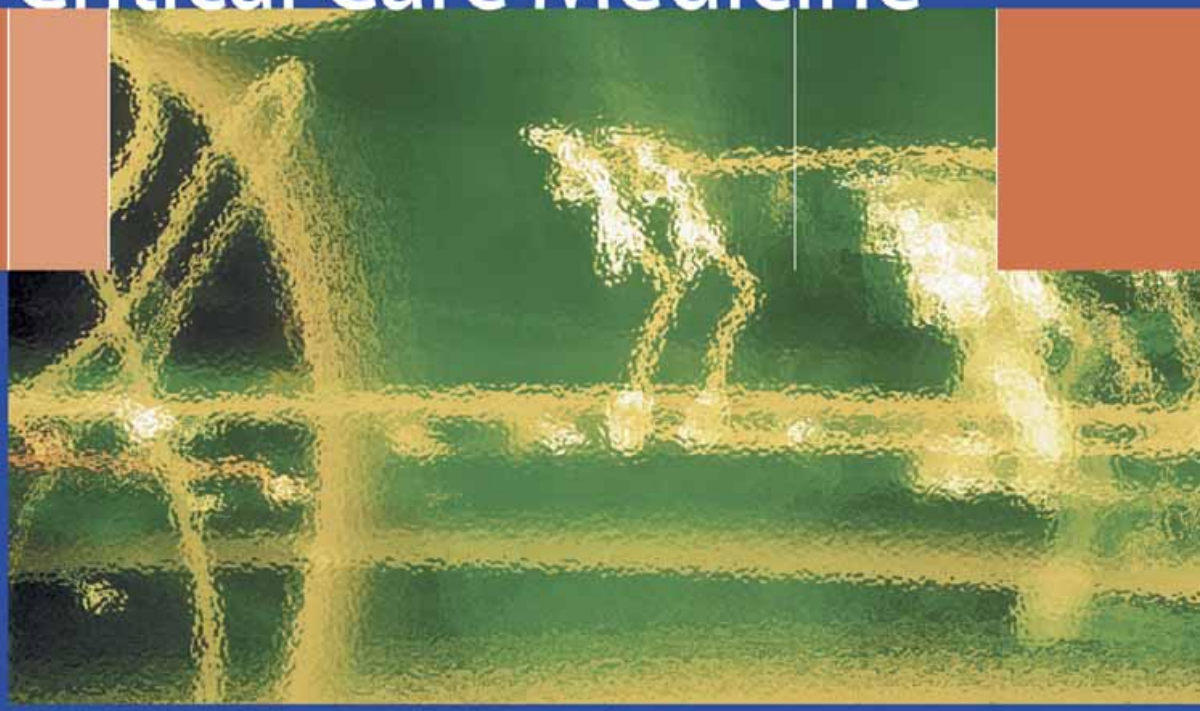
Antonino Gullo • José Besso
Philip D. Lumb • Ged F. Williams *Editors*

Intensive and Critical Care Medicine



WFSICCM
World Federation of Societies
of Intensive and Critical Care Medicine

Springer

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Preface

The World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM) has reached the age of maturity.

Physicians, nurses, and many others associated with the field of Intensive and Critical Care Medicine will be coming from all corners of the world to Florence, Italy in August, 2009 to celebrate the 10th quadrennial congress.

Every 4 years for the last 36 years, congresses in the magnificent venues of London (1973), Paris (1977), Washington (1981), Jerusalem (1985), Kyoto (1989), Madrid (1993), Ottawa (1997), Sydney (2001), and Buenos Aires (2005) have signified an ever-developing process which has resulted in the four pillars of the field of Intensive and Critical Care Medicine, namely partnership, ethics, professionalism, and competence.

The first pillar is based on a stronger interdisciplinary collaboration and a multiprofessional *partnership* in the field of Intensive and Critical Care Medicine. In recent decades, professional activity in medicine has been regulated by well-defined, universal principles, such as the welfare of the patient, autonomy, social justice, and the patient–physician relationship. The second pillar, *ethics*, has offered welcomed assistance to all these principles in establishing an ethics curriculum.

The third pillar, *professionalism*, is based on "the image of the ethical and moral conduct of those who practice the medical profession." Professionalism aspires to altruism, accountability, excellence, duty, service, honor, integrity, and respect for others. In order to maintain the highest level of professionalism, physicians and nurses must be committed to their own continuing education as a means of increasing both their knowledge base and manual skills. Equally important for achieving the best results possible is their willingness and ability to collaborate with others as a team with the goal of establishing continuity to assure the patients good medical practice and a better quality of care.

The fourth pillar, professional *competence*, is "the habitual and judicious use of communication, knowledge, technical skills, clinical reasoning, emotions, values, and the reflection in daily practice for the benefit of the individual and community

being served." Maintaining competence means continuing to learn as medical understanding and technologies rapidly change.

Coming from these reflections the Council of the WFSICCM, during the period 2001–2009, has alimented an important debate to develop a global communication network establishing a sort of bridge from the past to the present. The way into the future for the affiliated national societies is the planning of common strategies according to the objectives of the WFSICCM:

- To assist and encourage the cooperation of national societies for management of acute critical illness
- To promote the dissemination of knowledge, education programs, and scientific information
- To advise, upon request, national and international organizations
- To monitor the needs of the community
- To achieve a politically correct collaboration with governments, national health systems, and local authorities
- To support countries with limited resources
- To achieve equitable resource allocation
- To recommend desirable standards of training for intensivists, critical care personnel, emergency physicians, and nurses
- To provide information regarding opportunities for postgraduate training and research
- To ameliorate health care delivery and to promote the importance of intensive and critical care regionalization
- To implement the standards of care
- To encourage the establishment of safety measures, including procedures and equipment
- To achieve better accuracy regarding patient information
- To stimulate research into all aspects of intensive and critical care medicine
- To focus the importance of continuing education programs
- To consider mandatory the respect for ethics principles, the patient's welfare, and the quality of care
- To promote professional accomplishment by individuals, which will provide not only job satisfaction but also an improvement in the efficiency of the team
- To remark that intensive care nursing is younger than most healthcare specialties, but note that it already possesses a wealth of nursing knowledge and experience
- To increase the emphasis on the importance of improvement in competence, not only in terms of skills but also in behavior
- To maintain awareness about the priority and the mission of the WFSICCM: a good clinical practice

From 2001 the development agenda of the World Federation (WF) Council recognized the importance of promoting scientific and cultural integration across the world with prestigious editorial initiatives. Much success was achieved in Buenos Aires (2005) when the Council on the occasion of the 9th World Congress decided to publish its first book, from the beginning of the Federation Societies, edited by Springer: *Intensive and Critical Care Medicine – Reflections, Recommendations, and*

Perspectives. Education and standard of care were the pillars of the book. At that time each component of the Council contributed by updating chapter(s).

Florence (2009) will represent an important step in improving knowledge in the field of Intensive and Critical Care Medicine and reinforcing communication and good practice in the era of *partnership, ethics, professionalism, and competence*.

Everyone believes it is important to take advantage of the opportunity to take a leadership position on clinical decision-making. Prevention and management of life-threatening conditions in intensive and critical care and the importance of putting global strategies in place for surviving during and after natural or man-made disasters have become priorities.

As chairman of the Scientific Committee of the Florence 2009 meeting I am grateful to the Board and Colleagues of Italian Scientific Society (SIAARTI) and the Italian College of the Anesthesiologists (ICA), the Italian Society of Intensive Care (SITI) and the Italian Society of Nursing (ANIARTI) for their encouraging support during the long period of preparation of the World Congress. I would like to keep attention on the role of the Members of the WFSICCM Council for their active participation in assuring a bright future.

Besides, I wish to mention some distinguished persons for their institutional and active role in the success of the World Federation. Prof. José Besso is a special person full of humanity and devoted to optimizing the standards of care. I like to remember Prof. José Besso as superb and courageous President in the last mandate of WF (2005–2009). Further I offer sincere appreciation to the following individuals: Prof. Philip Lumb, for taking on the roles of both Editor-in-Chief of the Critical Care Journal and Past President of the WF (2001–2005), and for his very active presence and promotion of intercontinental cooperation; Prof. Edgar Jimenez, Treasurer of WF in the last 4 years (2005–2009), for his admirable efforts in pushing strongly for the globalization of WF and for his efforts to impart to everybody an understanding of the importance of maximizing communications between eastern and western countries; Prof. Ged Williams, as President of World Federation of Critical Care Nurses in the period 2001–2009, congratulations due, overall, for his important contribution to reinforce the independent, but collaborative role of nurses and the importance of their active cooperation in the care of critical illness. Moreover, my sincere gratitude to Phil Taylor, Executive Director of the WF, for his own enormous personal contribution to WFSICCM and for his continuing professional assistance to thousands and thousands of affiliates.

Particularly, I wish to express my sincere appreciation to the Council's Members who in the period 2001–2008 have worked intensively on the common project; so we were able to improve friendship, collaboration, and the strategic plan to get to the top in the critical care arena. Last but not least, a particular mention regarding Prof. Raffaele De Gaudio who had the merit and the power to drive thousands of physicians, nurses, students, and all allied people and companies interested to support the present and the future of the WFSICCM. On the other side, the Organizing and Scientific Secretary established a high spirit of cooperation and professionalism. My dear Raffaele, thanks a lot for the warm welcome in Florence and for showing us its magnificent heritage.

The working team is ready. Considering several assumptions, I think that we are at the right time to reach an exciting and remarkable goal: to continue the mission for serving critically ill patients and the community.

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Abbreviations

AECC	American European Consensus Conference
Aes	Adverse events
AGNB	Aerobic Gram-negative bacilli
AKI	Acute kidney injury
ALI/ARDS	Acute lung injury/Acute respiratory distress syndrome
AMSA	Amplitude Spectrum Area
ANCA	Antineutrophilic cytoplasmic antibodies
ANZICS	Australian and New Zeland Intensive Care Society
APACHE	Acute physiology and chronic health evaluation
APFCCN	Asia-Pacific Federation of Critical Care Nurses
APRV	Airway pressure release ventilation
APTT	Activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
ARDS	Adult respiratory distress syndrome
ASDI	Assurance in intensive care medicine
AT-III	Antithrombin-III
AUC	Area below the curve
AVPU score	Alert, Verbal, Painful, Unresponsive
BIS	Bispectral index
BMA	Bone marrow aspiration
BMI	Body mass index
CCNO	Critical care nursing organization
CDC	Center for Disease Control and Prevention
CFU	Colony forming units
CG	Clinical governance
CI	Colonization index
C-IAIs	Complicated intra-abdominal infections
Cmax	Maximum plasma concentration
CME	Continuing medical education
CNS	Central nervous system

CoBaTrICE	Competency Based Training in Intensive Care in Europe
CPP	Cerebral perfusion pressure
CPX	Cardiopulmonary exercise
CRBSI	Catheter-related blood stream infection
CRED	Center for Research on the Epidemiology of Disasters
CRH	Corticotropin-releasing hormone
CRP	C-reactive protein
CSE	Combined spinal epidural
CSF	Cerebrospinal fluid
CT	Computed tomography
CUSP	Comprehensive Unit-Based Safety Program
CVC	Central venous catheter
CVP	Central venous pressure
CVVH	Continuous veno-venous hemodiafiltration
DAD	Diffuse alveolar damage
DIC	Disseminated intravascular coagulation
DO_2	Oxygen delivery
DVT	Deep venous thrombosis
E. Coli	*Escherichia coli*
EBBP	Evidence-based best practices
EBP	Evidence-based practice
ECG	Electrocardiogram
ECMO	Extra corporeal membrane oxygenation
EfCCNa	European Federation of Critical Care Nursing Associations
EMCC	Emergency mass critical care
EMS	Emergency Medical Services
ESBL	Extended spectrum beta-lactamase
ESICM	European Society of Intensive Care Medicine
$EtCO_2$	End-tidal CO_2
FACTT	Fluid and Catheter Treatment Trial
FCCS	Fundamental critical care support course
FDA	Food and Drugs Administration
FDM	Fundamentals of disaster management
FFP	Fresh frozen plasma
FiO_2	Faction of inspired oxygen
FLECI	Federación Latinoamericana de Enfermería en Cuidado Intensivo
FSHRF	FSH-releasing factor
GABA	Gamma-aminobutyric acid
GFR	Glomerular filtration rate
GHRH	GH-releasing factor
GIT	Gastro-intestinal tract
GiViTI	Gruppo italiano per la Valutazione degli interventi in Terapia Intensiva
GMC	General Medical Council
Gp	General practitioner

GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
Hb	Hemoglobin
HCAI	Health care associated infections
Hct	Hematocrit
HES	Hydroxyethyl starch
HFOV	High frequency oscillatory ventilation
HICS	Hospital incident command system
HIV	Human immunodeficiency virus
HMGB-1	High mobility group box
HVA	Hazard-vulnerability analysis
IAIs	Intra-abdominal infections
ICD	Intensive care department
ICF	Informed consent form
ICM	Intensive care medicine
ICNARC	Intensive Care National Audit & Research Centre
ICP	Intracranial pressure
IFN	Interferon
IGF-1	Insulin-like growth factor receptor
IHI	Institute for Healthcare Improvement
INR	International normalized ratio
IOM	Institute of Medicine
IPS	Infection probability score
IRB	Institutional Review Board
IRR	Insulin receptor-related receptor
ISF	International Sepsis Forum
ITUs	Intensive therapy units
IUGR	Intrauterine growth retardation
JCAHQ	Joint Commission for Accreditation of Hospitals
LABIC	Latin American Brain Injury Consortium
LDH	Lactate dehydrogenase
LHRH	LH-releasing hormone
LiDCO	Lithium dilution cardiac output
LIS	Lung Injury Score
LMWH	Low-molecular-weight heparin
LOS	Length of stay
LP	Lumbar puncture
MAP	Mean arterial blood pressure
MCI	Mass casualty incident
$MgSO_4$	Magnesium sulphate
MIC	Minimum bacteria inhibiting concentration
MIF	Migration inhibiting factors
MIMMS	Major incident medical management and support
MODS	Multiple organ dysfunction syndrome
MRI	Magnetic resonance imaging

MRSA	Methicillin-resistant *Staphilococcus aureus*
MV	Mechanical ventilation
NANIN	National Association of Nurse Intensivists of Nigeria
NAS	Neonatal abstinence syndrome
NCA	Nurse or parent controlled analgesia
NDMS	National Disaster Medical System
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NO	Nitric oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
OPS	Orthogonal polarization spectral
PAC	Pulmonary artery catheter
PAOP	Pulmonary artery occlusion pressure
PAPR	Powered air purifier respirator
PCA	Patient-controlled analgesia
PCI	Percutaneous coronary intervention
PC-IRV	Pressure control inverse ration ventilation
PCT	Procalcitonin
PEEP	Positive end-expiratory pressures
PET	Positive emission tomography
PfEMP1	*Plasmodium falciparum* erythrocyte membrane protein 1
PI	Performance improvement
PiCCO	Pulse contour cardiac output
PICO	Patient, intervention, comparison, outcome
PICU	Pediatric intensive care unit
pK/pD	Pharmacokinetic / pharmacodynamic parameters
PNU1	Clinically defined pneumonia
PNU2	Pneumonia with specific laboratory findings
PNU3	Pneumonia in inmuocompromised patients
PPCM	Peri-partum cardiomyopathy
PPE	Personal protective equipment
PPM	Potentially pathogenic micro-organisms
PRL	Prolactin
PSA	Pressure swing adsorption
PtO_2	Oxygen partial pressure distribution
PTSD	Post traumatic stress disorder
QA/QI	Quality assurance/Quality improvement
QALYs	Quality Adjusted Life Years
QI	Quality improvement
rhAPC	Recombinant human activated protein-C
RIFLE	Risk, Injury, Failure, Loss and End stage
ROSC	Restoration of spontaneous circulation
RRT	Renal replacement therapy
SAFE	Saline versus albumin fluid evaluation
SAPS	Simplified acute physiology

SARS	Severe acute respiratory syndrome
SBI	Secondary brain injury
SCCM	Society of Critical Care Medicine
$ScvO_2$	Central venous oxygen saturation
SDD	Selective digestive tract decontamination
SICSAG	Scottish Intensive Care Audit Group
SIDS	Sudden infant death syndrome
SIRS	Systemic inflammatory response syndrome
SOD	Selective oropharyngeal decontamination
SOFA	Sequential Organ Failure Assessment score
SSC	Surviving Sepsis Campaign
START	Simple Triage and Rapid Treatment
SVR	Aystemic vascular resistance
TBI	Traumatic brain injury
TNF	Tumor necrosis factor
TNF-α	Tumor necrosis factor alpha
TQM	Total Quality Management
TRALI	Transfusion-related acute lung injury
TRH	Thyrotropin-releasing hormone
TRTS	Triage Revised Trauma Score
TTP	Thrombotic thrombocytopenic purpura
UC	Urinary catheter
UFH	Unfractioned heparin
US	Ultrasound
USC	University of Southern California
VAP	Ventilator associated pneumonia
VAS	Visual analog scale
VF	Ventricular fibrillation
VILI	Ventilator induced lung injury
VIP	Ventilation, infusion, and pumping
VO_2	Metabolic oxygen consumption
VRE	Vancomycin-resistant enterococci
WFCCN	World Federation of Critical Care Nurses
WFSICCM	World Federation of Societies of Intensive and Critical Care Medicine
WHO	World Health Organization

Section I
Introduction and Mission

History of Critical Care Medicine: The Past, the Present and the Future

1

G. Ristagno, M.H. Weil

Introduction

The term "Critical Care Medicine" was first introduced in the late 1950s at the University of Southern California (USC) from the concept that immediately life-endangered patients, the critically ill and injured, may have substantially better chances of survival if provided with professionally advanced minute-to-minute objective measurements. Such measurements were largely based on "real time" electronic monitoring of vital signs, hemodynamic and respiratory parameters, and complementary measurements on blood and body fluids. Care was increasingly delegated to a new generation of dedicated physicians, professional nurses, therapists, and clinical pharmacists in special care units. Since then, progress in the management of the acutely life-threatened patient has been accelerated by rapid advances in both monitoring and measurement technologies and the interventions that were triggered by them. Intubation and mechanical ventilation, hemodialysis, volume repletation guided by measurement of intravascular pressures and cardiac output, resuscitation by the routine use of chest compression, defibrillation and pacemaker insertion came into general use. These individual techniques had progressively evolved over the preceding decades by anesthesiologists in the operating room and postanesthesia recovery units and by cardiologists in the catheterization laboratory. Conventional methods of observation based on physical examination and largely manual measurement of vital signs at the bedside were therefore increasingly superceded by electronic techniques of quantitative monitoring and measurements. These methods of monitoring and measurements became not only acceptable practices but were remarkably rapidly implemented by hospitals and initially at defined in-hospital sites which were designated intensive care units (ICUs) or in some European countries, intensive

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therapy units (ITUs). In major centers, specialized units were later established in part contingent on the volume of patients eligible for specialized cardiac, respiratory, surgical, neurological, and later pediatric and neonatal care [1]. A variety of subsidiary or "step-down" units with less elaborate monitoring for intermediate care expanded the availability of monitored care to patients at lesser risk [2]. "Critical Care Medicine" as it became known in the USA, "Intensive Care," "Intensive Therapy" and "Reanimation" in some other countries remarkably rapidly became a new in-hospital practice discipline – within literally a decade. Within 25 years the discipline became a recognized subspecialty in which continuing on-site medical diagnosis and management of immediately life-threatening diseases and/or injuries was provided with high priority by advanced specialists recruited from internal medicine, general surgery, anesthesiology, and pediatrics. These specialists were intended to be physically on site, in part comparable to the well-established uninterrupted loyalty of anesthesiologists to a defined patient during surgical procedures [3]. At present, almost every medical and surgical practitioner now increasingly relies on critical care experts for the care of acutely life-threatened patients outside of the operating room in general or in specialized intensive care units.

When Did Critical Care Medicine Begin?

The beginning of critical care is debated, in part contingent on definitions of site or locale, the expertise and qualifications of providers, and the evolution of automated monitors and modern life support technologies. In the 1850s during the Crimean War, it was the site which defined the pioneering contribution of what became Critical Care by Florence Nightingale, who is generally viewed as the parent of professional nursing. Nightingale segregated the most severely battle injured soldiers and bedded them in close proximity to the nursing station so that they might receive more "intensive nursing care" [4]. Some 70 years later, in 1923, the concept of postoperative recovery was modeled by Dr. Walter Dandy who organized a neurosurgical postoperative care unit at Johns Hopkins Hospital in Baltimore, enlisting specialized nursing staff. Professional nurses therefore became the first bedside specialists rendering critical care under the direction of neurological surgeons. This initial intensive care also became a model for postoperative recovery units, which provided intensive postoperative management for military causalities during the Second World War [5]. Comparable postanesthesia recovery units evolved for postoperative management of patients in civilian practices in the 1950s, allowing for better outcomes after more invasive surgical procedures including cardiac and radical cancer operations. Again, it was the bedside expertise of specialist nurses, supported by anesthesiologists, who were later equipped with bedside monitors that triggered timely life support interventions and thereby improved management in the immediate postoperative interval.

Accordingly, there was a transition from site to expertise, both among medical specialists and especially anesthesiologists, and professional nursing. With respect to life support technologies, reference is often made to the poliomyelitis epidemics of

1940s and 1950s, in which the high incidence of bulbar polio with neuromuscular paralysis precluded spontaneous ventilation of the victims. The introduction of manual mechanical ventilation for such nonsurgical patients pioneered mechanical ventilation outside of the operating room. In one often quoted life support effort, Bjørn Ibsen in Denmark utilized manual methods of positive pressure ventilation by recruiting medical students who utilized bag ventilation for the victims [6]. Tracheostomy tubes were attached to a vented rubber bag which delivered air or oxygen mixtures when manually compressed. In our view, these lifesaving efforts, which preceded the use of positive pressure mechanical ventilation, however, are incorrectly cited by some historians as the beginning of critical care medicine. Although protracted manual ventilation as well as negative pressure tank respirators were used outside of the operating room, their applications were not focused on the management of the population of critically ill patients who we currently identify as the primary beneficiaries of modern critical care. More significantly, it was only after emergence of mechanical ventilators which were then widely utilized for management of the acute respiratory failure but beginning only in the late 1950s with the establishment of the earliest ICUs. Increasingly more sophisticated hemodynamic and respiratory methods of monitoring were introduced including quantitative measurements of ventilation, circulation, and metabolism, and the responses to interventions triggered by them. Examples include blood gases to guide concentrations of inspired oxygen and ventilator settings. Vascular pressures, both central venous and arterial together with cardiac output, served as basis for volume repletion and administration of vasopressor and inotropic drugs. Cardiac pacing following insertion of transvenous pacemakers and cardioversion and defibrillation are also major examples. Accordingly, the modern ICU had evolved in the late 1950s in a historical sequence beginning a century earlier with a site of care in proximity to and with the loyalty of professional nursing talent. Recruitment and training of special nursing and medical expertise followed in the mid-20th century. Increasing capability of professionals who were prepared to implement life support interventions followed the introduction of monitors, measurements, and life support technologies. The postanesthesia recovery units may be viewed, at least in part, as predecessors of the intensive care units as we know them today [7]. By 1958, and in our view largely as the result of newer methods of monitoring and measurements, the field of Critical Care Medicine/Intensive Care Medicine matured from a location into a defined clinical service, and within 25 years as a clinical specialty.

It was in 1958, at the Los Angeles County University of Southern California Medical Center, that one of the authors of this historical review (MHW) together with the late Dr. Herbert Shubin wondered why patients died unexpectedly after a heart attack, serious illness or injury, or postoperatively. In the absence of real time measurements of vital signs and alarms, professional providers were either not aware of the immediate life threats nor could they define with sufficient precision the immediate events that led to the fatal outcome. This “slipping away” in the absence of measurements or alarms therefore precluded the opportunity for prompt life saving interventions. Drs. Weil and Shubin, both cardiologists, implemented continuous monitoring of the electrocardiogram, blood pressure, pulse, breathing, and other vital

signs complemented by arterial and central venous pressures, urine flow, central and peripheral temperatures, and by intermittent measurements of blood gases from vascular sites. The assumption was that these monitors and measurements would provide the bedside team with the potential opportunity for timely actions. The VIP acronym [8], which orders the initial priority of life support, namely ventilation, infusion, and pumping was based on that early experience with the inventory of measurements. From that beginning, the USC team conceived of the concept of critical care professionals, both medical and nursing specialists, supported by engineers and technicians who would utilize monitors, measurements, and alarms in "real time" such as to have the capability for timely intervention and thereby greater likelihood of reversing immediate life threats. That concept was pioneered in a four-bed unit called the "Shock Ward." It became the prototype of the early ICU at the University of Southern California (Figs. 1.1–1.4). Initial emphasis reflecting the specialty interests of Drs. Weil and Shubin was on acute circulatory failure and especially cardiogenic shock [9]. Yet, the large incidence of sepsis and septic shock, which at that time was a poorly understood but major cause of early death, accounted for an increasing number of admissions to the Shock Ward. Within a decade, the service was expanded to multidisciplinary medical and surgical intensive care together with a cardiac care unit. It became a 42-bed "Center for the Critically Ill" at the University of Southern California and its affiliated Hollywood Presbyterian Medical Center. It also became an academic clinical service for the training of physicians, nurses, and technicians who were the early providers of intensive care, coronary care, trauma, and postoperative care.

Fig. 1.1 The "Shock Ward," University of Southern California, Los Angeles, 1958

Fig. 1.2 Computer room, University of Southern California

Fig. 1.3 Closed circuit TV camera to project printout from teletype to a TV monitor above the bed, University of Southern California

Fig. 1.4 Coronary Care, University of Southern California

With somewhat differing emphasis, the late Dr. Peter Safar, following the early tradition of Dandy [10] of neurosurgical care at John Hopkins University at the Baltimore City Hospital, developed a physician-staffed medical and surgical intensive care unit, also for management of patients with immediately life-threatening conditions [11], contemporaneously with our group. Peter Safar's unit was appropriately identified as a pioneering intensive care unit which emphasized bedside resuscitation interventions with emphasis on the management of airway and breathing but with somewhat lesser emphasis on technologies of monitoring and measurements. The elements of what emerged soon thereafter as the ABCs of CPR were major contributions of the Safar team [12,13]. The common denominator of both the Los Angeles and Baltimore units, however, was the commitment to dedicated care, on site, by physicians and specially trained professional nurses and technicians with preparedness for immediate lifesaving interventions for the most seriously ill and injured. The interventions included the VIP priorities of breathing, volume repletion, and circulatory support with early anticipation of neurologic recovery and control of infection. Both centers were committed not only to teaching, but to both clinical and laboratory research.

The Los Angeles team in emphasizing quantitative measurements of the circulation, focused on acute myocardial infarction, sepsis, and drug overdoses with interventions based on "real time" understanding of the myocardial failure, volume deficits, uncontrolled infection, and failure of adequate ventilation [14,15]. Los Angeles pioneered routines of bedside monitoring and measuring devices, including the earliest use of arterial and central venous catheters. Cardiac output was measured, initially by dye dilution techniques, and became routine for management of patients

with cardiovascular crises and especially circulatory shock. Titrated fluid and drug therapy, guided by hemodynamic measurements, became standards for management for these cardiovascular crises [16]. The "Shock Ward" in 1962 had already installed a dedicated digital computer system which facilitated and expedited hemodynamics and respiratory monitoring, infusion of fluids, and sampling of blood and urine. Medical records were partially automated and mechanically plotted even then. Infusion pumps programmed to deliver "fluid challenges" [17] were placed under computer control; urine flow was measured with an electronic urinometer; pressure transducers were automatically calibrated as were measurements of cardiac output, blood volumes, and blood lactate [18]. Detection and quantization of life-threatening cardiac arrhythmias were initially based on relatively primitive algorithms utilizing electrocardiographic heart rate and pulse rate. Respiratory frequencies were measured from pressure fluctuations in the superior vena cava or right atrium. Isotopic methods for measurements of plasma and red cell volumes, especially for detection of hypovolemic shock were of specific interest to the surgical members of the team, but their value was largely for research rather than routine clinical management. This contrasted with the STAT Laboratory concept born at USC (Fig. 1.5) for rapid measurements of blood gases, electrolytes, and arterial blood lactate, which proved uniquely helpful [19]. These have since been superceded by more automated compact and mobile analyzers, which now provide "point of care" testing.

