Severe HbE β-thalassemia (like β-thalassemia major).

The probability of getting HbE β-thalassemia from parents is shown in Table 5.

Hemoglobin E β-thalassemia

Hematological findings are similar to those of β-thalassemia major except the findings of Hb electrophoresis as follows:

- HbA: Absent or mildly present depending upon mutation type
- HbF: Increased (40–60%)
- HbE: 40–60%.

Mild HbE β-thalassemia:

- No significant clinical problems arise, so no treatment is required
- Hb electrophoresis and serum iron status are the parameters for diagnosis
- Hb level remains high (9–12 mg/dL).

Moderately severe HbE β-thalassemia:

- Steady state Hb level remaining at 6–7 g/dL
- Blood transfusion is required when anemia is precipitated by infection
- Iron chelation is required in patients with iron overload
- Careful monitoring and treatment of these patients allow survival up to old age.

Severe HbE β-thalassemia:

- They have the same clinical severity of thalassemia major
- Hemoglobin is very much low (4–5 g/dL)
- Treatment is as like as thalassemia major.

A scoring system is available for classifying HbE β-thalassemia as shown in Table 6. A total score of less than 4 is mild, 5–7 is moderate and greater than 8 is considered as severe HbE β-thalassemia.

Complications

- Extramedullary hemopoiesis:
  - Chronic anemia → stimulates erythropoiesis. Massive erythropoiesis (10–15 times normal) → bone resorption and extramedullary hemopoiesis in the spinal canal → paraplegia
- Cholelithiasis occurs in about 50% cases of HbE β-thalassemia
- Bone changes:
  - Hyperactive bone marrow → bones become distorted, fragile and thinner → prone to fracture
- Leg ulcers occur due to poor circulation
- Thrombophilia:
  - Thrombophilia → increased risk of thrombosis
- Renal complications:
  - Overactive bone marrow → increased production of uric acid.

Indications for Transfusion

- Delayed growth
- Cardiac complication
- Facial deformities
- Hypersplenism
- Decreased normal physical activities
- Hemoglobin less than 7 g/dL in 2 weeks interval.

Beta-thalassemia

Beta-thalassemia is divided into:

- β-thalassemia minor
- β-thalassemia intermedia
- β-thalassemia major.

Thalassemia Minor/Thalassemia Trait

Thalassemia trait has mild anemia, abnormal red cell indices with hypochromia, decreased MCV and very well number of target cells. Hypochromia is relatively marked considering mild or absent anemia. Hb electrophoresis shows increased HbA2. Blood film resembles iron deficiency but without significant anisocytosis which is usually found in iron deficiency anemia. Target cells are frequently found in peripheral blood film in thalassemia trait (Fig. 8). It is not uncommon to find iron deficiency with thalassemia trait in developing countries. Concomitant iron deficiency can be diagnosed by estimating serum iron, TIBC and serum ferritin. Thalassemia major can be differentiated from thalassemia minor clinically and hematologically. In thalassemia major, Hb is significantly reduced (3–5 g/dL), serum ferritin is increased, and serum bilirubin is slightly increased in comparison to thalassemia minor. Hb electrophoresis shows significant increase in HbF in comparison to thalassemia minor. The differences between thalassemia major and minor are shown in Table 7.

Table 6: Clinical scoring for classifying HbE β-thalassemia

Criteria	Status	Score	Status	Score	Status	Score
Hb at steady state (g/dL)	>7.5	0	6.0–7.5	1	<6	2
Age of onset (year)	>10	0	2–10	0.5	<2	1
Age of first transfusion (year)	>10	0	4–10	1	<4	2
Requirement of transfusion	Rare/none	0	Occasional	1	Regular	2
Size of spleen (cm)	<3	0	3–10	1	>10	2
Growth and development	Normal	0	±	0.5	Retarded	1
Splenectomy	No	0	Yes	2		

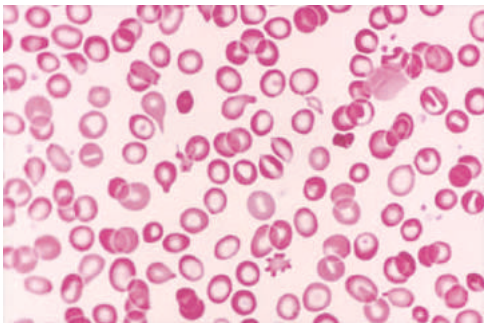


Fig. 8: Blood film of thalassemia minor showing target cell with microcytosis

Approach to screen thalassemia trait and to differentiate from iron deficiency and other abnormal Hb are shown in Figure 9.

Naked Eye Single Tube Red Cell Osmotic Fragility Test (NESTROFT) for detection of thalassemia trait: This method is useful for detecting β-thalassemia trait. It is cheap, simple and easy to perform. It is about 95.5% sensitive and 81% specific. It has high-negative predictive value (96–100%).

A positive NESTROFT is seen in other conditions like β-thalassemia trait, HbE and HbS.

NESTROFT procedure: It is performed by using 0.36% buffered saline solution. In another test tube, 2 mL of distilled water is used for test or control (Fig. 10A). A drop of venous blood is added to both the tubes and left undisturbed for half an hour at room temperature. After half an hour, both tubes are shaken and then held against a white paper on which a thin black line is drawn. The line is clearly visible through the contents of tube

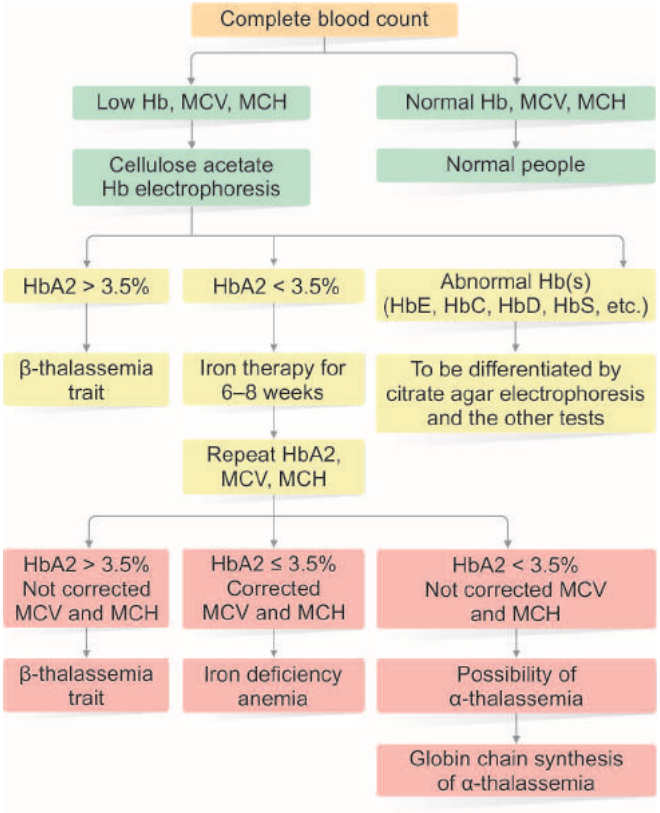


Fig. 9: Screening of thalassemia trait and abnormal hemoglobin

Abbreviations: Hb, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; HbA2, hemoglobin A2.

Table 7: Hematological parameters of β-thalassemia minor and major

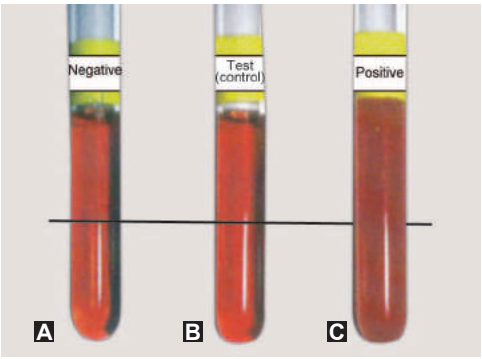
Parameters	**β-thalassemia minor or trait**	**β-thalassemia major**		
Hb estimation (g/dL)	Normal, mildly reduced, rarely <9.5 g/dL	Markedly reduced (3–5 g/dL)		
WBC count (total and differential)	Normal	Normal		
Platelet count	Normal	Normal or reduced in hypersplenism		
Reticulocyte count	Normal	Increased (5–10%)		
RBC indices:				
RBC count	Normal or increased	Decreased		
MCV	Decreased	Decreased		
MCH	Decreased	Decreased		
MCHC	Normal or slightly reduced	Decreased		
RDW	Normal	Increased		
Blood film:				
RBC	Hypochromia marked in comparison to anemia, target cells and mild anisocytosis	Marked anisopoikilocytosis, nucleated RBC, hypochromia, target cells		
Serum bilirubin	Normal	Slightly raised		
Serum ferritin	Normal	Increased		
NESTROFT	Positive (decreased)	Not required		
HPLC/Hb electrophoresis:			β^+	β^0
HbA	Decreased	Decreased	10–90%	Absent
HbF	Normal or slightly increased	Increased	10–90%	98%
HbA2	Increased (>3.5%)	Variable	1.5–4%	1.5–4%

Abbreviations: Hb, hemoglobin; WBC, white blood cell; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; NESTROFT, naked eye single tube red cell osmotic fragility test; HPLC, high performance liquid chromatography; HbA, hemoglobin A; HbF, fetal Hb; HbA2, hemoglobin A2.

containing distilled water due to breakdown of RBCs (Fig. 10A). If the line is similarly visible through the contents of the test tube with the buffered saline, the test is considered negative (Fig. 10B) that means hemolysis of RBCs occurred. If the line is not clearly visible, the test is considered positive (Fig. 10C) that means no hemolysis of RBCs occurred. A positive test indicates decreased osmotic fragility (resistant to hemolysis) suggestive of thalassemia trait.

Thalassemia Intermedia

This condition is usually due to compound heterozygous trait resulting in anemia of intermediate severity which usually does not require regular blood transfusion. Although primarily it is clinical diagnosis and requires monitoring of the child over time to see the clinical evaluation of the disease; however, it should be differentiated from thalassemia major by number of clinical and laboratory features as shown in Table 8.



Figs 10A to C: NESTROFT method of screening thalassemia. Thin black line visible through tube B (negative). Same line not visible through tube C (positive) due to no hemolysis suggestive of thalassemia trait

Table 8: Difference between thalassemia major and intermedia at presentation

	Thalassemia major more likely	Thalassemia intermedia more likely
Clinical		
Presentation (years)	<2	2
Hb level (g/dL)	<7	8–9
Hepatomegaly/ splenomegaly	Severe	Moderate to severe
Hematological		
HbF (%)	>50	10–50
HbA2	<4	>4
Molecular		
Type of mutation	Severe	Mild/silent
Coinheritance of α-thalassemia	No	Yes
Hereditary persistence of fetal Hb	No	Yes
XmnI polymorphism	No	Yes
β-thalassemia in one chromosome and Hb variant in other chromosome	No	Yes

Abbreviations: Hb, hemoglobin; HbF, fetal Hb; HbA2, hemoglobin A2.

Thalassemia Major

The condition is characterized by transfusion-dependent anemia, splenomegaly, bone deformities, growth retardation and hemolytic facies in untreated or inadequately treated individuals (Fig. 11).

Examination of peripheral blood film shows marked anisopoikilocytosis, microcytosis, hypochromia, target cells, schistocytes, nucleated RBCs and polychromatic cells (Fig. 12).

RBC indices:

- RBC count: Decreased
- MCV: Decreased
- MCH: Decreased
- Mean corpuscular hemoglobin concentration: Decreased
- RDW: Increased.

Reticulocyte count is also increased (5–10%). Serum bilirubin is raised with increased serum ferritin. Hb electrophoresis shows increase in HbF of variable degree and decrease in HbA in β^+-thalassemia (about 10–90%) whereas in β^0-thalassemia, HbA is absent.

Hemoglobin electrophoresis: This is done with paper and cellulose acetate where HPLC is not available. HPLC has become popular and very useful in quantification of HbA2 in β-thalassemia screening as well as for identification and quantification of other Hbs. In HPLC, Hbs are separated graphically (Figs 13A and B) and quantified by spectrophotometry utilizing sophisticated computer software. It is accurate, precise and fast.

Hemoglobin electrophoresis should be done before blood transfusion. If it is done immediately after blood transfusion, it interferes with the result. If blood transfusion is given to a patient, it is advised to wait up to 4 months (normal lifespan of RBC is 120 days) before Hb electrophoresis.

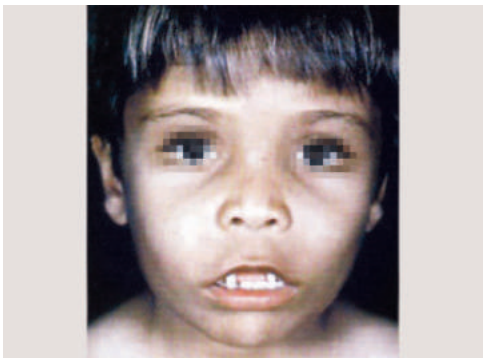


Fig. 11: Facial features of thalassemia

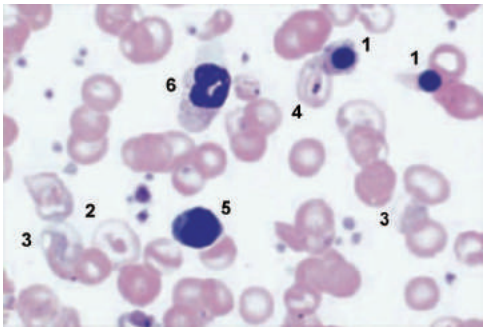
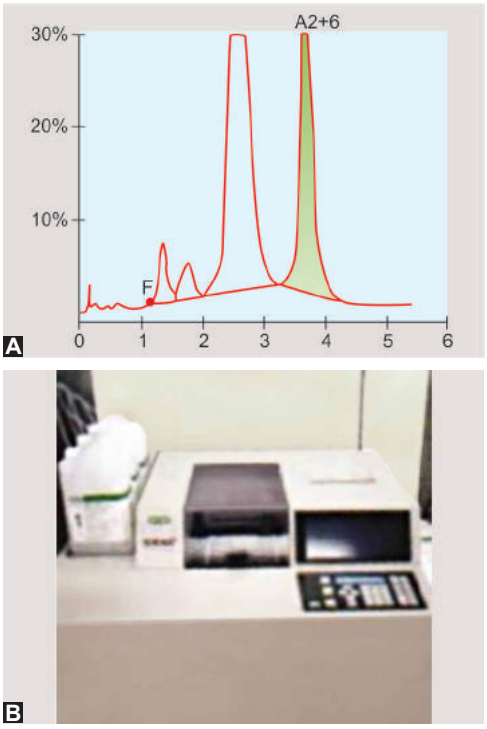


Fig. 12: Thalassemia major: (1) erythroblasts, (2) target cell, (3) polychromatic erythrocytes, (4) Howell-Jolly bodies (in a case of functional asplenia), (5) lymphocyte and (6) granulocyte



Figs 13A and B: High performance liquid chromatography (HPLC): (A) showing the curve of hemoglobins; (B) the HPLC machine

Radiological changes in thalassemia major:

Skeletal survey:

X-ray skull: Expansion of bone marrow and demineralization in the bone lead to trabeculae, in the skull bones become prominent giving hair on end appearance of skull bones (Fig. 14).

Osteoporosis and osteopenia also occur leading to increase in bone fragility and susceptibility to fracture (Fig. 15).

Management of thalassemia major: The two major components of management of thalassemia major are: (1) correction of anemia by regular blood transfusion and (2) management of iron overload by iron chelators.

- Definite treatment of thalassemia major is allogeneic hematopoietic stem cell transplantation (HSCT)
- Management of complications which includes cardiovascular complications, infection, growth, endocrine complications, skeletal complications, psychosocial support
- Genetic counseling.

Blood transfusion: Transfusion is given to children with severe anemia due to thalassemia to improve tissue oxygenation and to suppress ineffective erythropoiesis that causes many of the complications associated with thalassemia. In hypertransfusion regimen, the endogenous erythroid production is suppressed by maintaining a minimum pretransfusion Hb level of 9–10 g/dL and it is the commonest approach today. Supertransfusion program is aimed to maintain a pretransfusion Hb level between 11 g/dL and 12 g/dL with the intention of decrease in iron absorption from GIT. The frequency of red cell alloimmunization in chronically transfused children varies with the disease; number of transfusion given and ethnic background are often involved. Antibodies to common antigens of the Rh, Kell, and Duffy and Kidd systems are often involved. It may be desirable to phenotype the patients red cell antigens

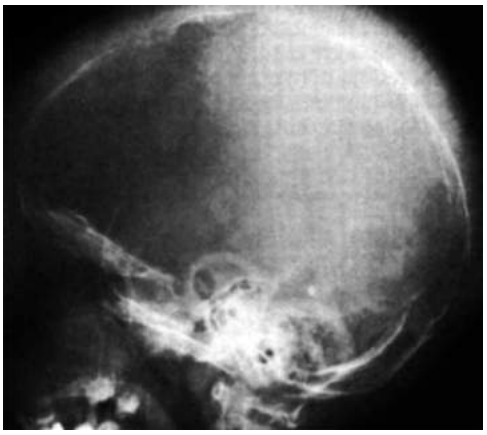


Fig. 14: X-ray skull showing typical hair on end appearance on skull vault in thalassemia

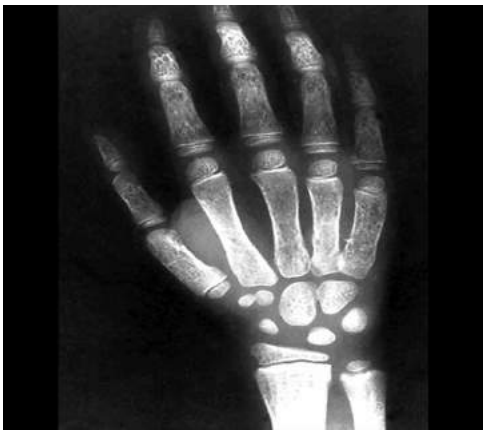


Fig. 15: X-ray of hand shows widened medullary cavities with coarse trabecular markings of the metacarpals and phalanges evident in thalassemia

as completely as possible before giving transfusion therapy and maintain a permanent record of the results. This can be helpful in selecting compatible blood if alloimmunization occurs. All patients with thalassemia should be transfused with ABO and Rh compatible blood, if available. Transfusion from first degree relative should be avoided because of the risk of developing antibodies that might adversely affect the later bone marrow transplant.

In patients who are already immunized and are at high-risk of developing additional antibodies, use of phenotypically matched units may be a reasonable approach. Leukocytes reduced blood transfusion should be considered for these chronically transfused patients to diminish development of alloimmunization to human leukocyte antigen (HLA) and to prevent febrile transfusion reactions. These children are not only frequently transfused but are possible future candidates of HSCT. It is considered by some clinicians that blood products that have been depleted to less than 5×10^6 leukocyte/unit to be cytomegalovirus (CMV) safe. All children on regular transfusion should be vaccinated against hepatitis B as early as possible.

Aim of blood transfusion: Current guidelines and the new Thalassemia International Federation (TIF) recommend:

- Maintaining an average of Hb 12 g/dL
- Maintaining pretransfusion Hb 9–10 g/dL
- That transfusion should prevent marrow hyperplasia, skeletal changes and organomegaly

- Red cell requirement should be adjusted to accommodate growth and hypersplenism if red cell requirement increased unexpectedly
- Iron chelation therapy should be considered after ten transfusions and once the ferritin level is 1,000 μg/L (if possible starting after 2 years of age).

Mainstay of therapy for β-thalassemia major is chronic hypertransfusion combined with iron chelation and supportive measures directed to the complication of expanded erythron and iron overload. Iron overload is the major cause of mortality and morbidity in thalassemia patient. Both transfused iron and excessive iron absorption from GIT are contributing to iron overload in thalassemia.

Management of iron overload:

- Serum ferritin is broadly related to body iron. When high, the following should be considered:
  - Iron overload
  - Inflammation
  - Hepatitis
  - Liver damage.

  In thalassemia intermedia, the degree of iron overload is underestimated. Ferritin levels related to low-risk are below 2,500 μg/L, preferably below 1,000 μg/L.
- Ranges of liver iron concentration (LIC) reflecting levels of risk:
  - Very low-risk = <1.8 mg/g dry weight
  - Low to moderate risk = 1.8–7 mg/g dry weight
  - Moderately high to high risk = 7–15 mg/g dry weight
  - Very high-risk = >15 mg/g dry weight.
- Total body iron stores = 10.6 × LIC (mg/g dry weight).
- Liver iron concentration is measured by:
  - Liver biopsy—indicated if ferritin levels deviate from expected trends, if coexistent hepatitis and if uncertain response to chelation.
- *Cardiac iron*: Reflected by heart function tests and measured by magnetic resonance imaging (MRI) T2.
- *Urinary iron*: Used to monitor desferrioxamine (DFO) or deferiprone (DFP) dose effects.

Assessment of myocardial iron load through imaging: The outcome of patients with cardiac siderosis cannot be predicted on the basis of serum ferritin as ferritin is not a suitable predictor of subclinical cardiac disease and cardiac decompensation can occur with serum ferritin level less than 2,500 μg/L. This may be due to the fact that the iron chelators remove iron from liver more rapidly than from the heart and also the possible genetic variation of various cardiac ions transport channels. Noninvasive quantification of myocardial iron can be done by cardiovascular magnetic resonance (CMR) imaging $T2^*$. MRI $T2^*$ is a measure of magnetic relaxation which is easier to measure than T2 and the extent of cardiac iron on MRI $T2^*$ provides useful insight into the severity of myocardial siderosis. Cardiac $T2^*$ value of less than 20 ms is indicative of iron overload, as below this level there is progressive decline in left ventricular (LV) function.

FerriScann®: It is a new noninvasive measure of LIC. It is done through MRI.

Liver iron concentration is the most accurate measure of total body iron score. In the past, LIC was only measured by liver biopsy, an invasive, often painful procedure. FerriScan® is alternative, noninvasive test. It is safer, painless and quick procedure. Nowadays FerriScan® has replaced liver biopsy because it is noninvasive, safe, painless and more accurate. However, it is not universally available particularly in developing countries. The FerriScan® method for measuring LIC has three simple steps (Figs 16 and 17):

Fig. 16: MRI FerriScanner

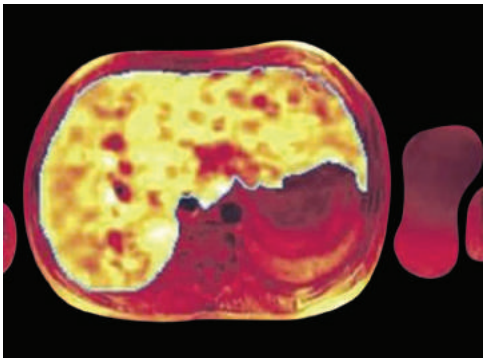


Fig. 17: Detection of images of liver iron concentration (LIC) by scanner

1. A set of images of liver are produced by a MRI scanner
2. Images are then sent to FerriScan® server at Australia via internet
3. The LIC is sent from Australia within 2 days.

Iron chelation: Every child who is maintained in a high transfusion regimen ultimately develops iron overload and dies of siderosis of the myocardium. Iron chelation is usually started after the patient has received more than 10–15 units of blood or serum ferritin level over 1,000 ng/mL. For this child, iron chelation program should be started earlier, i.e. first 2–3 years of age.

Iron chelating agents: Commonly practiced iron chelators are:

- Deferoxamine which is administered parenterally
- Deferiprone
- Deferasirox (DFX) which is administered perorally.

Desferrioxamine:

- Initiate treatment after first ten to twenty transfusions or ferritin level above 1,000 ng/mL
- If before 3 years of age, monitoring of growth and bone development is recommended
- Therapeutic index = Mean daily dose (mg/kg)—actual dose of each infusion × doses/7 days/ferritin (mg/L).
- Keep index less than 0.025 at all times

- Standard treatment:
  - Slow subcutaneous (SC) infusion over 8–12 hours
  - 10% DFO solution (5 mL water for each 500 mg vial)
  - Infusion pump (several types available)
- Standard dose:
  - Children 20–40 mg/kg (not exceeding 40 mg/kg)
  - Adults 50–60 mg/kg. Infuse 8–12 hours 6 nights minimum per week
- Alternative route: SC bolus—two SC boluses/day to a total daily dose of 45 mg/kg
- Vitamin C
  Dose limited to 2–3 mg/kg/day given orally at the time of infusion
- Intensive chelation with DFO—continuous 24-hourly infusion intravenous (IV) or SC
  Indications:
  - Persistently hig- serum ferritin
  - LIC greater than 15 mg/g dry weight
  - Significant heart disease
  - Prior to pregnancy or bone marrow transplantation (BMT)

  Dose: 50 mg/kg/day (up to 60 mg/kg/day)
- Indwelling catheters: danger of infection and thrombosis.

Deferiprone:
Standard dose:
- 75 mg/kg/day in three divided doses (up to 100 mg/kg/day)
- Vitamin C concomitant treatment not recommended. Weekly blood counts (more frequently if signs of infection) should be done for monitoring.

Combination therapy: In patients for whom monotherapy with DFO or DFP are not controlling body levels of iron or myocardial iron or in the presence of significant heart disease, combined regimes offer an alternative that can reduce iron levels in both the liver and heart. No recommendations as to which is the more effective combination can be made at present. Agranulocytosis may be more frequent in combination therapy, especially in simultaneous use.

Deferasirox: Desferrioxamine which is first effective iron chelator produced dramatic effect in children with thalassemia. However, DFO has poor oral bioavailability and half-life necessitating 12 hours of SC infusion. Although an oral iron chelator, DFP has short half-life and needs to be taken thrice daily, besides some troublesome side effects like arthralgia and neutropenia.

Deferasirox is a new efficacious, safe oral iron chelator and has an advantage of longer half-life and hence requires once daily administration leading to better compliance. It is also a good myocardial iron chelator as evidenced from investigations done using CMR by measuring myocardial T2*. It is more efficacious in moderate to severe cardiac iron overloaded patient. For myocardial iron, DFX has the ability to enter myocardial cells and chelate iron from these cells. It has been also observed from myocyte culture that it ensures therapeutic gain entering to myocytes and binds to labile intracellular iron leading to decreased free radicals production.
Recommended dose:
- Starting dose 20 mg/kg/day. After ten to twenty transfusions or iron intake of 0.3–0.5 mg/kg/day
- In pre-existing iron overload or iron intake greater than 0.5–30 mg/kg/day is recommended
- For patients with low rate of iron loading (<0.3 mg/kg/day), lower doses may be sufficient to control iron loading; some patients will still fail to achieve negative iron balance at a daily dose of 30 mg/kg/day of DFX, and studies are currently underway to assess the effectiveness and safety of higher doses.

Administration: Tablet dissolved in water (or apple juice), using a nonmetallic stirrer. Taken once a day before a meal.
Continuous monitoring is required.
Contraindicated in renal failure or significant renal dysfunction.

A comparison between these three drugs is mentioned in Table 9.

Newer Emerging Therapies for Thalassemia

Emerging therapies for thalassemia are:
- Allogeneic BMT—the curative modality

Table 9: Comparison between different iron chelators

Property	Deferoxamine (DFO)	Deferiprone (DFP)	Deferasirox (DFX)
Route	Subcutaneous/IV	Oral	Oral
Dose	25–50 mg/kg/day	75 mg/kg/day	20–30 mg/kg/day
Frequency and duration	Over 8–24 hours/day	3 times/day	Once daily
Excretion	Urine/feces	Urine	Feces
Plasma clearance ($t^{1/2}$)	20 minutes	53–166 minutes	1–16 hours
Adverse effect	• Local skin rash • Ototoxicity • Infections • Ophthalmic toxicity • Skeletal impairment	• Agranulocytosis • GIT disturbances • Elevated transaminase • Arthralgias	• GIT disturbances • Elevated transaminase • Raised creatinine • Rash • Proteinuria
Advantage	Long-term data available	Orally active	Orally active, only single dose and superior in removing iron from cardiac tissue
Disadvantage	Compliance may be a problem	Variable efficacy in removing hepatic iron	Acute renal failure Hepatic dysfunction
Monitoring	X-ray of long bone in growing children Annual eye and ear check up	Weekly CBC	Renal function test, liver function test and urinalysis monthly

Abbreviations: IV, intravenous; GIT, gastrointestinal tract; CBC, complete blood count.

- Pharmacologic manipulation of HbF level
- Gene therapy.

Allogeneic Bone Marrow Stem Cell Transplantation

Allogeneic HSCT still remains the only definitive, curative option for patients with thalassemia. Advances in transplantation biology have made it possible to perform haploidentical stem cell transplantation in patients with thalassemia who do not have HLA-identical related donor.

Pharmacologic Manipulation of HbF Switching

Hydroxyurea: Hydroxyurea has been found to increase Hb level in patients with β-thalassemia and SCD. Use of hydroxyurea is helpful in thalassemia intermedia though its role in thalassemia major is unsatisfactory.

Histone deacetylase inhibitors: Histone deacetylase inhibitors, butyrate and trichostatin A, activate γ-globin expression via a *p*38 mitogen-activating protein kinase (MAPK)-dependent mechanism.

Butyric acid analogs: The butyric acid analogs like arginine butyrate, sodium phenylbutyrate increase the potency and sustainability of the Hb switching effect.

Kit ligand (stem cell factor, Stemgen): Kit ligand with or without dexamethasone to cell cultures from patients with β-thalassemia intermedia and major causes:

- Increase in cell proliferation
- Reduces the percent of apoptotic cells and dyserythropoietic cells
- Induces marked increase of γ-globulin synthesis required for the production of HbF.

The main side effect of using Kit-ligand is severe allergic reaction.

Gene Therapy

Principle of gene therapy in thalassemia is to insert donor globin gene into the pluripotent hematopoietic stem cells in such a fashion that allows its tightly regulated but high-level expression only in the red cell lineage and only during the period of terminal erythroblastic maturation.

Complications of Thalassemia

Complications due to Blood Transfusion

- Nonhemolytic febrile transfusion reaction
- Allergic reactions
- Acute hemolytic reactions
- Autoimmune hemolytic anemia
- Delayed transfusion reactions
- Transfusion-related acute lung injury
- Transfusion-related graft versus host disease
- Transmission of infectious diseases.

Complications due to Iron Chelators

- Complications associated with DFO:
  - Local skin rash such as erythema, swelling and induration
  - With high-dose:
    - Hearing complications
    - Visual complications
    - Bony changes
- Complications associated with DFP:
  - Neutropenia
  - Pain and swelling of joints.
  - Gastrointestinal problems
  - Zinc deficiency
- Complications associated with DFX:
  - Acute renal failure
  - Cytopenia
  - Hepatic dysfunction.

Complications due to Disease Process

- Infection: Infection occurs due to:
  - Anemia
  - Splenectomy
  - Repeated transfusion with unscreened blood
- Cardiac complications
  Myocardial damage resulting in:
  - Arrhythmia
  - Cardiac failure
- Endocrine complications: Endocrine complications arise from iron deposition and toxicity to the endocrine tissues resulting in significant morbidity.
  The endocrine disorders arising from thalassemia are:
  - Growth retardation
  - Delayed puberty
  - Diabetes
  - Hypothyroidism
  - Hypoparathyroidism
  - Failure of sexual functions
  - Adrenal insufficiency
  - Osteoporosis
- Hepatic dysfunction:
  - Acute cholecystitis
  - Gallstones
- Bones and joint complications:
  - Arthritis
  - Osteoporosis.

Management of Complications Associated with Thalassemia

Growth and Endocrine Complications

Growth: Growth retardation is common in thalassemia major and severe E β-thalassemia. Patterns of growth are relatively normal until the age of 9–10 years when growth velocity begins to slow. Chronic anemia, transfusional iron overload, hypersplenism and chelation toxicity contribute to stunted growth in patients with thalassemia.

Diagnosis and investigations of short stature associated with thalassemia:

Diagnosis requires careful clinical evaluation to establish:

- Slow growth rates—growth velocity expressed in cm/year, below 1 standard deviation (SD) for age and sex (based on growth velocity charts)
- Height below the 3rd centile for sex and age (based on national growth charts)
- Signs of other pituitary hormone deficiencies (e.g. gonadotropins)
- Other possible causes of retarded growth.

Investigation of a child with thalassemia who has stunted growth is generally similar to that of a child without thalassemia.

Treatment

- Regular blood transfusion and iron chelation
- Folic acid supplementation
- Zinc supplementation.

Dietary management in thalassemia

- Diet of thalassemia patient should of low iron and also of foods that decrease the iron absorption. Foods with high iron content should be avoided. Calcium present in milk yogurt and cream decreases iron absorption and prevents osteoporosis. Tea and coffee also inhibit iron absorption
- Vegetables and fruits like orange with high vitamin C should be taken in between meals as vitamin C enhances iron absorption.

Delayed Puberty and Hypogonadism

Delayed puberty: Delayed puberty is defined as the complete lack of pubertal development in girls by the age of 13 and in boys by the age of 14.

Hypogonadism: Hypogonadism is defined in boys as the absence of testicular enlargement (less than 4 mL) and in girls as the absence of breast development by the age of 16.

In arrested puberty, annual growth velocity is either markedly reduced or completely absent and the testicular size remains 6–8 mL, and breast size at B3 in Tanner staging.

Investigations:

- Routine biochemical analysis
- Bone age (X-ray of wrist and hand)
- Thyroid function [thyroid-stimulating hormone (TSH) and free T4 (FT4)]
- Hypothalamic-pituitary-gonadal function:
  - Gonadotropin-releasing hormone (GnRH)
  - Stimulation test for luteinizing hormone (LH) and follicle-stimulating hormone (FSH)
- Sex steroids:
  - Serum testosterone
  - Serum 17β-estradiol
- Pelvic ultrasound (US) to assess ovarian and uterine size
- Transglutaminase antibodies
- In selected cases:
  - Growth hormone (GH) stimulation test
  - Insulin growth factor-1 (IGF-1)
  - Insulin growth factor-binding protein-3 (IGFBP-3)
  - Plasma zinc.

Treatment:

For girls: Oral administration of ethinyl estradiol (2.5–5 μg daily) for 6 months followed by hormonal reassessment. If spontaneous puberty does not occur within 6 months after the end of treatment, oral estrogen is reintroduced in gradually increasing dosages (ethinyl estradiol from 5 μg to 10 μg daily) for another 12 months.

For boys: Low dosages of intramuscular depo-testosterone esters (25 mg) are given monthly for 6 months, followed by hormonal reassessment. In patients with hypogonadotropic hypogonadism, treatment at a dose of 50 mg per month can be continued until growth rates wane. The fully virilizing dose is 75–100 mg of depo-testosterone esters every 10 days, administered intramuscularly.

Hypothyroidism

This may occur in severely anemic and/or iron overloaded patients, usually appearing in the second decade of life.

Signs and symptoms:

Preclinical hypothyroidism is asymptomatic. In mild and overt hypothyroidism, symptoms such as growth retardation, decreased activity, above normal weight, constipation, reduced school performance, cardiac failure and pericardial effusion may be encountered. The incidence of hypothyroidism is slightly higher in females.

Investigations:

- Serum TSH, free T3 and T4.

Treatment:

- Abnormal thyroid function may be reversible at an early stage through intensive chelation and good compliance
- Treatment depends upon the severity of organ failure. Subclinical hypothyroidism requires regular medical follow-up and intensive iron chelation therapy
- In patients with mild or overt hypothyroidism, L-thyroxine is given.

Impaired Carbohydrate Metabolism

Impaired glucose tolerance and diabetes mellitus may be the consequence of cell destruction secondary to iron overload, chronic liver disease, viral infection and/or genetic factors.

Investigations:

Oral glucose tolerance test (OGTT) should be performed annually from the age of puberty. For children, a dose of 1.75 g/kg (to a maximum of 75 g) is used for OGTT.

Treatment:

- Impaired glucose tolerance may be improved by a strict diabetic diet, weight reduction, where applicable, and possibly intensive iron chelation therapy
- In symptomatic patients, insulin treatment is normally required but metabolic control may be difficult to achieve
- The role of oral hypoglycemic agents remains to be fully determined.

Hypoparathyroidism

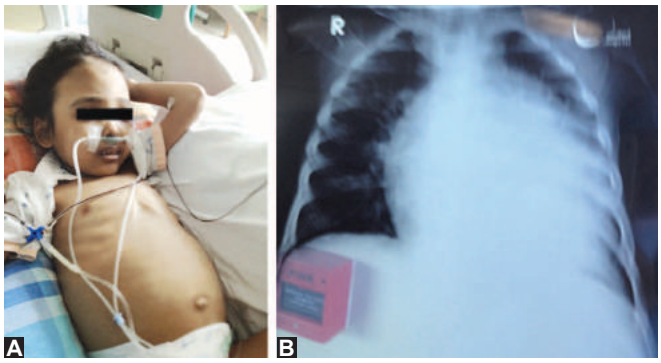
Hypocalcemia, due to hypoparathyroidism, usually begins after the age of 16 years.

The majority of patients show a mild form of the disease accompanied by paresthesia. More severe cases may demonstrate tetany, seizures or cardiac failure.

Investigations:

Investigations should begin from the age of 16 and should include:

- Serum calcium
- Serum phosphate and phosphate balance
- In cases with low serum calcium and high phosphate levels, parathyroid hormone should also be evaluated. Parathormone may be normal or low, with low readings for 1,25 dihydroxycholecalciferol (vitamin D)
- Bone radiology shows osteoporosis and malformations.



Figs 18A and B: (A) A 6-year-old girl of E β-thalassemia with abdominal distension due to hepatosplenomegaly, severe anemia with anemic heart failure and secondary malnutrition. (B) On the right chest X-ray (CXR) of same child showing cardiomegaly due to anemic heart failure

Treatment:

- Oral administration of vitamin D or one of its analogs
- Calcitriol, 0.25–1.0 μg, twice daily
- Weekly blood tests are required at the start of treatment, followed by quarterly plasma and daily urinary calcium and phosphate measurements
- In patients with persistently high serum phosphate levels, a phosphate binder (other than aluminum) may be considered
- Tetany and cardiac failure due to severe hypocalcemia require IV administration of calcium, under careful cardiac monitoring, followed by oral vitamin D.

Cardiac Complications of Thalassemia

- In the absence of effective iron chelation therapy, many patients sustain iron-induced myocardial damage resulting in cardiac failure, cardiac arrhythmia, progressive congestive cardiac failure or sudden death (Figs 18A and B).

Echocardiography: To assess cardiac status like right and left heart dimensions, biventricular function (LV fractional shortening and ejection fraction), estimated intracardiac pressures (pulmonary artery pressure, systolic and mean) and Doppler analysis of intracardiac flows.

Radioisotope studies: Multiple uptake gated acquisition: The use of multiple uptake gated acquisition (MUGA) to determine the overall left ventricular ejection fraction (LVEF) is an outmoded technique (both in requiring the use of radioactive isotopes and its high cost).

Investigations

Electrocardiogram: The electrocardiogram (ECG) is frequently abnormal, but changes are typically nonspecific. These changes commonly include:

- Depolarization changes in the T waves and ST segments of the anterior chest leads, and sometimes a preponderance of right ventricular voltages
- Biatrial enlargement—P wave abnormality
- Bundle branch block—alteration in QRS morphology
- Exercise ECG to detect cardiac arrhythmias or for assessing functional capacity
- 24-hour Holter ECG analysis: The standard method for detecting and investigating cardiac arrhythmias and their response to therapy.

Cardiac magnetic resonance imaging: The CMR scan provides a combination of morphological, functional information on the heart as well as—uniquely—quantitative estimates of tissue iron overload. As a result, CMR is rapidly becoming the tool of choice in the clinical assessment of patients with thalassemia.

Management strategy of cardiac complications: The therapeutic strategy to prevent or treat cardiac complication in patients with thalassemia involves a number of general measures, along with the particular cardiological interventions. Such measures might include:

- Maintenance of pretransfusional Hb level close to 9–10.5 g/dL in patients without heart disease, and 10–11 g/dL in patients with heart disease
- Regular iron chelation therapy and, for patients with high iron loads or cardiac disease, constant infusion regimens (SC or IV); consideration of combined chelation regimes using parenteral and oral chelators simultaneously
  Deferasirox currently found in published studies to be useful drug in chelating myocardial siderosis as evidenced by CMR and improving cardiac functions by showing improved LVEF and end-diastolic volume (EDV)
- Surveillance and adequate management of other causes of heart failure such as hypothyroidism, hypoparathyroidism, renal dysfunction, coincidental valve or structural heart disease, vitamin C deficiency
- Avoidance of unhealthy lifestyles, including smoking, lack of physical exercise and excess alcohol consumption in teenage in Western countries in particular.

Cardiological intervention and guidance are summarized as follows:

1. Asymptomatic patients with normal heart condition
   - No restriction to physical activity and body exercise.
2. Asymptomatic patients with moderate cardiac impairment
   - No restriction to physical activity
   - Medications:
     - Angiotensin-converting enzyme (ACE) inhibitors
     - Intensified iron chelation (SC or IV DFO 24 hours × 7 days/week)
     - Consider β-blocker, especially if arrhythmia is a problem.
3. Symptomatic patients with severe cardiac impairment
   - Restriction of physical activity
   - Slow blood transfusion with diuretics
   - Medications:
     - ACE inhibitors
     - Diuretics
     - Digitalis, if in atrial fibrillation prior to cardioversion.

Follow-up: The demonstration of impaired myocardial function might not only serve to alert the clinicians to give cardiac treatment, but it would also alert them to warn the individual patient that a much stricter adherence to chelation or initiation of more intensive chelation program to prevent progression to severe cardiac failure.

The frequency of follow-up for cardiological assessment depends on the age of the patient and the presence and severity of cardiac complications.

- Asymptomatic well-chelated patient with normal cardiac condition
  - Every year after 10–15 years of age.
- Asymptomatic, patients with moderately impaired cardiac function
  - Every 6–8 months, with particular attention to the functional tests that allow detection of impaired response to the stimulus.

- Patient with severe cardiac impairment
  - Every 1–4 months, depending on clinical conditions.

Prevention of cardiac complications: It is now well-established that intensive chelation can reverse even severe heart disease in thalassemia. It is much better to use chelation therapy to prevent heart disease occurring at all rather than starting once cardiac complications have already taken hold.

Infection in Thalassemia

Patients suffering from thalassemia are at a high-risk of development of infection. The causes that predispose patients to infection are:

Anemia

Anemia is the most important cause of infection such as pneumonia.

Splenectomy

Spleen is involved in protecting the body against infection especially against capsulated organisms like *Pneumococcus, Haemophilus, Meningococci*.

Iron Overload

Inappropriate iron chelation in patients with repeated transfusion leads susceptibility to severe infection. The documented organism in this regard is *Yersinia enterocolitica*.

Moreover, in viral hepatitis B and C, there is worst prognosis with high iron load.

Blood Transfusion

There is chance of transmission of hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) if blood is not properly screened.

Surgical Management of Thalassemia

Splenectomy

Invariably in all patients with thalassemia, there is splenomegaly causing mechanical discomfort. It is also the site of hemolysis. So splenectomy should be considered when:

- On oversized spleen—usually more than 6 cm in length resulting in discomfort
- An increasing amount of blood is required to transfuse a patient with no other medical problems, i.e. when the amount of blood required is increased by 1.5 times or more than 200–220 mL/kg/year of packed blood required to maintain average Hb level
- The age of the patient should be at least 5 years, as removing spleen increases the risk of infection as their immune system is not mature
- Appropriate immunization against *Meningococcus, Pneumococcus and Haemophilus* should be administered at least 2 weeks before splenectomy. Figure 19 shows abdominal scar mark of splenectomy in a thalassemic child.

Polyvalent pneumococcal polysaccharide vaccine together with lifelong oral penicillin should be offered to splenectomized thalassemic patients as they are more vulnerable to pneumococcal infection.

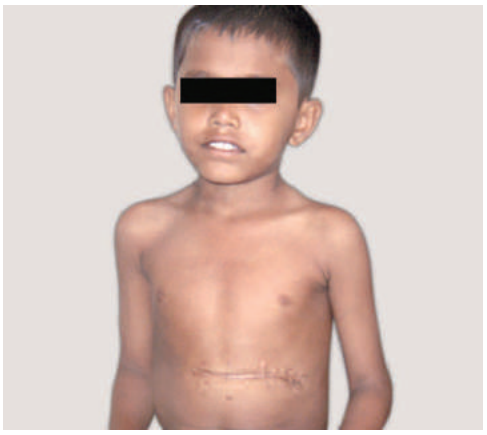


Fig. 19: Abdominal scar mark showing splenectomy done in thalassemic child

Prevention of Thalassemia

Creating Awareness

Public awareness regarding prevention of thalassemia.

Screening

Carrier detection by:

- Complete blood count with red cell indices (MCV, MCH, MCHC)
- Peripheral blood film
- Hb electrophoresis
- High performance liquid chromatography
- DNA test.

If screening is positive:

- If a man's screening is abnormal, then screening of the partner should be performed
- If both partners are found to be carrier of thalassemia, they should be referred for genetic counseling
- If a carrier woman becomes pregnant (early), her husband is asked to be tested. If the result is positive, then the couple needs to be counseled about the prenatal diagnosis to confirm the thalassemic status of the fetus.

Counseling

- Regarding general management of thalassemia patient
  - Diet:
    - Iron-rich food should be avoided
    - Raw tea/milk after each meal
    - Fruits, sugar and sweets should be avoided with foods
  - Hepatitis B vaccination
  - Serum ferritin test should be done after 10–20 times blood transfusion
  - Height, weight, liver function test (LFT), etc. should be examined every 3 months
  - Intelligence quotient (IQ) and psychosocial development to be assessed every year
  - Schooling—if Hb levels are maintained closed to recommended values
  - Work—to have positive attitude to their ability to work
  - Sexual and reproductive life

  - Nutrition—during growth, a normal energy intake with normal fat and sugar content is recommended
  - Recreational and physical activities should be encouraged
- Regarding genetic counseling
  - Prevention is the best option.
  - How to prevent the birth of thalassemia child.
- Identifying thalassemia carriers
  - Screen young people before marriage
  - For married couples, screen preconceptionally or early in the pregnancy
    - Screen first: Extended family of the patient (testing of the relatives of thalassemia patients), as the first degree relatives have higher risk of having an affected child compared to the general population
    - Screen second: Screening of all unmarried boys and girls.

Psychosocial Support

Psychosocial support is an important component on management, since the parents and the children are depressed mentally and financially, they require psychosocial support and family support. Various societies are available in different countries for offering psychosocial support together with medical support.

Prenatal Diagnosis

Prenatal diagnosis of thalassemia: There are three types of tests that can determine whether an unborn child has thalassemia:

1. Amniocentesis: Amniocentesis is performed in the second trimester of pregnancy, after about 15 (18–22) weeks' gestation. Using US as a guide, a trained obstetrician inserts a very thin needle through the mother's abdomen to withdraw 2–3 tablespoons of amniotic fluid. The fetal cells (cells from the unborn child) present in the fluid are then analyzed in the laboratory to determine whether the fetus has thalassemia.
   This test is used when the pregnancy is between 14 weeks and 16 weeks. It poses no significant risk to the mother. However, the test may cause a miscarriage—from a few days to a few weeks after the test.
2. Cordocentesis: Under US guidance, a fine needle is inserted through the abdomen into the fetal umbilical cord. About 2–3 mL of blood is aspirated and fetal blood is separated out in the laboratory. In skilled hands, 100% pure fetal cells are obtained from the first attempt in the majority of cases. Causes of failure in obtaining pure fetal blood include early gestational age less than 18 weeks, maternal obesity and posterior placenta. Early gestational age is also the most important cause of occurrence of serious complications in cordocentesis.
   Globin chain separation with gel electrophoresis is the usual laboratory method of detection. Early and specific diagnosis by molecular methods has almost completely replaced cordocentesis which is now mainly indicated only in pregnant patients who report late, in those in whom chorionic villus sampling (CVS) is inconclusive and when previous studies of at-risk couples are not available.

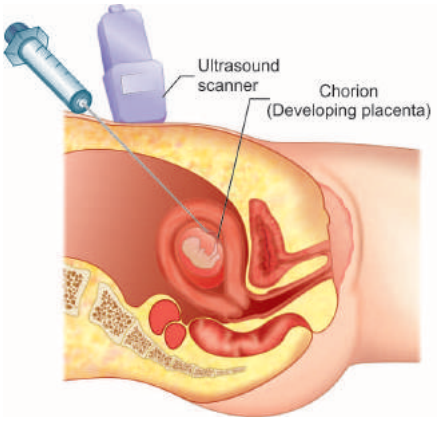


Fig. 20: Showing chorionic villus sampling procedure

3. Chorionic villus sampling (Fig. 20): The CVS can be performed somewhat earlier than amniocentesis, at about 10–11 weeks' gestation. Using US as a guide, the specialist obstetrician removes a small sample of the chorionic villi—cells that contain the same genetic information as the fetus and which will eventually form the placenta. The cells are removed either by a thin needle inserted through the mother's abdomen (transabdominal) or a thin catheter inserted through the vagina (transcervical). The cells are then analyzed and a diagnosis made.
   As with amniocentesis, CVS poses no significant risk to the mother. However, there is again a small risk of a miscarriage. If a miscarriage does occur, it can be difficult to know whether it was due to CVS, because many miscarriages happen naturally at around 12 weeks of pregnancy.
   There may be an increased risk of the baby's limbs being malformed if CVS is done very early in pregnancy, i.e. before the 8th week after the last menstrual period. However, there is no evidence of an increased risk of any malformation when CVS is carried out after the beginning of the 9th week after the last menstrual period. This is why the procedure is generally carried out after the beginning of the 10th week after the last period. Advantages are that sufficient tissue can be obtained for DNA diagnosis and result can be obtained within a few days. Less complications are found if therapeutic termination is done at this stage. The risk of fetal loss is 0.4–5%.

Alpha-thalassemia

Alpha-thalassemia is usually caused by gene deletion. The clinical phenotype depends on the number of genes deleted and the number of functional α-globin genes.

Alpha-thalassemia Major

The most severe α-thalassemia is α-thalassemia major also known as Hb Bart's hydrops fetalis is caused by deletion of all four α-genes. So no HbA (α2β2) can be produced. It presents as fetal hydrops due to fetal anemia which presents at midtrimester of pregnancy and results in death in utero.

Hemoglobin H (HbH) Disease

- Occurs only when three from two globin genes are deleted.
- Usually in thalassemia intermedia with mild to moderate anemia, splenomegaly and jaundice. Occasionally patients require blood transfusion.

Alpha-thalassemia Trait

- Two genes inactivated (aa/oo or ao/ao)
- Mild anemia with low RBC indices.

Silent Carrier

- One gene inactivated (aa/ao)
- Subclinical with occasional low RBC indices.

SICKLE CELL ANEMIA

Sickle cell disease is the collective name given to hemoglobinopathies in which HbS is inherited. HbS forms as a result of a point mutation in codon 6 of the β-globin gene which causes a change in the amino acid encoded from glutamine to valine. SCD is most common in patients whose parents are black and originate from tropical Africa or the Caribbean but it is also found in the Middle East and in low prevalence in most other parts of the world except for northern Europeans. In the United Kingdom up to 1 in 10 people of African or Caribbean descent have sickle cell trait and up to 1 in 60 have SCD giving a total of about 6,000 adult and children with SCD.

There are three forms of SCD: (1) Sickle cell anemia, (2) sickle cell disease and (3) sickle β-thalassemia.

1. Sickle cell anemia (HbSS)
   - Homozygous for HbS, i.e. virtually all their Hb is HbS
   - No HbA because they have no normal β-globin genes.
2. Sickle cell disease (HbSC)
   - Inherit HbS from one parent and HbC from the other parent (HbC is formed as a result of a different point mutation in β-globin)
   - No HbA because they have no normal β-globin genes.
3. Sickle β-thalassemia
   - Inherit HbS from one parent and β-thalassemia trait from the other
   - No normal β-globin genes and most patients can make no HbA and therefore have similar symptoms to those with sickle cell anemia.

Sickle cell trait:

- Inheritance of HbS from one parent and a normal β-globin gene from the other parent, approximately 40% of the Hb is HbS
- Do not have SCD but are carriers of HbS, so can transmit HbS to their offspring
- Asymptomatic is only identified as a result of blood tests.

CLINICAL FEATURES

- Sickle cell crisis
  - Vaso-occlusive crisis
    - Dactylitis (Fig. 21).
  - Bone crisis
    - Bone pain.
  - Abdominal crisis
    - Sickle cell gardle syndrome
    - Infarction of liver, spleen and lymph node resulting in capsular stretching.
  - Central nervous system crisis
    - Convulsions, vertigo, meningeal signs and cerebral infarction.
  - Pulmonary crisis
    - Acute chest syndrome.

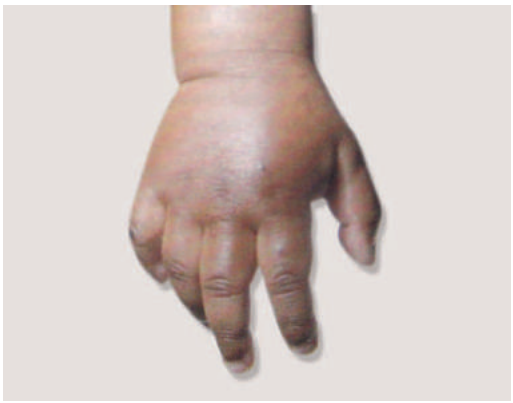


Fig. 21: Dactylitis in a case of sickle cell anemia

  - Hepatic sequestration crisis
    - Sudden onset of abdominal pain and splenomegaly, sometimes associated with shock.
- Priapism.
- Hematuria.

ORGAN DYSFUNCTION IN SICKLE CELL DISEASE

- Heart
  - Cardiomegaly
  - Myocardial dysfunction
  - Cor pulmonale.
- Lungs
  - Pulmonary fibrosis.
- Central nervous system
  - Cortical atrophy
  - Dilatation of ventricles
  - Permanent motor disabilities.
- Kidney
  - Papillary necrosis
  - Nephrotic syndrome
  - Renal infarction
  - Pyelonephritis
  - Renal medullary carcinoma.
- Liver
  - Cholelithiasis.
- Bones
  - Dactylitis
  - Osteonecrosis of femoral and humeral head
  - Fish mouth vertebra
  - Hair on end appearance.
- Eyes
  - Retinopathy.
- Ears
  - Sensorineural hearing loss.
- Skin
  - Leg ulcers over lateral and medial malleoli.

INVESTIGATIONS

- Complete blood count:
  - Hemoglobin is normal, except in those with coexisting thalassemia trait who may be slightly anemic
  - Mean cell volume and MCH are reduced in those with coexisting thalassemia trait.

- Blood film
  - The blood film may be completely normal or may show microcytosis or target cells. Sickle cells may be seen characteristically (Fig. 22). If a subject with sickle cell trait develops iron deficiency, target cells are often prominent
- Hemoglobin electrophoresis:
  - Hemoglobin S can be demonstrated by Hb electrophoresis or in HPLC.

MANAGEMENT

Emergency measures are required in sickle cell crises.

Management of Crises

The mainstay of treatment of painful crisis is:

- Analgesia—stepwise from paracetamol to opioids
- Antibiotics—IV cephalosporins if infection suspected
- Hydration—IV fluid as usually required.

Acute chest syndrome is responsible for 25% of death in children with SCD. In addition to analgesia, hydration and antibiotics, O_2 is required. Top up blood transfusion for significant anemia of 1–2 g below base level and exchange transfusion may be life-saving. Red cell transfusion is usually required for sequestration crisis.

General Management

- All patients with HBSS should receive oral penicillin V and folate supplement and immunization against *Streptococcus pneumoniae.*
- Hydroxyurea: It increases HbF level and improves RBC hydration which reduces frequency and painful chest crisis and myelosuppression.
- Transfusion: Every 3–4 weeks is indicated following acute stroke.
- Bone marrow/stem cell transplantation: This is potentially curative.

PLATELET DISORDERS

Normal circulatory platelet count is 150–400 × 10^9/L and does not vary with age. The average lifespan is 7–10 days. Platelets are disposed off in the spleen.

Platelets are developed from megakaryocytes in bone marrow by shedding cytoplasmic granules. Platelet production is under the control of growth factors including thrombopoietin and IL-6.

Absolute platelet does not correlate in a simple way with the hemostatic defects, as vascular factors are also involved and with high turnover a new active platelet may exist.

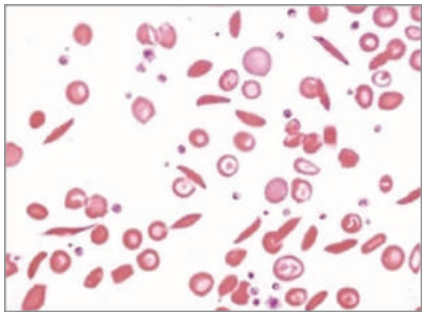


Fig. 22: Peripheral blood film showing sickle cells in sickle cell disease (SCD)

THROMBOCYTOPENIA

Thrombocytopenia may be caused by decreased production or decreased survival of circulatory platelets. Thrombocytopenia is the platelet count less than 150 × 10^9/L.

CAUSES OF THROMBOCYTOPENIA

Impaired Production

- Acquired
  - Bone marrow infiltration.
- Inherited
  - Aplastic anemia
  - Fanconi's anemia (FA)
  - Thrombocytopenia absent radius (TAR) syndrome
  - Wiskott-Aldrich syndrome.

Decreased Survival

- Immune-mediated
  - Immune thrombocytopenic purpura (ITP)
  - Autoimmune disorders
    - Systemic lupus erythematosus (SLE)
  - Infections, drugs and malignancy
  - Neonatal isoimmune or alloimmune or idiopathic thrombocytopenic purpura.
- Nonimmune-mediated
  - Disseminated intravascular coagulation (DIC)
  - Hemolytic-uremic syndrome (HUS)
  - Thrombotic thrombocytopenic purpura (TTP)
  - von Willebrand's disease (vWD) type 2b
  - Drugs
    - Valproate
    - Rifampicin
  - Liver disease
    - Kasabach-Merritt syndrome.

CLINICAL FEATURES OF THROMBOCYTOPENIA

Thrombocytopenia may result in bruising, petechiae, purpura and mucosal bleeding (e.g. epistaxis, bleeding from gum when brushing teeth).

Major hemorrhage in the form of severe GIT bleeding, hematuria and intracranial bleeding is less common. Purpura may also occur in presence of normal platelet count and in platelet dysfunction and vascular disorders (nonthrombocytopenic purpura).

Clinical features also depend on the severity of the platelet count.

- Mild (platelet count 50–150 × 10^9/L)
  - No risk of bleeding during operation or trauma.
- Moderate (platelet count 20–50 × 10^9/L)
  - Risk of bleeding during trauma or surgery
  - But low-risk of spontaneous bleeding.
- Severe (platelet count < 20 × 10^9/L)
  - Risk of spontaneous bleeding.

IMMUNE THROMBOCYTOPENIC PURPURA

Immune thrombocytopenic purpura is the commonest cause of thrombocytopenia in childhood. ITP is defined as immune-mediated thrombocytopenia not associated with drugs or other evidence of disease. Most cases are benign and self-limiting.

Immune thrombocytopenic purpura is classified as acute or as chronic if it persists for more than 6 months. Peak age of presentation is 2–5 years. Chronic ITP is more common in females.

Etiology and Pathogenesis

Acute ITP usually follows a viral infection or immunization. Pathogenesis involves a complex immune response combined with a relative failure of marrow compensation. Platelet antibodies coat the platelets which are being removed by reticuloendothelial system usually in the spleen.

Acute ITP

Clinical Features

- Abrupt onset of purpura or spontaneous bruising (Fig. 23), less commonly as epistaxis or bleeding from bowel or rarely from urinary tract
- Intracranial bleeding is a rare but severe complications occurring in less than 1% with prolonged severe thrombocytopenia
- Spleen may be palpable in 10% of cases
- The child is systemically well.

Differential Diagnoses

The differential diagnoses are:
- Acute leukemia
- Aplastic anemia
- Nonaccidental injury
- In older children, SLE may present with isolated thrombocytopenia.

Investigations

- Isolated thrombocytopenia in the range of $1–30 \times 10^9$/L
- Purpura with a platelet count greater than 30×10^9/L should search for an alternate diagnosis
- Any atypical clinical features such as hepatosplenomegaly or marked lymphadenopathy should prompt a bone marrow examination to exclude acute leukemia or aplastic anemia.

Management

- Most children require no treatment
- Approximately 80% of children recover within 6 weeks
- Severe hemorrhage from GIT and urinary tract occurs in 3–5% of cases. Intracranial bleeding occurs in less than 1% of cases. This cannot be predicted and cannot be prevented by treatment
- If there is no hemorrhage, hospitalization is not necessary

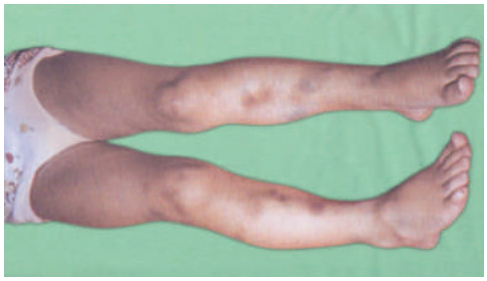


Fig. 23: Patient with immune thrombocytopenic purpura (ITP) showing bruise and petechiae in lower limbs

- Avoidance of antiplatelet medication such as nonsteroidal anti-inflammatory drugs (NSAIDs) and avoidance of exposure to contact sports are advised
- Parents should be provided with help for easy access to hospital in emergency.

In ITP, it is the patient rather than the platelet count to be focused for management as few circulatory platelets are more efficient.

Treatment options include:
- Steroids
  - Steroids are the first-line treatment
  - Oral prednisolone 1–2 mg/kg/day for 4 days or 1–2 mg/kg/day for 14 days.
- Intravenous immunoglobulin (IVIG):
  This raises the platelet count within 48 hours but side effects are common such as headaches and chills. IVIG is reserved for emergency management of patients with active bleeding who do not respond to steroids.

Chronic ITP (If Persist for >6 Months)

Management

- No treatment is given unless there is major bleeding
- Treatment is usually supportive
- The child should avoid contact sports and encouraged to do normal activities including schooling
- Splenectomy may be considered but has a 25% failure rate
- New therapies include monoclonal antibody (anti-CD20).

NEONATAL THROMBOCYTOPENIA

There are two types of neonatal thrombocytopenia:
1. Neonatal isoimmune thrombocytopenia.
2. Neonatal alloimmune thrombocytopenia.

1. *Neonatal isoimmune thrombocytopenia:* This occurs in infants of mother with active or previous ITP due to transplacental passage of antiplatelet antibodies. Antenatal maternal steroid treatment may improve the fetal platelet count.
2. *Neonatal alloimmune thrombocytopenia:* This usually occurs in HPA-1a positive fetus. However, only 6% of active mothers are sensitized.

Treatment Options

Treatment options include maternal infusion of immunoglobulin G (IgG), steroids and perinatal transfusion of immunogenically competent platelets.

PLATELET FUNCTION DISORDERS

- Inherited
  Falls in several groups:
  - Platelet membrane defect.
  - Disorder of adhesion:
    - Bernard-Soulier syndrome.
    - Is caused by lipoprotein Ib. Bruising and mucosal bleeding occur. Platelets are giant and few do not aggregate with ristocetin.
  - Disorder of aggregation: Glanzmann's thrombasthenia is due to abnormalities in lipoprotein 2b/3a. Episodic mucocutaneous bleeding and unprovoked bruising manifest soon after birth. Platelets fail to aggregate.

- Storage pool disorders:
  - Dense granules storage pool disease
  - Wiskott-Aldrich syndrome
  - Thrombocytopenia absent radius syndrome
  - Chédiak-Higashi syndrome.
- Acquired: Acquired disorder of platelet dysfunction occurs with:
  - Drugs:
    - Nonsteroidal anti-inflammatory drugs, frusemide, nitrofurantoin, cephalosporins
  - Renal and hepatic failure
  - Leukemia and myeloproliferative disorders.

ACUTE LEUKEMIAS

Among the childhood malignancies leukemia accounts for about 31% of all malignancies that occur in children less than 15 years of age. Among the leukemias, acute lymphoblastic leukemia (ALL) is the most common childhood cancer which is uniformly fatal but 80% curable with drugs alone.

Leukemia is defined as a group of malignant diseases in which genetic abnormalities in a hematopoietic cell give rise to an unregulated clonal proliferation of cells. The increased rate of proliferation of these cells and a decreased rate of spontaneous apoptosis follow results in disruption of normal marrow function leading to marrow failure.

CLASSIFICATION

Acute Leukemia

Acute leukemia constitutes 97% of all childhood leukemias and consists of the following types:

- Acute lymphoblastic leukemia—75%
- Acute myeloblastic leukemia (AML), also known as acute nonlymphocytic leukemia (ANLL)—20%
- Acute undifferentiated leukemia (AUL)—0.5%
- Acute mixed lineage leukemia (AMLL).

Chronic Leukemia

- Chronic lymphocytic leukemia
- Chronic myelocytic leukemia.

ACUTE LEUKEMIA

Epidemiology

Acute lymphoblastic leukemia occurs at a rate of 30–40 per million annually. Peak incidence observed among children of 2–3 years of age (>80 per million per year). The rate declines to 20 per million per year at the age of 8–10 years.

Risk Factors

The known primary risk factors are:

- Prenatal exposure to X-ray
- Postnatal exposure to high dose of radiation
- Down syndrome and other genetic conditions like neurofibromatosis (NF), Shwachman syndrome, Bloom syndrome and ataxia telangiectasia
- Inherited genetic polymorphism.

Clinical Features

Symptoms

- Initial presentation is brief and nonspecific like anorexia; fatigue, malaise and irritability often are present, as is an intermittent, low-grade fever. Bone or less often joint pain, particularly in the lower extremities, may be present
- As the disease progresses, signs and symptoms of bone marrow failure become evident with the occurrence of pallor, fatigue, exercise intolerance, bruising, or epistaxis, as well as fever, which may be caused by infection or the disease
- Organ infiltration
- Lymphadenopathy, hepatosplenomegaly, testicular enlargement or CNS involvement (cranial neuropathies headache, seizures)
- Severe anemia or mediastinal node comparison of the airways may cause respiratory distress.