In addition to Dr. Peter Safar's emphasis on the airway and ventilation which had such a prominent role in establishing the Safar-initiated priorities for cardiopul-

Fig. 1.5 The first STAT Laboratory with its primitive computer terminal

monary resuscitation, introduced by him in 1957, his commitment was most especially to both basic and clinical research on cerebral resuscitation. This was in part stimulated by Peter Safar's collaborative friendship with the late Russian resuscitation pioneer, V.A. Negovsky [20]. Indeed, Safar proposed that CPR would best be renamed for CPCR, i.e., cardiopulmonary cerebral resuscitation to highlight the importance of "brain preservation." His group pioneered studies on neuroprotection, beginning with drugs and especially barbiturates and based on evidence of benefit in victims of brain injury; he later pioneered the now important role of hypothermia in setting of cardiopulmonary resuscitation. In the years that followed, both our personal friendships and the increasing similarities and, even more, collaboration including the fellowship programs of both units, allowed us to train a majority of the early leaders of critical care medicine and critical care nursing worldwide.

During the late 1960s, Dr. Weil and Dr. Safar shared concepts with the early trauma surgeon/physiologist William Shoemaker who had extended the concept that care of the critically ill patients was applicable to surgical management and most especially to the management of life-threatening traumatic injuries. The reality was that medicine, surgery, anesthesia, and pediatrics were each affected in major ways by the emergence of Critical Care Medicine. Safar, Shoemaker, and Weil thereupon continued a series of personal dialogs, evolving the commonality of concepts and goals that prompted them to join efforts to improve care of patients with life-threatening conditions largely independently of specialty constraints. In 1967, Safar, Shoemaker, and Weil had an impromptu meeting on the Boardwalk of Atlantic City in conjunction with an annual meeting of the American Physiological Society. They subsequently corresponded regularly and our Los Angeles group then invited 28 medical leaders from diverse specialties representing internal medicine, cardiology, surgery, anesthesiology, and pediatrics to propose a multidisciplinary organization to implement and guide the field which evolved into the "Society of Critical Care Medicine." Its mission from the very beginning was to be multidisciplinary with its initial goal to foster the education of a new generation of physicians and surgeons from diverse specialties who would devote themselves to the care of the critically ill and injured. The additional mandate was to recruit, train, and provide professional identity to nursing and allied professionals as enfranchised members of the teams. The group saw its role as an agent which would develop standards and protocols for training, for routines of monitoring and measurement, for the organizational design of clinical units, and for protocols for appropriate life support interventions [21,22]. In the 38 years that have followed the initial Presidency of Weil followed by Safar, and then Shoemaker between 1972 and 1974 (Fig. 1.6), the Society now includes members from more than 80 countries with a total membership of 14,000, including physicians, specialist critical care nurses, critical care pharmacists/pharmacologists, respiratory therapists, veterinarians, and allied professionals.

Academic leadership in critical care medicine was assured early when "Critical Care Medicine" became the official journal of the Society of Critical Care Medicine in 1973 initially under the editorial direction of Dr. Will Shoemaker. Though American physicians played the major roles, both clinical and training programs rapidly expanded to industrialized countries and led to the first and second World

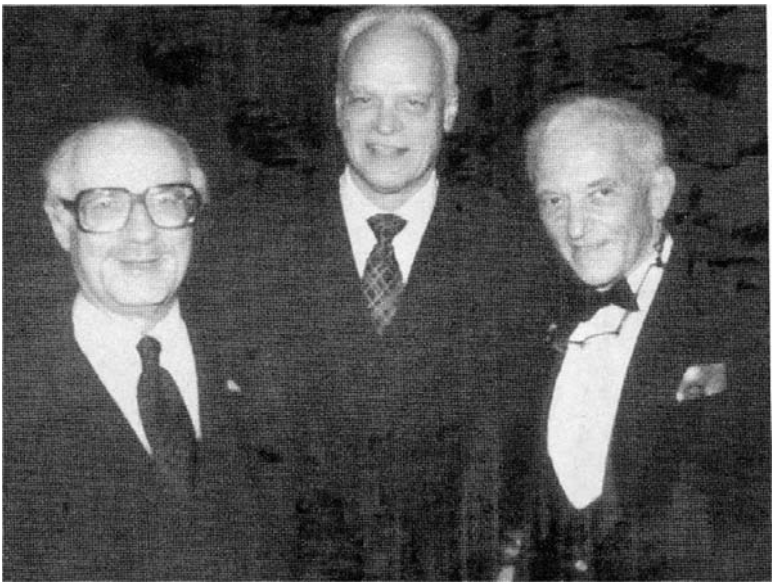
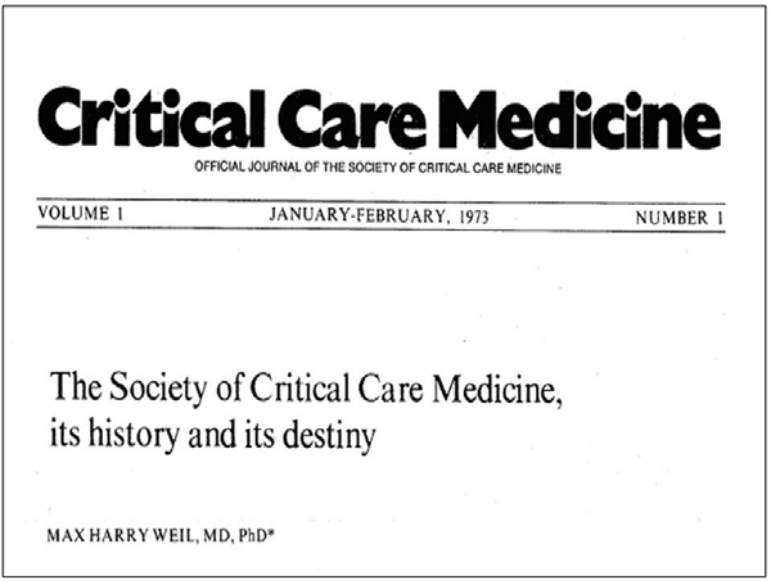


Fig. 1.6 The Initiators and first three Presidents of the Society of Critical Care Medicine (Weil 1st, Shoemaker 3rd, Safar 2nd)

Congresses in London and Paris and the formation of the "World Federation of Societies of Intensive and Critical Care Medicine." European, other North and South American, and Asian national Societies emerged within only a decade. Training in critical care was increasingly expanded from anesthesiology and cardiology to multidisciplinary programs and later as a subspecialty jointly with pulmonary medicine in the USA, though it evolved more often under the umbrella of anesthesiology in Europe. There was a strong medical rationale for multidisciplinary intensive care specialists who were in fact comprehensively trained generalists. The perception of one of the authors (MHW) expressed during his founding presidency of the Society of Critical Care Medicine (Fig. 1.7), was that there was no reason to separate the critical care specialist from his initial specialty: "It is perfectly reasonable that he/she remains a competent surgeon, anesthesiologist, cardiologist, or an infectious disease specialist. However, he/she should apply his/her specialty skills to the care of the critically ill and build bridges to the conventional specialties. This is an ideal opportunity to break down the barriers that isolate traditional departments… I look to conventional board certifications in internal medicine, pediatrics, surgery, or anesthesiology as a basis for entry into our field; though in time, a critical care specialist might have specific and selective subspecialty certification" [21].

Finally, in 1980, training standards were fully developed and subspecialty identity in Critical Care Medicine was achieved in the USA within but a short 15 years of the founding of the Society of Critical Care Medicine. A majority of industrialized countries promptly followed with programs for training critical care physicians within the specialties of anesthesiology, internal medicine, surgery, critical care medicine, emergency medicine, and reanimation.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The Society of Critical Care Medicine, its history and its destiny

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Fig. 1.7 Weil's "Presidential address," Society of Critical Care Medicine, 1973

The Present: Modern Critical Care Medicine and Intensive Care Units

It was remarkable that within 10 years of its inception, commitment to provide critical care in hospital settings was so rapid. Almost every major hospital had implemented the specialized facilities now known as ICUs or ITUs [23]. The practices evolved in parallel with advances in the understanding of life-support biology and as stated above, major advances in life-support technology [24]. In parallel with these advances, there was a novel, more aggressive interventional approach by physicians responsible for the acute life-threatened patient with the support of more effective monitors and measurements and the expansion of methods, drugs, and devices for resuscitation. The physician at the bedside of the critically ill patient may be confronted by an intimidating array of monitors. Nevertheless, when these complement the traditional methods of history and physical diagnosis, they allow for prompt and better insight and therefore understanding of the physiological disturbances and their severity than had previously been possible [1,25–27]. Both new concepts and new terminologies have evolved which define organ or system failures and priority routines for their reversals whether primarily respiratory, cardiac, or metabolic failure, for instance [28]. Interventions for respiratory failure, for instance, include intubation, airway care, oxygen, and mechanical ventilation. Sepsis "bundles" provide for the treatment of infection, shock, and multiorgan failure and protocols for reversal of heart failure and cardiac arrhythmias call for pharmacological, electrical, and mechanical interventions to sustain blood flows. Current training programs in critical care medicine therefore prepare the critical care specialist to intubate the trachea,

maintain mechanical ventilation, provide emergency airway intervention including fiberoptic bronchoscopy, maintain either external or internal temporary pacing, maintain appropriate hemodynamic and oxygen transport monitoring, and manage major fluid and electrolyte abnormalities. In instances of acute circulatory failure, the critical care physician increases vascular volume by systematic techniques of "fluid challenge," at the same time guarding against the risk of pulmonary edema and potentially fatal acute respiratory failure [8,29]. He supports myocardial function by pharmacological or mechanical interventions and if a life-threatening dysrhythmia presents itself, he or she must be prepared to use electrical methods by which an effective rhythm is restored [1]. The intensivist should also assure that timely subspecialty consultative services are provided in a redeeming professional manner and integrated with an overall patient care plan [3]. The optimal organization is that of a physician-staffed multidisciplinary team, including medical specialists, surgical specialists, anesthesiologists, nurse specialists, and allied technical personnel, which is committed to provide dedicated care of critically ill patients for 24 hours a day, 7 days a week [30].

In a remarkably rapidly moving discipline, critical care medicine trainees and, indeed, faculty, must not only maintain but acquire new knowledge and skills to provide state-of-the art care to critically ill and injured patients. Intensive care unit utilization with its extraordinary high cost must be optimized. Accordingly, the continuum of education in critical care medicine from residency through specialty training and ongoing throughout practice, supported by evidence-based practices with standardization of procedures became important. It is reassuring that the ICU is increasingly accepted as a patient-oriented/patient-centered collaborative professional environment receptive to peer-established standards [31–33].

At the time of this writing, contemporary ICUs vary not only from hospital to hospital with respect to physical structure and locale, but also with respect to the services that are provided, the staffing and the level of expertise of the providers, and the table of organization. Three levels of care are accordingly recognized, including capability to provide comprehensive care without major subspecialty presence for initial stabilization and hospitals that assure that in the absence of either comprehensive or stabilization capability maintain active transfer to assure access to the appropriate level of care. Large medical centers typically have multiple sites, more often separated by specialty or subspecialty. Smaller hospitals are more likely to have a single, multidisciplinary intensive care unit to which critically ill medical, surgical, cardiac, postoperative, and even pediatric patients are admitted. Earlier reticence on the part hospital staff to organized critical care has largely disappeared [32].

Designs of modern ICUs increasingly focus on the bedside rather than remote monitoring at the centralized nursing station. Local access to the patient at the bedside especially for mobile devices for monitoring, respirators, dialyses, cooling devices, etc., requires appropriate space [33]. Direct or indirect video monitoring is a major advantage but primarily in step down units where the nursing staff ratios are less than 1:2. Because of the commonly high incidence of false alarms, video confirmation at a central site is beneficial. Nevertheless, central monitoring is now largely obsolete for the care of the acutely life-threatened patient; it is the bedside nurse,

typically stationed between two beds or cubicles, who is in physical proximity and who is provided with direct vision to the patient, the monitors, and the terminal for recording together with ordinary supplies. The patient sites are therefore now designed fully to support the bedside nurse specialist who performs all necessary functions locally at the bedside and independently of the central station. In our view, a multiplicity of displayed analog and digital data may be counterproductive and there is increasingly persuasive agreement favoring simplification of measurements, and especially based on less invasive methods including the pulse oximetry with pulse rate, oxygen saturimetry, end-tidal PCO_2, and excepting in shock states, noninvasive methods. Except for coronary or cardiac care, the routine recording and display of the electrocardiogram is not likely to be beneficial. Finally, computerized patient charting, which allows for "paperless" data management, is emerging as a major asset.

The Future of Critical Care Medicine

The pulmonary artery flow directed (Swan-Ganz) catheter, in particular, may on occasion be of value in high-risk patients and especially in settings of circulatory shock [34]. Yet, such is invasive, expensive, and labor-intensive and increases the risks of serious complications, and especially infections. Comparable hemodynamic information may be obtained with newer methods of echocardiography including cardiac output and chamber volume, and Doppler techniques. This applies especially in settings of pulmonary hypertension and to the differential diagnosis of occult shock states, and the differentiation between hypovolemic, cardiogenic, distributive, and obstructive shock states [35,36]. End-tidal PCO_2 has emerged as an especially useful monitor and measurement of both respiration and hemodynamic status and specifically pulmonary blood flow and therefore cardiac output in critically ill patients [37–39].

Perhaps the greatest need is for better understanding of tissue perfusion in contrast to "macro" hemodynamics in critically ill patients [40]. The focus is on identifying hypoperfusion/ischemia during shock states. Large vessel pressures and flows including cardiac output measurements do not routinely address this need [41,42]. Tissue hypoperfusion is often masked by compensatory increases in cardiac output and near normal blood pressure values. Tissue ischemia when undetected has a high mortality [43]. Noninvasive measurements of buccal or sublingual mucosa partial pressure of carbon dioxide have been promising in both experimental and clinical settings, for identifying tissue ischemia with increases in tissue PCO_2. It is a more reliable and faster responding measurement than lactate measurement initially introduced by our group [41,44–45].

It is the microvessels and specifically the capillaries which serve as the ultimate exchange sites for vital metabolites. The availability of the Orthogonal Polarization Spectral (OPS) imaging technique [46], and further development of Sidestream Field Dark imaging [47], allows for direct and real time visualization of the microcircula-

tion including arterioles, venules, and capillaries. It has become a tool for quantitating systemic capillary blood flows and the effects of interventions on tissue perfusion [42,48]. Tissue ischemia heretofore more indirectly quantitated by increases in arterial blood lactate and even better by tissue capnometry are now better explained and quantitated by observing directly the selective decreases of blood flow in microvessels corresponding to capillaries.

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The Mission of the World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM)

2

P.D. Lumb

Introduction

The following editorial commentary from the British Medical Journal (BMJ) provides a fitting introduction to a discussion on the Mission and Values of the World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM).

"So what's the point of reading about healthcare challenges in developing countries? How does it help us practice better medicine and lead better lives?

Our answer is that medicine cannot be practiced in isolation. As the world becomes smaller, health care around the world has more, not less, in common. All healthcare systems struggle with the challenges of limited resources and growing demand. As well as providing clinically practical information…we think the BMJ has a role in presenting an international perspective on health care" [1].

The World Federation's Constitution (Approved at the 9th Quadrennial Meeting; Buenos Aires, 2009) provides the definition and purpose of the Federation as follows:

The aim of this Federation is to promote the highest standards of Intensive and Critical Care Medicine (ICCM) for mankind, without discrimination. In pursuit of this aim the Federation will:

1. Establish a world-wide cooperation between National and Multinational Societies of ICCM.
2. Assist and encourage the formation of new Societies of ICCM.
3. Sponsor World Congresses on ICCM at regular intervals, and support other Congresses of this nature as requested.
4. Promote activity, provide advice and cooperate with relevant bodies in the field of ICCM; disseminate scientific and educational information; establish the high-

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Antonino Gullo et al. (eds), *Intensive and Critical Care Medicine.*

est standards in patient care, training, equipment design and safety measures; and encourage research in this field.

5. Pursue by other lawful means all other activities which promote the objectives of the Federation.

However, this simplistic statement belies the importance and spirit of an organization founded in 1974 by a visionary group of critical care pioneers whose insight stimulated interest in the worldwide care of the critically ill and injured, irrespective of location, financial situation, race, or creed. The founders believed that the discipline of critical (intensive) care medicine would become a primary specialty rather than an addendum to the traditional practices of medicine, cardiology, and surgery. Today this vision is realized in their organization, which numbers over 50 member societies and represents over 50,000 multidisciplinary professionals involved in international critical care.

The Federation's first Congress was convened in London in 1974 under the leadership of Dr. Alan Gilston. In 1977, following the organization's second meeting in Paris, a seven member Constitutional Advisory Group was elected. Drs. Simon Bursztein (Israel), Alan Gilston (UK), Maurice Goulon (France), Ake Grenvik (USA), Claude Perret (Switzerland), Alberto Villazon (Mexico), and Robert Wright (Australia) were instrumental in forging international connections between interested critical care physicians and formalizing the organization's initial constitution ratified at the first General Assembly held at the 3rd WFSICCM Congress in Washington, DC in 1981. Subsequent quadrennial meetings have been held in Jerusalem (1985), Kyoto (1989), Madrid (1993), Ottawa (1997), Sydney (2001), and Buenos Aires (2005). The Tenth Meeting of the World Federation will be held in Florence in late August, 2009. The meeting will be hosted by the Italian Anesthesia and Critical Care Society (SIAARTI) and governed by the organization's General Assembly during which time its Executive Committee will be elected for a staggered eight-year term with half the committee rotating every four years. This insures international representation and administrative continuity. The organization's secretariat is headquartered in the UK and its incorporation and banking are in Switzerland.

Definition

In today's highly organized world of national critical care societies, it may be questioned whether an international organization can have validity and purpose. It is necessary only to review current international concerns to recognize the importance of a forum in which controversial and groundbreaking issues can be discussed in an impartial and collegial manner; surviving sepsis, strategies for mechanical ventilation, contradictory resuscitative strategies, use of expensive pharmaceuticals, and the appropriate emphasis on hand washing are all activities of importance and interest to critical care physicians worldwide. In addition, the WFSICCM has presented opinions to member organizations about the use of oxygen obtained from Pressure Swing Adsorption (PSA) techniques versus the more "pure" cryogenically prepared prod-

uct; the "contaminant" is nitrogen, and the opinion was that the marginally lower concentration product (93% vs. 98%) was medically appropriate and technically easier to manage for developing nations with less well-developed infrastructure and remote areas in which transportation of the refrigerated, liquid product is more complex and prone to mishap than a product prepared and moved in compressed gas tanks. This and other activities result in dissemination of information that otherwise may not be of interest to local organizations. Therefore, the WFSICCM is interested in promoting the following activities:

1. Establish world-wide collaboration between National and Multinational Societies of ICCM.
2. Assist and encourage the formation of new Societies.
3. Sponsor World Congresses and support others like Congresses as requested.
4. Promote multiprofessional and multinational interaction.
5. Provide advice and cooperate with relevant bodies in the field of ICCM.
6. Disseminate scientific and educational information.
7. Establish the highest context-correct standards in patient care, training, equipment design, and safety measures.
8. Encourage research and dissemination of new knowledge in the field of ICCM.
9. Establish accessible educational resources for all interested professional involved in ICCM.

To support these goals, the WFSICCM has sponsored the creation of the World Federation of Critical Care Nurses (WFCCN); established an international, peer reviewed, scientifically indexed publication, the Journal of Critical Care dedicated to exploring systems based practice; and cosponsored recent national meetings in Dubai, Brazil, India, and Uruguay. Additionally, the Federation has encouraged new member applications from both transnational and national critical care societies such as the Pan-Arab, Hungarian, Russian, Saudi, Emirates, and Egyptian Societies. Prize-winning abstracts from the Society for Complexity in Acute Illness and from national meetings in Brazil, Hungary, and Dubai have been published in the Journal of Critical Care.

The WFSICCM is unique among the world's critical care societies in that its members are national societies rather than individuals. This has led to a tradition of personal and national collaboration, respect, and trust with an integrity that lies beyond governments and national organizations. The Federation is committed to the promulgation and dissemination of common databases that are responsive to international validation with subsequent dissemination of all relevant information. The Federation supports a multiprofessional constitution and recognizes the essential partnerships that must exist among all members of the critical care teams in order to provide appropriate care to all patients. These tenets encompass an international fraternity of scientific knowledge, new discovery, and practical application of clinical expertise that is ultimately validated through outcomes data following therapeutic intervention. The organization thus amplifies multinational and multiprofessional creativity while continuing to depend upon individual discovery, practice, and communication. It enhances medical care through promotion of global education and research activities of all types, and fosters the excellence of national and multination-

al societies. In the international community of diverse and maldistributed resources, an additional focus that moves practice from "curing" to "caring," from technologically driven to humanism/holistic care is essential. The World Federation supports current global initiatives to create awareness of the simple but critical aspects of healthcare (e.g., World Health Organization hand washing campaign) that require minimal resources but provide maximum benefit in excess of costly therapeutic interventions.

It is increasingly important for an apolitical, nongovernmental organization to represent an evidence-based, outcomes-oriented membership with well-established traditions of information and resources sharing a common literature, language, and therapeutic options. The WFSICCM is established to provide that infrastructure and support it.

Standards of Care

Increasingly, it is recognized that international collaboration is necessary to treat global disease. The SARS epidemic provided a "wake-up call" to the critical care community, and the new reports of swine flu in Mexico, California, Kansas, and New York increase the likelihood that new, rapidly disseminated diseases will become frequent challenges for critical care practitioners and ancillary providers.

The WFSICCM sponsors multiple initiatives in support of these goals. Cosponsored national meetings provide venues in which the following items are discussed:

1. Promote site-specific standards of care (Surviving Sepsis translated to local conditions; presented in Brazil and Uruguay).
2. Develop relevant clinical protocols.
3. Provide continuing education programs.
4. Foster worldwide communication.
5. Implement clinical research initiatives.
6. Foster ethical standards and practice.
7. Develop databases.
8. Disseminate new information; the Journal of Critical Care.

Recommendations

Today's global critical care education requires adoption of a new curriculum and skill set. The clinician must be aware of and sensitive to many of the following administrative and instructional aspects of healthcare:

1. Population management with patient-centered care.
2. Team building; health care consortia.
3. Information-systems management.

4. Clinical-resource management.
5. Case-based learning/simulation.
6. Evidence-based implementation of therapeutic interventions.

It is also important to understand the timeliness and relevance of many aspects of evidence-based practice that, despite apparent relevance, become controversial and occasionally potentially dangerous. One example may be the worldwide acceptance of tight blood glucose control for all patients despite a relatively small initial sample experiment concentrating on specific patient populations. Wide dissemination of the protocols and excitement generated by "pay-for-performance" rewards created a widespread acceptance of the theory with improper application and methodology to maintain the surveillance necessary to minimize potential patient harm. Perhaps a more rational approach has evolved; certainly awareness has been raised for a significant problem that is now approached rationally.

The WFSICCM partners with established CCM societies and encourages them to participate in the development of global critical care. Sponsorship of innovative educational programs, stimulation of clinical research programs, and development of nationally relevant and internationally responsible practice guidelines are inescapable elements in facilitating and creating collaborative, transnational, and transorganizational partnerships.

"A good drug poorly delivered is diminished." This editorial comment in the March 10, 2001 edition of the BMJ highlights a problem involving not only delivery but also availability. The theme is continued in the subsequent edition (March 17) with the following comments: "Global inequities in health are the number one ethical issue of our age, argues Peter Singer, the Canadian bioethicist. Most of the sickness in the world is in the developing world, but most of the health care is in the developed world." The editorial continues by pointing out additional areas in which the global divide increases the "wellness" differences between countries and populations. Access to expensive technology and pharmaceuticals is often limited, and this further compromises the ability of local providers to halt the spread of deadly diseases. Pharmaceutical companies are under increased pressure not only to decrease product costs to the developing world but also to focus research and development on specific products for use in these areas. Unfortunately, this comes at a time in which profit margins have been cut, and especially in the USA, political pressure to further decrease cost and profit margin is intensifying. Therefore it is not only appropriate but also necessary for a global organization to proselytize and advocate for international standards in critical care practice and access.

In its Declaration of Rio de Janeiro, May 8, 1991, the World Federation adopted a number of principles defining its positions on ethical, administrative, and research activities in critical care medicine. These principles are at the core of the organization's beliefs and standards. The WFSICCM was the first international critical care organization to promulgate ethical standards, beginning with its Declaration of Helsinki in 1991. These standards are increasingly relevant today, and although requiring local modification, the general principles can be regarded as prescient and appropriate in today's increasingly technological world [2].

2

Conclusions

The WFSICCM represents approximately 50,000 physicians and nurses worldwide by facilitating communication between its 50 national society members. It is an organization of member societies of critical care medicine, and in this fashion is unique in the panoply of critical care societies. Indeed, as the recent SARS and current swine flu epidemics have occupied the attention of critical care practitioners, numerous "chat rooms" and "interdisciplinary" communication links have bridged the gap of ignorance that heralded the initial therapeutic response. It is the vision of the WFSICCM that in years to come, communication through international links established through multinational societies and linked communication strategies will further promote the necessary worldwide partnerships necessary to combat global diseases spread rapidly through personal travel and international commerce.

It is the mission of the WFSICCM to promote site-appropriate critical care services worldwide. There is an undeniable resource gap across critical care facilities, and even the most advanced countries report variable quality and outcome across regions; in part, this may be due to lack of appropriate resources and equipment. More often, however, it may be due to the lack of available and appropriately trained personnel. Internationally applicable outcome data capable of resolving these questions is difficult to obtain. It is likely that easier communication among peers will be valuable in changing the demographics of the current situation, and it is the WFSICCM's aim to encourage easy dialogue and clinical information exchange across international time, political, and national barriers in order to ameliorate some of the challenges inherent in managing our complex patients.

Hippocrates requests us "To hold him who has taught me this art as equal to my parents and to live my life in partnership with him, and if he is in need of money to give him a share of mine, and to regard his offspring as equal to my brothers in male lineage and to teach them this art – if they desire to learn it – without fee and covenant; to give a share of precepts and oral instruction and all the other learning to my sons and to the sons of him who has instructed me and to pupils who have signed the covenant and have taken an oath according to the medical law, but no one else." Surely with the appropriate additional currency of female lineage, the covenants described herein are equal to the task we face in international medicine. There can be no greater calling nor need than for international medical partnerships to flourish for the sake of the world's health. The international community is threatened and fragile; let its health be our first priority. "Physician heal thyself" is an exhortation familiar to us all; if indeed we are capable of this act in the context of our international professionalism, then perhaps we can move forward to the greater challenges inherent in the modern world in which advanced communications appear capable of creating as much havoc as hope.

The WFSICCM's vision is simple; it intends to be the international repository of critical information necessary to expand an individual clinician's horizon to a global scale. The challenges are significant, and to overcome the obvious obstacles will require individual participation across global boundaries. International data sharing

and national society partnerships are rational and cost-effective strategies that will insure the success of the global community. The WFSICCM intends to provide communication channels to increase the awareness of the international community's responsibility to participate in the acquisition and timely distribution of the information necessary to improve management of critically ill patients in whatever circumstance they are found. It is in this fashion that our world will become a smaller, friendlier, and healthier place.

Increased national and individual ownership for the World Federation's goals will develop from greater familiarity with the organization and its administration. In addition to the educational and communication facilities, the website will also provide important information about organizational structure, national membership, key contact information, and critical links to information sources hosted by society members. A calendar of international conferences and special events will be updated regularly; additional information will be solicited from individual members. A key component of the World Federation will be its utility to individual members, including their critical feedback and review. Research initiatives are increasingly costly with patient identity and privacy rules further complicating transfer of information. However, a great deal can be accomplished with appropriately designed questionnaires that cross national and regional boundaries; the WFSICCM can provide members the resources necessary to initiate appropriately powered and controlled studies. Further ideas will be developed through member participation and feedback.

Several questions may remain: Is there a role for a world-focused intensive care organization that will depend for its success upon support from national critical care societies, volunteerism from individual members, contributions from industry, consistency of production, and dissemination of new information in a timely, dependable, and credible manner? Are there benefits to be gained from a world organization that cannot be provided by national societies with international connections? Despite these and other important concerns, the values of a world focus and partnership among critical care professionals cannot be denied. There is intense competition among national societies to host the World Federation Congresses, and the participation of internationally recognized critical care physicians in local educational events is desired. Fiscal constraints and travel restrictions often militate against greater participation in many events, and the World Federation is the unique resource that can assemble the world's leading clinicians in an apolitical environment that fosters education, research, and the dissemination of new information. The mission is clear; the infrastructure is established; the vision is evolving; with international participation and support, the outcome is assured.

The World Federation exists:

- To do the right thing
- To eschew novelty for its own sake
- To determine best collaborative practice
- To work within ethical boundaries
- To understand compassion
- To transition from cure to care
- To be culturally sensitive

To understand the World Federation, it is essential to recognize these ideals as integral to its mission and purpose.

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Section II
Professionalism, Ethics and Evidence Based Practice

Professionalism

3

A. Gullo, P. Murabito, J. Besso

Medicine is "a calling, not a business"
Sir William Osler, The Reserve Of Life.
St. Mary's Hospital Gazette, 1907

Introduction and Implication

Medicine is more than the sum of our knowledge about disease. Medicine concerns the experiences, feelings, and interpretation of human beings in often-extraordinary moments of fear, pain, anxiety, and doubt. In this extremely vulnerable position, it is medical professionalism that underpins the trust the public has in doctors. Efforts to build professionalism must be based on a sharing of values over the long term. The career stage of learners must guide teaching efforts. Teachers must offer a clear cognitive base and discuss how learners interpret this in their actions and those of others. Role modeling is essential and empowers young physicians to participate in building the environment, expectations, and rewards which foster professionalism. A more appropriate reflection and several medical education initiatives have stressed the linkage between professionalism (profession, professional) and competence.

Clinical governance is the term applied to collecting all the activities that promote, review, measure, and monitor the quality of patient care into a unified and coherent whole. Professionalism is a major component of clinical governance; professionalism evolves over a career, not just during medical education [1]. The term "clinical governance" is an example of how professional learning can help doctors both cope with the imposed change and recognize their ongoing need to undertake a different and changing relationship with society, and it lays the foundations for coping with further change throughout their careers. Clinical governance aims to bring together managerial, organizational, and clinical approaches to improve the quality of care. Clinical governance may be succinctly defined as "corporate accountability for clinical practice" [2]. Effective clinical governance should therefore ensure: con-

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tinuous improvement of patient services and care; a patient-centered approach that includes treating patients courteously, involving them in decisions about their care, and keeping them informed; a commitment to quality, which ensures that health professionals are up to date in their practices and properly supervised where necessary; a reduction of risk from clinical errors and adverse events; as well as a commitment to learn from mistakes and to share that learning with others. The mission of the World Federation Societies of Intensive and Critical Care Medicine (WFSICCM) has for long time promoted better standards of care, humanism, and the capacity to develop educational programs for improving ethics and integrity, skills and competence, patient's safety, clinical governance, professionalism; and performing an appropriate and good medical practice [3].

Medical Professionalism in the Changing World

In the last decades the value and even the validity of medical professionalism have registered an increasing level of pressure in the community as result of changes in society and medicine itself. Delivery of health care has become increasingly complex as a consequence of invasive intrusion of government and the private sector into health care; so medicine has lost both autonomy and influence throughout the world [4]. The belief that physicians would be altruistic was greeted with skepticism by opinion leaders and social scientists, and medicine was accused of putting its own welfare above that of society [5,6].

Critical situations determined a defensive medicine. Adapting teaching styles to changing generational learning styles will further bridge the values gap. An erosion of public trust in the professions has brought increased attention to professionalism in all areas of work [7]. Since the late 1980s, there has been a change in the opinion of social scientists who become supportive of the concept of professionalism defined as the basis of medicine's contract with society [6,8,9].

Essential to this contract is public trust in physicians, which depends on the integrity of both the individual physician and the whole profession. However, as an example, new medical technologies and methods are entering the marketplace at dizzying speeds, increasing the complexity as well as the cost of health care. The concepts mentioned before remained a dark side; since, the inequality distribution of resources to get a poor organization and negative cost effectiveness of the health system. Academic medicine must assume greater responsibility and accountability for strengthening the resolve of future doctors to sustain their commitment to the ethic of professionalism. Medical education is facing a convergence of challenges defined by Albanese et al. as an apocalypse characterized by four negative elements: teaching patient shortages, teacher shortages, conflicting systems, and financial problems [10]. Recently, the working party of the Royal College of Physicians defined the nature and role of medical professionalism in modern society [11]. A combination of high-quality education, rigorous research, and extensive clinical experience matured according to the principles expressed by Sackett and Levi: Evidence-based medicine

is meant to assist clinical decision making by facilitating the formulation of focused clinical questions arising directly from patient care [12,13]. The term "profession" is defined as "A self-disciplined group of individuals who hold themselves out to the public as possessing a special skill derived from training or education, and who are prepared to exercise that skill primarily in the interest of others" [14]. The individuals in a profession are bound together by a shared commitment. Members of a profession regulate themselves. In medicine, physicians regulate themselves through state medical boards, as well as hospital committees and other peer-review groups. Those in a profession practice in accord with a code of ethics [15]. The term "professional" is a person who belongs to a group (a profession) which possesses specialized knowledge, skills, and attitudes which have been obtained after a long period of study and which are used to benefit other members of society [16]. The term "professional" can also be used as an adjective, e.g., a professional association, professional (or unprofessional) conduct or attitude. Professionalism may be defined in terms of the capacity to establish and maintain all the relationships appropriate to practice medicine with the physician-to-patients relationship at its core [17]. Professionalism is not a static structure within which we deliver medical care. Rather, it can be viewed as a dynamic framework derived from the interaction of many forces such as the tradition of healing, social change, rising medical challenges, and scientific advances, as well as the interests of members and subgroups within and outside the profession [18]. A comprehensive summary of the characteristics commonly associated with professionalism include "altruism, honor and integrity, caring and compassion, respect, relationship, responsibility, accountability, scientific knowledge, excellence and scholarship, and leadership. However, the exercise of medical professionalism is hampered by the political and cultural environment of health, which many doctors consider disabling. The conditions of medical practice are critical determinants for the future of professionalism. Equally, other members of the health care team – notably managers – have a reciprocal duty to create an organizational infrastructure to support doctors in the exercise of their professional responsibility. Just as the patient–doctor partnership is a pivotal therapeutic relationship medicine, so the interaction between doctor and manager is central to delivery of professional care. High-quality care depends on both effective health teams and an efficient health organization.

A Physician Charter and Fundamental Principles

A Physician Charter

The importance of professionalism for the future of medicine was underscored by the 2002 publication of the Medical Professionalism in the New Millennium: A "Physician Charter" [19]. The Charter's set of professional responsibilities includes commitments to professional competence, honesty with patients, confidentiality, maintaining appropriate relations with patients, improving quality of care, improving

access to care, just distribution of finite resources, scientific knowledge, maintaining trust by managing conflicts of interest and professional responsibilities.

The Charter was disseminated widely and has generated much response, but it is not without criticism. Reiser and Banner noted the absence of input from patients in developing the Charter and its lack of emphasis on the doctor's role of healer [20].

Their criticism is supported by recent work on patient complaints, indicating that patients have definite opinions about what they expect from care. Frequently mentioned complaints included disrespect, distrust, and miscommunication, all of which are opposites of important elements of professionalism. Using survey data, Mann et al. recently reported differing perceptions of students, faculty residents, and other health professionals about the extent to which their education met "noncognitive goals" and called for research exploring the basis for differing perceptions. The role of medical education is paramount in preparing future doctors to recognize and overcome these threats; to do so will require substantial change in the culture and environment of medical education [21].

Fundamental Principles (Table 3.1)

Principle of Primacy of Patient Welfare

This principle is based on a dedication to serving the interest of the patient. Market forces, societal pressure, and administrative exigencies must not compromise this principle.

Table 3.1 A decalogue of attitudes towards professionalism

- Maintaining professional competence
- Honestly with patients
- Patients' confidentiality
- Maintaining appropriate relationship with patients
- Improving quality of care
- Improving access to care
- Just distribution of finite resources
- Increasing scientific knowledge
- Maintaining trust by managing conflict of interest
- Fulfilling professional responsibilities, including selfregulation

Principle of Patient Autonomy

Physicians must have respect for patient autonomy. Patients' decisions about their care must be paramount, as long as those decisions are in keeping with ethical practice and do not lead to a demand for inappropriate care.

Principle of Social Justice

The medical profession must promote justice in the health care system, including the fair distribution of health care resources. Physicians should work actively to eliminate discrimination in health care, whether based on race, gender, socioeconomic status, ethnicity, religion, or any other social category.

Commitment to Maintain Professional Competence

Professional competency is defined as "the habitual and judicious use of communication, knowledge, technical skills, clinical reasoning, emotions, values, and reflection in daily practice for the benefit of the individual and community being served." Professional competence is multidimensional and the dimension of competence is a continually expanding. Physicians must be committed to lifelong learning and be responsible for maintaining the medical knowledge and clinical and team skills necessary for the provision of quality care.

There must also be a commitment to the application of knowledge and skills in interpersonal relations, decision making and physical performance consistent with the professional's practice role and public health, welfare, and safety considerations.

Commitment to Be Honest with Patients

The era of patient autonomy ended the traditional pattern of withholding information, which was characteristic of the previous era of paternalism.

In 1972, the Board of Trustees of the American Hospital Association affirmed A Patient's Bill of Rights, which states that the patient has the right to obtain from his physician complete current information concerning his diagnosis, treatment, and prognosis in terms the patient can be reasonably expected to understand [22]. Bioethicists favor full disclosure as a means of respecting patient autonomy [23]. Physicians must ensure that patients are completely and honestly informed before the patient has consented to treatment and after treatment has occurred. Physicians should also acknowledge that in health care, medical errors that injure patients do sometimes occur. Whenever patients are injured as a consequence of medical care, patients should be informed promptly because failure to do so seriously compromises patient and societal trust. Reporting and analyzing medical mistakes provide the basis for prevention and improvement strategies and for appropriate compensation to injured parties.

Commitment to Respect Patient's Confidentiality

Confidentiality has been defined by the International Organization for Standardization (ISO) as "ensuring that information is accessible only to those authorized to have access" and is one of the cornerstones of information security [24].

Confidentiality relates to the duty to maintain confidence and thereby respect privacy. Privacy relates to personal information that a person would not wish others to know without authorization. Under the ethical principle of respect for a person's autonomy, public health workers have an obligation to respect privacy. Privacy relates to a person's right to be free from the attention of the others. Confidentiality is the state of being secret, e.g., "you must respect the confidentiality of your patient's communications." In other words, confidentiality should be a fundamental right of patients in the health care setting [25].

Commitment to Maintaining Appropriate Relationships with Patients

Given the inherent vulnerability and dependency of patients, certain relationships between physicians and patients must be avoided. In particular, physicians should never exploit patients for any sexual advantage, personal financial gain, or other private purpose. What is a fiduciary relationship? The word fiduciary derives from the Latin word for "confidence" or "trust." The bond of trust between the patient and the physician is vital to the diagnostic and therapeutic process. It forms the basis for the physician–patient relationship. In order for the physician to make accurate diagnoses and provide optimal treatment recommendations, the patient must be able to communicate all relevant information about an illness or injury.

Physicians are obliged to refrain from divulging confidential information. This duty is based on accepted codes of professional ethics which recognize the special nature of these medical relationships.

Commitment to Improve Quality of Care

Physicians must be dedicated to continuous improvement in the quality of health care. The quality of care provided has a significant impact on these variables and continuous improvement in intensive care quality is the great challenge for the future (Table 3.2).

For this reason defining and measuring ICU performance are very complex tasks (Table 3.3).

Critical care physicians and nurses are involved in the quality improvement process according to Davidoff and Batalden assumptions; in contrast to the primary goals of science, which are to discover and disseminate new knowledge, the primary goal of improvement is to change performance [26,27].

One of the more popular models for measuring ICU performance is that developed by Donabedien, which includes three classic quality of care components: (1) structure (adequate organization), (2) process (formulation of medical professional standards), and (3) outcome (the classical outcome variable is mortality rate, but others have become more and more important, such as length of stay standardized for severity of illness and type of disease, the cost for surviving patients, the quality of life after discharge, etc.)

Table 3.2 Indicators of quality

• The incidence of nosocomial infections
• The complication rates of diagnostic procedures of invasive monitoring
• The unplanned readmission with 24 or 48 h after ICU discharge
• The postventilator survival after ICU discharge of COPD patients
• Unplanned extubation or intubation within 48 h
• The use of blood products or expensive drugs
• The effective cost per surviving patient
• Acute renal failure developing after ICU admission, etc.

Table 3.3 Eight essentials of performance measurement

1. Use a balanced set of measures
2. Make sure you measure what matters to service users and other stakeholders
3. Involve staff in determining the measures
4. Include both perception measures and performance indicators
5. Use a combination of outcome and process measures
6. Take account of the cost of measuring performance
7. Have clear systems for translating feedback from measures into a strategy for action
8. Measurement systems need to be focused on continuous improvement, not a blame culture

Commitment to Improve Access to Care

Medical professionalism demands that the objective of all health care systems be the availability of a uniform and adequate standard of care. A commitment to equity entails the promotion of public health and preventive medicine, as well as public advocacy on the part of each physician, without concern for the self-interest of the physician or the profession.

Commitment to Promote a Just Distribution of Finite Resources

While meeting the needs for individual patients, physicians are required to provide health care that is based on the wise and cost-effective management of limited clinical resources. While meeting the needs of individual patients, physicians are required to provide health care that is based on the wise and cost-effective management of limited clinical resources. The provision of unnecessary services not only exposes one's patients to avoidable harm and expense but also diminishes the resources available for others [19].

Commitment to Advance Scientific Knowledge

Much of medicine's contract with society is based on the integrity and appropriate use of scientific knowledge and technology. Physicians have a duty to uphold scientific standards, to promote research, and to create new knowledge and ensure its appropriate use.

Commitment to Maintaining Trust by Managing Conflicts of Interest

Medical professionals and their organizations have many opportunities to compromise their professional responsibilities by pursuit of private gain or personal advantage. Such compromises are especially threatening in the pursuit of personal or organizational interactions with for-profit industries, including medical equipment manufacturers, insurance companies, and pharmaceutical firms. Concerns have been raised about conflicts of interest compromising the objectivity of the doctors' decision making (e.g., prescribing practices) and the integrity of science and scientific research [21].

Commitment to Professional Responsibilities

As members of a profession, physicians are expected to work collaboratively to maximize patient care, be respectful of one another, and participate in the processes of self-regulation, including remediation and discipline of members who have failed to meet professional standards [19]. The Canadian Medical Association has developed and approved a Code of Ethics as a guide for physicians. The Code is an ethical document. Its sources are the traditional code of medical ethics such as the Hippocratic Oath, as well as developments in human rights and recent bioethical debates. Legislation and court decisions may also influence medical ethics.

The code has been prepared by physicians for physicians. It is based on the fundamental ethical principles of medicine, especially compassion, beneficence, nonmaleficence, respect for persons, and justice. It interprets these principles with respect to the responsibilities of physicians to individual patients, family and significant others, colleagues, other health professionals, and society. The code, as regards general responsibilities, refers to physicians, including residents and medical students (Table 3.4).

Integrative Team-Based Models and Continuing Education

Future clinicians who provide core services in the acute hospital setting will need new skill sets, which will be transdisciplinary and especially suited to a range of health care needs of hospital patients [28]. Physicians, nurses, pharmacists, managers, and other health care providers will develop team-based models of care that

Table 3.4 General responsibilities

1. Consider first the well-being of the patient
2. Treat all patients with respect; do not exploit them for personal advantage
3. Provide for appropriate care for your patient
4. Practice the art and science of medicine competently and without impairment
5. Engage in lifelong learning to maintain and improve your professional knowledge, skills, and attitudes
6. Recognize your limitations and the competence of others and when indicated recommend that additional opinions and services be sought

avoid gaps in knowledge and services. Essential skill sets will draw on anesthesia, internal medicine, surgery, accident and emergency medicine, basic sciences, and ethics where behavioral competencies will learn from the field of aviation and crew resource management [29]. Critical care medicine illustrates this development. Intensivists and critical care physicians have become the general practitioners of acute care. They have adopted multidisciplinary collaboration, contributed to system management within intensive care, and emphasized intervention at the first signs of clinical instability.

Integrative models with well-organized systems within intensive care units have reduced mortality and have resulted in significant improvement in the quality of care. Teaching the cognitive base of professionalism is not difficult. Establishing an environment where the process of socialization in its most positive sense can take place is much harder [30].

Competence to practice medicine includes the ability of physicians to demonstrate professionalism in all the relationships in which they engage. The taxonomy of domains was reported by Inui [31]. The 6 areas of professional competence are: patients' care and clinical reasoning; medical knowledge; practice-based learning and improvement, including information management; interpersonal and communications skills; professionalism, and systems-based practice, including economics and team-working [32].

The aim of the CoBaTrICE project (Competency Based Training in Intensive Care in Europe – Innovation Transfer) is to provide an International Competency Based Training program for Intensive Care Medicine in Europe and other world regions. The CoBaTrICE project was formed in 2003 to define outcomes of specialist training in intensive care, and to develop an international training program [33–36]. The project is partly funded by the European Commission (Leonardo Program) and supported by the European Society of Intensive Care Medicine (ESICM). The project is divided into four main phases.

1. A survey of national Intensive Care Medicine training programs across Europe and the other world regions.
2. The development of a comprehensive competency-based syllabus.
3. Development of assessment guidelines.

4. Connect the competency-based syllabus to an electronic portfolio.

The CoBaTrICE competencies define the minimum standards of knowledge, skills, attitudes, and behaviors required to perform a particular task, and the standard required for doctor performance to be identified as a specialist in intensive care medicine (ICM).

They have been developed with the intention of being internationally applicable but able to accommodate national practices and local constraints. They comprise 102 competence statements grouped in12 domains (Table 3.5).

CoBaTrICE has achieved this through a worldwide process of consultation and consensus-building, involving specialist physicians and trainees, nurses and allied health professionals, patients and their relatives, national and international organizations.

Table 3.5 CoBaTrICE domains

1. Resuscitation and initial management of the acutely ill patients
2. Diagnosis: Assessment, investigation, monitoring and data interpretation
3. Disease management
4. Therapeutic intervention/organ system support in single or multiple organ failure
5. Practical procedures
6. Perioperative care
7. Comfort and recovery
8. End of life care
9. Pediatric care
10. Transport
11. Patient safety and health systems management
12. Professionalism

Conclusions

The findings reported briefly in the present review also suggest avenues for future research of highly topical issues such as professionalism with particular evidence of the professional role of the physician regarding patient and community expectations on determining health priorities [37].

It seems a priority to understand the important differences between patients' and physicians' perspectives on key curricular concepts. The foundation "pyramid of professionalism" suggested recently by Parker and coworkers [38] represents the basis of an integrated and formal curriculum of medical ethics, law, and professionalism. This is a one-way direction for the WFSICCM and all allied people who are interested in modulating the trajectory of professionalism [39] and interpreting the essential meaning: "I know it when I see it" [40]. The door to manage professionalism is open.

Since Hippocrates, a dozen precepts have provided guidance for medical education and professionalism. Not so any more. The UK's General Medical Council (GMC) has specified 300 standards for undergraduate education and behavior in two reports. The first, Medical Students: Professional Values and Fitness to Practice, was published on March 11 [41]. The second, an update of Tomorrow's Doctor, is in preparation. Standards for professionalism, safety, and diversity are priorities [42]. It is mandatory for the WFSICCM to cover the gap.

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Ethics of Decision Making in Critical Care

4

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Introduction

This review will define the context of medical practice in the 21st century to highlight the challenge of managing patients with severe illness and at extremes of age where this was previously not possible. Equally, by virtue of the illness, these patients are often incapable of providing truly informed consent. For this reason there is a greater responsibility for the clinician to be the patient's advocate. Patient autonomy is always the first imperative for the clinician but the need to be aware of and responsive to the other ethical tenets will be addressed.

The Nature of the Patient

The patient of today typically presents with complex illnesses associated with major comorbid disease [1] and is often at extremes of age [2]. Comorbid disease and age have important adverse implications on the outcome from critical illness [1,2]. Our ability to manage these patients has, however, been significantly improved by advances in medicine. This reality has emerged because of better understanding of the pathogenesis of disease, better diagnostic tests, and more specific therapeutic options. The Surviving Sepsis Campaign guidelines are a typical illustration of this evolution [3]. The guidelines identify current insights into the pathogenesis of sepsis, delineate the role of diagnostic tests, and then emphasize a comprehensive approach to management [3]. General and specific treatment is recommended [4–7]. The role of novel therapy has also been identified [7].

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Such strategies have allowed clinicians to offer care to seriously ill patients with significant patient benefit.

By virtue of physical and/or mental incapacity, critical illness commonly limits the ability of the patient to be fully informed of the nature of their illness and its treatment. As a consequence surrogate consent is often the alternative route sought for the purpose of clinical treatment and research. This "consent" is indeed assent rather than true consent. In this situation, the clinician carries a far greater burden of responsibility because assent by a surrogate may at best be construed as tacit approval by the patient. Upholding the patient's right to autonomy is extremely challenging in this circumstance since there is only limited input from the patient.

The Emergence of Managed Care

In the last few decades and across the globe, there has been a dramatic increase in the cost of health care [8–11]. This has occurred in the face of variable human and material resources and has resulted in the rationing of health care including critical care [12–13]. The consequence of this tension is an increasing need for more efficient use of intensive care resources with emphasis on the team approach, rigorous scrutiny of treatment options, and significant input by policy makers in the quest for quality health care [12–14]. The clinician in this instance is challenged to be a part of a process which potentially is in conflict with the primary brief of the physician, i.e., to always act in the interest of the patient. If clinicians choose to distance themselves from such processes, it is inevitable that a fund/hospital manager will dictate the fate of patients via processes that are necessitated by economic reality but not accomplished with insight [8].

The Four Principles of Bio-Ethics

It is generally accepted that the four fundamental principles of bio-ethics, namely autonomy, beneficence, nonmalfeasance, and justice are the pillars of effective decision making in bio-ethics. There is debate about the relative importance of each of these based on basic principles [15] and on cultural differences [16].

1. Patient Autonomy

Autonomy implies the patient's right to be fully informed about the illness and the consequences of treatment, and equally promotes the patients right to choose to accept or refuse the proposed treatment. In critical care practice the principles maybe applied but appropriate modification is needed given the fundamental differences in clinical practice [17]. Central to our practice is the reality that autonomy cannot be exercised by the unconscious or sedated patient. Fully informed consent requires complete disclosure of all the relevant

information, including the risks and anticipated benefits of applying and with-holding all treatment options, which are then carefully considered by the patient who then chooses the appropriate course of action. The critically ill patient is incapable of fully participating in such a process. Family and friends are limited in their ability to make choices in the interest of the patient because they are burdened by the emotional challenge of severe illness, their variable insight into disease, and potential conflicts from personal preferences. As a result, the doctor carries the additional burden of being the patient's primary advocate. In this respect, the intensivist is the primary protagonist because of their greater contact with the patient and family during the intensive care phase of illness.

2. Beneficence

Beneficence is the imperative that the health care professional recommend therapy that is known to improve outcome from the illness. While it is intuitive that health care professionals act in the interest of the patient, the emergence of evidence-based medicine has prompted attention to careful selection of a treatment favored by the preponderance of available evidence. Even in the context of evidence-based trials, choices about treatment policies may not be applied without attention to the interest of individuals and broader society [18]. This contradiction is illustrated by the following debate. The Critical Care Society of Southern Africa published a position statement on the role of Drotrecogin-alfa in the management of sepsis [19]. The society recommended the use of the drug and suggested that a call center approach be adopted whereby all doctors wanting to use the agent would discuss the case with an on-call intensivist. This strategy was an attempt to ensure that all the fundamental steps in sepsis care are adhered to, that there were no contraindications to the use of Drotrecogin-alfa, and that the patient satisfied the criteria for the use of the drug. The argument against the use of this treatment was that the number needed to treat to save one life was not ethically justifiable given the desperate need for health care provision in other areas and the suggestion that these areas had greater cost efficacy [20].

3. Nonmaleficence

This tenet supports the principle of "first do no harm;" the imperative is to prevent harm from the primary disease and from the care that is offered. Modern critical care practice is characterized by invasive monitoring and multiple interventions and prolonged exposure to the intensive care environment. This multiple exposure is commonly associated with serious adverse effects that may significantly contribute to morbidity and mortality. These errors can occur before the patient reaches hospital [21], from failure to recognize severity of illness [22], controversies surrounding effective and safe treatment [23], and from deficiencies in drug administration [24]. Prevention of such insults requires attention to detail in training and implementation of control systems.

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4. Social Justice

The last tenet requires attention to the needs of society. In an era of cost containment and managed care, the demand for social consciousness is increasingly being placed on clinicians. This demand is in direct conflict with the clinician's quest to be the patient's strongest advocate. The alternative is for health care managers to assume this responsibility and carry the flag in the quest for greater good. The threat of the latter approach is that patient autonomy will be threatened by those least able to act in their interest. Increasingly, this pressure will require community participation in decision-making processes, particularly with respect to guidelines regarding allocation of limited resources and withdrawing of life support systems [25].

Managing Competing Ethical Imperatives

It is a basic instinct that compels most individuals to fight for survival and equally to demand the care needed for that purpose. If we subscribe to the view that the patient's wish is of primary consequence (patient autonomy) then are we as doctors obliged to concur and offer what is requested at all times? As clinicians we often see patients that are no longer benefiting from advanced life support and conversely we would submit that further treatment is an imposition of suffering (in conflict with beneficence and nonmalfeasance) and therefore not in the patient's interests. In this situation further treatment is unjustifiable because the patient is not benefiting from treatment. Withholding and or withdrawing treatment is in the patient's interest and is therefore appropriate. A purist might argue that adopting this position is flawed because we can never be absolutely certain and that all we might have are relative degrees of confidence. The test of futility is a difficult one [26]. The first submission must be that if there is doubt, then the patient must be given the benefit of the doubt. Objective outcome prediction systems are designed to predict the risk of death in groups of patients, not for individuals. For example, this may be true for single-point-in-time scoring systems such as APACHE II [27]. We do know, however, that three organ failures for three or more concurrent days is uniformly fatal [28]. Under these circumstances continuing treatment may be seen as delaying death rather than prolonging life. Equally, offering treatment to patients who are not likely to benefit denies care to those who are likely to benefit (when limited material resources exist) or induces budget expenditures which may be deemed to be unjustifiable.

The Effect of Limited Resources

Triage is the first consequence of limited resources and has been used by the military for centuries. It is ethically acceptable to apply the principles of triage when faced with limited resources [29]. There are three key principles that must be applied: first that treatment should be withheld when care is deemed to be futile; this decision is independent of the availability of resources. The second is to identify those that are in need of intensive care.

Thirdly, available resources should then be used on a first come, first serve basis.

This approach ensures that those unlikely to benefit do not have treatment imposed upon them and that those likely to benefit receive treatment as long as the resources are available. Clearly there will be patients who are denied treatment even though they are likely to benefit were it to be offered. This approach is clearly socially responsible but obviously does not satisfy patient autonomy. Again, adopting such a strategy should be affirmed by the broader community being served. Lastly, the intensivist is the key decision maker in these circumstances and is in the dubious position of being unable to satisfy patient autonomy but being socially just.

Conclusions

An era of unprecedented challenges awaits all health care practitioners. While protecting and upholding the rights of our patients will always be the primary prerogative of the practitioner, compelling economic realities dictate that our role needs to be diversified and the imperative to be socially just may take precedence in situations of limited resources. Perched above these is the need to offer treatment that is likely to benefit and prevent exposure to harm. In ensuring legitimacy to these processes, a broad-based, community-supported approach is probably the best route to ensure the rights and wishes of our patients and indeed, of ourselves.