Other Frequent Symptoms and Signs/Physical Examination

- Nonspecific general symptoms with acute onset
  - Reduced performance, fever, night sweats, fatigue, shortness of breath
  - Flu-like symptoms, anorexia, weight loss
  - Bone pain.
- Suppression of normal hematopoiesis
  - Anemia → malaise, fatigue, tachycardia, pallor
  - Thrombocytopenia → increased tendency to bleed, with petechiae and ecchymoses, hematomas, epistaxis
  - Granulocytopenia → skin infections, pneumonia, sepsis.
- Leukemic cell proliferation, organ infiltration: In order of frequency
  - Hepatomegaly and/or splenomegaly
  - Lymphadenopathy
  - Central nervous system/cranial bone, meningeal involvement (meningeosis leukemia) with headache, nausea, proptosis, vomiting, impaired vision (Fig. 24)
  - Central nervous system disorders
  - Mediastinal involvement with lymphadenopathy (Fig. 25)
  - Infiltration of parenchymatous organs with functional impairment (liver, kidneys, GIT, testes, etc.)
  - In the case of T-ALL: Mediastinal tumors, frequent skin infiltration.

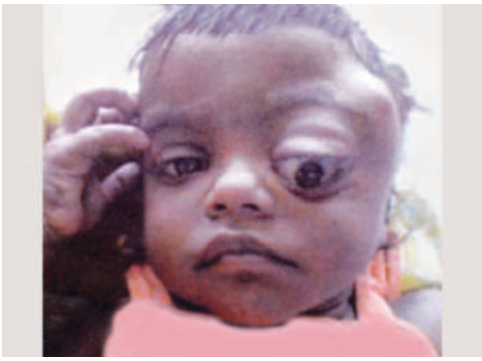


Fig. 24: Cranial bone (left temporal) involvement with proptosis in acute lymphoblastic leukemia

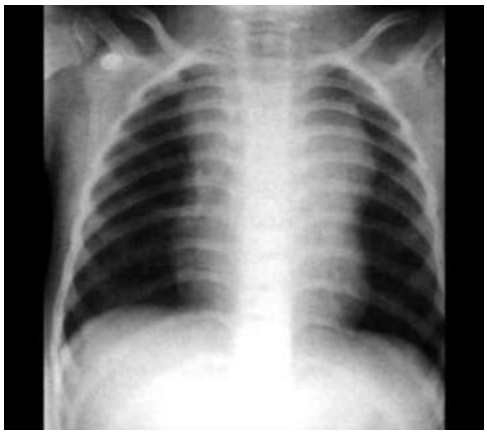


Fig. 25: Mediastinal lymph node involvement in acute lymphoblastic leukemia

Differential Diagnosis

- "Leukemoid reaction" due to infections or tumors
- Myelodysplastic syndrome
- Myeloproliferative syndrome, chronic myelogenous leukemia (CML) in blast crisis
- Acute myeloid leukemia or AUL
- Lymphoma with peripheral blood lymphocytosis, in particular high-grade non-Hodgkin's lymphoma (NHL)
- Pernicious anemia, vitamin B_{12}/folic acid deficiency
- Epstein-Barr virus (EBV) infection (infectious mononucleosis with atypical lymphocytes).

Laboratory Investigations

- Complete blood count:
  - Low Hb and platelet
  - Leukemic cells may or may not be present in peripheral blood film
  - Total leukocyte count may be high or normal or even decreased.
- Bone marrow aspiration and study: Bone marrow study confirms the diagnosis of acute leukemia (Fig. 26). An approach to laboratory diagnosis of ALL is shown in Figure 27.

Classification

FAB Classification

The French-American-British (FAB) classification (morphological) has been given in Table 10.

Flow Cytometric Immunophenotyping (Fig. 27)

Early pre-B ALL:

- Leukemic blast cells of early pre-B ALL resemble normal marrow B-cell precursors. These cells express CD19, cytoplasmic CD22 and CD79α.

Pre-B ALL:

- In pre-B ALL, cells express CD19, cytoplasmic CD22 and CD79α, and usually CD10 and TdT.

B-cell ALL:

- Commonly these cells have L3 morphology accord and express surface mu (μ) immunoglobulin heavy chain plus either κ or λ light chain.

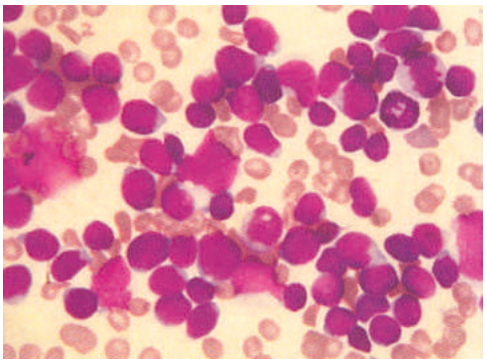


Fig. 26: Bone marrow showing blast cells containing round nuclei and scanty

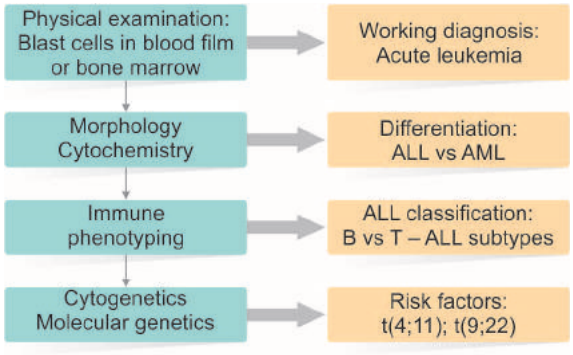


Fig. 27: Approach to laboratory diagnosis of leukemia
Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia.

Table 10: FAB classification

Type	Characteristics
L1	Small-cell acute lymphoblastic leukemia, small monomorphic cells with small nucleoli
L2	Polymorphocellular acute lymphoblastic leukemia, larger polymorph cells with one or more prominent nucleoli, low nucleus/cytoplasm ratio
L3	Large cells with prominent, poorly structured nucleoli and basophilic cytoplasm which is often vacuolated

- T-lineage ALL
- T-lineage ALL cells express CD7 and CD3.

Risk Stratification for ALL

Risk stratification for ALL has been shown in Table 11.

Table 11: Risk stratification of ALL

	T-cell type	B-cell type
Standard risk	• Thymic T-ALL • T-ALL (CD1a negative)	B-precursor ALL: • CR on day 26 (after induction I) and WBC < 30,000/μL • No pro-B or t(4;11)-positive ALL • No t(9;22)/BCR-ABL-positive ALL
High risk	Early T or mature T-ALL (CD1a negative)	B-precursor ALL: • CR after day 45 or WBC > 30,000/μL • Pro-B or t(4;11)-positive ALL
Very high risk (VHR)		• B-precursor ALL t(9;22)/BCR-ABL-positive ALL

Treatment of ALL

Treatment of leukemia comprises specific and supportive treatment.

Specific Treatment

- Multistage multiagent chemotherapy based on different protocols
- Hematopoietic stem cell transplantation.

Chemotherapy for the Treatment of ALL

Chemotherapy for ALL comprises three phases: (1) Remission induction, (2) consolidation or intensification and (3) systemic maintenance respectively.

Remission induction:

Objectives: Complete remission, i.e. reduction of the leukemic cell population to below the detection limit, recovery of normal hematopoiesis with normalization of blood count and bone marrow.

Drugs used: Vincristine, daunomycin, L-asparaginase, prednisolone.

Central nervous system prophylaxis: The concept of CNS prophylaxis is based on the fact that most children with leukemia have the subclinical CNS involvement at the time of diagnosis. This acts as a potential site of infiltration of leukemic cells. Early CNS prophylaxis helps to eradicate leukemic cells which have passed the blood brain barrier. CNS prophylaxis also increases the survival rates of leukemia. To prevent CNS involvement, intrathecally used drugs are methotrexate (MTX), cytarabine and hydrocortisone. Dexamethasone can also be used instead of hydrocortisone.

Consolidation:

Objectives: There is clear evidence that intensification has improved the long-term survival of patients with ALL especially those with high-risk disease. Early intensive consolidation is given to improve the remission quality.

Drugs used: Cyclophosphamide, daunorubicin, cytarabine, L-asparaginase, prednisolone, 6-mercaptopurine (6-MP). Use of these medications has resulted in prolonged period of granulocytopenia and the need for improved supportive care, liberal use of broad-spectrum antibiotics, blood products and use of GM-CSF.

Maintenance:

Objectives: Once remission is achieved, maintenance therapy is continued for 2–3 years. Without such therapy there is chance of relapse. A number of drug combination and schedules are used, some based on period reinduction, others on continued delivery of effective drugs as used in Table 10.

Drugs used: 6-MP, vincristine, MTX, daunomycin, L-asparaginase. Oral dexamethasone can be given in case of oral prednisolone. Total duration of maintenance therapy is 2 years for girls and 3 years for boys. It is imperative to monitor children for drug toxicity and compliance.

A dosage and schedule for chemotherapy (standard protocol) is mentioned in Table 12.

Table 12: An outline of standard protocolized treatment with multiagent chemotherapy in three phases

Phase	Drugs	Dose	Route	Schedule
Induction 1st month	Inj. vincristine	1.5 mg/m^2	IV	Once a week on D1 for 4 weeks
	Inj. daunomycin	20 mg/m^2	IV	Once a week for 4 weeks on D1, 8, 15 and 22
	Inj. L-asparaginase	6,000 IU/m^2	IM	Every alternate day for 9 days on D1, 3, 5, 7, 9, 11, 13, 15, 17 in 1st month
	Tab. prednisolone	40 mg/m^2/day	Oral	From D1–D28
	Intrathecal therapy			
	Inj. MTX	12 mg	IT	On D1, 8, 15, 22 is given in 5–10 mL of 0.9% NaCl solution
	Inj. cytosar	25 mg	IT	Vial contains 100 mg/2 mL and 0.5 mL is given
	Inj. hydrocortisone	12.5 mg	IT	
Consolidation (intensification) 2nd month	Cyclophosphamide	750 mg/m^2	IV	Given on D1 and D15 in the 2nd month
	Inj. daunorubicin/daunomycin	20 mg/m^2	IV	On D8 and D22
	Inj. cytarabine	100 mg/m^2	IV	On D1, 2, 3 and 4 on 1st week, D15, 16, 17, 18 on 3rd week
	Tab. 6-MP	75 mg/m^2	Oral	Daily
	Intrathecal therapy			
	A stated earlier in induction phase once in a week on D1, 8, 15, 22 similar to induction dose			
Systemic maintenance From 3rd month onward	Inj. vinblastine/vincristine	1.5 mg/m2	IV	Monthly on D1 every month for 24 months
	Inj. daunomycin	20 mg/ m2	IV	D1 every month for 6 cycles, 1st, 5th, 9th, 13th, 17th and 21st months
	Inj. L-asparaginase	6,000 IU/m2	IM	On D1, 3, 5 and 7 of every month in 1st, 5th, 9th, 13th, 17th and 21st month
	Tab. prednisolone	40 mg/m2	Orally	First 7 days in every month (after meal) up to completion of treatment regimen
	Tab. 6-MP	75 mg/m2/day	Orally	Daily for 24 months
	Tab. MTX	15 mg/m2	Orally	Once a week, missing every 4th week for total 12 weeks
	Intrathecal therapy			
	Once in every month on D1 with MTX, cytarabine and hydrocortisone at a dose mentioned earlier			

Abbreviations: D1, day 1; IV, intravenous; IM, intramuscular; MTX, methotrexate; IT, intrathecal; 6-MP, 6-mercaptopurine.

Supportive Treatment

- Provide explanation and offer counseling.
- Psychosocial support.
- RBC and platelet transfusion support will continue throughout treatment.
- Infection prevention, oral hygiene, patient care.
- Hepatitis B screening and vaccination.
- Start neutropenic regimen as prophylaxis against infections.
- Start hydration aiming for urine output greater than 100 mL/hour throughout induction therapy (*tumor lysis syndrome*—a special problem in B-cell or T-cell ALL).
- Start allopurinol to prevent hyperuricemia.

Treatment of Relapse

Relapse may be confined to bone marrow or the extramedullary. Treatment involves intensive reinduction and consolidation with further 2 years maintenance therapy. BMT is considered for high-risk cases.

Stem Cell Transplantation

Stem cell transplantation is becoming the main specific treatment of ALL along with several other hemopoietic diseases.

Other conditions where stem cell transplantation is indicated:

Allogeneic transplant:
- Severe aplastic anemia
- Chronic myeloid leukemia
- Acute myeloblastic leukemia in first complete remission
- Myeloid dysplasia
- ALL in first complete remission [Philadelphia positive ALL, infant ALL t (9;22)]
- Severe congenital immunodeficiency (SCID)
- Acute myeloblastic leukemia and ALL in second complete remission
- Thalassemia.

Autologous transplant:
- ALL (certain subtypes)
- Hodgkin's disease in second complete remission
- Non-Hodgkin's lymphoma in second complete remission
- Solid tumors such as neuroblastoma (NB).

Prognosis of ALL

Prognosis is improving to 80% overall survival (OS) in standard risk people. Molecular techniques are being developed to detect minimal residual disease, which will allow the patient to be allocated to more or less aggressive chemotherapeutic regimen at 28 days.

Bad prognosis is expected in following cases:
- Age less than 1 year or greater than 10 years at diagnosis
- A leukocyte count of greater than 50,000/μL at diagnosis
- T-cell immunophenotype
- Slow response to initial therapy
- Chromosomal abnormalities, including hypodiploidy, the Philadelphia chromosome, MLL gene rearrangements and certain mutations, including deletion of the IKZF1 gene.

New Therapeutic Concepts

Imatinib

BCR-ABL-positive ALL constitutes the poorest prognosis with a 5-year survival rate of 0–15%. BCR-ABL-tyrosine kinase inhibitors (imatinib, dasatinib) represent new treatment options for this entity → response rate in monotherapy is 60% median duration of remission for 2 months. Combination with chemotherapy may improve these results. The use of imatinib and dasatinib in the treatment of BCR-ABL-positive ALL is the subject of current trials.

Rituximab (Anti-CD20 Antibody Rituximab)

Rituximab is efficacious in the treatment of CD20-positive high-grade B-NHL. Efficacy and safety of rituximab in CD20-positive B-ALL and Burkitt's lymphoma is currently studied.

Alemtuzumab (Anti-CD52 Antibody)

The therapeutic benefit of alemtuzumab in the treatment of ALL is currently being tested in trials.

ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia is a rare form of childhood leukemia that accounts for 15–20% leukemia in children. The incidence increases with age and AML accounts for 90% of all leukemias in adults. AML is more complex and resistant disease than ALL.

ETIOLOGY AND PATHOGENESIS

Etiology is not known, the most important risk factor in childhood is Down syndrome which is associated with 10- to 20-fold risk of AML. Environmental risk factors include ionizing radiation and chemotherapeutic agents. Malignant cell is the myeloblast. A single myeloblast accumulated genetic changes which prevents further differentiation and further mutation lead to uncontrolled growth of an immature clone.

CYTOGENETICS AND MOLECULAR GENETIC ALTERATION

Specific cytogenetics is usually common and results in abnormally fusion proteins which cause the differentiation arrest. These are of great prognostic significance. Examples include unfavorable prognosis is monosomy 5 or 7 Del (5q) complex cytogenetics; favorable prognosis t(15;17); PML-RARA & acute promyelocytic leukemia.

CLASSIFICATION

The FAB divides AML into eight subtypes M0 to M7:

1. M0 – Undifferentiated
2. M1 – AML with minimal maturation
3. M2 – AML with maturation
4. M3 – Acute promyelocytic leukemia
5. M4 – Acute myelomonocytic leukemia
6. M5 – Acute monoblastic leukemia
7. M6 – Acute erythroblastic leukemia
8. M7 – Acute megakaryoblastic leukemia.

About 30–40% patients are with M1 and M2, and same percentage is M4 and M5. M3 type of AML constitutes 5–10% and M7 is probably associated with Down syndrome.

CLINICAL FEATURES AND INVESTIGATIONS

These are similar to those of ALL. Extramedullary including intrathoracic disease is less common, but involvement of gum and oral cavity is more frequent than ALL (Fig. 28). Presumptive diagnosis may be made by the examination of

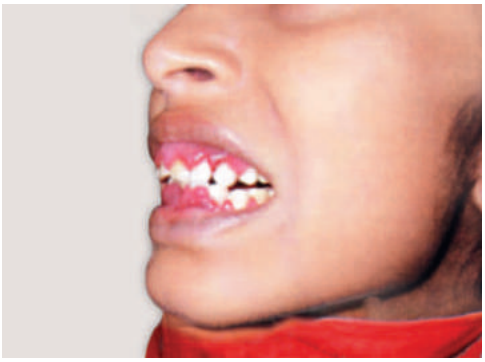


Fig. 28: Gum involvement in AML

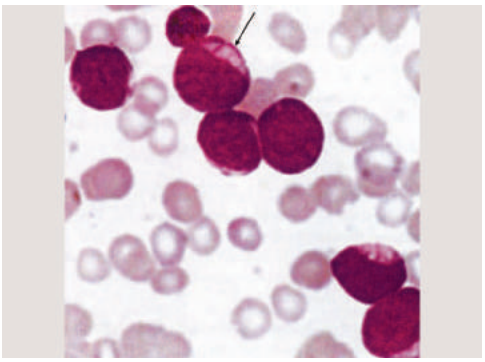


Fig. 29: Myeloblast containing Auer rod in AML (arrow)

peripheral blood film, which resembles ALL. Myeloblast may contain Auer rod (Fig. 29). The definite diagnosis requires bone marrow aspiration and biopsy. Diagnosis requires involvement greater than 20% blood or bone marrow is by leukemic myeloblast.

Preleukemic conditions such as myelodysplastic or myeloproliferative syndrome must be differentiated.

MANAGEMENT

Management involves induction with intensive chemotherapy followed by consolidation. Prolonged maintenance is not given.

Induction Chemotherapy

Induction chemotherapy involves 4–5 courses of therapy. The main drugs used for induction are cytosine arabinoside and anthracycline (doxorubicin or daunorubicin).

The *M3 subtype of AML (acute promyelocytic leukemia)* is treated in addition with the drug all-trans retinoic acid (ATRA) to prevent DIC. CNS prophylaxis is given.

For patients with high risk of relapse, allogeneic stem cell transplantation is usually recommended. OS in AML is only 50–60%.

APLASTIC ANEMIA

Aplastic anemia is a heterogeneous disorder characterized by pancytopenia with a hypocellular bone marrow in the absence of an inherited bone marrow syndrome. Majority of its cause is idiopathic (70–80%) and in 15–20% cases it is inherited, where the disease is familial and/or presents with one or more somatic abnormalities.

EPIDEMIOLOGY

Incidence of acquired aplastic anemia in Europe and North America is 2 per million, in East Asia 6.8 per million populations. There is significant difference in incidence in male and female. Age distribution is biphasic with peaks from 10 years to 25 years and greater than 60 years.

ETIOLOGY

About 80% causes are acquired and 20% are congenital or inherited.

Acquired

- Viral infection, e.g. EBV, CMV, human herpesvirus, HIV, parvovirus B, Hepatitis A and B virus, measles, mumps, rubella, varicella
- Drugs (mentioned in Table 13)—13%
- Toxins—5%
- Hepatitis associated aplastic anemia—5%
- Paroxysmal nocturnal hemoglobinuria
- Immune disorders, e.g. thymoma, eosinophilic fascitis, Graves' disease, SLE.

Inherited

- Blackfan-Diamond syndrome (autosomal dominant)
- Fanconi's anemia (autosomal recessive)
- Familial aplastic anemia
- Shwachman-Diamond syndrome.

PATHOPHYSIOLOGY

Three mechanisms are proposed in the pathophysiology of aplastic anemia:

1. An immune attack on the hemopoietic progenitor cells: Here T cell-mediated organ-specific destruction of bone marrow hemopoietic cells occurs, which is sometimes linked to viral infection or exposure to drugs or chemicals; often associated with over expression of HLA-DR2 as in other autoimmune diseases.
2. Inherent stem cell defect: In aplastic anemia, primary hematopoietic stem cell abnormalities are reduced the number of CD34+ cells, reduced multipotent and committed colony forming cells.

Table 13: Drugs responsible for development of aplastic anemia

Antibiotics	
	Chloramphenicol, sulfonamide, cotrimoxazole, linezolid
Anti-inflammatory	
	Gold, penicillamine, indomethacin, naproxen, sulfasalazine
Antithyroid	
	Thiouracil, carbimazole
Anticonvulsants	
	Carbamazepine, phenytoin
Antimalarial	
	Chloroquine
Antidiabetic	
	Chlorpropamide, tolbutamide
Others	
	Thiazides, mebendazole, allopurinol

3 Defects in bone marrow stroma or microenvironment:Abnormal secretion of hemopoietic growth factors found responsible for development of aplastic anemia.

CLASSIFICATION

Classification of aplastic anemia has been given in Table 14.

Table 14: Definition depending on the severity of aplastic anemia

Severe aplastic anemia (SAA)
• Bone marrow cellularity <25% or 25–30% with <30% residual hemopoietic cells • 2/3 of the following: – Neutrophil count <0.5 × 10^9/L – Platelet count <20 × 10^9/L – Reticulocyte count <20 × 10^9/L
Very severe aplastic anemia (vSAA)
• As for SAA but neutrophil count < 0.2 × 10^9/L
Nonsevere aplastic anemia
• Patient not fulfilling the criteria for severe or very severe aplastic anemia

CLINICAL FEATURES

Patients present with insidious onset of symptoms related to anemia, thrombocytopenia and neutropenia, i.e.:

- Progressive pallor
- Fever due to intercurrent infection
- Bleeding manifestations: Subcutaneous bleeding like petechiae, purpura, bruise, ecchymosis
- External bleeding like hematuria, epistaxis, melena.

Inherited marrow failure syndrome presents with some physical stigmata like short stature, skin pigmentation and skeletal anomalies.

Fanconi's Anemia

It is an autosomal recessive disorder characterized by upper limb radial bone (Fig. 30) deformity like absent/short radius, radial ray (triphalangeal thumb) (Figs 31A and B), café au lait spots, short stature, microphthalmia, cataracts, cardiac defects, gastrointestinal abnormalities. Patients with FA are susceptible for acute myeloid leukemia and squamous cell carcinoma.

Diamond-Blackfan Anemia

Autosomal dominant disorder characterized by snub nose, hypertelorism, radial ray (triphalangeal thumb), renal and cardiac defects.

Shwachman-Diamond Syndrome

It is an autosomal recessive disorder characterized by short stature, metaphyseal dysostosis, pancreatic exocrine failure with recurrent loose motion.

INVESTIGATIONS

- Full blood count:
  - Low Hb, pancytopenia with macrocytic RBC. Decreased reticulocytes.
- Bone marrow examination (Fig. 32):
  - Erythropoiesis is reduced or absent with marked dyserythropoiesis. Granulocytic cells and megakaryocytes are reduced or absent.

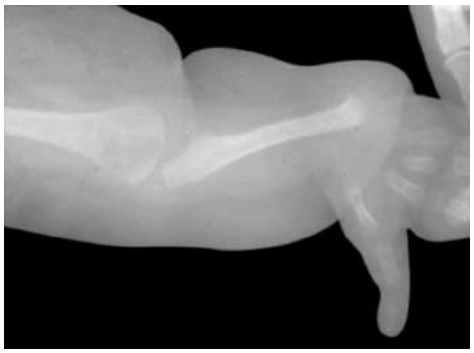
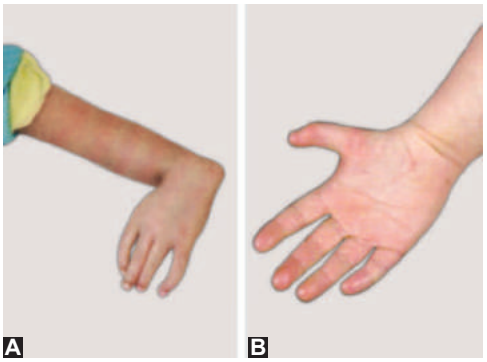


Fig. 30: X-ray of hand showing absent radius in Fanconi's anemia



Figs 31A and B: Absence of radius (radial ray appearance) in Fanconi's anemia

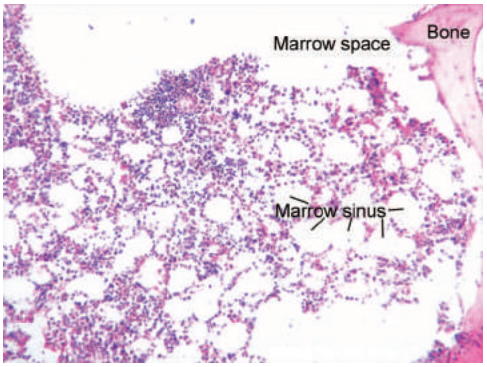


Fig. 32: Bone marrow biopsy showing marked hypoplastic marrow

- Others:
  - Serum vitamin B12 and folate level to exclude megaloblastic anemia
  - Liver function test to detect antecedent hepatitis
  - Viral serology:
    - Hepatitis A antibody
    - Hepatitis B surface antigen (HBsAg)
    - Hepatitis C antibody
    - Epstein-Barr virus
    - Cytomegalovirus
  - Flow cytometry for glycosylphosphatidylinositol (GPI)-anchored protein to detect paroxysmal nocturnal hemoglobinuria.

DIAGNOSIS

The above mentioned investigations are done to:

- Confirm diagnosis
- Exclude other possible causes of pancytopenia with a hypocellular bone marrow

- Exclude inherited aplastic anemia
- Screen for an underlying cause of aplastic anemia.

DIFFERENTIAL DIAGNOSIS

- Leukemia
- Lymphoma
- Atypical mycobacterial infection.

MANAGEMENT

Supportive

- Repeated blood transfusion to prevent major episode of bleeding and to correct anemia
  - Phenotypically matched RBC transfusion and single donor platelet units are preferred to prevent alloimmunization
  - Blood product from members of the patient's family is not advisable
  - All blood products should be properly filtrated and irradiated.
- Control of infection with antibiotics
- Broad-spectrum antibiotics and antifungal
- Prophylaxis for *Pneumocystis carinii* infection.

Specific

- Hematopoietic stem cell transplantation
- Immunomodulation
- Androgens.

Hematopoietic Stem Cell Transplantation

Indications and types:

- Patients with severe aplastic anemia
- Early HSCT from an HLA-matched sibling donor is the gold standard for treatment of patients with severe aplastic anemia (SAA)
- Matched unrelated donor (MUD) bone marrow transplant is considered when patient with SAA has no matched sibling donor but has a MUD and failed at least one course of antithymocyte globulin (ATG) and cyclosporine A.

Immunosuppressive Therapy

Indications:

- Nonsevere aplastic anemia is transfusion dependent
- Patients with severe or very severe disease having no HLA-identical sibling donor.

Agents:

The standard immunosuppressive regimen is a combination of ATG and cyclosporine.

- Antithymocyte globulin
  - 2.5–3.5 mg/kg/day for 4–5 days.

  Concurrent use of prednisolone 1–2 mg/kg/day and premedication with antihistamine and paracetamol is advised to combat serum sickness induced by ATG.
- Cyclosporine A
  - 6 mg/kg/dose twice daily for 12 months followed by very slow tapering.
- High-dose corticosteroid
  - Methylprednisolone of 20 mg/kg for a week tapered over a month. It is an alternative choice for patient who cannot afford ATG.

Androgen and Growth Factors

- Androgens induce remission in patients with nonsevere aplastic anemia.
- In cases of SAA, androgen has no role as a single agent.

Other Immunosuppressive Agents

For refractory aplastic anemia, alemtuzumab (Campath-1H) is currently under evaluation.

PROGNOSIS

Severe anemia can result in cardiac failure and neutropenia. Neutropenia can lead to bacterial and fungal infection. Severe bleeding can occur due to thrombocytopenia. The prognosis depends on severity and extent of cytopenia. Aplastic anemia is a serious disorder that frequently terminates to death with 6–12 months of presentation. Mortality rate is very high in different series from 60% to 80%. Death is due to severe bleeding and intercurrent infection. However, with HSCT regimen, most patients with SAA have 60–70% long-term survival rate.

LYMPHOMAS

Pediatric lymphomas are third most common group of malignancies in children and adolescents accounting for about 12% of all newly diagnosed cancer in this age group. About 60% of these are NHL and 40% are Hodgkin's lymphoma (HL). Lymphomas are uncommon below the age of 5 years and the incidence increases with age.

HODGKIN'S DISEASE

Hodgkin's lymphoma is a neoplasm of primarily B-cell lineage involving lymph nodes and the lymphatic system with unique clinical features, histologic, molecular and immune phenotype.

The recommended term "HL" encompasses two basic diseases: (1) A relatively common form now referred to as classical Hodgkin's lymphoma (CHL) and (2) the very uncommon disease of nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL). CHL is a malignant tumor that may be subclassified into histological groups sharing biologically and morphologically similar neoplastic cells, Hodgkin's Reed-Sternberg (H-RS) cells. NLPHL is in contrast viewed as an indolent tumor sharing features with some B-cell NHL.

Epidemiology

It is relatively uncommon in prepubertal children. The age-specific incidence of Hodgkin's disease exhibits a characteristic bimodal distribution. In the developed countries, the early peak occurs in the age group of 20–30 years and the second peak after the age of 50 years.

In developing countries, there are two forms: (1) Childhood form (<14 years) and (2) young adult form (15–44 years). It is uncommon below 5 years of age. Male to female ratio is 10:1 below 7 years and 1.1:1 above 12 years.

Etiology and Pathophysiology

They are multifactorial and consist of:

- Infectious agent: There is association of EBV infection. Fifty percent EBV positivity in HL in the United Kingdom.
- Genetic predisposition: There is a familial clustering with increased incidence in monozygotic twins and same sex siblings. Familial cases account for 5% of total.

Immune dysregulation: Association with HIV infection, immunodeficiency syndrome.

Socioeconomic factors: Incidence is inversely related to parental income and education in the United States of America.

Malignant B cell proliferates in reticuloendothelial and lymphatic systems and may invade lungs, bone, bone marrow, liver parenchyma and CNS.

Clinical Manifestations

- Lymphadenopathy: Common presentation. Manifested by nontender firm, rubbery, cervical or supraclavicular lymphadenopathy (Fig. 33) and usually some degree of mediastinal involvement.
- Depending upon nodal and extranodal involvement, there may be:
  - Signs of upper airway obstruction (dyspnea, hypoxia, cough)
  - Pleural or pericardial effusion
  - Hepatocellular dysfunction
  - Bone marrow infiltration (anemia, neutropenia or thrombocytopenia).
- Systemic symptoms, classified as *B symptoms* which are important for staging of disease are:
  - Unexplained fever greater than 39°C
  - Weight loss greater than 10% total body weight over 3 months
  - Drenching night sweats.
- Other less common features are:
  Pruritus, lethargy, anorexia or pain that worsens after ingestion of alcohol.

Classification

The majority of the tumor is composed of an infiltrate of inflammatory cells (histiocytes, plasma cells, lymphocytes, eosinophils, neutrophils) and fibrosis.

The World Health Organization (WHO) classifies HL into two broad categories:

1. Nodular lymphocyte predominant Hodgkin's lymphoma:
   - This type is generally asymptomatic and presents with localized nonbulky disease.
   - This type is characterized by large cells with multilobed nuclei referred to as popcorn cells.
2. Classical Hodgkin's lymphoma: Reed-Sternberg (RS) giant cell is the hallmark of CHL. RS giant cell is a binucleated or multinucleated giant cell that is often characterized by a bilobed nucleus (Fig. 34) with two large nucleoli, giving an owl eye appearance to the cells. There are four varieties of this subgroup; each characterized by the number of RS cells mentioned in Table 15.

Diagnostic Workup and Staging

Evaluation of a new patient includes:

- Careful physical examination with assessment of lymph node bearing areas
- Chest radiograph provides information about enlargement of mediastinum
- Computed tomography (CT) scan of the chest provides information about pulmonary parenchyma, chest wall, pleura and pericardium which may not be apparent in plain CXR
- CT scan of abdomen and pelvis may show involvement of viscera and lymph nodes.

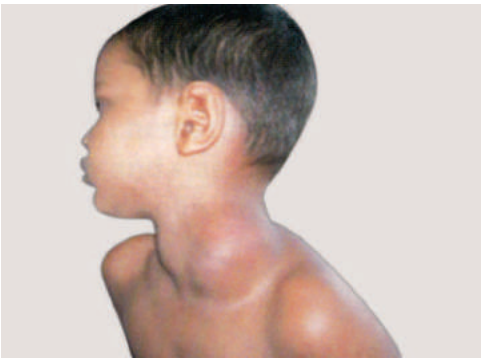


Fig. 33: Lymph node involvement in Hodgkin's lymphoma

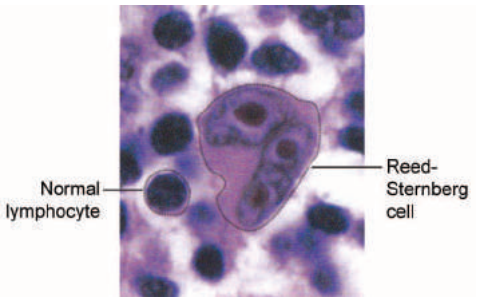


Fig. 34: Film showing Reed-Sternberg giant cell in Hodgkin's lymphoma

Table 15: Histological classification of and prognosis of Hodgkin's lymphoma

Histology	Occurrence (%)	Pathology RS	Other	Prognosis
Lymphocyte predominance	10–15	Rare	Predominance of normal appearing lymphocytes, few RS cells, No fibrosis	Excellent
Nodular sclerosis	20–50	Frequent "lacunae"	Lymphoid nodules collagen bands that divides lymphoid tissue into nodules	Very good
Mixed cellularity	5–15	Numerous	Pleomorphic infiltrates paucity of lymphocytes	Good
Lymphocyte depletion	5–15	Often	Paucity of lymphocytes fibrosis and necrosis common but diffuse	Poor

Abbreviation: RS, Reed-Sternberg giant cells.

Bone marrow biopsy to detect advanced stage (III and IV) is required in all children with systemic symptoms.

Ann-Arbor staging system for Hodgkin's lymphoma (Fig. 35) has been shown in Table 16.

Management

Hodgkin's lymphoma is one of the most curable of childhood malignancies. Radiation therapy and chemotherapy alone or in combination are used. Modern strategies focus on minimizing late effects of therapy while maintaining cure rates.

Treatment modalities vary from total nodal radiation therapy to chemotherapy to combination—chemoradiotherapy with significant improvement of survival rates throughout the last three decades.

Currently chemotherapy alone with/without low-dose involved-field radiotherapy (IFRT) is preferred for treatment of Hodgkin's disease.

Determinants of volume of radiation and intensity/duration of chemotherapy are prognostic factors at presentation including presence of constitutional symptoms, disease stage and bulk.

Common regimens of chemotherapy are:

1. Nonalkylating—doxorubicin (adriamycin), bleomycin, vinblastine and dacarbazine (ABVD).
2. Hybrid regimen with lower dose of alkylators, doxorubicin and bleomycin such as:
   - Cyclophosphamide, vincristine, procarbazine, prednisolone/doxorubicin, bleomycin and vinblastine (COPP/ABV)
   - Doxorubicin, bleomycin and vinblastine, etoposide (DBVE)
   - Bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, prednisolone, procarbazine (BEACOPP).
   - Vincristine, doxorubicin, methotreaxate and prednisolone (VAMP).

Prognosis

Patients with favorable prognostic factors and early-stage disease have an event-free survival (EFS) of 85–90% and an OS at 5 years is greater than 95%. Prognosis after relapse depends on the time from completion of treatment to recurrence, site of relapse (nodal vs extranodal) and presence of B symptoms at relapse. Patients whose disease relapses greater than 12 months after chemotherapy alone or combined modality therapy have the best prognosis, and their relapses usually respond to additional standard therapy, resulting in a long-term survival of 60–70%.

Poor prognostic markers are:

- Advanced stage of disease (stage IIB, IIIB or IV disease)
- The presence of B symptoms
- The presence of bulk disease
- Extranodal extension
- Male sex
- Erythrocyte sedimentation rate (ESR) > 50 mm in 1st hour
- Hb <10.5 g/dL
- WBC count 15,000/μL or less
- Absolute lymphocyte count < 600/μL
- Albumin <4 g/dL.

NON-HODGKIN'S LYMPHOMA

Childhood NHL encompasses a heterogeneous group of proliferation of lymphoid tissue, usually manifested by bulky extramedullary (usually extranodal) disease with or without significant dissemination. It is more common lymphoma than Hodgkin's and accounts for 7% of all childhood cancers. As the distinction between HL and NHL is arbitrary, they range from clinically localized disease to overt leukemia. At present leukemia is considered when there is marrow involvement at a threshold level (typically blast cells count >25%) irrespective of bulky extramedullary disease, whereas

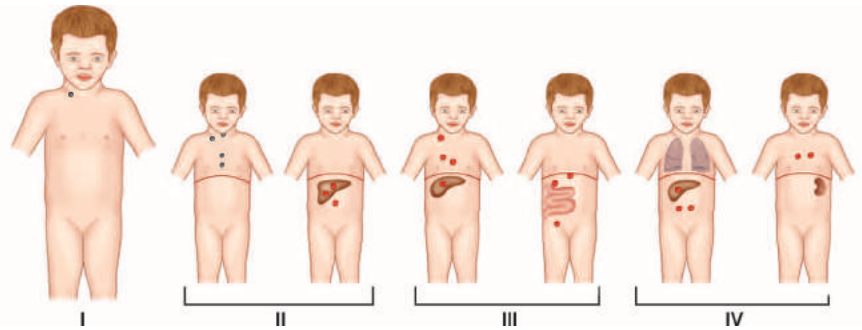


Fig. 35: Diagram showing anatomical stages for Hodgkin's disease. Red dots showing lymph node and organ involvement

Table 16: Ann-Arbor staging system for Hodgkin's lymphoma

Stage	Involvement
I	Single lymph node region (1) or one extralymphatic site (IE)
II	Two or more lymph node regions on same side of the diaphragm (II) or one or more lymph node regions on same side of diaphragm plus local extralymphatic extension (IIE)
III	Lymph node regions of both sides of the diaphragm (III) which may be accompanied by local extralymphatic extension (IIIE)
IV	Diffuse involvement of one/more extralymphatic organs/sites
A	No B symptoms
B	Presence of B symptoms: (1) unexpected weight loss >10% baseline during 6 months before staging, (2) recurrent unexplained fever >38°C, (3) recurrent night sweats
X	Bulky tumor

stage IV lymphoma constitutes tumor accompanied with bone marrow involvement less than 25% blast cells.

Epidemiology

- Sex: Male to female is 2.5:1 overall and over 3:1 in ages 5–14 years.
- Age: All age groups are vulnerable, peaks at ages 15–19 years. More common in white males with peak incidence in second decade.
- Risk factors
  - Viral infection: The most common childhood malignancy is associated with AIDS. It occurs in children younger than 4 years if HIV is vertically transmitted. EBV is also associated with NHL.
- Genetic:
  - Immunological defects:
    - Bruton type of sex-linked agammaglobulinemia
    - Common variable agammaglobulinemia
    - Severe combined immunodeficiency ataxia telangiectasia
    - Bloom syndrome
    - Wiskott-Aldrich syndrome
    - Autoimmune lymphoproliferative syndrome (ALPS).
- Post-transplant immunosuppression:
  - Post bone marrow transplantation (especially with use of T-cell depleted marrow)
  - Post solid organ transplantation.

Lymphomatoid Papulosis

Drugs

Diphenylhydantoin, infliximab and other immunosuppressive agents.

Radiation

Children treated with chemotherapy and radiotherapy for HL.

Etiology and Pathogenesis

Viral Infection and Immunosuppression

Immunocompromised individuals are at risk of developing NHL. Infection with EBV and HIV has been shown to be associated with NHL.

Geographic Location

Sub-Saharan Africa is the endemic zone of developing Burkitt's lymphoma.

Genetic

During normal lymphocyte development, the loci for the genes involving immunoglobulins or T-cell receptor (TCR) molecules undergo recombination enhancing immunologic diversification.

Chromosomal and Molecular Rearrangement

The most common abnormality is the t(8;14) translocation which juxtaposes the c-myc (bcl-2) gene to immunoglobulin locus regulatory elements leading to overexpression of c-myc.

Classification

About 90% of childhood NHLs are "high-grade" tumors and can be classified into one of four main categories by histology, cytogenetics and immunophenotypes:

- Burkitt/Burkitt-like (45–50%): A mature B-cell lymphoma.
- Lymphoblastic (25–30%): T-cell (90%), pre-B cell (10%).
- Large-cell diffuse (15–20%): B-cell.
- Large-cell anaplastic (10–15%): T-cell (70%), null cell (20%), B cell (10%).

Clinical Manifestations

Clinical manifestations of childhood NHL depend primarily on pathological subtype and sites of involvement.

Abdomen

Primary site of NHL is abdominal, involving the ileocecal region, appendix, ascending colon or some combination of these sites. Children present with:

- Abdominal pain and distension
- Nausea and vomiting
- Bowel changes
- Palpable masses
- Intussusception
- Hepatosplenomegaly
- Obstructive jaundice
- Inferior vena cava obstruction (Fig. 36)
- Ascites or peritonitis
- Rarely bleeding from gut.

Head and Neck

In 13% of cases, there is enlargement of the cervical node(s) and parotid gland, jaw swelling and unilateral tonsillar hypertrophy. The disease may present with nasal obstruction, rhinorrhea, hearing difficulty and cranial nerve palsies.

Mediastinum

Large superior mediastinal mass gives rise to:

- Edema of the neck and face
- Marked dyspnea
- Orthopnea
- Dizziness
- Headache
- Dysphagia

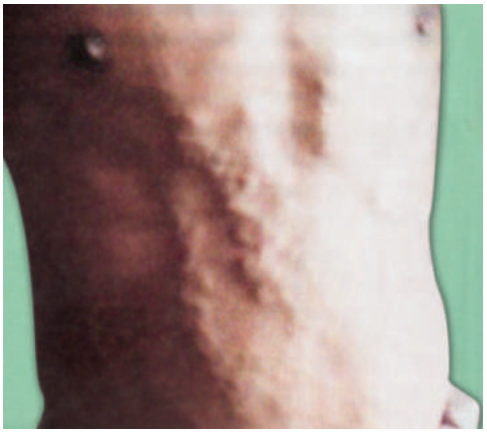


Fig. 36: Visible tortuous veins in anterior abdominal wall and chest in due to inferior vena cava obstruction in non-Hodgkin's lymphoma

- Epistaxis
- Altered mental status and syncope.

Diagnosis

Since NHL is a rapidly growing neoplasm, early and rapid diagnosis is essential. Selection of appropriate node or mass for histopathological examination is important. Histopathology is the primary means of definitive diagnosis and should be supplemented if possible, immunophenotyping and cytogenetic study. The diagnosis should be made with less invasive procedure like per cutaneous needle aspiration of accessible lymph nodes if the clinical condition of the patient is not suitable for biopsy particularly under general anesthesia.

Laboratory Investigations

- Tissue tests
  - Surgical biopsy for cytochemical, immunologic, cytogenetic and molecular studies
  - Bone marrow aspiration and biopsy (bilateral)
  - Spinal fluid, peritoneal, pericardial or pleural fluid examination—cytochemical, immunologic, cytogenetic.
- Laboratory tests
  - Complete blood count
  - Serum electrolytes (calcium, phosphorous, magnesium)
  - Evaluation of renal function [urinalysis, blood urea nitrogen (BUN), uric acid, creatinine]
  - Evaluation of hepatic function [bilirubin, alkaline phosphatase, alanine transaminase (ALT), aspartate aminotransferase (AST)]
  - Lactic dehydrogenase level
  - Soluble IL-2 receptor levels (if possible)
  - Viral studies: HIV antibody, hepatitis A, B, C serology, CMV antibody, varicella antibody, herpes simplex virus (HSV) antibody.
- Radiologic tests
  - Chest radiograph
  - CT scan of the chest
  - CT scan of the abdomen and pelvis with contrast
  - Positron emission tomography (PET) scan
  - Magnetic resonance imaging when clinically indicated, especially for bone involvement (e.g. vertebrae).

Management

The dramatic improvement in the survival of patients with NHL is because of development of highly effective multiagent chemotherapy and supportive care. Surgery has limited role in treatment other than diagnostic purpose. Radiotherapy is also restricted to emergency situations, e.g. superior vena cava syndrome or spinal cord compression. Chemotherapy is the mainstay of treatment.

The Saint Jude staging scheme is used to guide treatment and to inform prognosis.

Stage I

- Single tumor or nodal area is involved, excluding the abdomen and mediastinum.

Stage II

- Single extranodal site and regional node involvement
- Two or more nodal areas on the same side of the diaphragm
- Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm
- Primary gastrointestinal tumor usually in the ileocecal area with or without involvement of associated mesenteric nodes (resectable).

Stage III

- Two extranodal sites on opposite sides of diaphragm
- Two or more nodal areas above and below the diaphragm
- Primary intrathoracic tumors (mediastinal, pleural, thymic)
- Extensive intra-abdominal disease
- Paraspinal or epidural tumors.

Stage IV

- Central nervous system or bone marrow involvement.

Treatment

Chemotherapy is the mainstay of treatment.

- Lymphoblastic lymphoma is treated with regimen similar to those of ALL, i.e. cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)
- Burkitt's lymphoma and anaplastic large cell lymphoma are treated with brief intensive courses [e.g. cyclophosphamide, vincristine, MTX and prednisolone (COMP)]
- Central nervous system involvement necessitates intrathecal therapy, and radiotherapy is used for residual disease
- Other principles are combining drugs of different mechanism of action; high-dose intensity over time by keeping the treatment interval short; an efficient CNS-directed therapy to address the strong tendency to invasion to CNS. Therapeutic strategies that adhere to this principle of the rapidly repeated 4–7 days courses composed of corticosteroid, vincristine, cyclophosphamide, high-dose of MTX, cytarabine, doxorubicin, etoposide and triple drug (MTX, cytarabine, corticosteroid) intrathecal therapy result in longtime remission rate up to 90% in large multicenter study.

Supportive Therapy

All patients need administration of IV fluid as twice the maintenance rate, usually without potassium. Sodium bicarbonate should be added to IV fluid to achieve moderate alkalinization of urine. These measures enhance excretion of tumor metabolites. Allopurinol is used to prevent or correct hyperuricemia. In high-risk situation (extreme elevation of LDH and/or uric acid) or evidence of impaired renal function at presentation considers administration of recombinant urate oxidase (rasburicase). The patient's laboratory value should be monitored for tumorlysis throughout initial therapy. If fever is present, it may reflect the underlying malignancy. However, consider beginning of empiric broad-spectrum antibiotic coverage until sepsis or focal infection (due to bowel perforation) is excluded.

Prognosis

Although the effective treatment protocol for different subtypes of early stages of NHL have 90% cure rate, for late stages it is about 50–60%. Therapy carries significant toxicity and adequate supportive care is required to deliver high-dose of chemotherapy safely to children.

NEUROBLASTOMA

In children, NB is the most common extracranial solid tumor ranging from 8% to 10% of all childhood cancers. Although the incidence is 1 case per 7,000 live births in industrialized countries, rates in low income countries are less clear.

Neuroblastoma is aggressive tumor originating from neural crest-derived sympathetic nerve cells.

ETIOLOGY AND PATHOGENESIS

The cause is unknown, but the genetic factors are important. Numerous genetic factors have been identified. NB has strongly correlated with disease outcome. Two germline mutations are involved in familial predisposition of development of NB: (1) anaplastic lymphoma kinase (ALK) and (2) PHO X 2B 2B genes. Advanced diseases with poor outcome are associated with MYCN oncogenes. MYCN testing is currently considered as standard part of the diagnosis as it clearly has biological and treatment importance.

PATHOLOGY

Neuroblastoma arises from neural crest-derived cells in the sympathetic chain. Most common site is suprarenal gland. Next common site is sympathetic chain of posterior mediastinum.

Neuroblastoma is the most common extracranial round, small, blue cell tumor of childhood. NB arises from neural crest-derived cell of the sympathetic chain. The spectrum of neuroblastic cell differentiation and maturation is represented by three histopathological subtypes: (1) NB, (2) ganglioneuroblastoma and (3) ganglioneuroma. NB tends to calcify.

Neuroblastoma is slightly more prevalent in boys compared to girls 1.1:1.

CLINICAL FEATURES

Presenting symptoms are highly variable and often nonspecific and vague. The clinical manifestations are primarily dependent on location of the primary and metastatic tumor. Approximately 65% of primary tumors arise in the abdomen, remaining are seen in thoracic, cervical or pelvic regions. Clinical features depend upon primary site, the presence of metastasis and associated metabolic disturbances caused by catecholamine secretion. Presenting features may include:

- Local effects:
  - Abdominal swelling, constipation, bladder dysfunction
  - Dyspnea, difficulty in swallowing, visible cervical swelling, limping and pain from cord compression, Horner's syndrome
  - Catecholamine: Sweating, hypertension, pallor, diarrhea.
- Metastasis:
  - Proptosis (Fig. 37) and periorbital ecchymoses called raccoon eyes (Fig. 38)
  - Blueberry muffin skin (stage IV-S), pallor, bone pain
  - Nervous system:
    - Opsoclonus-myoclonus syndrome (OMS) (dancing eye syndrome with cerebellar ataxia).

OPSOCLONUS-MYOCLONUS SYNDROME

It is a paraneoplastic syndrome associated with NB, found in 2–3% of patients with NB. It is a nonepileptic movement disorder that may mimic status epilepticus. OMS (Fig. 39) is also known as dancing eye syndrome, which features opsoclonus (rapid involuntary multidirectional unpredictable conjugate eye movement), myoclonus, ataxia and irritability. It may be idiopathic but 20–50% of affected children are found to have neoplasm, most commonly NB. A humoral autoimmune process causing symptoms has been implicated.

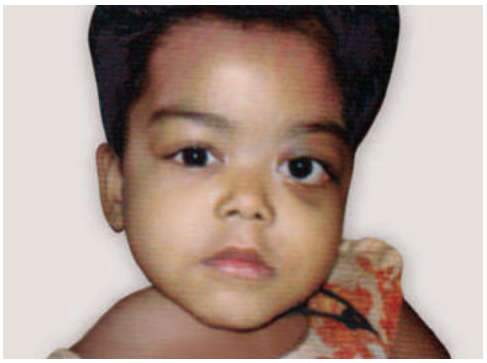


Fig. 37: Child with neuroblastoma showing proptosis of left eye

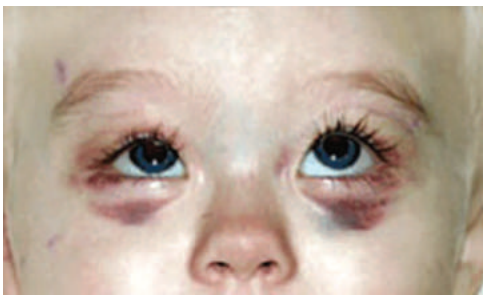


Fig. 38: Periorbital ecchymoses (raccoon eyes)

Fig. 39: A child showing involuntary multidirectional eye movement suffering from opsoclonus-myoclonus syndrome (OMS)

Difference between seizure attack and OMS is frequently difficult. In OMS, consciousness is not impaired like epilepsy and child is responsive to voice despite florid jerks of eyes and limbs. The nature of eye movement is also different than that of seizure. In seizure there is usually unilateral gaze movement, while in OMS there is multidirectional movement.

Prognosis of OMS

Neuroblastoma associated with OMS has excellent prognosis. But opsoclonus-myoclonus may relapse. Up to two-thirds may end up to developmental delay with wide range of behavioral problems.

DIAGNOSIS OF NB

A complete physical examination to evaluate any mass, adenopathy, bony defects, organomegaly and a careful assessment of neurological assessment for paralysis.

INVESTIGATIONS

A wide range of investigations may be necessary.

- *Genetic analysis*: MYCN amplification, gene analysis for DNA ploidy.
- *Blood tumor markers for NB*: Neuron-specific enolase, LDH.
- Urine catecholamines, vanillylmandelic acid (VMA) and homovanillic acid (HVA) to creatinine ratio raised in 80%.
- Imaging (Figs 40 to 43):
  - Evidences of metastasis may be seen on MRI, CT scan or even in plain X-ray (Fig. 40)
  - The imaging modality of choice for delineation of primary tumor is the scan of chest, abdomen and pelvis and further evaluation of spine for paraspinal tumors. Recent studies suggest that 18F-fluoro-2-deoxyglucose (18F-FDG) PET scan has been useful for lower stage of patient
  - *X-ray chest and abdomen*: May show calcification.
  - Contrast intravenous urography (IVU) may show rotation of kidney due to pressure effect and calcified mass (Fig. 41)
  - *Iodine-131-metaiodobenzylguanidine (131I-MIBG) scan*: It remains the gold standard for high-stage disease. This is taken up by the NB cells and is useful for identification of primary tumor and metastasis, also used as treatment (Fig. 42)
- Bone marrow aspiration: Bilateral bone marrow aspiration is necessary as disease infiltration may be patchy. NB cells are grouped as rosette form (Fig. 44)
- Biopsy: The lesion/lymph node may be accessible for biopsy. Tissue and bone marrow material are subjected to histological, cytogenetic and molecular analysis. Characteristic neuroblastoma cell in the form of rosette can be seen on bone marrow study (Fig. 44).

DIFFERENTIAL DIAGNOSIS

- Neurofibromatosis:
  - Although intrathoracic NF tumor appears similar to NB radiologically, they tend to be more nodular in outline and grow along the course of intercostal nerves resulting in characteristic indentation along the inferior costal margin.
- Wilms' tumor (WT):
  - Tends to feel smooth on palpation in contrast to nodular feel of a NB
  - No calcification is found in imaging studies in contrast to NB.
- Cervical adenitis and lymphoma:
  - May be challenging to distinguish from cervical NB.

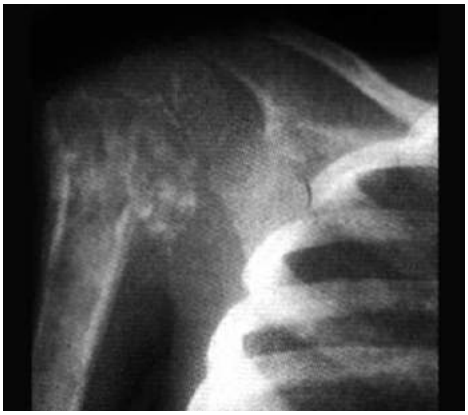


Fig. 40: X-ray showing metastasis in humerus in neuroblastoma

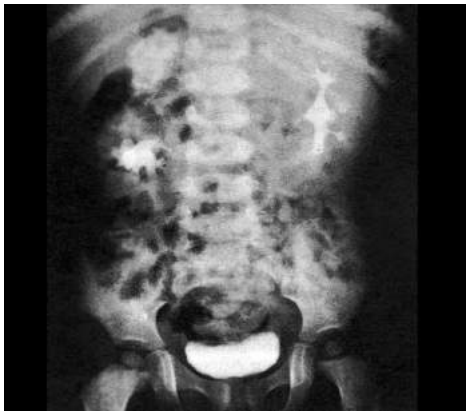


Fig. 41: Contrast X-ray IVU showing calcified mass above upper pole of right kidney which is rotated about transverse axis. Left pyelogram is normal

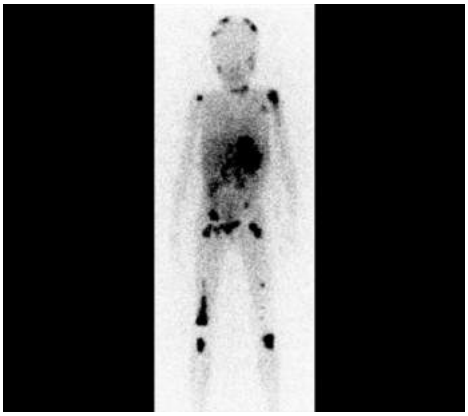


Fig. 42: Metaiodobenzylguanidine (MIBG)–avid neuroblastoma. Increased uptake of radiolabeled tracer can be detected in multiple sites of disease, including bone and soft tissue

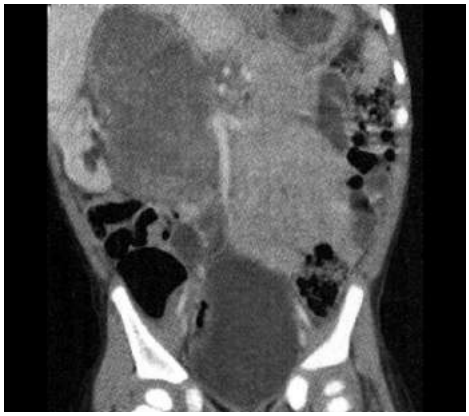


Fig. 43: CT scan showing large tumor above right kidney (neuroblastoma)

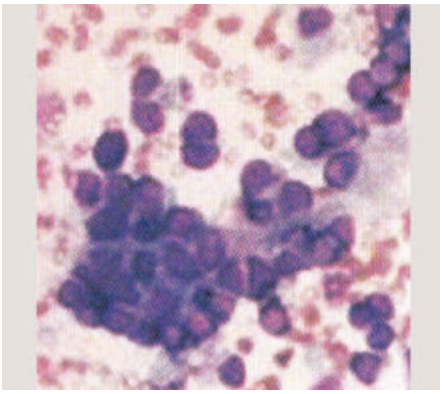


Fig. 44: Bone marrow infiltration with neuroblastoma (NB) cells. Bone marrow with rosette formation with NB cells is characteristic

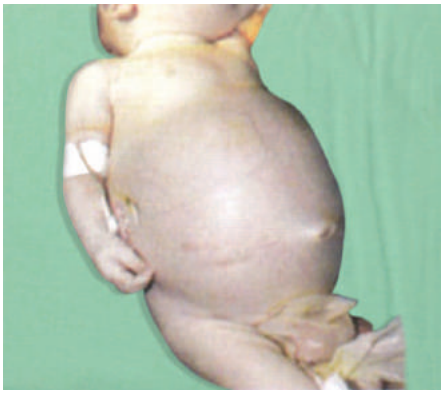


Fig. 45: Maximum liver enlargement due to metastasis in liver due to stage 4S disease. The child has favorable outcome if MYCN mutation is negative

TREATMENT

Treatment includes drugs, chemotherapy, surgical excision or combined depending upon staging of NB and risk factors involved. One or more cytotoxic drugs are given depending upon staging.

Chemotherapeutic Agents

Chemotherapy includes vincristine and alkylating agents in combination with anthracycline and epipodophyllotoxin. Widely used regimens are:

- Vincristine, cisplatin, teniposide and cyclophosphamide (OPEC).
- Cyclophosphamide, doxorubicin and vincristine (CADO).
- Cisplatin and teniposide-vincristine, cyclophosphamide and doxorubicin (PE-CADO).

Treatment depends on staging of NB as follows: Staging (Tables 17 and 18).

International Neuroblastoma Staging System (INSS)

Stage 1 (Low-risk)

- Surgery alone.
- Survival rate is greater than 95%.

Stage 2 or 3 (Intermediate-risk)

- Age greater than 1 year, no MYCN amplification
- Surgery combined with intensive chemotherapy
- Survival rate is 75–85%.

Stage 4 and MYCN Amplification (High-risk)

- A combination of surgery, high-dose chemotherapy with stem cell rescue and radiotherapy (either external or internal radioactive MIBG)
- Survival rate is less than 40%.

Stage 4S

- Infants less than 1 year of age can spontaneously regress or resolve into ganglioneuroma (Fig. 45)
- Chemotherapy oral for life-threatening symptoms. Oral cyclophosphamide with IV adriamycin or vincristine is sufficient
- Survival is greater than 90%.

Table 17: Staging of neuroblastoma

Stages	Involvement
Stage 1	Localized disease, surgically excised
Stage 2A	Localized disease, incompletely excised. No lymph node involved
Stage 2B	Localized disease, incompletely excised. Lymph nodes positive
Stage 3	Unresectable, unilateral tumor extending across midline
Stage 4	Any primary tumor with dissemination (except 4S)
Stage 4S	In child <1 year: Localized tumor (1-2B) with dissemination to liver, skin or bone marrow

Table 18: International Neuroblastoma Risk Group (INRG) staging system revised

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors* and combined to one body compartment
L2	Locoregional tumor with presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastasis confined to skin, liver and/or bone marrow

*Image-defined risk factors are surgical risk factors detected by imaging studies that make safe, complete resection of the tumor is impractical at the time of diagnosis.

PROGNOSIS

Prognosis varies greatly by risk group.

- Patients with low-risk (stage 1 and 4S), OS rate is 95%
- Patients with intermediate-risk (stage 2 and 3), survival rate is 87%
- Patient with high-risk (stage 4 and MYCN amplification) disease (<5%).

WILMS' TUMOR

Renal tumors comprise approximately 6% of all childhood cancers and nearly 10% of all malignancies among children aged 1–4 years. WT (nephroblastoma) is the most common primary renal tumor of childhood and the sixth most common childhood malignancy in the United States.

EPIDEMIOLOGY

Male to female ratio is 0.92:1.00 in unilateral WT and 0.6:1.00 in bilateral WT.

Wilms' tumor, clear cell sarcoma of the kidney and malignant rhabdoid tumor of the kidney occur predominantly in younger children and are rarely seen after 10 years of age. The majority of renal tumors occurring in adolescents are renal cell carcinomas. Approximately 78% of children with WT are diagnosed at 1–5 years of age, with a peak incidence occurring between 3 years and 4 years of age. Median age of presentation is 44 months in unilateral disease and 32 months in bilateral disease. WT is usually sporadic, but 1% of cases are familial.

Association with other diseases, WT is closely associated with following syndromes:

- The Wilms' tumor-aniridia-genital anomalies-mental retardation (WAGR) syndrome
- Denys-Drash syndrome
- Beckwith-Wiedemann syndrome
- Hemihypertrophy
- Trisomy 18.

ETIOLOGY AND PATHOGENESIS

Two WT genes have been identified: (1) *WT1* (chromosome 11p13) and (2) *WT2* (11p15). Moreover, loss of heterozygosity at chromosome 1p and 16q confers worst prognosis.

Wilms' tumor arises from metanephric blastema cells, primitive embryonic renal tissue. These tissues usually disappear after birth but persist in children with WT as "nephrogenic rest." It typically arises as an intrarenal solid or cystic mass which displaces the collecting system and extends to the renal vein (40% cases). It is bilateral in 6% cases. Tumor spreads to lungs and liver via lymphatic and vascular routes.

CLINICAL FEATURES

Often present as asymptomatic abdominal mass which is smooth, firm, fixed in position and may extend across the midline. Other features include abdominal pain, fever, anemia, hematuria and hypertension.

Metastasis

Wilms' tumor spreads both locally and hematogenously.

Local Spread

Local spread occurs to renal hilar structures and penetrates renal capsule. This type of spread may cause invasion to renal vein resulting in thrombosis in inferior vena cava.

Hematogenous Spread

Hematogenous spread occurs to lungs and liver most commonly.

DIFFERENTIAL DIAGNOSIS

- Neuroblastoma.

INVESTIGATIONS

- Complete blood count
- Urine R/M/E
- Imaging:
  - *US*: To evaluate abdominal mass and identify involvement of renal vein, inferior vena cava and liver.
  - *CXR*: To detect pulmonary metastasis.
  - *CT scan/MRI*: CT/MRI of chest and abdomen allows distinction of nephroblastoma from NB, assessment of lymph nodes, other kidney involvement and liver/pulmonary metastasis.
- Biopsy: Tissue from the tumor is examined histologically and using cytogenic and molecular techniques. Histopathological examination provides information whether the tumor is favorable or not.

Favorable

- Presence of epithelial, stromal and blastemal elements
- Low-risk (90%).

Unfavorable

- Anaplastic and blastemal subtypes
- High-risk (10%).

STAGING

There are two staging systems available.

1. Prechemotherapy staging consisting of five cases developed by National Wilms' Tumor Study Group (NWTSG) (Fig. 46 and Table 19).
2. Postchemotherapy-based system developed by International Society of Pediatric Oncology (SIOP).

TREATMENT

Treatment includes surgery, chemotherapy and radiotherapy depending upon the stage and histology of the tumor.

Surgery

All children have surgery at some stage. It is both a diagnostic and therapeutic option.

Chemotherapy

Chemotherapy includes vincristine or several months of an anthracycline-based regimen. Postoperative chemotherapy is determined by the extent of surgical resection (complete and incomplete) and histology.

Radiotherapy

Radiotherapy may also be given to the area of affected kidney or the whole abdomen and for the lung metastasis.

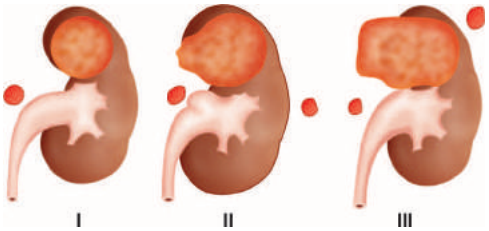


Fig. 46: Diagram showing three pre-chemotherapy stages (out of 5 stages) of Wilms' tumor

Table 19: Prechemotherapy staging of Wilms' tumor
Stage I
• Tumor is limited to the kidney and completely excised • The tumor does not rupture before or after removal • The vessels of the renal sinuses are not involved beyond 2 mm • There is no residual tumor apparent beyond the margin of excision
Stage II
• Tumor extends beyond the kidney but is completely excised • No residual tumor is apparent at or beyond the margin of excision • Tumor thrombus in vessels outside the kidney is stage II if the thrombus is removed en bloc with the tumor
Stage III
• Residual tumor confined to the abdomen • Lymph nodes in the renal hilum, the periaortic chains or beyond, are found to contain tumor • Diffuse peritoneal contamination by the tumor • Implants are found on the peritoneal surfaces • Tumor extends beyond the surgical margins either microscopically or grossly • Tumor is not completely resectable because of local infiltration into vital structures
Stage IV
• Presence of hematogenous metastases or metastases to distant lymph node
Stage V
• Bilateral renal involvement at the time of initial diagnosis

PROGNOSIS

Wilms' tumor is a curable disease with a 5-year survival rate above 90%. The prognosis for patients with WT is related not only to the stage of the disease at diagnosis, the histopathological features of the tumor, patients' age and tumor size but also to the team approach provided to each patient by the pediatric surgeons, radiation oncologist and pediatric oncologists.