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Evidence-Based Medicine in Critical Care

5

P.F. Kotur

"Good judgment comes from experience;
and often experience comes from bad judgment."
Unknown

Introduction

The knowledge and skills obtained during the course of study in the medical school are insufficient to carry on a life-long successful practice. To make clinical decisions, the practicing physician, even today is largely dependent on his obsolete knowledge and expertise derived from unsystematic observations made during his training period, which can be as old as his medical course itself. It needs to be updated periodically with the findings of new scientific/medical research. The scientific research has to be translated into clinical practice for improving the patient care provided to the community. Patient's values are rarely acknowledged and current practices are often outdated, with the result that the patient rarely gets the best currently available care. It is exactly 30 years since Archie Cochrane uttered the following words that sparked the "Evidence-Based Medicine" movement: "It is surely a great criticism of our profession that we have not organized a critical summary, by specialty or subspecialty, adapted periodically, of all randomized controlled trials" [1]. Today the practice of EBM has grown into the most popular paradigm or tool of translation of research into practice The application of Evidence-Based Medicine (EBM) principles can help us with this daunting task that challenges us daily to offer the "Best" patient care.

Definition

EBM is an approach to caring for patients that involves the nonconscientious, explicit, and judicious use of the clinical research literature combined with an understand-

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ing of pathophysiology, clinical experience, and patient preferences to aid in clinical decision-making. EBM de-emphasizes (but does not eliminate) intuition, unsystematic clinical experience, and physiologic reasoning as sufficient grounds for clinical decision-making and emphasizes the systematic evaluation of evidence from clinical research [2].

EBM has thus been defined as the optimal integration of the best research evidence with clinical expertise and patient values [3]. Best research evidence is generally derived from patient-centered clinically relevant research. Clinical expertise would include the ability to use the mastered clinical skills and past experiences to evaluate the unique health state of the patient, assess the risks and benefits of potential interventions, and incorporate personal values and expectations into clinical decision making. The unique preferences, concerns, and expectations brought to the clinical encounter by an individual patient represent the third component to be integrated into the clinical decision-making process. Triangulation of these three elements results in the forging of an alliance between clinicians and patients for optimizing clinical outcomes and quality of life.

Ever since the introduction of EBM about 3–4 decades ago, more and more physicians have been accepting the same in their practice day by day. Along with its increasing acceptance and popularity this new paradigm of medicine has undergone subtle but noticeable changes (the process continues) because newer thoughts and innovations are constantly being added to it by new users. EBM continued to evolve, to address a number of issues including scientific underpinnings, moral stance and consequences, and practical matters of dissemination and application, thus turning out to become less pretentious and more practical [4].

Goal of EBM

The initial goal of EBM was to minimize the use of nondocumentary knowledge and reasoning in clinical practice; however, no time was lost to realize the importance of the de-emphasized factors and there were suggestions to also include the nondocumentary evidence in the practice of EBM. Thus, EBM evolved (after several philosophical debates) beyond its initial (mis)conception, that it might replace traditional medicine. As a result the focus was shifted to integrating pathophysiologic knowledge, clinical expertise, and patient preferences in making decisions regarding the care of individual patients. This shift marked a critical but necessary step regarding the value of alternative forms of medical knowledge and reasoning. EBM is now attempting to augment rather than replace individual experience and understanding of basic disease mechanisms. As a result, the evidence was automatically classified into External evidence and Internal evidence. “External” refers to evidence tracked down from valid literature; “internal” refers to evidence existing within the clinician in the form of his expertise, pathophysiological understanding of a disease, and also his intuition. Now EBM is also defined as the explicit use of valid external evidence combined with the prevailing internal evidence [5]. Dissemination and incorporation

of valid clinical research findings into medical practice with an eye towards improvisation of patient care is the ultimate goal of EBM.

How Does One Practice EBM?

A clinician who wants to practice EBM must be able to understand the patient's circumstances or predicaments (including issues such as social support and financial resources), to identify gaps in his medical knowledge and frame questions to fill those gaps, to conduct an efficient literature search, to critically appraise the research evidence, and to apply that evidence to patient's care. This whole process has been divided into five simple steps, which if followed systematically can bring about a very successful outcome and a desired improvement in the patient's care [3].

I will proceed with a practical demonstration of the practice of EBM in five steps using an example of a clinical problem which we encountered recently in our KLES Hospital, Belgaum, India.

Clinical Scenario

A 12-year-old, only male child of a school teacher was admitted with a h/o accidental ingestion of an organophosphorus compound 4 h previously.

On admission the patient was comatose but hemodynamically stable. The clinician used his past experience, knowledge, skills, and expertise and treated the patient with an infusion of atropine; despite that, the patient started developing respiratory paralysis in the next 2 h. Again the clinician used his expertise, anticipated the respiratory paralysis, and put him on ventilatory support. He was being mechanically ventilated. At that point the consultant recognized the gap in his knowledge and he identified the same. The consultant wanted to administer an injection of pralidoxime but was not sure of the dosage and the mode of administration (a single bolus dose or an infusion). Thus the need has arisen: finding out an appropriate therapy for O.P. poisoning.

The Five-Step Approach for Practicing EBM

Step 1 – Framing a Proper, Pertinent, Focused, and Answerable Question

The first and foremost step in the practice of EBM is to convert the need for information into a patient-focused, pertinent, relevant, and answerable question. This need for information may be related to finding the optimal critical care management (Therapy) in the presence of a specific disease process, or to find out the possible sequelae (and their management), or to predict the outcome or to Diagnose a clinical

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problem, or to answer a query put forth by a patient or a patient's relative to know the course (Prognosis) of a clinical condition. A very useful tool (PICO model) that could be adopted in the process of formulating a proper/pertinent/focused question has been described [3,5].

PICO Model – Four Criteria System

- **P** – Patient problem: How would I describe a group of patients similar to mine?

In this clinical situation it is a male pediatric patient (12 years) who has developed organophosphorous poisoning following its ingestion.

- **I** – Intervention strategy: Which main intervention, prognostic factor, or exposure am I considering?

Here the intervention is therapy with pralidoxime in optimum dosage.

- **C** – Comparison: What is the main alternative to compare with the intervention?

Here in our patient, it is the dosage of pralidoxime, i.e., small dose versus big dose and it is the mode of administration (methodology). i.e., Single bolus dose versus Infusion.

- **O** – Outcome: What can I hope to accomplish, measure, improve, or affect?

In this scenario, recovery from O.P. poisoning and a decrease in morbidity and mortality would be the primary concern of the clinician. The physician would be interested in reducing the chances of the patient going into intermediate syndrome. He would be looking for evidence for minimizing mortality, duration of ICU stay, the need and duration of ventilation, time to recover from unconsciousness, the odds of developing intermediate syndrome, and infections.

In addition to the four PICO criteria, there are two additional criteria to be considered while formulating the question:

- Type of Question: How would I categorize this question? Is it related to etiology, diagnosis, therapy, or prognosis? In this example the question is about the therapy of O.P. poisoning.
- Type of Study: The other consideration is the type of study that will answer a therapy question. Various study designs provide specific answers. Tables 5.1 and 5.2 provide the guidelines for choosing the type of study design for each category of questions.

Table 5.1 Type of question and the corresponding study design

Type of question	Suggested best type of study → in decreasing order of importance
Therapy	RCT→ cohort → case control → case report/series
Diagnosis/clinical exam	Prospective, blinded comparison with a gold standard
Etiology/harm	RCT → cohort → case control → case report/series
Prognosis	Cohort study → case control → case report/series
Prevention	RCT→ cohort → case control → case report/series

Table 5.2 Type of question pertaining to a clinical encounter

Diagnosis	How to select and interpret diagnostic tests
Therapy	How to select treatments to offer patients that do more good than harm and that are worth the effort and costs of using them
Prognosis	How to estimate the patient's likely clinical course over time and anticipate likely complications of disease
Harm/etiology	How to identify causes for disease (including iatrogenic forms)

Ours is a therapy-related question and will be formulated using RCT study designs.

The pertinent, answerable, focused question is (Table 5.3):

So our question is: "In the drug therapy of organophosphorous poisoning, in a 12-year-old male child, should pralidoxime be administered as a single bolus dose or as an infusion and in what dosage to prevent the chances of development of intermediary syndrome?"

Table 5.3 PICO-Model example

In the drug therapy of	Categorizes that this is a therapy question	
O.P. poisoning	Patient's problem	
In a 12-year-old male	Categorizes the type of patient	**P**
Administration of pralidoxime	Intervention	**I**
Single dose vs. Infusion and Small vs. Big	Comparison	**C**
Good outcome/Recovery is understood or hidden	Outcome	**O**

Step 2 – Searching the Literature

The second step in the process is to locate the "best" evidence to answer the question. The clinician has two basic choices for finding the evidence. He may search through the "traditional" print resources like textbooks or journals or "browse" online electronic databases. What is of paramount importance is answering the question in the shortest possible time and in the most efficient manner. Manually searching through voluminous literature is an unenviable task requiring immense periods of time, a commodity that is in limited supply given the potentially life-threatening situation that the patient is facing. Browsing the online electronic medical databases seems the most logical option to pursue.

There are a number of online information resources that the clinician may tap to find the evidence. These include: textbooks, journals, patient profiles, practice guidelines issued by specialty boards, EBM reviews, and databases of indexed publications.

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"Medline" a premiere biomedical database published by the National Library of Medicine, USA, is the most popular (probably because it's free) and most exhaustive database. Citations may be retrieved by author's name, medical subject headings, and text words from titles or abstracts.

There are several search engines that enable the clinician to browse this database. The "Pubmed" service hosted by the same agency has several additional features and is probably the most versatile search engine for exploring Medline. This search offers a number of "browsers" (Clinical Queries, MesH, etc.) for searching the information. Additionally it also permits narrowing down the search by application of limits (type of publication, language, age group, period of publication, etc.)

Using the MeSH browser and restricting the search to publications in English and with abstracts available of Randomized Controlled Trials it was possible to locate the following article which appears to be the "best" evidence to answer our question. "Johnson S, Peter JV, Thomas K, Jeyaseelan L, Cherian AM: Evaluation of two treatment regimens of Pralidoxime (1 gm single bolus dose vs. 12 gm infusion) in the management of organophosphorus poisoning. J Assoc Physicians of India 1996 Aug: 44 (8):529–531."

Step 3 – Critical Appraisal of the Literature

To know whether the evidence is the best available or not is the next step. Critical appraisal of the article is an important step in the whole process. It is essential that clinicians must master the skills of critical appraisal of the literature if they are to apply evidence-based medicine to the daily clinical problems they encounter. Most busy clinicians do not have hours to spend critiquing an article. However, they do need a brief and efficient screening method of determining whether the information is valid and applicable to their practice. By applying this "Fast Track" appraisal it is possible to approach the literature confidently and base clinical decisions on evidence rather than hope! The critical appraisal of literature involves 3 stages: (1) screening for initial validity and relevance, (2) determining the intent of the article; and (3) evaluating the validity based on its intent. Validity of the literature pertains to determining the closeness to the "Truth." Different kinds of errors can creep in during the conduct of a study [6]. There are many ways/methods of eliminating these errors in the study such as: blinding, randomization, using placebo-controlled groups, minimizing loss to follow-up of patients, and treating the data by appropriate statistical analysis, etc. The clinician should ascertain whether the authors have used these methods to minimize the errors in the study or not.

The article that was tracked down is a prospective randomized placebo controlled clinical trial of pralidoxime in two similar groups of patients (control group–low dose and study group–high dose). Block randomization is used to give equal chance to all the patients to participate in the study in either arm of the trial. The investigators were not blinded to the two groups which if done would have made the results even more valid. The 72 patients who entered the trial were properly accounted for at the time of analysis and are attributed to at its conclusion indicating proper follow up

in all the patients. The article is quite relevant to the clinical problem as it addresses the clinical scenario that is confronting the clinician. The intent of the article is to evaluate two treatment regimes of PAM in the management of O.P. poisoning. The next thing to determine is the strength of the outcome. How large was the treatment effect? The incidence of intermediate syndrome and the ventilator requirement was significantly higher in the high-dose group. This was an equivalence study designed to show that the low dose was as effective as the high dose. The results attain higher significance as the low-dose group fared better than the high-dose group, even though the research hypothesis was in the reverse direction.

Step 4 – Integrating the Evidence with Clinical Expertise and Patient Values

EBM, by definition, is the optimal integration of best research evidence with clinical expertise, and the patient's biology and values.

The best-documented critically appraised research evidence is already with the clinician. The physician has already exercised his expertise arising from prior knowledge and past experience in treating his patient by starting an infusion of atropine, and putting the patient on mechanical ventilation. He now has to take into consideration the patient values also.

Lastly, the study is quite beneficial to our patient; because the treatment effect is quite precise in bringing down the risk of prolonged ventilation, intermediate syndrome, time required to regain consciousness, the cost of therapy, and the duration of ICU stay. PAM is very expensive. It is imperative for the clinician to find a cost-effective and yet effective treatment. The patient's father, being a primary school teacher with limited earnings, could not afford the exuberant cost of large volumes of the drug. Hence, the outcome of this research study is very much relevant and beneficial in solving the clinical dilemma and also taking into consideration thepatient's values.

Step 5 – Evaluating the Process

Once the therapy is administered the clinician needs to evaluate the previous four steps. Was he able to formulate a focused question? Was he able to devise a precise search strategy for locating the evidence? Did he use the most appropriate resource? Were more pertinent resources like practice guidelines available to him? Did the "evidence" work for his patient? The final step is to reassess the strategy and take it onwards from there. The clinician should document the outcomes of the application of the evidence, and based on his experiences and those of his colleagues should be able to develop management protocols. Beyond this he must also collaborate with professional bodies in developing practice guidelines. This last step completes the feedback loop of EBM [3].

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Benefits of EBM

The greatest advantage of EBM is that it minimizes the errors in patient care, reduces the cost of treatment to the patient, and most importantly it optimizes the quality of patient care. Further, the skills learnt in practicing EBM are the very same ones needed for being a life-long, self-directed learner. The habit of accessing literature on a daily basis is the best guarantor of ensuring advancement of knowledge and keeping abreast of scientific progress.

Limitations in Adopting EBM

There are three major challenges in adopting EBM. First and foremost, technology and online information resources must be available to the clinician. Research-based evidence is generated at an exponential rate, yet it is not readily available to clinicians. When it is available, it is applied infrequently. The sheer volume of research-based evidence is one of the main barriers to better use of knowledge. The problem is compounded by the inability of clinicians to afford more than a few seconds at a time in their practices for finding and assimilating evidence [7].

This issue seems to be resolving due to the rapid pace at which the information technology revolution is occurring. Personal computers are becoming cheaper, internet costs are declining, and a number of health portals and databases are offering free access to electronic journals and periodicals. This will enable a practitioner to collect evidence on a daily basis sitting at home and or at his clinic.

The second challenge for the clinician lies in learning the skills required for accessing the medical literature and finding the best evidence therefrom. Once the evidence has been located, he must be able to determine the validity of the evidence found. This will require an understanding of the epidemiological study designs and concepts of biostatistics. Readers must take personal responsibility for judging the validity and clinical importance of the medical literature. Though medical educators have embraced EBM since its introduction as an innovative approach to medical education, the task of teaching clinicians the basic skills of EBM remains challenging [8].

The most important challenge in adopting EBM is an attitudinal one. A systematic review [1] of studies examining the information-seeking behavior of physicians found that the information resource most often consulted by physicians is textbooks, followed by advice from colleagues. The textbooks we consult are frequently out of date, and the advice we receive from colleagues is often inaccurate [7]. Change in attitude will take place only when there is realization that clinical performance depends upon regular updating of knowledge and does not merely accrue through years of clinical experience.

Other potentially negative impacts of EBM are:

1. Evidence may be viewed as static rather than dynamic. Guidelines are increasingly influencing medical practice, yet these guidelines require frequent review and

revision to incorporate new literature. The use of out-of-date guidelines may be associated with decreased quality of care compared with the use of more recent evidence.

2. Clinical observation and experience are placed last in the evidence hierarchy with the randomized controlled trial held as the standard for clinical intervention. The hierarchical discourse of medical knowledge produces opposition rather than collaboration between researcher, clinician, and patient. Alleviating perceptions of dominance and creating connections produces cohesion within medical communities. Evidence to practice and practice to evidence redefines EBM as a circular integration of best research evidence, clinical expertise, and patient values [9].
3. No amount of empiric evidence can tell us what we ought to do in any particular situation as decisions regarding what ought to be done are value based. The necessary gap between clinical research and medical practice means that evidence can never directly dictate care; evidence cannot tell us when it is best to ignore the evidence. The current boundaries of EBM are generally defined in relation to obstacles to the development, dissemination, and incorporation of medical evidence, and approaching EBM from a philosophical perspective may allow a more rigorous delineation of the promises and pitfalls of EBM [10].

Relevance of the EBM to the Developing World

Most of the reviews produced to date address health conditions that are priorities in the developed world and not the major health concerns of the developing world [11]. Lots of doubts are being expressed about the relevance, suitability, and transferability of the evidence evolved in the developed countries for application in the developing countries. There is a definite ground for these doubts and what we need is not the "best" evidence but the most "appropriate evidence." Most effective treatment as per an RCT conducted in an affluent country may not be the most effective treatment when provided in the developing world and it is quite essential to know which interventions work, which do not work, and which are likely to be harmful [12]. This is especially important in situations where health problems are severe and the scarcity of resources (like the ones needed for the practice of Critical Care) make it vital that they are not wasted [13].

Special Considerations for Evidence-Based Critical Care Medicine

1. Because of the paucity of valid, randomized clinical trials to help the practice of Evidence-Based Critical Care (EBCC) Medicine, many decisions in ICUs/CCUs are based on evidence from pathophysiologic reasoning or evidence obtained from studies on animals, healthy volunteers, or observational studies focusing on physiologic (arterial blood pressure, heart rate, pulmonary artery occlusion pres-

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sure) or patient (mortality, morbidity, functional status) outcomes. EBM sees evidence broadly. There is always evidence; however, it is often unsystematic or physiologic. Dispersed literature sources and insufficient clinical research data enhance the need for evidence-based critical care, whereas the need to make critical decisions under the pressure of time challenges the application of EBCC .

2. Literature sources. The Database pertaining to critical care medicine is dispersed across multiple specialties (anesthesia, medicine, pediatrics, surgery, etc.) journals, as well as basic science journals such as Cell, Shock, and Circulation journals. This diversity increases the need for efficient methods and search engines to access and search relevant literature.
3. Both the breadth of knowledge required for the practice of EBCC and the diverse sources of critical care literature not only demand efficient access and but also efficient critical appraisal strategies for evaluation of relevant literature.
4. Need for rapid decisions. The need to make rapid clinical decisions in critical care areas may complicate the application of EBM [14], especially when the best external evidence found may not be in agreement with the internal evidence. In case of conflicting internal and external evidence, clinicians may have several options. They may change their mind and align it with the external evidence. They may determine that the external evidence is not sufficiently convincing and remain with the original decision. Or, they may choose to discuss with the patient the conflict between the internal and external evidence in a manner that enables the patient to take part in the decision-making process. This last approach is recommended because patient preferences are considered an essential component of the evidence-based decision making process and decisions often need to be made in the practice of critical care, in the absence of clear research findings [5].
5. In the ICU, decisions are routinely made faster than in a general medical ward, and there are few data regarding whether EBM can be applied practically where rapid decisions are required. There is some data suggesting that EBM treatment and diagnostic protocols may be used effectively even in the treatment of acute processes such as acute respiratory distress syndrome. Without such protocols, practical applications of EBM in ICUs will be limited to problems we see repeatedly. There are facilitations like a self-sufficient EBM trolleys containing a portable computer with an internet connection, which can be wheeled into any critical area.
6. In procedure-oriented specialties such as critical care, the skill of the provider and hospital-level factors may affect risk and should be considered in the risk/benefit analysis.

Conclusions

The promise offered by EBM in providing optimal patient care to all critically ill patients has to be exploited by all practicing physicians. Formulation of a pertinent question relevant to the clinical encounter, tracking down the best available docu-

mentary and nondocumentary evidence to answer the question (and validating the same), incorporation of the prevailing internal evidence with patient values, making correct clinical decisions, and keeping in mind the philosophical limitations of evidence-based medicine, are the primary responsibilities of the physicians who like to be life-long, self-directed learners. Needless to say, a total commitment and a willingness to undergo attitude change have to be exhibited by all practicing physicians who like to be competent all the time in their careers. Failure to accomplish this runs the real risk of producing a cult of physicians who cannot help but offer outdated and nonoptimal patient care.

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Section III
Clinical Governance

Clinical Governance: Definitions and Recommendations

6

G. Offenstadt

Definition of Clinical Governance

Quality improvement (QI) has become a central tenet of healthcare and a statutory obligation in many countries worldwide. Clinical governance (CG) has been introduced in 1998 as a new approach to QI by the UK National Health Service (NHS), which built on it a whole reform program. CG is a system through which NHS organizations are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish [1]. The opportunities for improvement are similar in many countries despite the large differences in the underlying financing organization and delivery of health care. The ten commandments of CG were described originally [2] as follows.

A quality organization will ensure that:

1. Quality improvement processes (e.g., clinical audit) are in place and integrated with the quality program for the organization as a whole.
2. Leadership skills are developed at the clinical team level.
3. Evidence-based practice is in day-to-day use with the infrastructure to support it.
4. Good practice, ideas, and innovations (which have been evaluated) are systematically disseminated within and outside the organization.
5. Clinical risk reduction programs of a high standard are in place.
6. Adverse events are detected and openly investigated, and the lessons learned promptly applied.
7. Lessons for clinical practice are systematically learned from complaints made by patients.
8. Problems of poor clinical performance are recognized at an early stage and dealt with to prevent harm to patients.

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9. All professional development programs reflect the principles of clinical governance.
10. The quality of data collected to monitor clinical care is itself of a high standard.

Whatever the originality of the concept [3], CG has to be understood as a basis for good clinical care, ensuringsafe, effective, and up-to-date care.

Quality is not easy to define, but it can now be measured and improved. The involvement of doctors is essential and special training is required which connects quality methods with applied medical research [4]. It is interesting to recognize that improving the quality of patient care does not require entirely new systems, and that people work best if they are given a worthwhile job and are allowed to get on with it [5].

Clinical governance is about the clinical process and its governance; it depends on doctors and managers working together, each realizing that they have the potential to gain from such collaboration. Managers have to accept that doctors make decisions that cost money and that doctors know more about what works for patients than they do.

Only recently the concept that bad systems, not bad people, lead to the majority of errors and injuries has become a mantra in healthcare. Good care is dependant on the organization and environment in which clinicians work. The more complex any system is the more chances it has to fail. Because of the new technologies, the new medications, and the new medical devices there is a permanent struggle to contain the potential of errors. The implementation of a system approach is difficult within a highly individualized environment encompassing many subcultures, each with its own priorities, rules, and traditions [6].

We agree with the three main challenges proposed by Donaldson [7] for the next decade:

1. Make quality and safety the common currency so that it is on an equal footing with money and productivity.
2. Put clinicians in leadership roles with full responsibility for assuring and improving the quality and safety of their services.
3. Build the understanding, expertise, and track record on safety in health care to the level of other high-risk industries.

The difficult question is how to optimize quality of care while minimizing cost. Cost-containment efforts have created strong pressure to use the most cost-effective care possible. At the same time it is increasingly difficult to develop widely accepted health policies and maintain public consent. The chairman of the Britain's National Institute for Health and Clinical Excellence, known as NICE, said recently "We are not trying to be unkind or cruel. We are trying to look after every body" [8].

All these principles apply to critical care medicine.

Critical care medicine has matured rapidly within the last 40 years all over the world. Research into critical illness has been a major stimulus to the evolution of the discipline. Critical care had also focused attention on difficult ethical issues such as aggressive care offered to potentially terminally ill patients.

The financial cost of critical care is an issue because it is an increasingly expensive. While widely available in developed countries, it is scarce in developing countries where it is often restricted to those who can afford to pay. A rapidly aging population and public expectation places an even greater demand on critical care. It rep-

resents a large proportion of hospital costs, which tend to dominate health expenditure. It is estimated that 1–2% of hospital budgets in the UK is spent treating approximately 100,000 critically ill patients [9]. In the USA more than 20% of hospital budgets is expended on the care of intensive care patients [10]. Health expenditure in developed countries varies from 15% of the gross domestic product in the USA, through 11% in France, to 8% in the UK [11].

ICU services are widely distributed but there is considerable diversity in the way intensive care departments are structured and in the teaching of critical care [12]. Nevertheless, national and international critical care societies have provided recommendations for best ICU management [13–15]. In some countries, France for example, official texts have defined ICU organization [16].

Recommendations for Intensive Care Departments

The intensive care department (ICD) is a well-defined entity of medical activity and care, operating independently from other departments in the hospital. It has a defined geographical location concentrating manpower facilities, professional skills, technical equipment, and the necessary space. The objectives of an intensive care department are the monitoring and support of failing vital functions in acutely ill patients in order to perform adequate diagnostic measures and medical or surgical therapies to improve outcome. The patient population may present with a large variety of pathologies, but share the potential reversibility in one or more threatened vital functions.

1. An intensive care department must be localized in a hospital comprising appropriate departments, assuring that the multidisciplinary needs of intensive care medicine are met. Not every hospital must conceive their ICD facilities in the same way, with the same capabilities and identical structure and equipment. ICDs must be adapted to the region and the hospital they serve in size, staffing, and technology. A department of intensive care should accommodate at least 6 beds (8 beds in France and 10 beds in the Paris area).
2. The responsibility for the department and the administrative and medical management belongs to a full-time physician, with the position as head of a department. The head of the ICD has a formal education and training in intensive care medicine. He (she) is assisted by physicians qualified in intensive care medicine. Their number will be calculated based on the number of beds in the department; number of shifts per day; the level of care; and as a function of clinical, research, and teaching work load. The regular medical ICDs staff treat patients using state-of-the-art techniques and may consult specialists in different medical, surgical, or diagnostical disciplines whenever necessary. The regular medical staff has the task of coordinating the referring physician and consulting medical specialists. The staff members of the ICD take over the medical and administrative responsibilities of the care of the patients admitted to the unit. They define admission and discharge criteria, and bear the responsibility of diagnostic and therapeutic protocols to standardize care in the department. An important task of the medical

staff is to supervise and teach the doctors in training. The continuity of medical care in the department during nights, weekends, and holidays is assured by the regular medical staff of the department on a 24-h-per-day basis.

3. Intensive care medicine is the result of an intensive cooperation between doctors and nurses. An efficient communication system has to be organized between the medical and nursing staff of the department. The nursing staff is managed by a head nurse, who oversees the functions and quality of the nursing care. The head nurse should have extensive experience in intensive care nursing and should be supported by a deputy head nurse able to replace him (her).
4. One dedicated physiotherapist should be available per 12 beds on a 7-day-per-week basis.
5. Maintenance, calibration, and repair of technical equipment in the department have to be organized.
6. A radiology technician should be on call around the clock. Dietician should be on call during normal working hours. One medical secretary is required per 12 intensive care beds. A specialized group of cleaning personnel should be available for the intensive care department.
7. Objective criteria are required to evaluate the activity of care.
   - Minimal clinical data: indicating type of pathology, diagnosis, demographic data, occupancy rate, mean length of stay, mortality.
   - Minimal nursing data: indicating the level of nursing activity.
   - Severity and organ system failure scores.
   - Overview of technical procedures (percentage of patients on artificial ventilation, hemodialysis, etc.).

A critical minimal mass for each disease category is necessary to maintain medical and nursing expertise at adequate levels.

These guidelines correspond to the concept of the "closed unit" with a full-time intensivist.

This "closed unit" model is usual in Europe and Australia but uncommon in the USA [12,17,18], where it is also called the "team model" and supported by the Society of Critical Care Medicine. The barriers to this standard of care in USA could be due to a shortage of intensivists and cultural differences [19]. The reluctance of other physicians to support the intensivist model comes from loss of authority, patient control, and personal incomes [20]. A reliance on other health care professionals, on telemedicine, electronic monitoring, and regionalization [21] are suggested to overcome these difficulties [18].

ICU Performance and Quality Improvement

Measures

Defining ICU performance is a complicated but compulsory task. It requires quantification of parameters not limited to patient health outcomes but also economic,

psychosocial, and ethical and institutional outcomes [22]. In each category there is a debate about the different parameters depending on their importance (linked to clinical important outcome), validity, reliability, responsivity (sensitive to change), interpretability, and finally the difficulty of their acquisition. It is important to take in to account for their interpretation the case mix of the patients, which is not always constant across time periods in the same ICU and of course may be different from one ICU to another.

There are a variety of measures that every ICU should collect.

Among medical outcomes measures, survival rate in ICU, in hospital, and in long term are used. It is possible to correctly appreciate the performance for patient cohorts by using the standardized mortality ratio, which is the ratio of observed mortality rate to the mortality rate predicted by severity scores. However, this ratio is unable to predict mortality for the individual patient. Complications rates related to care, medical errors, rate of nosocomial infections, and compliance to hand hygiene may be reported.

There is a clear need to improve the ability of doctors and nurses to disclose errors of care. Threat of malpractice liability is a significant barrier to error reporting. Every error has at least one root cause, and every cause can be eliminated only if the error is revealed. Adverse events and near misses should be reported. Confidentiality is protected through anonymous reporting from any personal computer with internet access [23].

The other measures may be for economic outcomes: resources consumption in ICU, cost-effectiveness of care, etc.; for psychosocial and ethical outcomes: quality of life among survivors, satisfaction of the patient, of the family, etc.; for institutional outcomes: staff satisfaction, turn over rate, etc.

Quality Improvement

QI is an attitude and culture. The foundation of successful QI is strong motivation, teamwork, and leadership [24]. Achieving safe care requires efficacy (identifying what works), appropriate use, and no errors [25].

The Donabedian's [26] model to improve quality includes 3 quality of care components: structure, process, and outcome. Structure is defined as a way care is organized (open or closed ICU); process refers to what is done or not done for patients and their families. We already spoke about outcomes, which refer to the results achieved.

It is necessary to create structures and implement processes in the ICU to allow the application of evidence-based best practices and create an environment of patient safety. In fact, most of the problems result from flaws in institutional processes and not from inadequate performance by individuals [27].

In 1998, several large US health care purchasers formed the Leapfrog Group to initiate breakthroughs in patients safety and improve the overall value of health care. This group support the notion that the quality of care in hospital ICUs is strongly influenced by whether intensivists are providing care and the staff organization in the ICU. This group requires this condition for hospitals that treat their beneficiaries

[28]. Multiple investigations have shown that outcomes are better in closed ICU systems. Mortality rates, length of stay, and hospital costs are significantly lower in hospitals with closed ICUs managed exclusively by board-certified intensivists [29–32]. A competent intensivist's proximity and the ability to see the patient at all hours are the most important parameters for maximizing care. Critically ill patients deserve care by the most experienced provider regardless of the time of the day [33–35].

Implementation of Evidence-Based Best Practices

Time has to be provided. Two types of time are required: integrated time, which gives sufficient space to considered quality issues during routine work, and shared time to allow clinicians to meet to report on QI [36]. Intervention to improve implementation of evidence-based best practices include education, audit with feed back, clinical practice guidelines, reminders, order sets, computerization, and a combination of these interventions [37].

Errors in order writing are the most common sort of medical error [38]. They may be decreased by computerized physician orders.

Adherence to guidelines and protocol is often poor. To improve compliance is to ensure that they have been adapted to local practices and accepted by health care providers. Simply having written a protocol is not sufficient and probably less important than having a close, motivated working group of health care providers [39].

An example of structural change is the participation of a Senior Pharmacist in the morning work rounds, which reduces avoidable drug errors by 65% [40] and cost [41].

The Institute of Health Improvement has been created to help institutions to improve implementation of evidence-based best practices. This Institute promotes the approach of "bundles" of care defined as a small, straightforward set of practices – generally 3 to 5 – that, when performed collectively and reliably, have been proven to improve patient outcomes [42].

Quality improvement has little chance of success without the understanding, the participation, and in many cases the leadership of individual doctors. The presence of the Head Physician of the Department is often mandatory. Performance improvement is expensive but everyone has to be convinced that the money is well spent. One should remember that the priority for an intensivist is to be a good worker in the field of basic care. In this respect unlimited time and personal commitment towards the patient and his family are essential.

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Optimization of Limited Resources and Patient Safety

7

A.O. Gallesio

Introduction

A rational resource allocation is today an imperative for intensive care medicine; resource allocation, in the intensive care unit (ICU) context, is more related to human resources availability and organization, mainly the number of trained nurses, than technology and supplies. For optimizing resources we must focus on redesigning and improving work processes. Adverse events and medical errors have arisen as a formidable problem since November, 1999, when the US Institute of Medicine released a report on medical error, "To Err is Human;" this publication was followed by several studies [1–4]. Technology complexity has improved patient prognosis but also has increased exponentially the possibility of errors and adverse events.

Errors and adverse events have several consequences:

1. Resources spent in treating adverse events and errors are huge and hinder rational resources allocation.
2. An excessive utilization of finite resources violates, from a social and institutional point of view, bioethics principles such as beneficence, nonmaleficence, and equity.
3. Patient autonomy may also be involved because the bulk of resources are consumed by chronically critically ill patients. These patients continue to be treated, many times without any chance of recovering, resulting in futility management.

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ICU Mission, Vision and Strategic Plan

The *mission* of ICUs was first defined as the recovering of a patient with a high risk of dying. Changing concepts in bioethics and rehabilitation made a change in the ICU mission definition necessary. In 1997, the American Thoracic Society Bioethics Task Force summarized these changes as the achievement of three main objectives [5] (Table 7.1):

1. Management and allocation of ICU resources must meet the mission of the unit, and this is a responsibility of the ICU director.
2. *Vision* is how the organization wishes to see itself in the future and which are the objectives to reach.
3. *Strategic plan* is the way and the steps the ICU must carry out in order to reach the vision.

Mission, vision, and strategic plan must agree with the general hospital mission and objectives, and the whole ICU team must collaborate in their definition.

Table 7.1 Mission of an intensive care unit

Objectives	Outcome
Resuscitation and preservation of human life	Actual mortality against expected mortality
To provide suitable rehabilitation as soon as the patient begins to recover from his critical condition	Morbidity and quality of life after discharged
To provide palliative care and affective support to the nonrecoverable patient and his family	Futility. There is no validated instrument to measure futility so far

Processes

Daily tasks in the ICU will be carried out through steps which are often a result of the organization culture. Processes may or may not be defined; we may say that they may be either implicit in the ICU daily practice, or explicit, because they have been discussed and designed consciously.

The definition of the main ICU processes are the cornerstone of resources management because they define not only the way in which the critically ill patient will be assisted, but also the responsibilities of each member of the team.

Definition of processes comes from management and the business area. A process is defined by the Merriam Webster online Thesaurus [6] as "an usually fixed or ordered series of actions or events leading to a result." In the ICU scenario the central processes are patient admission and daily assistance.

The process of admission of a patient to an ICU will always be the initial input to

the unit: this request will trigger all other processes. The most basic process scheme of a patient admission to the ICU may be described in a few steps:

1. Request for a patient admission to the ICU
2. Allocation and checking of the room or area in which the patient will be admitted
3. Patient reception
4. Patient medical and nurse assessment
5. Decision about diagnostic and vital support procedures
6. To inform either patient or family
7. Therapeutic, diagnostic, and vital support planning fulfillment
8. Nursing care
9. Patient monitoring
10. Has the patient an emergency before next daily medical staff assessment? If yes go to step 4
11. Has the patient died? If yes go to the discharge process
12. New daily staff assessment
13. Does the patient need to continue staying in the ICU? If yes go to step 4, if not go to the discharge process
14. Patient discharge process. Patient and/or family information
15. Get the room or area ready for the next admission
16. Consumed resources registration and statistic analysis

Resources Allocation

Resources allocation is a consequence of at least four main factors:

1. Patient population to be admitted
2. Pathology case mix
3. Human resources organization and processes definition
4. Local resources availability

Resources are an essential part of the structure of ICUs. Normally human resources account for between 45 and 60% of ICU costs everywhere in the world; supplies, including drugs, account for approximately the other 30 to 35% [7].

Human Resources

Intensive utilization of human resources (manpower) is a characteristic of medicine but caring for the critically ill patient requires even more human resources. A nurse/patient relationship of at least 1:2 has been proposed as necessary for thorough care of the critically ill patient. ICU-specialized medical staffing with a 24-hour on duty presence in the ICU has also been shown to result in better outcomes and decreased costs [8].

Usually the ICU health team is made up of specialized nurses and physicians, but

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also technicians have an important role in carrying out mechanical ventilation and hemodynamic monitoring; specialized nutritionists, pharmacists, physiotherapist, and other specialties complete the list of professionals involved in ICU tasks. ICUs must be headed by a specialist in intensive care; also the nurse team head should have training in intensive care.

Nursing Teams

Nursing is the most scarce resource in the ICU. This is a worldwide problem, but it affects developing and undeveloped countries more seriously [7]. A report from the Pan American Health Organization [9] in 2005 showed that the shortage of nurses in Latin America threatened the quality of health care throughout the region. The report has attributed this situation, at least in South America and the Caribbean, to deteriorating working conditions; many nurses must have two jobs in order to meet their daily needs. In the USA, it has also been reported that the availability of professional nurses is declining as health services are becoming increasingly specialized, and this shortage will grow substantially in the next 10 years. A report of the US Health Resources and Services Administration says that "To meet projected growth in demand for RN services, the U.S. must graduate approximately 90% more nurses from U.S. nursing programs relative to the baseline graduate projections" [10]. The study estimates that the shortage of nurses will reach 275,000 by 2010 and to 800,000 by 2020.

A report "Overview of the Nursing Workforce in Latin America" [9] highlighted the fact that the pattern of nursing shortages mirrors other health inequities in the region. In Haiti, for example, there are only 1.1 nurses for every 10,000 inhabitants, compared with 97.2 per 10,000 in the USA. The report affirmed that fifteen countries have fewer than 10 nurses per 10,000 people, and the regional average is 30 per 10,000. Emigration is also a problem in Latin America. Peru's national nursing association reports that in the last 4 years, more than 5,000 nurses – 15% of the nursing workforce – have emigrated, primarily to Spain, Italy, and the USA. The increased demand for nurses is also in large part due to growing life expectancy and population aging.

The Ministry of Health of Argentina reported [11] that the country currently has 65,806 nurses in the federal and provincial public health system; the total number of nurses is approximately 83,000, equivalent to 22 nurses/10,000 inhabitants compared to 87 and 95 in Canada and the USA, respectively. Of the 65,806 nurses working in the public health system only 7% have a university certificate; 30% have a tertiary certificate with 3 years of study and 63% are only auxiliary nurses with 1 year of study. A 7-year program for training 45,000 new professional nurses was launched in October, 2008.

We do not have the exact figure regarding the shortage of critical care nurses worldwide; the figures are contrasting among countries and areas in the world. Many countries have reported a lack of trained nurses. In 2001, a published study of critical care nursing organizations in 23 countries found that staffing levels, followed by

working conditions, were the two most important issues and priorities facing critical care nurses at that time [12]. In that study all 23 responding countries identified staffing levels as the most important issue for their country's critical care nurses. The researchers have recently found that these issues remain among the most important issues to critical care nurses in 51 countries of the world. Other studies have shown similar results [13–17].

This scenario has begun to improve in recent years in many countries because of government actions stimulating the choice of nursing as a professional career, and also by the intervention of several actors in the critical care field:

1. The national societies of intensive care that have initiated nursing ICU training courses and have introduced a regular nursing meeting in the societies' critical care annual national congress.
2. Hospitals are giving a major importance to the ICU staff service continuous education.
3. Nonprofit organizations and industry that support and promote different kinds of training and grants.

The most commonly used score worldwide to establish the magnitude of the daily tasks a nurse may execute with respect to a patient is the simplified Therapeutic Intervention Scoring System (TISS). The original version of TISS had 76 items and was built based on the complexity of care intervention that each single patient needs [18]. This score was reduced to 28 items (TISS 28) by Miranda et al. [19,20]. It has been stressed that one nurse can not carry out a TISS score of more than 40–50 points.

Recently Miranda et al. [21] reassessed the TISS 28 score. They changed the score based on a different concept; they proposed that the time spent in many nursing activities are not necessarily related to the complexity of care. TISS 28 was mainly based on this type of intervention and not on the real time that is necessary to carry out a particular care action. Many nursing activities are not necessarily related to severity of illness but to the time spent in simple care. Five new items and 14 subitems describing nursing activities in the ICU were added to the list of therapeutic interventions. New activities accounted for 60% of the average nursing time; the new scoring system, Nursing Activities Score, explained 81% of the nursing timeversus 43% in the TISS 28. It is necessary to validate this new score in new samples and in different populations.

Medical Team

Medical responsibilities in the ICU are essentially to provide life support of the critically ill patient through diagnostic and therapeutic interventions. Follow-up of patients admitted to the unit is the role of the medical staff.

1. *ICU director*: This responsibility must be held by a professional specialist in intensive care. He must overview the whole management of the ICU. He must also supervise and define ICU processes regarding patient care and ICU administrative and technical support.

2. *Staff physicians*: The ICU director must be supported by doctors qualified in intensive care. The number of doctors must be determined based on the number of ICU beds and on the ICU complexity. An assistant doctor for each 6–8 beds is recommended.
3. *24-hour on-duty physician*: The presence of a 24-hour on-duty physician in the ICU will depend on hospital organization. Large university-affiliated hospitals with many in-training residents and fellows, and specialized well-trained nurses and technicians are capable of running without an intensivist continuously on duty in the unit; however, a specialist in intensive care must be on call.

This kind of organization is not the case in other countries where well-trained nurses are scarce and where respiratory and homodynamic technicians on duty in the ICU do not exist at all. A physician trained in intensive care stays on duty in the unit 24 hours a day. Complex tasks such as mechanical ventilation or hemodynamic monitoring are carried out by the on-duty physician.

Resources have been shown to be better allocated in well-organized units that are managed by intensive care specialists and run with a closed model than in those units running with an open model [22].

Pharmaceuticals

Medication is an important component of ICU resources utilization. The national costs of pharmaceuticals in the USA has been calculated to have risen from 6 to 15% yearly [23] since 1997; more than 70% of this increase in costs is due to new drugs approval [24]. Pharmaceutical costs represent 4–7% of hospital expenses. The impact of this increase is even more striking in the ICU; drug utilization in these areas reach 38.4% of total pharmaceutical hospital costs and are currently increasing faster than total hospital drugs costs, 12% vs. 6% [25]. The cost of ICU drugs should not be viewed only in terms of acquisition costs; adverse drug effects (ADE) also have a significant impact on hospital costs. Although the rate of preventable and potential ADE are greater in ICU patients, the event rate is no different when adjusted for the number of drugs administrated. This result suggests that methods that reduce the overall number of drugs in the ICU is a way to reduce the incidence of ADE in critical care areas.

In many countries pharmaceutical costs are approximately 30–35% of total ICU costs; employee wages represent approximately another 48–55%.

The bulk of drugs used in the ICU are associated with only a few therapeutic procedures; approximately 80% of the total drug utilization is associated with interventions seen in Table 7.2.

Technology

Definition of the technology to be incorporated is a responsibility of the ICU director. Only few hospitals have written policies for incorporating technology; these writ-

Table 7.2 Drug utilization associated with interventions

Drugs	Therapeutic intervention
Colloid and crystalloids	Blood volume expansion
Blood components	Transfusions
Analgesics and sedatives	Pain management
	Sedation for adapting to mechanical ventilation
Gastric H^+ secretion inhibitors	Prevention and treatment of gastrointestinal bleeding
Heparins	Prevention of deep venous thrombosis and pulmonary thromboembolism

ten policies should take into account the institution's vision, mission, and strategic plan. This assertion is much more important in countries with limited resources, because it may imply a substantial resources savings. Unfortunately this is frequently not the case, and it often happens that marketing pressures from industry promote unnecessary purchases of technology.

Often the director of an ICU is left alone at the moment of deciding about the purchase of new technology; neither medical, administrative, nor engineering departments are included in a committee that permits a serious discussion about: (1) the need for incorporating a new technique, (2) whether it is cost-effective, and (3) an analysis of the financial viability of the acquisition.

The ICU director must find out if at least a cost-effectiveness, cost/utility, or cost/benefits analysis has been carried out about the utility of the new technique. If these studies do in fact exist and support its use, it must still be kept in mind whether or not the conclusions are valid regarding available human resources and the economic conditions of the country where the facility is located. The Society of Critical Care Medicine (SCCM) has established guides regarding technology evaluation and use (Table 7.3).

The financial viability of introducing new technologies includes not only purchase price, but also maintenance and repair costs.

Patient Safety and Resource Allocation

Two studies have carefully analyzed the incidence of adverse events and errors in the ICU scenario: The Safety Study in the USA and The Sentinel Evaluation Study in Europe.

The objective of the Safety Study [26] was to study prospectively and descriptively the incidence of Adverse Events (AEs) and serious Medical Errors (MEs) that occur in two tertiary ICUs with a high degree of complexity. The AEs and serious

Table 7.3 Evaluation of new technology

What basic science principles support a certain technology?
Are the indications for the use of the new technology clearly indicated by the manufacturing company?
Are secondary advantages defined for frequent users?
Does the new technology really comply with the indications proposed by the manufacturing company?
What is the scientific information available to support its use?
Is scientific information available on key concepts about the new technology?
Does this information consider: surviving, morbidity, length of stay in the ICU, benefits and complications?
How much are the costs of introducing the new technology, including initial capital, operative costs, costs of human and non human resources to be used, and indirect costs?
How does the technology affect the total daily cost of the patient?
Does new technology require of specially trained staff, such as knowledge in basic sciences or specific experience for its safe use?
Adapted from [37]

MEs were measured as events every 1,000 patient-days. AEs occurred in 79 patients (20.2%), including 66 (55%) that were not preventable, and 54 (45%) that could have been prevented; there were also 223 serious MEs. The incidence of AEs and MEs were discriminated as follows: all AEs, 80.5 per 1,000 patient days; preventable AEs, 36.2 per 1,000 patient days; and serious MEs, 149.7 per 1,000 patient days. A further analysis showed that 13% of AEs caused risk of death and could have been ultimately fatal. Eleven percent of MEs caused serious risk to the patient's life. The most frequent serious ME occurred during the process of therapeutic interventions, primarily medications (61%). If we add AEs and serious MEs, they total 230.2 episodes per 1,000 patient days, so a patient staying for 3 days in the ICU would likely suffer an AE or an ME.

The Sentinel Events Evaluation (SEE) Study [27] was published in 2006. A sentinel event was defined as an incident that harmed or could harm the patient. The categories of sentinel events were classified as follows:

1. Medication: wrong drug, dose, or route of administration
2. Erroneous handling of airway:
   Unplanned extubation
   Airway obstruction
   Artificial air lost by the tube cuff
   Immediate reintubation
3. Errors in handling catheters, guides, bags of intravenous fluids
4. Probes and drains: departures and accidental catheter drainage, improper disconnections, etc.

5. Failures in equipment: pumps, ventilators, monitors, dialyzers, oxygen supply, etc.
6. Disconnection, turning off, or inappropriate setting of alarms

The study included 1,913 patients; 584 events were registered that affected 391 patients. A stepwise multiple logistic regression model was constructed. Variables that were significantly associated with the occurrence of a sentinel event were patient-to-nurse ratio, risk time, any organ dysfunction/failure more frequently in sepsis [28], and NEMS item-specific intervention in the ICU [29]. The magnitude of resources used because of adverse events and medical errors has been published recently [30]. Fifty-six medical intensive care patients were evaluated with matched controls; the cost of an adverse event was \$3,961 (p = 0.010) and the increase in length of stay was 0.77 days (p = 0.048). Extrapolating to annual costs, the increase expenditure was \$853,000 for all adverse events in the medical ICU. Similarly, for 52 cardiac ICU patients, the cost of an adverse event was \$3,857 (p = 0.023), corresponding to an amount of \$630,000 annual costs. On average, patients with events in the cardiac ICU had an increase of 1.08 days in length of stay (p = 0.003).

ICU Improving Quality Committee (IQC)

The first step for avoiding MEs and AEs is to establish an ICU improving quality committee with strong support of hospital and the ICU directives. Nurses, medical staff, technicians, pharmacists, administrative personnel, and housekeeping staff must be represented in this committee. The committee must call for participation of other hospital sectors and departments according to the problem subjected to analysis.

Once the ICU quality committee has been launched, there are at least three steps to implement in order to reach the main objective of installing a culture of patient safety:

1. Promote the voluntary, anonymous, nonpunitive report of adverse events and errors, involving the whole UCI team. This initiative will surely also change the team culture of facing up to errors [31].
2. Choose a suitable pattern of quality indicators in order to follow up the ICU performance.
3. Organize a reasonable way of periodically auditing indicators performance.

In order to get better resources allocation and avoid AEs and MEs, four main types of documents have been developed for daily tasks description: (1) standards of practice, (2) flow charts, (3) protocols, and (4) checklists.

1. *Standards of Practice* must be seen as rules that define an acceptable minimum standard of the practice the violation of which is associated with general to bad praxis.
2. *Flow charts* enable integration of several aspects of the patient care process in a coherent plan that allows a linear continuity. They must also include alarms for avoiding processes errors.

3. *Protocols* are much more specific. Their instructions are explicit and can be followed by medical nurses and other professionals. They should be specific for individual hospitals and adapted to local conditions. Protocols must have a high level of consensus because they often are resisted by the ICU team as they leave little freedom for personal decisions.
4. *Checklists* are lists of items and steps to be controlled for checking the appropriateness of carrying out a particular task. A recently published WHO checklist for surgery room control is an example of this kind of instrument.

Bioethics Considerations

We have traditionally recognized four bioethics principles, the two first deriving from the Hippocratic oath:

1. *Beneficence*: Beneficence may be described as the positive expression of nonmaleficence. This principle highlights the concept that we have a positive obligation to advance the health care interests and welfare of others and to assist others in their choices to live life to the fullest.
2. *Nonmaleficence*: Nonmaleficence derives from one of the most traditional of medical guidelines that goes back to the time of the Hippocratic oath: First of all, do no harm.
3. *Autonomy*: Put most simply, autonomy affirms that we ought to be the authors of our own fate and to make our own decisions and to control what is done to ourselves.
4. *Justice*: In relation to health care, justice may be described as the allocation of health care resources according to an equity standard.

In 1999, The Tavistock group proposed and published [32] what we may call an extension of bioethics principles; they are intended to be applied to different actors of the health delivery process: (1) people who work in health care delivery systems, (2) health care organizations, (3) insurers, employers, and governments, and (4) the community.

These ethical principles take into account several considerations:

1. Health care is a human right.
2. The care of individuals is at the center of health care delivery but must be viewed and practiced within the overall context of continuing work to generate the greatest possible health gains for groups and communities.
3. The responsibilities of the health care delivery system include the prevention of illness and the alleviation of disability.
4. Cooperation with each other and those served is imperative for those working within the health care delivery system.
5. All individuals and groups involved in health care, whether providing access or services, have the continuing responsibility to improve quality and equity in resources distribution.

Singer [33], referring to medical errors and resource allocation, says that ethical analyses have focused on the obligation to disclose and report an error when it occurs

[34]. However, disclosure, though important, does not provide a solid ethical basis for the development of a culture of safety in medicine and the author proposed following the Tavistock draft statement [35]. It is interesting that this author included a suggestion about the role of physicians, who work in complex institutions, must make decisions about medical errors and resource allocation: "In developing a culture of safety, clinicians will need to act as role models for their students by applying these principles themselves the next time they encounter a medical error. [Health care leaders will need to] feel personally responsible for error [and] declare error reduction to be an explicit organizational goal, and devote a significant proportion of the board and management agenda to achieving this goal" [36].

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Improving Quality of Care in ICUs

8

A. Garland

Introduction

The care of critically ill patients in Intensive Care Units (ICUs) is an important component of health care in developed countries, because it is common, expensive, and increasing.

The starting point for efforts to improve health care is to recognize that problems of quality are common and serious. They include: (a) failure to receive recommended care, (b) unnecessary interventions, and (c) medical errors and hospital-acquired complications [1,2]. Other areas of poor performance include communication and teamwork [3], and palliative and end-of-life care [4].

Another problem is widespread variation in practice and outcomes not explained by patient or illness characteristics. It is illogical to believe that doing the same thing a multitude of ways can lead to better outcomes than doing them in a uniform manner consistent with the best available evidence; thus such variation is evidence that suboptimal care is common.

For these reasons, we must make vigorous efforts to critically examine and improve ICUs. Because quality is a vague term, I will instead use the more operational concept of ICU performance, discussing Performance Improvement (PI).

Identifying how well a given ICU performs requires quantitation of relevant, objective indices of performance. However, it is challenging to define or measure such indices. In fact, the meaning, scope and measurement of performance in health care have evolved and broadened over the past 2 decades. Some of the most widely used approaches to improving performance in health care have proven ineffective. This chapter will discuss both the conceptual basis and practical aspects of a superior method of evaluating and improving ICU performance.

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Defining ICU Performance

The two main principles of assessing ICU performance are: (1) evaluate multiple parameters spanning the domains of ICU performance (Table 8.1), and (2) use performance measures that are primarily important to patients and society, or that have a proven relationship to such primary measures.

Every measure of ICU performance has important limitations. While most ICU PI efforts assess short-term outcomes such as hospital mortality rate and ICU length of stay (LOS), long-term survival and quality of life are most important to people. Indeed, "improved" short-term mortality and LOS can merely reflect shifting the place of death [5]. Accordingly, ICU PI efforts should try to assess longer-term, patient-centered outcomes.

Complication and error rates are commonly used measures of ICU performance. However, before using such parameters as indicators of ICU performance, great care

Table 8.1 Domains and measures of ICU performance

Domains	Measures
Medical outcomes	Survival or mortality rates – ICU, hospital, 30-day, 1-year, longer-term
	Complication rates related to care
	Medical errors
	Adequacy of symptom control
Economic outcomes	Resource consumption–ICU, hospital, post-hospital
	Cost-effectiveness of care
Psychosocial and ethical outcomes	Long-term functioning and quality of life among survivors
	Patient satisfaction
	Family satisfaction
	Concordance of desired and actual end-of-life decisions
	Appropriateness of medical interventions provided
Institutional outcomes	Staff satisfaction and turnover rate
	Effectiveness of ICU bed utilization
	Satisfaction of others in the hospital with the care and services supplied by the ICU
	Efficiency of processes/procedures/functions involved in ICU care

must be taken to ensure a true relationship to relevant outcomes. Since only a fraction of medical practices have been rigorously proven to be efficacious [6], deviations from recommended practice may have no such relationship.

Because ICU care is expensive, resource consumption should be part of ICU PI efforts. A measure balancing simplicity and information content is ICU LOS, though as discussed, this has important limitations. Cost-effectiveness is a more relevant parameter but requires resources beyond those of most local PI efforts.

Effective use of ICU beds is important because they are a limited and expensive resource. Though there is little data to help us understand what constitutes appropriate ICU triage, possible measures of triage performance include: (a) the percentage of ICU patients who are admitted to ICU for "monitoring only," i.e., not requiring use of the special active interventions that are used there, (b) the fraction of patients who die within 6 h of entry, or otherwise represent an exercise in medical futility, and (c) patients who remain in an ICU longer than their need for its special capabilities.

Though satisfaction of ICU patients, their families, and those who work in the ICU are all legitimate indices of ICU performance, they are rarely measured because they require questionnaires that are unfamiliar and time-consuming.

ICU readmission rate is not included in Table 8.1 because it is a questionable measure of ICU performance. Although readmitted patients have higher mortality rates and longer lengths of stay [7], for it to be a meaningful surrogate requires that: (a) premature ICU discharge caused a subsequent detrimental outcome due to a problem that was present during the time in the ICU, and (b) the outcome would not have occurred if the patient had remained longer in the ICU. There are no data that have demonstrated this [7]. The optimal readmission rate is unknown, and a low one could indicate that most patients are remaining in the ICU longer than necessary, increasing costs of care and possibly exposing them to increased risk of dying.

Measuring ICU Performance

PI requires collection of high quality data about performance measures, and statistical analysis of that data. Many PI efforts analyze adverse events (AEs) suffered by individuals. However, it is fundamental that detection and analysis of individual AEs cannot be used to measure performance. Instead, the rate of negative outcomes, such as death, errors, complications, staff turnover, family dissatisfaction, etc., is what truly represents ICU performance. Such rates are calculated by dividing the number of individual events by the number of at-risk patients, patient-days, or other appropriate denominators. The goal is always to improve these rates.