CLOTTING DISORDERS

HEMOPHILIA

Hemophilia is a clotting disorder resulting from deficiency of one of the clotting factors. There are two types of hemophilia:

1. Hemophilia A (classic hemophilia)—deficiency of factor VIII (FVIII)
2. Hemophilia B (Christmas disease)—deficiency of factor IX (FIX).

Epidemiology

Prevalence is 1:10,000 for hemophilia A and 1:35,000 for hemophilia B. As both hemophilia A and B are X-linked recessive disorders, they affect males exclusively. Female becomes affected rarely if there is extreme lyonization or if there are two independent mutations.

Etiology

Hemophilia A and B are X-linked recessive disorders. The genes for FVIII and FIX are located on the long arm of the X chromosome in bands q28 and q27 respectively.

Mutation of FVIII gene (F8) interferes with the synthesis, stability or function of the proteins generating a spectrum of severity in the phenotype determined by the level of activity. A flip inversion mutation in intron 22 of F8 accounts for 45% of all serious cases of hemophilia A.

Pathophysiology

The role of the coagulation system is to produce a stable fibrin clot at sites of injury. The clotting mechanism has two pathways: (1) Intrinsic and (2) extrinsic. FVIII and FIX circulate in an inactive form. When activated, these two factors cooperate to cleave and activate factor X, a key enzyme that controls the conversion of fibrinogen to fibrin.

Clinical Features

In the neonatal period:

- Severe hematoma, prolonged bleeding from the umbilical cord or umbilical area
- Intracranial hemorrhage (1–2%)

Beyond neonatal period, bleeding is uncommon in infants until they become toddler.

In young child:

- Trauma-related soft tissue hemorrhage (Fig. 47)
- Bleeding from gum during eruption of teeth
- Prolonged bleeding from circumcised wound (Fig. 48).

Older children:
Hemarthrosis (Fig. 49).

- Hematoma

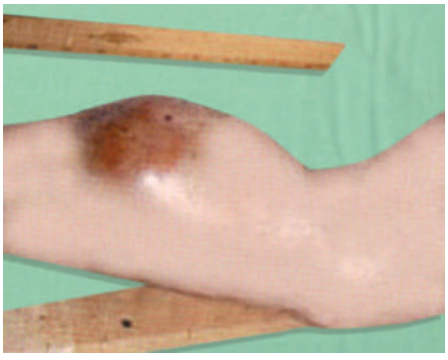


Fig. 47: Intramuscular hematoma on right cuff muscles seen in hemophilia patient

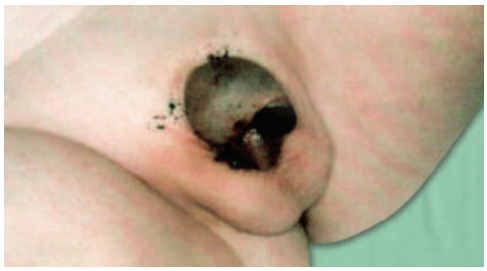


Fig. 48: Postcircumcision hematoma in hemophilia A

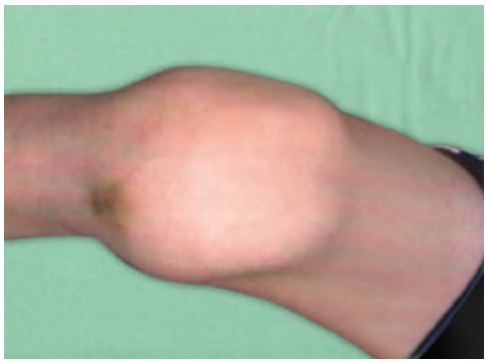


Fig. 49: A swollen knee joint (hemarthrosis) in hemophilia patient

- Bruise can occur with hematoma, but petechiae usually do not occur as because petechiae are clinical manifestation of capillary leaking or platelet disorders
- Arthropathy due to recurrent joint bleed.
  Clinical features related to hematoma (pressure symptoms):
  - Sciatica
  - Neurological deficit in the lower limb can occur if there is hematoma in the iliopsoas or inguinal region due to pressure effect.

Clinical Severity

Hemophilia has been classified into three types based on factor activity (Table 20).

1. Severe disease:
   - Factor activity less than 1% (< 0.01 IU/mL).
   - Age group younger than 1 year.
   - Spontaneous bleeding (1–2 episodes per week), predominantly in joints and muscles.
   - Incidence is 43–70% of all hemophilia.
2. Moderate disease:
   - Factor activity 1–5% (0.01–0.05 IU/mL)
   - Age group 1–2 years
   - Occasional spontaneous bleeding (1–2 episodes in a year)
   - Severe bleeding with trauma, surgery
   - Incidence is 15–26% of all hemophilia.
3. Mild disease:
   - Factor activity greater than 5% (>0.05 IU/mL)
   - Age group older than 2 years
   - Severe bleeding with major trauma, surgery
   - Incidence is 15–31% of all hemophilia.

Diagnosis

Hemophilia should be suspected in patients presenting with a history of easy bruising in childhood:

Table 20: Severity, factor activity and hemorrhage type in hemophilia

Classification	Factor activity	Type of hemorrhage
Mild	<5%	Major trauma or surgery
Moderate	1–5%	Mild-moderate trauma
Severe	<1%	Spontaneous, hemarthrosis

- Spontaneous bleeding (particularly into the joints and soft tissues)
- Excessive bleeding following trauma or surgery
- Family history of hemophilia.

Accurate diagnosis of hemophilia requires the following:

- Detailed history with special attention to:
  - Age of onset of bleeding
  - Site of bleeding
  - Whether bleeding spontaneous/trauma related (number of episodes/month or year)
  - Target joints, if any
  - Other affected members in the family.
- Complete physical examination with particular care to record range of motion, deformities (if any) and muscle strength at the knees, hips and elbows.

Laboratory Investigations

- Coagulation studies:
  - Activated partial thromboplastin time (APTT) is prolonged
  - Bleeding time, prothrombin time and platelet count are normal.
- FVIII and FIX activity assay
- von Willebrand's factor assay: The combination of low FVIII and low vWF may indicate vWF deficiency as the primary diagnosis.
- A DNA-based diagnosis is possible in 95% of cases. Common flip inversion is seen in 50% of patients with severe FVIII deficiency.
- Carrier detection by molecular analysis is more reliable than methods based on assays of coagulation activity.

Differential Diagnosis

- von Willebrand's disease.

Management

The aims of management include:

- Prevention of life-threatening bleeds and chronic joint damage
- Facilitation of social and physical well-being
- Avoidance of harm by exposure to blood product.

Management involves prophylactic therapy to normalize hemostasis, treatment of bleeding episodes and treatment of patients who developed FVIII inhibitors.

Medical Management

General management includes:

- Prevention of bleeding
  - To prevent bleeding, following should be avoided:
    - Intramuscular injections
    - Aspirin and other NSAIDs
    - Contact sports.

  - To prevent bleeding following must be addressed carefully:
    - Local treatment with ice application and local pressure
    - Early factor correction
    - All invasive procedures should be done under factor cover (clotting factors or concentrate/desmopressin (DDAVP) should be given to achieve appropriate factor level)
    - Use of DDAVP/epsilon-aminocaproic acid (EACA)/tranexamic acid
    - Hepatitis A and B immunization
    - Educate teachers and parents
- Acute bleeding should be treated as early as possible (preferably within two hours)
- Only uncomplicated mild/moderate bleeding episodes can be managed at home
- Patients with severe bleeding should be treated in hospital
- To hemophilia void trauma, all patients should adjust lifestyle as much as possible
- Regular exercise should be encouraged to promote strong muscles, protect joints and improve fitness.

Management of Hemostasis (Table 21)

Primary prophylaxis is the better mode of management. Patients with severe hemophilia are given FVIII or FIX three times weekly in hemophilia A and twice weekly in hemophilia B to reduce risk of bleeds. This results in less deformity and allows the child to play normally. It is expensive mode of treatment but provides good quality of life. All children should receive hepatitis vaccination subcutaneously and parents are counseled regarding injury prevention.

Products available for FVIII and FIX replacement therapy include plasma-derived products, monoclonal antibody purified and recombinant FVIII (rFVII).

Hemostasis is achieved with replacement therapy aimed at correcting the coagulation factor deficiency.

A variety of products are available for replacement therapy. Due to lack of safe viral elimination and chance of volume overload, use of fresh frozen plasma (FPP) and cryoprecipitate is limited.

FVIII Products

Many rFVIII are available.

Advantages:

- Elimination of viral contamination.
- Effectiveness same as plasma-derived concentrate.
- Continuous infusion decreases the amount of factor used which is cost effective.
- Can be used to control hemostasis as well as for prophylaxis.

Cryoprecipitate:

A 30–50 mL of cryoprecipitate should contain at least 80 IU FVIII activity.

Indications:
It should be used for replacement therapy in FVIII deficiency and vWD.

Disadvantages:

- Storage at or below –30°C
- Infusion as early as it reaches at room temperature.
- Contains fibrinogen, FVIII and vWF but no FIX. So not suitable for treatment of hemophilia B.

Cryosupernatant/Lyophilized Prothrombin Complex Concentrate (PCC)

Leftover plasma after preparation of cryoprecipitate contains factors II, VII, IX, X (the prothrombin complex). It is not available commonly.

Fresh Frozen Plasma

Fresh frozen plasma contains all clotting factors in near normal quantities. Each mL of FFP contains 1 IU of FVIII and FIX. It should be transfused over 15–20 minutes as soon as it reaches room temperature. In emergency when FIX is unavailable, only FFP can be used. Cryoprecipitate does not contain FIX and therefore should not be used.

To achieve a target of 30% of FVIII which is required for the management of hemarthrosis, a dose of 50 U/kg every 12–24 hours for 1–2 days is required. A major bleed, e.g. intracranial hemorrhage, the target of achieving the factor level is 80–100% correction. The dose needed to achieve this target is 50 U/kg every 8–12 hours for approximately 7–12 days. The dose regimens of FVIII and FIX requirement are shown in Table 21. EACA or tranexamic acid may be effective as adjunct therapy in mild cases of hemophilia.

Other Modalities of Management

Desmopressin Vasopressin Analog or 1-Deamino-8-D-Arginine Vasopressin

Desmopressin is considered as the treatment of choice for *mild to moderate hemophilia* but it is not effective in

Table 21: Replacement therapy for hemorrhage in hemophilia A and B

Site of bleeding	Required factor level (%)	Dose in hemophilia A	Dose in hemophilia B
Joint	30–50	20–40 U/kg/day	30–40 U/kg/day q2d
Muscle	40–50	20–40 U/kg/day	40–60 U/kg/day q2d
Oral mucosa	50, add EACA	25 U/kg/day	50 U/kg/day
Epistaxis	80–100, then 30 until healed	40–50 U/kg, then 30–40 U/kg/day	80–100 U/kg, then 70–80 U/kg/day q2d
Gastrointestinal tract	100, then 30 until healed	40–50 U/kg, then 30–40 U/kg/day	80–100 U/kg, then 70–80 U/kg/day q2d
Genitourinary tract	100, then 30 until healed	40–50 U/kg, then 30–40 U/kg/day	80–100 U/kg, then 70–80 U/kg/day q2d
CNS	100, then 50–100 for 10–14 days	50 U/kg, then 25 U/kg/day q12 h or continuous infusion	100 U/kg/day, then 50 U/kg/day
Trauma or surgical site	100, then 30–50 until healed	50 U/kg, q12 h or continuous infusion	100 U/kg/day, then 50 U/kg/day

Abbreviations: EACA, epsilon-aminocaproic acid; CNS, central nervous system.

severe hemophilia. It stimulates a transient increase in plasma FVIII level and results in sufficient hemostasis to stop a bleeding episode. Onset of action is 30–60 minutes after IV administration (0.3 μg/kg) and 60–90 minutes after intranasal administration. Several doses of DDAVP may be needed to infuse every 12–24 hours before tachyphylaxis is observed. DDAVP is also available in oral form as 0.1 mg and 0.2 mg tablets.

Antifibrinolytic Agents

Tranexamic acid and EACA are used as adjunctive treatment of mucosal bleed.

Contraindications:

- In cases of renal bleeding
- Concurrently with nonactivated or activated prothrombin complex concentrate (APCC) as because it causes potential thrombotic complications.

Gene Therapy

Hemophilia A and B are ideal disease states to target for gene therapy since they are caused by mutations in single identified genes, a slight increase in clotting factor levels in vivo can convert severe hemophilia into milder disease.

Pegylated Factor VIII

The use of low molecular weight polyethylene glycol (PEG) containing liposomes as carriers for rFVIII results in the prolongation of hemostatic efficacy.

Inhibitors in Hemophilia

Inhibiting antibodies (inhibitors) directed to FVIII and FIX are formed in about 25% of severely affected hemophilia A and 1–3% of children with hemophilia B. The antibodies that develop in patients with hemophilia A are usually of mixed subclass with a dominant contribution of immunoglobulin G4 (IgG4). This presents with poor response to treatment.

The antibodies bind to infused FVIII, thereby reducing its half-life and neutralizing its coagulant activities resulting in an increased bleeding time that does not respond to FVIII replacement therapy.

Management of Inhibitors in Hemophilia

General Measures

- Monitoring all patients (especially in children newly diagnosed for hemophilia) every 3–6 months for the development of inhibitors
- No surgical procedure or joint aspiration should be done without prior checking for inhibitors
- If there is no response to appropriate replacement therapy, treat for inhibitors.

Control of Hemorrhage in Inhibitors of Hemophilia

Control of hemorrhage consists of adequate replacement of the deficient coagulation factor protein so as to prevent or reverse acute bleeding episodes. A multiple varieties of standard and modified FVIII, FIX and recombinant activated factor VIIIa (rVIIIa) concentrates are available. Treatment option includes the agents that bypass the defect such as recombinant activated factor VIIa (rFVIIa).

Factor VIII

Large dose of FVIII is required in life-threatening hemorrhage to swamp the inhibitor.

Recombinant Factor VII

Recombinant factor VII (rFVII) is highly effective in the management of spontaneous bleeding episodes which are life-threatening. The dose is 200–300 μg/kg.

Activated Prothrombin Complex Concentrates

Activated prothrombin complex concentrates are effective in the treatment of 90% of bleeding episodes and in the management of bleeding during major surgery. The effective dose is 100 U/kg twice per day. Antifibrinolytic agents such as tranexamic acid should not be administered concurrently with APCCs.

Antifibrinolytic Therapy

The recommended dose of tranexamic acid is 35 mg/kg/8 hours.

Plasmapheresis/Immunoadsorption

Plasmapheresis can be used to reduce inhibitor titers to allow effective therapy with FVIII.

Immunosuppression

Rituximab (anti-CD20 monoclonal antibody) therapy may be considered as an adjunct therapy to reduce inhibitor titers.

von WILLEBRAND'S DISEASE

von Willebrand's disease is the most common inherited bleeding disorder caused by quantitative or qualitative deficiency of vWF.

EPIDEMIOLOGY

Incidence of vWD is about 125 per million with severe disease affecting about 0.5–5 per million. There is no variation of incidence regarding race. Both male and female are equally affected.

PATHOPHYSIOLOGY

Inheritance for most common form is autosomal dominant, but molecular genetics remain complex and not fully resolved.

The genes for vWF are located on chromosome 12p. Expression of vWF gene is restricted to megakaryocytes, endothelial cells and possibly placental syncytiotrophoblast. Plasma concentration of vWF is 10 mg/mL. It is released from platelet and endothelial cells upon various stimuli (Fig. 50). It has two main functions in hemostasis:

1. Formation of platelet plug as an adhesion protein that diverts circulatory platelets to the sites of vascular injury through larger multimers.
2. Stabilizing and protecting of platelet plug from inactivation and clearing by forming a noncovalent complex with the procoagulant protein FVIII in plasma.

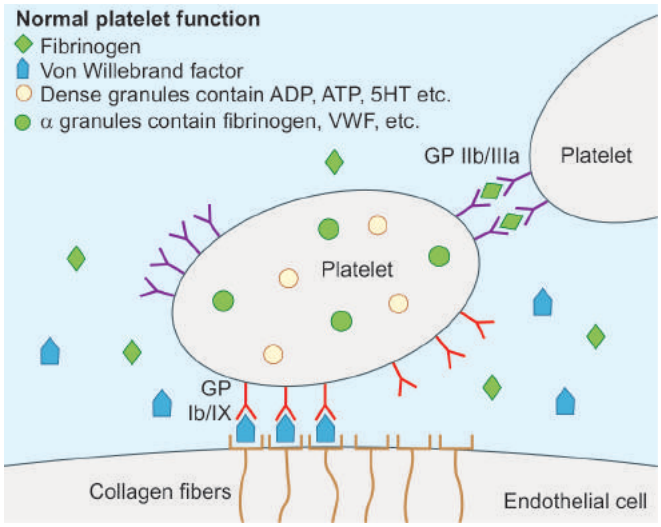


Fig. 50: Diagram showing platelet functions

So qualitative or quantitative deficiency of vWF leads to disruption of:

- Primary hemostasis due to failure of platelet aggregation and adherence to vessel wall
- Secondary hemostasis due to destabilization of FVIII.

CLASSIFICATION

von Willebrand's disease is divided into three main categories (Table 22):

1. Type I or partial quantitative deficiency
2. Type II or qualitative deficiency
   - Type II is again subcategorized into IIA, IIB, IIN and IIM based on the characteristics of the dysfunctional vWF.
3. Type III or total deficiency.

Table 22: Classification and frequency of von Willebrand's disease (vWD)

Types		Description	Frequency (%)
I		Partial quantitative deficiency of normal vWF	70–80
II		Quantitative defects in vWF	15–20
	IIA	Decreased platelet-dependent vWF function with lack of HMWM	10–20
	IIB	Increased binding affinity for platelet glycoprotein 1B	3–5
	IIM	Decreased platelet-dependent vWF function with normal vWF multimers	1–2
	IIN	Decreased vWF affinity for factor VIII	1–2
III		Complete deficiency of vWF	~1 per million

Abbreviation: vWF, von Willebrand's factor; HMWM, high molecular weight multimers.

CLINICAL FEATURES

Prolonged bleeding after minor trauma to skin and mucous membrane is characteristic of vWD.

- Most common symptoms include nose bleeds (Fig. 51), skin bruises (Fig. 52) and hematoma
- Prolonged bleeding from trivial wounds, oral cavity bleeding, excessive menstrual bleeding
- Bleeding are often exacerbated by ingestion of aspirin and ameliorated by the use of oral contraceptive.

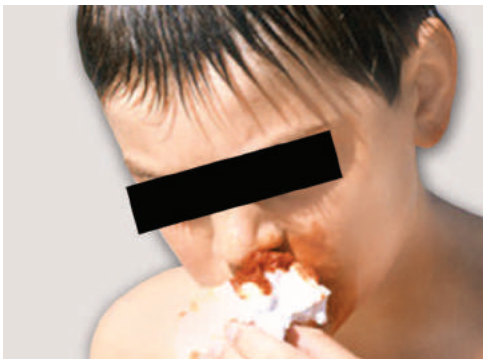


Fig. 51: Unwarranted nose bleeding in von Willebrand's disease

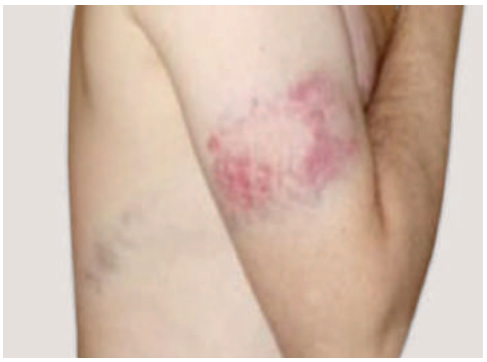


Fig. 52: Easy bruise in von Willebrand's disease

DIFFERENTIAL DIAGNOSIS

- Hemophilia A or B
- Platelet function defect
- Platelet type pseudo-vWD
- Bernard-Soulier syndrome
- Fibrinolytic defect
- Antiplatelet drug ingestion.

LABORATORY INVESTIGATIONS

- Normal bleeding time and normal APTT in type I vWD
- Bleeding time prolong in type II (IIA, IIB, IIM)
- Prothrombin time and thromboplastin time are normal
- *Platelet count*: Normal, but low in type IIB
- *Activated partial thromboplastin time*: Prolonged or at upper end of normal range
- *FVIIIc*: Reduced or low normal in type I, IIB
- *vWF antigen*: Reduced
- *vWF activity* (measured by ristocetin-induced platelet aggregation, acts by causing vWF to bind to platelet): Impaired, but enhanced in type IIB
- vWF antigen or vWF activity measurement is more reliable to confirm vWD in clinically suspected case where bleeding time, APTT and platelet count are normal.

MANAGEMENT

Patients with vWD do not normally require regular treatment but should be advised against use of aspirin and NSAIDs. While type III and II forms are easily identifiable, the diagnosis of type I disease still poses a significant problem. The two main treatment options are DDAVP and transfusion therapy. Optimal therapy depends on subtype and severity.

Severe Disease: Type III or Type IIB

Best treated with vWF and FVIII concentrate. Consider cryoprecipitate or platelet transfusion for severe uncontrolled bleeding.

Mild Disease

DDAVP promotes release of vWF from storage pools from endothelial cells. It is useful in most patients with quantitative deficiency. It may be given IV, SC or intranasally. It is contraindicated in type IIB because of thrombocytopenia and possible thrombotic complications. The side effects are seizure and hyponatremia which limit its use in young children.

DISSEMINATED INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation is the uncontrolled activation of the coagulation and fibrinolytic pathways.

ETIOLOGY

There are numerous causes of DIC which includes:
- Severe infection, e.g. meningococcal septicemia
- Intravascular hemolysis, e.g. ABO incompatibility
- Liver disease
- Malignancy.

PATHOPHYSIOLOGY

Three main pathological processes involved in DIC are:
1. Initiation of fibrin deposition
2. Amplification role of thrombin
3. Propagation of fibrin deposition.

Initiation of Fibrin Deposition

In DIC, extrinsic pathway of coagulation provides generation of thrombin. The tissue factor accumulates on activated platelets by binding to platelet P-selectin which results in thrombin generation.

Amplification Role of Thrombin

Thrombin amplifies inflammation and clotting by activation of platelets, and factors V, VIII and IX.

Propagation of Fibrin Deposition

Fibrinolysis is suppressed secondary to sustained increase in plasma levels of plasminogen activator inhibitor type 1 (PAI-1). Pathophysiology of DIC is shown in Figure 53.

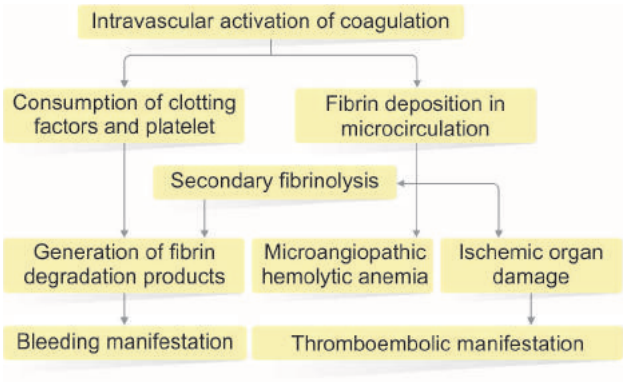


Fig. 53: Pathophysiology of disseminated intravascular coagulation (DIC)

CLINICAL FEATURES

The disturbed coagulation of DIC can manifest clinically at any point in the spectrum from bleeding to thrombosis.
- Bleeding tendency characterized by bleeding from puncture site, surgical incisions. Purpura, petechiae and ecchymoses and necrotic skin patches (Fig. 54) are characteristics of DIC.
- Thromboembolic phenomena with hematuria, oliguria leading to renal failure.
  - Gastrointestinal tract: Diarrhea, abdominal distension, ileus (Fig. 55), melena
  - Central nervous system: Internal hemorrhage, convulsion
  - Chorionic villus sampling: Hypotension, shock.
- Pallor or jaundice secondary to hemolytic anemia.

All the features may not be present in the same child.

LABORATORY INVESTIGATIONS

No single test is diagnostic for DIC. The presence of thrombocytopenia and hypofibrinogenemia (50% reduction) is the most sensitive laboratory marker.

Screening tests for DIC are:
- Complete blood count and peripheral blood film show schistocytes and thrombocytopenia (Fig. 56)
- *Prothrombin time*: Prolonged
- *Activated partial thromboplastin time*: Prolonged
- *Thrombin time*: Prolonged
- *Fibrinogen*: Low
- *Fibrin degradation products or D-dimer*: Increase.

A scoring system for evaluation of DIC has been proposed (Table 23).

Fig. 54: Necrotic skin patches seen in disseminated intravascular coagulation

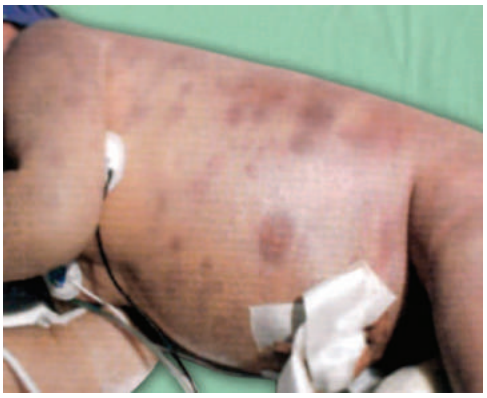


Fig. 55: Abdominal distension due to ileus with extensive ecchymoses

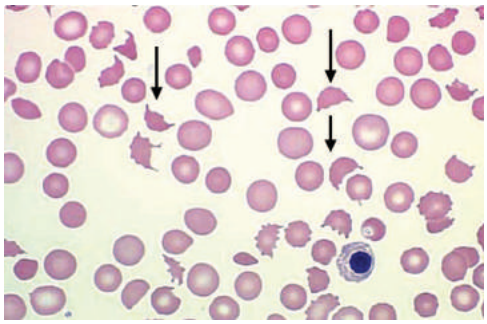


Fig. 56: Blood film of DIC showing schistocytes (arrows)

Table 23: Scoring system for overt disseminated intravascular coagulation (DIC)

Risk assessment	
Does the patient have an underlying disorder (like sepsis) known to be associated with overt DIC?	
If Yes	Proceed
If No	Do not use this algorithm
Order global coagulation tests	
Prothrombin time, platelet count	
Score the test result	
Platelet count	Score 0 = >100 × 10^9/L Score 1 = <100 ×10^9/L Score 2 = <50 ×10^9/L
Elevated fibrin markers, e.g. D-dimer, fibrin degradation product (FDP)	Score 0 = No increase Score1 = Moderate increase Score 2 = Highly increase
Prolonged prothrombin time (PT)	Score 1 = >35 sec but < 65 sec Score 2 = >65 sec
Fibrinogen level	Score 0 = >1 g/L Score 1 = <1 g/L
Calculate score	
Score >5	Compatible with overt DIC; repeat score daily
Score <5	Suggestive for nonovert DIC; repeat next 1–2 days

TREATMENT

- Treatment of the underlying cause is a priority and options to control bleeding include FPP and platelets as first line of treatment
- Management of aggravating factors like shock, hypotension, hypoxia and acidosis should be corrected
- Cryoprecipitate, fibrinogen concentrate and anticoagulant concentrate remain the other forms of intervention
- Coagulopathy may be compounded by vitamin K deficiency. Hence vitamin K should be given
- In case of sepsis, antibiotics are required.

Fresh Frozen Plasma

Fresh frozen plasma can be used if there is coagulation defect and the patient is bleeding, the dose is 15 mL/kg. Specific deficiency in fibrinogen despite FFP replacement may be corrected by cryoprecipitate or fibrinogen concentrate.

Platelet Transfusion

Platelet transfusion is given to patients with active bleeding and platelet count is less than 50 × 10^9/L.

Cryoprecipitate

Cryoprecipitate (fibrinogen 15 mg/bag)—1 bag/5 kg will raise fibrinogen level by 70 mg/dL.

Anticoagulants

In typical cases of DIC, therapy with heparin has not proved useful and may be harmful.

Anticoagulant Factor Concentrate

Protein C, Activated Protein C (APC) and Antithrombin

The level of both antithrombin and protein C is decreased in DIC. It is reasonable to think that administration of these anticoagulants may have a beneficial effect in the management of DIC. Patients with severe sepsis with DIC may be treated with recombinant human APC (continuous infusion 25 µg/kg/h). However, patient with platelet count of less than 30 × 10^9/L should not be given this product.

FEBRILE NEUTROPENIA

Patients with neutropenia and fever are grouped in febrile neutropenia. The patients are categorized into two groups: first category involves neutropenia secondary to bone marrow failure syndrome (single or multilineage), cyclical neutropenia or benign neutropenia of infancy (autoimmune neutropenia) and second category involves neutropenia secondary to administration of chemotherapy. Usually neutropenia secondary to chemotherapy is referred as *febrile neutropenia*.

DEFINITION

The Infectious Diseases Society of America (IDSA) has defined febrile neutropenia with the following two parameters:

1. Neutropenia:
   - Neutrophil count of less than or equal to 500 cells/mm^3 or
   - A count of less than 1,000 cells/mm^3 with a predicted decrease less than 500 cells/mm^3.
2. Fever: In a neutropenic patient, a single measurement of oral temperature of greater than 38.3°C or a temperature of greater than 38.0°C for 1 hour.

RISK STRATIFICATION

Assessment should be done at presentation of fever which may determine:

- The need for type of empirical antibiotic administration (oral or IV)
- The need for hospitalization (inpatient or outpatient)
- Duration of antibiotic therapy.

Most high-risk patients should be hospitalized initially for empirical therapy, whereas low-risk patients may receive oral empirical therapy at home (Table 24). Table 24 shows the criteria for risk stratification.

LABORATORY INVESTIGATIONS

Initial Lab Investigations Nonspecific to Condition

- Complete blood count with ESR and blood film
- C-reactive protein
- Renal function tests

Table 24: Risk group assignment in patients with febrile neutropenia

Low-risk for severe infection	High-risk for severe infection
ANC ≥100/mm^3	ANC <100/mm^3
AMC ≥100/mm^3	Toxic appearance
Normal chest X-ray	Comorbid conditions*
Near normal hepatic and renal function test	Abnormal chest X-ray
Duration of neutropenia of < 7 days	Abnormal hepatic or renal function tests
Resolution of neutropenia expected in <10 days	Resolution of neutropenia expected >10 days
No intravenous catheter site infection	Intravenous catheter in situ
Early evidence of bone marrow recovery	Malignancy not in remission
Malignancy in remission	Signs of CNS infection
Peak temperature of <39.0°C	
No neurological or mental change	
Nontoxic appearance and no abdominal pain	
No comorbid complication*	

*Shock, hypoxia, pneumonia or other deep organ infection, vomiting or diarrhea.
Abbreviations: ANC, absolute neutrophil count; AMC, absolute monocyte count; CNS, central nervous system.

- Liver function tests
- Coagulation studies
- Blood urea
- Serum creatinine
- Serum electrolytes
- Liver transaminases
- Serum bilirubin
- Serum amylase
- Radiological and imaging studies:
  - Depend on organ systems of presentation like X-ray, US scan or CT scan of chest, abdomen, etc.
- Culture
- Microbiological:
  - Rapid antigen tests as indicated, which may include group A streptococcus, *Clostridium difficile, Cryptococcus,* respiratory syncytial virus (RSV), influenza virus, adenovirus and parainfluenza virus.

Additional Tests as per the Suspected Conditions

B-Cells Evaluation

Immunological:
- Immunoglobulin level.
- Immunoglobulin G subclass.
- Isohemagglutinin.

Culture:
- Blood culture.

Imaging:
- X-ray/CT scan of chest for thymus.

Serological:
Antibody production after vaccination (e.g. diptheria, meningococcus, etc.).

T-cells Evaluation

Immunological, if indicated:
- Lymphocyte subpopulation
- Delayed hypersensitive reaction assay.

Culture:
- Blood culture daily, other culture if required.

Imaging, if indicated:
- CT scan/X-ray chest for thymus.

Serological if indicated:
- Mitogen stimulation assay.

Phagocytic Evaluation

Immunological:
- Absolute neutrophil count (ANC)
- Number of CD11 (a, b and c subset) and CD18 β-receptor, if indicated and available.

Culture:
- Blood culture daily, other culture if required.

Imaging:
- CT scan/X-ray chest for thymus.

Serological:
- Chronic granulomatous disease assay.

MANAGEMENT

Fever with neutropenia requires hospital admission, cultures and IV antibiotics.

Antibiotic Therapy

Empirical Antibiotic Therapy

High-risk patients should be hospitalized for IV empirical antibiotic therapy. Recommended monotherapy includes antipseudomonal β-lactam agents like cefepime, carbapenem (meropenem or imipenem-cilastin) or piperacillin-tazobactam. Other antimicrobials added to initial regimen to control complications are aminoglycosides, fluoroquinolones and/or vancomycin.

Initial modified empirical therapy is considered for patients at risk for infection with the following antibiotic-resistant organisms:
- Methicillin-resistant *Staphylococcus aureus* (MRSA): Early addition of vancomycin, linezolid or daptomycin.
- Vancomycin-resistant enterococcus (VRE): Early addition of linezolid or daptomycin.
- Extended-spectrum β-lactamases (ESBLs): Early use of carbapenem.
- *Klebsiella pneumoniae carbapenemases* (KPCs): Early use of polymyxin—colistin or tigecycline.

Low-risk patients should receive initial oral or IV empirical antibiotic dose in hospital settings.

Duration of therapy: Duration of therapy depends on organisms and site of infection. Appropriate antibiotics

are given at least during the neutropenia (until ANC is > 500 cells/mm^3) or longer if clinically necessary.

If patient is afebrile with resolved clinical signs of nondocumented infections and initial course of antibiotics completed but still neutropenic should be given appropriate oral antibiotic prophylaxis until marrow recovery.

Prophylactic Antibiotic Therapy

High-risk group: Appropriate prophylaxis should be given.
Low-risk group: Not routinely recommended.

Antifungal Therapy

Pre-emptive Antifungal Therapy

High-risk patients: Empirical or pre-emptive antifungal therapy is recommended if fever persists or recurring after 4–7 days of antibiotics.

Low-risk patients: Routine use of empirical antifungal therapy is not recommended.

Antifungal Prophylaxis

- *High-risk patients*: Prophylaxis for Candida is recommended in high-risk patients.
  Prophylaxis for aspergillosis must be offered for patients who are undergoing intensive chemotherapy for acute myeloid leukemia and myelodysplastic syndrome.
- *Low-risk patients*: Not recommended.

Antiviral Prophylaxis

Patients undergoing allogeneic HSCT or leukemia induction therapy and are seropositive should receive a HSV prophylaxis with acyclovir.

Hematopoietic Growth Factors (G-CSF or GM-CSF)

- Not generally recommended for treatment of established fever and neutropenia.

TUMORS OF THE CENTRAL NERVOUS SYSTEM

Central nervous system tumors are the second most common childhood malignancy after leukemia. About 20–25% of all childhood malignancies are CNS tumor and a major cause of cancer-related death.

EPIDEMIOLOGY

Incidence is about 35 cases per million children under 15 years of age. Major lesions are infratentorial (60–70%) and rest are supratentorial (30–40%).

ETIOLOGY

Etiology of CNS tumors is not known. There is some predilection in certain conditions like:

- Turcot's syndrome
- Neurofibromatosis type 1
- Tuberous sclerosis
- Von Hippel-Lindau syndrome
- Previous cranial radiotherapy
- Gorlin's syndrome.

CLASSIFICATION

The WHO has classified CNS tumor vividly. Here main types of CNS tumors are mentioned:

- Gliomas
  - Astrocytoma (90%)
    - Low-grade glioma (30%)
    - Moderate-grade glioma (astrocytoma) (45%)
    - High-grade glioma (glioblastoma multiforme) (10%)
    - Brain stem glioma (<5%) (Figs 57 and 58)
  - Ependymoma (10%).
- Primitive neuroectodermal tumors (PNETs)
  - Supratentorial: Pineoblastoma
  - Infratentorial: Cerebellar medulloblastoma.
- Craniopharyngioma.

CLINICAL FEATURES

Some common signs and symptoms are encountered in a variety of CNS tumors. These are as follows:

- Headache: Headache worsens in the morning, improves throughout the day suggestive of CNS malignancy. In younger child, headache presents as irritability.
- Seizures: Usually focal.
- Mental disturbances:
  - Somnolence
  - Irritability
  - Behavior or personality change
  - Decreased school performance.
- Impaired vision:
  - *Diplopia (6th cranial nerve palsy)*: Presents as blinking or intermittent strabismus
  - Strabismus and ptosis (Fig. 57)
  - *Papilledema due to raised intracranial pressure (ICP)*: Presents as intermittent blurred vision
  - *Perinaud's syndrome*: Failure of upper gaze, setting sun sign, large pupils and decreased constriction to light.
- Cranial enlargement
- Cranial nerve abnormalities
- Disturbances of gait and balance
- Vomiting (often early morning).
- Endocrine abnormalities: Midline CNS tumors (supratentorial) due to effects of the hypothalamus or pituitary gland or visual pathway.
- Diencephalic syndrome:
  - Presents with sudden failure to thrive or emaciation in children aged 6 months to 3 years

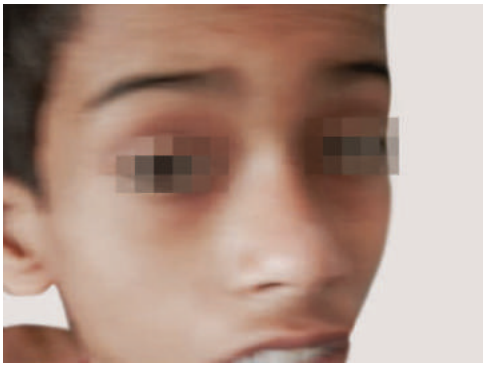


Fig. 57: Left-sided ptosis and medial squint in a child with CNS tumor

  - Caused by hypothalamic tumor in the anterior portion of hypothalamus or anterior floor of third ventricle.
- Spinal tumors may present with:
  - Spinal deformity
  - Back pain
  - Gait disturbances
  - Sensory abnormalities
  - Muscle power/tone abnormalities
  - Sphincter impairment.

LABORATORY INVESTIGATIONS

- Imaging:
  - CT scan: About 95% CNS tumors are detected by CT scan. Bony destruction and calcification are evident by CT scan (Fig. 58)
  - Magnetic resonance imaging scan: MRI is superior to CT scan in tumor localization especially posterior fossa tumor (Figs 59A and B)
  - Magnetic resonance spectroscopy: Useful in distinguishing malignant and necrotic areas
  - PET scan: Helps in determination of transformation of low-grade tumor (primarily glial) to a higher grade neoplasm and separation of post therapy, especially postradiation, treatment effects from tumor progression.
- Colony-stimulating factor analysis: Following parameters are studied from CSF analysis in suspected case of CNS tumors:

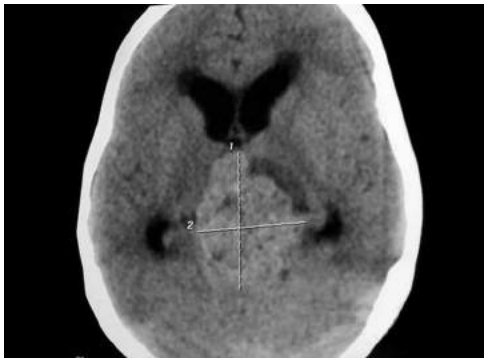
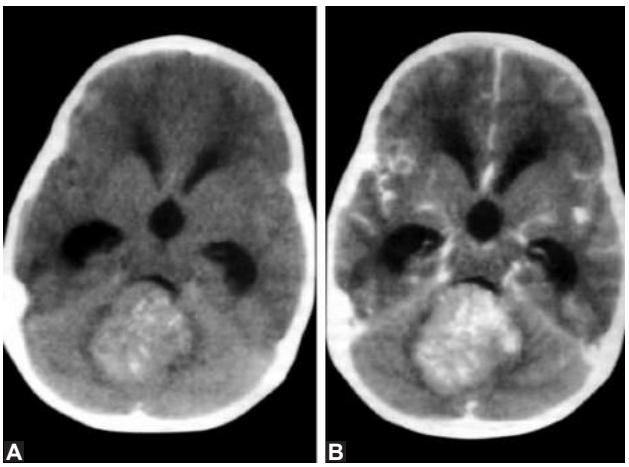


Fig. 58: Axial CT of brain of the child showing space-occupying lesion (SOL) involving brain stem (supratentorial) encroaching bilateral thalamus



Figs 59A and B: Axial CT of the brain showing a large posterior fossa mass, homogeneously enhancing after contrast material injection, associated with triventricular hydrocephalus in a 6-year-old female

  - Cell count with cytocentrifuge for cytology of tumor cells
  - Glucose and protein
  - Alpha-fetoprotein (AFP)
  - Human chorionic gonadotropin (hCG).

  (Both AFP and hCG may be elevated in nongerminomatous CNS germ cell tumors)
- Immunohistochemistry: Immunohistochemical markers help in establishment of diagnosis of ambiguous cases of pediatric CNS tumors.
- Bone marrow and others:
  Bone marrow and bone scan are indicated in patients with medulloblastoma/embryonal tumors and supratentorial PNET, because of risk of extraneural dissemination.

MANAGEMENT

Prior to start treatment for CNS tumor following evaluation must be done:

- Ophthalmologic and endocrine assessment
- Audiogram
- Glomerular filtration rate (GFR) prior to chemotherapy
- Routine hematological and biochemical assessment before starting chemotherapy
- Sperm cryopreservation should be considered for adolescent males undergoing intensive chemotherapy.

MODALITIES OF MANAGEMENT OF CNS TUMORS

Neurosurgery

Surgery is usually the first step of treatment of most of the tumors.

Radiotherapy

Most of the children (usually above 3 years of age) require radiotherapy.

Chemotherapy

Routine adjuvant chemotherapy is indicated for primitive embryonal tumors, high-grade gliomas, intracranial germ cell tumors, low-grade gliomas of optic pathway affecting vision or other low-grade gliomas presenting at a very young age and/or progressing despite radiotherapy.

OVERVIEW OF MANAGEMENT OF INDIVIDUAL CNS TUMORS

Low-grade Glioma

- Most are cured by surgery alone
- Unresectable tumors are treated with radiotherapy or chemotherapy in older children.

High-grade Glioma

- Occurs in older children
- These are often supratentorial and completely unresectable
- Prognosis is poor.

Brain Stem Glioma

- Inoperable
- Response to radiotherapy and chemotherapy is variable
- Median survival less than 1 year.

Ependymoma

- Can be removed completely by surgery
- Radiotherapy or chemotherapy is used in addition in cases of inoperable tumors
- Survival rate is greater than 70%.

Primitive Neuroectodermal Tumors

- Resection and craniospinal radiotherapy are the basis of treatment with additional chemotherapy
- Survival rate for localized medulloblastoma is 50% in less than 3 years but 80% in greater than 3 years
- Long-term morbidity is due to prolonged radiotherapy.

Craniopharyngioma

- Completely resectable in most cases (80%).
- Survive for a long time but with significant complications like hypothalamic dysfunction, vision impairment and behavioral problems.

LANGERHANS CELL HISTIOCYTOSIS

Langerhans cell histiocytosis (LCH) is characterized by aberrant proliferation of a cell type normally found as epidermal histiocytes—the Langerhans cell (LC). In 1953 having identified abnormal histiocytes in three-related syndromes, eosinophilic granuloma of bone, Letterer-Siwe disease and Schüller-Christian disease, Lichtenstein grouped them together as "histiocytosis X (HX)"-related manifestation of a single nosologic entity.

Novel intracellular granules called "Birbeck granules" in histiocytosis in HX lungs and bone lesions were recognized in 1950s. Tissues characteristically involved in LCH are bone, skin, lung, liver, spleen, bone marrow, lymph nodes and the hypothalamic pituitary regions. Depending upon organ involvement, staging distinguishes between single-system (SS) and multisystem (MS) disease. In the context of MS disease, involvement of certain tissues—bone marrow, liver, spleen and lungs—so-called risk organ positivity (MSRO+), is associated with a worse prognosis. In case of SS, bony or nodal disease several sites can be involved, which is then described as multifocal (MF) disease (Fig. 60).

Epidemiology and Etiology

There is still debate about whether the disease is malignant or reactive as the natural history ranges from spontaneous remission to chronic reactivating disease to multiorgan failure through rapidly progressive, fatal condition. There are reports of LCH occurring in association with other malignancy. Children previously treated for T-cell ALL may develop LCH; the cells share genetic rearrangements with the original leukemic clone. After treatment of LCH with etoposide, patient may develop AML, a therapy-induced second malignancy.

- A genetic predisposition may exist in some cases
- There is no convincing evidence implicating specific environmental factors or infectious agents, although several studies have looked at the role of viruses in the etiology of LCH
- Cigarettes have been implicated in a particular form of lung LCH seen predominantly in young adults

Langerhans cell histiocytosis is a rare disease. French study has given an estimated annual incidence of 4 per million children (age 0–14 years).

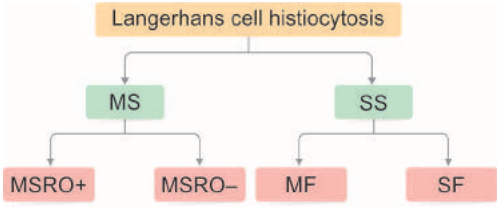


Fig. 60: Staging of Langerhans cell histiocytosis (LCH)

Abbreviations: MS, multisystem; SS, single-system; MSRO+, multisystem risk organ positive; MSRO−, multisystem risk organ negative; MF, multifocal; SF, single focus

Presentation

the time interval between onsets of symptoms and diagnosis is variable. The shortest time is for patients with MSRO+ disease (median 9, range 3.1–26.7 weeks). Presentation depends on organ involvement and staging at presentation.

Single-system LCH Presentation

In SS-LCH, common presentations are:

1. Bone involvement (previously known as eosinophilic granuloma)
   - Skull is most commonly involved (painless lump fluctuant on examination)
   - Proptosis due to lesion in orbit
   - Aural discharge due to mastoid involvement
   - Cervical pain and torticollis due to lesion of odontoid peg.
2. Cutaneous presentation (present in 3–10% of SS type of LCH)
   - May present as eczematous rash (Fig. 61)
   - In neonate may present as vesicles with wheal and flare (Fig. 62).

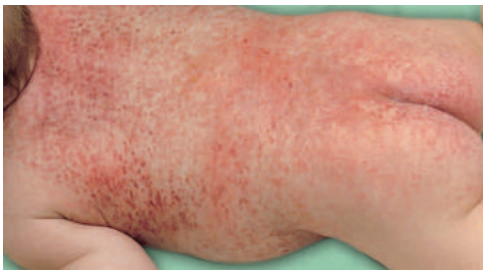


Fig. 61: Rash in multisystem type of LCH showing skin lesion mimicking seborrheic dermatitis

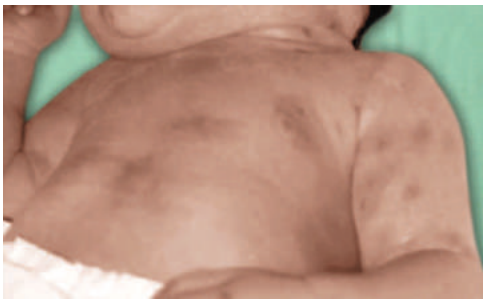


Fig. 62: Neonatal cutaneous Langerhans cell histiocytosis showing vesicles with surrounding inflammatory wheals

3. Other rare presentation of SS-LCH
   - Localized lymphadenopathy
   - Increased thirst due to diabetes insipidus (DI) due to posterior pituitary involvement.

Multisystem LCH Presentation

Multisystem Risk Organ Negative (MSRO−):

Up to 50% present with bone involvement.

Other manifestations:

- Skin disease (Fig. 61)
- Increased thirst due to DI due to posterior pituitary lymph node involvement.

Multisystem Risk Organ Positive (MSRO+):

- Mostly present in infancy with extensive skin rash with failure to thrive
- Up to 50% have bony lesions
- Risk organ involvement presents as cytopenia (bone marrow infiltration), increased liver enzyme due to liver involvement, respiratory distress due to lung involvement and hepatosplenomegaly.

Diagnosis and Staging

detailed history is important to ascertain past or current symptoms indicating involvement of a particular organ system which should include odd rashes, atypical musculoskeletal pain, aural discharge and excessive thirst.

The diagnosis of LCH is confirmed by the characteristic morphology and the presence of CD1a or CD207 (langerin) positive histiocytic cells.

The presence of Birbeck granules in tissue biopsy (skin, bone, lung, etc.) is also diagnostic which is currently rarely used.

Further Investigations

investigations should include skeletal survey, liver enzymes, abdominal US, urine osmolarity, biopsy of the skin, bone, lymph nodes, MRI of brain for the purpose of staging of LCH and to know the extent of the disease.

Skin

A punch biopsy should be obtained from an area of clearly active disease.

Lymph Node Biopsy

Lymph nodes draining involved bone or skin may be affected. Occasionally LCH may occur in isolated nodes.

Skeletal Survey for Bone Involvement

Plain X-ray of the majority of bone lesions will demonstrate the characteristic punched out (Fig. 63), radiolucent appearance. Having found a lesion, CT or MRI may help ascertain the extent and character of the lesion prior to biopsy. Recently, whole-body PET CT and MRI have been proposed as more sensitive modalities.

Investigations of Hypothalamic-pituitary Axis

In the absence of symptoms, a normally concentrated early morning urine is adequate to exclude DI in a child with LCH;

Fig. 63: X-ray skull showing typical moth-eaten appearance of skull bone found in LCH

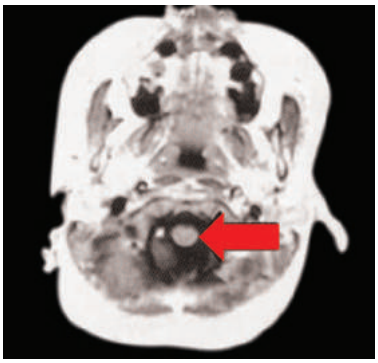


Fig. 64: Magnetic resonance imaging (MRI) of brain showing thickening of the stalk (red arrow) and absence of posterior bright spot of pituitary gland

otherwise a formal water deprivation test is necessary. MRI of brain should be done. MRI features compatible with pituitary LCH should be seen which is characterized by thickening of the stalk and absence of posterior bright spot (Fig. 64).

Lungs

As it is often asymptomatic, lung involvement should be considered in all cases of MS disease. X-ray chest may show interstitial infiltrations. A classical honeycomb lung appearance may be seen with progression to reticulonodular changes followed by cyst formation. A high resolution CT scan of chest will give more clear picture of lung infiltration.

Liver and Spleen

The presence of hepatosplenomegaly or abnormal LFTs is required for staging purpose. In some cases, US, cholangiography and liver biopsy may be indicated.

Treatment

Single-system LCH

A single bony lesion may heal spontaneously after biopsy or respond to recurettage and injection of methylprednisolone acetate.

Bony lesions are generally exquisitely sensitive to oral prednisolone. A high-dose steroids may be required, especially in MF type of SS. A lesion in a base of skull or facial bone with significant intracranial extension or proptosis is designated “special site” disease. Pamidronate has been proposed for refractory cases and appears to be particularly helpful when pain is an issue.

Multisystem LCH

- Multisystem LCH, seen mainly in young patients (aged < 2 years), requires treatment with steroids and chemotherapy (vinblastine, etoposide or MTX)
- MSRO+ disease may have poor outcome. High-dose AML type of therapy is required in such cases
- Bone marrow transplantation is considered in poor prognosis patients if a suitable donor is found
- Diabetes insipidus is treated with DDAVP
- Orthodontic reconstruction is needed for loss of teeth
- Children with ear involvement should be followed up for regular audiometry and assessment. Early diagnosis of hearing loss and the use of hearing aids can significantly improve outcome.

Skin

For skin lesions, topical steroid and emollient can be used. Depending on the severity and extent of involvement, scarring can result in up to 30% of children who have had skin disease.

Prognosis

Greater than 80% survive long-term without significant sequelae. Survivor of MS or CNS disease may have lasting disabilities.

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18 Pediatric Dermatology

SKIN DISORDERS IN NEONATE

Normal Changes in Newborn Skin

The skin of the newborn is different from that of the adult. Neonatal skin is less hairy, has less sweat and sebaceous gland secretions. It is thinner, having fewer intercellular attachments and fewer melanosomes.

Transient Eruptions of the Newborn

These are number of innocent rashes occuring in infants. They are usually transient.

Transient Vascular Phenomena

Transient vascular phenomena may appear during the first 2–4 weeks of life. Acrocyanosis and cutis marmorata are the vascular phenomena developed may be due to cold stress.

Acrocyanosis

The hands and feet become variably and symmetrically blue in color without edema or other cutaneous changes.

Cutis Marmorata

Cutis marmorata is characterized by reticulated cyanosis or marbling of the skin, which symmetrically involves the trunk and extremities. Persistent cutis marmorata beyond the neonatal period signifies the presence of:

- Trisomy 18
- Down syndrome
- Cornelia de Lange syndrome
- Hypothyroidism
- Other causes of central nervous system induced neurovascular dysfunction.

Harlequin Color Change

- Etiology unknown
- When the infant lies horizontally and the dependent half of the body turns bright red in contrast to the pale upper half. Color shifting occurs when the infant is rolled from side to side
- This phenomenon lasts from seconds to 20 minutes
- Recurrences are common until 3–4 weeks of life.

BENIGN PUSTULAR DERMATOSES

Several pustular lesions are benign in nature. These are as follows:

Erythema Toxicum Neonatorum (ETN)

- Erythema toxicum neonatorum is most common in term infant (70%)
- Usually appears on the second or third day of life
- These are erythematous, blotchy macules and papules of 2–3 mm diameter, which may evolve over several hours into pustules on a broad erythematous base to give affected infants a "flea-bitten" appearance (Fig. 1)
- Lesions may be isolated or clustered on the face, trunk and proximal extremities, and usually fade over 5–7 days
- Laboratory investigations:
  - Eosinophilia in 15–20% cases
  - Wright's stain of pustule shows sheets of eosinophils and occasional neutrophils.

Transient Neonatal Pustular Melanosis (TNPM)

- Transient neonatal pustular melanosis occurs in 4% neonate
- Black male infants are frequently involved

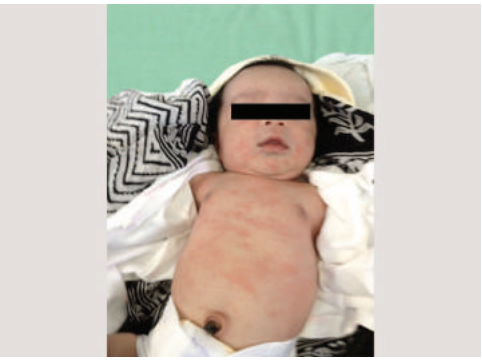


Fig. 1: An infant showing erythema toxicum over chest and trunk

- Transient neonatal pustular melanosis appears as 2–5 mm diameter pustules on a non-erythematous base on the chin, neck, upper chest, sacrum, abdomen and thighs. After several days, lesions develop a central crust, which desquamates to leave a hyperpigmented macule with a collarette of fine scale
- Investigation:
  - Wright's stain of the pustular smear shows numerous neutrophils and rare eosinophils.

Acropustulosis of Infancy

- Chronic, recurrent pustular eruption that appears on the palms and soles, but may also involve the scalp, trunk, buttocks and extremities
- In some infants scabies infestation may precede the onset of eruption
- Investigation:
  - Histopathology of the lesions reveals sterile, intraepidermal pustules
  - Wright's stain shows numerous neutrophils and occasional eosinophils.
- Treatment:
  - Oral dapsone (1–3 mg/kg/day)
  - Topical corticosteroids.

Eosinophilic Pustular Folliculitis (EPF)

- Rare, self-limiting vesiculopustular eruption of infancy
- It occurs almost exclusively in boys of age 5–10 months and can recur for months to years
- It is characterized by recurrent episodes of 2–3 mm diameter follicular white vesicle sand pustules on a red base on the scalp and forehead
- Investigation:
  - Wright's stain preparations of material from pustules show large numbers of eosinophils, but no evidence of bacterial, fungal or viral organisms.
- Treatment is symptomatic.

Other Papulopustular Rashes

Benign pustular dermatoses are different from herpes simplex infection by the absence of multinucleated giant cells on Wright-stained smears of pustular contents. Negative-Gram stain and potassium hydroxide preparations exclude bacterial and candidal infection.

Other innocent papulopustular rashes include sebaceous gland hyperplasia, miliaria, milia and acne.

Sebaceous Gland Hyperplasia

- Commonly found over the nose and cheeks of term infants
- Results from maternal or endogenous androgenic stimulation of sebaceous gland growth
- Papules are of multiple number, yellow in color and 1–2 mm in diameter
- Eruption resolves within 4–6 months.

Miliaria

- Occurs frequently in term and preterm infants after the first week of life in response to thermal stress
- Miliaria results from obstruction to the flow of sweat and rupture of the eccrine sweat duct
- Lesion's eruption crops in the intertriginous areas, scalp, face and trunk. In older infants, lesions appear most commonly in areas of skin occluded by tight-fitting clothing.

The following types of miliaria occur in the neonate:

- *Miliaria crystalline*: Superficial, 1–2 mm diameter vesicles appear on noninflamed skin when the duct is blocked by keratinous debris just beneath the stratum corneum
- *Miliaria rubra (prickly heat)*: Small papules and pustules develop due to the obstruction in the mid epidermis (Fig. 2)
- *Miliaria profunda*:
  - Deep-seated papulopustular lesions
  - The duct ruptures at the dermal-epidermal junction.

Milia

- The lesions are pearly, yellow, 1–3 mm diameter papules on the face, chin and forehead (Fig. 3)
- Histology reveals miniature epidermal inclusion cysts that arise from the pilosebaceous apparatus of vellus hairs
- Milia usually resolve during the first month of life without treatment. Persistence beyond several months, possibility of the oral-facial-digital syndrome or hereditary trichodysplasia (Marie Unna hypotrichosis).

Acne

- Mild acne develops in up to 20% of newborns (Fig. 4)
- Usually closed comedones (white heads) predominate
- Open comedones (black heads), red papules, pustules and (rarely) cysts may also occur
- Lesions in volute spontaneously within 1–3 months, so no treatment is required
- Topical acne preparation may be indicated in severe cases.

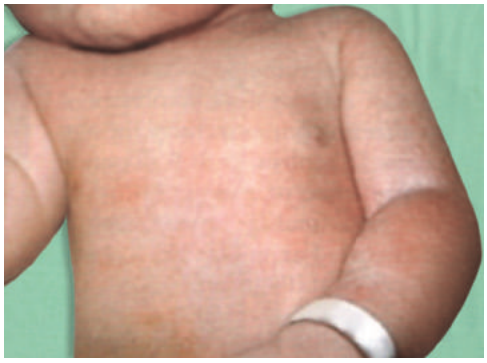


Fig. 2: Miliaria rubra

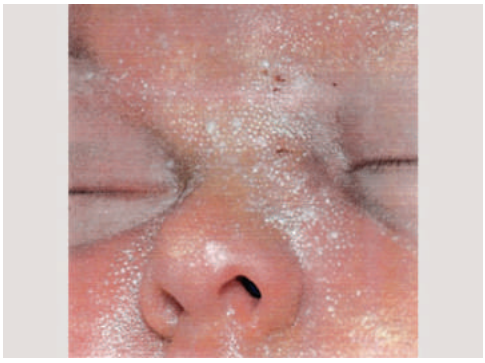


Fig. 3: Milia

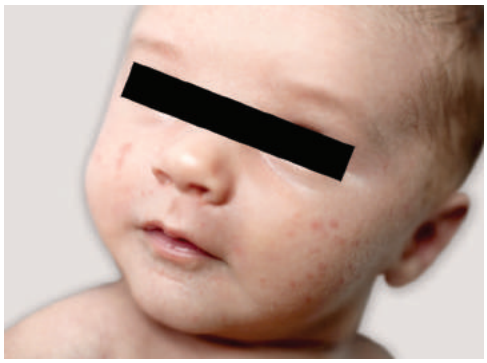


Fig. 4: Neonatal acne

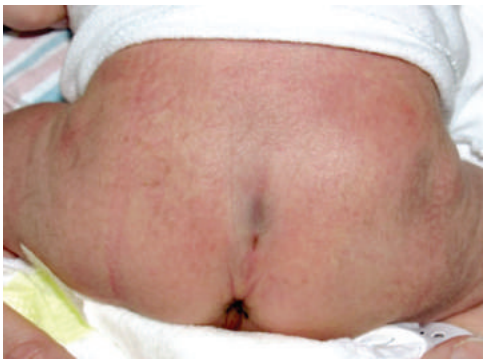


Fig. 5: Sacral dimpling a common mostly benign finding in neonate

Subcutaneous Fat Necrosis of the Newborn

- Rare, self-limited process that usually occurs in otherwise healthy full-term and post-mature infants.
- Discrete red or hemorrhagic nodules and plaques up to 3 cm in diameter appear most commonly over areas exposed to trauma, such as the cheeks, back, buttocks, arms and thighs, during the first few weeks of life. The lesions occasionally become fluctuant, drain and heal with atrophy
- Lesions are usually painless, occasionally tenderness may be present
- Difficult deliveries, hypothermia, perinatal asphyxia and maternal diabetes predispose to the development of fat necrosis
- Histopathology demonstrates necrosis of fat with a foreign body giant cell reaction. Remaining fat cells contain needle-shaped clefts, and calcium deposits are scattered throughout the subcutis
- Nodules usually resolve without scarring in 1–2 months.

MINOR ABNORMALITIES OF NEONATAL SKIN

Periauricular Sinuses, Pits, Tags and Cysts

- Failure of fusion of brachial arches or clefts gives rise to periauricular sinuses, pits, tags and cysts occur.

Dimpling

- Dimpling is commonly found over bony prominences, especially the sacral area (Fig. 5).
- Deep dimples in conjunction with sinus tracts or other cutaneous lesions (such as lipomas, hemangiomas, nevi and tufts of hair) may be associated with lumbosacral spinal anomalies.

Supernumerary Nipples

- May appear unilaterally or bilaterally anywhere along a line from the mid axilla to the inguinal area
- Malignant change may occur.

Supernumerary Digits

- Usually asymptomatic and familial.
- Most commonly as rudimentary structures at the base of the ulnar side of the fifth finger.

Umbilical Granuloma

- Commonly occurs during the first few weeks of life

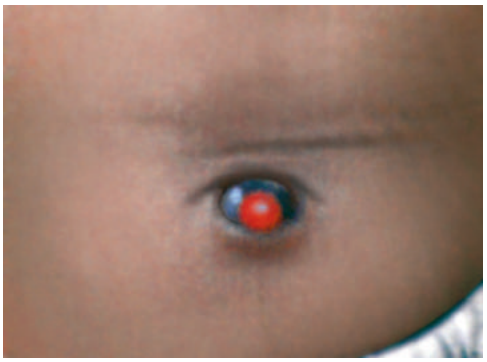


Fig. 6: Umbilical granuloma

- The open surface of a fallen cord epithelializes and scars down in an additional 1–2 weeks. Excessive moisture and low-grade infection may result in the growth of exuberant granulation tissue to form an umbilical granuloma (Fig. 6)
- Treatment:
  - Cauterization with copper sulfate
  - Repeated desiccation with repeated applications of isopropyl alcohol.

SKIN DISORDERS IN CHILDREN

Atopic Dermatitis

It is a common condition severely affecting 1–2% of school children. It is a chronic inflammatory skin disease in children who have genetic propensity of immunoglobulin E (IgE) mediated type I response (atopy) to environmental allergens, hence the term atopic dermatitis. The same atopic process is involved in hay fever and childhood asthma.

Etiology and Pathophysiology

- *Atopy*: 70% have a family history of atopy (eczema, hay fever or asthma). Immune abnormality is the primary immunological abnormality with production of allergen specific IgE. Various allergens such as animal or foods may exacerbate eczema. Th1 to Th2 system abnormality is found with increased production of Th2 cytokines which stimulate B cells to produce IgE and activate mast cells that cause increased vascular permeability.
- *Infection*: Endotoxin from *Staphylococcus aureus* (*S. aureus*) which colonize in the skin may trigger atopic dermatitis
- *Skin barrier function*: Dry skin predisposes to abnormal access of antigen, local infection and atopic dermatitis.

Clinical Features

- Usually appears 50% below 1 year of age and 90% under 5 years of age
- Early presentation include:
  - Erythema, scaling, intense itching, excoriation, weeping, secondary infection and sleep deprivation due to itching
- A family history of atopy is significant
- Examination:
  - The location and characteristics of lesion vary according to the age
  - In infants (below 2 months) face (Fig. 7) and scalp are usually affected
  - May affect any part of the skin but flexural regions are more affected
  - Child between 18 and 24 months (Fig. 8), flexures of knees and elbows are commonly involved
  - Thickening of skin (lichenification) over bony prominence may be detected
  - The papular form of skin lesion may be found over extensor surface particularly in Asian or black children
  - Allergic pleats (Fig. 9) may be detected as prominent in infraocular skin creases (Dennie-Morgan fold)
  - Hypopigmentation of face called pityriasis alba (Fig. 10) may be found.
- Late signs:
  - Late signs are characterized by lichenification and pigmentation changes (Fig. 11).