Systematically identifying AEs is difficult. Chart review and incident reports filed by clinical staff are unreliable [8]. Therefore, PI requires establishing reliable methods of systematically collecting data on the performance parameters being surveyed. Both the denominator and numerator must be accurate. This topic is beyond our scope, but has been addressed elsewhere [9].

To quantitate ICU performance we calculate the rate for binary variables such as

AEs, and the mean or median for continuous variables such as a 0–100 patient satisfaction scale. Such values are then compared to benchmarking standards, such as the value in other ICUs, or in that same ICU during a prior time interval. Care must then be taken to base conclusions only on sufficiently large samples; for example, many ICUs track monthly infection rates, but because the monthly number of cases are low, they overinterpret impressive looking changes seen over 1 or 2 months on their graph.

Performance measures can be influenced by patient demographics, comorbidities, and type and severity of acute illness. These factors are cumulatively referred to as case-mix. While raw data is not incorrect, it is problematic for comparing ICU performance between samples having different case-mix. Thus PI efforts should try to collect at least some case-mix variables. In general they should include patient age, gender, race, the presence or absence of important comorbid states, the organ system most responsible for ICU admission, and ICU admission source. With more data collection resources, or for special PI projects, one would consider collecting additional case-mix data.

The simplest way to use case-mix variables is to evaluate whether they are statistically similar between the time periods (or ICUs, or patient populations) being compared; if so then it is reasonable to compare raw values of the performance parameters. When case-mix is dissimilar, it is best to adjust for the observed differences. Computational and statistical methods for such adjustment is also beyond our current scope, and has been addressed elsewhere [9].

Finally in this section, interpretation of any ICU performance parameter must be compared against something. That could be external comparison with other ICUs, or internal comparison in your own ICU's performance in an earlier time interval. The latter is easier, and quite satisfactory for the purpose of continuous performance improvement. Though external comparison can be facilitated by membership in a consortium, two other methods are simpler. Using a ready-made system such as SAPS or APACHE to calculate a severity-adjusted parameter in your ICU, such as standardized mortality ratio, is equivalent to retrospective benchmarking against the patient cohort upon which those equations were created. Even simpler is to compare the performance variable of interest in your ICU to values reported in the literature from other ICUs.

Framework for Improving ICU Performance

To improve ICU performance we must: (1) measure indices of ICU performance, (2) make interventions aimed at improving those measures, and then (3) remeasure the indices to document the effect of the intervention. This section will develop a framework for understanding the interventions required to improve ICU performance.

A powerful framework for improving medical care is adapted from Berwick [10]. He tells us that we must: (1) know what works, (2) use what works, and (3) do well what works.

Knowing what works requires reading and appropriately interpreting the medical literature. Given the limitations of current knowledge, and the nature of statistical inference used to draw conclusions in medicine [11] we must accept that the "best evidence" is a moving target.

However, the single biggest problem in health care is the frequent failure to adhere to evidence-based best practices (EBBP). Even simple, universally accepted practices such as aspirin and beta-adrenergic blockers after acute myocardial infarction are often forgotten, leading to many unnecessary deaths [12].

Ensuring that all patients receive every applicable EBBP requires a paradigm shift. In the current, physician-centered paradigm of medical care, each physician is entirely responsible and free to guide care as they will, regardless of whether their choices concur with best practices, and independent of effective accountability. Yet there are too many important things to learn and remember to expect that any physician will always do all the right things. Such a system is not rational, and is not in the best interests of patients or physicians. Instead, it is necessary to create structures and implement processes in the ICU that ensure that every patient, every time, receives every applicable EBBP.

Indeed, the performance of complex organizations, such as ICUs, is determined by their structure. Only 15% of errors and problems are a result of inadequate performance by individuals; 85% of the opportunities for performance improvement relate to flaws in institutional systems and processes which hinder the ability of individuals to perform their jobs well [13].

In this concept of improving performance by altering the system itself, often called Total Quality Management (TQM), every structure, process, activity, interaction, function, and relationship, clinical and nonclinical, that influences the ICU in any way is open to scrutiny and change. In most ICUs the existing systems and processes make it easy for well-meaning people to make mistakes, and hard to do things efficiently and correctly the first time; the goal of TQM is to reverse this situation.

Within TQM it is understood that performance is a moving target that can be improving all the time, even in the absence of identified problems. But TQM represents a major paradigm shift, and is often actively opposed by physicians. TQM does not respect existing professional standards, instead it continually demands development of new ones which are more effective. It emphasizes teamwork and standardization over individual autonomy [14]. Thus it asks physicians and other professionals to alter their mindset regarding their place in the health care system; away from viewing themselves as singular individuals with skills that set them apart from their similarly-trained colleagues, to that of an "equivalent actor" [14].

Systems-oriented PI is very different from the Quality Assurance/Quality Improvement (QA/QI) method that is still used in many ICUs. QA/QI strives to address individual errors, AEs, or other problems that are noted. Since problems are addressed only if they are noted and after they occur, QA/QI is reactive, instead of proactive. In fact, both components of QA/QI are seriously deficient: identification of individual problems [8], and root cause analysis [15]. To make matters worse, instead of simplifying the overly complex and mistake-prone processes that are the true cause, many hospitals respond to severe AEs by adding additional layers aimed

at eliminating the possibility of that particular problem; this frequently creates an even more complex and maladaptive system that becomes more prone to a variety of other mishaps. Despite decades of use, the published, peer-reviewed literature does not support the notion that QA/QI or root cause analysis are effective in improving the performance of health care systems.

On the other hand, the ICU is an opportune place to establish a systems-oriented PI environment. The details of implementing such a program are beyond the scope of this chapter, but discussed elsewhere [16].

Dramatic examples exist demonstrating the power of TQM to improve relevant outcomes [17]. Indeed, not only does measuring performance promote improvement, but the benefits of implementing a TQM program extend beyond the targeted performance projects [18].

Strategies to Improve Performance

Strategies shown to be effective by existing, published evidence are convenient, ready-made tools that individual ICUs can adopt. There should be no hesitation in making changes that have credible literature support even if your ICU does not have the resources needed to carefully validate their local efficacy.

Changes to ICU Structures and Processes not Directly Related to Specific Technical Aspects of Care

Numerous structures and processes comprise every ICU, with many differences even between ICUs that seem similar. To date, few elements of ICU organization have been well studied, and there are many more questions than answers. The best-studied organizational element is the question of "closed" versus "open" ICUs [19]. Others include 24-hour intensivist presence [20,21], telemedicine [22], use of a daily goals sheet [23], pharmacist participation in ICU rounds [24], nurse–physician collaboration [25], different nurse staffing ratios [26], implementation of a rapid response teams [27], and availability of an intermediate care unit [28].

Some interventions represent radical departures from current practice and are challenging to implement. As discussed, improving ICU performance requires a genuine openness to new ideas and ways of doing things, and a commitment to beneficial change. The PI groups of every ICU should evaluate this literature now and as it evolves, and implement beneficial structural changes that are feasible with available resources.

Strategies to Increase Use of Evidence-Based Best Practices

The opportunity to improve ICU care by uniform implementation of existing EBBPs is enormous [29]. Strategies to increase use of EBBPs include education, audit with

feedback, clinical practice guidelines, reminders, order sets, computerization, and combinations of these interventions. One of the most consistent themes in implementation research is that combining multiple strategies is more effective than individual ones [30]. Much more of such translational research is needed.

Traditional continuing medical education (CME), such as didactic education, rounds, meetings, and symposia, does not materially change practice or improve care [30]. Audit with feedback refers to a summary of recent clinical performance that is communicated back to practitioners. The body of literature assessing this intervention is of poor quality, generally showing only small benefits [31].

Practice guidelines aim to increase use of EBBPs by making them known and available to clinicians. They are not effective without concomitant use of other strategies to ensure that they are actually used [30].

Reminders about a specific patient, provided at the point of care, are one of the most effective ways of improving adherence to recommended practices [30]. The main limitation is effecting reliable and timely delivery of reminders to clinicians. The best way to deliver reminders is via computers incorporating expert systems (see below). Unfortunately, such systems are very expensive.

Another approach to increasing use of EBBPs is prefabricated order sets. For example, an order set incorporating all current EBBPs to reduce ventilator-associated pneumonia could be applied, by default, to all newly intubated patients. Notably, some implementations of this concept have failed because order sets were not implemented unless they were actively chosen, i.e., "off by default." In many cases "on by default" is better, so that EBBPs are implemented unless explicitly switched off [32]. Although caution must be exercised in choosing EBBPs that should be on by default, concern that it would cause more harm than good is misplaced, in light of evidence that errors of omission are much more prevalent than errors of commission [33]. Just as for reminders, computerization offers a superior way to utilize prefabricated order sets to improve use of EBBPs.

Information Technologies in Performance Improvement

Computers are powerful tools for PI. Unlike people, they can keep track of almost limitless amounts of information, never forget, and are essentially flawless in performing their assigned tasks.

Computers can reduce information overload by acquiring, integrating, displaying, and analyzing clinical data. Online access to textbooks and journals replaces trips to the hospital library. An increasing amount of medical knowledge is accessible via hand-held devices. Bar code labeling of medications and blood products reduces errors [34].

Errors in order writing are the most common type of medical error [2], and computer order entry dramatically reduces such errors and their consequences [35]. As discussed, computers facilitate the powerful strategies of clinical reminders and prefabricated order sets for increasing use of EBBPs.

Computer-aided decision support systems have access to patient data and provide clinicians with "expert" medical advice. For example, when the physician enters an order for gentamicin into the computer ordering system, it automatically accesses the patient's age, current weight, and creatinine value, and recommends a dosing regimen. When drug levels become available from the laboratory computer, the system would automatically update the recommendation. Most studies have shown benefits from using such highly competent systems, especially if they are designed with certain usability characteristics [36].

The potential of computers to the ICU patients extends beyond providing advice. Computers can automatically adjust devices such as ventilators to maintain optimal parameters in a way impossible for humans [37]. The ability of computers to continuously monitor and analyze the entire ICU data stream in real-time makes them superior to people for tasks such as early detection of physiologic instability, adverse events, and surveillance for care practices outside of established guidelines.

The future promises even more—an automated ICU environment in which some EBBPs are effected without the need for humans to remember to order or even remember them. For example, a computer could automatically elevate the head of the computer-controlled bed for a patient it senses is on computer-regulated mechanical ventilator, receiving enteral feedings being delivered by a computer-controlled infusion pump.

In addition to assisting in care of individual patients, computers are a powerful piece of a mature systems-based PI programs. Computerized clinical ICU databases can be queried to identify relationships between variables that suggest opportunities for improving performance that are not obvious even to those intimately involved in day-to-day care [38]. Computers can automatically calculate scores and predictions from systems like APACHE or SAPS, and perform adjustment for case-mix.

The current barriers to more widespread adaptation of information technologies include a paucity of commercially available systems, high cost, poor human interfaces, and opposition from clinicians.

Conclusions and Recommendations

Every ICU should collect data on a variety of relevant measures of ICU performance. Efforts to detect individual adverse events and errors must not be substituted for systematically collecting data and calculating cumulative measures of performance. If there are insufficient resources to acquire and adjust for case-mix differences, one should use unadjusted (raw) data without apology; unadjusted data cannot possibly be more misleading than having no performance data at all. A simple and reasonable performance comparison is against the same ICU in successive time intervals.

Improving ICU performance requires a paradigm shift away from the discredited notion that poor performance is due to deficient individuals. Instead it requires a systems-oriented approach of studying and changing the ICU structures and processes that make it easy for people to make mistakes and hard for people to do their jobs well, in order to transform them into the opposite. These ideas must become an inte-

gral part of the ICU's routine activities; its concepts and methods must be incorporated into the culture of the ICU.

Even the smallest ICU should have an appropriately constituted, multidisciplinary, systems-oriented Quality Circle that meets at least monthly. The Quality Circle should quantitatively assess ICU performance, improving it by implementing changes to ICU structures and processes designed to standardize care and ensure uniform use of evidence-based best practices.

Although it is not preferred, in place of the effort needed to identify and collect data on an outcome of primary relevance, one can substitute the lesser effort to collect information about an associated process-related variable. An ongoing program of such small-scale efforts, Plan-Do-Study-Act cycles, can produce large improvements in performance [39]. Even an ICU with literally no data collection resources can use systems principles by implementing interventions shown effective in the medical literature, without actually assessing the local benefits of those practices. Of course, such humble versions of PI should be accompanied by ongoing efforts to convince the hospital's administration that providing resources to improve ICU performance is money well spent.

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Scoring Systems

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R.P. Moreno, A.C. Diogo, S. Afonso

"The power and the beauty of science do not rest upon infallibility, which it has not, but on corrigibility, without which it is nothing"
Howard Gruber

Introduction

Intensivists, the physicians that practice the art and science of intensive care medicine, have a challenging task. Our field of action presents unique characteristics that make it distinct from most fields of medicine: we deal with a quite heterogeneous population, with our patients presenting a wide range of ages, comorbid diseases, reasons for seeking medical care, and specific needs for care. Moreover, the time window for our interventions is measured often in minutes rather than in days or months. For this reason, we traditionally practice our specialty inside special places in the hospital, the so-called Intensive Care Units (ICUs) where all the technical and human expertise are assembled together in order to optimize the science and art of preventing, detecting, and managing patients at risk or with already-established critical illness in order to achieve the best possible outcomes of care. This task is a complex process, carried out on a very heterogeneous patient population, and influenced by several variables that include religious and cultural background, different structures and organizations of the health care systems, and major differences in the baseline characteristics of the populations.

These facts, particularly the heterogeneity in patient characteristics, dependent on the chronic health status and the degree of physiologic reserve of the patient but also on the acute insult or disease responsible for the acute situation and on the timing and characteristics of medical care applied until admission to the ICU, make the evaluation of the effects of any clinical or nonclinical practices in the critically ill patient a challenging task. In other words, when we want to standardize different groups of patients, we need always to use risk adjustment methods, which allow us

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to take into account all of the characteristics of patients known to affect their outcome, irrespective of the treatment received. The objective of this article is to review the principles of risk adjustment in the critically ill patient.

Definition

The art and science of severity evaluation and later of outcome prediction become in the 1980s one of the icons of intensive care medicine. Although not exclusive to our area of knowledge (see, e.g., the extensive use by pediatricians of the APGAR score [1] or the use by cardiologists of the Killip and Kimball score in patients with acute myocardial infarction [2]), instruments such as the Acute Physiology and Chronic Health Evaluation (APACHE) model [3] or the Simplified Acute Physiology Score (SAPS) [4] become as commonplace to intensivists as the pulmonary artery catheter or the mechanical ventilator.

Given the scope of this review, we will focus only on general severity scores and general outcome prediction models. Other similar instruments exist, such as the organ dysfunction/failure scores (developed to quantify over time the presence and severity of the dysfunction and failure of several organs and systems), disease-specific scores (to be used only in certain diseases or conditions), or nursing workload use scores (developed to quantify nursing workload use in the ICU).

For the purpose of this review, we will use the following definitions:

1. Severity scores are instruments that aim at stratifying patients based on their severity, assigning to each patient an increasing number of points (or score) as their severity of illness increases.
2. Prognostic models, apart from their ability to stratify patients according to their severity of illness, aim at predicting a certain outcome – usually the vital status at hospital discharge – based on a given set of prognostic variables and a certain modeling equation. Other outcomes, both in the short-term and in the long-term can eventually be considered, but are of little interest for the patients, their families, and the health care providers.

Needs and Standards of Care

The need for general severity scores and general outcome prediction models varies according to purpose of the use. As methods to control – in the statistical meaning of the term – for the heterogeneity of different patients and patient populations, they have different but complementary applications at the level of the individual patient and at the level of the ICU.

At the individual patient level, these instruments are used mainly to describe the severity of the individual patient's illness; for ensuring comparability of the severity of illness in epidemiological studies; as inclusion or exclusion criteria for clinical tri-

als; at management level to identify patients with a very low risk to develop complications; or patients too sick to benefit from treatment in the ICU, the socalled potentially futile or ineffective care [5,6]; and for the use of specific therapies (e.g., total parenteral nutrition or drotrecogin alfa (activated) [7].

At the ICU level, these instruments are used mainly for comparisons, either inside the same institution or among different institutions, settings, or countries. They have also been used to understand the effects of organization and management on ICU outcomes [8], decisions in end-of-life care [9], quality-of-life after ICU discharge [10], or to understand the patterns and characteristics of ICU practice related to better cost-effectiveness ratios [11,12]. They have been used to describe the variations in risk-adjusted mortality in different parts of the world [13] and constitute the basis for several national benchmarking systems, such as the Intensive Care National Audit & Research Centre (ICNARC) in the UK, the Austrian Center for Documentation and Quality Assurance in Intensive Care Medicine (ASDI) in Austria, or the Gruppo Italiano per la Valutazione degli interventi in Terapia Intensiva (GiViTI) in Italy.

The evaluation of case-mix (characteristics of the admitted patients) and outcomes (the results of care in the ICU) are crucial parts in the structural description and evaluation of an ICU, both as part of routine evaluation or as part of a formal audit [14]. Although currently available severity scores and outcome prediction models are probabilistic in nature, and have not been conceived to be used alone in the complex process of decision-making in individual patients, their use as auditing tools is unquestionable [15–19].

Due to several methodological problems which have been discussed elsewhere [20], intensivists should learn to dissociate conceptually the evaluation of the individual patient from the evaluation of the ICU. This issue, which was called recently by us the "paradox of outcome evaluation in intensive care" [21], has been omnipresent in our field since the original descriptions of the first general severity scores and outcome prediction models, and has resulted in two mistakes.

First, we use for individual patient assessment only data collected at admission or on the first 24 h in the ICU, when we know that for accurate patient assessment we should rely on daily assessment of the severity of illness.

Second, we use for ICU assessment only patient-related data, do not take into account ICU characteristics that are known to affect the performance, such as the organizational characteristics of the ICU.

Both these problems have been addressed in recent years. Regarding the evaluation of the individual patient, general severity scores are being slowly but consistently replaced by organ dysfunction/failure scores and at the moment, we can foresee two main developments in this field for the next few years: first, the incorporation in these models of biological variables, such as cytokines, immunological parameters, or other markers of inflammation, to allow a more precise diagnosis, stratification, and evaluation of patients with certain conditions. All these variables have been proven to have prognostic significance [22–27] but there is still the need to combine them with other patient characteristics to achieve a superior descriptive (and predictive) capability; second, the definition of the minimum amount of data needed for the daily assessment of

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the severity of illness [28, 29], combining eventually these organ dysfunction/failure scores with data derived from general outcome prediction models [30], and for the quantification of our ability to intervene in the process (the effectiveness of our clinical practice) [31]. This is a challenging task probably because the multiple organ dysfunction/failure syndrome is a complex nonlinear system [32] and will require eventually the use of new, nonlinear, statistical approaches [33–35].

Regarding the evaluation of the ICU, although our ability to control for baseline patient characteristics is still incomplete, resulting potentially in unstable predictions [36], and a growing body of evidence suggests that the patient genetic characteristics are one of the major outcome predictors of disease susceptibility and outcome [37–39], one of the main determinants of patient outcome in intensive care is the ICU organizational characteristics.

The number and qualifications of the medical doctors attending the critically ill patient have been shown to be associated with very large differences in the outcome of severe illness. This fact was demonstrated, for example, by Blunt et al., who found a case-mix-adjusted reduction in mortality of 73% with the introduction of 24-h intensivist cover in the ICU [40], and by Dimick et al. who demonstrated that daily rounds by an intensivist were associated with a decrease in the length of stay, a decrease in the hospital cost, and a decrease in the rate of complications after esophageal resection, after adjusting for case-mix and other hospital characteristics [41]. These data, which confirmed a previous paper by Pronovost et al., who showed that the organizational characteristics of the intensive care unit were related to outcomes of abdominal surgery [42], turn this issue of ICU staffing and qualifications into something important which certainly needs certainly research. Although the best way to provide 24-h coverage of all critically ill patients by a senior intensivist is still a matter of debate, new solutions have been tried and evaluated [43]. For those who remember Fisher's old question "Intensive care: do intensivists matter?" [44], now we have an objective answer: "yes, they do!" Interestingly, in a different database, Hans Rothen and our group also demonstrated that organizational characteristics do have a significant impact not only on risk-adjusted mortality but also on risk-adjusted use of resources [11]. The role of nursing staff was also not forgotten, with Amaravadi et al. demonstrating an increase in the risk of several postoperative pulmonary and infectious complications and an increase in the use of resources in patients after esophageal resection if the patient/nurse ratio was high [45]. The best way to incorporate these and other ICU organizational characteristics in our models should also be explored, with emerging modeling techniques being used, linking outcomes and costs [11,46–48].

Interestingly, general outcome prediction models have also been very important to understand the changing prognostic determinants of the patient with critical illness, allowing the researcher to document a decrease in recent years of the impact of deranged physiology on hospital mortality, a fact that can be attributed to the increasing effectiveness of ICU interventions in recent years [49]. Less and less true is the old quote from Sir William Osler that "*Patients do not die of their disease. They die of the physiological abnormalities of their disease*," and this change is due to the science and art of intensive care.

Evidence-Based Models

All severity scores and general outcome prediction models in use today have been developed based on strong evidence about the prognostic determinants in the critically ill patient and share some common methodological characteristics:

1. Developed in large databases: (APACHE II/III/IV/MPM III: patients from North American ICUs; SAPS II/MPM II: patients from European and North American ICUs; SAPS 3: worldwide population; the ICNARC model: patients from the UK).
2. Developed using logistic regression to choose and weight the variables (in some models controlling for the clustering of patients inside ICUs through the use of logistic regression with random effects or multilevel modeling, in other cases just assuming the – false – conditional independence of observations on the outcome of interest).
3. All variables accessed at patient-level.
4. All variables accessed at ICU admission (SAPS 3, MPM II, and III) or at 24 h after ICU admission (SAPS II, APACHE II, III, and IV).
5. Providing the user with one (or more) equation(s) to predict, at patient level, the outcome at hospital discharge (with one global equation or one global and several regional equations).
6. Providing the user with one equation to predict, at patient level, the length of stay in the ICU (APACHE III and IV).

These aspects, at their best and assuming the absence of major statistical errors in their development, represent the actual state of the art in outcome prediction in intensive care. They reflect the databases in which they have been developed and are based on the evidence of the relationship between the values of the predictive variables, the observed outcomes, and the mathematical link between both. Although the end results are always an approximation, approximation is the basis of the exact sciences, as told by Bertrand Russell "*An exact science is dominated by the idea of approximation, you only have to be right*."

Recommendations

All the general outcome prediction models can, at best, only predict exactly what would be the behavior of a certain group of patients matching exactly a similar group of patients in the development population. This implies that an adequate choice of the development population is a crucial step – probably the most important step – in the building of these models and later on the process of choosing a certain model to be used in a certain ICU.

This fact divided the scientific community into two groups, which we previously named the "lumpers" and the "splitters" [50]. On one side, the first group of model developers used only data from a very restricted geographic location. This fact holds true especially for all the APACHE models, from the APACHE II to the IV version

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[3,51,52], and to the new MPM III0 model [53]. Apart from an easier access to compatible databases, researchers chose this strategy mainly to decrease the variability in the sample and to focus on their main market. It is always easier to work with a more homogeneous sample, where we assume that all the known and unknown factors that affect prognosis present only a random variation in their distribution in the participating ICUs. This homogeneity allows for more precise estimates of the effects of the variables in the outcome of interest (vital status at ICU discharge), creates a bigger market for the developed instruments, and allows the set-up of global benchmarking systems, in which ICUs can be evaluated based on the observed to predicted mortality ratio in order to generate league tables. So, by focusing in on limited regions of the globe to develop and calibrate the severity scores and the outcome prediction models, researchers who support this approach have had to keep track and to worry not just about changes in baseline epidemiology, but also changes in health delivery and therapeutic options and the resultant changes in outcomes.

This approach has been followed, for example, by the developers of the APACHE systems (where even several updates in the predictive equations have been performed without changing the name of the score), as described by Zimmerman et al. from the Cerner Corporation, which runs the APACHE database [52]. Also, in some areas of the world, country-specific models have been developed and used with great success, such as the ones proposed by Rowan [54] and more recently by Harrison [55] in the UK.

The price paid by these researchers is that the results of these methodologies should not and cannot be extrapolated to other settings (e.g., to patients in South America or in Australasia): the genetic background of the patients is different, the epidemiology of diseases is different, life-styles are different, organization and delivery of medical care is different, and the availability and use of medical technology are different. These factors can make a difference, as demonstrated very clearly by Paulo Bastos in Brazil, working with the APACHE III system [56,57]. Also, as times passes, changes in the baseline characteristics of the admitted patients, in the circumstances of the ICU admission, and in the availability of general and specific therapeutic measures slowly introduced an increasing gap between actual mortality and predicted mortality [58]. Overall, in the last years of the twentieth century, there was an increase in the mean age of the patients admitted to ICU, with a larger number of chronically sick and immune-suppressed patients and also an increase in the number of admissions due to sepsis [59,60]. At the same time, outcome from major diseases, such as acute myocardial infarction or sepsis, consistently improved [60], which further impacted this miscalibration. So, by focusing in on limited regions of the globe to develop and calibrate the severity scores and the outcome prediction models, researchers who support this approach have had to keep track and to worry not just about changes in baseline epidemiology, but also changes in health delivery and therapeutic options and the resultant changes in outcomes.

On the other extreme, the “splitters” argue that heterogeneity, although making the work of model developers more difficult, is crucial in order to understand the differences in outcome determinants and outcomes among different regions of the world. Therefore, when building a model, these researchers looked to the database as an instrument to better reflect important differences in patients’ and health care sys-

tems' baseline characteristics that are known to affect outcome. These include, for example, different genetic markers, different styles of living, and a heterogeneous distribution of major diseases within different regions of the world, as well as issues such as access to the health care system in general and to intensive care in particular, or differences in availability and use of major diagnostic and therapeutic measures within the ICUs.

Although the integration of ICUs outside Europe and the USA surely increased the representativeness of the resultant databases, such as the SAPS 3 database developed by Moreno et al. [61] or the Ventila database developed by Esteban et al. [62,63], it must be acknowledged that the extent to which these databases reflect the case-mix in ICUs worldwide cannot be determined yet, since they have not been randomly selected and are consequently not necessarily representative of their respective regions of the world. It is noteworthy, however, that, even with major methodological limitations on the local or global representivity of these databases, they had a key role in understanding differences among different geographical areas regarding issues such as the basic epidemiology of critical care [13], the epidemiology in the use of certain therapeutic techniques such as mechanical ventilation [62–65], the impact of medical technology on improving outcomes [57], differences in the prevalence and prognostic determinants of severe infection and sepsis [66,67], the compliance with evidence-based advances in respiratory care [68], and the importance of religious affiliation and culture regarding end-of-life decisions [9,69].

The construction of these large databases has been accompanied by the development in certain areas of the globe of large registries, which now consist of hundreds of thousands of patients such as the Intensive Care National Audit and Research Centre (ICNARC) in the UK, or the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database in Australia and New Zealand. Already sometimes these databases are truly representative of a given population, by including all the patients in a given region of the world, such as the Scottish Intensive Care Audit Group (SICSAG), which reports data from all the ICUs in the country [70].

Consequently, apart from their role in documenting patient outcomes and comparing ICUs from different regions using risk-adjusted mortality and generating benchmarking scores for quality assurance or management purposes [71], these types of instruments and databases have a very important role in research and teaching. They allow the researcher to see the differences between different patient groups [61], to try to find the causes for these differences [11,72], and more important than all to try explain the differences [73]. To achieve these aims we must assure that a large degree of heterogeneity remains in the database, a mandatory condition to perform research on the differences.

Conclusions

Two crucial steps exist in the choice and correct application of a general severity score and general outcome prediction model.

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First, the choice of the best model for a certain geographical region and a certain type of ICU: Is the model able to control for the main patient characteristics related to mortality in that population? Has the reference population been well chosen and are the models well calibrated to this population?