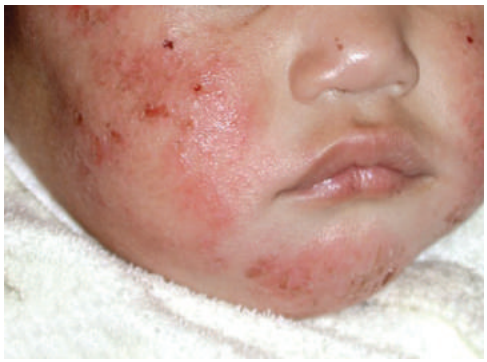
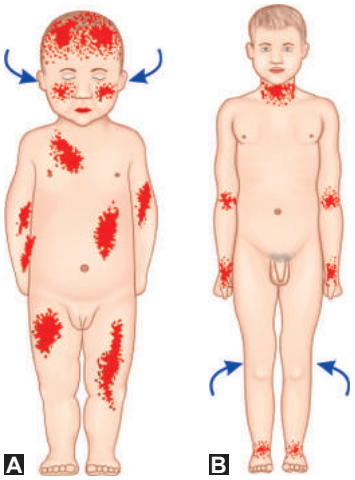


Fig. 7: Face of a child showing the lesions of atopic dermatitis



Figs 8A and B: Area of distribution of eczema. (A) In infant the areas are cheeks, scalp and behind ear; (B) Beyond infancy: skin flexure, particularly antecubital and popliteal fossae

Fig. 9: Dennie-Morgan fold seen in a child with atopic asthma and atopic dermatitis

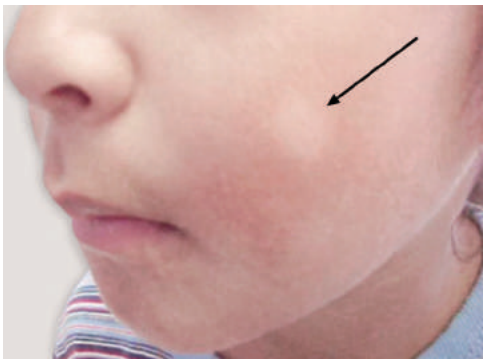


Fig. 10: Pityriasis alba (arrow)

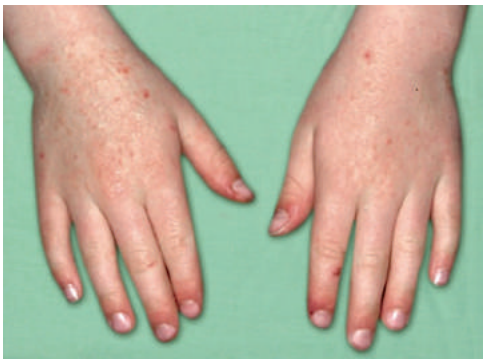


Fig. 11: Discrete lichenified papules on the dorsum of hands

Severity of Eczema

On the bassis of severity, eczema is classified as mild, moderate or severe as shown in Table 1. Its impact on quality of life and psychosocial wellbeing is given in Table 2.

Table 1: Skin/physical severity	
Clear	
	Normal skin, no evidence of active eczema
Mild	
	Areas of dry skin, infrequent itching (with or without small areas of redness)
Moderate	
	Areas of dry skin, frequent itching, redness (with or without excoriation and localized skin thickening)
Severe	
	Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking and alteration of pigmentation)

Table 2: Impact on quality of life and psychosocial well-being with atopic dermatitis	
None	
	No impact on quality of life
Mild	
	Little impact on everyday activities, sleep and psychosocial wellbeing
Moderate	
	Moderate impact on everyday activities and psychosocial well-being, frequently disturbed sleep
Severe	
	Severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep

Investigations

No investigation exists, although high IgE level is supportive. Allergy testing is generally not indicated.

Management

A step approach of management is used which depends upon severity.

General measures:

Diet:

- Exclusive breast-feeding during the first 6 months of life lowers the incidence of eczema in childhood
- Women who have breast-feeding children with eczema should be informed that it is not known whether altering mother's diet is effective in lowering the effect of the condition
- Offer 6–8 weeks trial of hydrolyzed protein formula or amino acid formula in place of cow's milk formula for bottle-fed infants aged under 6 months with moderate to severe eczema that has not been controlled with optimum topical corticosteroids and emollients. Children with cow's milk-free diet for longer than 8 weeks should be referred for specialist dietary advice.

Other measures

- Avoidance of trigger factors
- Clothing: Loose cotton clothing is preferable over synthetic or woollen fabric
- Avoid excessive heat
- Keep nails short and rub itchy-skin with palm of hand rather than scratch
- Napkin should be changed frequently
- Keep nappy area clean and dry
- Emollients:
  - Petroleum jelly
  - Liquid paraffin
  - Urea
  - Consider emulsifying ointment, soap substitute and bath oil
  - Zinc barrier cream: It can be added to protect the skin against moisture.

Specific measures: Stepwise treatment of atopic dermatitis

Mild:

- Emollients
- Mild potency topical corticosteroids

Moderate:

- Emollients
- Moderate potency topical corticosteroids
- Topical calcineurin inhibitors
- Bandages

Severe:

- Emollients
- Potent topical corticosteroids
- Topical calcineurin inhibitors
- Bandages
- Phototherapy
- Systemic therapy

Topical steroid: 1% hydrocortisone initially increase potency as required in exacerbation.

Topical calcineurin inhibitor (tacrolimus): 0.03% tacrolimus, particularly useful in face.

Sedative and histamine: To ease night-time itching and sleep deprivation.

Dry bandages and medicated dressings: Dry bandage with topical emollient with or without topical steroid in uninfected skin can be used in moderate to severe eczema.

Complications of Atopic Dermatitis

- Secondary bacterial infection.

Nappy Rash (Napkin Dermatitis)

Dermatitis that affects the area covered by nappy is termed as nappy rash or napkin dermatitis.

Clinical Features and Etiology

- Nappy rash results from prolonged occlusive contact of urine and feces with skin. Inner thigh and genitalia are affected as these areas remain the under cover of nappy. Flexures are not usually affected (Fig. 12). The pattern of involvement appears as the shape of W. The dermatitides are characterized by acute changes (erythema, edema and vesiculation) and/or chronic changes (scale, lichenification and increased or decreased pigmentation) in the skin
- Microscopically, these disorders show infiltration of the dermis with inflammatory cells, variable thickening of the epidermis and scale.

Differential Diagnosis and Complications of Nappy Rash

- Candidiasis:
  - In case of candidiasis, skin folds are involved with satellite lesions. The area becomes red and scaly (Fig. 13).
- Secondary bacterial infection with *S. aureus*.
- Extensive infantile seborrheic dermatitis (Fig. 14).

Treatment

- Nappy rash can be treated with greasy emollient and topical corticosteroid preparation with 1% hydrocortisone
- If complicated by fungal infection, topical antifungal (fluconazole) can be used
- Topical antibiotic like fusidic acid with topical steroid in case of secondary bacterial infection with *Staphylococcus*
- An antibiotic may be required in severe bacterial infection.

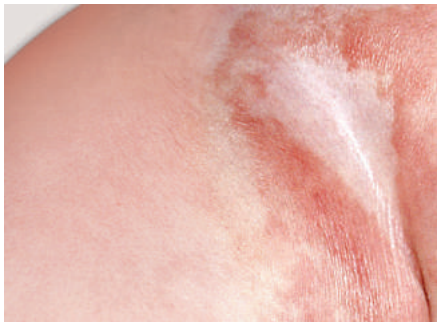


Fig. 12: Uncomplicated napkin rash (flexural are not affected)

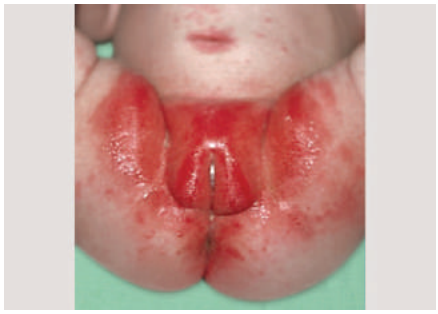


Fig. 13: Napkin rash in an infant due to candidal infection affecting skin folds (flexurals) with satellite spots

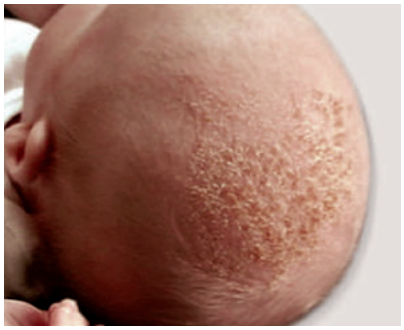


Fig. 14: "Cradle cap" seborrheic dermatitis

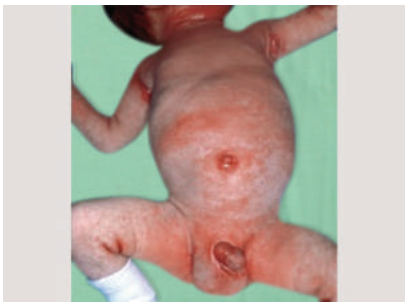


Fig. 15: Extensive seborrheic dermatitis

Prevention

As nappy rash or napkin dermatitis results from prolonged exposure to nappy, it can be prevented by using disposable nappies and frequent changing of nappies. Other measures include exposure and use of protective cream.

Infantile Seborrheic Dermatitis

Clinical Features

- Usually infants under 3 months of age are affected
- It starts as thick yellow scales on the scalp called "cradle cap" (Fig. 14) then spread to behind the ears, the folds of neck, axillae and nappy area (Fig. 15)
- Flexural folds in the groin may be involved.

Treatment

Seborrheic dermatitis can be treated with:

- Emollients (aqueous cream).
- Hydrocortisone (0.5–1%) alone with or without imidazole.

Psoriasis

Psoriasis is a chronic inflammatory disease characterized by well-demarcated erythematous plaques that demonstrate a characteristic silvery scaling. Psoriasis occasionally begins as persistent diaper dermatitis. There may be considerable clinical overlap with seborrheic dermatitis.

Epidemiology

- One-third of adults with psoriasis report onset in childhood
- Highest incidence is found among the Caucasians, black then Asian populations.

Etiology and Pathogenesis

The etiology of psoriasis is multifactorial. Major gene for psoriasis susceptibility is thought mainly to be located on chromosome 6, the site of *human leukocyte antigen* (HLA) class I (associated with early onset disease) and class II (late onset disease) antigens which are thought to produce different subtypes of the disease. Environmental factors have also a significant role.

There is over and underexpression of certain proteins in psoriatic lesions. The effects of these expressions are threefold:

- Abnormal keratinocyte differentiation
- Hyperproliferation of the keratinocyte
- Inflammatory infiltration.

The actions are mediated by activated T cells and dendritic cells that are present in psoriatic plaques. These cells release proinflammatory cytokines which trigger a cascade of cytokines that lead to keratinocyte proliferation, neovascularization and vasodilation.

Clinical Features

- Infants remain well, and the eruption may be asymptomatic
- Although lesions may disseminate to the trunk and extremities, the rash may continue in the diaper area alone for months
- The eruption is typically bright red, scaly and well-demarcated at the diaper line
- Lesions tend to persist or recur for months
- Itch is variable but mostly not a significant symptom.

Clinical Subtypes

Guttate psoriasis:

- Commonest type
- Sudden onset of multiple small "rain drop" like red papules of 0.5–2 cm diameter on trunk, face and limbs. Sometimes it may occur 1–4 weeks following β-hemolytic streptococcal infection. Lesion usually resolves in 3–4 months.

Plaque psoriasis:

- In this type, there develops thick, larger, scaly, erythematous plaque predominantly on extensor surface of elbow, knee and scalp.

Flexural psoriasis:
- Lesions are macerated and scales are little
- Often involves the napkin areas first.

Nail psoriasis (Fig. 16):
- May precede skin lesion
- Lesions are superficial pits, onycholysis and subungual hyperkeratosis.

Differential Diagnosis

Differential diagnosis includes other papulosquamous disorders of childhood which include:
- Atopic dermatitis
- Discoid eczema (nummular dermatitis)
- Tinea corporis
- Lichen planus
- Drug reactions
- Pityriasis rosea
- Pityriasis rubra pilaris.

Diagnosis

Psoriasis primarily is diagnosed clinically and classified on the basis of morphology. It presents mostly as well-demarcated erythematous lesions with fine or coarse "silvery" scaling (Fig. 17). Psoriasis in the nappy areas will generally have no scale and the diagnosis is made on the "salmon-pink" color of the erythema and the well-demarcated borders of the plaques.

Investigations

Skin biopsy is the only way to confirm the diagnosis.

Treatment:

Topical treatment:
- Emollient and soap substitutes to reduce scaling and pruritus
- Dithranol: Available as cream preparation. It is useful for large thick plaques
- Coal tar
- Topical steroid: Can be used as monotherapy for management of itch.

Systemic therapy:

- For severe, resistant or complicated psoriasis systemic drugs, like ciclosporin, retinoids and anti-TNF antibodies, may be used.

Phototherapy:

- Narrow band ultraviolet B (UVB) phototherapy or psoralen + UVA (PUVA), but long-term risk of skin cancer.

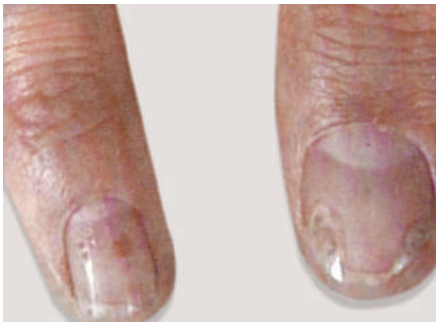


Fig. 16: Psoriatic fingernails

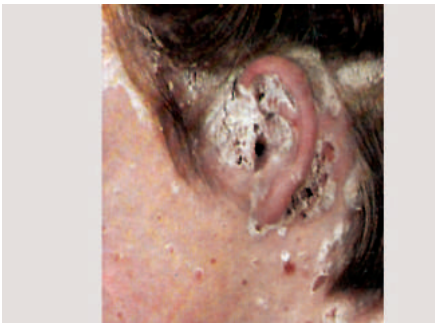
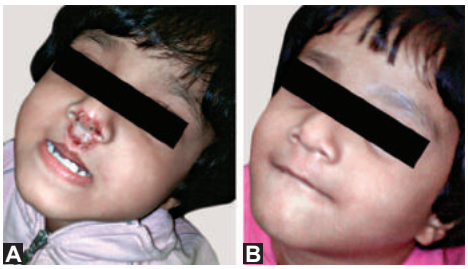


Fig. 17: Silvery scaling of psoriasis



Figs 18A and B: (A) Impetigo contagiosa before treatment; (B) Same child after treatment with topical antibiotic

INFECTIOUS DISEASE OF SKIN

Infections and infestations of the skin form a large proportion of skin diseases in children, especially in the tropics, but also in temperate areas. Major infections include bacterial, viral and fungal infection.

Bacterial Infections

Impetigo

Impetigo contagiosa (Figs 18A and B): Impetigo contagiosa is a common superficial infection in children producing classical appearances of inflammation with yellowish crusting and superficial erosion.

Causative agents:
- Frequently by *S. aureus*, or by *Streptococcus pyogenes* (*S. pyogenes*) or a combination of the two
- Streptococcal impetigo presents with fever, malaise or lymphadenopathy.

Treatment:
- Topical antibiotics like mupirocin and fusidic acid for localized impetigo
- Systemic treatment: Flucloxacillin, erythromycin or cephalosporin

Bullous impetigo: It is a superficial infection caused by an exfoliative toxin-producing strain of *S. aureus*.

Clinical features:
- The eruption arises at the site of inoculation and presents first with mild discomfort or irritation, evolving rapidly to fragile fluid or pus filled blisters that produce little crusting when they rupture.

Treatment:
- Topical antibiotics for bullous impetigo.
- Systemic antibiotics: Flucloxacillin, erythromycin or cephalosporin depending on antistaphylococcal sensitivity.

Staphylococcal Scalded Skin Syndrome (SSSS)

It is the systemic infection caused by Staphylococcus involving soft tissues, with or without throat involvement (it is also discussed in Chapter "Infectious Disease").

Clinical features

- Fever.
- Skin discomfort mostly starting in the flexures.
- Affected skin is erythematous rapidly develops epidermal loss (Fig. 19).

Diagnosis

Diagnosis of bullous impetigo and SSSS is clinical. Following investigation may be done:

- Surface swab for culture and sensitivity
- Full thickness skin biopsy (rarely done in clinical practice) will demonstrate acantholysis of the epidermis as well an epidermal split within the subcorneal upper epidermis.

Treatment

General measures

- Keeping the skin surface dry and clean
- Application of dressing in case of severe erosion.

Specific measures

- No topical antibiotic for SSSS
- Intravenous (IV) antibiotics for severe SSSS: Flucloxacillin or cephalosporin depending on antistaphylococcal sensitivity.

Toxic Shock Syndrome (TSS) (also discussed in Chapter "Infectious Disease").

S. aureus is the causative agent for TSS. The bacterial enterotoxin, TSS toxin-1, is also the cause of a severe illness with widespread eruption in neonates, when the condition is termed neonatal toxic shock syndrome-like exanthematous disease.

Clinical features:

- General malaise
- High pyrexia
- Shock
- Diffuse macular pale erythematous eruption
- Desquamation follows approximately 2 weeks later.

Necrotizing Fasciitis

It is the soft tissue infection caused by a variety of organisms including *S. aureus* (including methicillin-resistant strains), *S. pyogenes, Klebsiella pneumoniae* and other bacteria such as *Bacteroides* species. Predisposing factors include diabetes, malnutrition, preexisting superficial skin infection and IV cannulae.

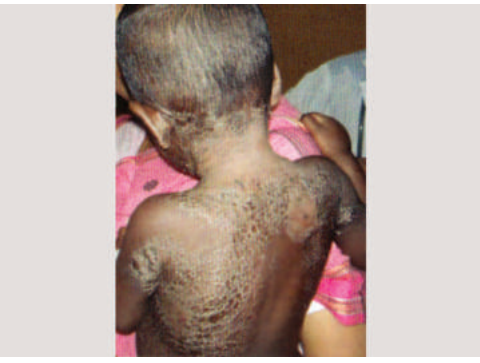


Fig. 19: Manifestation of staphylococcal scalded skin syndrome

Clinical features:

- Lesion starts with a small skin infection such as a boil or surface wound, evolving into localized cellulitis then spreads rapidly. Areas of purplish discoloration can be seen within the cellulitic area
- High fever
- Marked general malaise.

Treatment:

- General supportive measures: Analgesic to control pain
- Surgical treatment: Surgical removal of gangrenous tissue
- Antimicrobial therapy: IV broad spectrum, including antistaphylococcal and antistreptococcal antibiotics should be started immediately and before sending sample for culture and sensitivity.

Viral Infections Affecting Skin (Also Discussed in Chapter "Infectious Disease")

Herpes Simplex

Herpes simplex virus usually affects skin and mucous membrane.

- Herpes simplex Type I: Usually causing herpes of the mouth, lips and nongenital skin
- Herpes simplex Type II: Predominantly affects the genital area.

Clinical features:

Primary infection:

- May be subclinical, but recurrent episodes present with lesions on the vermillion border of the lip, perioral skin, nasal mucosa or cheek
- Prodromal phase of fever, malaise and tender lymphadenopathy typically occurs 3–7 days following exposure
- In children: Gingivostomatitis with mouth ulceration, vesicles over the lips, sore throat and fever
- Dysphagia and drooling due to edema, pain and ulceration of the oropharyngeal membranes.

Reactivation: Reactivation may be precipitated by various factors including fever, UV light, trauma and the menses.

Treatment:

- No treatment is required, as the episodes are self-limiting with lesions crusting over and healing in 2–6 weeks
- Antiviral, like aciclovir, famciclovir or valaciclovir, may be used.

Complications:

- Herpes keratitis
- Encephalitis
- Eczema herpeticum (Kaposi varicelliform eruption).

Neonatal herpes:

- Incidence is 1 in 2,000–5,000 deliveries
- Localized or disseminated small 1–3 mm vesicles are present at birth or appear on the skin up to 7 days after delivery and may progress to large, 1 cm bullous lesions (Fig. 20).

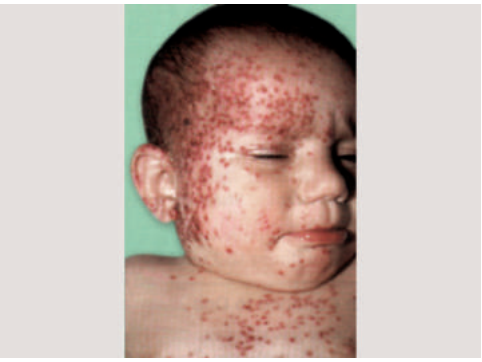


Fig. 20: A case of generalized neonatal herpes

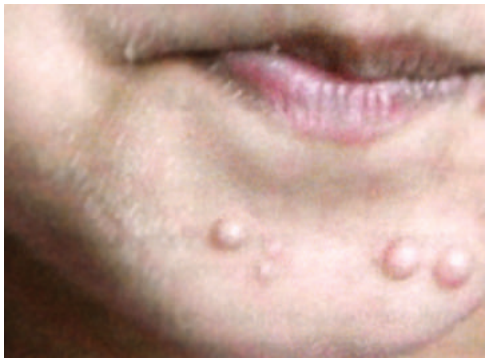


Fig. 21: Molluscum contagiosum

- Keratoconjunctivitis and chorioretinitis may occur
- Infection is acquired from mothers with active infection of the cervix, vulva or perineum at the time of delivery
- Disseminated infection may present with encephalitis, liver or adrenal involvement.

Varicella Zoster (Chickenpox) (Also Discussed in Chapter "Infectious Disease")

- Typically affects children under the age of 10 years
- Spread is by droplets from the upper respiratory tract or contact with infected vesicular fluid
- Crops of lesions appear initially on the trunk and spread to the face, scalp and limbs
- Lesions begin as faint erythematous macules that progress to edematous papules and then to vesicles within 24–48 hours. Individual lesions develop crusts that shed to leave shallow erosions. Crops of lesions appear to reveal several stages of lesion at any one time. Lesions may involve the mucous membranes of the conjunctiva, oral cavity or nasal mucosa
- Complications are high fever, encephalitis, pneumonia, hepatitis or disseminated intravascular coagulation in immune-compromised patients
- Treatment:
  - Only supportive treatment is required.
  - Antibacterial chemotherapy may be required to treat secondary bacterial infection.
  - Systemic IV antiviral therapy is required in immune-compromised patients with complications.

Molluscum Contagiosum

Molluscum contagiosum is caused by a type of pox virus.

Source of infection: Occurs following contact with an infected individual or contaminated object, for example swimming pools.

Vulnerable group: Common in patients with disorders of T cell function, particularly:

- Atopic dermatitis
- Congenital immunodeficiency
- Lymphoproliferative disorders
- HIV infection.

Incubation period: Up to 6 months.

Clinical features:

- Asymptomatic flesh-colored papules with a central depression (umbilication) appear on the skin, predominantly on the face and neck (Fig. 21).

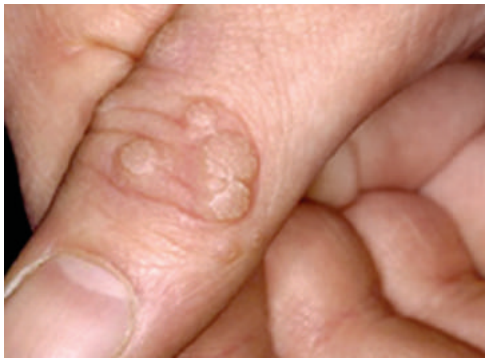


Fig. 22: Warts on hand: Typical hard, raised, verrucous tumor with irregular horny surface

- In children, molluscum are seen quite commonly on the genital, perineal and surrounding skin and do not indicate abuse unless there are other suspicious features.

Outcome: Individual lesions often become inflamed or eczematous shortly before resolving spontaneously after about 2 months.

Viral Warts

Warts are caused by human papilloma virus. The incidence is high between the ages of 12 and 16 years.

Incubation period: Average incubation period is 4 months (range between 1 and 20 months).

Clinical features and types:

Common warts:
Discrete flesh-colored papules having a rough surface and may occur anywhere on the skin, but are particularly common on the hands and feet.

Plane warts:

- Often persistent flesh-colored, flat spots mainly occur on the face, hands and limbs (Fig. 22)
- May be pigmented and slightly raised
- Lesions often occur in lines of trauma such as those corresponding to scratching (the Koebner phenomenon).

Plantar warts (verrucas):

- Verrucas can penetrate deeply into the soles of feet due to body-weight pressure
- May be painful and impair walking
- Thrombosed capillaries are often seen as black specks on their surface, which aids with differentiation from simple corns.

Mosaic warts:
Mosaic warts are particularly resistant to treatment and present as plaques of roughened skin on the soles and palms that are usually asymptomatic.

Anogenital warts:
- Anogenital warts in children are usually caused by autoinoculation and are rarely secondary to sexual abuse
- Vertical infection to the newborn may occur following delivery through an infected birth canal.

Treatment of warts: Treatment is not usually required. Following are the options for cosmetic purpose:
- Topical preparations containing salicylic acid or glutaraldehyde
- Cryotherapy
- Cryospray for children.
  Treatment should be repeated at 2–4 weeks interval.

Prognosis and outcome of warts: Warts involute spontaneously, and in children virtually all warts disappear within 3 years.

Fungal Infection

In childhood, skin manifestation of superficial fungal infection include: dermatophytes, tinea versicolor and candidiasis.

Dermatophytes

Dermatophytes caused by fungi that parasitize keratin-rich structures such as the outer layer of the epidermis (stratum corneum), hair and nails.

Tinea capitis:
- Fungal infection of the skin and hair of the scalp that primarily affects prepubertal children between the ages of 3 and 7 years
- *Trichophyton tonsurans* (*T. tonsurans*) and *Microsporum canis* (*M. canis*) are the causative agents
- More common in boys probably due to shorter hair
- Incubation period is 1–3 weeks.

Clinical features:
- May be localized ringed form (Fig. 23) to one or more areas or may be diffused
- Alopecia with variable degree of erythema and scaling (Fig. 24)
- There may be boggy, tender plaque with pustules and a purulent discharge and overlying alopecia (kerion) (Fig. 24).

Diagnosis:
Microscopic observation of fungal elements in specimens of infected skin and hair.

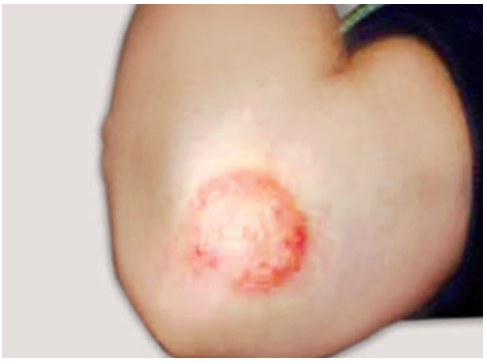


Fig. 23: Fungal infection of skin (ringworm)

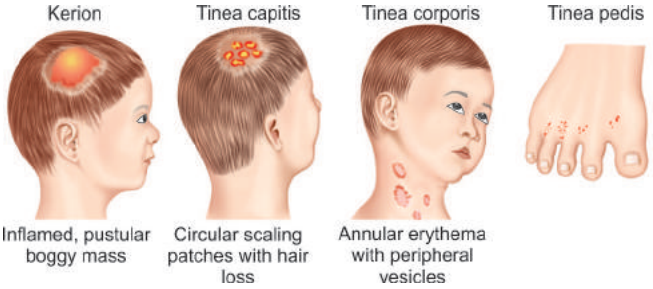


Fig. 24: Site and distribution of infection by dermatophytes

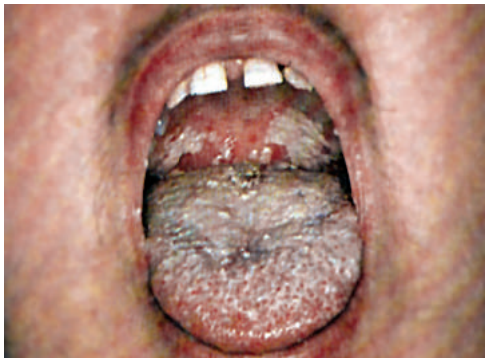


Fig. 25: Oral candidiasis: Erythema, edema and whitish coating of raucous membranes

Treatment:
- Griseofulvin: 10–20 mg/kg per day for minimum 6 weeks to a maximum period of 2–3months.
- Topical: Use of ketoconazole 2% shampoo twice weekly can effectively reduce infectivity.

Candidiasis

Newborns are susceptible to candidal infections mainly present as oral thrush or nappy rash candidiasis but may occur as intertrigo, vulvovaginitis, angular cheilitis or nail fold involvement (paronychia). It is acquired from the infected maternal vagina during birth, also from the skin of the mother's breast or hands, or from inadequately sterilized feeding bottles or pacifiers.

Clinical features:
Adherent white patches over the tongue, soft and hard palate and buccal and gingival mucosae which may be painful (Fig. 25). Nappy rash may occur with satellite spots simultaneously.

Diagnosis:
- Mostly clinical
- Examination of oral plaque under microscope
- Fungal culture.

Treatment:
Nystatin oral suspension four times daily for 1–2 weeks.

Tinea Versicolor/Pityriasis Versicolor

This is a common superficial skin infection in adolescents, caused by the yeast forms of the lipophilic fungus *Malassezia furfur*, rarely affects prepubertal children.

Clinical features:
- Multiple asymptomatic, oval, scaly macules (Fig. 26) distributed mainly over the sebum-rich skin on the upper

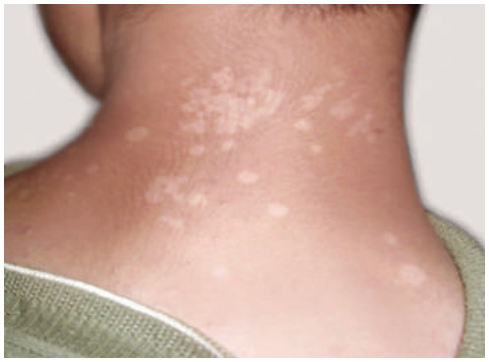


Fig. 26: Tinea versicolor with hypopigmented lesions

trunk and proximal arms, occasionally extending to the face and neck
- Lesions may be hypopigmented or hyperpigmented.

Differential diagnosis:
- Vitiligo
- Pityriasis alba
- Postinflammatory hypopigmentation or hyperpigmentation, pityriasis rosea.
- Tinea corporis.

Diagnosis:
Microscopy and culture of skin scrapings from the affected area.

Treatment:
Topical: Selenium sulfide 2.5% shampoo applied for 10 minutes daily over 1–2 weeks and/or ketoconazole 2% shampoo as a single application or used daily for 3 days.

Prognosis:
Response is good to treatment but recurs commonly.

SCABIES

Scabies is one of the common dermatological diseases in children. Scabies is caused by the mite *Sarcoptes scabiei* var. *hominis*.

Mite Biology and Life Cycle

- The scabies mite is an obligate parasite that burrows in the epidermis of human skin, on average within 30 minutes after first contact
- The adult mite burrows at 0.5 to 5.0 mm per day into the stratum corneum and deposits feces in its path; female mites also lay eggs
- Eggs hatch into larvae within 2–3 days, which then leave the burrow to mature on the skin surface. In 10–11 days, females mature into egg-laying adults
- The total life span of the adult female is approximately 5 weeks
- Adult mites have eight legs, making them easily distinguishable from less mature larval forms which have six legs
- During maturation on the skin surface, larval mite forms are capable of burrowing into the patient's epidermis or moving to a different host
- Mites can crawl as fast as 2.5 cm per minute on warm skin
- Scabies mites can survive off the human host and remain capable of infestation for an average of 24–36 hours at room conditions (21°C and 40–80% relative humidity) and up to 19 days in a cool, humid environment.

Transmission

Transmission of the mite from person to person is most likely within households in which close contact such as bed-sharing permits the mites to move directly from skin to skin.

Epidemiology

Scabies is a worldwide disease.
- All races and social classes in every climate from the coldest to the hottest regions are affected. Individuals of all ages are susceptible to scabies, but it is most common in the young, remains frequent in the older children and young adults, and thereafter sharply declines
- Highest prevalence is in children under 2 years old
- Scabies is found primarily in poor and overcrowded conditions but can affect all socioeconomic status without regard to level of hygiene.

Clinical Features

- Generalized pruritus of recent onset
- Characteristic eruption of scabies presents as pruritic papules, vesicles, pustules and linear burrows (Fig. 27). However, most patients only have an admixture of the primary lesions along with excoriations, eczematization, crusting and secondary infection
- Other members of the family particularly caretakers of child are similarly frequently affected (Fig. 28)
- Nocturnal itch is very characteristic of scabies

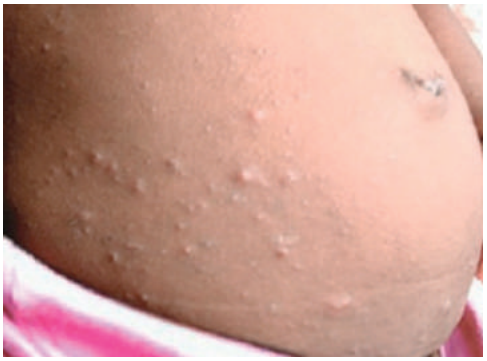


Fig. 27: Scabietic papules over the skin of abdomen

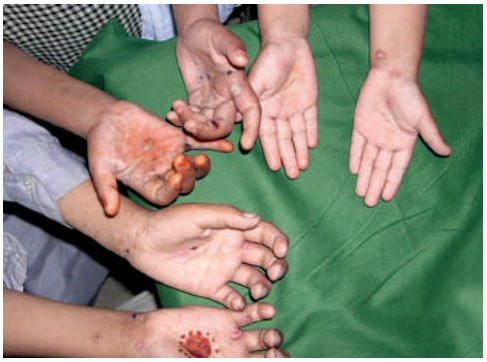


Fig. 28: Scabies affecting many members of same family

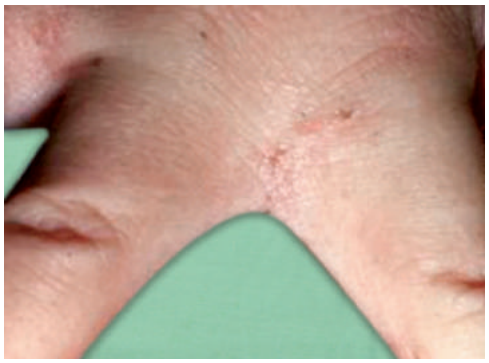


Fig. 29: Small linear burrow between fingers in scabies

- The pathognomonic scabies burrow (Fig. 29) is an elevated white and serpiginous tract measuring 0.3–0.5 mm by 10 mm length. Excoriations, crusting and eczematization may completely obscure these and any other primary lesion
- In infants, head, neck, palms and soles are involved.

Differential Diagnosis

Papular Urticaria

- Commonly affects young children between the ages of 2 and 10 years
- It manifests as scattered, excoriated papules and urticated lesion on the exposed parts. The lesion principally occurs on the lower legs and arms. This condition is basically an allergic condition and caused by the blood-sucking insects
- It can be differentiated from scabies by the absence of burrows and haphazard distribution of lesions.

Atopic Dermatitis

- Atopic dermatitis is characterized by itching and vesicopapular eruption predominantly in the flexors
- Lichenification and excoriations are seen in chronic patients
- Scabies can be differentiated by the presence of burrows and web space involvement.

Lichen Planus

Lichen planus presents as an itchy, violaceous papular eruption on the flexor aspects of the forearm, legs and back. The lesions may also occur in the oral cavity.

Dermatitis Herpetiformis

It is an itchy, chronic, symmetric, vesicopustular eruption predominantly involving the extensor aspects of the upper and lower extremities.

Infantile Acropustulosis

Characteristic lesions of acropustulosis of infancy are sterile vesicles and pustules in the palms and soles.

Investigation

Diagnosis of scabies is confirmed by the demonstration of the mite, eggs or the fecal pellets (scybala) in skin scrapings.

Diagnosis

Diagnosis of scabies is dependent upon the characteristic clinical features and demonstration of mite, egg or fecal pellete. Following features are diagnostic of scabies:

Suggestive Features

- Distribution of the lesions
- Burrows
- Nocturnal pruritus
- Contact cases
- Response to therapy.

Definitive Features

Microscopy of skin scrapings
Skin biopsy.

Treatment of Scabies

Both the mother/caretaker and the infant should be treated together. Proper instruction for the use of drugs should be provided to caregiver. Following instructions should be provided to parents/patients:

- The agent should be applied on a clean dry skin by the parent or under parental supervision
- The medication provided should be rubbed into the skin. All parts of the body from head downward, whether involved or uninvolved should be treated
- Treatment is best done at night before going to bed.
- Avoid touching any mucosa (oral or ocular) with your hands.
- Change underclothing and sheets the next day and launder them
- Everyone in the house should be treated at the same time
- Babysitter and caretakers also should be treated
- Itching may persist for few days after treatment but never reapply the medication without doctor's advice
- Report to your doctor after 1 week
- Always keep the medication out of reach from the children.

Drugs for Scabies Treatment

Topical agents:

- Permethrin 5% cream:
  - Very effective in infants over 2 months of age
  - It should be applied at bedtime and washed off in the morning
  - Treatment should be repeated after a week
- Lindane (gamma benzene hexachloride) 1% lotion or cream:
  - It should be always applied to cool dry skin
  - It acts on the central nervous system of the insects leading to increased excitability, convulsions and death
  - Lindane is not recommended in children under 10 years of age
- Benzyl benzoate 10% and 25% lotion or emulsion
- Precipitated sulfur 2–10% ointment.

Oral Drug:

- Ivermectin:
  - It is the only oral remedy of scabies
  - Ivermectin should be used with caution in children of age under 2 years old.

Instructions for the Use of Drugs Used for Scabies

1. *Lindane 1% lotion*: Apply thinly to the whole body from head to neck down and wash off completely after 8 hours

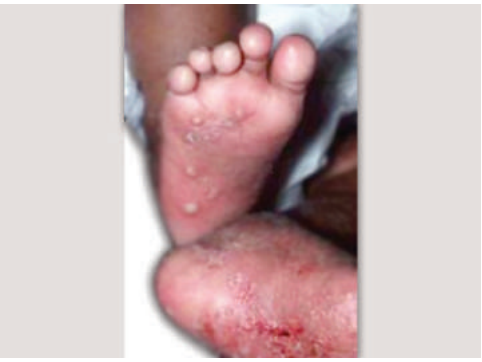


Fig. 30: Papulovesicular and pustular skin lesion in infected scabies

2. *Permethrin 5% cream*: Apply to whole body from the neck down and wash off after 8–14 hours
3. *Ivermectin*: 200 μg/kg administered orally for two doses at an interval of 2 weeks.

Complications of Scabies

- Superadded bacterial infections usually with *Streptococcus,* occasionally *Staphylococcus* (Fig. 30).
- Poststreptococcal glomerulonephritis following infection of scabies with *Streptococcus*
- Leukocytoclastic vasculitis.

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19 Joint and Bone Disorders

JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disease with significant long-term morbidity and mortality. It is previously known as juvenile rheumatoid arthritis (JRA).

Definition

It is defined as arthritis of unknown etiology beginning before the child's 17th birthday and persisting for at least 6 weeks and where known causes have been excluded. The hallmark of clinical presentation is arthritis.

Depending upon the number of joint involvement and other clinical features, JIA has been classified in various ways. On the basis of most recent consensus of task force on JIA of International League of Association for Rheumatology (ILAR), the classification of JIA has been recently made which is summarized in Table 1.

Etiology

Juvenile idiopathic arthritis is a complex polygenic multifactorial disease where multiple genes and environmental factor play role in causation of the disease.

Genetic Factors as Predisposing Factors

Various genetic factors are involved in various types of arthritis.

- Early onset (<5 years) oligoarthritis
  HLA DR5, DR6, DR8 and A2
- Late onset oligoarthritis
  HLA B27, rheumatoid factor (RF) positive polyarthritis, DR4, DW4, DR1.

Table 1: Subtypes of JIA (ILAR classification of JIA) and clinical features

Subtypes	Criteria
Oligoarthritis	Arthritis of four or fewer joints within the first 6 months
• Persistent	Affecting not more than four joints throughout the disease process
• Extended	Extending to affect more than four joints after the first 6 months
Polyarthritis	Arthritis of five or more joints within the first 6 months
• RF positive	Rheumatoid factor positive
• RF negative	Rheumatoid factor negative
Systemic arthritis	
Arthritis with or preceded by quotidian (daily) fever for at least 3 days, accompanied by one or more of: • Evanescent erythematous rash • Lymphadenopathy • Hepatomegaly and/or splenomegaly • Serositis (mandatory exclusion of infective and malignant condition; arthritis may not be present early in course)	
Psoriatic arthritis	
Arthritis and psoriasis or arthritis with at least two of: • Dactylitis • Nail pitting or onycholysis • Psoriasis in first-degree relative	
Enthesitis-related arthritis	
Arthritis and enthesitis or arthritis or enthesitis with two of: • Sacroiliac joint tenderness or inflammatory lumbosacral pain • HLA B27 antigen positivity	

Environmental Factors as Trigger Agents

Various infectious particularly viral: Parvovirus B19, rubella and *Mycoplasma pneumoniae* are involved in the pathogenesis of JIA.

Psychosocial Stress

Physical trauma.

Pathophysiology and Pathogenesis of JIA

Two important factors are involved:

1. Autoimmunity:
   - Failure of T cell and B cell to differentiate between foreign and self-antigen resulting in self-tissue damage
   - The chronic arthritides which include JIA are generally considered T cell-mediated
   - Activated T cells undergo differentiation which by Th1 response promotes inflammation by activating B cells like monocytes, macrophages, synoviocytes and osteoclast
   - Activated T cell may stimulate cytokine cascade to release proinflammatory cytokines by Th2 response.
2. Cytokines:
   - Proinflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), IL-6 are produced by macrophage and monocytes
   - TNFα in particular stimulates the production of cytokines mediators of inflammation
   - TNFα stimulates synoviocytes resulting in pannus formation, activation of osteoclast with articular erosion and reduced bone density (Fig. 1).

Clinical Significance of Understanding Pathophysiology of JIA

Therapeutic Cytokine Modulation

The understanding of pathophysiological pathways that control JIA or adult rheumatoid arthritis helped to discover biological agents that can replicate, mimic or block culpable molecules and so promote or inhibit cellular activity or proliferation of these agents. Cytokine antagonists have shown greatest promise, and TNF blockade has been identified as a dramatic clinical benefit in many children with JIA.

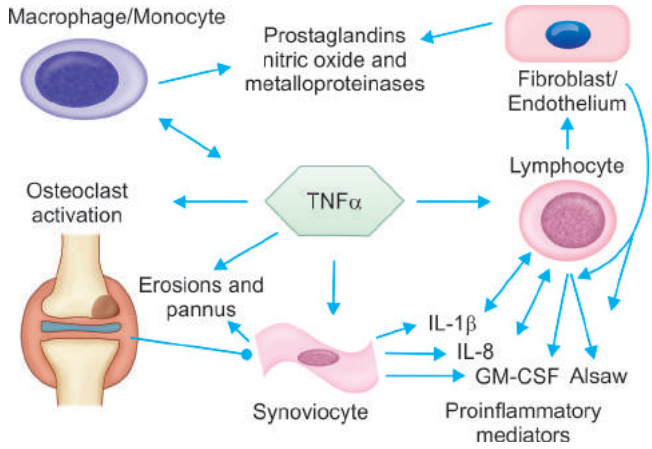

Fig. 1: TNF-α activity. Macrophages and monocytes are a major source of TNF-α, which in turn acts on these and other cells to stimulate the production of biochemical, enzymatic and cytokine mediators of inflammation. Further cellular activity ensues. Specifically TNF-α acts on synoviocytes resulting in pannus formation and together with the activation of osteoclasts, this results in articular erosions and reduced bone density

Clinical Features

Characteristics Clinical Features of JIA Which are Different from Adult Rheumatoid Arthritis

Clinical features depend on type of JIA as mentioned in Table 1. It differs from adult rheumatoid arthritis in the following ways:

- Unlike adult rheumatoid arthritis, clinical features of JIA can be subtle or misleading
- Typical pain and joint swelling may be absent
- Joint stiffness may not be appreciated in children, but may be manifested by poor activity after night rest or prolonged inactivity
- Pain may be manifested by irritability
- In systemic JIA, joint involvement takes place long after initial presentation of nonarticular features like fever, skin rash and splenomegaly
- Muscle wasting near involved joint may precede clinical evidence of arthritis
- Potentially blinding uveitis (in oligoarticular JIA) initially remains asymptomatic, hence require regular ophthalmological screening during subclinical phase.

Oligoarticular JIA

- Previously called pauciarticular JIA
- Commonest types (60% of patients)
- Two subtypes:
  1. Persistent: Affecting not more than four joints throughout the disease process
  2. Extended: To affect more than four joints after the first 6 months
- Usually big joints, like knee, elbow and ankle, are affected by age 3–5 years
- Children may develop blinding anterior uveitis (Fig. 2), more commonly seen in girls. Antinuclear antibody (ANA) is present in 75% of such disease
- Sacroiliitis or spondylitis often occurs. More common in older (8 years) boys with HLA-B27 positivity.

Polyarticular JIA

- Rheumatoid factor negative polyarticular JIA:
  - Thirty percent of JIA patients

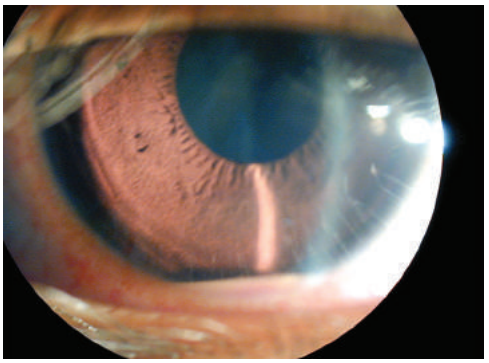

Fig. 2: Anterior uveitis with hypopyon in a child suffering from oligoarticular JIA

- Characterized by five or more joints involvement within first 6 months
- Onset at any age in childhood
- Diagnosis of exclusion:
  - Immunoglobulin M (IgM) RF negative 3 months apart.
- Multiple large joint knee, ankle and elbow are more affected; small joints are less affected (Fig. 3)
- Joint swelling leads to limited mobility
- Tenosynovitis and bursitis of fingers and feet
- Flexion of contraction of knee, hip and elbow.

- Rheumatoid factor positive polyarticular JIA:
  - Age of onset is teen age or early adolescent
  - Severe deforming symmetrical arthritis affecting mostly small joints of hands and feet like metacarpophalangeal and 1st interphalangeal joint (Fig. 4). May results in short stature
  - Cervical spine and temporomandibular joint
  - Rheumatoid nodule
  - Rheumatoid factor positive
  - X-ray: Erosion of bones.

Systemic Onset of JIA

- Ten percent of JIA
- Male-female ratio equal
- Clinical features:
  - Systemic features precede joint involvement by weeks to months
  - Fever is essential with high (39–40°C), intermittent nature with twice daily peak
  - Rash: Present with rash, evanescent maculopapular with central thickening (Fig. 5)
  - Hepatosplenomegaly
  - Lymphadenopathy
  - Serositis: Pleural effusion, pericardial effusion.

Diagnosis

History

- Gradual onset of clinical features:
  - Limping, pain, cry or irritability on touching the involved joint, malaise
  - Stiffness of involved joints particularly after rest or prolonged inactivity
  - Stiffness may not be typically elicited. May be appreciated by parent's observation that the child is lazy to walk in the morning but actively mobile in the afternoon
  - Loss of use of affected joints
- History of fever, rash, weight loss (systemic JIA)
- Family history of psoriasis, colitis
- History of antecedent infection, sore throat, upper respiratory tract infection.

Examination

Anthropometry: Look for short stature (Fig. 4) and wasting (weight by height).

- Gait:
  - Limping gait may be present
  - Circumducting gait may be present in advanced disease due to increased limb length

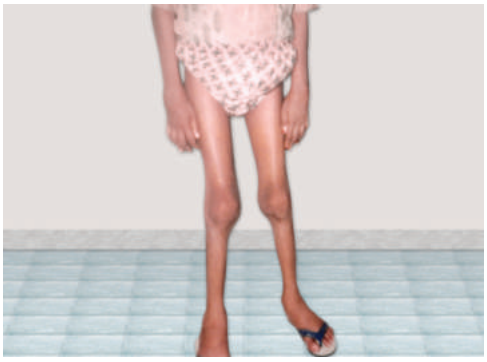

Fig. 3: Polyarticular JIA affecting both knee joints and joints of hand and atrophy of quadriceps muscles proximal to knee joints

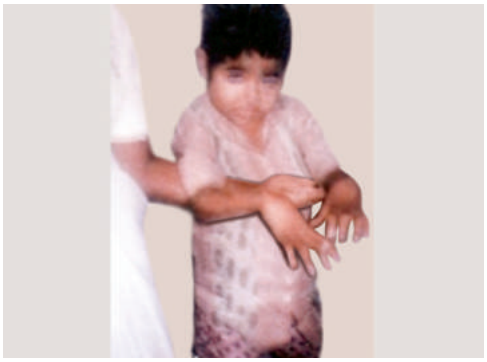

Fig. 4: Polyarticular JIA affecting both hands with deformity and causing short stature

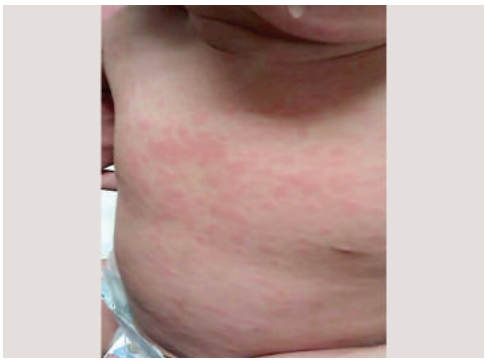

Fig. 5: Macular evanescent rash in systemic onset JIA

- Muscle bulk:
  - Examine muscle bulk around the affected or surrounding joint
  - Wasting of the muscle may precede inflammatory signs of nearby joint (Fig. 3)
- Assess the muscle strength (MRC grade 1 to 5)
- Joint examination:
  - All joints should be examined for evidence of inflammation: swelling, redness, warmth, pain on movement
  - Joint movement restriction
  - In advanced or neglected cases, look for fixed flexion deformity particularly in knee, hip, elbow and wrist (Fig. 4)
  - Measure the degree of fixed flexion deformity by goniometry.

Laboratory Investigations

Investigation should be done depending upon the type of JIA.

- Full blood count (FBC):
  - May show anemia (normochromic, normocytic). If severe anemia and thrombocytopenia consider leukemia
  - Leukocytosis found in systemic onset JIA
  - Neutrophilia: Systemic JIA or sepsis
  - *Erythrocyte sedimentation rate* (ESR)/*C-reactive protein* (CRP): Normal or elevated. Acts as surrogate marker of disease activity. High ESR with thrombocytopenia suggests leukemia
- Antinuclear antibody:
  - Positive usually in oligoarticular JIA
- Immunoglobulin M rheumatoid factor:
  - Not useful for screening
  - Negative for all types of JIA except polyarticular RF positive JIA
  - Useful for prognosis only
- Liver function test:
  - Usually done before and during methotrexate (MTX) treatment
- Imaging:
  - Plain X-ray of affected joint:
    - Soft tissue swelling around the joint, look for any erosion and bony overgrowth
  - Ultrasound:
    - Helpful for confirming synovitis and joint effusion
  - Magnetic resonance imaging (MRI):
    - Useful for atypical monoarthritis
    - Gadolinium enhanced MRI: It is the gold standard for diagnosis of synovitis but cannot differentiate from sepsis
- Synovial fluid aspirate:
  - Culture if sepsis suspected.

Management

Current Strategy, Approach and Advances in Management of JIA

- A holistic approach to management is essential
- A multidisciplinary team should be involved with specific expertise in pediatric rheumatology which includes physiotherapist, occupational therapist, orthopedic surgeons, psychologist and social service personnel. Major shift in management approach is early aggressive therapy with expectation of not only to control inflammation but also to switch it off
- Early use of disease-modifying antirheumatic drugs (DMARDs) like methotrexate, sulfasalazine with better outcome
- Intraarticular corticosteroids are used much earlier in addition to other systemic therapy
- Current biological treatment (cytokine blockade): Created a major breakthrough in the management of refractive and severe JIA
- The use of stem cell transplantation in intractable disease.

Aims of JIA Treatment

- Rapid induction of disease control to prevent joint damage
- To maximize physical function
- To achieve normal lifestyle of patients by improving quality of life and psychosocial wellbeing of the patient.

Treatment

- Treatment regimens are individualized depending upon subtypes of JIA and according to individual response
- However, therapeutic pyramid with gradual addition of more active treatment has been reversed nowadays
- Currently early aggressive intervention is preferred as it may result in long-term disease suppression.

Early Use of DMARDs

Methotrexate*:*

- Weekly methotrexate (MTX) is an established treatment of JIA
- In polyarticular JIA, MTX is the mainstay of treatment and used as a first-line agent either alone or with initial pulse of methylprednisolone and/or with intra-articular steroids
- It is also used in oligoarticular JIA
- Role of MTX in systemic onset JIA is unclear
- Weekly dose of 10–15 mg/m^2, maximum 25 mg/m^2
- Duration: Until remission, usual duration is around 1 year
- Route: Oral or subcutaneous. If the dose requirement is greater than15 mg/m^2, then subcutaneous route is preferred
- Side effects: It is safe in children; MTX is better tolerated in children than adult. Nausea may be infrequently found which can be minimized by giving MTX in divided dose. Folic acid (1 mg) supplementation decreases the side effects of MTX. Hematological abnormalities are rare. Transient elevation of liver enzyme may be present.

Other DMARD:

Sulfasalazine:

- Early use of sulfasalazine is effective in oligoarticular and polyarticular JIA
- Poor efficacy in systemic JIA
- Rash, gastrointestinal side effects and leukopenia (frequently up to one-third found), which necessitates discontinuation and hence not used as first-line DMARD in JIA.

Intra-articular injection of corticosteroid:

- Intra-articular injection currently recommended in earlier disease course
- Can be used alone or in combination with other systemic treatment
- Significant benefits when used in oligoarticular or large joints of polyarticular JIA
- Multiple simultaneous injections are preferred
- Triamcinolone hexacetonide or triamcinolone acetonide (TA) are used.

Minimizing Pain and Stiffness Using Nonsteroidal Anti-inflammatory Drugs *(NSAIDs) along with DMARD*

- Ibuprofen: 30–40 mg/kg/day in three divided doses
- Naproxen: 5–15 mg/kg/day in two divided doses
- Diclofenac: 1.5–2.5/kg/day in three divided doses
- Piroxicam: 0.3–0.5 mg/kg/day once daily
- Aspirin: Should be avoided for the risk of developing Reye syndrome.

Treatment should be continued for 6–8 weeks.
In oligoarticular JIA, screening for uveitis is initially done 3 monthly by an ophthalmologist.

Steroids (nonarticular steroid)

- In systemic JIA pulse IV steroid (methyl prednisolone) with DMARD
- Oral steroid: Used in systemic JIA 1–2 mg/kg/day in divided doses until fever and pain settle then gradually taper. Alternate day dose and steroid sparing agents can be used.

Biological Therapy

Therapeutic cytokine modulation: Therapeutic cytokine modulation appears that established therapies may exert an effect via cytokine modulation. Biologic agents have been developed to restore immune homeostasis via several strategies including stimulation or blockade of production (as with steroid), binding of soluble cytokines (e.g. TNFα) blockade, interference with receptor binding [e.g. recombinant IL-1receptor antagonist (IL-1ra)] and inhibition of signal transduction (as with leflunomide). Cytokine blockade has become the mainstay and this has been achieved by using monoclonal neutralizing antibodies, recombinant soluble cytokine receptors and other cytokine binding proteins called immunoadhesins.

Tumor necrosis factor blockade: TNFα is considered to be at the fulcrum of many inflammatory pathways and as such, targeting it is thought to manipulate these wide influences. Two anti-TNF inhibitors are licensed.

Etanercept:

- Etanercept is a human soluble TNFα receptor, attached to human IgG
- It neutralizes TNF by binding with naturally occurring TNF receptors and may also exert its effects by binding other cytokines
- It is administered by subcutaneous injection twice weekly, for an indefinite period and may be used with or without methotrexate
- It is licensed for use in children aged 4–17 years.

Infliximab:

- Infliximab is a chimeric human-murine monoclonal antibody that binds both soluble and cell bound TNFα
- Infliximab is given by IV infusion and in combination with methotrexate to avoid tachyphylaxis to the murine component.

Risk from TNF blockade:

- Etanercept is well-tolerated in children
- The usual side effects are headache, nausea, abdominal pain and vomiting
- There is risk of infection presumed theoretically.

Physiotherapy

- Physical therapy helps in relieving pain
- Enables posture and joint mobility
- Improves muscle strength
- Prevents fixed flexion deformity.

Occupational Therapy

- Helps therapy taken to tailor according to need of the child.

Psychosocial Support

Psychologist/psychiatric involvement and social services are necessary particularly in disabling polyarticular JIA.

Stem Cell Transplantation

Autologous stem cell transplantation (ASCT) has been used in the last decade to treat unresponsive severe JIA or JIA only controlled by unexpectable steroid cost. Intensive immunosuppression followed by ASCT has the potentiality to sustain complete remission or marked improvement in children with refractory progressive JIA.

Core Variables of Outcome Criteria for JIA

Six core components are used to define improvement or assess disease flare. The criteria are as follows:

1. Physician's global assessment of disease activity.
2. Parent/patient assessment of overall wellbeing/disease activity.
3. Erythrocyte sedimentation rate.
4. Number of joints with active arthritis.
5. Number of joints with limited range of movement.
6. Functional ability (Childhood Health Assessment Questionnaire, CHAQ).

The following definitions are frequently used in assessing disease activity of JIA on the basis of presence or absence of components of six core variables.

Flare

Definition of disease flare has been defined based on the following criteria:

- A minimum of 40% worsening in a minimum of two out of six components, with no more than one component improving by 30%.

Improvement

Improvement is defined as greater than 30% improvement in at least three of six core set variables, with no more than one of the remaining variables worsened by 30%.

Definition of Remission of the Disease

Remission is a controversial concept in JIA. The criteria for remission or relapse have never been operationally defined. However, the following criteria may be undertaken to define diseases remission.

"Inactive disease" includes the following:

- No active arthritis
- No fever, rash, serositis
- No splenomegaly
- No generalized lymphadenopathy attributable to JIA
- No active uveitis
- Normal ESR or CSR
- A physician's global assessment of disease activity rated at the best score possible for the instrument used.

Differential Diagnoses

There are many differential diagnoses of chronic arthritis which include the following (Table 2).

Out of these in Indian subcontinent, rheumatic fever, leukemia and tuberculosis (TB) are the most important differential diagnoses.

Table 2: Differential diagnoses of JIA	
Infective	
Bacterial	Septic arthritis, osteomyelitis
Viral	Parvovirus B19, rubella
However, they are acute in nature rather than chronic	
Tuberculous arthritis	
Postinfective	
Rheumatic fever • Presence of subcutaneous nodule, erythema marginatum and features of carditis favors the diagnosis of acute rheumatic fever • Antistreptolysin O (ASO) titer may be raised in both the conditions • An arthritis of >12 weeks duration, involvement of small and large joint, presence of cervical spine involvement and presence of hepatosplenomegaly, lymphadenopathy favors the diagnosis of JIA	
Reactive arthritis	
Malignancy	
Leukemia: Acute lymphoblastic leukemia can sometimes have an arthritic presentation and mistaken of having JIA. Bone marrow aspiration therefore carried out to exclude leukemia	
• Neuroblastoma • Primary bone tumor	
Connective tissue disorder	
• SLE • Juvenile dermatomyositis • Vasculitis: HSP, Kawasaki disease	
Hematological	
• Hemophilia • Sickle cell disease	
Orthopedic	
• Perthes disease • Slipped femoral epiphysis	
Hypermobility	
• Marfan syndrome • Ehler-Danlos syndrome • Benign hypermobility	

In TB: Tubercular arthritis is usually monoarticular, may be confused with oligoarticular (monoarticular) JIA. In such cases, TB workup investigations (including Mantoux test) for evidence of TB should be sought.

Differences between rheumatic fever and JIA have been listed in Table 3.

Complications

- Uveitis:
  - Anterior uveitis is the most significant complication of oligoarticular JIA
- Growth retardation and short stature:
  - Localized growth abnormalities are more commonly observed and are likely a direct result of active arthritis. Linear growth retardation (sort stature) is a major complication of JIA
  - Accelerated growth at the ossification center because of inflammation may result in overgrowth of the affected limb and longer limb on the affected side.
- Bone abnormalities:
  - Children with JIA are at risk of osteopenia and osteoporosis, leading to an increased risk of fracture.

Prognosis

Prognosis of JIA varies with severity, type of JIA and management offered.

Oligoarticular

- Usually good
- Eighty percent normal at 15 years
- Uveitis is the most important complication and potentially blinding
- Children with HLA B27 may later develop ankylosing spondylitis and other spondyloarthropathy.

Polyarticular

- Variable prognosis
- Aggressive treatment with MTX and biological treatment have improved prognosis dramatically
- Intra-articular steroid causes 70% remission in 1 year, 40% remission in 2nd year
- Seropositive (RF positive) behaves like adult rheumatoid arthritis with erosive deforming arthritis.

Systemic

- Prognosis is extremely variable
- Monocyclic variety: Do well with no significant disability
- Recurrent variety: Polycyclic and persistent variety up to one-third will have permanent disability
- Amyloidosis may occur as a late complication which is difficult to treat.

Table 3: Differences between JIA and rheumatic fever

Criteria	Juvenile idiopathic arthritis	Rheumatic fever
Age of onset	1 year or older (both sex), girls are mostly affected during childhood and adolescence	5–15 years both sex
Onset	Insidious	Sudden
Joint involvement	Small. Large joints are also involved	Large (knee, ankle, elbow and wrist)
Symmetry	Both symmetrical and asymmetrical depending upon subtype	Asymmetrical
Cause	Multifactorial	Immune response to group A β-hemolytic streptococcus
Chronicity	Present	Recurrence of attack may occur
Muscle atrophy, deformity	Present	Absent
Migratory polyarthritis	Rare	Common
Cardiac involvement	Myocarditis or pericarditis may occur rarely	Pancarditis is common
Chorea	Uncommon	Common
Extraarticular manifestations like adenopathy, polyserositis, hepatosplenomegaly, iridocyclitis	Common	Uncommon
Lab investigations	RF or ANA may be positive	Raised ASO titer Positive throat culture for group A β-hemolytic streptococcus
Response to aspirin	Full therapeutic response takes 4 weeks to occur, but prednisolone relieves pain within 72 hours.	Dramatic response. Pain and fever relief occurs within 12–24 hours.

HENOCH-SCHÖNLEIN PURPURA

Henoch-Schönlein purpura (HSP) is a self-limiting IgA medicated systemic vasculitis that affects skin, joints, gastrointestinal tract and kidney. All organs can be affected, but the purpuric skin lesions are necessary to make the diagnosis.

Epidemiology

Henoch-Schönlein purpura is the commonest vasculitis seen in children. The incidence of HSP is about 10 cases per 100,000 per year. It affects all ages, but 90% of cases are found in those less than 10 years of age, with the median age at presentation being 6 years. Kidney involvement occurs in 30–50% patients.

Etiology

Etiology of HSP is not clearly understood. Upper respiratory tract infection often precedes HSP. Hence, it is thought that an inflammatory process initiated particularly by β-hemolytic Streptococcus triggers the pathogenesis of HSP. Other organisms involved are measles, parvovirus B19, rubella, mumps, Coxsackievirus, *Mycoplasma*, adenovirus, Staphylococci and *Campylobacter jejuni.*

Pathogenesis

The cause of HSP is not clearly understood. Some hypotheses suggest that IgA has a fundamental role in the pathogenesis of the disease because on skin or renal biopsies the deposition of IgA (IgA1 isotype) has been found in the wall of skin capillaries and in the glomeruli. Diminished glycosylation of the hinge region of IgA1 has been reported in patients with HSP and IgA1 molecules with diminished hinge region glycosylation are prone to aggregate into macromolecular complexes that can activate the alternative pathway of complement.

Clinical Features

Henoch-Schönlein purpura presents with purpuric rash with involvement of joints and accompanying abdominal pain which appear within 1–2 days of each other. The manifestations are:

- Cutaneous:
  - Rash: Palpable purpuric rash appears in crops over pressure bearing or dependent areas especially malleoli of ankle, dorsum of legs and glutei (Fig. 6)
  - Edema: Subcutaneous edema over scalp, periorbital region, dorsum of hand and feet, scrotum
- Gastrointestinal:
  - Colicky and periumbilical pain
  - Gastrointestinal hemorrhage:
    - Hemorrhage may be occult, or may cause hematemesis, melena or frank bleeding per rectum
    - Hemorrhagic pancreatitis
  - Bowel ischemia and infarction, fistula, stricture
  - Intussusception is an important compilation

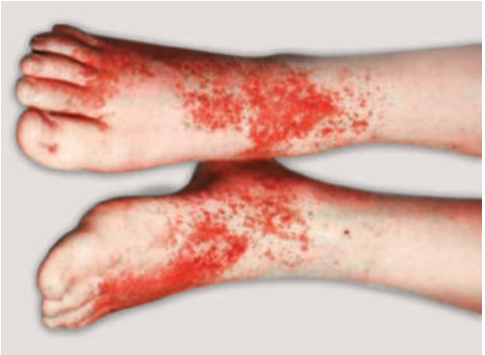

Fig. 6: Typical rashes in HSP

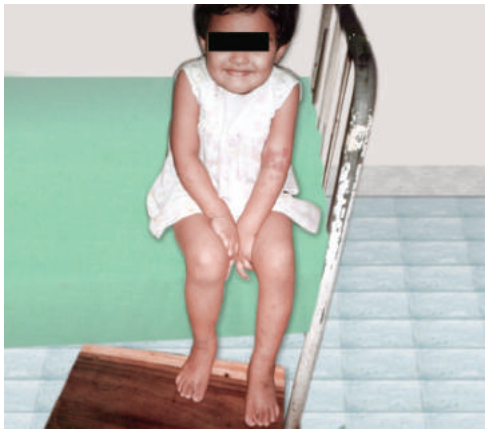

Fig. 7: Vasculitic skin lesions and swollen joints of knee and elbow of a young girl with HSP

- Joints:
  - Joint symptoms are periarticular swelling, pain and limitation of movement (Fig. 7)
- Lung:
  - Pulmonary hemorrhage, pleural effusion, chylothorax
- CNS:
  - Headache
  - Encephalopathy
  - Seizure
  - Cerebral vasculitis
  - Cerebral hemorrhage
  - Ataxia.
- Eyes:
  - Episcleritis, scleritis, keratitis, anterior uveitis
  - Central retinal vein occlusion and central retinal artery occlusion
- Renal (discussed in detail in Chapter Nephrology):
  - Renal involvement in HSP, known as HSP nephritis, occurs within 3 months of onset of HSP in about 20–40% patients. The manifestations are microscopic and macroscopic hematuria and proteinuria
- Genitourinary:
  - Orchitis, epididymitis.

Infantile HSP

Other name is Sedelmayer syndrome. It is not so common. The distinctive features are:

- Purpura:
  - Purpura of acute onset
  - Ecchymoses and inflammatory edema of limb and face
- Cutaneous:
  - Cutaneous manifestation occurs in medallion-like pattern on the face, extremities and auricle.