Second, the correct application of the chosen model: can we evaluate and register all the data needed for the computation of the models? Can the models be used in the large majority of our patients? Is the sample size enough to draw meaningful differences? Several researchers, especially Kathy Rowan in the UK, demonstrated the importance of these "minor issues" such as the definitions of the variables, the timeframes for the evaluation and registration of the data, the frequency of measurement and registration of the variables, the applied exclusion criteria, and the data handling before analysis on the performance of general outcome prediction models [74]. These issues seem trivial but can have a huge impact on the performance of a model. It should also be noted that all existing models have been calibrated for nonautomated, i.e., manual data collection. The use of electronic patient data management systems (with high sampling rates) has been demonstrated to have a significant impact on the results [75,76]: the higher the sampling rate, the more outliers will be found and thus scores will be higher.

So, in conclusion, in recent years we assisted the development of a new generation of general outcome prediction models. More complex than their old counterparts, relying heavily on computerized data registry and analysis (although the SAPS 3 model can be still computed easily by hand), incorporating more extensively the reasons and circumstances responsible for ICU admission, these instruments have now to be evaluated outside their development populations.

The choice between them remains largely subjective and depends on the reference database that the user wants to use: the USA centers participating in the APACHE III database or a more heterogeneous sample of ICUs across all major regions of the globe. The absence of any fee regarding the SAPS 3 model and the existence of equations specific for each region of the world should be weighed against the paid participation in a continuous database program, which provides a more professional support and analysis of the data. However, even in regions that participated in their development, a model's behavior can be less than perfect, as recently demonstrated by Barbara Metnitz et al. in a large cohort of patients admitted to Austrian ICUs [77].

No matter the model chosen, users should keep in mind that the accuracy of these models is dynamic and should be periodically retested, and that when accuracy deteriorates they must be revised and/or updated. Also, their use should be complementary and not alternative to the use of clinical evaluation, since both predictive methods are prone to error [78], especially in the individual patient [79]. But, concerning the future, we are optimistic, since, as Sir Winston Churchill said once "*Every day you may make progress. Every step may be fruitful. Yet there will stretch out before you an ever-lengthening, ever-ascending, ever-improving path. You know you will never get to the end of the journey. But this, so far from discouraging, only adds to the joy and glory of the climb*."

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Section IV
Nursing Perspectives

Nursing Workforce Management in Intensive Care

10

G.F. Williams

Introduction

Intensive care nurse shortages and nursing shortages generally have been documented in many countries around the world [1–4].

In 2001, a published study of critical care nursing organizations in 23 countries found that staffing levels, followed by working conditions, were the two most important issues and priorities facing critical care nurses at that time [5]. In that study all 23 responding countries identified staffing levels as the most important issue for their country's critical care nurses. The researchers repeated the study in 2005 and found that staffing levels and working conditions remain among the most important issues to critical care nurses in 51 countries of the world [6]. A similar study is being conducted again in 2009 and similar results are expected [7], although the current world-wide financial crisis may influence this slightly as economic recessions often result in more nurses wishing to work to supplement the family income and subsequently the nursing shortage is less evident during the recession period [8].

The need for intensive care workforce and workload management systems is a common concern of many, yet in 2003 when the World Federation of Critical Care Nurses (WFCCN) was requested by its Council to develop guidelines on critical care nursing workforce requirements, few countries actually had documented workforce guidelines in place; Australia [9] and the UK [10] were notable exceptions.

Finding common, consistent, and (hopefully) evidence-based approaches to nursing workforce and workload management issues is of particular importance to all groups interested in intensive care… not just nurses, physicians, hospital administrators, and other departments that depend on a responsive intensive care service, but also the community at large and of course our patients and their families.

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Antonino Gullo et al. (eds), *Intensive and Critical Care Medicine.*

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Definition

The WFCCN describes a critical care nurse as a person who holds a recordable or registered nursing qualification in their own country and contributes to the field of critical care nursing [11]. Further, critical care nursing is specialized nursing care of critically ill patients who have manifest or potential disturbances of vital organ functions. Critical care nursing means assisting, supporting, and restoring the patient towards health, or easing the patient's pain and preparing them for a dignified death. The aim of critical care nursing is to establish a therapeutic relationship with patients and their relatives and to empower the individuals' physical, psychological, sociological, and spiritual capabilities by preventive, curative, and rehabilitative interventions [11].

Although sometimes the terms critical care and intensive care are used interchangeably, it is helpful to clarify the nomenclature. In this context, it is useful to first consider what is meant by an "intensive care unit" (ICU). For the purpose of this discussion, it is understood to mean a centralized location within a hospital environment where the sickest patients (critically ill) with severe organ failure are treated, advanced technological support is provided, and specialized staff provide the workforce. Usually, nurse-to-patient ratios are significantly higher than those found in general ward areas. In this context, "intensive care" is provided within an intensive care unit, and refers to the specialized interventions that are required to care for critically ill patients. By definition, the nature of this work is "intensive," and requires multiprofessional teamwork.

Critical care is an expansive term that incorporates all areas of high intensity care. While intensive care is included under this umbrella term, other acute areas such as, but not limited to, emergency departments, recovery rooms, and coronary care units are covered also. The term is very broad, and generally includes all areas of high care, where "high" can be defined as care over and above that normally provided in a general ward area. As with intensive care units, these critical care areas are usually centralized, and provide higher levels of technological support and multiprofessional expertise than that found on general wards.

Intensive care nursing workforce management has been identified as having similar characteristics to general nursing although more complex and difficult for the following reasons:

- Patient care is labor intensive, many patients requiring one nurse 24 h per day [12].
- Aspects of the role can be very demanding and stressful, resulting in burnout and frustration; hence, many intensive care nurses move on to other roles [13].
- Many critical care nurses are highly qualified and experienced but their remuneration and career choices do not reflect this fact compared with other nursing positions or other jobs that they could perform for more money and recognition [14].

It is the large numbers of highly skilled nurses required to deliver safe care in these intensive care environments that make the workforce demands and management so critical to care delivery. Good planning and management of workloads and workforce in a critical care nursing environment will lead to staff job satisfaction and retention.

Needs

The intensive care nurse works in a complex and ever-changing environment, necessitating constant observations that involve assimilation, interpretation, and evaluation of specialized information and subtle changes in patient condition as well as technology and monitoring outputs [15].

The relationship between the nurse:patient ratio, skill level of staff, and the quality of patient care and adverse events (errors) both in nursing and in intensive care specifically have been borne out through numerous studies. Such research helps to inform what may be considered safe and reasonable workloads or workforce standards in intensive care. For instance, it has been shown that a reduction in the number of registered nurses providing direct patient care is associated with complications, such as nosocomial infections [16], an increased risk of central line infection rates, pressure sore incidence, falls and use of physical restraints [17], medication errors, patient injuries, and death [18], while a higher ratio of registered nurses to nonregistered nurses in the skill mix improves patient care outcomes [19–21].

Ruth Endacott, a leading critical care nurse researcher who has worked both in the UK and Australia, proclaims that managing and supporting the transition of patients from mechanical ventilation is one of the pivotal roles of the intensive care nurse [22] and the time taken to wean patients from mechanical ventilation dramatically increases when nurse:patient ratios are reduced. Further research supporting this assertion by Peter Provonost and colleagues have shown that the presence of fewer critical care nurses is independently associated with postoperative complications [23] and increased risk for respiratory-related complications after abdominal surgery [24], while Thorens et al. showed that unnecessary delays in weaning and extubation from the ventilator may lead to unnecessary increase in length of stay and complications [25]. Good patient care appears to be associated with an appropriate ratio of highly skilled critical care nurses in the intensive care environment. Endacott also states "the 1:1 nurse:patient ratio has been the central tenet of endeavouring to maintain the level of qualified nurse and this level of staffing was stated as an explicit requirement in the recent Department of Health Guidelines of Intensive and High Dependency Care (UK)" [22].

It may be argued that a lesser nurse:patient ratio could be tolerated and compensated for by the addition of sophisticated monitoring equipment and alarms at the bedside and therefore reduce the need for 1:1 bedside nursing. Such an assertion lacks a solid evidence base, in fact the opposite may be true. Firstly, more technology requires more supervision and management, secondly, a Hong Kong study of ICUs found that 51% of incidents were detected by direct observation compared with 27% detected by a monitor [26] and in an Australian study, bedside staff observing the patient, chart, or equipment detected 83% of incidents, whereas 8% of incidents were detected by monitors [27]. So while complex technology and monitoring systems are essential to contemporary critical care practice, they remain yet another adjunctive tool for the nurses and cannot (at least for now) be considered a substitute for experienced and skilled direct patient care provided by a critical care nurse at the bedside.

A number of dependency scoring systems have been developed for critical care patient acuity and staff allocation measures in different countries and cultures around the world [28–30]. Although useful as a means to consistently measure workload trends retrospectively and over time, dependency scoring systems do not reflect the totality of the nursing work performed in an ICU and at best may only be used as a guide to workload measurement [15,31]. Like any scoring tool they may only provide a point in time indication of activity, they do not provide a response to the appropriate workforce necessary to respond to such activity.

It is clear, however, that most guidelines do acknowledge and support the need for the experienced senior critical care nurse in charge to determine the appropriate staffing mix and number for each patient and for the shift at any given time [9,10,12,15,32].

However, allocation of appropriate nursing staff numbers and skill mix to the workload anticipated varies substantially between individual clinicians, ICUs, cultures, and countries and has been a dilemma for managers for some time [33]. In a yet-to-be published study of over 50 countries it was found that for a described set scenario of 10 ventilated patients in an ICU, quite different staffing arrangements were suggested by the respondents. Economic, political, bureaucratic, and personal values and opinions were suggested to influence the variance [7]. What was striking for the researchers is that many countries still do not have documented standards to inform appropriate staffing levels for critical and intensive care units despite the evidence suggesting the high risk to patients when low staffing levels are allowed to remain and the fact that the WFCCN critical care nursing workforce guidelines have been available since 2005 [34].

Standards

The central principles of the WFCCN: Declaration of Buenos Aires, Position Statement on the Provision of Critical Care Nursing Workforce are outlined in Table 10.1. These are similar to the principles outlined in previously identified documents that inform the expected workforce arrangements in individual countries that have developed workforce standards in ICUs [9,10].

As outlined earlier there is a growing body of literature supporting the development of nursing workforce standards; however, the challenge for many critical care nursing organizations and leaders is finding an acceptable process for the development of a critical care nursing workforce standard within a given country that will be acceptable to critical care nurses, doctors, hospital administrators, governments, and the community at large.

Developing National Critical Care Nursing Workload and Workforce Standards

As outlined by Williams et al. in 2006, no patients, nurses, unit, hospitals or counties are alike and hence idiosyncrasies and other sensitivities must be recognized when

Table 10.1 Central Principles – WFCCN: Declaration of Buenos Aires, Position Statement on the Provision of Critical Care Nursing Workforce. Adapted from [34]

1. Every patient must be cared for in an environment that best meets his or her individual needs. It is the right of patients whose condition requires admission to a critical care unit to be cared for by registered nurses. In addition the patient must have immediate access to a registered nurse with a postregistration critical care nursing qualification (refer to WFCCN Declaration of Madrid on the provision of critical care nursing education)
2. There should be congruence between the needs of the patient and the skills, knowledge, and attributes of the nurse caring for the patient
3. Unconscious and ventilated patients should have a minimum of one nurse to one patient. High dependency patients in a critical care unit may have a lesser nurse patient ratio. Some patients receiving complex therapies in certain critical care environments may require more than one nurse to one patient
4. When calculating nurse-to-patient ratios and roster requirements in critical care, consideration and care must be given to the skill sets and attributes of nursing and support colleagues within the nursing shift team as they vary and require re-evaluation with fluctuations in patient care requirements
5. Adequate nursing staff positions must also be in place to assist with nursing education, in-service training, quality assurance and research programs, management and leadership activities, and where institutionally required, external liaison and support services beyond the confines of the critical care unit
6. Critical care nurses should focus their labor on roles and tasks that require advanced skill, expertise, and knowledge of best practice in patient care. Therefore, adequate numbers of support staff should be employed to preserve the talents of critical care nurses for patient care and professional responsibilities wherever possible
7. Flexible workforce strategies and incentives should be employed by management to recruit, retain, and remunerate expert critical care nurses at the patient bedside, and to ensure appropriate succession planning for future leadership needs. Additionally, contingencies should also be in place to respond to fluctuating and unexpected demands on the critical care service

attempting to develop a set of standards or guidelines for a national critical care nursing workforce [35].

The following process is recommended which utilizes the WFCCN: Declaration of Buenos Aires, Position Statement on the Provision of Critical Care Nursing Workforce and follows the methodology utilized by Williams and Clarke [12], which was in turn used to inform the Australian College of Critical Care Nurses workforce guidelines [9]. The methodology developed by Williams and Clarke has been independently acknowledged as a suitable methodology to establish specialty nursing guidelines in Australia and possibly elsewhere [32,36].

Suggested steps in establishing National workforce guidelines for Critical Care Nursing are:

1. Review all available relevant literature using the following search words: critical/intensive care, workforce/staffing, nurse/nursing.

2. Identify a set of existing guidelines that will form a template or basis upon which to start (WFCCN position statement [34] is recommended).
3. Identify a large cross-section of critical care nursing leaders from across the country who represent the following:
   - Regional interests and idiosyncrasies (i.e., state or province)
   - Subspecialty interests (e.g., pediatric, cardio-thoracic)
   - Sector interests (i.e., clinical, management, education, academia). Above all the panel members must have strong credibility and influence in the eyes of all stakeholders including clinical nurses and doctors, hospital managers, unions, government officials, etc.
4. Utilize a modified Delphi Technique [37]. Send the first draft guideline to all panel members for comment on each aspect or recommendation of the draft guideline. Use feedback to confirm the obvious areas of agreement and identify those aspects where consensus looks unlikely at this stage.
5. Develop a second draft; highlight the areas of consensus stating there is no need to change these statements. Also share the different perspectives of the group where consensus is not currently possible. This is a good time to facilitate a teleconference or face-to-face meeting (if logistically possible) to clarify consensus statements for each of the statements as best as possible.
6. Develop a third draft; this time send a survey to the panel members asking them to rate their approval/support for each statement or recommendation on a scale of 1–10 where 1 means, I do not agree at all, and 10 means I fully support the statement. Develop a mean score and range for each statement and circulate to the panel. Williams and Clarke accepted statements once they were able to get mean consensus scores above 7 out of 10 [12].
7. Facilitate a consensus forum, preferably at a conference where there will be a large number of opinion leaders and utilize the experience and "fresh eyes" of the forum to critique and comment on the document. Modify the document where good suggestions on wording, presentation, or content are made.
8. Circulate the fourth and final draft to the panel for any final comment.
9. Publish and print the document in an attractive format and font and keep it simple and easy to read. The document should have a covering note from the professional organization sponsoring the document and have it signed by an appropriate dignitary, either the chair of the panel, the president of the professional organization, or both.
10. Publish articles announcing the new guidelines in as many journals, newsletters, and websites as possible with linkages to the original authorized version of the document, preferably on the professional organizations' website. Send hard copies of cover letter and guideline to the Minister for Health, Hospital CEOs, and Directors of Nursing, interested media outlets, and any other relevant stakeholders in your country.

Be prepared to be praised, criticized, ignored, and challenged about the document! Taking a stand and setting a standard at a national level is a brave leadership action. You must be prepared to defend the standard not with emotion and defiance, but with calm, reasoned logic and evidence that is almost irrefutable… good luck!

Recommendations

The recommendations of the WFCCN: Declaration of Buenos Aires, Position Statement on the Provision of Critical Care Nursing Workforce are outlined in Table 10.2. The rec-

Table 10.2 Recommendations from the WFCCN: Declaration of Buenos Aires, Position Statement on the Provision of Critical Care Nursing Workforce. As a minimum, the critical care unit should maintain or strive to achieve the following nursing workforce requirements

1. Critically ill patients (clinically determined) require one registered nurse at all times
2. High dependency patients (clinically determined) in a critical care unit require no less than one registered nurse for two patients at all times
3. Where necessary extra registered nurses may provide additional assistance, coordination, contingency (for late admission, sick staff), education, supervision, and support to a subset of patients and nurses in a critical care unit (sometimes referred to as ACCESS nurse)
4. A critical care unit must have a dedicated head nurse (otherwise called Charge Nurse or similar title) to manage and lead the unit. This person must have a recognised postregistration critical care nursing qualification. It is also recommended the Head Nurse/Nurse in Charge have management qualifications
5. Each shift must have a designated nurse in charge to deputize for the head nurse and to ensure direction and supervision of the unit activities throughout the shift. This person must have a recognised postregistration critical care nursing qualification.
6. A critical care unit must have a dedicated nurse educator to provide education, training, and quality improvement activities for the unit nursing staff. This person (s) must have a recognized postregistration critical care nursing qualification
7. Resources must be allocated to support nursing time and costs associated with quality assurance activities, nursing and team research initiatives, education, and attendance at seminars and conferences
8. Adequate support staff within the critical care area including: administrative staff, support staff to assist with manual handling, cleaning and domestic duty staff and other personnel exist to allow nursing staff to focus on direct patient care and associated professional requirements
9. Appropriately skilled and qualified medical staff are appointed and accessible to the unit for decision making and advice at all times. A medical director is appointed to work collaboratively with the head nurse in order to provide policy/protocol, direction, and collaborative support
10. Remuneration levels for nursing staff are such that they are competitive with similar professions in the country and are scaled in such away as to reward and retain qualified, experienced, and senior critical care nurses
11. Appropriate, accessible, and functional levels of equipment and technology are available and maintained to meet the demands of the expected patient load at any given time and nursing staff are adequately trained and skilled in the application of such equipment and technology
12. Adequate occupational health and safety regulations should be in place and enforced to protect nurses from hazards of manual handling and occupational exposure
13. Organized and structured peer support and debriefing procedures are in place to ensure nursing staff support and well-being following critical incident exposure

ommendations are simple to follow and self-explanatory although may need modifying in individual countries or regions to suit local needs.

While the recommendations strongly support the provision of experienced and highly skilled critical care nurses, it is acknowledged that this is not always possible and especially in a teaching hospital environment where there is always going to be novice and inexperienced nurses in the critical care environment. Therefore, supervision of junior, inexperienced, and untrained staff in the critical care unit requires skilled assessment by the senior critical care nurse in charge. The WFCCN workforce guidelines provide for ACCESS nurses in addition to those nurses allocated to a patient. Williams and Clarke [12] describe the role of the ACCESS nurse as providing additional assistance, coordination, contingency (for late admission or sick staff), education, supervision, and support to a subset of patients and nurses in a critical care unit. Staff meal breaks, admissions of additional patients during a shift, and education and support for junior, inexperienced, and locum staff are daily issues that require the provision of additional experienced critical care nurses to ensure appropriate and continuous supervision, monitoring, and care at all times…this is within the role of the ACCESS nurse [12].

The WFCCN supports clear nurse:patient ratios that are clinically determined and applied by the critical care nurse in charge; this reflects the Australian College of Critical Care Nurses position that also describes nurse:patient ratios for critical care and high-dependency care patients [9]. A number of other nursing associations and government reports do not support nurse:patient ratios and provide more general descriptions and principles to inform staffing needs in the critical care area [10,15,38]. The provision of ratios lessens the risk of ambiguity in what is acceptable practice, whereas, if taken out of context ratios can be expensive or under representative.

A qualified critical care nurse in the context of the WFCCN position statement has undergone formal education and training in a university, teaching hospital, or similar institution of credible education and teaching reputation. While it is beyond the scope of this chapter to discuss the educational requirements of the critical care nursing workforce, WFCCN have established the Declaration of Madrid: Position Statement on the Provision of Critical Care Nursing Education [39]. Similar consensus processes are required for the development of education standards also at a national level. Again, it is recommended to utilize the WFCCN statement as a base guideline and modify according to the idiosyncrasies and sensitivities of the local area.

Conclusions

A developing body of evidence and consensus is emerging throughout the world of critical care that emphasizes the need for measurable, transparent, documented, and accountable nursing workforce and workload guidelines to ensure appropriate and safe levels of care. Furthermore, the evidence is overwhelming that major system

failings, serious patient harm, death, and litigation [40,41] may result from the absence of appropriate critical care nursing workforce standards.

The WFCCN: Declaration of Buenos Aires, Position Statement on the Provision of Critical Care Nursing Workforce attempts to provide universal guidance on the principles governing critical care nursing workforce requirements. In those countries where such formal guidelines do not exist, it is necessary for nursing organizations and leaders to work with hospital administrators, health departments, and governments to establish written standards of nursing workforce and staffing requirements to ensure an appropriate and safe level of care to the patients they serve.

Critically ill patients are but some of the most vulnerable people in our community. If we are unable to describe the level of care and safety we ought to afford this group in our community… God help the rest of us!

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Intensive and Critical Care Nursing Perspectives

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Introduction

The essential characteristic traits of a professional were first explored by Flexner [1] and others in the early 1900s. Researchers attempted to refine the traits of the "true" professions of law, medicine, and the clergy, and began comparing other groups of workers to these professions [2,3]. In 1969, Etzioni [4] labelled nursing a "semiprofession" concurrent with changes in conceptualization of the nature of professions by others [5–6]. However, contemporary opinion is that nursing has since achieved full professional status in many countries [7]. Kimball's comprehensive historical analysis identified that expertise, service, and associations were the three essences of a profession [8]. Nursing is now well recognized as a profession and intensive and critical care nursing is regarded as a subspecialty of the nursing profession.

Kimball's three tenets of a profession: expertise, service, and association make a helpful contribution to the identification of specialties within the profession of nursing. It is arguable that critical care nursing is its own profession within the broader umbrella of nursing. Critical care nursing requires advanced clinical expertise, knowledge, and cutting edge and complex services to the community. In recent years, the critical care nursing profession has organized itself into many associations throughout the world. Indeed, of the ten criteria that the International Council of Nursing (ICN) identified in 1992, as a requirement for an area of nursing to be considered a specialty, was the formation of a professional association.

Historically, critical care nursing organization (CCNO) leaders from around the world have established forums at various international critical care congresses. In particular, the need for, and value of, a stronger international network of CCNOs has

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been discussed at a series of forums that have been held during the World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM) congresses since 1985 (Table 11.1).

Table 11.1 History of formal international dialogue aimed at forming stronger international networks between critical care nurses and critical care nursing organizations (CCNOs)

1985	4th World Congress of Intensive and Critical Care, Tel Aviv. Australia critical care nurses ask to be admitted to the World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM)
1989	5th World Congress, Kyoto. Australia and USA applications are accepted by the WFSICCM. Sarah Sandford (USA) and Lorraine Ferguson (Australia) ask for a nursing position on the board
1993	6th World Congress, Madrid. CCNOs from Australia, USA, Britain and Spain are formally admitted to the WFSICCM and a Nursing member (Belinda Atkinson, England) is appointed to the board. Madrid Declaration on the Preparation of Critical Care Nurses is announced and signed. CCNOs pledge to improve international communication, collaboration and expansion
1994	American Association of Critical Care Nurses (AACN) Global Connections Conference, Toronto. CCNOs meet during this conference, share visions, and pledge to improve international communication, collaboration, and expansion
1997	7th World Congress, Ottawa. CCNOs meet during this conference, share visions and pledge to improve international communication, collaboration and expansion
2000	British Association of Critical Care Nurses Global Connections Conference, Edinburgh. Ged Williams presents results of the world CCNOs survey and outlines possibilities for a World Federation of Critical Care Nursing Organizations
2001	30 October, a meeting of 75 critical care nurse leaders from 15 countries form a meeting at the 8th World Congress on Intensive and Critical Care in Sydney, Australia to form the World Federation of Critical Care Nurses

A small number of critical care nursing organizations have attempted to use WFSICCM as a vehicle to establish a nursing network, and in 1993 WFSICCM established its first nursing position on the fifteen-member board of directors. Its intention was that this appointment would help to drive such a development. Since then, Australia (1993–2006) and the USA (1993–2001) have held long-term CCNO memberships of WFSICCM, and a small number of other CCNOs from Spain, Britain, and Canada have held short-term memberships.

Between 1999 and 2001 a group of interested critical care nursing leaders from various regions of the world formed a team to conduct the first world-wide survey of CCNOs and their activities [9]. The aims of the survey were to:

- Obtain an overview of their CCNO and its activities in their country.
- Identify the major issues and concerns for critical care nurses in their country.
- Determine their organization's interest in being part of an international communication network.

- Identify their organization's interest in supporting the establishment of an International Society of Critical Care Nursing Organizations.
- Obtain their perspective on the mission of such a society.

Based on the findings from the survey, in which there was significant support for the establishment of a world organization to represent critical care nurses, critical care nurse leaders from several countries collaborated with the intention of forming an international society of critical care nursing organizations. On October 30, 2001, at the 8th World Congress on Intensive and Critical Care held in Sydney, Australia, 75 nursing leaders from fifteen countries met to discuss and approve the Declaration of Sydney: The Constitution of the World Federation of Critical Care Nurses (WFCCN) [10]. For the first time in their history, national CCNOs and critical care nurses world-wide had a formally elected representative body, which was able to represent their perspectives and needs at an international level. In 2005, ICN admitted WFCCN into its Council as a member society.

Definition

Critical care nursing has been loosely defined as a specialty of nursing which is focused on the care and treatment of critically ill patients [11,12]. This generally encompasses nurses working in intensive care units, whether generalized units, or specialized units such as coronary care units, postanesthetic recovery rooms, emergency departments, and even those who work with air-medical and retrieval teams. WFCCN defines a critical care nurse as a person who holds a recordable or registered nursing qualification in their own country and contributes to the field of critical care nursing [10]. This definition acknowledges the fact that in many countries critical care nursing, as a specialized profession, is not well developed and may not, therefore, be associated with formal specialist qualifications.

Around the world, many critical care nurses have developed professional organizations, associations, and groups to provide support networks for the specialty and those nurses who identify with it. The more established associations are able to trace their beginnings back to the 1960s and 1970s, some 10 years or more after the establishment of intensive care units in their respective countries [13–15]. While it is assumed that many of these associations of critical care nurses have well-defined roles and functions within their country, little documented literature exists that describes these associations and their functions. In fact, in 2001, when the first world-wide survey was conducted [9], the authors were unable to locate a single reference or index of known CCNOs. Without appropriate information, it was difficult to gain a perspective of the challenges and issues commonly faced by critical care nurses.

Once formed, WFCCN developed a database of CCNOs and defined critical care nursing as: "Specialized nursing care of critically ill patients who have manifest or potential disturbances of vital organ functions. Critical care nursing means: assisting, supporting, and restoring the patient towards health, or easing the patient's pain and

preparing them for a dignified death. The aim of critical care nursing is to establish a therapeutic relationship with patients and their relatives and to empower the individuals' physical, psychological, sociological, and spiritual capabilities by preventive, curative, and rehabilitative interventions" [10].

Furthermore, in the WFCCN constitution, a CCNO is defined as: "…an association, society, or federation of critical care nurses. In countries where no such group exists, it is a separate critical care nurses section within a health professional association or a subgroup of the national nurses association which has in both cases its own constitution, regulations, and rules" [10].

Although sometimes the terms critical care and intensive care are used interchangeably, it is helpful to clarify the nomenclature. In this context, it is useful to first consider what is meant by an "intensive care unit" (ICU). For the purpose of this discussion, it is understood to mean a centralized location within a hospital environment where the sickest patients (critically ill) with severe organ failure are treated, advanced technological support is provided, and specialized staff provides the workforce. Usually, nurse to patient ratios are significantly higher than those found in general ward areas. In this context, "intensive care" is provided within an intensive care unit, and refers to the specialized interventions that are required to care for critically ill patients. By definition, the nature of this work is "intensive," and requires multiprofessional teamwork.

Critical care is an expansive term that incorporates all areas of high intensity care. While intensive care is included under this umbrella term, other acute areas such as, but not limited to, emergency departments, recovery rooms, and coronary care units are covered also. The term is very broad, and generally includes all areas of high care, where "high" can be defined as care over and above that normally provided in a general ward area. As with intensive care units, these critical care areas are usually centralized, and provide higher levels of technological support and multiprofessional expertise than that found on general wards.