Diagnostic Features of HSP

- Classification criteria for HSP
- Palpable purpura (mandatory) in the presence of at least one of the following four features:
  1. Diffuse abdominal pain.
  2. Arthritis (acute) or arthralgia.
  3. Renal involvement (any hematuria and/or proteinuria).
  4. Any biopsy showing predominant IgA deposition.

Differential Diagnosis

- Immune thrombocytopenic purpura
- Acute post-streptococcal glomerulonephritis
- Systemic lupus erythematosus (SLE)
- Septicemia
- Disseminated intravascular coagulation
- Hemolytic-uremic syndrome
- Papular purpuric gloves and socks syndrome.

Investigations

- Complete blood count:
  - Hemoglobin (Hb): Low
  - Erythrocyte sedimentation rate (ESR): High
  - White blood cells (WBCs): Increased with shift to left
  - Platelet count: May be elevated
  - Film: Normochromic normocytic anemia
- Blood urea and serum creatinine: Increased level indicates acute nephritic syndrome
- Urinalysis:
  - Microscopic or gross hematuria
  - Variable proteinuria
- Serology:
  - Antinuclear antibody: Negative
  - Rheumatoid factor: Negative
  - Complement level (C3 and C4): Low
  - Serum IgA: Elevated
- Skin biopsy:
  - Leukocytic vasculitis involving capillaries and venules of upper and mid-dermis
  - Deposition of IgA and occasionally C3 and fibrinogen on the perivascular region seen on immunofluorescence study.

Renal Biopsy

A renal biopsy is indicated only in children with persistent or significant renal manifestations.

Indications for diagnostic renal biopsy in children with HSP are:

- Nephritic/nephrotic presentation
- Raised creatinine, hypertension or oliguria
- Heavy proteinuria [urine albumin to creatinine ratio (U_a:U_{cr}) persistently greater than 100 mg/mmol] on an early morning urine sample at 4 weeks
- Serum albumin not necessarily in the nephrotic range
- Persistent proteinuria (not declining) after 4 weeks
- Impaired renal function (GFR <80 mL/min/1.73 m^2).

Diagnosis of HSP

Henoch-Schönlein purpura is diagnosed predominantly by presenting features. Table 4 demonstrates the diagnostic criteria for HSP.

Treatment of HSP

Most children with HSP follow a relatively benign course and do not require hospital admission. Treatment aimed at predominantly relieving the symptoms except for renal disease which may be associated with long-term complications.

Treatment is supportive, i.e. maintenance of adequate hydration, nutrition and electrolyte balance.

Table 4: EULAR/PRINTO/PRES criteria for diagnosis of HSP

Mandatory criteria
Purpura
Purpura (commonly palpable and in crops) or petechiae, with lower limb predominance, not related to thrombocytopenia*
At least one of the following:
Abdominal pain
Diffuse abdominal colicky pain with acute onset assessed by history and physical examination. May include intussusception and gastrointestinal bleeding
Histopathology
Typically leukocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit
Arthritis or arthralgia
Arthritis of acute onset defined as joint swelling or joint pain with limitation on motion. Arthralgia of acute onset defined as joint pain without joint swelling or limitation on motion
Renal involvement
Proteinuria >0.3 g/24 hr or >30 mmol/mg of U_a:U_{cr} on a spot morning sample; Hematuria or red blood cell casts: >5 red blood cells/high power field or red blood cells casts in the urinary sediment or ≥2 + on dipstick

*For purpura with atypical distribution, a demonstration of IgA deposit in a biopsy is required
Abbreviations: EULAR, European League Against Rheumatism; PRES, Paediatric Rheumatology European Society; PRINTO, Paediatric Rheumatology International Trials Organization.

- Analgesics: To relieve joint involvement. Simple analgesics, like paracetamol or NSAIDs, can be used.
- Glucocorticoids: Though it relives pain dramatically, it is not routinely used. A short-term use of glucocorticoid is effective in relieving pain of epididymo-orchitis
- Prednisolone: Prednisolone may be used to control gastrointestinal symptoms as well as hemorrhage. There is no evidence that corticosteroid therapy is effective in treating the purpura, shortening the duration of the disease, or preventing recurrences or the development of nephritis
- Immunosuppressive agents: These are required along with IV methylprednisolone to control fatal complication like pulmonary hemorrhage.

Prognosis

Henoch-Schönlein purpura is a self-limiting disease but 33% have recurrence of symptoms. A long-term outlook in children with HSP is predominantly related to renal disease. Although renal involvement in most cases is mild and self-limited, it has been claimed that about 1% of patients progress to end stage renal failure.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus is a chronic autoimmune disease that can involve any organ system, and may lead to significant morbidity and even mortality. Juvenile-onset SLE (JSLE) differs from the adult form in terms of severity, variation in organ involvement and gender ratio.

Epidemiology

- Childhood onset SLE (cSLE) is a rare disease with an incidence of 0.3–0.9 per 100,000 children-years and a prevalence of 3.3–8.8 per 100,000 children
- Childhood onset SLE is frequently reported in Asians, African Americans, Hispanics and Native Americans
- Median age of onset of cSLE is between 11 and 12 years
- SLE is rare in children younger than 5 years
- Like most autoimmune conditions, SLE is more prevalent in females. In childhood SLE female to male ratio is around 5:1 in contrast to 9:1 seen in adult SLE (aSLE) which may be influenced by sex hormones during puberty.

Etiology

It is of unknown etiology but is characterized by autoantibodies against nuclear antigens, such as antinuclear antibodies (ANA) and double stranded DNA (dsDNA). Elevated levels of anti-dsDNA antibodies are more common in cSLE than aSLE. An estimated 92% of children with infantile SLE show positive test for anti-dsDNA antibodies. Antihistone and antiribosomal P protein antibodies are all more frequently observed in cSLE than aSLE. Antinucleosome antibodies, autoantibodies against intranuclear antigens exposed by apoptosis, have been implicated in the pathogenesis of lupus nephritis with cSLE, and global SLE disease activity in general RF is positive in 10–54% of cSLE patients. Hormonal, environmental and genetic factors play a contributory role in the development of SLE. Individuals with SLE may have a genetic susceptibility to disease as almost half of all children with SLE have a family history of autoimmunity. Environmental factors including drugs, ultraviolet light exposure, pregnancy and response to infectious stimuli such as viruses, also play a role. C1q deficiency is a rare inherited complement deficiency and these patients have an almost certain chance of developing SLE over their lifetime.

Pathophysiology of SLE

An exaggerated immune response, characterized by an immune reaction against the body's own cellular and nucleic antigens (thus autoantibody formation), underpins the pathophysiology of JSLE. Commonly observed nucleic autoantibodies include ANA, dsDNA and extractable nuclear antigens (ENA) including anti-Sm, anti-RNP, anti-Ro and anti-La antibodies. This response involves hyperactive immune cells and dysregulated immune pathways, reduced clearance of immune complexes and reduced tolerance to antigenic stimuli. Monocytes and macrophages secrete chemokines, cytokine and growth factors, causing inflammation and damage to both healthy and target tissues.

Clinical Features

Systemic lupus erythematosus can affect any organ system, and leads to glomerulonephritis and central nervous system (CNS) involvement arguably more often in cSLE than aSLE.

Constitutional Symptoms

Nonspecific constitutional symptoms are fever, fatigue, anorexia, weight loss, alopecia and arthralgias. Hepato-splenomegaly and lymphadenopathy may also occur.

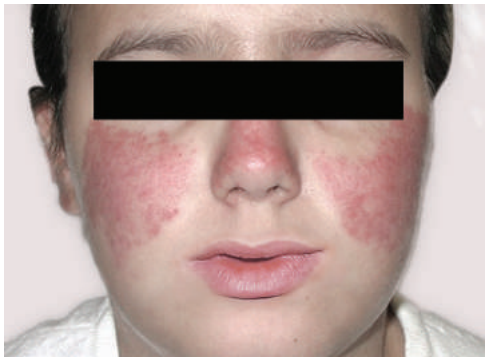

Fig. 8: Malar (butterfly) rash in a patient with SLE

Mucocutaneous

- The hallmark of SLE is the malar, or butterfly, rash (Fig. 8)
- The rash is generally described as erythematous, raised, nonpruritic and non-scarring. It often extends over the nasal bridge, affects the chin and ears, sparing the nasolabial folds
- Discoid rash is rare in cSLE.

The skin manifestations of SLE are listed in the Table 5.

Musculoskeletal

- Arthralgia and arthritis
- Avascular necrosis
- Bone-fragility fractures
- Secondary pain amplification.

Renal

- Minimal proteinuria and microscopic
- Hematuria to nephrotic range proteinuria
- Urinary casts
- Severe hypertension
- Peripheral edema
- Renal insufficiency or acute renal failure
- SLE most commonly affects the glomerulus (i.e. lupus nephritis), with rare involvement of the renal interstitium.

In 2003, International Society of Nephrology/Renal Pathology Society (ISN/RPS) working group classified lupus nephritis as discussed in Table 6.

Neuropsychiatric

Systemic lupus erythematosus can involve both the central and peripheral nervous systems, with 19 distinct neuropsychiatric SLE (NPSLE) syndromes as described in Table 7.

Hematological

- Anemia
- Mild leukopenia (WBC count 3000–4000/mm^3) is the most common hematologic manifestation and is usually due to lymphopenia (<1,500 cells/mm^3) and, less frequently, neutropenia mild (<150,000 platelets/μl) to profound (<10,000 platelets/μl)
- Thrombotic or thromboembolic event:
  - The most common events are deep venous thrombosis, cerebral vein thrombosis and pulmonary embolus.

Table 5: Dermatological manifestation of SLE

Rash	• Malar (butterfly) rash • Annular erythema • Discoid lupus erythematosus • Maculopapular and/or linear (nonspecific) rash • Bullous lupus (rare)
Photosensitivity	
Alopecia	
Raynaud phenomenon	
Palmar/plantar/periungual erythema	
Livedo reticularis	
Vasculitis	• Petechiae • Palpable purpura (leukocytoclastic vasculitis) • Chilblains/nodules • Digital ulcers

Table 6: ISN/RPS classification of lupus nephritis

Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis
Class IV	Diffuse segmental (IV-S) or global (IV-G) lupus nephritis
Class V	Membranous lupus nephritis
Class VI	Advanced sclerosing lupus nephritis

Note: Lupus nephritis is discussed elaborately in the nephrology section

Table 7: Neuropsychiatric SLE syndromes

Central nervous system	• Aseptic meningitis • Cerebrovascular disease • Demyelinating syndrome • Headache • Movement disorder (chorea) • Myelopathy • Seizure disorder • Acute confusional state • Anxiety disorder • Cognitive dysfunction • Mood disorder • Psychosis
Peripheral nervous system	• Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome) • Autonomic disorder • Mononeuropathy, single/multiplex • Myasthenia gravis • Neuropathy, cranial • Plexopathy • Polyneuropathy

Gastrointestinal Involvement

- Abdominal pain (epigastric) and discomfort
- Abdominal vessel vasculitis, with or without bowel perforation
- Sterile peritonitis in fewer than 10% of patients, leading to abdominal pain and ascites, pleuritis and pericarditis
- Pancreatitis.

Cardiopulmonary Features

- Serositis:
  - Pleuritis presenting with shortness of breath and pleuritic chest pain
  - Pericarditis presents with tachycardia, precordial or retrosternal chest pain and the inability to lie flat.
- Other:
  - Myocarditis
  - Noninfective (Libman-Sacks) endocarditis
  - Interstitial pneumonitis
  - Pulmonary hemorrhage
  - Pulmonary hypertension.

Vascular Manifestations

Cutaneous vasculitis may manifest as small, tender nodules of the digits, or palpable purpura (leukocytoclastic vasculitis) of the lower extremities, while retinal vasculitis (cotton-wool spots) and a small vessel CNS vasculitis are rare but recognized.

Differential Diagnosis

The differential diagnoses of SLE are discussed inTable 8.

Table 8: Differential diagnosis of SLE

Infection		
	Viral exanthematous disease	Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Parvovirus B19, human immunodeficiency virus (HIV), human herpes virus 6 (HHV-6)
	Bacterial	Sepsis *(Streptococcus, Salmonella), Brucella, Leptospira*
	Other	• Q fever (Coxiella) • Tuberculosis (mycobacterial) • Lyme disease (spirochetal) • Toxoplasmosis (protozoan)
Malignant		
	• Leukemia • Lymphoma (Hodgkin/non-Hodgkin) • Neuroblastoma • Langerhans cell histiocytosis	
Autoimmune or inflammatory		
	• Juvenile idiopathic arthritis (Systemic onset JIA with rash) • Juvenile dermatomyositis • Acute rheumatic fever • Sarcoidosis • Hemolytic uremic syndrome	
Other		
	Chronic (widespread) pain syndrome	

Diagnosis of SLE

Criteria for diagnosis of SLE according to the American College of Rheumatology is mentioned in Table 9. If 4 of these 11 criteria are fulfilled at any time, then the diagnostic specificity of SLE is 95%.

Investigation for SLE

The laboratory investigations and their finding in SLE are discussed in Table 10.

Management of SLE

The aims of treatment are to achieve symptomatic resolution, disease control and improved quality of life by reducing disease progression and preventing further tissue damage. The care of a child or adolescent with SLE requires a multidisciplinary approach and ideally involves rheumatology, a primary care physician, nephrology (for any patient with renal disease), adolescent medicine, psychiatry and psychology, nursing, social work, and physical and occupational therapy.

General Supportive Measures

- Dietary modification to minimize risk of cardiac complication
- Appropriate exercise
- Control of blood pressure in hypertensive patients
- Calcium and vitamin D supplementation to prevent osteoporosis in long-term corticosteroid therapy
- Use of sunscreen in patients with photosensitivity.

Pharmacologic Therapy

Pharmacologic treatment is tailored to the severity and extent of disease manifestations. The agents used are NSAIDs, corticosteroids, hydroxychloroquine.

NSAIDs: NSAIDs are usually used to relief pain and arthritis.

Hydroxychloroquine (HCQ): All patients should receive unless contraindicated.

Dose: 5–7 mg/kg/day

Corticosteroids: Corticosteroids are the main stay of treatment. Optimal dose in children is unknown. Severe disease may require high doses of IV methylprednisolone (e.g. 30 mg/kg/day for 3 days) or high doses of oral prednisone (1–2 mg/kg/day).

Steroid-sparing immunosuppressive drugs: Steroid-sparing immunosuppressive agents are often used in the treatment of pediatric SLE. These include methotrexate, leflunomide, azathioprine, mycophenolate mofetil and cyclophosphamide. Methotrexate, leflunomide and azathioprine are often used to treat persistent moderate disease, including arthritis, significant cutaneous or hematologic involvement and pleural disease. Immunosuppressive treatment regimens usually consist of a period of intensive induction of remission therapy over 6–12 months to achieve disease quiescence followed by a period of long-term maintenance therapy to control disease and prevent disease flares.

Induction treatment options include IV corticosteroids (e.g. IV methylprednisolone) and long-term high-dose oral corticosteroids (e.g. 1–2 mg/kg/day, followed by gradual weaning regime) combined with a disease-modifying agents like IV cyclophosphamide for major organ involvement in cSLE, with azathioprine or methotrexate for milder or moderate disease.

Immunosuppressive agents:

Corticosteroids:

- Induction and maintenance therapy
- All moderate to severe cases; may be required for mild unremitting disease.

Cyclophosphamide:

- Induction therapy, usually IV
- Moderate to severe disease with organ involvement.

Table 9: Diagnostic criteria for SLE
Malar rash
Flat or raised erythema over the malar eminences, spares the nasolabial folds
Discoid rash
Erythematosus raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur
Photosensitivity
Rash following sunlight exposure, by history or physician observation
Oral ulcers
Oral or nasopharyngeal ulceration, usually painless
Arthritis
Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion
Serositis
• Pleuritis: Convincing history of pleuritic pain or rub on auscultation or evidence of pleural effusion or • Pericarditis: Documented by electrocardiogram, echocardiogram or rub
Renal disorder
• Persistent proteinuria >0.5 g/d or >3+ if quantitation not performed, or • Cellular casts may be red cell, hemoglobin, granular, tubular, or mixed
Neurologic disorder
• Seizures in the absence of offending drugs or metabolic derangements, or • Psychosis in the absence of offending drugs or metabolic derangements
Hematologic disorder
• Hemolytic anemia with reticulocytosis, or • Leukopenia <4000/mL on two or more occasions, or • Lymphopenia <1500/mL on two or more occasions, or • Thrombocytopenia <100,000/μL
Immunologic disorder
• Antibody to native DNA, or • Antibody to Sm protein, or • Antiphospholipid antibodies either anticardiolipin antibodies, presence of the lupus anticoagulant, or false-positive serologic test for syphilis
Antinuclear antibody
Presence of ANA by immunofluorescence or an equivalent assay

Table 10: Laboratory investigations and their finding in SLE	
Direct Coombs test	May be positive, with hemolytic anemia
Urea and electrolytes	Abnormal renal function
Liver function test, bone profile	Hypoalbuminemia, elevated transaminases
Creatinine kinase	May be elevated
Lactose dehydrogenase	May be elevated
C-reactive protein	Often normal, unless concurrent infection (useful for differential diagnosis)
Erythrocyte sedimentation rate	Usually elevated
Complement (C3, C4)	Often reduced
Immunoglobulins G, A, M	May get hypogammaglobulinemia
Antinuclear antibodies	Positive (seen in over 90% of SLE patients)
Anti-dsDNA	Often positive and if present may reflect disease activity
Antiextractable nuclear antigens (anti-ENA; including anti-Sm, anti-RNP, anti-Ro and anti-La)	May be present
Anticardiolipin antibodies IgG, IgM	May be present
Urinalysis	Protein, blood, casts
Urine albumin creatinine ratio	Important in quantification or proteinuria

Mycophenolate mofetil:
- Induction and maintenance therapy
- Moderate to severe disease.

Azathioprine:
- Maintenance treatment
- Mild, moderate or severe disease.

Methotrexate:
- Maintenance therapy
- Musculoskeletal symptoms.

Newer Therapy

Newer therapy includes the biological agents. These agents are targeted to B cell function.

Rituximab: Rituximab is a monoclonal antibody that binds and kills active B cells, is effective for the treatment of cytopenias and rheumatologists also use this drug in combination with other immunosuppressants for other disease manifestations.

Belimumab: Belimumab is an anti-B lymphocyte stimulator antibody, was recently shown to be effective for the treatment of mild to moderate symptoms in adult SLE population but not recommended yet for children.

Vaccination

All vaccines are strongly recommended except for live vaccines [such as the measles, mumps and rubella (MMR) vaccine], which are contraindicated whilst on immunosuppressive agents including corticosteroids.

Complications

The complications are:
- Infection with encapsulated bacteria including *Pneumococcus, Meningococcus, Haemophilus influenzae* type B and *Salmonella*
- Macrophage activation syndrome.

Death may occur due to infection and complications of glomerulonephritis and neuropsychiatric disease and pulmonary hemorrhage. Over the long term, the most common causes of mortality include complications of atherosclerosis and malignancy.

Prognosis

The 5-year survival rate for pediatric SLE is greater than 90%. However, given their long burden of disease, children and adolescents with SLE face a high risk of future morbidity and mortality from the disease and its complications, especially atherosclerosis and malignancy.

GENETIC SKELETAL DISEASES

Achondroplasia

Achondroplasia is an autosomal dominant genetic disease characterized by short stature with disproportionate shortening of the proximal limbs (also discussed in section endocrinology of chapter "Growth and Its Disorder").

Epidemiology

- Incidence is 1 in 15,000–45,000
- Male:Female ratio is equal
- Associated with increased paternal age (>35 years).

Etiology and Pathogenesis

- Eighty percent cases are due to de novo mutation of fibroblastic growth factor receptor 3 (FGFR3)
- Mutation causing activation of FGFR3 resulting in decreased endochondrial ossification and inhibited proliferation of chondrocytes in growth plate cartilage. Nearly all cases are caused by mutation causing substitution of arginine for glycine at position 380 (G380R). Inheritance is autosomal dominant (AD) with full penetrance.
- Activation of the FGF3 receptor causes decreased endochondral ossification and inhibited proliferation of chondrocytes in growth plate cartilage. This leads to failure of long bone growth and abnormal formation of skull and vertebrae.

  Allelic variants

  Different mutations in FGFR3 cause distinct phenotypes hypochondroplasia, thanatophoric dwarfism, and severe hypochondroplasia with developmental delay and acanthosis nigricans.
- There are three distinct phenotype other than typical achondroplasia:
  1. Hypochondroplasia.
  2. Thanatophoric dwarfism.
  3. Severe achondroplasia.

Clinical Features

Antenatal:

Shortening of limb on ultrasound scan at third trimester.

Postnatal:
- Head and neck (Fig. 9):
  - Large head (macrocephaly)
  - Frontal bossing
  - Flat nasal bridge
  - Contracted skull base
- Normal trunk
- Limbs:
  - Proximal (rhizomelia) shortening of limb
  - Limited elbow extension
  - Brachydactyly
  - Trident hands (Fig. 10).

Fig. 9: A 10-year-old girl of achondroplasia with short stature, short proximal limbs, large head with frontal bossing

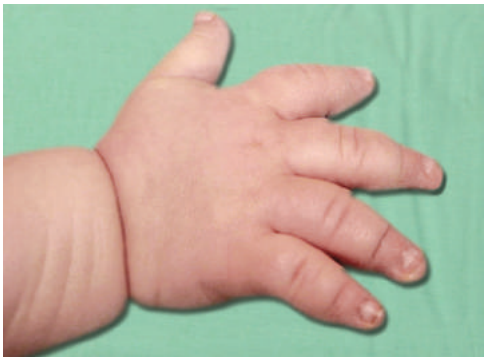

Fig 10: Trident hand in achondroplasia

Diagnosis

Diagnosis is based on presenting features and imaging studies.

- At birth skeletal survey reveals:
  - Large calvarium with narrow foramen
  - Small skull base
  - Short vertebral bodies with wide intervertebral discs
  - Square-shaped long bone
  - Irregular growth plate
  - Trident hand
  - Broad short metacarpals and phalanges
- Prenatal ultrasound:
  - Progressive discordance between femur length and biparietal diameter
- Genetic testing:
  - Genetic testing may be done to detect mutation.

Complication: Affects Several Systems

- *CNS*: Hydrocephalus in 5% due to stenosis of sigmoid venous sinus
- *Musculoskeletal*: Delayed motor development due to hypotonia. Wadding gait with exaggerated lumbar lordosis and bow legs
- *Obesity*
- *Respiratory system*: Recurrent otitis media and sleep apnea.

Treatment

Treatment is only supportive.

Medical:

- Monitoring of growth and head circumference
- Weight control to avoid obesity
- Treatment of ear infection and dental overcrowding
- Monitoring of development of hydrocephalus with cranial ultrasonogram at birth and at 2, 4 and 6 months.

Surgical: Surgical treatment is required in the following indications:

- Limb shortening
- Spinal stenosis
- Kyphosis
- Craniomedullary compression
- Symptomatic bow legs or knock knees.

Genetic counseling: It is for autosomal dominanat (AD, two in one offspring affected) with high new mutation. If both parents have achondroplasia than each child has 1:4 chance of being homozygous affected with potential lethality (hydrops fetalis).

Hypochondroplasia

Hypochondroplasia is autosomal dominant disorder. Penetrance is 100 percent; height range in mild hypochondroplasia may overlap that of the general population, but radiographic changes are present. Majority of cases are sporadic; recurrence risk in offspring is <0.01 percent for unaffected parents. An association with advanced paternal age has been reported. Gain of function mutations in the fibroblast growth factor receptor 3 (FGFR3) gene, a negative regulator of bone growth, leads to the characteristic skeletal findings. Seventy percent of cases are caused by an A or G nucleotide substitution for C at position 1620, resulting in a lysine-forasparagine substitution (N540K). Hypochondroplasia has also been discussed in chapter "Growth Disorders" (Short Stature).

Osteogenesis Imperfecta

Other name is brittle bone disease. Osteogenesis imperfecta (OI) is characterized by increased bone fragility. The clinical spectrum ranges from mild to severe and lethal. Osteogenesis imperfecta is generally a new mutation and is inherited in an autosomal dominant pattern, except for rare instances of type III disease that are inherited in an autosomal recessive pattern.

Etiology and Pathogenesis (Table 11)

Mutation of either of the two genes encoding type I collagen results in OI.

Diagnostic Evaluation

Diagnosis is made on the basis of clinical features and radiological investigation. Sometimes it may be difficult to differentiate coexisting child abuse from osteogenesis imperfecta. The modes of investigations are:

- X-ray of limbs: Irregular wavy ribs, deformed long bones with multiple fractures (Fig. 14)
- Skin biopsy: Collagen synthesis analysis in cultured dermal fibroblasts
- Bone mineral density: Dual energy X-ray absorptiometry (DEXA) may be normal
- Bone biopsy: Variable histology may be evident

Table 11: Classification of osteogenesis imperfecta

Type	Description
Type I	Generalized demineralization; increased bone fragility, sometimes with secondary deformities (Fig. 11); retarded ossification of the cranial vault, blue sclera (Fig. 12), deafness
Type II	Generalized demineralization with multiple fractures (Figs 13 and 14); thick, short crumpled shafts of the long bones; rectangular femora with a wavy appearance; severe retardation of calvarial bone formation; short, thick ribs with continuous beading It is perinatally lethal
Type III	Generalized osteopenia; short, deformed long tubular bones with broad metaphyses and thinner diaphyses; retarded calvarial ossification; thin ribs with discontinuous fractures
Type IV	Generalized demineralization; increased bone fragility, sometimes with secondary deformities; bowed long bones; retarded ossification of the cranial vault

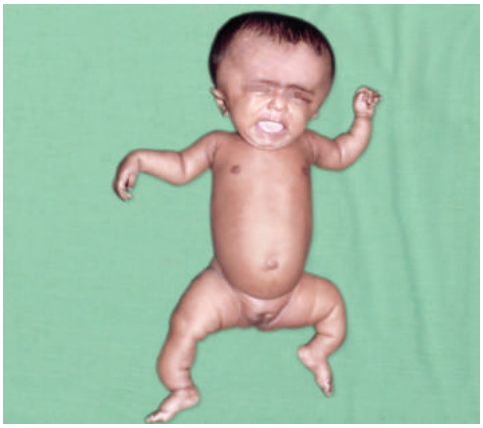

Fig. 11: Angulated deformities due to underlying multiple fractures in osteogenesis imperfecta

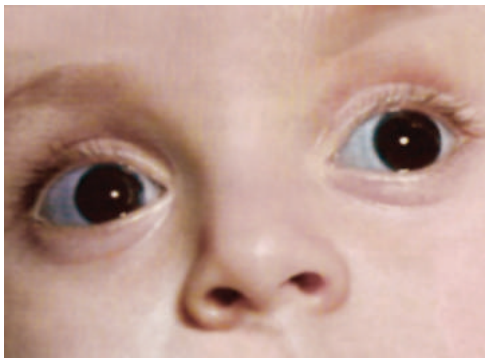

Fig. 12: Blue sclera in osteogenesis imperfecta

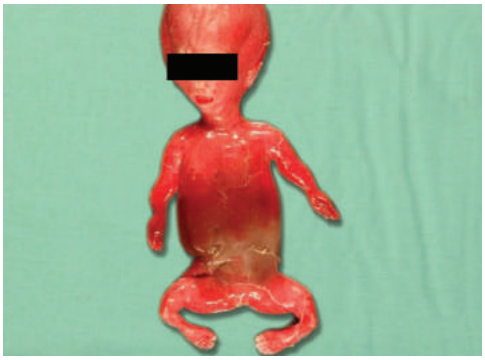

Fig. 13: Postmortem photograph shows deformed extremities, finding that are consistent with fractures

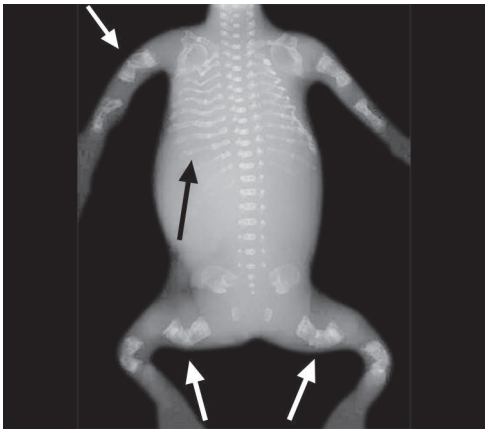

Fig. 14: Radiograph showing wavy ribs (black arrow) and irregular deformed long bones (white arrows) due to multiple fractures

- Genetic testing: Not readily available. Here mutation analysis of collagen genes done.

Management

Medical treatment: To prevent and treating fractures and maximizing independent mobility and weight-bearing and developing optimal bone mass following strategies are taken:

- Advice and counseling of parents on handling
- Use of wheel chairs, braces and mobility aids
- Optimal nutrition (supplementation of calcium and vitamin D)
- Fracture care
- Regular hearing test every 3 years from age 7 years
- Dental follow-up
- Drugs:
  - Bisphosphonate: Cyclical administration of pamidronate reduces bone pain and fracture rate and increases bone mineral density

Surgical treatment: Surgical intervention includes:

- Intramedullary rod placement to improve weight-bearing in children with bow legs
- Spinal fusion to correct scoliosis.

Prognosis

Prognosis is variable. Most children and adults with OI lead productive and active lives. Severe form may cause permanent disability.

Thanatophoric Dysplasia

Thanatophoric dysplasia is the most common lethal skeletal dysplasia. It is of two types: Type I and Type II.

Inheritance is autosomal dominant. Both types are caused by mutations of the gene encoding FGFR3.

Clinical Features

- Polyhydramnios may be present in 50% cases
- Disproportionate dwarfism with very short extremities (Fig. 15)
- Dysmorphic face:
  - Disproportionately large head
  - Depressed nasal bridge
  - Prominent forehead
  - Protruding eyes
- Normal trunk length
- Narrow thorax
- Platyspondyly, short bowed long bones, distinct flattening of vertebral ossification centers (Fig. 16) less severe in Type II than in Type I
- Secondary skull deformity due to the premature closure of cranial sutures.

Type I:

- Lower extremity bowed in Type I

Type II

- Cloverleaf skull deformity
- Lower extremity may be straight.

Prognosis and Treatment

It is a lethal disorder (thana means deadly). There is severe hypotonia and severe respiratory problem after birth and the baby usually dies during neonatal period.

Fig. 15: A newborn with thanatophoric dysplasia

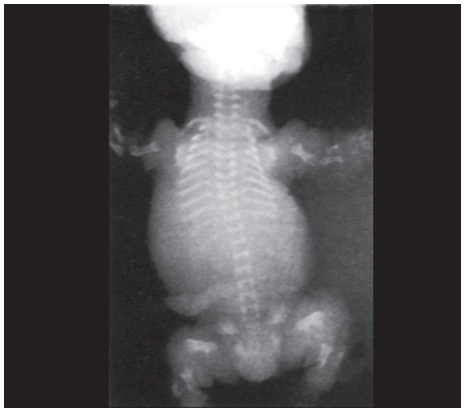

Fig. 16: X-ray of thanatophoric dysplasia showing short narrow ribs, short bowed long bones with cupped spur-like irregular flaring of metaphysis (land telephone receiver deformity), short flattened vertebrae with wide intervertebral disc space

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20 Drug Overdoses and Poisoning

PRINCIPLE OF MANAGEMENT OF POISONING

Most patients with self-poisoning require only general care and support of the vital systems. Additionally a few drugs are required. It is challenging to identify poisoned patient at an early stage, who are at risk of developing serious complications and who might potentially benefit from an antidote or treatment to increase elimination of the poison. Following strategies are usually followed:

- Provide immediate supportive treatment [resuscitation with airway, breathing and circulation (ABC) measures]
- Use of appropriate antibiotic if available
- Attempt to reduce poison absorption
- Perform toxicological investigations
- Nontoxicological investigation if required
- Increase elimination of poison by urine alkalization, multiple-dose activated charcoal and hemodialysis.

AIRWAY, BREATHING AND CIRCULATION MEASURES

Airway and Breathing

- Remove food, vomit, secretion and dentures from patient's mouth, pharynx and tongue
- Prevent tongue fall back
- Nurse the patient in left lateral position to minimize risk of aspiration
- If respiratory depression is present, insert an oropharyngeal airway tube and supplemental oxygen should be administered
- Intubation is required if cough or gag reflex is lost
- If ventilation remains inadequate after intubation, as shown by hypoxemia and hypercapnia, intermittent positive pressure ventilation (IPPV) should be instituted.

Circulation

- Hypotension is a recognized feature of acute poisoning, but classical features of shock like tachycardia and pale cold skin develop rarely
- To treat hypotension first step is that patient should be placed with head down position (foot end is elevated 15 cm above head end)
- If there is no improvement, infusion of crystalloid solution should be started
  - Marked hypotension should be treated with volume expander like gelatins, or etherified starches (e.g. hetastarch, hexastarch)
  - Central venous pressure and urine output should be monitored
  - Inotropes like dopamine and dobutamine should be used, if the above measures fail to maintain blood pressure.

Care of Unconscious Patients

- Nurse the patient in lateral position with lower leg straight and the upper leg flexed
- Airway should be kept clear by removing any obstructive object, vomit or dentures, and by backward pressure on the mandible
- Care of the mouth and pressure areas should be taken
- Some routine investigations should be done like serum electrolytes, glucose, hepatic and renal function, measurement of carboxyhemoglobin, methemoglobin and cholinesterase activity.

OTHER MEASURES

Body Temperature

Hypothermia

Hypothermia is defined when rectal temperature falls below 35°C. To prevent hypothermia:

- The patient should be covered with a "space blanket"
- Intravenous and intragastric fluid should be given in normal temperature.

Hyperthermia

To prevent hyperthermia, cloth should be removed and sponging with tepid water should be done to promote evaporation.

Rhabdomyolysis

Rhabdomyolysis can occur from pressure necrosis in drug-induced coma.

Convulsions

Convulsions may occur in poisoning due to tricyclic antidepressant (TCA), mefenamic acid or opioids. Duration of convulsion is of shorter duration. For prolonged period of convulsion, IV diazepam 10–20 mg should be administered. If convulsion is not controlled with repeated dose of diazepam, a loading dose of phenytoin (15 mg/kg) should be administered. Blood pressure and electrocardiogram (ECG) should be monitored.

Stress Ulceration and Bleeding

Stress ulceration of stomach can be prevented by administering IV H_2-receptor antagonists or proton pump inhibitor.

SPECIFIC MEASURES

Specific Antidote

Specific antidotes are available for a few number of poisons. These are given in Table 1.

Reduction of Poison Absorption

Inhaled

Removal from the toxic atmosphere.

Skin

- Removal of contaminated clothes
- Washing of affected skin with plenty of water.

Gut Decontamination

- Gastric lavage
  - Gastric lavage should not be employed routinely in the management of poisoned patients
  - Gastric lavage should only be considered if a patient has ingested a potentially life-threatening amount of a poison and the procedure can be undertaken within 1 hour of gestation
  - It can be offered up to 4 hours in poisoning with salicylates, anticholinergic and iron
  - Gastric lavage is contraindicated in cases of ingestion of hydrocarbon and corrosive agents
- Single-dose activated charcoal
  - Activated charcoal adsorbs a wide variety of compounds and drugs, e.g. aspirin, carbamazepine, aminophylline, digoxin, barbiturate, phenytoin, paracetamol
  - It cannot adsorb strong acids and alkalis, ethanol, ethylene glycol, iron, lithium, mercury and methanol
  - It should be administered only if a patient has ingested a potentially toxic amount of a poison up to 1 hour previously.

Table 1: Various poisoning and their respective antidotes

Poison	Antidote
Paracetamol	N-Acetylcysteine, Methionine
Opioids	Naloxone
Lead (inorganic)	Sodium calcium edetate, DMSA
Digoxin and digitoxin	Digoxin specific antibody fragments
Benzodiazepine	Flumazenil
Arsenic	Dimercaprol
Beta-adrenoceptor blocking drugs	Atropine, glucagon
Organophosphorus compounds (OPC)	Atropine, pralidoxime
Warfarin and other anticoagulants	Vitamin K1
Cyanide	Oxygen, dicobalt edetate, hydroxocobalamin, sodium thiosulfate
Ethylene glycol	Fomepizole, Ethanol
Iron salts	Desferrioxamine

Abbreviation: DMSA, dimercaptosuccinic acid

Increasing Poison Elimination

- Forced diuresis
- Urine alkalinization
  Most drugs, particularly unionized, lipid soluble molecules, are largely reabsorbed by the renal tubules. Increasing the concentration of ionized drug in the urine should reduce reabsorption and further elimination. This is achieved by manipulating urine pH which enhances ionization and hence elimination of weakly acidic compounds such as salicylate, phenobarbital, and chlorophenoxy herbicides
- Multiple dose activated charcoal: Multiple doses of activated charcoal aid the elimination of some drugs from the circulation by interrupting their enterohepatic circulation and also by adsorbing the drug that has diffused into the intestinal juices
- Dialysis
  - Peritoneal dialysis increases the elimination of poisons such as ethylene glycol and methanol but is much less efficient than hemodialysis
  - Hemodialysis is indicated for the treatment of acute renal failure.
- Hemoperfusion: It involves the passage of blood through an adsorbent material, e.g. activated charcoal.

PARACETAMOL POISONING

Paracetamol is a widely used over-the-counter antipyretic and analgesic.

TOXIC DOSE

- Acute ingestion: More than 200 mg/kg
- Chronic ingestion: 50–150 mg/kg/day for 2–8 days.

MECHANISM OF TOXICITY

Acetaminophen is metabolized in liver by cytochrome P-450 mixed-function oxidase enzyme yielding a toxic metabolite (NAPQI) which is detoxified rapidly by glutathione in liver cells. In case of overdose, NAPQI production exceeds glutathione, the macromolecules directly injure hepatocytes.

CLINICAL PRESENTATION

- Stage I (0.5–24 hours):
  - Nausea
  - Vomiting
  - Diaphoresis
  - Pallor
  - Malaise.
- Stage II (24–72 hours):
  - Initial symptoms subside
  - Hepatic dysfunction develops.
- Stage III (3–7 days):
  - Progressive hepatic encephalopathy: Jaundice, confusion
  - Hyperammonemia, and
  - Bleeding diathesis.

DIFFERENTIAL DIAGNOSIS

- Reye's syndrome
- Hepatitis

INVESTIGATIONS

- Liver function tests
- Acetaminophen level: Usually done 4 hours after ingestion.

MANAGEMENT

General

Decontamination

- Gastric lavage within 1 hour of ingestion
- Use ipecac if other toxic coingestion is evident
- Activated charcoal:
  - For all patients within 4 hours of ingestion of acetaminophen
  - It can be considered beyond 4 hours if the preparation is sustained release or delayed release form.

Specific

N-acetylcysteine (NAC) is the specific antidote for acetaminophen. NAC provides maximum efficacy if administered within 8 hours of ingestion of acetaminophen.

Dose

Oral loading dose 140 mg/kg, followed by 70 mg/kg q4h for 17 doses, and diluted 1:4 in a carbonated beverage, per oral or through nasogastric tube.

Other Antidote: Methionine

Complications:

- Fulminant hepatic failure
- Renal failure
- Anaphylaxis if NAC is used intravenously.

Prognosis

There may be no toxicity of single ingestion of less than 150 mg/kg of acetaminophen. Hepatocellular necrosis and fulminant hepatic failure may develop in chronic ingestion.

BENZODIAZEPINE POISONING

Benzodiazepine (BZD) are commonly indicated in controlling seizure, anxiety, alcohol withdrawal, insomnia, control of drug-associated agitation as muscle relaxants and preanesthetic preparation. As they are used widely, abuse is common.

TOXIC DOSE

The toxic:therapeutic ratio for BZDs is very high. For example, oral overdoses of diazepam have been reported in excess of 15–20 times the therapeutic dose without serious depression of consciousness. However, respiratory arrest has been reported after ingestion of 5 mg of triazolam and after rapid intravenous injection of diazepam, midazolam, and many other BZDs. Also, ingestion of another drug with central nervous system (CNS)-depressant properties (ethanol, barbiturates, opioids, etc.) will produce additive effects.

MECHANISM OF TOXICITY

Benzodiazepines enhance the action of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). They also inhibit other neuronal systems by poorly- defined mechanisms. The result is generalized depression of spinal reflexes and the reticular activating system. This can cause coma and respiratory arrest.

Cardiopulmonary arrest may occur after rapid injection of diazepam, possibly because of CNS-depressant effects or because of the toxic effects of the diluent propylene glycol.

Death from BZD overdose is rare unless the drugs are combined with other CNS-depressant agents such as ethanol, opioids, or barbiturates.

CLINICAL FEATURES

Depending on the compound, onset of CNS depression may be observed within 30–120 minutes of ingestion. The presenting features are:

- Lethargy
- Slurred speech
- Ataxia
- Coma
- Respiratory arrest
- Hyporeflexia and
- Midposition or small pupils
- Hypothermia.

INVESTIGATIONS

- Specific drug level of intoxicant
- Other investigation include
  - Glucose, arterial blood gases, and pulse oximetry.

DIAGNOSIS

Diagnosis is based on the history of ingestion or recent injection.

DIFFERENTIAL DIAGNOSIS

Poisoning with other sedative-hypnotic agents, antidepressants, antipsychotics, and narcotics.

MANAGEMENT

Prehospital Care

- Supplemental oxygen
- Intravenous access
- Rapid blood sugar
- Naloxone, if diagnosis is unclear or an opiate coingestion is suspected.

Emergency Department Care

- Continuation of supportive care and monitoring (e.g. cardiac monitoring, oximetry, vital signs)
- Decontamination
  - Ipecac syrup is contraindicated for prehospital use because of the risk for CNS depression and subsequent aspiration with emesis
  - Gastric lavage is not recommended but may be considered if the presence of a lethal coingestant is suspected and the patient presents within 1 hour of ingestion
  - Single-dose activated charcoal is recommended for gastrointestinal (GI) decontamination in patients who

present within 1 hour of ingestion or in symptomatic patients when the time of ingestion is unknown.
- Respiratory depression may be treated with assisted ventilation.

Specific

Flumazenil is the selective competitive antagonist of the GABA receptor and the only available specific antidote for BZD.

Dose

0.002–0.02 mg/kg IV q1m.

Contraindications

- Documented hypersensitivity
- Chronic BZD use
- Patients using BZDs to control a potentially life-threatening condition, e.g. intracranial pressure, status epilepticus.

Precautions

Patients on BZDs for prolonged periods may experience seizures; monitor for resedation and unmasking of seizure.

BARBITURATE POISONING

Barbiturates are used as hypnotic and sedative agents, for the induction of anesthesia, and for the treatment of epilepsy and status epilepticus.

TOXIC DOSE

The toxic dose of barbiturates depends on the type of drug, the route and rate of administration, and individual patient tolerance. In general, toxicity is likely when the dose exceeds 5–10 times the hypnotic dose.

MECHANISM OF TOXICITY

All barbiturates cause generalized "depression of neuronal activity" in the brain by interacting with a barbiturate receptor. These lead to enhanced GABA-mediated chloride currents and result in synaptic inhibition. Hypotension occurs with a large dose. Hypotension is caused by depression of central sympathetic tone as well as by direct depression of cardiac contractility.

CLINICAL FEATURES OF BARBITURATE POISONING

The symptoms depend on the drug and route of administration.

Mild to Moderate Intoxication

- Lethargy
- Slurred speech
- Nystagmus and
- Ataxia are common.

With Higher Doses

- Hypotension
- Coma
- Respiratory arrest
- Deep coma
  - The pupils are usually small or midposition
  - All reflex activity lost
  - Hypothermia
  - Hypotension and bradycardia.

INVESTIGATIONS

- Serum levels of phenobarbital
- Others include electrolytes, glucose, blood urea nitrogen (BUN), creatinine, arterial blood gases or pulse oximetry, and chest X-ray.

DIAGNOSIS

- History of ingestion
- Overdose should be suspected in any epileptic patient with stupor or coma.

MANAGEMENT

General Supportive Measures

Emergency Care

- Protect the airway and assist ventilation (see airway), if necessary
- Treatment of coma, hypothermia, and hypotension.

Decontamination

- Administer activated charcoal orally if conditions are appropriate
- Gastric lavage is not necessary after small to moderate ingestions if activated charcoal can be given promptly.

Enhanced Elimination

- Alkalinization of the urine increases the urinary elimination of phenobarbital but no other barbiturates
- Hemodialysis or hemoperfusion may be necessary for severely intoxicated patients who are not responding to supportive care.

Specific Measures

There is no specific antidote for barbiturate poisoning.

HYDROCARBON POISONING

Hydrocarbons are used widely as solvents, degreasers, fuels and lubricants. Hydrocarbons include organic compounds derived from petroleum distillation as well as many other sources, including plant oils, animal fats, and coal. Subcategories of hydrocarbons include aliphatic (saturated carbon structure), aromatic (containing one or more benzene rings), halogenated (containing chlorine, bromine, or fluoride atoms), alcohols and glycols, ethers, ketones, carboxylic acids, and many others.

TOXIC DOSE

The toxic dose is variable, depending on the agent involved and whether it is aspirated, ingested, injected, or inhaled (Table 2).

Table 2: Toxic doses of hydrocarbons

Pulmonary aspiration	Few milliliters
Ingestion	As little as 10–20 mL
Injection	Less than 1 mL

MECHANISM OF TOXICITY

Hydrocarbons may cause direct injury to the lung after pulmonary aspiration or systemic intoxication after ingestion, inhalation, or skin absorption.

Aspiration

- Chemical pneumonitis is caused by direct tissue damage and disruption of surfactant. Aspiration risk is greatest for hydrocarbons with low viscosity and low surface tension (e.g. petroleum naphtha, gasoline, turpentine).

Ingestion

- Aliphatic hydrocarbons and simple petroleum distillates such as lighter fluid, kerosene, furniture polish, and gasoline are poorly absorbed from the GI tract and do not pose a significant risk of systemic toxicity after ingestion as long as they are not aspirated
- Aromatic and halogenated hydrocarbons, alcohols, ethers, ketones, and other substituted or complex hydrocarbons are capable of causing serious systemic toxicity, such as coma, seizures, and cardiac arrhythmias.

Inhalation

- Causes intoxication as a result of systemic absorption or by displacing oxygen from the atmosphere.

Injection

- Injection into skin, subcutaneous tissue, or muscle may cause a severe local inflammatory reaction and liquefaction necrosis.

Topical Contact

- Skin and eye contact can cause local irritation. Dermal absorption can be significant for some agents but is insignificant for most of the simple aliphatic compounds.

CLINICAL FEATURES OF HYDROCARBON POISONING

Pulmonary Aspiration

- Immediate onset of coughing or choking
- Chemical pneumonitis characterized by respiratory distress, including tachypnea, retractions, grunting, wheezing, rales, hypoxia, and hypercarbia
- Death may ensue from respiratory failure, secondary bacterial infection, and other respiratory complications.

Ingestion

- Abrupt nausea and vomiting
- Occasional hemorrhagic gastroenteritis.

Systemic Toxicity

- Confusion
- Ataxia
- Lethargy
- Headache
- Syncope, coma, and respiratory arrest
- Cardiac arrhythmia
- Hepatic and renal injury.

Injection

- Local tissue inflammation, pain, and necrosis
- Severe scarring and loss of function.

Skin or Eye Contact

- Local irritation
- Burns
- Corneal injury
- Defatting dermatitis on chronic skin exposure.

Diagnosis

Diagnosis is based on following parameters:

- History of exposure
- Aspiration pneumonitis
  - Presence of respiratory symptoms such as coughing, tachypnea, and wheezing
- Systemic intoxication
  - Appropriate systemic clinical manifestations.

Investigation

Aspiration Pneumonitis

- Arterial blood gases
- Oximetry
- Chest X-ray.

Suspected Systemic Toxicity

- Electrolytes
- Glucose
- BUN and creatinine
- Liver transaminases
- ECG monitoring.

MANAGEMENT

Emergency Care

General

- Maintenance of an open airway and assist ventilation, if necessary
- Administration of supplemental oxygen
- Monitoring of arterial blood gases or oximetry, chest X-ray, and ECG and admit symptomatic patients to an intensive care setting.

Pulmonary Aspiration

- Asymptomatic patients should be kept under observation for 4–8 hours
- Administration of supplemental oxygen. Treatment of bronchospasm and hypoxia if occur
- Steroid and prophylactic antibiotics should not be used.

Ingestion

- Supportive and symptomatic.

Decontamination

Inhalation:

- Moving the victim to fresh air
- Administration of supplemental oxygen.

Skin and eyes:

- Removal of contaminated clothing and washing exposed skin with water and soap
- Irrigation of exposed eyes with copious water or saline and perform fluorescein examination for corneal injury.

Ingestion

- For systemic toxins, consider aspiration of the liquid via nasogastric tube and administration of activated charcoal.

Specific Treatment

- There is no specific antidote for aspiration pneumonitis
- Specific drugs or antidotes may be available for systemic toxicity of some hydrocarbons (e.g. acetylcysteine for carbon tetrachloride and methylene blue for methemoglobin formers) or their solutes (e.g. chelation therapy for leaded gasoline and antidotes for pesticides, etc.).

KEROSENE POISONING

Kerosene is widely available in rural areas of developing countries and used as cooking fuel and for lighting. Kerosene poisoning is the most common household poisoning in developing countries accounting 61–82% of recorded poisoning in childhood. It is bought and kept in food bottles especially fruit and soda bottles which attract children, who think that they are drinking their usual beverage.

Epidemiology

- Kerosene poisoning is more common in developing countries like South Africa, Asia etc.
- Usually lower socioeconomic group are the sufferers
- Rural children are more affected than urban.

Mode of Poisoning

Accidental ingestion is the most common mode of poisoning.

Pathophysiology

Kerosene is the volatile hydrocarbon and is inhaled into lungs as the child drinks it and during vomiting or gastric lavage. Inhalation into and excretion from the lungs produces a chemical pneumonitis and pulmonary edema. Hydrocarbon may interact with pulmonary surfactant, resulting in alveolar collapse. Cyanosis develops quickly due to:

- Displacement of alveolar gas by vaporized hydrocarbon
- Bronchospasm due to irritation may contribute to the ventilation perfusion abnormalities with resultant hypoxia.

A very little amount even 0.2 mL of kerosene can produce chemical pneumonitis.

Toxic Dose

Toxic dose is 30 mL and fatal period is usually 24 hours.

Clinical Features

- May be asymptomatic
- Ingestion immediately produces burning sensation in the mouth and pharynx as well as nausea and vomiting
- Kerosene odor in the breath and vomitus
- Fever
  - Temperature elevates within few hours and subsides within 24–48 hours. Antibiotics are required if temperature rises after 48 hours
- Respiratory manifestation
  - Respiratory manifestation present within 30 minutes, progression occurs over first 24 hours and subsides between 2nd day and 5th day but onset of symptoms may be delayed by 12–24 hours if aspiration is less extensive
  - Cyanosis
  - Tachypnea
  - Nasal flaring
  - Supra clavicular, intercostal retraction and chest indrawing
  - Bronchospasm, consolidation and crackles
- Nausea, vomiting, abdominal pain and diarrhea by increasing peristalsis (Fig. 1)
- Encephalopathy
- Myocarditis in rare cases.

Diagnosis

Diagnosis is made on the basis of:

- Meticulous history
- Physical examination
  - Smell of kerosene in breath and vomitus, fever,
  - Respiratory symptoms and/or CNS manifestation.

Investigations

- Chest X-ray
  - It shows the radiological evidence of pneumonitis
  - It may be evident as early as 30 minutes or may not be apparent until 6–12 hours
  - X-ray changes are graded (Table 3)
- Pulse oximetry to detect oxygen saturation
- Complete hemogram: Leukocytosis.

Management

All patients should be hospitalized for at least 24 hours irrespective of severity.

Fig. 1: Cough, vomiting and abdominal pain in a child following ingestion of kerosene kept in bottle frequently used domestically for lighting hurricane in rural areas

Asymptomatic Cases

Patients should be admitted for observation and may be discharged after 24 hours if no symptoms develop.

Symptomatic Cases

Asymptomatic patients who develop symptoms within 24 hours of observation should be managed according to following guidelines:

- Evaluation and maintenance of ventilator status
  - Administration of oxygen to all patients with respiratory symptoms
  - Some patients with respiratory failure may require intubation and ventilator support
- Prevent contamination from skin
  - Removal of contaminated cloth
  - Washing of skin with copious amount of water
- Antibiotics
  - Antibiotics should not be used routinely, rather reserved for occurrence of secondary infection of the affected lung which is detected by reappearance of fever on 3rd to 5th day after ingestion
- Nutritional support to maintain adequate nutrition
- Corticosteroids, activated charcoal, cathartics, mineral oil and olive oil have no beneficial effect.

Complications

- Immediate complications:
  - Pneumothorax
  - Subcutaneous emphysema
  - Empyema
  - Pneumatocele: Develops in recovery phase and resolve slowly over 6–9 months
  - Secondary infection with bacteria
- Long-term complications.

Prognosis

- Most children survive without complication and sequela
- Some progress rapidly to respiratory failure and death.

Prevention

Preventive measures include:

- Storage of kerosene in designated containers above ground level out of reach of children
- Emphasizing on adult supervision of children.

TRICYCLIC ANTIDEPRESSANT POISONING

Tricyclic antidepressant poisoning remains a significant cause of childhood morbidity and mortality. Sometimes, the drug ingested has been prescribed for the child concerned or a sibling for the treatment of nocturnal enuresis.

Table 3: Grades of chest X-ray for kerosene poisoning

Grade-0	Normal X-ray
Grade-1	Minimal unilateral perihilar infiltration
Grade-2	Bilateral infiltration (Fig. 2)
Grade-3	Confluent, fluffy shadows on one or both sides
Grade-4	Extensive bilateral infiltration with consolidation and/or pleura effusion (Figs 3 and 4)

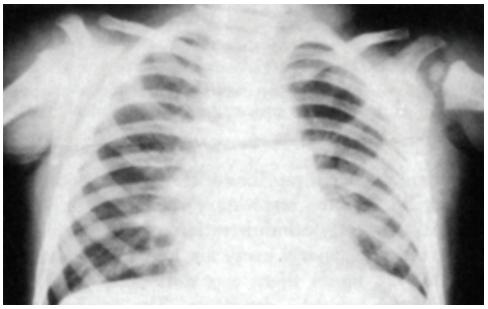


Fig. 2: Bilateral hilar and basilar increased vascular marking (Grade-2)

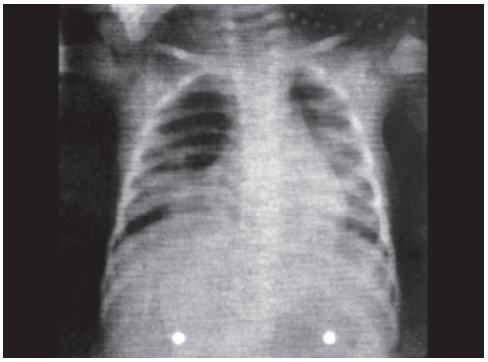


Fig. 3: Bilateral pneumonic consolidations in kerosene poisoning (Grade-4)

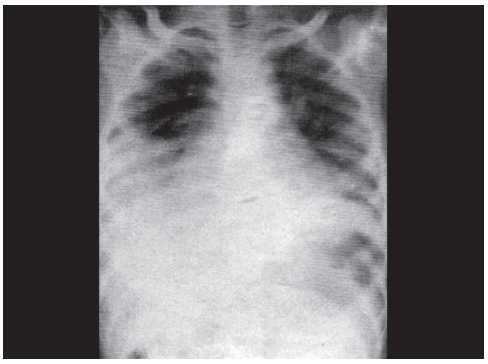


Fig. 4: Right-sided pleural effusion in kerosene poisoning (Grade-4)

ADVERSE EFFECTS

- Sinus tachycardia
- Conduction disorders
- Dry mouth, blurred vision
- Agitation, confusion, convulsions, coma
- Respiratory depression
- Hypotension.

TREATMENT

Methods to Prevent Absorption

Gastric lavage and activated charcoal may be of value for up to 12 hours after overdose because of impaired gastric emptying due to the anticholinergic effects of tricyclic antidepressants.

Supportive Measures

- In severe cases, intubation and/or mechanical ventilation will be required

- Hypotension should be corrected by volume expanders and inotropes
- If cardiac arrhythmias supervene sodium bicarbonate should be infused intravenously, even if metabolic acidosis is not present. If this fails, lignocaine may be given, although it may depress myocardial function further
- Convulsions are usually short-lived, but if they persists diazepam 2.5–10 mg may be given IV
- Metabolic acidosis should be corrected with sodium bicarbonate IV
- Confusion during the recovery period often requires sedation; diazepam is effective
- Physostigmine and mesylate cannot be recommended as their action is short-lived and they may induce serious complications.

PROGNOSIS

The severity of intoxication may be gauged from:

- The clinical features, particularly the degree of coma and cardiovascular impairment
- Associated metabolic disturbances, e.g. metabolic acidosis
- The width of the QRS complex on ECG: If more than 0.11s, the patient is severely poisoned
- The plasma tricyclic concentration: If more than 1,000 µg/L, the child is severely poisoned.

FOLLOW-UP

No follow-up is required.

IRON POISONING

Approximately 5% children admitted to hospital from suspected acute poisoning have taken iron in UK between 1968 and 1983.

Adverse Effect

- Initial: Vomiting, diarrhea, hematemesis, melena, acute gastric ulceration
- Latent period of improvement
- Hours later: Drowsiness, coma, shock, liver failure with hypoglycemia and convulsions
- Long-term: Gastric strictures.

Treatment

Prevention of Absorption

- Gastric lavage should be undertaken if more than 10 mg/kg body weight of elemental iron has been ingested less than 4 hours previously
- Although desferrioxamine (2 gm in 1 liter of water) is customarily added to the lavage fluid or left in the stomach after lavage, its value is unproven although it is unlikely to be harmful.

Supportive Measures

- Measures to correct hypovolemia, hypotension and hepatorenal impairment will be required in a few cases
- Convulsions, if persistent, may be aborted by diazepam 2.5–10 mg IV
- Metabolic acidosis may be corrected by the infusion of IV sodium bicarbonate.

Desferrioxamine

- If the serum iron concentration is more than 90 nmol/L (5 mg/L) and the patient is symptomatic, desferrioxamine should be considered. However, the value of desferrioxamine in acute iron poisoning has not been evaluated as part of any formal clinical trial
- Desferrioxamine is administered in a dose of 15 mg/kg body weight/hour IV. A maximum of 80 mg/kg body weight should be administered in any 24 hour period. Such a regimen should not lead to complications such as hypotension, although rashes and anaphylaxis have occasionally been reported
- Desferrioxamine may be discontinued when the orange/red color imparted to the urine by ferrioxamine disappears as this implies that iron is no longer available for chelation
- Desferrioxamine appears to be safe in pregnancy and may save the lives, both of the mother and her child.

Prognosis

- A child who does not develop one of the following clinical features within 6 hours of ingestion of iron is not at risk of serious toxicity: vomiting, diarrhea, leukocytosis more than 15×10^9/L, blood glucose more than 8.3 mmol/L or a positive abdominal X-ray for iron
- Hematemesis, hypotension, metabolic acidosis, coma and shock are poor prognostic features
- If the serum iron concentration is more than 90 nmol/L (5 mg/L) for less than 6 hours after overdose, clinical features are likely to be present and the child may need treatment with desferrioxamine.

Follow-up

Follow-up is not required.

ORGANOPHOSPHORUS COMPOUND POISONING

Organophosphorus compounds (OPCs) are readily incorporated in the pesticides. Most of the rural people are dependent on agriculture so pesticides are easily available and thus poisoning with OPCs is common in rural areas.

MECHANISM OF TOXICITY

Organophosphorus compounds are the inhibitors of esterase. Phosphorylation of acetyl cholinesterase inhibits its catalytic function. As a result, there is accumulation of hydrolyzed acetylcholine (Ach) at muscarinic, nicotinic and central sites of nervous system form the pharmacological basis of acute cholinergic crisis.

TYPES OF ORGANOPHOSPHORUS COMPOUND POISONING

Acute Poisoning

This may occur due to intake of a toxicant in a single occasion which occurs because of suicide attempts or accidental ingestion.

Subacute Poisoning

Subacute poisoning occurs due to repeated exposure to or intake of smaller dose into system over a short period of time.

Chronic Poisoning

Chronic poisoning refers to cumulative effect occurring from repeated exposure to or intake of small amount pesticides over a long period of time.

CLINICAL FEATURES OF ORGANO–PHOSPHORUS COMPOUND POISONING

Muscarinic Effects

- Gastrointestinal
  - Nausea, vomiting, abdominal pain, diarrhea, fecal incontinence
- Respiratory
  - Pulmonary edema, hypotension
- Cardiovascular
  - Bradycardia, hypotension
- Eyes
  - Blurring of vision, meiosis (Figs 5A to D)
- Genitourinary
  - Frequency of micturition, incontinence
- Others
  - Increased sweating, salivation and lacrimation (Figs 5 and 6).

Nicotinic Effects

- Skeletal
  - Muscle twitching, fasciculation, cramps, weakness including respiratory muscles
- Sympathetic ganglion
  - Pallor, tachycardia, hypertension
- Central nervous system
  - Giddiness, tension, anxiety, restlessness, difficulty in concentration, confusion, slurred speech, insomnia, headache, tremor, apathy, withdrawal and depression, drowsiness, night mares, ataxia, generalized weakness, coma (Fig. 7), Cheyne-Stokes breathing, convulsion, depression of respiratory and circulatory centers
  - Delayed complications: Permanent peripheral neuropathy.

Intermediate Syndrome

Patients may develop proximal muscle weakness 2–4 days after the resolution of the acute cholinergic crisis. This is often first noted as neck weakness, progressing to proximal limb weakness and cranial nerve palsies. Respiratory muscle weakness and respiratory arrest may occur abruptly. The intermediate syndrome is thought to be caused by a redistribution of lipophilic pesticides or result from inadequate oxime therapy. Symptoms may last 1–2 weeks and do not usually respond to additional treatment with oximes or atropine.

Fig. 6: Hyperhidrosis (sweating)

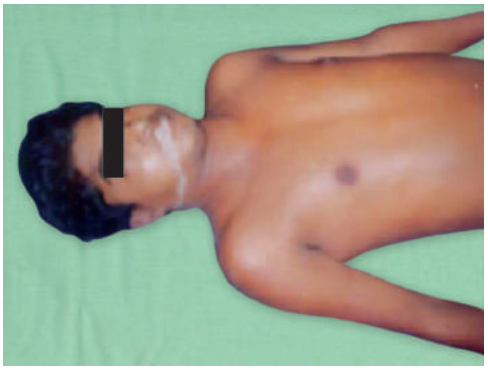


Fig. 7: An unconscious child with acute organophosphorus compound (OPC) poisoning

Investigations (Table 4)

Table 4: Investigation results for organophosphorus compounds

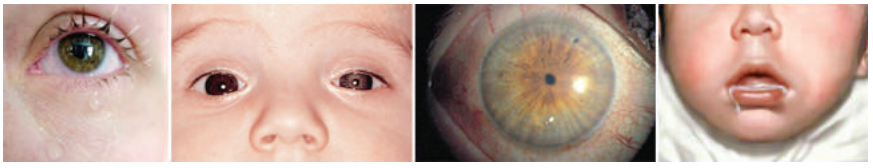
Complete blood count	Leukocytosis
Blood sugar	Hypoglycemia
Liver function test	Increased prothrombin time
Serum electrolytes	Hypokalemia
Urine R/M/E	Proteinuria
Serum amylase	Raised
ECG	Arrhythmia
Chest X-ray	Pulmonary edema

Abbreviations: ECG, electrocardiography; R/M/E, routine/microscopy/examination

MANAGEMENT

General

- Initial stabilization of patient by maintaining respiration and other vital signs
  - Clearing the airway
  - Maintenance of adequate ventilation
- Supportive management
  - Decontamination



A B C D

Figs 5A to D: Clinical features of organophosphorus compound (OPC) poisoning (muscarinic effects); (A) Lacrimation, (B) Meiosis, (C) Meiotic pupil, (D) Salivation with drooling

- Removing the patient from source
  - Removing of clothes
  - Reduction of exposure
    - Gastric lavage within 1 hour of ingestion
    - Use ipecac if other toxic coingestion is evident
    - Activated charcoal:
      - ◊ For all patients within 4 hours of ingestion of acetaminophen
      - ◊ It can be considered beyond 4 hours if the preparation is sustained release or delayed release form
  - Management of respiratory insufficiency
  - Maintenance of circulation
  - Treatment of convulsion and other complications
  - Fluid and electrolyte balance
  - Control of infection
  - Maintenance of nutrition
  - Control of body temperature.

Specific

Administration of specific antidotes. There are two antidotes in the treatment of OPC poisoning.

1 Atropine: Atropine is the antidote of choice which reverses the muscarinic features.
2. Oxime: Oximes (pralidoxime) are the cholinesterase reactivator. Oxime reactivates cholinesterase inhibited by organophosphate and reverses the nicotinic features.

Atropine

Atropine is the physiological antidote of OPCs. It antagonizes the effects of acetylcholine reversing the excessive parasympathetic stimulation by competing for identical binding sites at muscarinic receptors.

Signs of atropinization are as follows:
- Mydriasis
- Tachycardia
- Flushing
- Dry mouth and nose
- Anhidrosis
- Bronchodilation.

Dose:

In Mild Poisoning :
Initial test dose is 0.01 mg/kg through IV route and observe for signs of atropinization.

In Moderate to Severe Poisoning:
Dose of atropine should be repeated if there is no response to loading test dose. Repeated dose of 0.02–0.05 mg/kg every 10–30 minutes should be given until signs of atropinization occur.

In Most Severe Case:
If above regimens are inadequate to reverse the toxicity, a continuous intravenous infusion of atropine at a doses of 0.02–0.08 mg/kg/hour is required and titrated against the response.

Maintenance of Atropinization

Atropinization should be maintained for at least 24–48 hours. Then the drug is gradually withdrawn by decreasing the dose.

Oximes

Oximes are the specific biochemical antidote of OPC intoxication. Pralidoxime is used in conjunction with atropine in moderate and severe poisoning.

Dose: World Health Organization (WHO) recommended dose is 30 mg/kg as a loading dose of pralidoxime over 10–20 minutes, followed by a continuous infusion of 8–10 mg/kg/hour until clinical recovery.

During the management, patient should be under intensive follow-up regarding:
- Vital signs
- Signs of atropinization
- Toxicity of atropine and oxime
- RBC and plasma acetylcholinesterase level
- Recurrence of symptoms on withdrawal of antidote
- Restart the treatment promptly if recurrence occurs
- Patient's general condition.

COMPLICATIONS

Complications may be due to toxic effects of atropine (Table 5).

PROGNOSIS

Deaths from severe organophosphate poisoning usually occur within the first 24 hours in untreated cases and within 10 days in treatment failure cases. Recovery occurs usually within 10 days if there is no anoxic brain damage. There may be residual sequelae.

Causes of Death in Organophosphorus Compound Poisoning

- Immediate death
  - Seizure
  - Complex ventricular arrhythmias
- Death within 24 hours
  - Due to respiratory failure as a result of acute cholinergic crisis in untreated severe case
- Death within 10 days of poisoning
  - Due to respiratory muscle paralysis in intermediate syndrome
- Late death
  - Late death may occur up to 15 days after intoxication secondary due to ventricular arrhythmias.

Table 5: Complications due to toxic effects of atropine

Peripheral effects	Central effects
• Dry mouth • Mydriasis • Blurred vision • Hot dry skin • Tachycardia	• Hyperpyrexia • Restlessness • Anxiety • Excitement • Hallucination • Delirium • Mania • Cerebral depression • Coma

DROWNING

Drowning is the third leading cause of death worldwide, accounting for 7% of all injury-related deaths, 96% of these deaths occuring in low-income and middle-inclome countries.

DEFINITION

Many misleading terms like drowning, near drowning prevailed before the adoption of definition of drowning. In 2002, the World Congress on Drowning developed guidelines for the definition of drowning. The new definition of drowning is "a process resulting in primary respiratory impairment from submersion/immersion in a liquid medium." The previous terms like "near drowning," "wet drowning," "dry drowning" and "secondary drowning" are not used after the definition has been compiled.

"Drowned" is the term reserved for those persons who die from drowning.

EPIDEMIOLOGY

- Drowning is the third leading cause of unintentional injury death globally
- Over 96% of drowning deaths occur in low and middle-income countries
- The rate of fatal drowning in low and middle-income countries is six times higher than in high-income countries
- In Asia alone, the drowning rate is 20 times higher than in developed countries
- Rate of mortality varies with location, age group, activity, and type of water
- Gender prevalence of drowning is twice in boys than girls
- For people with epilepsy, the risk of drowning is 15–19 times as high as the risk for those who do not have epilepsy.

DROWNING: GEOGRAPHICAL FACTOR

The geography has established water as a common feature of the landscape. Ponds and ditches (small holes that fill with water during the rainy season) are in abundance in both rural and urban areas. Open water bodies are used for bathing, washing, drinking, agriculture, raising fish and for children to play in. Closed vessels such as large buckets and troughs are used for porting, cooking and water for livestock.

- Drowning is the leading cause of death in children aged 1–17 years
- Age is a major risk factor for drowning. The highest rate of fatal drowning are found in the 1–4 year age group, when children start to walk and venture away from supervision
- Rate of drowning are higher in rural populations, most likely due to the relatively high number of water sources in rural areas compared to urban areas.

Risk factors for drowning are:

- Male sex
- Age of less than 14 years
- Alcohol use
- Low income
- Poor education
- Rural residency
- Aquatic exposure
- Risky behavior
- Lack of supervision.

PATHOPHYSIOLOGY

A drowning episode begins upon submersion/immersion. Initially, there is a period of panic, struggle to stay above water, and voluntary breath holding. Hypercarbia and hypoxia eventually drive an involuntary gasp of air. If water is aspirated, laryngospasm may occur, causing further ventilation difficulties but temporarily preventing aspiration. If the victim is not rescued, this phase is followed by a period of involuntary respiratory efforts accompanied by aspiration of water, which may persist for many minutes before respiratory arrest. Convulsions and muscle spasms may occur before eventual cardiac arrest and death. The sequence of cardiac rhythm deterioration is usually tachycardia followed by bradycardia, pulseless electrical activity and finally asystole. The whole drowning process, from submersion or immersion to cardiac arrest, usually occurs in seconds to a few minutes, but in unusual situations, such as hypothermia or drowning in ice water, this process can last for an hour (Fig. 8).

MANAGEMENT

Aims of treatment are to:

- Prevent progression of hypoxia
- Prevent hypothermia and
- Minimize cardiovascular impairment
- Rescue and in-water resuscitation
  - Only expert or highly trained rescuer should attempt in-water resuscitation
  - Immediate rescue may be carried out by the bystanders using reaching to the drowning person with an object such as a pole, towel, or tree branch or throwing a buoyant object
  - Emergency medical help should be sought immediately
  - Drowning persons with only respiratory arrest usually respond after a few rescue breaths. If there is no response, the person should be assumed to be in cardiac arrest and be taken as quickly as possible to dry land, where effective cardiopulmonary resuscitation (CPR) can be initiated

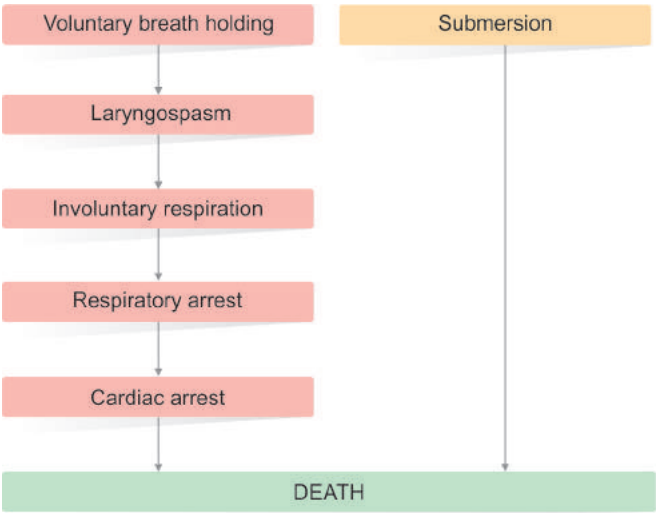


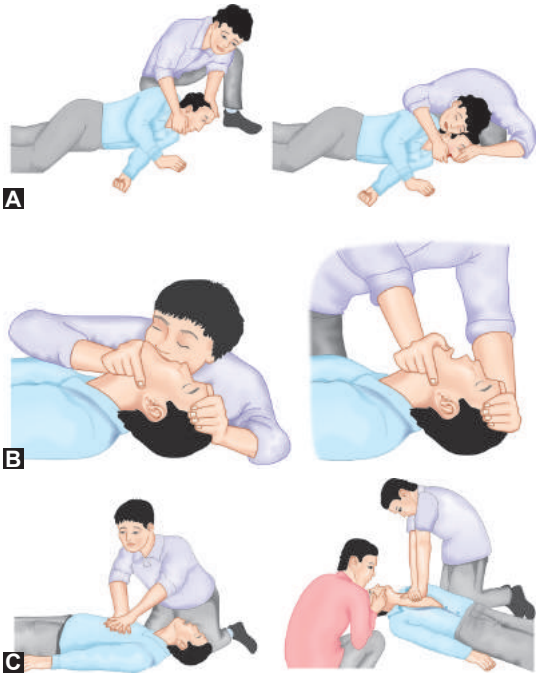
Fig. 8: Sequences of events following drowning

- When rescuing a person from the water, rescuers should try to maintain the person in a vertical position while keeping the airway open, which helps to prevent vomiting and further aspiration of water and stomach contents

- Initial resuscitation on land
  - On land, the drowned person should be placed in a supine position, with the trunk and head at the same level (usually parallel to the shoreline), and the standard checks for responsiveness and breathing should be carried out
    - If the person is unconscious but breathing, the recovery position (lateral decubitus) should be used (Fig. 9A)
    - If the person is not breathing, rescue ventilation is essential
  - Cardiac arrest is tried to be managed by CPR. Keep head and trunk at the same level. If no instrument is available, perform mouth to mouth breathing (Fig. 9B). Start with five initial rescue breaths, followed by 30 chest compressions, and continuing with two rescue breaths and 30 compressions (Fig. 9C) until signs of life reappear, the rescuer becomes exhausted, or advanced life support becomes available.

Initiation of Cardiopulmonary Resuscitation

- Persons with respiratory distress or respiratory arrest in order to prevent cardiac arrest
- Initiate CPR in persons who have been submerged for less than 60 minutes and who do not have obvious physical evidence of death (rigor mortis, body decomposition, or livor mortis).



Figs 9A to C: Initial resuscitation of drowning; (A) First establish breathing; (B) Keep head and trunk at the same level by placing one hand over the forehead behind the head and two fingers of other hand behind cheeks, keep nose close with other fingers. Perform mouth to mouth breathing, if no instrument is available. If chest moves during mouth to mouth breathing then the procedure is expected to be satisfactory; (C) Give 30 chest compressions after 5 initial rescue breaths

Discontinuation of Cardiopulmonary Resuscitation

- Continue basic life support unless signs of life reappear, rescuers are exhausted, or advanced life support team takes over
- Continue advanced life support until patient has been rewarmed (if hypothermic) and asystole has persisted for more than 20 minutes
  - Active efforts to expel water from the airway (by means of abdominal thrusts or placing the person head down) should be avoided because they delay the initiation of ventilation and greatly increase the risk of vomiting, with a significant increase in mortality.

Advanced Prehospital Care

In addition to providing immediate basic life support, it is important to alert advanced-life-support teams as soon as possible. Because of the wide variety of clinical presentations of drowning, a classification system of six grades with higher numbers indicating more severe impairment, can help to stratify risk and guide interventions.

Care at Emergency Department

- The majority of drowning persons aspirates only small amounts of water and recover spontaneously
- After securing an airway and stabilizing the patient with adequate circulation, a nasogastric tube should be inserted and thermal insulation of the patient should be provided
- A full physical examination should be carried out
- Metabolic acidosis is usually corrected by the patient's spontaneous effort to increase minute ventilation or by setting a higher minute ventilation (30–35 liters per minute) or a higher peak inspiratory pressure (35 cm H_2O) on the mechanical ventilator
- Following investigations should be carried out:
  - Chest X-ray
  - Arterial blood gas analysis
  - Serum electrolytes
  - BUN
  - Hematocrit
- Hospitalization is recommended for all patients with a presentation of grade 2–6
- Patients with a presentation of grade 3–6 (hypotension, shock, rales on chest auscultation, submersion for >1 hour, etc.) who usually need intubation and mechanical ventilation, are admitted to an intensive care unit (ICU).

Treatment at Intensive Care Unit

Intensive care is required for those drowned patients on grade 3–6.

- Respiratory system
  - Treatment of drowned person is similar to that of treatment of acute respiratory distress syndrome (ARDS).
  - Prophylactic antibiotic should be administered to prevent pneumonia
  - In some patients, pulmonary function deteriorates so dramatically that adequate oxygenation can be maintained only with the use of extracorporeal membrane oxygenation.
- Cardiovascular system
  - In most persons who have been rescued from drowning, the circulation becomes adequate after oxygenation,

rapid crystalloid infusion, and restoration of normal body temperature
  - If volume replacement with a crystalloid infusion fails to restore hemodynamic adequacy, ECG can help inform decisions about the use of inotropic agents, vasopressors, or both
  - Early cardiac dysfunction can occur in patients with a presentation of higher grade (grade 4–6)
- Nervous system
  - Permanent neurological damage is the worst complication of drowning. Intensive assessment and care should be provided with the goals of achieving normal values for glucose, partial pressure of arterial oxygen, and partial pressure of carbon dioxide, with avoidance of any situation that increases brain metabolism.

Prognosis

Prognosis depends on:
- The duration of submersion,
- Quality and promptness of resuscitation
- Clinical status upon arrival to the emergency department, 10% may have long-term sequelae.

Depending upon the duration of submersion, the risk of death or severe neurological sequelae is given in Table 6.

PREVENTION OF DROWNING

It is estimated that more than 85% of cases of drowning can be prevented by supervision, swimming instruction, technology, regulation and public education. The following measures can be taken to prevent drowning (the first eight messages in each section are from the International Open Water Drowning Prevention Task Force).

Keep Yourself Safe

- Learn swimming and water-safety survival skills
- Always swim with others
- Obey all safety signs and warning flags
- Never go in the water after drinking alcohol
- Avoid inflatable swimming aids, such as "floaters"; know how and when to use a life jacket
- Swim in areas with lifeguards
- Know the weather and water conditions before going in the water
- Always avoid shallow or unfamiliar water feet first
- Do not overestimate swimming capability
- Know how to stay away from rip currents, which are involved in more than 85% of drowning events at the beach.

Keep Others Safe

- Help and encourage others, especially children, to learn swimming and water-safety survival skills
- Swim in areas with lifeguards
- Set rules for water safety
- Always provide close and constant attention to children you are supervising in or near water
- Know how and when to use a life jacket, especially for children and weak swimmers
- Learn first-aid and CPR
- Learn safe ways of rescuing others without putting yourself in danger
- Obey all safety signs and warning flags
- Fence in a pool on four sides and install a self-closing, self-latching gate, measures that reduce the incidence of drowning by 50–70%
- Provide a warning sign for shallow water in a pool.

Table 6: Risk of death depending upon the duration of submersion

Time duration	Risk of death
0–5 min	10%
6–10 min	56%
11–25 min	88%
>25 min	Nearly 100%

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21 Procedures

PERIPHERAL VENOUS CANNULATION

Insertion of an indwelling IV cannula in a peripheral vein.

Indications

Administration of fluids and drugs.

Equipment Required

- Alcohol swab
- 24G (yellow) cannula
- Extension set flushed with saline
- 5 mL syringe with saline
- Cannula dressing/sterile strips
- Splint
- Cotton wool.

Procedure

- Identify a suitable vein (common sites include dorsum of hands and feet, antecubital fossa, long saphenous vein at ankle and temples of scalp); a fiberoptic (cold) light is helpful in preterms (Fig.1). Shave with a safety razor if using a scalp vein
- Clean the skin with an alcohol swab
- Stabilize the vein by pulling the skin taut
- Hold the limb and squeeze gently, proximally or apply a tourniquet
- Insert the cannula at an angle of 30° to the skin, bevel upward, and advance slowly until a vessel is hit, and there is flashback of blood into the hub
- Advance the plastic Teflon® cannula into the vein and remove the stylet

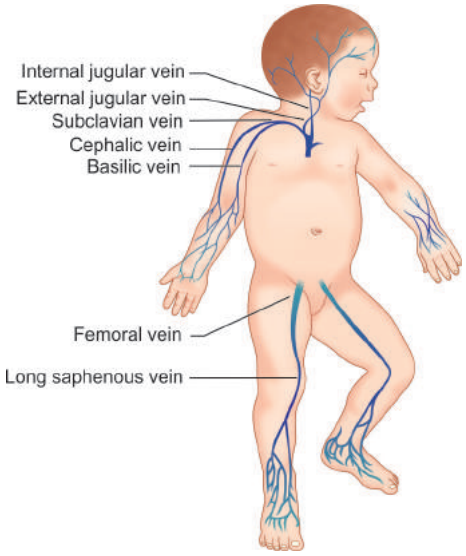


Fig. 1: Veins for intravenous infusion or sampling in infants

- Collect blood directly into bottles or aspirate with needle and syringe
- Fix the cannula to the skin with tapes/sterile strips (Fig. 2), while occluding the vessel with pressure proximally
- Attach the extension set and flush with saline
- Cover with a clear dressing
- Use a splint to immobilize the limb and bandage if the baby is active.

Helpful Hints

- Practice makes perfect! Three strikes and out! Stop after three attempts and ask for help!
- Peripheral veins should be used initially and save larger veins for central access (e.g. long saphenous and antecubital fossa veins)
- In fact in preterm babies, do not use the long saphenous for peripheral lines.

SCALP VEINS

- These are often used in children aged below 2 years and work best in young infants
- Find a suitable scalp vein (usually in the midline of the forehead, the temporal area, or above or behind the ear)
- Shave the area if necessary and clean the skin with an antiseptic solution. The assistant should occlude the proximal to the site of puncture. Fill a syringe with normal saline and flush the butterfly set. Disconnect the syringe and leave the end of the tubing open. Introduce the butterfly needle as described above. Blood flowing back slowly through the tubing indicates that the needle is in the vein
- Care should be taken not to cannulate an artery, which is recognized by palpation. If there is a pulsatile spurting of blood, withdraw the needle and apply pressure until bleeding stops, then look for a vein.

FEMORAL AND INTERNAL JUGULAR CENTRAL VENOUS LINE INSERTION

Indications

Long-term administration of drugs, fluid or total parenteral nutrition (TPN) (should not be inserted in a septic baby unless

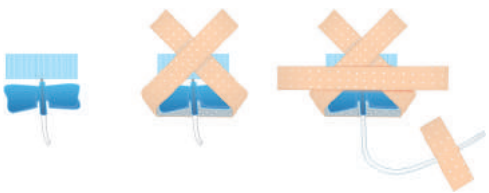


Fig. 2: A method of fixing a butterfly winged needle in infants

there is good antibiotic cover). Should only be attempted by someone experienced with this procedure.

Equipment Required

- Measuring tape
- Sterile gown and drapes
- Central venous line pack (24G or 27G line) +/– 24G (yellow) cannula
- Dressing pack (forceps, swabs, pot)
- Antibacterial solution, e.g. chlorhexidine
- 10 mL syringe and saline and 21G (green) needle
- Skin closure strips
- Clear dressing.

Procedure

Aseptic techniques:

- Wash up, put on sterile gown and gloves
- Attach three-way taps to each lumen of the line and prime with saline
- Clean the skin with antibacterial solution and wash off with saline before applying sterile drapes.

Femoral Vein

Femoral vein landmarks: Aim just medial to the pulsation of the femoral artery (midway between anterior superior iliac spine and symphysis pubis) at the inguinal ligament in the groin. Insert the needle and syringe at 30–45° angle and aiming for the umbilicus while aspirating.

Internal Jugular Vein

- Position the baby supine with a 20° tilt, head down, and the head turned away from the side of insertion
- Insert needle and syringe at the junction of the sternal and clavicular heads of sternocleidomastoid muscle, anterior, and lateral to the carotid artery at a 30° angle, aiming for the nipple (Figs 3 and 4)
- When there is blood flashback, remove the syringe
- Ensure blood flows freely and pass the guide wire through the needle (it should pass easily) and advance 10–15 cm. If the guide wire gets caught, withdraw slightly, rotate, and re-advance

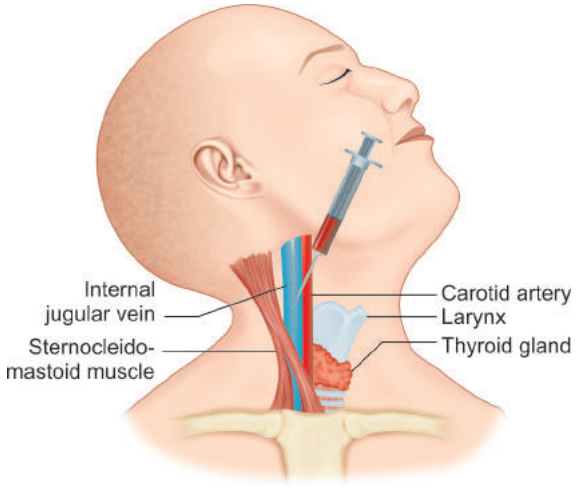


Fig. 3: Site of insertion of a central venous catheter using the internal jugular vein

- Remove the needle over the guide wire while controlling blood loss at the puncture site with a swab (care not to withdraw the wire inadvertently)
- Larger bore lines require a dilator to be passed over the guide wire and into the vein to widen the lumen using a corkscrew movement
- Insert the line over the guide wire (keep an eye on the distal end of the guide wire at all times and ensure it's not lost in the vein)
- Remove the guide wire
- Fix the line to the skin with sutures and a clear dressing
- Check line position with an X-ray.

UMBILICAL VESSELS CATHETERIZATION

Principles

- This is a fully sterile procedure
- If possible, explain to parents why procedure is necessary
- The cord is like a smiley face: Two small round eyes (arteries) and one large floppy mouth (vein)
- The venous line should end up past the liver (not in the heart); the arterial line above T10 (ideal T8), and below the arch of the aorta
- Securing the line is critical.

Procedure: Points to Remember

- Ask an assistant to hold the cord clamp up in the air. Clean the stump thoroughly with cleaning fluid; then hold the clean end and wash the end your assistant has just held
- A long stump enables more attempts but makes it more difficult to thread your line.

Umbilical Artery Catheterization (Fig. 5)

- The artery will need to be dilated to a depth of around 1 cm. Do this very gently, or the artery will tear
- Fill the umbilical line with 0.9% saline
- Gently insert up to distance in cm according to the formula: weight in kg × 3+9
- Carefully suture the stump with umbilical line. A good method is using an elastoplast flag at the base of the line and suture this to the stump (Fig. 5).

Umbilical Vein Catheterization (Fig. 6)

This procedure can be used for resuscitation or exchange transfusion which is usually possible in neonates in the first few days of life. In some circumstances, it might be possible upto 5 days of life.

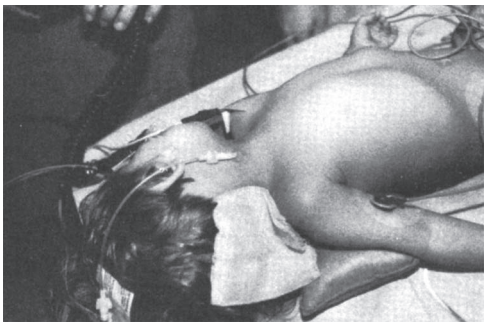


Fig. 4: A catheter in the internal jugular vein inserted for central venous pressure monitoring. The catheter has not yet been secured

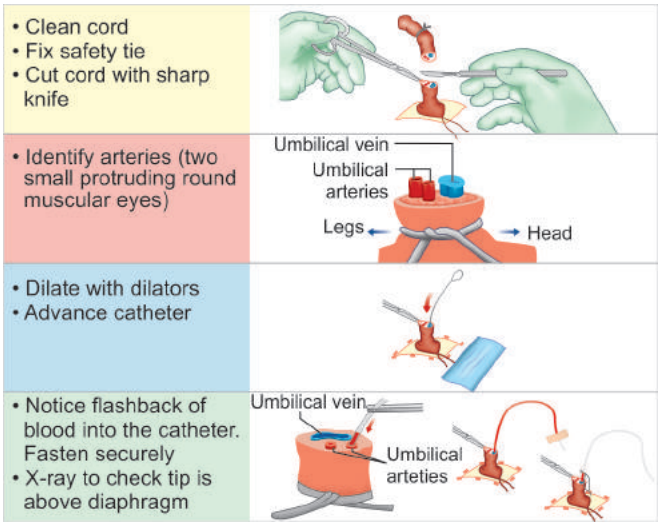


Fig. 5: Umbilical artery catheterization

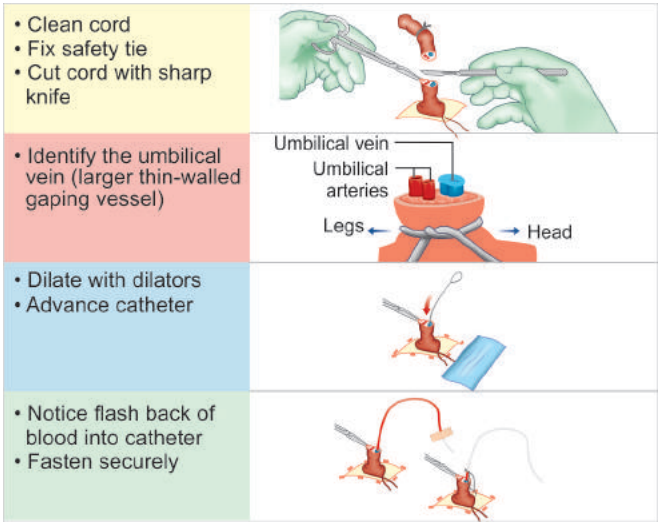


Fig. 6: Umbilical vein catheterization

- Attach a sterile syringe to a 5 Fr gauge catheter and fill with sterile 0.9% saline, then close the tape to prevent air entry (which may cause an air embolus)
- Clean the umbilical cord and surrounding skin with an antiseptic solution and then tie a suture around the base of the cord
- Cut the cord 1–2 cm from the base with a sterile scalpel. Identify the umbilical vein (larger gaping vessel) and umbilical arteries (two thicker walled vessels apart from the vein) and then hold the cord (near the umbilical vein) with sterile forceps
- Hold near end of catheter with sterile forceps and advance it into the vein (it should pass easily) for 4–6 cm
- Check that catheter is not kinked and that blood draws back easily, if there is a block pull gently on the cord, pull back the catheter partly and reinsert
- Secure with two sutures into the cord leaving 5 cm long suture ends. Tape suture and catheter
- Secure this by taking extreme care not to damage the arterial line if done
- Ask the nurses to tape "goalpost" and label the lines as given in Figure 7

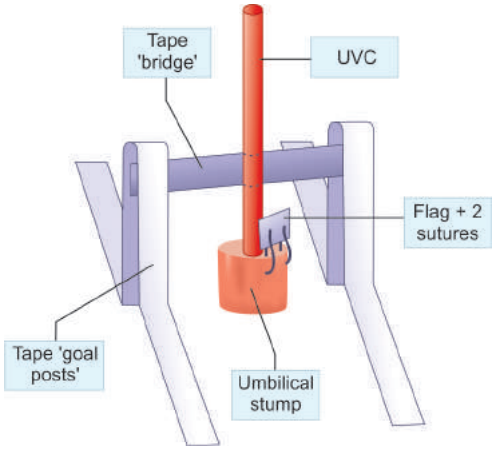


Fig. 7: Umbilical vein catheter taping
Abbreviation: UVC, umbilical venous catheter

- Check the position of lines with an AXR—the venous line goes straight up and the arterial line goes inferiorly and then turns up
- After removal, apply pressure to the umbilical stump for 5–10 minutes.

EXCHANGE TRANSFUSION

Indications

- Hemolytic disease of newborn e.g.:
  - Rh incompatibility
    - Cord Hb less than 10 gm/dL
    - Cord bilirubin greater than 5 mg/dL
    - Rate of rise of bilirubin 0.5 mg/dL/hour
  - ABO incompatibility
- Sepsis
- Disseminated intravascular coagulopathy
- Polycythemia (partial exchange transfusion)
- Aims of exchange transfusion in hemolytic disease of newborn:
  - To correct anemia
  - To reduce hyperbilirubinemia
  - To remove unifixed antibodies
  - To remove damaged and antibody coated red blood cells (RBCs).

Prerequisite for Exchange Transfusion

- Informed written consent of parents
- Blood grouping and cross matching with donor blood
- All materials for umbilical venous vessels catheterization exchange transfusion, resuscitation should be ready
- Setup should be air-free
- Exchange transfusion should be done under radiant warmer in neonatal intensive-care unit (NICU)
- Umbilical catheterization should be done and stabilize catheter before exchange transfusion.

Choice of Blood

- Rh-incompatibility: Always Rh negative blood:
  The best choice is "O" negative or ABO compatible with baby (e.g. mother's Rh, baby's ABO)

- ABO-incompatibility: Only O blood should be used for exchange and Rh compatible with baby (preferably with O-positive blood. Mother-ABO, baby → Rh).

Procedure

There are various ways or technique to carry out exchange transfusion. These are as follows:

- Ideally withdraw blood through umbilical artery catheter (UAC) and replace consciously via umbilical venous catheter (UVC) using a three-way tap
- Umbilical artery catheter or UVC can be used to withdraw blood and a second large venous line used to infuse the fresh blood
- An exchange transfusion can be performed as an "in and out" (push-pull technique) exchange via a single UVC or UAC with a four-way tap. If UVC is the only access then withdraw and replace alternatively.
- Use a closed circuit technique to prevent air embolism.

Techniques of Exchange via Umbilical Venous Catheter

This is well-practiced technique in developing countries. Umbilical vein catheterization is easier than umbilical artery catheterization as it is single and larger and thin-walled. UAC insertion is more difficult.

Equipment Required

- Sterile drapes and gown
- Umbilical catheter set (scalpel holder, artery forcep, tooth forcep, dilator, needle holder, swabs)
- Antibacterial solution, e.g. chlorhexidine
- Cord ligature
- 20 mL disposable syringe
- Four-way tap or stop cock
- If four-way tap is not available then two three-way stop cocks are required which are connected end-to-end to make a four-way stop cock (Figs 8 and 9)
- Umbilical catheter
- Suture (3-0 silk)
- Saline set leading to empty saline bag into which patient's blood will be expelled.

Procedure

- Three persons are needed. First person will do push-pull technique of exchange blood transfusion
- Another person must keep a written record of each infusion and withdrawal of cumulative volume, third person for supervision of the procedure
- Umbilical vein catheterization is done first (see UVC procedure)

Fig. 8: Three-way stop cock used in exchange transfusions

- Length to be inserted = 2 × weight in kg + 5 cm + stump length in cm
- Using excessive force may create false passage within the cord
- If there is a resistance at 2 cm then UCV may be in portal sinus. Withdraw slightly and re-inset
- Tip of line should be in the inferior vena cava (above diaphragm) but not into right atrium and not in the liver (confirmed by X-ray).

Fix the catheter by putting a suture through the stump and skin (avoiding the vessels and avoiding tying to the catheter). A purse string type of suture can also be given.

Blood Volume for Exchange Transfusion

Volume = Double volume in mL: 2 × 85 × body weight in kg (volume of blood newborn is approximately 85 mL/kg).

Each time total in and out of blood:

- <1 kg = 5 mL aliquots
- 1–2 kg = 10 mL
- >2 kg = 15 mL
- >3 kg = 20 mL.

After Insertion of Umbilical Venous Catheter

- One way of stop cock (four-way tap) is connected with distal end of umbilical catheter and another (opposite) end is connected to 20 mL disposable syringe (Fig. 10)
- Distal sideway from the operator is connected to donor blood set
- Proximal sideway is connected to a saline set leading to an empty saline bag into which patient's blood is expelled out and discarded
- One round should be made to confirm the functioning of the exchange transfusion set up. Then exchange is done by push-pull technique

Fig. 9: Two three-way stop cocks are attached end-to-end to make four-way stop cock

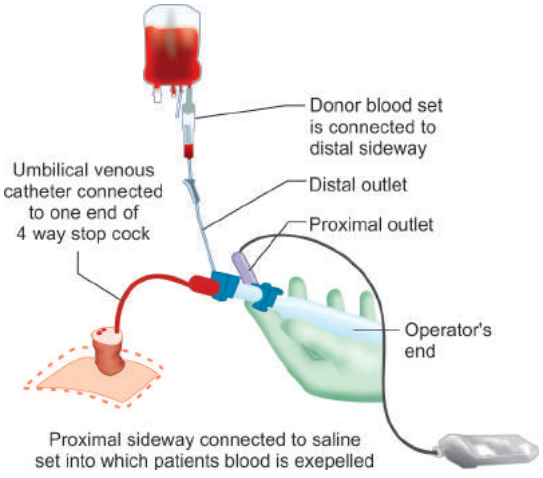


Fig. 10: Procedure of exchange transfusion

- The defined amount of blood (mentioned above) is withdrawn first from the patient slowly and steadily. It is then expelled out through proximal sideway outlet by keeping the inlet closed
- Then 15 mL of donor's blood is drawn from the suspended bag through distal sideway outlet, keeping the proximal one closed and this drawn blood is pushed slowly to the infant
- If the baby is symptomatically hypocalcemic, 1 mL/kg of calcium gluconate can be given very slow IV with cardiac monitoring
- First and last aliquots of blood should be withdrawn to keep in negative balance
- Agitate the donor blood at 10–15 min interval so that cells do not settle
- Monitor the vital signs at regular interval SPO_2, temperature, respiratory rate—½ hourly, perform ECG monitoring
- Should be careful about air bubble in lines.

Special Attention

- Do not perform exchange transfusion through umbilical vein if tip is in portal circulation—chance of necrotizing enterocolitis (NEC)
- Take about 1 hour to perform exchange transfusion in a vigorous baby, longer in sick baby
- If baby is ventilated, need to increase fraction of inspired oxygen (FiO_2) during exchange
- Donor blood warm at 34–35°C
- The need for giving calcium and sodium bicarbonate is controversial. Planned to administer if baby is symptomatic or laboratory investigations are suggestive
- Feeding: May be attempted half the usual feed after 2 hours, full after 4–6 hours, if stable.

Investigations During Exchange Transfusion

- Before exchange transfusion (with first withdrawal blood):
  - Serum bilirubin (direct and indirect)
  - Full blood count (Hb%)
  - Serum. electrolytes, serum calcium, blood glucose, blood gas, serum creatinine.
- During exchange transfusion:
  - Blood glucose and blood gas
- After exchange transfusion:
  - Blood glucose, serum electrolytes, serum calcium, serum bilirubin, Hb%
- Six hour after exchange transfusion:
  - Serum bilirubin, Hb%, serum electrolytes, serum calcium, blood glucose
- Subsequently: only serum bilirubin 6–12 hourly (individualizing timing according to rate of rise of bilirubin and patient).

Complications

Immediate Complications

- Perforation
- Hemorrhage
- Embolism (air)
- Cardiac arrhythmia [due to stimulation of sinoatrial (SA) node]
- Hypothermia
- Hypoglycemia
- Hypocalcemia
- Hyperkalemia
- Volume imbalance
- Anemia, polycythemia, thrombocytopenia
- Collapse, acidosis/alkalosis.

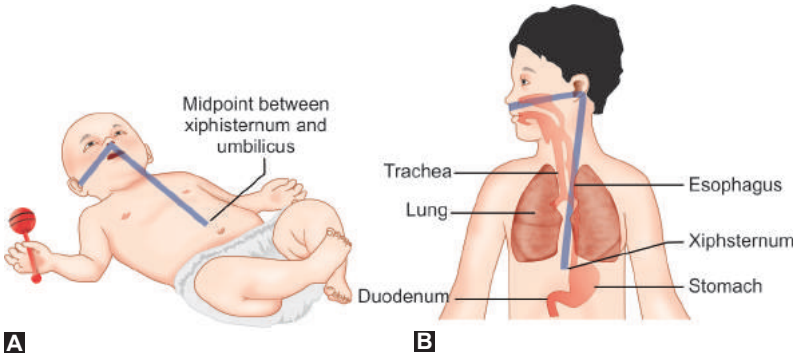
Late Complications

- Infection, NEC
- Portal vein thrombosis
- Portal hypertension.

INSERTION OF A NASOGASTRIC TUBE (FIGS 11A AND B AND TABLE 1)

Procedure

- Select an appropriately sized nasogastric (NG) tube (≤8 kg, 6 Fg; ≥8 kg, 8 Fg), sterile water; measuring tape, permanent marker pen, 50 mL syringe; tape; pH paper. Consider appropriate sedation
- Open packaging and remove the guide wire from within the tube; flush the tube with 10 mL of sterile water, then lubricate the guide wire with sterile water and reinsert into the tube (NB: do not use a gel lubricant as this may affect the accuracy of the pH paper response)
- Using a tape measure, determine the length of the tube that needs to be inserted: for an infant less than 1 year, measure from the nose to the ear to the mid-point between the xiphisternum and umbilicus, continuing to the right iliac crest, and mark the tube at this length; for a child greater than 1 year measure from the nose to the ear to the sternum, continuing to the right iliac crest
- Elevate the bed to 15–30° and if clinical condition allows turn patient on their side with left side up; aspirate the NG tube already in situ



Figs 11A and B: Measuring a nasogastric (NG) tube. (A) For infants and newborns; (B) For children

Table 1: How to confirm correct nasogastric (NG) tube position

Confirmatory test result	Action
Positive aspiration of gastric contents (pH <5.5 using pH paper) and correct length of tube	Accept placement as correct
Unable to obtain aspirate of gastric contents despite correct external length of tube	• If possible, offer drink to child and re-aspirate • Inject 2–5 mL of air and re-aspirate • Inject 2–5 mL 0.9% saline, position child on their side and re-aspirate
Unable to obtain aspirate of gastric contents and incorrect external length of tube	Reposition tube to correct length and re-aspirate; if no aspirate, follow steps 1–3 above
Unable to obtain aspirate of gastric contents and correct external length of tube	Confirm satisfactory placement by chest/abdominal X-ray or remove tube and re-site, then repeat confirmatory tests

- Use sterile water to lubricate the tip of tube; it is often easier and more comfortable to insert the NG tube through the same nostril as the NG tube
- Aspirate a small amount of stomach contents with a syringe to confirm that the tube is in place. If no aspirate is obtained, inject air down the tube and listen over the abdomen with a stethoscope

7. If there is any doubt about the location of the tube, withdraw it and start again.

LUMBAR PUNCTURE (FIGS 12 AND 13)

- Position of the child:
  - There are two possible positions:
    - The child lying down on the left side (particularly for young infants)
    - In the sitting position (particularly for older children).

Lumbar Puncture When the Child is Lying on the Side

- A hard surface should be used. Place the child on the side so that the vertebral column is parallel to this surface and the transverse axis of the back is vertical
- The assistant should flex the back of the child, pull up the knees toward the chest, and hold the child at the upper back between the shoulder and buttocks so that the back is bent. Hold the child firmly in this position. Make sure that the airway is not obstructed and the child can breath normally. Take particular care in holding young infants. The assistant should not hold a young infant by the neck and should not flex the neck which may cause airway obstruction
  - Check the anatomical landmarks:
  - Locate the space between the third and fourth or between vertebra which is at the junction of the line between the iliac crests and the vertebral column
- Prepare the site:
  - Use aseptic technique. Scrub the hands and wear sterile gloves
  - Prepare the skin around the site with an antiseptic solution
  - Sterile towels may be used
  - In older children who are alert, give a local anesthetic (1% lidocaine) infiltrate in the skin over the site
- Perform the lumbar puncture (LP):
  - Use an LP needle with styled (22G gauge, 1.5 inch for a young infant)

    Or
  - 20 gauge for an older infant and child; if these are not available, hypodermic needles may be used). Insert the needle into the middle of the intervertebral space and aim the needle toward the umbilicus
  - Advance the needle slowly. The needle will pass easily until it encounters the ligament between the vertebral processes. More pressure is needed to penetrate this ligament, less resistance is felt as the dura is penetrated. In young infants this decrease in resistance is not always felt, so advance the needle very carefully
  - Withdraw the needle and stylet completely and put pressure over the site for a few seconds. Put a sterile dressing over the needle puncture site.

If the needle is introduced too far, a lumbar vein may be punctured. This will result in a "traumatic tap" and the spinal fluid will be bloody. The needle should be withdrawn and the procedure repeated in another disc space.

TRANSURETHRAL CATHETERIZATION

Indications

- Close monitoring of urine output/fluid balance

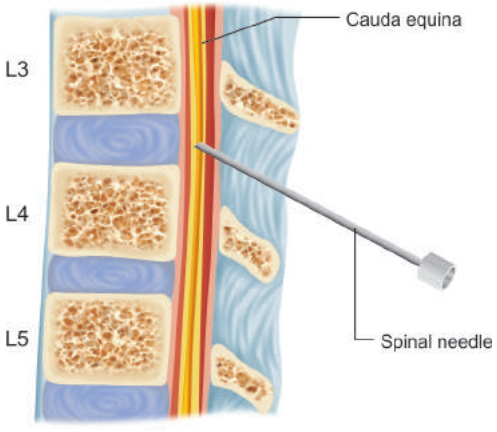


Fig. 12: Lumbar puncture anatomy

Fig. 13: Lumbar puncture procedure

- Urinary retention
- Obtain uncontaminated urine for microbiology.

Equipment Required

- Sterile dressing pack
- Urinary catheter (3–5 Fr) or feeding tube (5 or 6 Fr)
- Umbilical catheters (2–3 Fr) are sometimes used in very small babies, although this is not recommended by nephrologists/urologists
- Sterile lubricant gel
- Tape.

Procedure

- Aseptic technique
- If sample required for microbiology have a universal container ready for a clean catch sample, as spontaneous urination during the procedure is not uncommon
- Position the baby supine with hips abducted (assistant will need to hold the legs in position)
- Clean the external genitalia and perineum with antibacterial solution and wash off with saline (do not pull back the foreskin in males)
- Insert the lubricated catheter/feeding tube through the urethra! meatus (unable to directly visualize in males) and advance slowly until urine flows from the catheter
- Attach catheter to collecting bottle
- Fix catheter to anterior abdominal wall and one leg with tape (penis pointing upward in boys!).

Complications

- Urethral trauma, hematuria and urethral stricture
- Infection.

SUPRAPUBIC ASPIRATION OF URINE (FIGS 14 AND 15)

Indications

- To obtain uncontaminated urine for microbiology.

Equipment Required

- Antibacterial solution, e.g. chlorhexidine and saline
- Sterile dressing pack
- 23G (blue) needle
- 10 mL syringe
- Universal container.

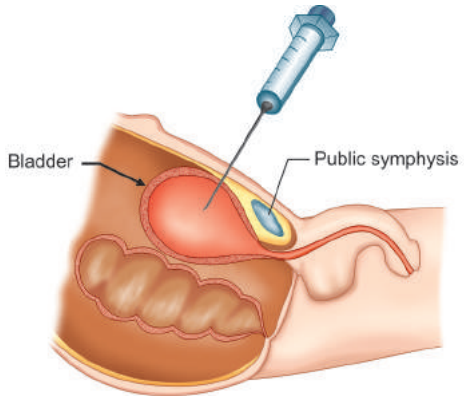


Fig. 14: Suprapubic aspiration of urine

Procedure

- Confirm bladder is filled by palpation or ultrasound (US) scan
- Have a universal container ready for a clean catch sample, as spontaneous urination during the procedure is not uncommon
- Aseptic technique
- Position the baby supine with hips abducted (assistant will need to hold the legs in position)
- Clean the skin of lower abdomen with antibacterial solution and wash off with saline. Use an alcohol swab if looking for fungi
- Insert needle with attached syringe at 90° to the abdominal wall, 1 cm above the symphysis pubis in the midline
- Advance needle slowly to depth of 1–2 cm, while aspirating continuously until urine aspirates
- Aspirate as much urine as possible
- Remove needle and apply pressure to puncture site
- Test at cot-side with urine analysis stick and send remainder for microbiology (culture and sensitivity).

Complications

- Bladder trauma and hematuria
- Bowel puncture.

VENTRICULAR TAP

Indications

- As for LP and administration of intrathecal antibiotics
- Removal of cerebrospinal fluid (CSF) in a baby with rapidly increasing head circumference, but not fit for ventriculoperitoneal shunt insertion.

Equipment Required

- As for LP + safety razor.

Procedure

- Perform cranial US to estimate angle and depth for insertion. Tap side that has largest ventricle or, if equal, right (non-dominant) side shave the hair around the point of insertion (lateral angle of the anterior fontanelle) with aseptic technique
- Position the baby supine and assistant holds the head in the midline and very still
- Remember to monitor the baby's condition throughout the procedure. Clean the skin with antibacterial solution and

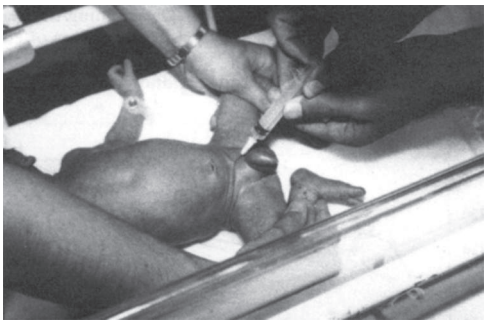


Fig. 15: Demonstration of the angle and site of insertion of the needle for suprapubic aspiration (SPA) of urine in a newborn

wash off with saline. Insert the needle and advance at the angle, and to the distance estimated from scanning, aiming for the inner canthus of the opposite eye, there is a definite "give" when entering the ventricle
- Remove the stylet and measure pressure with manometer and collect samples as for LP
- Drain 10–15 mL/kg CSF in cases of hydrocephalus and remeasure pressure
- Replace stylet, withdraw needle, and apply pressure with gauze before using an adhesive spray.

Helpful Hints

- Use US guidance if there is any difficulty finding the ventricle
- Use the same needle track if repeating the procedure.

ENDOTRACHEAL INTUBATION (FIGS 16 TO 18)

Indications

- Provide definitive and secure airway for ventilation
- Administration of surfactant.

Equipment Required

- Laryngoscope + straight blades (size 0 or 1)
- Continuous heart rate and O_2 saturation monitoring
- Endotracheal tube (ETT) including a size above and below
- Ventilation equipment and gas supply (facemask + self-inflating bag or breathing system, e.g. Neopuff/Ayre's T-piece)
- Introducer (optional)
- Fixation device, or ties and flange
- Suction system with Yankauer sucker/1 OFG (black) suction catheter
- Ensure good IV access and appropriate drugs for intubation (in elective cases)
- Ventilator ready to use (tubing, connectors, settings).

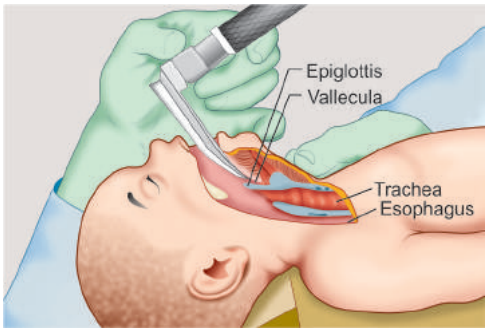


Fig. 16: Endotracheal tube in position

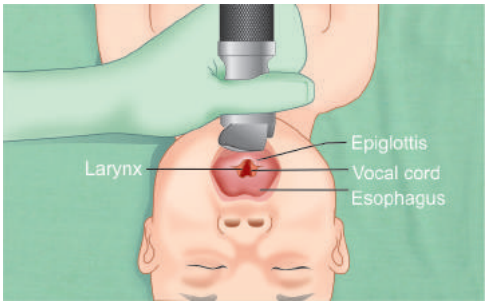


Fig. 17: View of the vocal cords

Procedure

- Requires careful supervision until confident. Insert introducer if required into ETT (not protruding from end) and bend around connector. Hold laryngoscope in left hand, open blade and check light source
- *Step 1*: Position the baby supine with head midline and slightly extended (can use a rolled-up nappy under neck)
- *Step 2*: Suction the oropharynx to clear secretions
- *Step 3*: Pre-oxygenate baby for 3 min
- *Step 4*: Elective intubations: Administer drugs for intubation, e.g. fentanyl (5 µg/kg), atropine (20 µg/kg) then suxamethonium (2 mg/kg) (NB: muscle relaxants should only be used by someone competent with bag-mask ventilation)
- *Step 5*: Insert blade so the blade lies in the midline (Fig. 16)
- *Step 6*: Lift the epiglottis by a vertical movement of the laryngoscope to expose the vocal cords (Fig. 17)
- *Step 7*: Hold ETT in right hand, introduce into right corner of mouth and pass the tip of the ETT through the cords (Fig. 18) under direct vision until the thick black marking lies just below the cords (1–2 cm). The assistant continuously monitors O_2 saturation and heart rate, and advises when to resume mask ventilation (at 30 sec if intubation procedure duration exceeds 30 seconds, or if the child is bradycardic or saturation and HR falling precipitously) and return to step 1
- *Step 8*: Remove introducer and start ventilating through ETT with bag/breathing system
- *Step 9*: Look for good chest movement, improving O_2 saturation and listen for bilateral and equal breath sounds. If there is no improvement in saturation and heart rate then remove the tube and start bagging without delay, and return to step 1
- *Step 10*: Firmly hold the ETT at the lips. Fix the ETT with a preformed fixation device or suturing flange to ETT, and tying flange to a hat
- *Step 11*: Trim ETT to reduce dead space
- *Step 12*: Connect to ventilator and observe chest movement
- *Step 13*: Check ETT position with chest X-ray (tip half-way between clavicles and carina)
- *Step 14*: Document in case notes: View of cords, number of attempts, size of ETT and length from tip to lips.

Helpful Hints

- If in doubt that tube is in the correct place, take it out!
- Endotracheal tube length: Approximate wt + 6 cm at lips, less reliable under 1 kg (Table 2)
- Overextending the neck can obscure the view of the cords
- Cricoid pressure (gentle downward pressure on the cricoid cartilage) may improve view of the cords

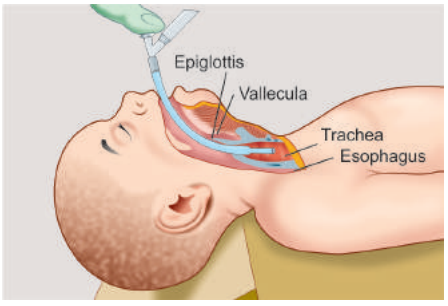


Fig. 18: Tracheal intubation of a neonate showing the position of the laryngoscope blade

Table 2: Size and length of endotracheal tube (ETT)

Weight (kg)	Gestation (weeks)	ETT size (cm)
<1	<28	2.5
1–3	28–34	3.0
>3	>34	3.5

- Do not use excessive force to pass the ETT through closed or tight cords
- If air entry is greater on the right, slowly withdraw ETT until air entry is equal.

Complications

- Local trauma to mouth and oropharynx
- Pneumothorax
- Airway edema and subglottic stenosis
- Nasal damage (with nasal ETT).

SURFACTANT ADMINISTRATION

What is Surfactant?

- It is a natural substance produced in utero by the developing lungs after 24 weeks of gestation by type-II alveolar cells.
  - It consists of phosphatidylcholine and proteins
  - It forms a monolayer over the alveolar surface. It (1) lowers the surface tension to reduce the work of expansion, and (2) prevents atelectasis
- Types of surfactants for clinical use:
  - Natural:
    - Porcine lung derived → Curosurf®
    - Bovine derived → Survanta®
  - Synthetic:
    - Exosurf (phosphatidylcholine + hexadecanol + tyloxapol)
    - Artificial lung expanding compound
- Indication:
  - Ventilated baby less than 32 weeks gestation, if continues to be oxygen dependent
  - Gestation less than 30 weeks, a first dose soon after birth after lung is aerated and requires ventilation at that time
  - Established respiratory distress requires ventilation with more than 40% FiO_2 to maintain partial pressure of oxygen (PaO_2) >90%
- Survanta® dose: 100 mg/kg or 4 mL/kg 1–3 doses, within 48 hours, 6 hourly
- Second dose—national should be given within 6 hours of first dose
- Exosurf: 67.5 mg/kg or 5 mL/kg, 12 hourly, 2–3 doses
- Curosurf®: 100 mg/kg or 1.25 mL/kg, 12 hourly, 2–3 doses.
- How to administer surfactant? (Fig. 19)
  - Counseling and consent of parents for administration of Survanta®
  - Setup: Level-III NICU
  - Baby should be intubated and on mechanical ventilation
  - Clear the trachea of mucus
  - Preoxygenate the lungs to minimize the risk of cyanosis during administration
  - Instill the necessary dose of Survanta® (surfactant) down the ETT while maintaining respiratory support

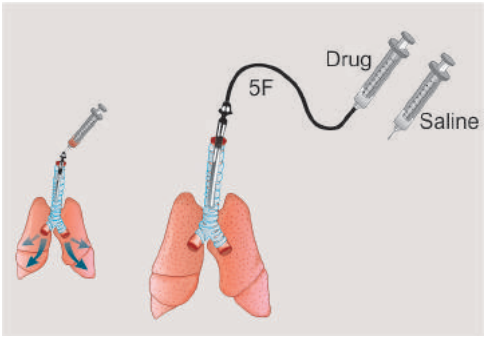


Fig. 19: Procedure of administration of surfactant

  - Changing the position of the baby during or after instillation may improve distribution
  - The ventilator settings need to be adjusted after giving surfactant.

MOBILE TRANSFUSION

Requirements

- 50 mL syringe
- Butterfly needle
- Blood transfusion set
- Blood bag with anticoagulant.

Procedure

- This procedure is considered when very small volume of blood is to be transfused for neonates and infants
- First blood grouping of the donor and recipient is done and cross-matched
- The physician has to wash hands thoroughly then put on gloves
- Then with strict aseptic precautions, 3 mL of anticoagulant is down for each 20 mL of blood transfusion in a 50 mL syringe from the anticoagulant containing blood bag
- After proper local aseptic care, donor's blood is drawn in the syringe by a 19G butterfly needle with a ratio of anticoagulant: Blood equal to 3:17
- The blood bag is then emptied of the rest of the anticoagulant and the blood from the syringe is transferred to the blood bag and then transfused as usual method.

Complications

Minimum complications other than usual hazards of blood transfusion

BONE MARROW ASPIRATION (FIGS 20 TO 22)

- Parts: Trocar (stillete) with knob
- Cannula
- Adjustable guard
- Site of aspiration:
  - Any age: Anterior and posterior iliac crest
  - Birth to 2 years: Medial aspect of upper end of tibia
  - 6 years or older: Sternum (menubrium sterni).

Procedure

- First consent should be taken before doing the procedure
- The guard of the aspiration needle has to be fixed about 1/2 the depth of bone

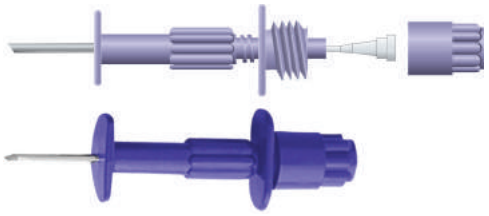


Fig. 20: Bone marrow aspiration needle with trocar and cannula

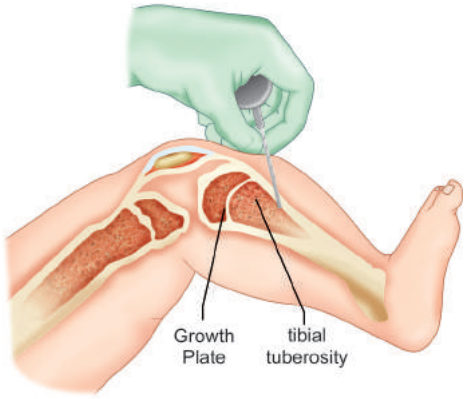


Fig. 21: Site of bone marrow aspiration in child

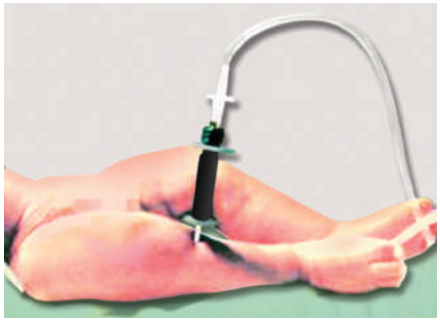


Fig. 22: Bone marrow underway

- The patient has to lie down in prone position for iliac crest site or on his back for menubrium sterni
- Physician should wear mask, gown and gloves
- After putting skin wash and draping, with all aseptic precautions local anesthesia (2% xylocaine) is infiltrated upto periosteum after locating the puncture site
- Then aspiration needle is pushed through the skin vertically down by screwing method until bone is penetrated
- A sudden loss of resistance indicates that the needle entered in the marrow space
- Then the stillete is removed and a syringe is attached to the cannula
- Marrow is aspirated by negative suction and needle is withdrawn and puncture site is pressed and seated with sterile swab.

Indications of Bone Marrow Aspiration

- Diagnostic:
  - Leukemia
  - Aplastic anemia
  - Idiopathic thrombocytopenic purpura (exclusion of differential diagnosis)
  - Secondary marrow infiltration by:
    - Lymphoma
    - Myelofibrosis
  - Kala-azar (LD body)
  - Storage disease (e.g. Gaucher's disease)
  - Secondary malignancies
  - Therapeutic: bone marrow transplantation.

Contraindications

- Local skin infection
- Known case of hemophilia
- Thrombocytopenia.

Complications

- Suction pain (local)
- Over penetration
- Hemorrhage
- Injury to deep structures (great vessels)
- Introduction of infection (osteomyelitis)
- Shock (vasovagal/hemorrhagic).

Bone Marrow Aspiration Method

- Aspiration
- Trephine biopsy
- Combined.

Self-inflating Ambu Bag

- *Parts:* Mouth piece/mask
- AMBU bag proper
- O_2-connector
- O_2-connector
- Pop-up valve (safety valve).

Uses

- Neonatal resuscitation in case of:
  - Perinatal asphyxia
  - Recurrent asphyxia
  - Severe respiratory distress syndrome
  - For cardiopulmonary recitation—due to any cause
  - Respiratory failure from any cause
    - Severe pneumonia
    - Severe acute asthma
    - Poisoning
    - Guillain-Barré syndrome (GBS)
    - Head injury
    - Bulbar poliomyelitis.

Contraindications

- Diaphragmatic hernia
- Tracheoesophageal fistula (except high variety)
- Eventration of diaphragm
- Hiatus hernia.

Peritoneal Dialysis

Indications

- Fluid overload associated with hypertension, pulmonary edema or heart failure
- Persistent hypercalcemia (>7 mmol/L or ECG change or not responds to therapy)
- Severe metabolic acidosis—unresponsive to medical treatment
- Blood urea >50 mg/dL/blood urea nitrogen >100–150 mg/dL

- Serum creatinine: >500 µmol/L
- Severe uremia with risk of encephalopathy
- Anuria more than 3 days
- Inborn error of metabolism, for example:
  - Urea cycle disorder
  - Maple syrup urine disease
  - Congenital form of lactic acidosis
  - Salt poisoning.

Procedure

Pre-requisition:

- Informed written consent
- Bleeding time (BT), clotting time (CT), prothrombin time (PT), platelet count should be normal
- Blood grouping and cross matching
- Open IV channel and maintain with 10% dextrose in quarter strength normal saline
- Bladder should be empty
- Transfer the patient at dialysis room with medicine and equipment (PD catheter with set, dialyzing fluid, local anesthetics, surgical blades, sterile gloves, kidney tray with artery forceps, etc.).

Preparation of Patient:

Patient should be lying on supine position

- Bladder should be empty
- Maintain proper aseptic precaution
- Site of puncture: Midline or left flank at the level of umbilicus beyond the rectus abdominis lateral margin
- Initial inject local anesthetics
- Stab given by surgical blade
- Introduction of peritoneal dialysis (PD) catheter: Direction toward right iliac fossa and attach with PD set.

Amount of fluid given in each cycle:

- 20–30 mL/kg, holding time: 30–60 minutes
- Total duration: 72 hours.

Composition of PD fluid:

- Na^+: 141 mmol/L
- Cl^-: 101 mmol/L
- Ca^{++}: 3.5 mmol/L
- Mg^{++}: 1.5 mmol/L
- Acetate: 45 mmol/L
- Glucose: 1.5%.

Following substances are absent in PD fluid:

- K^+, SO_4, PO_4, urea, creatinine.

Complications

- Infection: Peritonitis
- Bleeding after insertion of catheter
- Perforation of bowel or bladder
- Abdominal pain
- Leakage around the catheter
- Difficult drainage—may be due to kinking of catheter, catheter blockage—by omental plugging, fibrin clots
- Loss of ultrafiltration
- Loss of protein (0.5–1 mg/L)
- Electrolyte imbalance, hyperglycemia, hypothermia hypotension.

Benefits

- Fluid removal
- Urea and creatinine clearance
- Hypercalcemia correction
- Toxin clearance.

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22 Drug Therapy in Children

Some important and frequently used drugs in children, with their doses and routes of administration:

ANTIMICROBIALS

ANTIBIOTICS

Drug	Route	Doses and time/day	Availability, generic and some trade (local) names
Penicillins Procaine penicillin • Pneumonia • Acute rheumatic fever • Post-streptococcal Acute glomerulonephritis	IM	25,000–50,000 IU/kg/day Neonates 50,000 IU/kg/day Once daily	Inj. procaine penicillin 4,00,000 IU/vial Inj. G procaine penicillin 4,00,000 IU/vial (Gonoshastha Pharmaceuticals Ltd.), Pronapen
Benzathine penicillin Prophylaxis of rheumatic fever. Acute glomerulonephritis, streptococcal pharyngitis	IM	<27 kg: 600,000 LacI U >27 kg: 1,200,000 IU Once in every 3 weeks	Penidure LA (Wyeth) 1.2 million1,200,000 IU, BPEN (Opsonin) 600,000, Benzapen (Square Pharmaceuticals Ltd.), 1,200,000 IU, 2,400,000 IU/vial
Benzyl penicillin IPD	IV/IM	Streptococcal pharyngitis 100,000–200,000 units/kg/day in four divided dose For severe infection, 200,000–300,000 IU/kg/day in four to six divided doses	Injection benzyl penicillin penicillin G, Crystalline penicillin 5,00,000–10,00,000 units/vial (Renata)
Penicillin V (phenoxymethylpenicillin)	Oral	10 mg/kg 6 hourly for 10 days For rheumatic fever prophylaxis 200,000 IU (125 mg) twice daily	Syrup: 125 mg/5 mL, Penvik® (Square Pharmaceuticals Ltd.), Crystapen V (GSK) Tablet 250 mg (Penvik, Crystapen V)
Ampicillin	Oral/IV	100–200 mg/kg/day in three to four divided dose Meningitis: 200–400 mg/kg/day in four divided dose	Capsule 250 mg, Ampicin (Square Pharmaceuticals Ltd.), Ficillin (Sanofi-Aventis) Syrup 125 mg/5 mL (Ampicin, Ficillin) Injection 500 mg/vial (Ampicin, Ficillin)
Amoxycillin	Oral/IV	25–50 mg/kg/day three divided dose	Capsule 250 mg Fimoxyl (Sanofi-Aventis), Moxacil (Square Pharmaceuticals Ltd.), Tycil® (Beximco Pharma) Syrup: 125/5 mL (Fimoxyl, Moxacil, Tycil) Drop: 100 mg/mL (Fimoxyl, Moxacil, Tycil) Injection 500 mg/vial (Fimoxyl, Moxacil)
Amoxycillin + Clavulanic acid	Oral/IV	20–40 mg/kg/day Amoxycillin in three divided doses, Double strength (DS, Fort) Amoxclav (DS, Fort) can be given in two divided doses	Tablet 375 mg (Amox 250 mg, Clav 125 mg) Tablet 625 mg (Amox 500 mg, Clav 125 mg) Tablet: 1.250 g (Amox 1 g, Clav 250 mg), Moxaclav® (Square Pharmaceuticals Ltd.), Amoxyclav, Augmentin (GSK) Suspension: Amox 125 mg, Clav 31.25/5 mL Fimoxyclav (Sanofi-Aventis), Moxaclav (Square Pharmaceuticals Ltd.) Suspension: Augmentin (125/31 and 250/62 in 5 mL) Suspension: Moxaclav fort/Fimoxyclav DS (Amoxi 400 mg and Clav 57.5 mg/5 mL) Injection: Amoxyclav 600 (Amox 500 mg, Clav 100 mg) Injection: Fimoxyclav 600 mg (Sanofi-Aventis)

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Drug	Route	Doses and time/day	Availability, generic and some trade (local) names
Piperacillin antipseudomonas and *Klebsiella* penicillin	IV/IM	100–300 mg/kg/day in four divided dose	Injection: Pipracil: 1 g, 2 g, 4 g/vial In combination with Tozabactam. Tazocin (Wyeth). Injection containing piperacillin 2 g and tazobactam 250 mg
Carbenicillin antipseudomonas penicillin	IV/IM	200–300 mg/kg in four divided dose	Injection Piopen 1 g powder vial
Ticarcillin antipseudomonas penicillin	IV/IM	200–300 mg/kg/day in four divided dose	Injection: Ticar 1 g, 3 g, 5 g/vial Injection: Timentin (GSK) 1.6 g vial, ticarcillin 1.5 g, Clavulanic acid 100 mg, 3.2 g vial, ticarcillin 3 g, clavulanic acid 200 mg
Cephalosporins First generation Cephalexin	Oral	25–50 mg/kg/day in four divided dose	Capsule: 250, 500 mg Syrup: 125 mg/5 mL Drops: 100 mg/mL Ceporex (GSK), Acelex (Acme)
Cefadroxil	Oral	30 mg/kg/day in two divided doses	Capsule: 250, 500 mg Suspension: 125 mg/5 mL Adora (Incepta Pharmaceuticals Ltd.), Arocef® (SKF)
Cepharidine	Oral/IV/IM	25–50/kg/day in three to four divided doses	Capsule: 250 mg, 500 mg Suspension: 125 mg/5 mL Drop: 125 mg/1.25 mL Injection: 250 mg, 500 mg vial Sefrad® (Sanofi-Aventis), Sefril (Acme), Lebac™ (Square Pharmaceuticals Ltd.)
Second generation cefaclor	Oral	20–40 mg/kg/day (maximum 2 g) in three divided doses	Capsule: 250 mg, 500 mg Suspension: 125 mg/5 mL Biocef® (Novartis), Lorasef® (Square Pharmaceuticals Ltd.)
Cefuroxime	IV/IM Oral	50–100 mg/kg/day in three divided doses	Tablet: 250, 500 mg (as axetil) Suspension: 125/5 mL (as axetil) Injection: 750 mg vial (as sodium salt) Kilbac (Incepta Pharmaceuticals), Zinnat (GSK), Furocef (Renata) available as axetil in tablet and suspension and as sodium salt in injection form
Third generation cefotaxime	IV/IM	100–150 mg/kg/day in two to three divided dose Meningitis: 200 mg/kg/day in two to three divided dose	250 mg/500 mg/1 g vial Injection Taxim (Acme), Maxcef (Square)
Ceftriaxone • Meningitis • Typhoid • Septicemia	IV/IM	50–100 mg/kg in one to two divided dose 100 mg/kg/day in meningitis septicemia	250 mg, 500 mg, 1 g, 2 g vial Axon (Aristopharma), Arixon (Beximco pharma), Traxon (Opsonin), Rocephin (Roche), Rofecin (Radiant), Aciphin (ACI), Ceftrix (Novo), Trizon (Acme), Ceftron (Square Pharmaceuticals Ltd.), Exiphin (Incepta Pharmaceuticals Ltd.)
Ceftazidime • Pseudomonas	IV/IM	50–100 mg/kg/day Meningitis: 150 mg/kg/day in two to three divided dose	250 mg, 500 mg, 1 g vial Injection: Fortum (GSK), Tazid (Square Pharmaceuticals Ltd.) Injection: Ceftazim (Aristopharma)
Cefixime	Oral	10 mg/kg Two divided dose 20 mg/kg/day in typhoid	Capsule: 200 mg, 400 mg Tablet: 200 mg Syrup: 100 mg/5 mL, as DS or XL as 200 mg/5 mL Cef-3 (Square Pharmaceuticals Ltd.), Cefim-3® (ACI), Roxim (Eskayef), Roxim XL (200 mg/5 mL), Afix (Aristopharma), Afix-DS (200 mg/5 mL), Triocim (Beximco), Fix-A (Acme), Emixef (Incepta), Cebex® (Novo Health Care and Pharma Ltd.), Ceftid (Opsonin), Zemicef (Popular Pharmaceuticals Ltd.)

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Drug	Route	Doses and time/day	Availability, generic and some trade (local) names
Cefpodoxime Proxitil	Oral	8 mg/kg/day in two divided doses 16 mg/kg/day in two divided doses in typhoid	Capsule: 100 mg, 200 mg Tablet: 100 mg, 200 mg Suspension: 40 mg/5 mL, 80 mg/5 mL Drop: 20 mg/mL Texetil (Aristopharma), Ximeprox (Incepta Pharmaceuticals Ltd.), Vercef® (Beximco Pharma) drop, suspension, Caps. Texetil DS (80 mg/5 mL), Ximeprox DS (80 mg/5 mL)
Fourth generation Cephalosporin Cefepime	IV/IM	100–150 mg/kg/day in two to three divided doses	500 mg, 1 g, 2 g Maxipime 1 g (Square Pharmaceuticals Ltd.) Forgen (Aristopharma) 500 mg, 1 g, 2 g
Aminoglycosides Amikacin	IV/IM	10–15 mg/kg/day in two to three divided doses	2 mL vial 100 mg, 250 mg/2 mL Injection Kacin® (ACI) Injection: Psudonil (Drug International Ltd.)
Gentamycin	IV/IM	<7 days 1.5–2.5 mg/kg/dose >7 days 1.5–2.0 mg/kg/dose two to three times	Ampule 20 mg/2 mL, 80 mg/2 mL Injection Genacyn® (Square Pharmaceuticals Ltd.), Injection Gentin (Opsonin Pharma Ltd.), Invigen® (Beximco Pharma) 100 mL, 0.08% w/v
Netilmicin sulfate	IV/IM	2.5–3.0 mg/kg/dose 12 hourly	300 mg/2 mL vial Injection: Netromycin (Schering-Plough)
Kanamycin	IV/IM	15 mg/kg/day 12 hourly	500 mg/1 g vial Injection: Kantrax Injection: Kanacyn Injection: Kanamycin (Meiji Seika)
Tobramycin (UTI pneumonia)	IV/IM nebulization, eye drop and ointment, eye drop	2.5–5 mg/kg/day in two to three divided dose Diluted solution with concentration of 2 mg/mL should be infused over 15–30 min Eye drop: Two drops three to four times daily	Vial 40 mg/mL and 80 mg/2 mL Injection: Tobramycin (non-proprietary) Tobi (Novartis) Nebulized solution 60 mg/mL Eye drop: Intobac (Aristopharma), Tobrex (Alcon Laboratories)
Streptomycin	IM	25–40 mg/kg/day one or two dose	Injection streptomycin sulfate 1 g vial (Renata)
Cotrimoxazole SMT and TMP	Oral	6–20 mg TMP/kg/dose 12 hourly	Tablet 480 mg (SMT 400 mg + TMP 80 mg) Tablet DS (SMT 800 + TMP 160) Suspension SMT 200 mg+ TMP 40/5 mL Cotrim® (Square Pharmaceuticals Ltd.) Suspension and Tablet, Cotrim DS (Tablet), Fisat (Sanofi-Aventis) (Suspension and Tablet), Fisat DS (Tablet), Megatrim (Beximco) Suspension and Tablet, Megatrim DS (Tablet)
Chloramphenicol (*Haemophilus influenzae*, typhoid, typhus)	IV/IM, oral, eye drop	25–50 mg/kg/day in four divided dose Eye drop and ointment Eye drop 3–4 hourly	Capsule 250 mg Injection 1,000 mg/vial Suspension 125/5 mL Medophenicol (Medochemie) 1 g ampule, Kemicitin (Pfizer) 1 g vial Capsule Fionicol 250 mg (Sanofi-Aventis), Suspension Opsomycetin (Opsonin) Eye drop/ointment, SQ Mycetin® (Square Pharmaceuticals Ltd.), A-Phenicol (Acme), Supraphen (Gaco Pharmaceuticals Ltd.)
Doxycycline	Oral	5 mg/kg/day (max 200 mg/day)	Capsule 100 mg, avoid in children < 8 years Doxicap (Renata), Doxin (Opsonin)
Macrolides Erythromycin	Oral	30–50 mg/kg/dose in two to four divided dose	Tablet 250 mg, 500 mg Suspension 125 mg/5 mL, 250 mg/5 mL (DS) Pediatric drop 200 mg/5 mL Amycin (Aristopharma) Tablet, Suspension, Drop, Amycin DS (250 mg/5 mL Suspension), Etrocin (Beximco) Tablet, Suspension, Erythrox (Renata) Tablet, Suspension Eromycin (Square Pharmaceuticals Ltd.) Tablet Suspension, Drop, Acos (Radiant Pharmaceuticals), Tablet, Suspension

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Drug	Route	Doses and time/day	Availability, generic and some trade (local) names
Azithromycin	Oral/IV	10 mg/kg/day once 20 mg/kg/day (typhoid)	Tablet 250/500 mg Azith (Novartis), AZ (Aristopharma), Azicin (Opsonin), Azin (Acme), Azithrocin (Beximco) Zibac (Popular) IV (PF syringe) 200 mg/5 mL Injection Zibac, Macrozith PFS (Silva Pharmaceuticals Ltd.) Suspension 200 mg/5 mL Azin, Azythrocin
Clarithromycin	Oral/IV	15 mg/kg/day in two divided dose in slow IV infusion Oral dose 1 hour before meal in two divided dose (15 mg/kg/day)	Tablet 250 mg/500 mg Klaricid (Unimed), Binoclar (Novartis), Claricin (Acme) IV 500 mg vial (Klaricid, Novartis) Infused over 60 minutes after reconstitution in 10 mL of solvent supplied and diluting and infusing it with DA or DNS
Quinolones Ciprofloxacin	Oral/IV	15–30 mg/kg/day in two divided dose	Tablet: 250/500/750 Aprocin (Aristopharma Ltd.), Neofloxin (Beximco), Ciprocin (Square Pharmaceuticals Ltd.), Ciprox (Opsonin) Suspension 250 mg/5 mL (Aprocin, Neofloxin) Injection 200 mg/100 mL infusion (Neofloxin, Ciprox IV)
Levofloxacin	Oral/IV	5–10 mg/kg/day Single dose (two doses below 5 year)	Tablet 250 mg/500 mg/750 mg Suspension 50 mg/mL Evo® (Beximco), Levoxin (Incepta Pharmaceuticals Ltd.), Levox (Opsonin), Urilev (Techno drugs) IV 500 mg/100 mL infusion (Urilev, Leviflox)
Nalidixic acid	Oral	50 mg/kg/day four divided dose	Tablet 500 mg Suspension 300 mg/5 mL Nalid (Square Pharmaceuticals Ltd.), Naligram (Acme), Utirex (Opsonin)
Metronidazole (anaerobic infection, anti-protozoal infection), *Helicobacter pylori* along with proton pump inhibitor and clarythromycin or amoxicillin	Oral/IV	7–10 mg/kg three times (orally) IV infusion 7.5–10 mg/kg (1.5 mL/kg) 8 hourly	Tablet: 200/400 mg, Amodis (Square Pharmaceuticals Ltd.), Amotrex (ACI)), Filmet (Beximco), Dirozyl (Acme) Suspension 200 mg/5 mL, Flagyl (Sanofi-Aventis) Injection: 500 mg/100 mL (Flagyl, Filmet)
Flucloxacillin	Oral/IV	50–100 mg/kg/day in four divided doses	Capsule: 250/500 mg Dry syrup: 100 mg/5 mL A-Flox (Acme), Fluclox (ACI), Flucloxin (SKF), Phylopen (Square Pharmaceuticals) Injection: 250/500 mg vial (A-Flox, Phylopen)
Linezolid (MRSA)	Oral/IV	30 mg/kg/day orally in three divided dose IV slowly in infusion 10 mg/kg 8 hourly	Tablet: 400 mg/600 mg, Injection: 2 mg/mL, 300 mL Dry syrup: 100 mg/5 mL Arlin (Beximco), Linozid (Orion), Inj. Zyvox (Pharmacia)
Pivmecillinam sodium (invasive diarrhea, UTI)	Oral	40–50 mg/kg/day in three to four divided dose	Tablet 200 mg Alexid (Aristopharma Ltd.), Selexid (Leo)
Nitrofurantoin (UTI)	Oral	5–7 mg/kg/day in four divided dose 1 mg/kg/day for UTI prophylaxis	Tablet 50/100 mg, Nintoin (Incepta Pharmaceuticals Ltd.)
Clindamycin (serious anerobic infection)	Oral/IV infusion	IV- neonate 15–20 mg/kg/day in two to four divided dose Postneonate 15–40 mg/kg/day in three to four divided dose	Capsule: 150 mg/300 mg Clindacin, (Incepta Pharmaceuticals Ltd.) Injection 300 mg/2 mL, 600 mg/4 mL Clindacin vial (Incepta Pharmaceuticals Ltd.)
Meropenem	IV	15 mg/kg 8 hourly (tds) Higher dose in meningitis, sepsis (35–40 mg/kg tds)	500 mg/1 gm/vial Meronem (ACI), Specbac (Square Pharmaceuticals Ltd.), Meronix (Novo)

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Drug	Route	Doses and time/day	Availability, generic and some trade (local) names
Imipenem with Cilastin	IV	50 mg/kg/day in three divided dose	IV infusion 500 mg Imipenem with 50 mg Cilastin Tenam, Premaxin (MSD), Imbac (Aristopharma) 500 mg Imipenem and 50 mg Cilastin
Vancomycin	IV	10–15 mg/kg/dose three to four times daily	Injection: 1 g and 500 mg vial Vanmycin (Incepta Pharmaceuticals Ltd.) Vancomycin (DBL)
Anti-TB Drugs			
Rifampicin	Oral	10 mg/kg/day once daily before breakfast	Tablet: 450 mg Firifam (Sanofi) Tablet: 450 mg Rimactane (Novartis) Suspension: 100 mg/5 mL Rifcin (Pharmadesh) Rifatan (Gaco)
Isoniazid (INH)	Oral	5–10 mg/kg/day once daily before breakfast	Tablet: 100 mg/300 mg Servizid, 300 mg (Novartis)
Rifampicin + INH	Oral	Once daily dose similar to Rifampicin and INH	Tablet: Rifazid 150 mg (Sanofi)/Rimactazid (Novartis) 150 mg (Rifampicin 150 mg + INH 100 mg) Tablet: Rimactazid 300 mg/Rifazid 300 mg (Rifampicin 300 mg + INH 150 mg) Tablet: Rifazid 450 mg/Rimactazid 450 mg (Rifampicin 450 mg + INH 300 mg)
PZA	Oral	25–35 mg/kg once daily before breakfast	Tablet: 500 mg (PZA-Ciba Novartis), Firazin, (Sanofi)
Ethambutal	Oral	15-25 mg/kg once daily before breakfast	Tablet: 400 mg Servambutal (Novartis), Fiambutal (Sanofi)
Antiviral			
Acyclovir	Oral cream (skin) drop (eye)	100–200 mg/day in four divided dose orally	Tablet: 200 mg Virux (Square Pharmaceuticals Ltd.) Suspension: 200 mg/5 mL Eye ointment: 3% Clovir (Ibne Sina) Eye drop: 3%, Cyclovex (Opsonin)
	IV Herpes simplex encephalitis	15 mg/kg/dose three times daily	Injection: 250 mg vial/500 mg vial, Zovirux (GSK) Infusion over 1 hour
	IV Herpes zoster (immunocompro-mised)	10 mg/kg/dose three times daily	
Ganciclovir (CMV retinitis)	IV	5–10 mg/kg/day two divided dose for 14–21 days for treatment, 7–14 days for prevention. Maintenance therapy 5–6 mg/kg/day IV once daily until adequate recovery	Injection Cymevene (Roche) 500 mg/vial
Antifungal Drugs			
Ketoconazole	Oral	3–6 g/kg/day once daily	Tablet: 200 mg Ketoral (Square Pharmaceutical Ltd.), Ketocon (Opsonin)
Fluconazole	Oral	Initially 6 g/kg/day then 3 mg/kg/day for 7–14 days once daily	Tablet: 50/150 mg Capsule: 50/150 mg Dry syrup: 50 mg/5 mL Omastine (Beximco), Flugal (Square Pharmaceuticals Ltd.), Canazole (ACI), Fluconal (Acme)
Nystatin (oral thrush)	Oral	Neonate: 100,000 IU four times daily topically (1 mL four times) Child: 400,000 IU four times daily orally/topically 7–10 days	Drop: 100,000/mL Nystatin, Candex (Square Pharmaceuticals Ltd.) Tablet: 500,000/IU, Canstat (Jayson Pharmaceuticals Ltd.)

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Drug	Route	Doses and time/day	Availability, generic and some trade (local) names
Griseofulvin	Oral	10 mg/kg/day once daily	Tablet: 150 mg/250 mg/500 mg, Grisovin (GSK), Fulcinex (ACI)
Flucytosine	Oral/IV	100–150 mg/kg/day in four divided dose IV infusion slowly over 20–40 minutes	Tablet: 500 mg Injection: 10 mg/mL, 250 mL/vial Ancotil (Meda)
Amphotericin	IV	Initially 1 mg/kg/day in two to three divided dose followed by 250 µg/kg/day IV infusion slowly	50 mg vial, Fungizone (Squibb)
Clotrimazol	Topical (cream) for skin and vaginal cream	Two to three times	Cream: Canesten (Square Pharmaceuticals Ltd.), Neosten (Beximco)
Econazole	Topical (cream) for skin and vaginal cream	Two to three times	Cream: Pevaryl (Sanofi-Aventis)
Antiparasitic (Antimalarial)			
Quinine	Oral/IV	IV initially 20 mg/kg over four hours followed by 10 mg/kg 8–12 hourly, 8 hour after loading dose Oral: 10 mg/kg 8 hourly for 7 days	Tablet: 300 mg, Jasoquin (Jayson) Injection: 60 mg/mL, 300 mg/5 mL ampule Jasoquin (Jayson)
Chloroquine	Oral	Initially 10 mg base/kg (maximum 600 mg/days) followed by 5 mg base/kg (maximum 300 mg/days), after 6 hour. Single dose of 5 mg base/kg on day 2 and day 3	Tablet: 250 mg, Avloquine (ACI), Jasochlor (Jayson)
Sulfadoxine + Pyrimethamine	Oral	Pyrimethamine 25 mg + Sulphadoxine 500 mg Child under 4 year: half tablet single dose 4–8 year: one tablet single dose 9–14 year: two tablet single dose Adult: three tablet single dose	Tab. Pyrimethamine 25 mg + Sulfadoxine 500 mg Malacide (Square), Sulfamin (Jayson Pharmaceuticals Ltd.)
Mefloquine (Resistant Malaria)	Oral	15–25 mg/kg single dose	Tablet: 250 mg Lariam (Roche), Meflon (ACI)
Primaquine (exoerythrocytic anti-malarial)	Oral	250 µm/kg once daily for 14 days Adult 15 mg/day once daily for 14 days	Tablet: 15 mg, Jasoprim (Jayson), Kanaprim (Globe)
Artemether (severe malaria, MDR malaria)	Injection	3.2 mg/kg IM on day 1 1.6 mg/kg IM for 3–5 days	Ampule 80 mg/mL, Paluther (Sanofi-Aventis)
Artemether + Lumefantrine	Oral	Body weight: 5–15 kg 1 Tablet stat followed by 1 tablet each on 8, 24, 36, 48 and 60 hours (total 6 tab. over 60 hours) Body weight 15–25 kg two tab. initially followed by five further dose of two tablet on 8, 24, 36, 48 and 60 hours (total 12 tablet over 60 hours) Body weight 25–35 kg three tab. initially followed by same regime three tablet (total 18 tablet over 60 hours)	Tablet Artimether 20 mg + Lumefantrin 120 mg Arexel (Jayson), Coartem (Novartis)
Antiprotozoal Antiamebic, Anti-trichomonas, Antigiardiasis and others			
Metronidazole (for amebiasis blastocystosis, balantidiasis)	Oral/IV	7.5 mg/kg tds orally IV 7.5 mg/kg (1.5 mL/kg) 8 hourly for 7 days	Tablet: 200 mg/400 mg Suspension: 200 mg/5 mL Dirozyl, Filmet Injection: 500 mg/5 mL (Filmet, Flagyl)

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Drug	Route	Doses and time/day	Availability, generic and some trade (local) names
Nitazoxanide (broad spectrum antihelminthic and antidiarrheal)	Oral	1–3 year: 100 mg twice daily for 3 days 4–11 year: 200 mg twice daily for 3 days	Suspension: 100 mg/5 mL Tablet: 500 mg Nitazox (Incepta Pharmaceuticals Ltd.), Nitoxin (Aristopharma Ltd.), Zox® (Square Pharmaceuticals Ltd.)
Secnidazole	Oral	30 mg/kg, 1–3 dose once daily	Tablet 500 mg/1 g Secnid (Square Pharmaceuticals Ltd.), Secnidal
Niclosamide	Oral	Beef and fish tape warm 40 mg/kg once maximum 2 g Dwarf tape warm 40 mg/kg orally qd for 7 days, maximum daily dose is 2 g	Tablet 500 mg, (Praziquantel)
SAG, Treatment of KA, PKDL, KATF	Injection IM	KA 20 mg/dose IM, IV once daily for 20 days KATF: Pentamidine should be given IM three times/week for 5 weeks then start SAG 20 mg/kg IM daily for 30 days PKDL—SAG 20 mg/kg/day IM for 20 days followed by 10 days rest in each cycle—total 6 cycle	Injection 100 mg/mL in 10 mL bottle Stibatin (GSK), Stiboson (Jayson Pharmaceutical Ltd.)
Pentamidine isethionate For treatment of kala-azar treatment failure (KATF) and *Pneummocystis carinii* pneumonia	Injection IM/IV in deep IM/IV infusion	3 mg/kg/day <12 year, 4 mg/kg/day >12 year. Every alternate day IM for 5 weeks then from thsixth week start SAG IM daily for 30 days. *Pneumocystis carinii* pneumonia treatment Infants/child 4 mg/kg/day IM or IV for 14–21 days *Pneumocystis carinii* prophylaxis: 4 mg/kg/day IM or IV every 2–4 weeks	Injection: 300 mg/via (Pentacarinat (Sanofi),
Diethylcarbamazine (in filariasis)	Oral	1 mg/kg single dose on day 1, 2 mg/kg/day in three divided dose on day 2, 3–6 mg/kg/day in three divided dose on day 3, 6 mg/kg/day in three divided dose on days 4–14	Tablet: 50 mg (Benocide), Notezine (Sanofi-Aventis)
Albendazole (broad spectrum antihelminthic)	Oral	>2 year 400 mg/single dose before meal	Tablet: 200 mg/400 mg Alben (SKF), Alben DS
Mebendazole (Treatment of ascariasis hook warm, pin warm, trichuriasis)	Oral	Pin warm 100 mg once, may be repeated in second week, Round warm, hook warm and trichuriasis 100 mg 12 hourly for 3 consecutive days second course if needed in 3–4 weeks	Tablet: 100 mg. Suspension: 100 mg/5 mL Ermox, (Square Pharmaceuticals Ltd), Meben (Sanofi-Aventis)
Pyrantel pamoate (treatment of pin warm, hook warm and round warm)	Oral	11 mg/kg once may be repeated after 2 weeks For hook warm 11 mg/kg once daily for 3 consecutive days	Tablet: 125 mg Syrup: 50 mg/mL Melphin (Beximco), Delentin (Renata)
Drugs Used in Neurological Disorders			
Phenobarbital	Oral/IV	In neonatal seizure: 20 mg/kg IV slowly stat. If seizure continues for 30 minutes: Give further 10 mg/kg IV Maintenance dose is not required in neonatal seizure unless underlying seizure disorder present If seizure persists 3–5 mg/kg/24 hour IV or PO in divided dose In status epilepticus: 20 mg/kg IV slowly (dilute at least 20 mg/mL and infuse at max: 1 mg/min). Additional 5 mg/kg may be considered Maintenance: 3–5 mg/kg/24 hour divided in two doses	Tablet: 30 mg/60 mg Gardinal, Bardinal, Epinal Suspension: 15 mg/5 mL Barbit (Incepta pharmaceuticals Ltd.), Epinal (Square Pharmaceutical Ltd.) Injection: 200 g/mL ampule Injection: Barbit (Incepta Pharmaceuticals Ltd.) Inj. Norbital (Opsonin) Gardinal, Phenobarbital (Nonproprietory)

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Drug	Route	Doses and time/day	Availability, generic and some trade (local) names
Phenytoin and phosphenytoin	Oral/ IV (Phosphenytoin)	Neonatal seizure (second line) Loading dose: 20 mg/kg IV over 30 minutes give second dose if seizure not controlled after 30 min Status epilepticus (over 1 month age)—18 mg/IV (slow infusion over 30 min with cardiac monitoring) Maintenance: 5–10 mg/kg/24 hour oral or IV in two divided dose	Tablet: 100 mg Diphedan, Pheytoin (Nonproprietory), Epantoin (Pfizer) Suspension: 125 mg/5 mL IV ampule Phosphenytoin 75 mg/mL equivalent to 50 mg phenytoin sodium Epanutin (Pfizer)
Valproate	Oral/IV (not universally available)	20–40 mg/kg/day in two divided doses In status epilepticus: 20 mg/kg IV slowly	Tablet: 200 mg/300 mg/500 mg Syrup: 200 mg/5 mL Epilim chrono (Sanofi-Aventis), Valex (Incepta), Epival (Unimed) IV Injection: 400 mg vial (Epilim IV Sanofi-Aventis)
Benzodiazepines Diazepam (Muscle relaxant, status epilepticus, neonatal tetanus, intermittent prophylaxis of febrile seizure)	Oral/IV and PR	For antispasmotic 0.1–0.3 mg/kg 12 hourly In status epilepticus: IV: 0.2–0.3 mg/kg/dose given over 2–3 min: may repeat every 30 min to maximum total dose of 10 mg Rectal: 0.5 mg/kg than 0.2–0.5 mg/kg in 10 minutes Intermittent prophylaxis for febrile seizure 0.3–0.5 mg/kg orally or rectally 8 hourly at onset of fever up to 48–72 hours In neonatal tetanus, 0.1–0.2 mg/dose IV every 3–6 hours then titrate	Tablet: 5 mg/10 mg Sedil (Square Pharmaceuticals Ltd), Easium (Opsonin) Supplementary: 10 mg (Easium) Injection: 10 mg/2 mL (Sedil)
Midazolam (status epilepticus)	Oral/Buccal/IV	150–200 µg/kg loading dose followed by continuous infusion, 2 µg/kg start, increasing in 4 µg/kg/min, increments every 30 min Maximum 30 µg/kg/min (PICU setting only) Maintenance dose: 5–20 µg/kg/min, Buccal use: single dose 300 µg/kg (maximum 10 mg) particularly useful for out of hospital treatment for prolonged seizure	IV solution 10 mg/5 mL or 10 mg/2 mL Dormicum (Roche) Tablet: 7.5 mg/15 mg Dormicum (Roche), Milam (SKF) Buccal liquid (non-proprietary, not universally available) oral liquid 10 mg/mL (100 mL)
Clobazam	Oral	1 mg/kg/day in two divided doses	Tablet: 10 mg Frisium (Sanofi-Aventis), Clobam (Square Pharmaceuticals Ltd.)
Clonazepam (absence seizure, myoclonic seizure, Lennox-Gastaut, phobic disorder)	Oral	0.01–0.03 mg/kg/day in two divided dose	Tablet: 0.5 mg and 2 mg Disopan (Incepta Pharmaceuticals Ltd.), Rivotril (Roche), Leptic (Acme)
Lorazepam (status epilepticus)	IV/PR sublingually	0.05–0.1 mg/kg/dose (maximum 4 mg)	Tablet: 1 mg/2.5 mg (Ativan) Injection: Lorazepam 4 mg/mL (Ativan) Lorapam (Popular)/Lorazepam
Ethosuximide (absence seizure)	Oral	15–40 mg/kg/day in two divided doses	Tablet, Capsule 250 mg Syrup: 250 mg/5 mL Zarontin (Pfizer)
Topiramate	Oral	Starting dose 1 mg/kg/day increasing every 1–2 weeks Maintenance 5–15 mg/kg/day two divided dose 1–2 weeks in two divided dose	Tablet: 25 mg/50 mg Topamax® (janssen-Cilag), Topirva (Incepta)

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Drug	Route	Doses and time/day	Availability, generic and some trade (local) names
Levetiracetam	Oral/ IV infusion	Starting dose 20 mg/kg in two divided dose increasing every 2 weeks by 10 mg/kg (maximum 30 mg/kg twice daily) Maintenance: 40 mg/kg/day in two divided doses	Tablet: 250 mg/500 mg, 1 g Eletam (Uni med), Erata, Keppra (UCB Pharma) Oral solution: 500 mg/5 mL (Eletam, Keppra) IV infusion: 100 mg/mL, 5 mL vial (Eletam IV infusion, Unimed) Dilute before use for IV infusion
Vigabatrin	Oral	Starting dose 50 mg/kg/day in two divided doses, increasing if required every 48 hours to 100 mg/kg up to 150 mg/kg/day	Tablet: 500 mg Sabril® (Sanofi-Aventis)
Lamotrigine	Oral	With valproate: Add on therapy Starting dose: 0.15 mg/kg/day gradually increasing every 2 weeks until control achieved Maintenance: 1–5 mg/kg/day Without valproate Double the above dose	Tablet: 25 mg/50 mg/100 mg, Lamictal (GSK), Lamitrine (ACI)
Pregabalin	Oral	75 mg every 24 hours over 12 years Maintenance: 300 mg/24 hours	Capsule: 75 mg/150 mg, Lyrica (Pfizer), Pregaben (Incepta Pharmaceuticals Ltd.)
Gabapentin	Oral	Starting dose: 10 mg/kg/day once daily increasing every 3–5 days Maintenance: 30–40 mg/kg/day in once or in two divided doses	Capsule: 100 mg/300 mg/400 mg Neurontin (Pfizer) Tablet: 300 mg/600 mg Gabapen (Incepta Pharmaceuticals Ltd.), Gabatin (Renata), Algia (Beximco)
Carbamazepine	Oral	Starting dose 5 mg/kg/day in two divided dose increasing 5 mg/kg/day every 5–7 days Maintenance: 20 mg/kg/day in two divided doses	Tablet: 200 mg, CR Tablet: 200 mg Tablet: Tegretol (Novartis), Tablet: Tegretol CR Syrup: 100 mg/5 mL (Tegretol)
Oxcarbazepine	Oral	Starting dose 5 mg/kg/24 hourly in two divided dose increasing weekly by 5 mg/kg/day. Maintenance: 24–40 mg/kg/day in two to three divided doses	Tablet: 300 mg/600 mg, Leptal (Healthcare Pharma), Trileptal (Novartis)
Paraldehyde (refractory seizures)	IV/ IM/PR	Loading: 150–200 mg/kg Maintenance: 20 mg/kg/hour 0.1–0.2 mL/kg/dose 0.35 mL/kg/dose (use glass syringe only)	Paraldehyde 5% solution by adding 1.75 mL Paraldehyde to a total vol. of 35 mL in 5% dextrose saline Can cause tissue damage and sloughing This route should be reserved for exceptional circumstances Use freshly opened bottle. Injection Paraldehyde 1 g/mL (5 mL ampule). Reduce dose once desired effect is obtained
Piracetam	Oral	40 mg/kg in three divided dose	Tablet: 800 mg Suspension: 500 mg/5 mL Piratam, Neurolep (Square Pharmaceuticals Ltd.), Memopil (ACI)
Melatonin (nonepileptic drug used in seizure)	Oral	Under 2 years: 2.5–5 mg Over 2 years: 2.5–10 mg At night (for sleep wake cycle disorders) and 30 minute prior to procedure	Capsule and CR Tablet: 3 mg Filfrash (Incepta Pharma), Melatonin (Sundown natural)
ACTH (infantile spasm)	IM	Starting 500 µg or 40 IU/IM on buttock on alternate day increasing up to 750 µg/60 IU in 2 weeks. Gradually decreasing by 25% in 2 weeks	Injection 40 IU ACTH equivalent to 500 µg of Synacthen® (tetracosactide) depot (Alliance)
Prednisolone (infantile spasm, epileptic encephalopathy)	Oral	Starting dose 2–4 mg/kg/day once daily Maintenance 4 mg/kg weekly over several months	Tablet 5 mg, 10 mg, 20 mg Cortan (Incepta Pharmaceuticals Ltd.), Cortef (Aristopharma Ltd.) and Precodil (Opsonin) Suspension: 5 mg/5 mL, 15 mg/5 mL (Precordil-5, Precordil-15)

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Drug	Route	Doses and time/day	Availability, generic and some trade (local) names
Methyl prednisolone (pulse remission initiating in noninfectious CNS inflammation)	IV infusion	30 mg/kg IV infusion once daily for 3 days usually followed by maintenance course of oral prednisolone	Vial 500 mg powder for reconstitution Solu-Medrone®, (Pharmacia)
Dexamethasone To reduce intracranial pressure in cerebral tumor, also given in pyogenic meningitis just before or with initiation of antibiotics	IV	1–1.5 mg/kg/day in 2–4 divided doses (to reduce intracranial pressure) In bacterial meningitis: 0.4 mg/kg/dose every 12 hours for 48 hours	Ampul 5 mg/1 mL, Oradexon® (Organon), Decason (Opsonin)
Baclofen (treatment of spasticity and dystonia)	Oral	0.75 mg/kg/day in three divided dose with weekly increase Maximum: 2 mg/kg/day	Tablet: 10 mg, Lioresal, (Novartis) Liquid 25 mg/5 mL
Botulinum toxin A (treatment of focal dystonia or localized spasticity)	IM	As required	200 IU/mL, Botox (Allergan) 100 IU/mL Dysport (Ipsen)
Intravenous immunoglobulin IVIG Used in GBS, ADEM	IV infusion	In GBS 400 mg/kg/day for 3–5 consecutive days or total dose 2 g/kg, either as a single dose or fractionated over 3–5 consecutive days	2.5 gm/vial, Octagam® (Octapharma)
Drug Used in Neuropsychiatric Condition			
Haloperidol (chorea, tic, agitation)	Oral/IM/SC	0.025–0.05 mg/kg/day (maximum 0.15 mg/kg/day) in two to three divided doses followed by 1–3 mg/dose every 4–8 hours	Tablet: 5 mg Halop (Opsonin), Peridol (Square Pharmaceuticals Ltd.) Injection: 5 mg/mL (Peridol)
Procyclidine (acute dystonia)	Oral/IM/IV/SC	IV/IM/SC Below 2 years: 0.5–2 mg 2–10 years: 2–5 mg 10–18 years: 5–10 mg	Ampule: 10 mg/2 mL, Kemadrin (GSK) Tablet: 5 mg Kemadrin, Perkinil (Square Pharmaceuticals Ltd.)
Resperidone (chorea, tic, acute disturbed behavior)	Oral	Starting dose 1 mg/24 hour in two divided doses Weekly increase by 1 mg if required Acute disturbed behavior 2 mg/24 hours	Tablet: 1 mg, 2 mg, 4 mg Rispolux (Novartis), Resco (Drug International)
Methylphenidate (ADHD)	Oral	Starting dose over 6 year 5–10 mg/24 hours Maintenance: 1–2 mg/kg/24 hour typically at 8 am to 1 pm	Controlled release Tablet: 10 mg, Ritalin (Novartis) Modified release Tablet: (not universally available) Tablet: Concerta XL (Janssen-Cilag) Capsule: Equasym XL (Shire)
Chlorpromazine (psychosis, tourette syndrome, chorea)	Oral/IV	1–2 mg/kg/dose	Tablet: 10 mg, 25 mg, 50 mg, 100 mg, 200 mg Syrup: 25 mg/5 mL Injection: 25 mg/mL Largactil (Sanofi-Aventis)
Imipramine (anti-depressant, anti-enuresis)	Oral	Starting dose 1 mg/kg/day, maximum 5 mg/kg/day Enuresis > 6 years 25–50 mg at bed time	Tablet: 25 mg, Tofranil (Novartis)
Nortriptyline	Oral	10–25 mg at bed time for enuresis age >6 years	Tablet: 10 mg, 25 mg Apresin (Beximco), Nortrilen (Lundbeck)

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Drug	Route	Doses and time/day	Availability, generic and some trade (local) names
Some Useful Drugs Used in Cardiac Disorders			
Digoxin	Oral/IV	0.02–0.05 mg/kg/day Preterm: 0.02/mg/kg (total daily dose) Term neonate: 0.02–0.03 mg/kg/day (total) Infant and child: 0.03–0.04 mg/kg (total) IV 75% of oral dose Digitalization: Half of TDD initially followed by one-fourth of TDD, every 8–12 hours × two doses	Tablet: 0.25 mg Digoxin, Digoxen (Drug International), Lenoxin (GSK) Drop: 0.05 mg or 50 µg/mL, Centoxin (Opsonin) Injection: 0.5 mg/2 mL, Lenoxin (GSK)
Adrenaline	IV for neonatal resuscitation	For neonatal resuscitation 0.1–0.3 mL/kg/dose (1 in 10,000 dilution) Maximum 0.5 mL/dose Never use 1:1,000 solution To make 1:10,000 dilution, mix 1 mL of Adrenalin with 9 mL distilled water	Adrenaline/Epinephrine 1:1,000 as hydrochloride (1 mg/mL) Adrenaline in 1:10,000 dilution (non-proprietary) IM infection for self-administration 150 µg, 300 µg, 500 µg of single dose containing adrenaline 1 mg/mL (Anapen 500, 300, 150) Adrenaline auto-injector 0.3 mg. adrenaline 1 mg/mL (EpiPen®, ALK-Abello)
	IV for cardiac arrest	For cardiac arrest 0.01–0.03 mL/kg/dose (1:10,000 dilution maximum 0.5 mL/dose IV)	
	IV infusion for severe hypotension, IM	For hypotension 0.5 µg/kg/min increasing until desired effect achieved	
	SC for giant urticaria, angioedema, anaphylaxis	For urticaria and anaphylaxis 0.1–0.3 mL/kg/dose SC/IM. For self-administration (auto injector) 150 µg IM for child <30 kg, 300 µg for child >30	
	Croup, bronchiolitis	Nebulized adrenalin (1:1,000) in severe croup and bronchiolitis Dose: 400 µg/kg maximum 5 mg may be repeated after 30 min, if necessary	
Phosphodiesterase inhibitors Milrinone (used in refractory CCF)	IV	50 µg/IV infusion 375–750 ng/kg/min up to 12 hours Maximum 1–1.15 mg/kg	Injection: Milrinone 1 mg/mL, Primacor (Sanofi-Aventis)
Angiotensin-converting Enzyme Inhibitors			
Captopril	Oral	0.1–0.5 mg/kg/day in 2–3 divided dose	Tablet: 25 mg, 50 mg Cardopril (Beximco), Capril (Opsonin)
Enalapril	Oral	0.1–1 mg/kg/dose single	Tablet: 5 mg, 10 mg Anapril (SKF)
Angiotensin II receptor blocker	Oral	0.5–1 mg/kg/dose single	Tablet: 25 mg, 50 mg Losartan (Popular Pharma), Angiolock (Square Pharmaceuticals Ltd.)
Beta-Blocker			
Metoprolol	Oral	0.2 mg/kg/day gradually increasing to maximum dose of 1–2 mg/kg/day in two divided doses	Tablet 50 mg, Betaloc (Drug International), Metaloc (Renata)
Carvedilol	Oral	0.1 mg/kg/day increase every 2 weeks Maximum dose 0.5–1 mg/kg/day in two divided doses	Tablet: 6.25 mg, 12.5 mg, 25 mg Carvida (Delta Pharmaceuticals), Carvista (Incepta Pharmaceuticals Ltd.), Carvil (Tecno Drugs)

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Drug	Route	Doses and time/day	Availability, generic and some trade (local) names
Propanolol Anti-arrhythmic, anti-hypertensive also used in migraine	Oral/IV	Dose for oral use: 0.5–1 mg/kg/24 hour in 3–4 divided dose titrated upward to 2.5 mg/kg/24 hour for 3–5 days Dose for IV 0.01–0.1 mg/kg/dose infused over 10–15 minutes Maximum dose 1 mg infant and 3 mg in children Migraine prophylaxis 0.6–2 mg/kg/day in three to four divided dose maximum 4 mg/kg/day	Tablet: 10 mg, 40 mg, 80 mg, Indevar (ACI), Propranol (Opsonin) Ampule: 1 mg/mL- Propranol (Indevar, ACI), Ampule: 1 mg/mL Propranol (Inderal, Astra)
Nifedipine (anti-hypertensive, anti-arrhythmic, calcium channel antagonist)	Oral	0.25–0.5 mg/kg/dose (maximum 10 mg) in four divided dose	Capsule, Tablet: 10 mg Nificap (Drug International), Adalat (Bayer), Nifin (Acme) slow release Nidipin SR 20 mg (Square Pharmaceuticals Ltd.)
Nitroprusside (anti-hypertensive CCF)	IV	0.3–0.5 µg/kg/min titrating dose to desired effect	Injection: 10 mg/mL, 25 mg/mL (Nonproprietary)
Prostacyclin (Prostaglandin E2 for duct dependent CHD)	IV infusion	2–20 ng/kg/min (dilute 0.3 mL with normal saline to match a 150 µg/kg/50 mL solution) 1 mL/hour = 0.05 µg/kg/hour	1 mg/1 mL Ampule 0.75 mL Dinoprostone, Prostin E2 (Pharmacia), Alprostadil 500 µg/mL ampule, Prostin VR (Pharmacia)
Indometacin for PDA closure	IV	0.2 mg/kg/ doses preferably IV 8 hourly × three doses	Injection: Indocid PDA (Idis Pharma) 1 mg vial
Diuretics (Used in CCF and Hypertension)			
Furosemide (Loop diuretic)	Oral/IV	1–4 mg/kg/orally 1–4 mg/kg/IV Stat, 6–12 hourly depending on response	Tablet 40 mg, Lasix (Sanofi-Aventis), Fusid (Square Pharmaceuticals Ltd.), Frusin (Opsonin) Oral solution 20 mg/5 mL (Frusin) Injection 20 mg/2 mL (Lasix, Fusid, Frusin)
Spironolactone (K^+ sparing diuretic)	Oral	1–3 mg/kg, 8 hourly	Tablet 25 mg Aldactone (Pharmacia), Pilactone (Sanofi-Aventis)
Furosemide + Spironolactone Refractory edema CCF	Oral	Depends on clinical condition and desired response (see above doses)	Tablet Furosemide 20 mg and Spironolactone 50 mg Frulac (Orion), Lacitone (General Pharma), Edenil 20 (containing 20 mg Furosemide) and Edenil 40 (containing 40 mg Furosemide) (SKF)
Inotropic drugs Dopamine Shock/hypotension/heart failure	IV infusion in 5% dextrose	Initially 2–5 µg/kg/min gradually increasing up to 20 µg/kg/min	Dopamine HCL vial (Unimed & Unihealth) 40 mg/mL (5 mL ampule)
Dobutamine	IV infusion	2.5–10 µg/kg/min increased up to 20 µg/kg/min (adjusted according to response)	Ampule: 250 mg/5 mL, 250 mg/20 mL Dobuject, (Leiras), Dobutamine HCL (Unimed & Unihealth)
Antiarrhythmic Drugs (SVT)			
Adenosine	IV infusion	100 µg/kg up to 300 µg/kg depending on response	Injection 3 mg/mL, 2 mL vial Adenocor (Sanofi- Aventis)
Flecainide	IV infusion/Oral	2 mg/kg/over 10 minutes IV infusion Orally: 2–3 mg/kg/day in 2–3 divided dose	Injection: Flecainide acetate 10 mg/mL, 14 mL ampule Tambocor (3M) Tablet Flecainide acetate 50 mg, 100 mg (Tambocor)
Amiodarone	IV/Oral	2 mg/kg loading dose over 10 minutes	Tablet 100 mg amiodarone (non-proprietary) Injection 50 mg/mL, 3 mL ampule Cordarone X (Sanofi-Aventis)
Verapramil	IV/Oral	Age-over 1 year 100–300 µg/kg IV slowly	Injection 2.5 mg/mL, 2 mL vial Oral solution 40 mg/5 mL Injection Cordilox 2.5 mg/mL (Dexel) Tablet 40 mg (Credilox)
Propanolol	IV/Oral	10–100 µg/kg infused over 10–15 minutes Orally: 0.1–1 mg/kg/day in two divided dose	Injection: Propanolol 1 mg/mL 1 mL ampule Indever (ACI), Inderal (Astra) Tablet: 10 mg, 40 mg Indever, Inderal (Astra), Propranol (Opsonin)

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Drug	Route	Doses and time/day	Availability, generic and some trade (local) names
Some Useful Drugs used in Respiratory Disorders			
Salbutamol (β2 agonist quick acting bronchodilator)	Oral/inhaled (MDI)/Nebulized/ Injection (SC and IV)	0.1–0.4 mg/kg/day PO, tds 1–2 puff of 100 µg, qds-tds 0.15–0.2 mg/kg/dose of nebulized solution (preferably oxygen given at 6 L/minute), frequency depends on severity (from every 30 minute to 6–12 hourly)	Tablet: 2 mg, 4 mg Syrup: 2 mg/5 mL Azmasol (Beximco), Brodil (ACI), Respolin (Jayson), Asmolex (Aristopharma) Inhaler: (MDI 100 µg/meter inhalation) Salbutamol nebulized solution 5 mg/mL, Ventolin (GSK), Sultolin (Square) Salbutamol solution in single nebule 2.5 mg/2.5 mL nebule (Ventolin) Ampule for injection: 50 µg/mL (Ventolin, GSK)
Levosalbutamol	Oral nebulized	0.1–0.4 mg/kg/day in 2–3 divided dose orally. Nebulized from 0.31 mg twice daily (2–11 years)	Tablet: 1 mg, 2 mg Syrup: 1 mg/5 mL Purisal (Incepta Pharmaceuticals Ltd.), Levostar (Square Pharmaceuticals Ltd.), MDI Puff 50 µg/puff (Levostar inhaler) Nebulized solution 0.31 mg, 0.63 mg, 1.25 mg in 3 mL solution- Purisal nebulized solution (Incepta Pharmaceutical Ltd.)
Salmeterol (long-acting β2 agonist)	Inhaler	25 µg/12 hourly	1 puff, 12 hourly Bexitrol (Beximco), Serevent (GSK)
Combination Salmeterol + Fluticosone	Inhaler	1 puff, 12 hourly dose depends on age and severity	Salmeterol 25 µg Fluticosone 50 µg, 125 µg, 250 µg, 500 µg Inhaler Bexitrol F 25/125, 25/250 (Beximco Pharma), Ticamet-125 MDI (25 µg Salmeterol and 125 µg Fluticosone (Square Pharmaceuticals) and Ticamet-250 (25 µg Salmeterol and 250 µg Fluticosone) MDI (Square Pharmaceuticals) Evohaler seretide (Salmeterol/Fluticosone) 25/50, 25/125, 25/250 (GSK) Accuhaler seretide (Salmeterol/Fluticosone) 50/100, 50/250, 50/500 (GSK)
Ipratromium bromide	Nebulized/ MDI	100–500 µg/dose in nebulized form four times daily MDI < 6 years 20 µg tds, >6 years 40–50µg tid	Nebulized solution 250 µg/mL (30 mL), Iprex solution (Square Pharmaceuticals), atrovent solution (Boehringer) MDI- 20 µg/dose Ipramid (Beximco), Iprex (Square Pharmaceuticals Ltd.)
Injection. Aminophylline Acute severe asthma (currently not well-recommended for children as first-line treatment) Apnea of prematurity	IV infusion/Oral	In acute severe asthma: Loading 5 mg/kg/dose IV with equivalent volume of 5% dextrose/saline as a bolus over 20 minutes, then 0.5–0.7 mg/kg/hour In apnea of prematurity: loading 4 mg/kg than 1.5–3 mg/kg every 8–12 hour or 0.7 mg/kg/hour	Injection 125 mg/5 mL ampule, Cardophylin (Sanofi-Aventis) Tablet 100 mg (Cardophylin) Slow release Tablet 600 mg, Aminophylline retard (Novartis)
Budesonide	Inhaled (MDI) nebulized	MDI 50–400 µg bd Nebulized 250–500 µg bd (3 months to 12 years)	MDI 100 µg/dose MDI (Aeronid Beximco Pharma) Nebulized solution 0.5 mg and 1 mg Budicort (Incepta Pharmaceuticals), Pulmicort (Astra-Zenesa) nebulized solution
Fluticasone	Inhaled (MDI)	>4 year 50–100 µg bid up to 200 µg bid	MDI 50 µg, 100 µg, 250 µg Flixotide (GSK):50 µg/ accentuation Flaso Cozycap (Square Pharmaceuticals Ltd.) : 100 and 200 µg/dose Other preparation (combination) Ticamet 250 (Square Pharmaceuticals Ltd.): Fluticasone 250 µg + Salmeterol 50 µg) with Cozycap. Salflu (Acme): Fluticasone 250 + Salmeterol 100 µg with Rotahaler
Beclomethasone	Inhaled (MDI)	50–100 µg, 100–200 µg two to four times	MDI 50 µg, 100 µg, 250 µg/accentuation Decomit HFA- MDI 50 µg and 100 µg/puff (Beximco Pharma) Becotide- MDI (GSK) 50 µg and 100 µg/puff
Cromolyn	Inhaled	20 mg one to two puff (5 mg per MDI/ puff)	Cromolyn 1 mg, 5 mg inhaler, Intal 1 and 5 (Sanofi-Aventis) Intal 20 mg Rotacap, Fanil Capsule 100 mg (Square Pharmaceuticals Ltd.)

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Drug	Route	Doses and time/day	Availability, generic and some trade (local) names
Monteleukast	Oral	4 mg <5 year 5 mg 5–10 year 10 mg >10 years once daily	Tablet 4 mg, 5 mg, 10 mg Monas (Acme Lab), Montair (Incepta Pharmaceuticals Ltd.), Provair (Unimed and Unihealth), Lumona (SKF) Granules in sachet containing 4 mg Monteleukast (Lumona 4 sachet)
Ketitofen	Oral	6 month to 2 years 0.5 mg BID >2 year: 1 mg BID	Tablet: 1 mg Syrup: 1 mg/5 mL Alarid (Square Pharmaceuticals Ltd.) Tofen (Beximco), Toti (SKF), Minia (Novo)
Injection 50% magnesium sulfate (acute severe asthma)	IV infusion	0.1 mL/kg IV infusion in 20 minutes followed by 0.06 mL/kg/hour until acute condition improves	50% magnesium sulfate in 5 mL vial, G magnesium sulfate (Gono Shastho Pharma), Minjet
Injection Hydrocortisone (acute severe asthma)	IV	4 mg/kg 6 hourly	Injection 100 mg in 2 mL Cotson (Opsonin), Hydrocortisone medo (Medocheme), Solucortef (Pfizer)
Prednisolone (acute severe asthma)	Oral	1–2 mg/kg/day Single/divided dose for 4–7 days	Tablet: 5 mg, 10 mg, 20 mg Cortan (Incepta Pharmaceuticals Ltd.), Cortef (Aristopharma), Precordil (Opsonin) Suspension: 5 mg in 5 mL Syrup: Cortan, Precordil 5 Suspension: 15 mg/5 mL (Precordil 15)
Analgesia Oral Preparation			
Paracetamol	Oral/IV/suppository	15/20 mg/kg 6 hourly IV infusion 15 mg/kg over 15 minutes	Tablet 250 mg, 500 mg Napa (Beximco) Ace (Square Pharmaceuticals Ltd.), Fast (Acme), Tamen® (SKF), Reset (Incepta Pharmaceuticals Ltd.), Xpa (Aristopharma) Extended release Paracitamol- 665 mg (Napa Extend) Combination: Paracetamol 500, Caffeine 65 mg (Napa Extra, Ace Plus) Suspension: 120 mg/5 mL (Reset, Napa, Ace) Pediatric Drop: 80 mg/mL (Drop Napa, Drop Ace) Supplementary: 60 mg, 125 mg, 250 mg, 500 mg Renova (Opsonin), Napa, Ace IV infusion 1 g (Napa, IV injection)
Ibuprofen	Oral	7.5–10 mg/kg/dose three to four times daily after meal	Tablet: 200 mg, 400 mg, Inflam (Sanofi-Aventis), Profen (Acme) Syrup: 100 mg/5 mL Inflam, Profen
Naproxen	Oral	5–7 mg/kg/dose two to three times daily after meal	Tablet 250 mg, 500 mg Naprosyn (Roche/Radiant), Naprox (SKF), Anaflex (ACI) In combination with Esmoperazole 20 mg (Naprosyn Plus) Syrup: 125 mg/5 mL (Naprosyn, Anaflex)
Indometacin (PDA, rheumatoid arthritis)	Oral/Suppository/IV	For PDA closure = 0.1–0.25 mg/kg/dose preferably IV 8 hourly × three doses (12 hourly × three doses) Anti-inflammatory 1–2 mg/kg/day in two to three divided doses	Capsule: 25 mg, Indomet (Opsonin) Supplement: 100 mg (Indomet) Injection: Indocid 1 mg vial (Idis Pharma)
Diclofenac	Oral/Suppository/Injection	1 mg/kg/dose 8 hourly Maximum 3 mg/kg/dose (avoid in case of suspected dengue)	Tablet: 25 mg, 50 mg Slow release Tablet: 100 mg Supplementary: 12.5 mg and 50 mg Injection: 75 mg/3 mL (rarely used in children) Voltalen (Novartis), Voltalen SR (75 mg, 100 mg) Supplementary: Voltalen, Ultrafen (Beximco), Clofenac (Square), Diclofen (Opsonin)

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Drug	Route	Doses and time/day	Availability, generic and some trade (local) names
Mefenamic acid	Oral	>6 month 25 mg/kg/day in three divided doses	Tablet: 250 mg and 500 mg Capsule: 250 mg and 500 mg Suspension: 250 mg/5 mL (double strength) Fenamic (Beximco), Flamic (Globe), HPR (Pacific), HPR-DS (500 mg) Suspension: HPR, Fenamic (250 mg/5 mL)
Morphin	IV/IM/SC	Neonate 40–100 µg/kg >1 month 100–200 µg/kg maximum 10 mg than follow with infusion of 20 µg/kg/hour	15 mg/1 mL ampule
Naloxone (Opioid antagonizer)	IV	Neonate and child 0.1 mg/kg IV maximum 2 mg If no response repeat every 2–3 minutes until desired effect	Injection: 0.4 mg/mL, Narcan/Narcan Neonatal, Boots (Zuellig)
Antiemetic and Prokinetic			
Domperidone	Neonate: 100–300 µg/kg	four to six times daily before feeds	Tablet: 10 mg Drop: 5 mg/mL Suspension: 5 mg/5mL Supplementary: 15 mg, 30 mg Tablet: Apuldon (Aristopharma), Motigut (Square Pharmaceuticals Ltd.), Deflux (Beximco), Don A (Acme) Suspension: Apuldon, Motigut, Deflux, Don A Supplementary: Don A (15 mg, 30 mg)
	1 month to 12 years: 200–400 µgm/kg	three to four times daily before food	
	12 year–18 year: 10 –20 mg	three to four times daily before food	
Erythromycin	3 mg/kg	Four times a day	Tablet: 250 mg, 500 mg Suspension: 125 mg, 250 mg/5 mL Drop: 200 mg/5 mL Tablet, Suspension and Drop: Amycin (Acme), Etrocin (Beximco), Eromycin (Square Pharmaceuticals Ltd.)
Metoclopramide (currently discouraged to use in pediatric practice due to extrapyramidal side effects)	Neonate:100 µg/kg twice daily	Every 6–8 hour twice daily	Tablet: 10 mg Syrup: 5 mg/5 mL Drop: 1 mg/mL Motilon Tablet, Syrup, Drop (Sanofi-Aventis), Maxolon (Amidpharm)
	1 month to 1 year: 100 µg/kg	Two to three times daily	
	1–3 year: 1 mg	Two to three times daily	
	3–5 year: 2 mg	Three times daily	
	5–9 year: 2.5 mg	Three times daily	
	9–18 year: 5 mg	Three times daily	
	15–18 year: 10 mg	Three times daily	
Ranitidine	Neonate: 2 mg/kg	Three times daily	Tablet: 150 mg, 300 mg Syrup: 75 mg/5 mL Ampule: 50 mg/2 mL Gepin (Drug International), Asinr (Sanofi-Avenyis), Neoceptin R (Beximco), Neotack (Square Pharmaceuticals Ltd.) Tablet, Syrup, Ampule
	1–6 month: 1 mg/kg	Three times daily	
	6 months to 12 years: 2–4 mg/kg	Twice daily	
	12–18 year: 150 mg	Twice daily	
Lansoprazole	Under 30 kg: 0.5–1 mg/kg Over 30 kg: 15–30 mg	Once daily at morning	Capsule: 15 mg, 30 mg Tablet: Aslan (Unimed & Unihealth), Lansec (Drug international), Lansodil (Acme Lab)
Omeprazole	Neonate: 700 µg/kg 1 month to 2 year: 700 µg/kg up to 3 mg/kg	Once daily	Capsule: 10 mg, 20 mg, 40 mg Powder: 20 mg/sachet Capsule Ansec (Novo), Cosec (Drug International), Omenix (Incepta Pharmaceuticals Ltd.) Losectil (SKF) Injection 20 mg, 40 mg/vial (Ansec, Omenix)

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Drug	Route	Doses and time/day	Availability, generic and some trade (local) names
Esomeprazole	0.5–1 mg/kg from 6 month	Once daily	Tablet: 20 mg, 40 mg Injection: 20 mg/IV Tablet: Nexum (Square) Asector (Novo), Emep (Aristopharma Ltd.), Esonix (Incepta Pharmaceuticals Ltd.) Injection: Nexum 20 mg, 40 mg/vial
Topical Preparation (Cream Ointment) for Dermatological Disorders			
Antibiotic Fusidic acid	Topical (over affected skin)	three times daily/four times daily	Cream, ointment, Facid (SKF), Fusidate (Aristopharma), Fusidin (Leo)
Mupirocin	Topical (over affected skin)	three times daily	Ointment, Bactroban (GSK), Bactoderm (Unimed & Unihealth), Trego (Incepta Pharmaceuticals Ltd.)
Nitrofural	Topical (over affected skin)	three times daily	Cream, Furasep (Beximco)
Polymyxin B (witsh bacitracin, neomycin)	Topical (over affected skin)	three times daily	Ointment, Nebanol Plus® (Square Pharmaceuticals Ltd.)
Silver sulfadiazin (Burn)	Topical (over affected skin)	three times daily	Cream Dermazin (Novartis), Silcream (Jayson Pharma)
Povidone-iodine	Topical (over affected skin)	three times daily	Ointment, solution, cream (Betadin Ointment (Win-Medicare), Povisep cream, Povisep Solution, Viodine® solution and cream (Square Pharmaceuticals Ltd.)
Steroids Hydrocortisone	Topical (over affected skin)	three times daily	Cream, ointment 1% hydrocortisone cream Zocort® (ACI), cream Unicort (Gaco), cream, Topicort® (Square Pharmaceuticals Ltd.)
Triamcinolone	Topical (over affected skin)	three times daily	Cream, ointment 0.1% Triamcinolone, Aristocort (Aristopharma Ltd.), Cenolon (Incepta Pharmaceuticals Ltd.)
Mometasone and Clobetasone	Topical (over affected skin)	three times daily	Mometason cream, ointment, lotion Elocon (Schering-Plough) Elocan (General Pharma) Clobetasone cream, Eumovate (GSK)
Non-steroidal anti-inflammatory Tacrolimus	Topical (over affected skin)	three times daily	Ointment 0.03%, 0.1%, 0.3% Tacrolim (Incepta Pharmaceuticals Ltd.), Tacrol (Acme), Remus (Square Pharmaceuticals Ltd.)
Antibiotic + steroid Fusidic acid + Betamethasone	Topical (over affected skin)	three times daily	Cream, ointment Fucicort (Leo)
Fusidic Acid + Hydrocortisone	Topical (over affected skin)	three times daily	Cream, ointment Fucidin H (Leo), Fusidate H (Aristopharma Ltd.), Facid HC (SKF)
Neomycin + Hydrocortisone	Topical (over affected skin)	three times daily	Ointment Framycort (Sanofi-Aventis)
Neomycin + Betamethasone	Topical (over affected skin)	three times daily	Cream Neobet (Acme), Betnovate-N (GSK), Betnovate-N Rectal (GSK)
Antifungal Miconazole	Topical (over affected skin)	three times daily	Cream Fungidal (Square Pharmaceuticals Ltd.), Miconex (ACI), Micozole (Gaco)
Clotrimazole	Topical (over affected skin)	twice daily/three times daily	Cream Canesten (Square Pharmaceuticals Ltd.), Clotrim (Acme), Fungin (Ibne Sina)
Econazole	Topical (over affected skin)	twice daily/three times daily	Cream Econate (Incepta Pharmaceuticals Ltd.) Pevaryl (Sanofi-Aventis)

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Drug	Route	Doses and time/day	Availability, generic and some trade (local) names
Tioconazole	Topical (over affected skin)	three times daily	Cream Conasyd (Renata)
Terbinafine	Topical (over affected skin)	three times daily/once/twice daily/	Cream Lamisil (Novartis), Tarbex (Beximco), Mycofin (SKF)
Combination of antifungal + Steroid Miconazole + Hydrocortisone	Topical (over affected skin)	three times daily	Cream Fungidal HC (Square Pharmaceuticals Ltd.), Mic-HC (Globe)
Econazole + Triamcinolone	Topical (over affected skin)	three times daily	Cream Pevisone (Sanofi-Aventis), Fungista (Drug International), Enazole Plus (Biopharma)
Antiscabies Permethrin	Topical (over affected skin)	Topical once over all skin surfaces, allowed to remain on lesion for 10 hours. May be reapplied after 1 week	Cream: 5% Lotrix (GSK), Scabex (Square Pharmaceuticals Ltd.), Elimate (Incepta Pharmaceuticals Ltd.)
Crotamiton	Topical (over affected skin)	Apply over affected skin repeat application in 24 hour and cleanse in 48 hour	Cream: 10% and 10% Lotion Eurax (Novartis), Crodex (Gaco), Chronix (Unimed & Unihealth)
Combination (Permethrin + Crotamiton)	Topical (over affected skin)	Apply over affected skin repeat application in 24 hour and cleanse in 48 hour	Cream: 10% and 10% lotion Unix C (Unimed & Unihealth), Lorix Plus (Opsonin), Elimate Plus (Incepta Pharmaceuticals Ltd.)

Abbreviations: IPD, invasive pneumococcal disease; UTI, urinary tract infection; SMT, sulphamethoxazole; TMP, trimethoprim; MRSA, methicillin-resistant *Staphylococcus aureus*; INH, isonicotinylhydrazine; PZA, pyrazinamide; CMV, cytomegalovirus; MDR, malaria drug resistance; SAG, sodium antimony gluconate; KA, kala-azar; PKDL, post-KA dermal leishmaniasis; KATF, kala-azar treatment failure; PR, per-rectal; GBS, Guillain-Barré syndrome; ADEM, acute disseminated encephalomyelitis; ADHD, attention deficit hyperactivity disorder; CCF, congestive cardiac failure; CHD, congenital heart disease; SVT, supraventricular tachycardia; MDI, metered dose inhaler, IV, intravenous; IM, Intramuscular; SC, subcutaneous

23 Chart

ASSESSING NUTRITIONAL STATUS (SD)

WEIGHT FOR AGE

Boys' weight (kg)					Age (months)	Girls' weight (kg)				
-4SD	-3SD	-2SD	-1SD	Median		Median	-1SD	-2SD	-3SD	-4SD
1.63	2.04	2.45	2.86	3.27	0	3.23	2.74	2.24	1.75	1.26
1.55	2.24	2.92	3.61	4.29	1	3.98	3.39	2.79	2.19	1.59
1.76	2.62	3.47	4.33	5.19	2	4.71	4.03	3.35	2.67	1.99
2.18	3.13	4.08	5.03	5.98	3	5.40	4.65	3.91	3.16	2.42
2.73	3.72	4.70	5.69	6.68	4	6.05	5.25	4.46	3.66	2.87
3.34	4.33	5.32	6.31	7.30	5	6.65	5.82	4.98	4.15	3.31
3.94	4.92	5.89	6.87	7.85	6	7.21	6.34	5.47	4.60	3.73
4.47	5.44	6.41	7.37	8.34	7	7.71	6.80	5.90	5.00	4.09
4.92	5.89	6.85	7.82	8.78	8	8.16	7.22	6.29	5.35	4.42
5.30	6.27	7.24	8.21	9.18	9	8.56	7.59	6.63	5.66	4.70
5.62	6.60	7.58	8.56	9.54	10	8.92	7.92	6.93	5.93	4.94
5.88	6.88	7.87	8.87	9.86	11	9.24	8.22	7.20	6.17	5.15
6.09	7.11	8.12	9.14	10.15	12	9.53	8.48	7.43	6.39	5.34
6.26	7.30	8.34	9.38	10.41	13	9.79	8.72	7.65	6.57	5.50
6.40	7.46	8.53	9.59	10.65	14	10.03	8.93	7.84	6.74	5.64
6.51	7.60	8.69	9.78	10.87	15	10.25	9.13	8.01	6.89	5.78
6.60	7.72	8.84	9.96	11.08	16	10.45	9.31	8.17	7.04	5.90
6.68	7.83	8.98	10.13	11.28	17	10.64	9.49	8.33	7.18	6.02
6.76	7.93	9.11	10.29	11.47	18	10.83	9.65	8.48	7.31	6.14
6.83	8.04	9.25	10.45	11.66	19	11.01	9.82	8.64	7.46	6.27
6.91	8.15	9.38	10.61	11.85	20	11.19	9.99	8.80	7.60	6.41
7.00	8.26	9.52	10.78	12.04	21	11.37	10.16	8.96	7.75	6.54
7.08	8.37	9.65	10.94	12.22	22	11.55	10.33	9.12	7.90	6.68
7.17	8.48	9.79	11.10	12.41	23	11.73	10.50	9.28	8.05	6.82
7.84	8.97	10.09	11.22	12.34	24	11.80	10.62	9.45	8.28	7.10
7.85	9.03	10.20	11.37	12.54	25	12.01	10.81	9.61	8.40	7.20
7.87	9.09	10.30	11.52	12.74	26	12.23	10.99	9.76	8.53	7.29
7.89	9.15	10.41	11.68	12.94	27	12.43	11.17	9.91	8.65	7.39

Contd...

Contd...

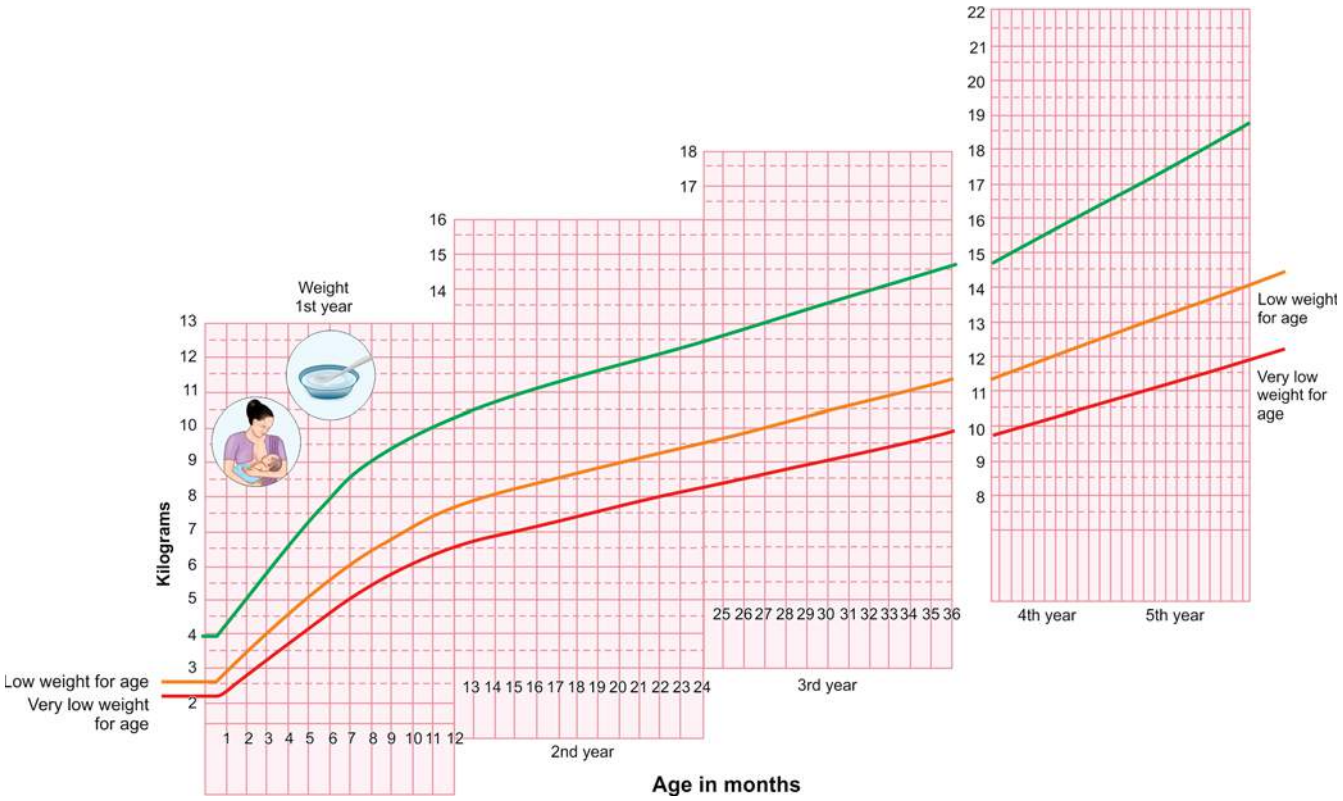
Boys' weight (kg)					Age (months)	Girls' weight (kg)				
-4SD	-3SD		-1SD				-1SD		-3SD	-4SD
7.91	9.22	10.52	11.83	13.13	28	12.63	11.35	10.06	8.77	7.48
7.94	9.28	10.63	11.98	13.33	29	12.83	11.52	10.21	8.89	7.58
7.97	9.36	10.74	12.13	13.52	30	13.03	11.69	10.35	9.01	7.67
8.00	9.43	10.85	12.28	13.71	31	13.22	11.85	10.49	9.13	7.76
8.04	9.51	10.97	12.43	13.89	32	13.40	12.01	10.63	9.24	7.85
8.09	9.58	11.08	12.58	14.08	33	13.58	12.17	10.76	9.35	7.94
8.13	9.66	11.20	12.73	14.26	34	13.76	12.33	10.90	9.46	8.03
8.18	9.75	11.31	12.88	14.44	35	13.93	12.48	11.03	9.57	8.12
8.24	9.83	11.43	13.03	14.62	36	14.10	12.63	11.15	9.68	8.21
8.29	9.92	11.55	13.18	14.80	37	14.27	12.78	11.28	9.79	8.29
8.35	10.01	11.67	13.32	14.98	38	14.44	12.92	11.41	9.89	8.38
8.42	10.10	11.79	13.47	15.16	39	14.60	13.06	11.53	9.99	8.46
8.48	10.19	11.91	13.62	15.33	40	14.76	13.20	11.65	10.10	8.54
8.55	10.29	12.03	13.77	15.51	41	14.91	13.34	11.77	10.20	8.62
8.62	10.39	12.15	13.91	15.68	42	15.07	13.48	11.89	10.29	8.70
8.70	10.48	12.27	14.06	15.85	43	15.22	13.61	12.00	10.39	8.78
8.77	10.58	12.40	14.21	16.02	44	15.37	13.74	12.12	10.49	8.86
8.85	10.68	12.52	14.35	16.19	45	15.52	13.88	12.23	10.58	8.94
8.93	10.79	12.64	14.50	16.36	46	15.67	14.00	12.34	10.68	9.01
9.01	10.89	12.77	14.65	16.53	47	15.81	14.13	12.45	10.77	9.09
9.10	11.00	12.90	14.79	16.69	48	15.96	14.26	12.56	10.86	9.16
9.18	11.10	13.02	14.94	16.86	49	16.10	14.39	12.67	10.95	9.23
9.27	11.21	13.15	15.09	17.03	50	16.25	14.51	12.77	11.04	9.30
9.36	11.32	13.28	15.23	17.19	51	16.39	14.63	12.88	11.13	9.37
9.45	11.43	13.40	15.38	17.36	52	16.53	14.76	12.98	11.21	9.44
9.54	11.54	13.53	15.53	17.52	53	16.67	14.88	13.09	11.30	9.51
9.64	11.65	13.66	15.67	17.69	54	16.81	15.00	13.19	11.38	9.57
9.73	11.76	13.79	15.82	17.85	55	16.95	15.12	13.29	11.46	9.64
9.82	11.87	13.92	15.97	18.02	56	17.09	15.25	13.40	11.55	9.70
9.92	11.99	14.05	16.12	18.18	57	17.24	15.37	13.50	11.63	9.76
10.02	12.10	14.18	16.26	18.34	58	17.38	15.49	13.60	11.71	9.82
10.11	12.21	14.31	16.41	18.51	59	17.52	15.61	13.70	11.79	9.88
10.21	12.33	14.44	16.56	18.67	60	17.66	15.73	13.80	11.87	9.94
10.31	12.44	14.57	16.71	18.84	61	17.81	15.85	13.90	11.95	9.99
10.41	12.56	14.70	16.85	19.00	62	17.96	15.98	14.00	12.02	10.04
10.50	12.67	14.84	17.00	19.17	63	18.10	16.10	14.10	12.10	10.10
10.60	12.78	14.97	17.15	19.33	64	18.25	16.23	14.20	12.17	10.15
10.70	12.90	15.10	17.30	19.50	65	18.40	16.35	14.30	12.25	10.20
10.79	13.01	15.23	17.45	19.67	66	18.56	16.48	14.40	12.32	10.25
10.89	13.13	15.36	17.60	19.84	67	18.71	16.61	14.50	12.40	10.29
10.99	13.24	15.49	17.75	20.00	68	18.87	16.74	14.60	12.47	10.34
11.08	13.35	15.63	17.90	20.17	69	19.03	16.87	14.70	12.54	10.38
11.18	13.47	15.76	18.05	20.34	70	19.19	17.00	14.81	12.62	10.42
11.27	13.58	15.89	18.20	20.51	71	19.36	17.13	14.91	12.69	10.46
11.36	13.69	16.02	18.35	20.69	72	19.52	17.27	15.01	12.76	10.50

Contd...

Contd...

Boys' weight (kg)					Age (months)	Girls' weight (kg)				
-4SD	-3SD		-1SD				-1SD	-2SD	-3SD	-4SD
11.45	13.80	16.15	18.51	20.86	73	19.70	17.41	15.12	12.83	10.54
11.54	13.91	16.29	18.66	21.03	74	19.87	17.55	15.22	12.90	10.57
11.63	14.02	16.42	18.81	21.21	75	20.05	17.69	15.33	12.97	10.61
11.71	14.13	16.55	18.97	21.38	76	23.23	17.83	15.43	13.04	10.64
11.80	14.24	16.68	19.12	21.56	77	20.42	17.98	15.54	13.11	10.67
11.86	14.35	16.81	19.28	21.74	78	20.61	18.13	15.65	13.18	10.70
11.96	14.45	16.94	19.43	21.92	79	20.80	18.28	15.76	13.24	10.72
12.04	14.56	17.07	19.59	22.10	80	21.00	18.44	15.87	13.31	10.75
12.12	14.66	17.20	19.75	22.29	81	21.20	18.59	15.99	13.38	10.77
12.19	14.76	17.33	19.90	22.47	82	21.41	18.76	16.10	13.45	10.79
12.26	14.86	17.46	20.06	22.66	83	21.62	18.92	16.22	13.52	10.81
12.33	14.96	17.59	20.22	22.85	84	21.84	19.09	16.34	13.58	10.83
12.39	15.06	17.72	20.38	23.04	85	22.06	19.26	16.46	13.65	10.85
12.46	15.15	17.85	20.54	23.24	86	22.29	19.43	16.58	13.72	10.86
12.52	15.25	17.97	20.70	23.43	87	22.53	19.61	16.70	13.79	10.87
12.57	15.34	18.10	20.87	23.63	88	22.76	19.79	16.82	13.85	10.88
12.63	15.43	18.23	21.03	23.83	89	23.01	19.98	16.95	13.92	10.89
12.68	15.52	18.35	21.19	24.03	90	23.26	20.17	17.08	13.99	10.90
12.72	15.60	18.48	21.36	24.24	91	23.51	20.36	17.21	14.06	10.91
12.77	15.69	18.61	21.52	24.44	92	23.77	20.55	17.34	14.13	10.92
12.81	15.77	18.73	21.69	24.65	93	24.03	20.75	17.48	14.20	10.92
12.84	15.85	18.85	21.86	24.86	94	24.30	20.95	17.61	14.27	10.93
12.87	15.92	18.98	22.03	25.08	95	24.57	21.16	17.75	14.34	10.93
12.90	16.00	19.10	22.20	25.30	96	24.84	21.37	17.89	14.41	10.94
12.92	16.07	19.22	22.37	25.52	97	25.12	21.58	18.03	14.49	10.94
12.94	16.14	19.34	22.54	25.74	98	25.41	21.79	18.18	14.56	10.94
12.96	16.21	19.46	22.71	25.97	99	25.70	22.01	18.32	14.63	10.95
12.97	16.28	19.58	22.89	26.19	100	25.99	22.23	18.47	14.71	10.95
12.98	16.34	19.70	23.06	26.43	101	26.29	22.45	18.62	14.79	10.96
12.98	16.40	19.82	23.24	26.66	102	26.59	22.68	18.77	14.87	10.96
12.99	16.46	19.94	23.42	26.90	103	26.89	22.91	18.93	14.95	10.97
12.99	16.52	20.06	23.60	27.14	104	27.20	23.14	19.08	15.03	10.97
12.98	16.58	20.18	23.78	27.38	105	27.51	23.38	19.24	15.11	10.98
12.98	16.64	20.30	23.97	27.63	106	27.82	23.61	19.40	15.20	10.99
12.97	16.70	20.43	24.15	27.88	107	28.14	23.85	19.57	15.28	11.00
12.96	16.82	20.67	24.53	28.39	109	28.79	24.34	19.90	15.46	11.02
12.95	16.87	20.80	24.72	28.65	110	29.11	24.59	20.07	15.55	11.03
12.94	16.93	20.93	24.92	28.91	111	29.44	24.84	20.24	15.65	11.05
12.93	16.99	21.05	25.12	29.18	112	29.78	25.10	20.42	15.74	11.06
12.91	17.05	21.18	25.32	29.45	113	30.12	25.36	20.60	15.84	11.08
12.90	17.11	21.31	25.52	29.72	114	30.45	25.62	20.78	15.94	11.10
12.89	17.17	21.45	25.72	30.00	115	30.80	25.88	20.96	16.04	11.12
12.88	17.23	21.58	25.93	30.28	116	31.14	26.14	21.15	16.15	11.15
12.87	17.30	21.72	26.14	30.57	117	31.49	26.41	21.33	16.25	11.18
12.86	17.36	21.86	26.36	30.86	118	31.84	26.68	21.52	16.36	11.21
12.86	17.43	22.00	26.57	31.15	119	32.19	26.95	21.72	16.48	11.24

Abbreviation: SD, standard deviation



WEIGHT FOR LENGTH

World Health Organization/National Center for Health Statistics normalized reference weight-for-length (49–84 cm) and weight-for-height (85–110 cm), by sex

Boys' weight (kg)					Length (cm)	Girls weight (kg)				
-4SD 60%	-3SD 70%		-1SD 90%				-1SD 90%		-3SD 70%	-4SD 60%
1.8	2.1	2.5	2.8	3.1	49	3.3	2.9	2.6	2.2	1.8
1.8	2.2	2.5	2.9	3.3	50	3.4	3	2.6	2.3	1.9
1.8	2.2	2.6	3.1	3.5	51	3.5	3.1	2.7	2.3	1.9
1.9	2.3	2.8	3.2	3.7	52	3.7	3.3	2.8	2.4	2
1.9	2.4	2.9	3.4	3.9	53	3.9	3.4	3	2.5	2.1
2	2.6	3.1	3.6	4.1	54	4.1	3.6	3.1	2.7	2.2
2.2	2.7	3.3	3.8	4.3	55	4.3	3.8	3,3	2.8	2.3
2.3	2.9	3.5	4	4,6	56	4.5	4	3.5	3	2.4
2.5	3.1	3.7	4.3	4.8	57	4.8	4.2	3.7	3.1	2.6
2.7	3.3	3.9	4.5	5.1	58	5	4.4	3.9	3.3	2.7
2.9	3.5	4.1	4.8	5.4	59	5.3	4.7	4.1	3.5	2.9
3.1	3.7	4.4	5	5.7	60	5.5	4.9	4.3	3.7	3.1
3.3	4	4.6	5.3	5.9	61	5.8	5.2	4.6	3.9	3.3
3.5	4.2	4.9	5.6	6.2	62	6.1	5.4	4.8	4.1	3.5
3.8	4.5	5.2	5.8	6.5	63	6.4	5.7	5	4.4	3.7
4	4.7	5.4	6.1	6.8	64	6.7	6	5.3	4.6	3.9
4.3	5	5.7	6.4	7.1	65	7	6.3	5.5	4.8	4.1
4.5	5.3	6	6.7	7.4	66	7.3	6.5	5.8	5.1	4.3
4.8	5.5	6.2	7	7.7	67	7.5	6.8	6	5.3	4.5
5.1	5.8	6.5	7.3	8	68	7.8	7.1	6.3	5.5	4.8

Contd...

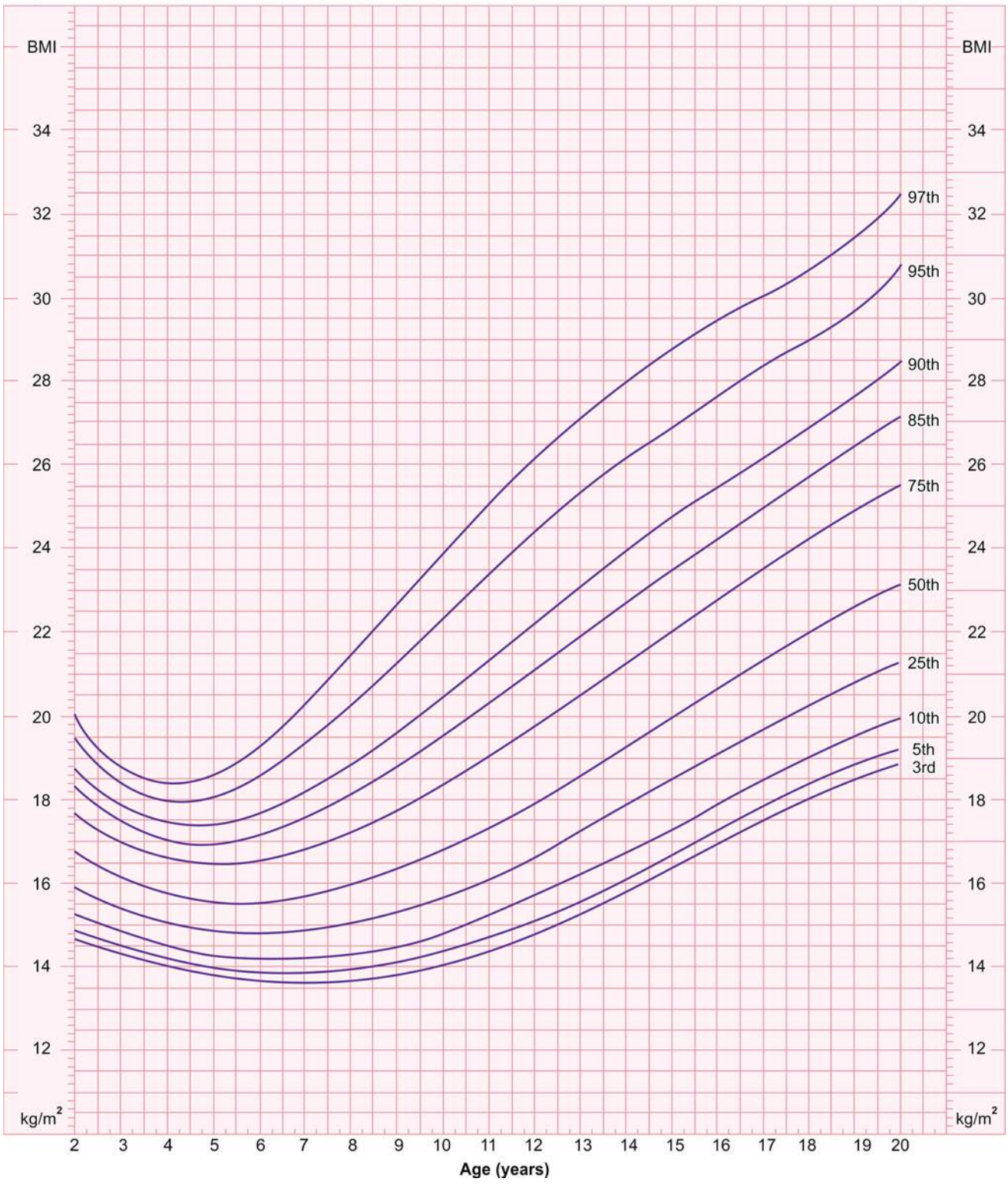
Contd...

Boys' weight (kg)					Length (cm)	Girls weight (kg)				
-4SD 60%	-3SD 70%	-2SD 80%	-1SD 90%	Median		Median	-1SD 90%	-2SD 80%	-3SD 70%	-4SD 60%
5.3	6	6.8	7.5	8.3	69	8.1	7.3	6.5	5.8	5
5.5	6.3	7	7.8	8.5	70	8.4	7.6	6.8	6	5.2
5.8	6.5	7.3	8.1	8.8	71	8.6	7.8	7	6.2	5.4
6	6.8	7.5	8.3	9.1	72	8.9	8.1	7.2	6.4	5.6
6.2	7	7.8	8.6	9.3	73	9.1	8.3	7.5	6.6	5.8
6.4	7.2	8	8.8	9.6	74	9.4	8.5	7.7	6.8	6
6.6	7.4	8.2	9	9.8	75	9.6	8.7	7.9	7	6.2
6.8	7.6	8.4	9.2	10	76	9.8	8.9	8.1	7.2	6.4
7	7.8	8.6	9.4	10.3	77	10	9.1	8.3	7.4	6.6
7.1	8	8.8	9.7	10.5	78	10.2	9.3	8.5	7.6	6.7
7.3	8.2	9	9.9	10.7	79	10.4	9.5	8.7	7.8	6.9
7.5	8.3	9.2	10.1	10.9	80	10.6	9.7	8.8	8	7.1
7.6	8.5	9.4	10.2	11.1	81	10.8	9.9	9	8.1	7.2
7.8	8.7	9.6	10.4	11.3	82	11	10.1	9.2	8.3	7.4
7.9	8.8	9.7	10.6	11.5	83	11.2	10.3	9.4	8.5	7.6
8.1	9	9.9	10.8	11.7	84	11.4	10.5	9.6	8.7	7.7
7.8	8.9	9.9	11	12.1	85	11.8	10.8	9.7	8.6	7.6
8.1	9.2	10.3	11.5	12.6	87	12.3	11.2	10.1	9	7.9
8.3	9.4	10.5	11.7	12.8	88	12.5	11.4	10.3	9.2	8.1
8.4	9.6	10.7	11.9	13	89	12.7	11.6	10.5	9.3	8.2
8.6	9.8	10.9	12.1	13.3	90	12.9	11.8	10.7	9.5	8.4
8.8	9.9	11.1	12.3	13.5	91	13.2	12	10.8	9.7	8.5
8.9	10.1	11.3	12.5	13.7	92	13.4	12.2	11	9.9	8.7
9.1	10.3	11.5	12.8	14	93	13.6	I2.4	11.2	10	8.8
9.2	10.5	11.7	13	14.2	94	13.9	12.6	11.4	10.2	9
9.4	10.7	11.9	13.2	14.5	95	14.1	12.9	11.6	10.4	9.1
9.6	10.9	12.1	13.4	14.7	96	14.3	13.1	11.8	10.6	9.3
9.7	11	12.4	13.7	15	97	14.6	13.3	12	10.7	9.5
9.9	11.2	12.6	13.9	15.2	98	14.9	13.5	12.2	10.9	9.6
10.1	11.4	12.8	14.1	15.5	99	15.1	13.8	12.4	11.1	9.8
10.3	11.6	13	14.4	15.7	100	15.4	14	12.7	11.3	9.9
10.4	11.8	13.2	14.6	16	101	15.6	14.3	12.9	11.5	10.1
10.6	12	13.4	14.9	16.3	102	15.9	14.5	13.1	11.7	10.3
10.8	12.2	13.7	15.1	16.6	103	16.2	14.7	13.3	11.9	10.5
11	12.4	13.9	15.4	16.9	104	16.5	15	13.5	12.1	10.6
11.2	12.7	14.2	15.6	17.1	105	16.7	15.3	13.8	12.3	10.8
11.4	12.9	14.4	15.9	17.4	106	17	15.5	14	12.5	11
10.6	12	13.4	14.9	16.3	102	15.9	14.5	13.1	11.7	10.3
10.8	12.2	13.7	15.1	16.6	103	16.2	14.7	13.3	11.9	10.5
11	12.4	13.9	15.4	16.9	104	16.5	15	13.5	12.1	10.6
11.2	12.7	14.2	15.6	17.1	105	16.7	15.3	13.8	12.3	10.8
11.4	12.9	14.4	15.9	17.4	106	17	15.5	14	12.5	11
11.6	13.1	14.7	16.2	17.7	107	17.3	15.8	14.3	12.7	11.2
11.8	13.4	14.9	16.5	18	108	17.6	16.1	14.5	13	11.4
12	13.6	15.2	16.8	18.3	109	17.9	16.4	14.8	13.2	11.6
12.2	13.8	15.4	17.1	18.7	110	18.2	16.6	15	13.4	11.9

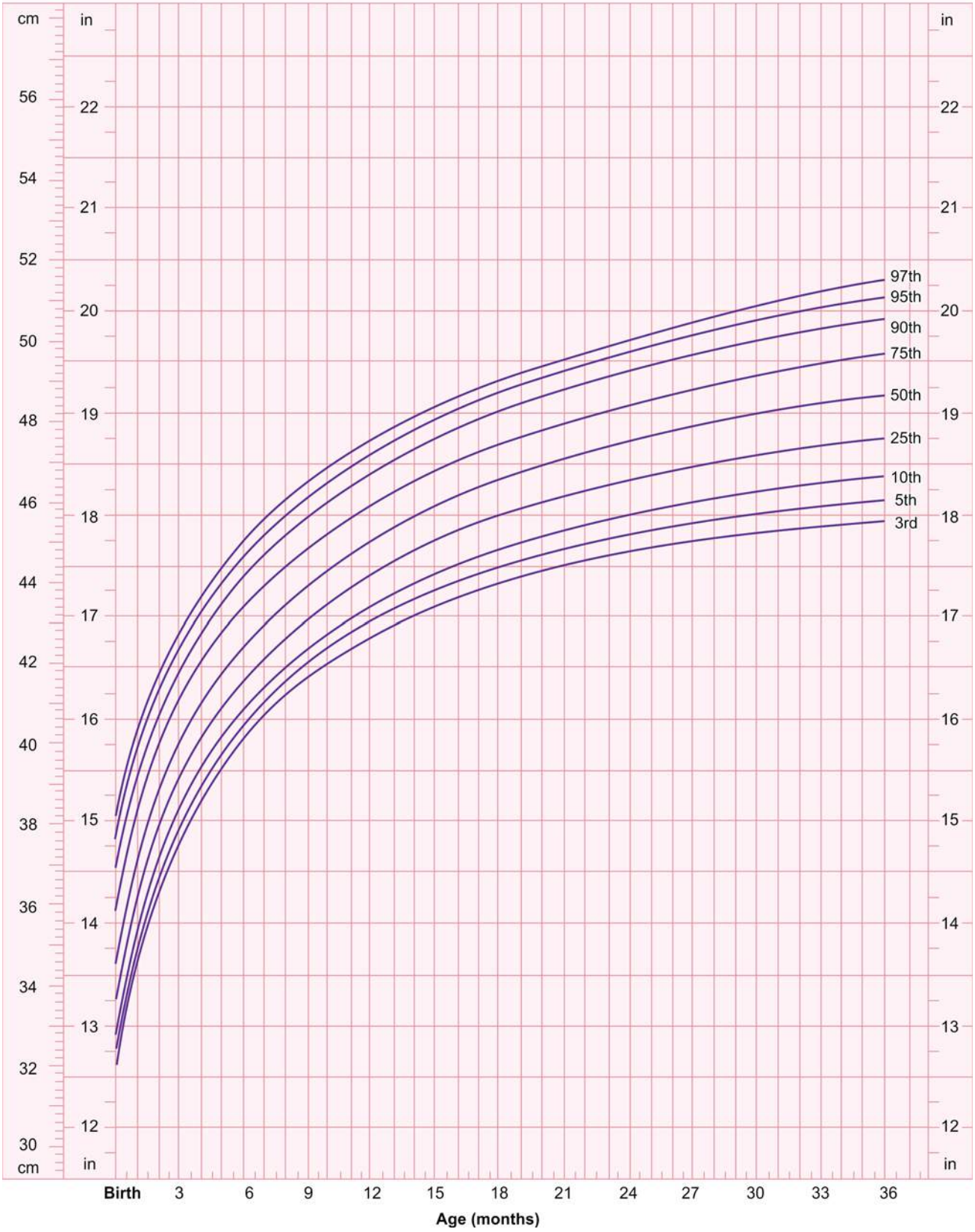
Source: Gorstein J, Sullivan K, Yip R, et al. Issues in the assessment of nutritional status using anthropometry. Bull World Health Organ. 1994;72(2):273-83.

Note: Length is measured below 85 cm; height is measured 85 cm and above. Recumbent length is on an average 0.5 cm greater than standing height, although the difference is of no importance to the individual child. A correction may be made by deducting 0.5 cm from all lengths above 84.9 cm, if standing height cannot be measured.

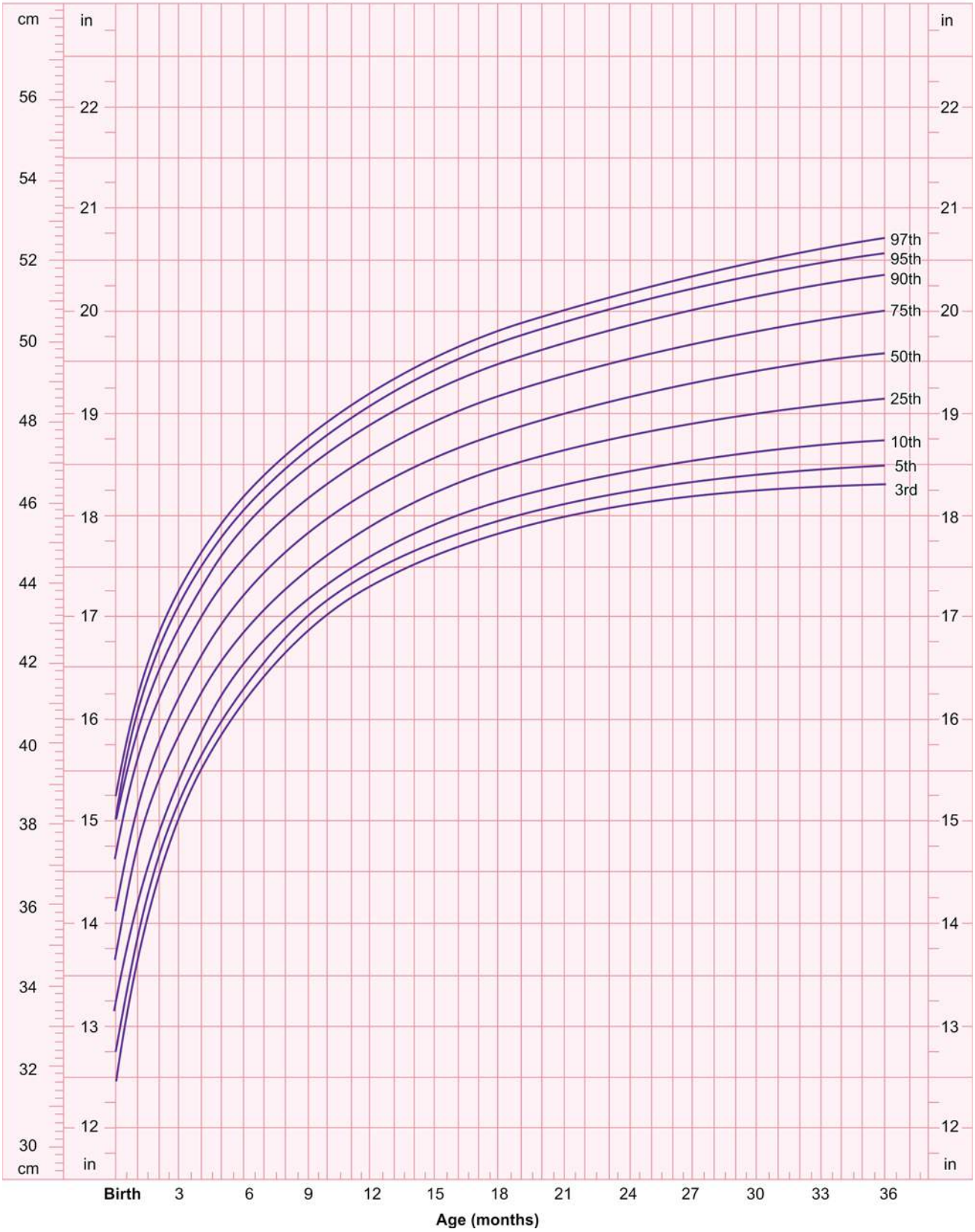
Body mass index-for-age percentiles: Boys, 2 to 20 years



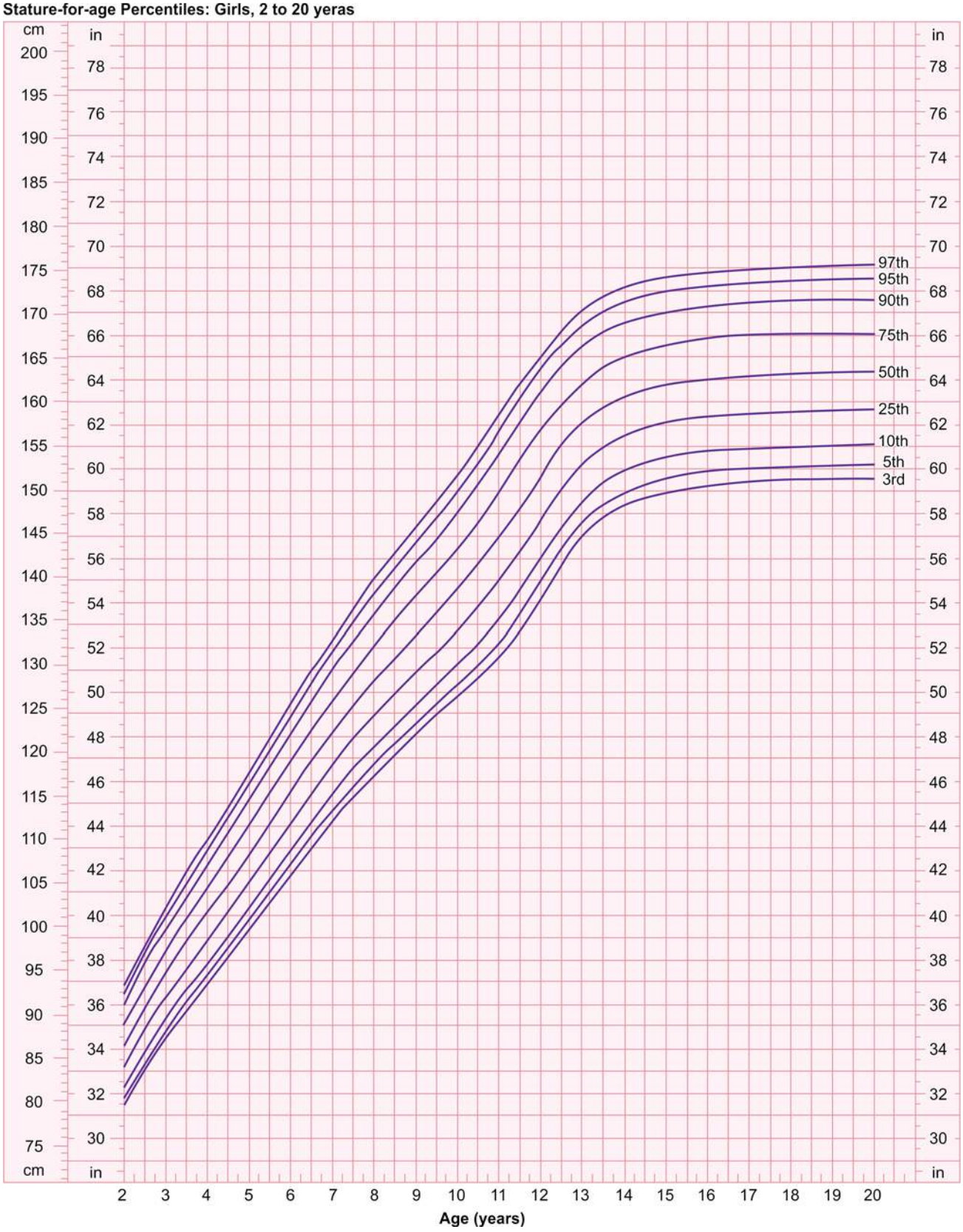
Head circumference-for-age Percentiles: Girls, Birth to 36 months



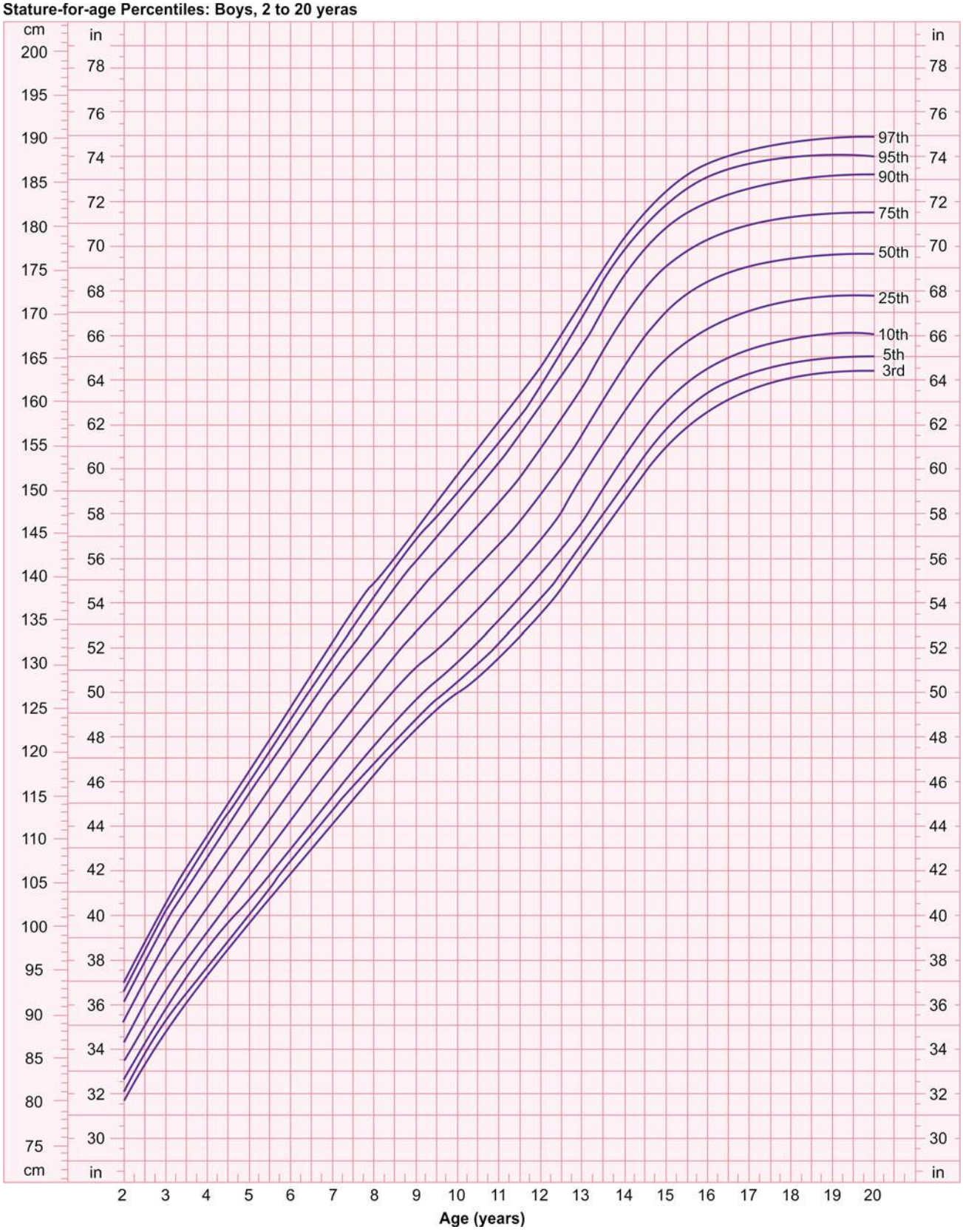
Head circumference-for-age Percentiles: Boys, Birth to 36 months



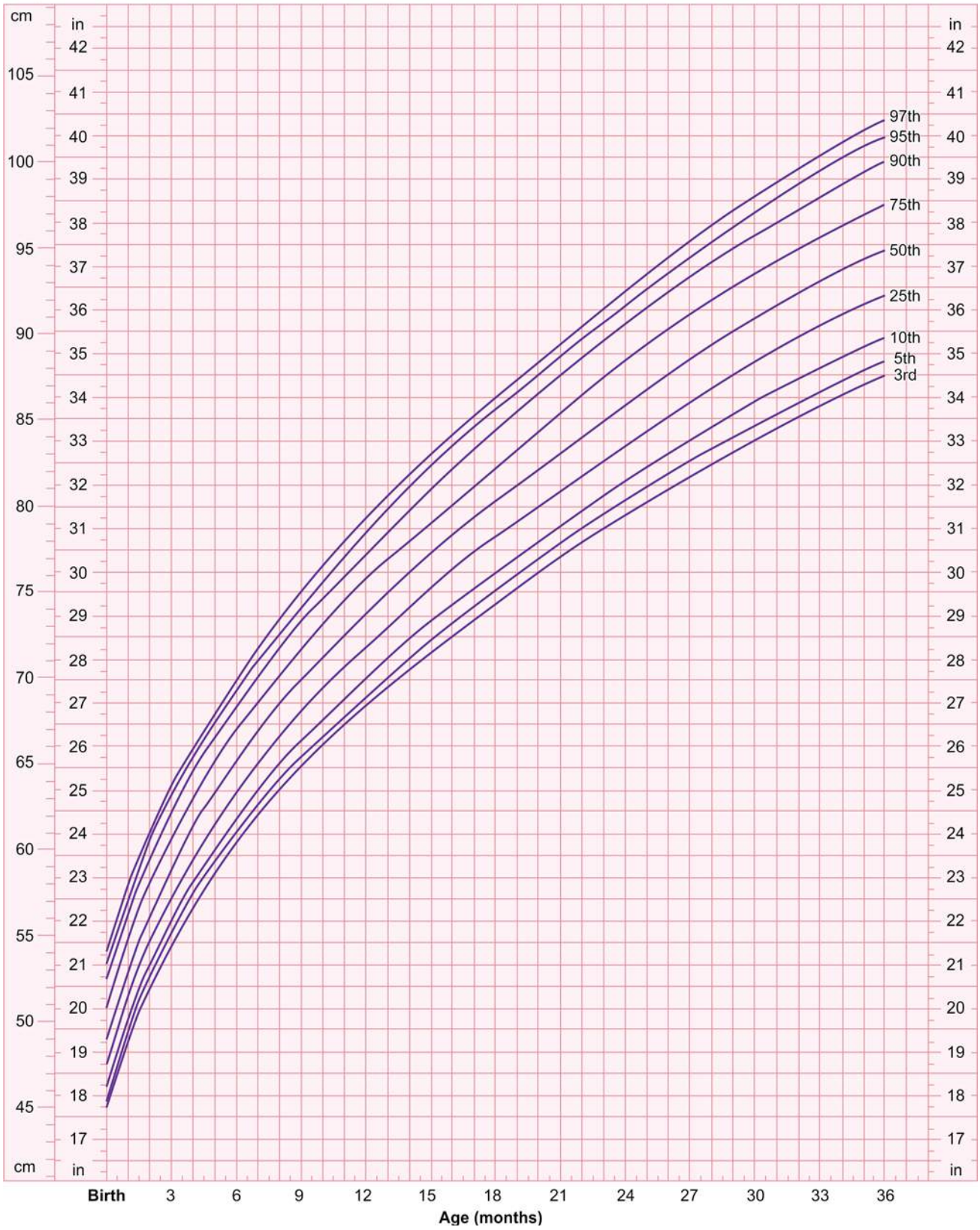
Stature-for-age Percentiles: Girls, 2 to 20 yeras



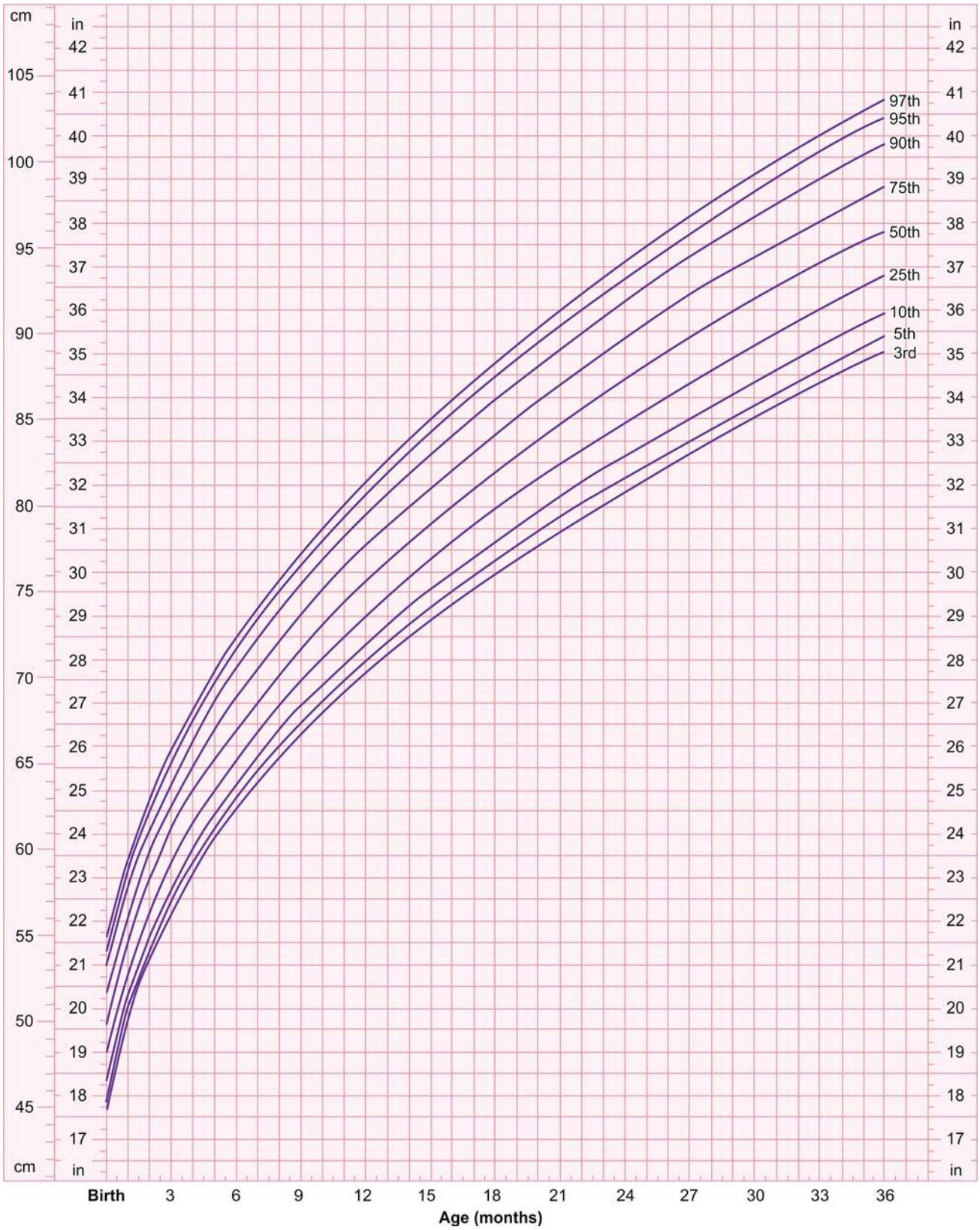
Stature-for-age Percentiles: Boys, 2 to 20 yeras



Length-for-age Percentiles: Girls, Birth to 36 months

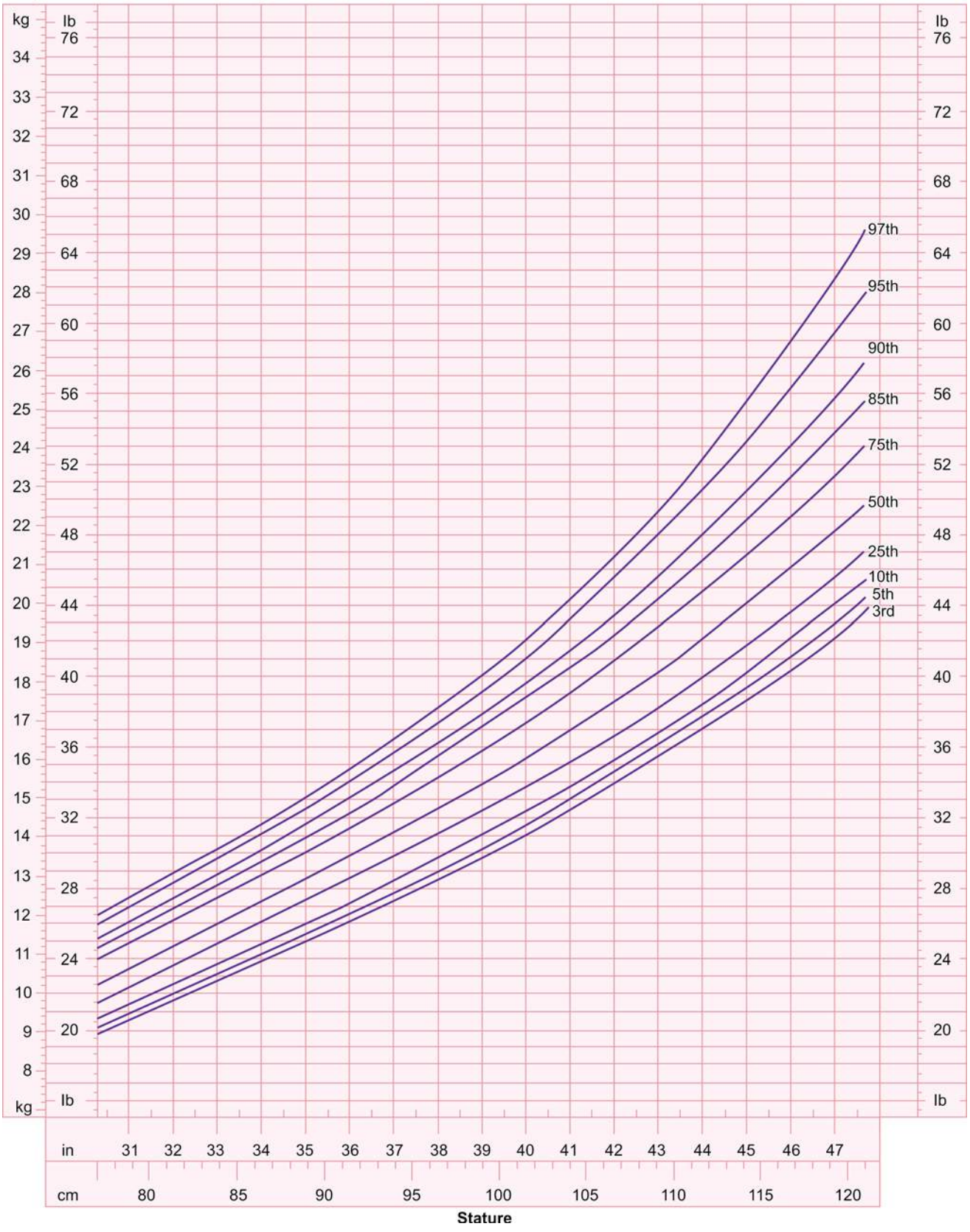


Length-for-age Percentiles: Boys, Birth to 36 months

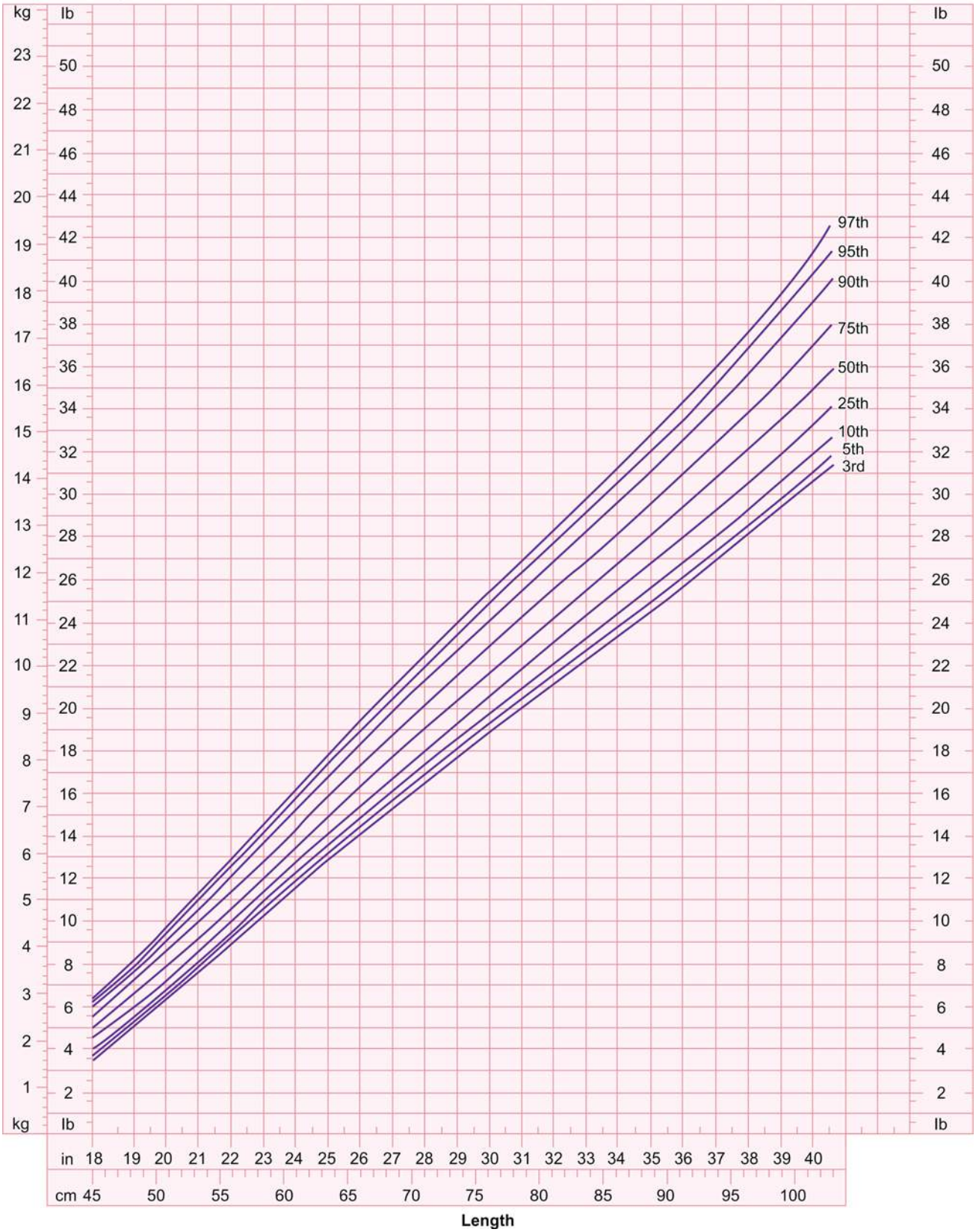


Weight-for-stature Percentiles: Girls

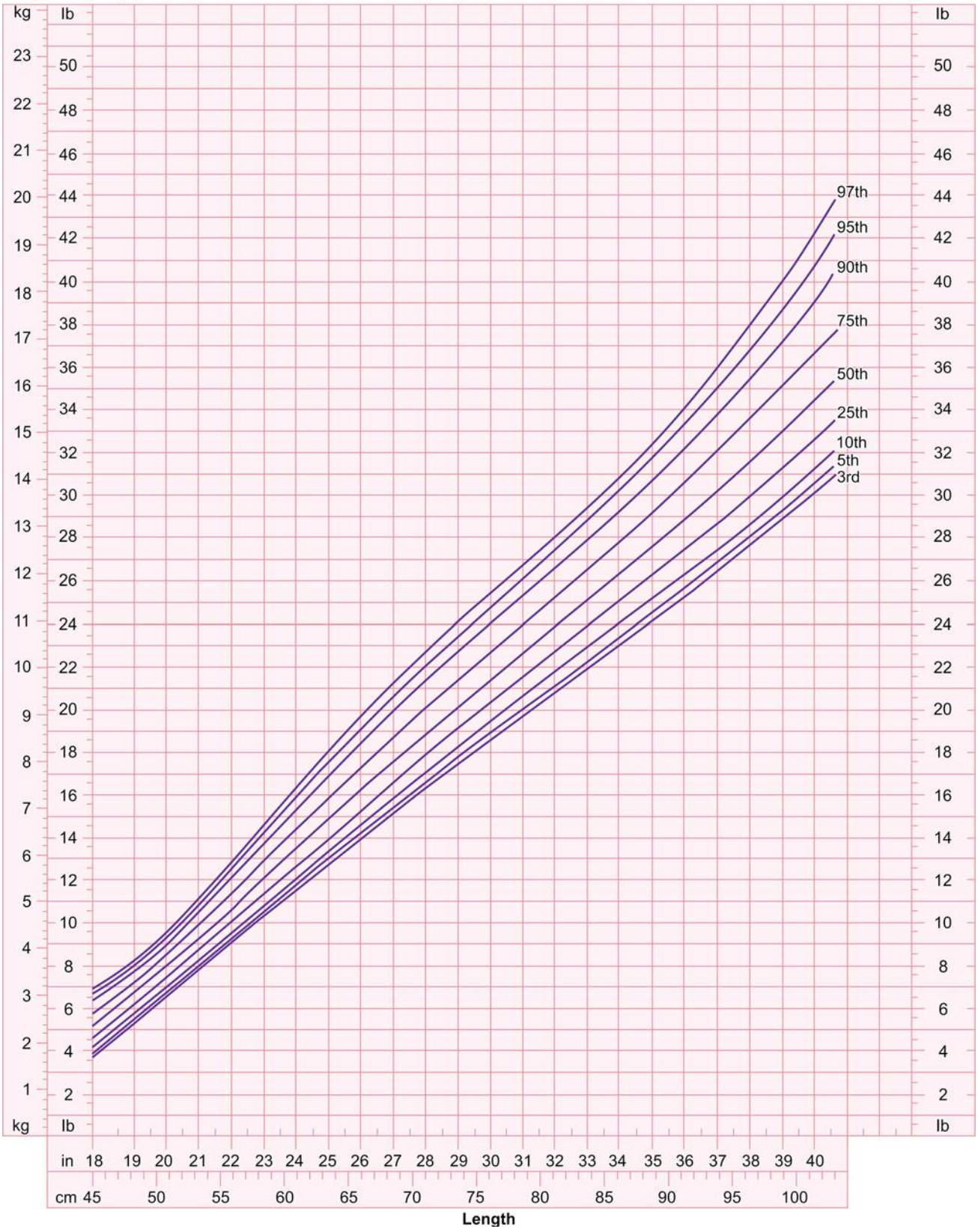
Weight-for-stature Percentiles: Boys



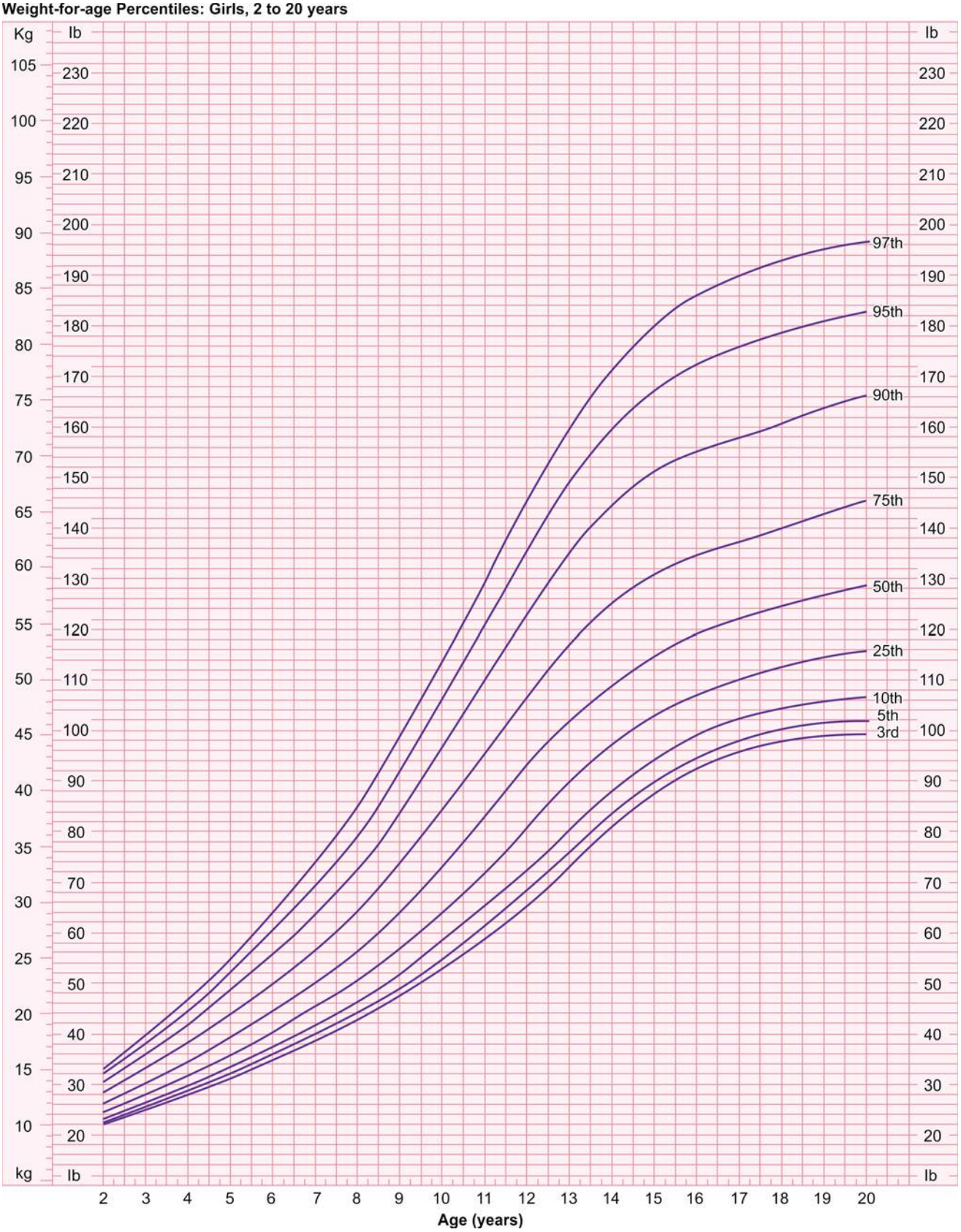
Weight-for-Length Percentiles: Boys, Birth to 36 Months



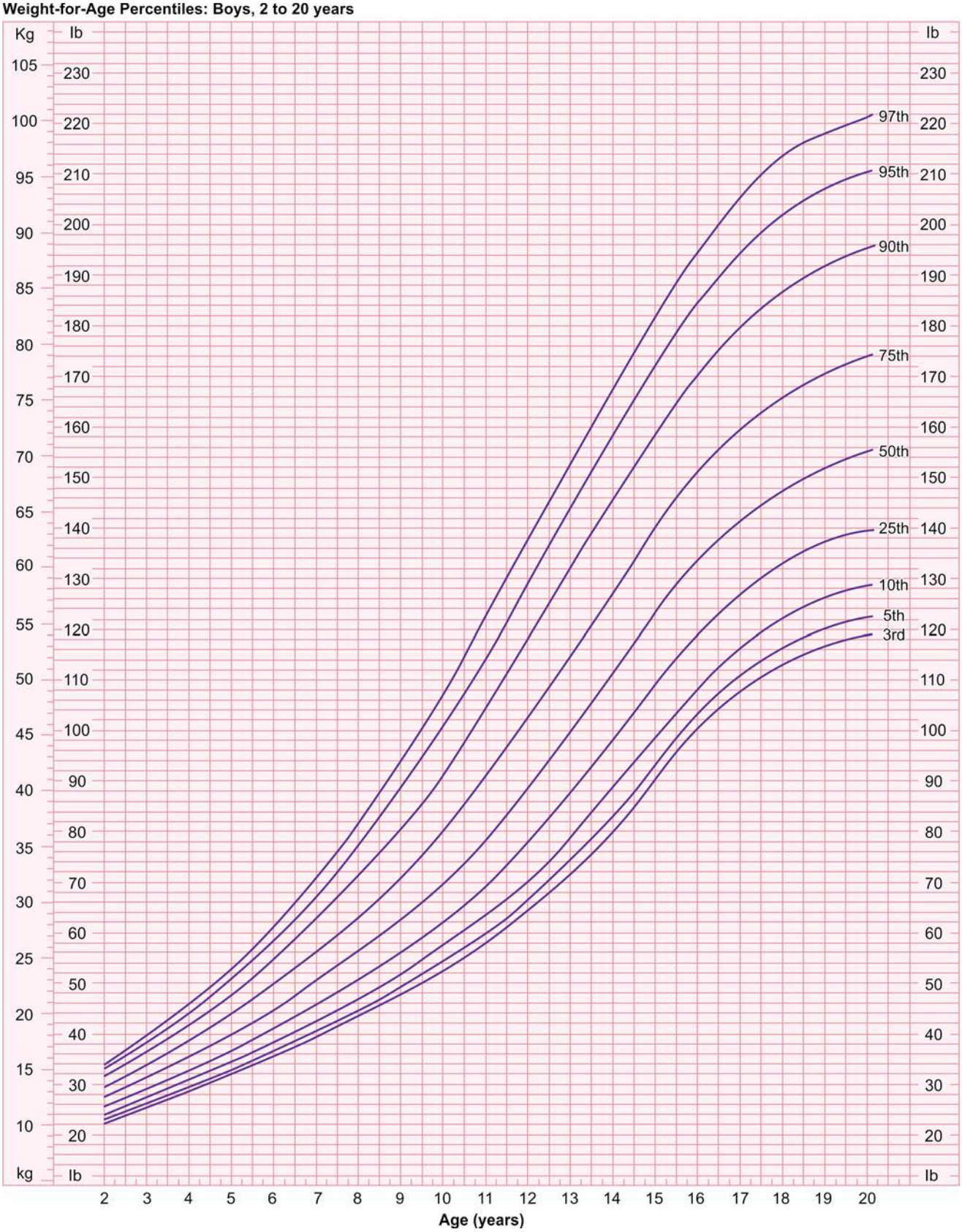
Weight-for-Length Percentiles: Girls, birth to 36 Months



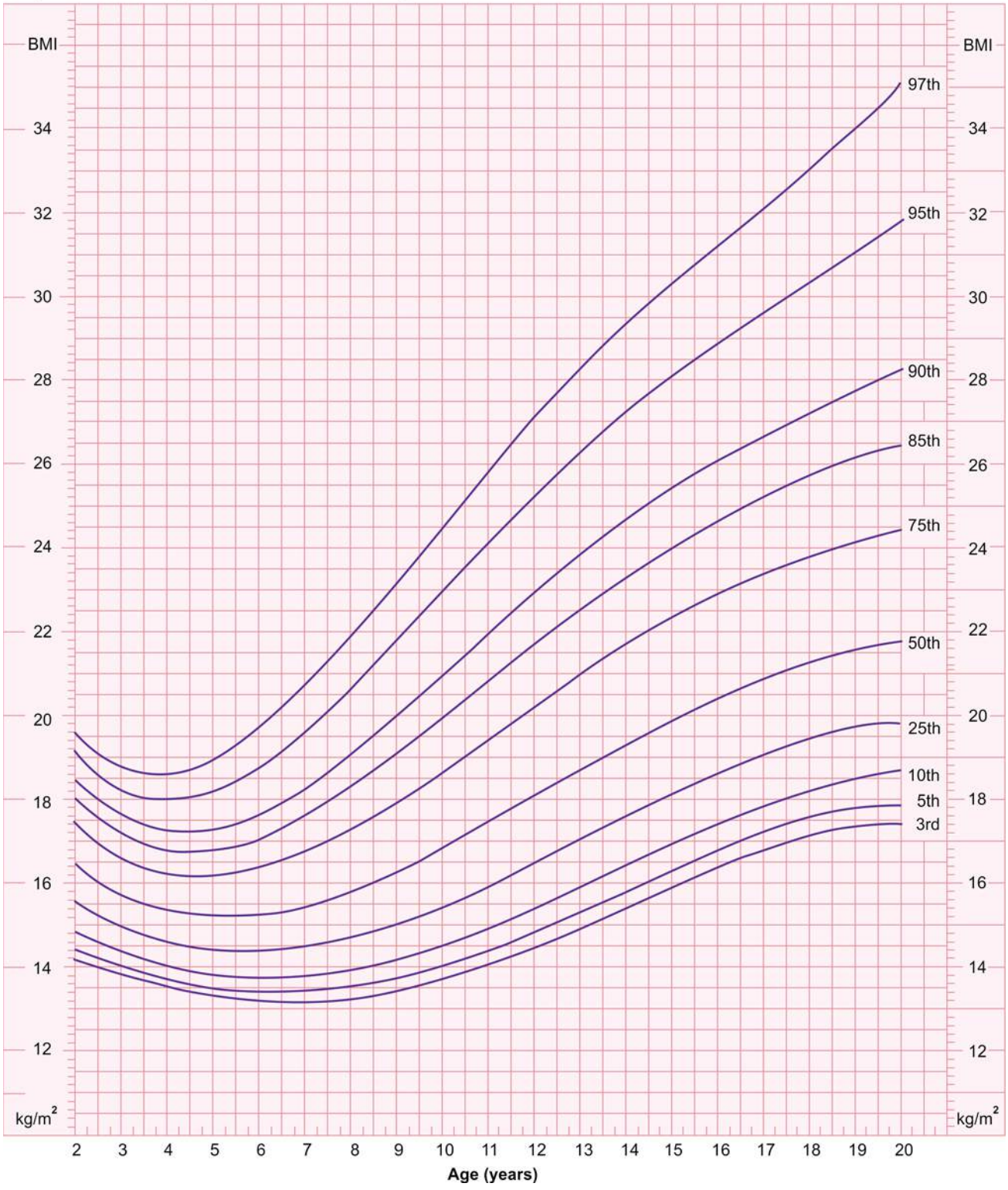
Weight-for-age Percentiles: Girls, 2 to 20 years



Weight-for-Age Percentiles: Boys, 2 to 20 years



Body mass index-for-age percentiles: Girls, 2 to 20 years



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