Needs

Through the first world-wide study of critical care nursing in 2001 [9], and the second world-wide study in 2005 [16], it was possible to survey CCNOs and critical care nursing leaders in 23 and 51 countries respectively. The surveys enabled the perspectives and the needs of CCNOs and critical care nurses in many parts of the world to be analyzed. A third survey has commenced in 2009; however, not all data had been analyzed at the time of writing.

Based on the WFCCN surveys, Table 11.2 provides a summary of the issues of most importance to critical care nurses. The scores provided by the participants were averaged and rank ordered in each study year. Clearly, staffing levels was the most important issue in both surveys. Other important issues in both periods were working conditions, wages, access to educational programs, and development of formal practice guidelines. The one issue that changed dramatically was the issue of team-

Table 11.2 Mean and rank order responses for important issues for critical care nurses participating in the survey in 2001 and 2005 (participants were asked to score their opinion of each issue: 1 = not important, 10 = very important)

Issue	Ranking 2005	Av. Score 2005	Ranking 2001	Av. Score 2001
Staffing levels	1	8.9	1	9.24
Teamwork	2	8.9	7	8.29
Wages	3	8.6	4	8.52
Working conditions	4	8.6	2	8.86
Access to educational programs	5	8.6	3	8.76
Formal practice guidelines/ competencies	6	8.3	5	8.38
Facilities and equipment	7	8.1	12	7.24
Use of technologies	8	7.9	11	7.38
Work activities/roles	9	7.9	6	8.33
Relationships with doctors	10	7.8	9	7.76
Extended/advanced practice	11	7.7	8	7.90
Formal credentialing process	12	7.6	10	7.60
Relationships with other nursing groups	13	7.6	13	6.90
Relationships with other health care groups	14	7.5	14	6.76

work. However, it was not precisely clear what the issue was, i.e., whether teamwork in the ICU environment was poor, or whether there was a need for strong teamwork structures and behaviors, which was important and therefore valued more highly in the second survey. Others have studied and written on this topic recently [17–19] and it is likely to remain an important issue in the third survey.

Table 11.3 summarizes the main services and activities provided by national CCNOs, and participants were asked to rate the importance of each. In this question, the top four priorities did not change between the two surveys despite the diversity of responding countries and the number of responding countries. Professional representation, developing standards for education courses, provision of national conferences, and provision of practice guidelines were what critical care nurses most wanted from their CCNO.

In Table 11.4, the main services/activities provided by WFCCN and the awareness and importance of these were examined. Clearly, opinions have changed over time. In 2001, prior to the formation of WFCCN there was a strong emphasis by respondents on the formation of a website, the need for international nursing conferences, and the provision of study/education grants. Then, in 2005, the importance

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Table 11.3 Services/activities provided by National Critical Care Nursing Organizations (respondents) and importance attached to each (1 = not important, 10 = very important)

Issue	Ranking 2005	Av. Score 2005	Ranking 2001	Av. Score 2001
Professional representation	1	9.3	1	8.75
Standards for educational courses	2	9.2	3	8.67
National conferences	3	9.2	2	8.67
Practice standards/guidelines	4	8.8	4	8.40
Website	5	8.8	14	6.79
Workshops/education forums	6	8.8	5	8.29
Research grants	7	8.2	15	6.43
Local conferences	8	8.5	8	7.81
Journals	9	8.5	7	7.93
Initiating/conducting or leading research studies	10	8.4	10	7.58
Credentialing process	11	8.2	6	8.25
Training/skill acquisition course	12	8.2	11	7.42
Research grants	13	8.2	15	6.43
Study/education grants	14	7.9	12	7.00
Newsletters	15	7.3	9	7.73
Industrialization/union	16	5.8	13	7.20

and focus on the provision of guidelines was much stronger. However, all issues ranked highly. This signalled a growing need and desire for WFCCN to take a leading role in the development of international activities on behalf of critical care nurses.

Five domains of nursing commonly referred to are professional activity, clinical practice, education, research, and management; in no particular order. The issues, needs, and ambitions of CCNs may vary from individual person, hospital, country, and region; however, some of the common and well-described issues are summarized below under the five main domains of nursing.

Professional Activity

The WFCCN has synergistic relationships with regional critical care nursing organizations namely: European Federation of Critical Care Nursing Associations (EfCCNa), Federación Latinoamericana de Enfermería en Cuidado Intensivo (FLECI), and Asia-Pacific Federation of Critical Care Nurses (APFCCN). Together

Table 11.4 Services/activities provided by World Federation of Critical Care Nurses: awareness and importance attached to each (1 = not important, 10 = very important)

Issue	Ranking 2005	Av. Score 2005	Ranking 2001	Av. Score 2001
Standards for educational courses	1	8.9	4	8.74
Standards for workforce	2	8.9	4	8.74
Professional representation	3	8.7	8	8.52
Journal (through CONNECT journal)	4	8.6	7	8.43
Website (http://www.wfccn.org)		5	8.6	1 9.19
International conferences	6	8.6	2	8.90
Initiate, conduct or lead research studies	7	8.5	6	8.57
Research grants	8	8.4	NA	NA
Study/education grants	9	8.3	3	8.86

these organizations identify different activities depending on their regional priorities and capacity to respond. Where there is an identified need to cooperate on a specific issue, the federations will work together towards a single outcome, and in other situations may work independently depending on the nature of the activity.

In many countries of the world, there are no CCNOs, or the CCNO is limited in its capacity to respond to needs. In these countries CCN leaders attempt to support their CCNO and utilize the existing infrastructure of the broader nursing professional bodies. For instance in Nigeria, which is among the poorest fifty countries of the world, the National Association of Nurse Intensivists of Nigeria (NANIN) works with the Nursing and Midwifery Council of Nigeria to identify issues of shared interest and support each other in finding possible solutions to issues such as education and training, remuneration, recognition of qualifications, and workload management. Poverty and lack of privilege may be barriers to professional growth but even in countries like Nigeria, the spirit of its CCNs ensure growth and development of professional activity through NANIN despite the barriers!

Clinical

While somewhat similar, the role of CCNs in clinical practice differs considerably worldwide due to several factors: availability of technology and medical resources, intensity of medical conditions, access to education and training opportunities, and clinical practice standards.

Use of complex technology is commonplace among large academic medical centers in countries with strong economies and carries with it the need to educate and

train CCNs with regard to equipment management, associated patient assessments, related diagnostics, and methods of integrating technological demands into provision of routine nursing care.

Medical resources such as use of healthcare informatics systems, support personnel (therapists, nurse assistants, etc.), use of advance practice nursing roles such as nurse practitioners, clinical consultants and outreach/hospital liaison nurses, and availability of competent physician practitioners also contributes to clinical practice needs of CCNs [20].

The intensity of patients' medical conditions also contributes to the learning needs of CCNs worldwide. In centers providing more basic care that is primarily limited to stabilization without extensive curative therapy, learning needs are clearly directed toward measures that support these methods. While in centers that provide extensive curative and even experimental treatment, CCNs are likely to need ongoing, regularly updated information on changes in protocols and methods that are among the most complex in medical care. The limits of resources will affect the scope of practice and therefore the level of active treatment that will be made accessible to patients in ICUs. However, the limits on resources and scope of practice do not mean that the fundamental education, care, skill, and expertise of the clinical nurse need to be any different from those CCNs working in sophisticated, well-resourced ICUs. Indeed, many sophisticated ICUs in the developed world are now heavily populated with nurses (and doctors) who have received their basic and post-graduate education and training in developing and third world countries (Fig. 1)!

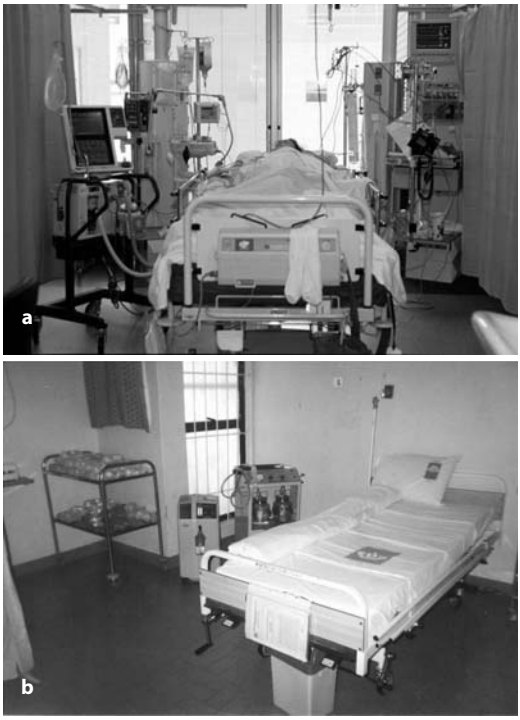

Fig. 11.1a,b (**a**) A typical ICU cubical in Melbourne, Australia, (**b**) a typical ICU cubicle in Kano, Nigeria

Education

Access to educational programs for CCNs remains an important issue for CCNs of the world (Table 11.2). Provision of educational standards, practice standards and guidelines, and educational forums are important activities that CCNs expect of CCNOs (Table 11.3), although provision of training and skill acquisition courses is not something CCNs expect of CCNOs, presumably because these are activities CCNs may see as the responsibility of employers or education institutions.

In 2005, the WFCCN developed the Declaration of Madrid: Position Statement on the Provision of Critical Care Nursing Education [21]. This document outlines the shared expectations of many critical care nursing representatives from around the world whose ambition was to establish a commonly held view on the minimum expectations of CCNs wishing to obtain a specialist qualification in the field of critical care nursing. Much evidence exists to support the notion that appropriately qualified and educated CCNs will ensure higher quality care and outcome for their patients [22].

The growth of critical care education in developing countries has shown tremendous promise. For instance in Colombia, there are currently nine graduate degree programs that lead to a qualification in critical care nursing, of which seven programs specialize in adult care and two specialize in pediatric care [23]. In Nigeria, the first ICU nursing training program was provided in 1972 as a 28-week program with 27 days of theory with the remainder practical experience [24]. In South Africa a postbasic diploma course in intensive care nursing was first offered at the Johannesburg Hospital in 1966 [25]. In many other countries CCNs are Masters- and Ph.D.-prepared practitioners in all fields of practice within the critical care subspecialty. Regrettably, in many parts of the world we simply do not know how many postbasic critical care nursing courses exist. Knowing the gap is the first step to addressing the need, and measuring the gap is a role for the WFCCN and other regional multinational CCNOs.

Research

The growing international emphasis on evidence-based practice (EBP) has created urgency in the need for CCNs to develop skills related to clinical inquiry and research. While research is best learned through formal academic education, EBP skills can be well supported within most practice settings when there is a commitment within the healthcare institution to nurturing a “culture of inquiry” among nursing staff. Resources that best support such a culture include provision of internet access directly within the nursing care unit, training of nursing personnel on methods to search electronic databases for evidence, purchase of institutional subscriptions to key electronic databases such as Cochrane and CINAHL, and provision of education to nursing personnel on critical appraisal and synthesis of research. As critical care continues to grow in complexity in the coming years, an ability to use EBP methods will be essential among CCNs.

Relatively new developments in critical care nursing research are the establishment of EBP practice guidelines informed by multinational teams of CCN experts [26–28].

Finally, a pragmatic initiative to facilitate access to current, free EBP and educational material on the internet has been established by Dr. Ruth Kleinpell on behalf of the Society of Critical Care Medicine [29]. The initiative is to discover and catalogue all known educational and EBP websites with information relevant to critical care practice on a single website so that they can be easily accessed. Initiatives such as this will make research and EBP material readily accessible to CCNs world wide…provided they have access to reliable internet, a factor that still requires more attention in the developing world.

Management

Staffing levels, teamwork, wages, and working conditions are the four most important issues identified by CCNs in Table 11.2. These are all within the scope of the managers and leaders of critical care. WFCCN has established workforce guidelines, which are covered in greater detail in chapter "Nursing Workforce Management in Intensive Care". The role of managers in the critical care environment is essential to the orderly coordination of activities of safety and quality of patient care and service delivery. The link between excellent patient care and outcome and multidisciplinary teamwork, collaboration, and management is well documented [30,31]. Furthermore, the provision of well-educated and -supported nurses at the bedside reduces harm and improves the patient's chance of survival. For these reasons WFCCN maintains a strong focus on the development of workforce and education standards and the provision of evidence-based documents to help empower managers to lobby for appropriate resources and standards of practice to support both their patients and the staff delivering care to those patients [22].

Finally, it is essential that managers can create suitable measures of workload and productivity in order to demonstrate the quality of care and performance of the team. This is not always easy, and a future goal for critical care nursing might be the establishment of universal measures of the quality of critical care nursing.

Standards

Articulating a standard of nursing professional practice and collaborative behavior is difficult in a world setting as the diversity of language, culture, religion, and expectations are varied. Nevertheless, the WFCCN has attempted to establish standards and expectations through the formation of a constitution whose philosophy is: "To assist critical care nursing associations and nurses without distinction of any kind, such as race, color, sex, language, religion, political or other opinion, national or social origins, property, birth, or other status in the pursuit of the objectives of the WFCCN" [10].

WFCCN Objectives

The WFCCN has identified ten objectives that help to focus the organization and its members on common goals and outcomes:

1. To represent critical care nurses and critical care nursing at an international level.
2. To improve the standard of care provided to critically ill patients and their families throughout the countries of the world.
3. To advance the art and science of critical care nursing in all countries throughout the world.
4. To promote cooperation, collaboration, and support for critical care nursing associations and individuals.
5. To improve the recognition of critical care nursing throughout the world.
6. To maintain and improve effective cooperation between all health professionals, institutions, agencies, and charities who have a professional interest in the care of critically ill patients.
7. To establish standards for the education, practice, and management of critical care nursing.
8. To foster and support research initiatives that advance critical care nursing and patient/family care.
9. To encourage and enhance education programs in critical care nursing throughout the world.
10. To provide conferences, written information, and continuing education for critical care nurses.

Standards of clinical practice and professional activity and behavior maybe expressed through various forms, settings, and at various levels. For instance, many hospitals and ICUs have policies and procedures to help guide individual clinicians in their tasks and procedures at the unit and hospital level. National CCNOs may have policies, procedures, and guidelines or position statements that inform the collective expectations and standards of the critical care nursing profession in their respective countries, and most western contemporary countries have developed quite sophisticated and comprehensive standards that are readily accessible through their respective websites and documents [32–35]. However, standards, position statements, and guidelines that purport to represent the opinion of a multinational region or the international community of critical care nursing are still in their infancy. The European Federation of Critical Care Nursing Associations (EfCCNa) and WFCCN have commenced such activity, with guidelines being established for workforce [36,37], education [21–38], rights of the patient [39], family presence during resuscitation [24], and sepsis [27].

It is too early to evaluate the effectiveness of such guidelines and positions statements, although it is clear from the WFCCN survey in 2005 [16] that the position statements on workforce [36] and education [21] were considered to be the most important activities provided by WFCCN at that time.

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Recommendations

While it is acknowledged that a lot of exciting activity has occurred in the last decade in terms of the formation of multinational and international critical care nursing organizations and the collaborative work and activity of many critical care nurses, it is clear there remains much work to be done, and this will never end!

Based on the views of the participants of the first two world-wide surveys and the collective experience of the authors and others, we suggest the following pursuits and activities to be important for the ongoing development of the critical care nursing world during the next decade:

- Continue to assist countries that do not have a CCNO to develop collegial networks internally and externally so that a sustainable structure is established to facilitate the development of clinical professional practice standards in critical care.
- Continue to strengthen the regional federations of Europe, Latin-America, Asia and beyond.
- Stronger and well-established CCNOs of the world need to take responsibility for sharing their resources, interest, and expertise with critical care nursing groups in not-so-developed countries especially in Eastern Europe, Asia and the subcontinent, Africa, and Arabic countries.
- Continue to identify those areas of practice where world-wide guidelines and position statements may be helpful and bring together leaders in the field to help establish strong evidence-based guidelines that are freely accessible on the internet.
- Find ways of making educational programs and other learning opportunities freely accessible to all, and especially those in developing countries.

Conclusions

The formation of multinational federations of critical care nursing organizations and extensive access to the internet has enabled greater communication, collaboration, and cooperation among critical care nursing organizations and leaders of the world. Furthermore, it is now also possible for these organizations to provide a broader perspective and representation of the issues, opinions, and needs of the critical care nursing world as we have attempted in this chapter.

The ambition for further growth in activity to occur at an international level is only limited by the extent to which our collective creativity and commitment to such activity will limit us and our representative organizations.

We have seen many great initiatives in professional activity, clinical practice, education, research, and management in the world of critical care nursing this last decade or more. From the perspective of critical care nursing, the world is our oyster and we have much more to look forward to in the coming decades.

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Section V
Central Nervous System, Circulation and Kidney

Central Nervous System Monitoring

12

F.M.B. Maciel

Introduction

The primary objective of intensive care is to prevent and treat secondary brain injury (SBI) caused by hypotension, hypoxia, or hyperthermia. We will focus this chapter on traumatic brain injury (TBI) and our objective will be the treatment and prevention of SBI using a neuroprotective strategy to maintain cerebral perfusion in order to meet the brain's oxygen and metabolic demands. Elevated intracranial pressure (ICP) is an important cause of SBI and associated with very poor outcome after TBI. Elevated ICP can be related to brain edema, vascular engorgement, cerebral contusion, or intracranial mass lesions. The prevention and control of raised ICP and the maintenance of cerebral perfusion pressure (CPP) are essential therapeutic goals after TBI. ICP monitoring has developed an essential role in the treatment of TBI, despite the incredible absence of class-1 studies and its use is only recommended by international consensus guidance [1].

ICP Monitoring

ICP is a very complex variable. Recent consensus (Brain Trauma Foundation) indication for ICP monitoring in TBI include: patients in coma (Glasgow Coma Scale score of 8 or less) with an abnormal head CT scan; patient in coma with a normal head CT scan but at least two other risk factors for elevated ICP (age over 40 years, pathologic motor posturing, systolic BP under 90 mmHg); and in other head injured patients at the physician's discretion [2].

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There is around a 60% chance of raised ICP in patients with these risk factors. Although there are again no class-1 studies, there is some clinical evidence supporting the use of ICP to assess prognosis after severe TBI, to guide therapeutic interventions, and to detect earlier intracranial mass lesions. ICP monitoring is accepted as a low-risk procedure, a decisive clinical decision-making tool, and a high-yield and cost effective intervention during TBI management.

Techniques

ICP cannot be precisely estimated from any specific clinical feature or CT finding and must be actually measured [2]. Different methods of ICP monitoring have been described (Table 12.1) but two methods are commonly used at the bedsideintraventricular catheters and intraparenchymal catheter-tip micro-transducer systems. An intraventricular catheter, connected to a standard pressure transducer via a fluid filled catheter is the "gold standard" method for monitoring ICP. Ventricular catheters measure global ICP and have the additional advantages of allowing periodic external calibration, administration of drugs, and therapeutic drainage of cerebrospinal fluid (CSF). However, installation may be difficult and their use is complicated by an infection rate up to 11% [4]. Microtransducer-tipped ICP monitors can be located in the brain parenchyma or subdural space, either via a cranial access device (skull bolt) or during a neurosurgical procedure. They are almost as accurate as ventricular catheters and are reliable and easy to use at the bedside [1]. Their infection rates are much lower but the measured pressure may not be representative of true CSF pressure, due to the intraparenchymal pressure gradients that are very common after TBI [1]. In vivo calibration is not possible but the zeroing during surgical installation lies within a clinically acceptable range and is usually as low as 1 mmHg after 5 days of continuous use [1].

Table 12.1 Intracranial pressure monitoring catheters. Modified from [1]

Method	Advantages	Disadvantages
Intraventricular	• Gold standard • Measures global values • Allows drainage of CSF • In vivo calibration	• Insertion may be difficult • Most invasive method • Risk of hematoma
Microtransducer system	• Intraparenchymal/ subdural placement • Low complication risk • Low infection risk	• Small zero drift over time • No in vivo calibration • Measures local pressure
Epidural catheter	• Easy to insert • No penetration of dura	• Limited accuracy • Rarely used

CSF, Cerebral spinal fluid

Absence of Consensus

There is no general consensus on the benefits of ICP monitoring and intense variability in its application. There are also important differences between different centers regarding treatment modalities guided by ICP levels. In the USA, for instance, ICP monitors were placed in only 58% of patients who fulfilled established criteria for monitoring, and therapies to reduce ICP were routinely applied in those patients in whom ICP was not monitored [5]. In a survey carried out by the European Brain Injury Consortium, ICP monitoring was undertaken in only 37% of eligible patients [6] and, in a Canadian study of severe TBI, only 20% of neurosurgeons believed that outcome was affected by ICP monitoring [6]. The Latin American Brain Injury Consortium (LABIC) is now conducting a randomized controlled clinical trial (RCCT) comparing TBI patients with and without ICP monitoring.

Treatment of Intracranial Hypertension

High ICP and low CPP result in cerebral ischemia after TBI and are associated with increased mortality and worse outcome in survivors [7]. Consensus guidance recommends that ICP above 20–25 mmHg should be aggressively treated using a multimodal approach [3].

Sedation and Analgesia

Sedation and analgesia are two crucial components of TBI management [8]. They minimize pain, anxiety and agitation, reduce cerebral metabolic rate, and facilitate mechanical ventilation. Propofol is a widely used sedative agent because it reduces ICP, has profound cerebral metabolic suppressive effects, allows easy control of sedation levels and ICP, and permits rapid wake-up [8]. Other combinations of Midazolam, Fentanyl, and morphine are also very popular.

Hyperventilation

$PaCO_2$ is a major determinant of cerebral vessel diameter, with its reduction causing cerebral vasoconstriction and therefore a reduction in cerebral blood volume and ICP. Although it has been widely used in the treatment of elevated ICP, it is thought that it can worsen regional ischemia, particularly in the first 24 h after TBI. The routine application of hyperventilation is discouraged and a $PaCO_2$ target of 30–35 mmHg should be used in the first instance. Hyperventilation to lower levels should always be carried out in association with cerebral oxygenation monitoring to avoid cerebral ischemia. Acute hyperventilation is relatively safe only for short-term use (<30 min)

and is effective in controlling severely raised ICP while a neurosurgery procedure is prepared. It can also be used in threatened or actual brain herniation.

Hyperosmolar Therapy

Mannitol in bolus (0.5 g/kg) effectively treats elevated ICP and improves outcome, although it has never been subject to an RCCT against placebo [9]. It has at least two mechanisms of action: its plasma-expanding effects causes an increase in cerebral microcirculatory flow and is responsible for the rapid onset of action, and its osmotic effect reduces cerebral edema by drawing water across the blood–brain barrier into the vascular space. Treatment driven by ICP increase is much more effective than treatment oriented by clinical signs [9]. Repeated administration could result in high osmolality (>320 mOsm/l), renal, and neurologic complications.

Hypertonic saline is very effective, even better than mannitol, and its actions are not related just to the hyperosmotic effects, but also to hemodynamic, vasoregulatory, endothelial, immunological, and neurochemical actions [10]. It is efficient in controlling ICP resistant to mannitol and is associated with fewer side effects. However, there are no large RCCTs comparing mannitol and hypertonic saline. Furthermore, there are many concentrations available (1.7–29.2%) and the optimal concentration to lower elevated ICP has not been defined [11]. Based on our own data, we suggest a 3 ml/kg loading bolus in a 7.5% concentration.

Moderate Hypothermia

Moderate hypothermia (33–35°C) has efficient neuroprotective effects in animal studies but human trials have been disappointing, mainly because of infection. We must control this morbidity, which is not that simple, before using it again in humans. In addition, high temperatures are associated with worse outcomes after TBI and are the most important cause of secondary brain injury. Core temperature and cerebral temperature should be continuously monitored and pyrexia must be prevented and aggressively treated.

Barbiturates

Barbiturates lower ICP by many mechanisms and, although there is no good evidence that they improve outcome after TBI [12], there has been a resurgence of interest in the use of high-dose barbiturate therapy for the treatment of refractory intracranial pressure [13]. Hypotension is a frequent complication of treatment, and drug accumulation leads to delayed recovery and difficulties in rapid clinical assessment when the drug is discontinued. Continuous EEG monitoring can be used to titrate barbiturate infusion and minimize side effects.

Neurosurgical Procedures

The removal of an expanding intracranial mass lesion is the goal of neurosurgical treatment after TBI. An external ventricular catheter allows drainage of CSF and, because intracranial compliance is reduced, removal of even small CSF volumes can result in a dramatic decrease in ICP. Decompressive craniectomy is an extensive procedure where a large area of the skull vault is removed, and the dura is opened wide to allow brain expansion, with a consequent ICP reduction. There is divided opinion on the relative benefits and risks of the operation [14]. Our group strongly recommends this method, but it must be performed in a small window of time (<8 h after TBI) and the duraplasty must be large and wide to be effective. This controversial issue is currently being addressed by an RCCT—the Rescue ICP study (www.rescue-icp.com).

Controversies

Like all difficult cases and diseases this issue has many controversies and we will address each one.

What is the Target ICP?

Although it is very well recognized that raised ICP correlates with higher risk of mortality and morbidity, not all patients with intracranial hypertension have poor outcome [15]. There is therefore a fundamental dilemma about which patients should be treated and at what ICP level. Furthermore, recent evidence suggests that the duration of intracranial hypertension and its fast response to treatment could be better predictors of neurological outcome than isolated and absolute ICP values [16]. It has also recently been demonstrated that brain resuscitation after TBI based exclusively on control of ICP levels and CPP does not prevent cerebral hypoxia in more than 20% of patients [17]. This is unsurprising because monitoring of ICP and CPP does not tell the whole story. They are global measurements and sometimes a small but very important cerebral region is suffering very much without global modifications. It is impossible to know in an individual patient whether the targeted ICP or CPP is enough to allow the brain's metabolic demands to be met at a particular moment in time [1]. There is preliminary evidence that therapy directed towards maintenance of brain tissue oxygenation as well as ICP and CPP is associated with reduced mortality after TBI [18].

Does ICP Monitoring and Management Improve Outcome?

In a retrospective study, an "aggressive" management protocol was associated with decreased risk of mortality and shorter length of hospital stay, although there were no differences in functional status in survivors after discharge [5]. Another large retrospective study also concluded that ICP monitoring was associated with significantly decreased mortality [18] but two surveys [19, 20] and one prospective study [21] did not show benefits from ICP monitoring. In general, all studies demonstrated that the use of ICP increased intensity of treatment without clear evidence of improvement in outcome [1].

Complications of Treatment

Conventional approaches to the management of TBI have concentrated on a reduction in ICP to prevent secondary cerebral ischemic injury, but there has been a shift in emphasis from primary control of ICP to a multifaceted approach of maintenance of CPP >70 mmHg and brain protection [1]. The Brain Trauma Foundation now recommends that the CPP target after severe TBI should lie between 50–70 mmHg [3] instead of the previous suggested value >70 mmHg. The previous aggressive attempts to maintain CPP >70 with volume overload and vasopressors caused a fivefold increase in the occurrence of acute lung injury.

Multimodal Monitoring

In addition to the evidence that the control of ICP and CPP may improve outcome after severe TBI, it is also possible that targeting treatment only towards changes in these two variables might be inappropriate because, when changes do occur in these measurements, irreversible ischemic brain damage may already have occurred [1]. So, besides the pressures, it is also necessary to monitor the adequacy of cerebral perfusion, such as measurements of cerebral oxygenation (jugular venous oximetry and brain tissue oxygen tension) and metabolic status (cerebral microdialysis). Monitoring of several variables simultaneously, the multimodal monitoring (MM), allows cross validation between monitors, artifact rejection, and greater confidence in making the right clinical decision. Developments of MM have allowed a movement away from rigid physiological target setting after TBI toward an individually tailored, patient-specific approach. This new vision provides early warning of impending brain ischemia, prevents secondary brain injury, and guides targeted therapy.

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Definition, Monitoring, and Management of Shock States

13

J.-L. Vincent

Introduction

Circulatory shock is the clinical syndrome corresponding to acute circulatory failure, and can arise from a number of disease processes. The key feature of all forms of circulatory shock is an inability for tissues and cells to get enough oxygen in relation to their oxygen needs, ultimately resulting in cell death. Circulatory shock thus represents a critical condition where rapid and effective treatment can make the difference between life and death. In this chapter, we will briefly review the definition and pathophysiological classification of shock, principles of monitoring in patients with shock, and general management strategies.

Definition and Characteristics

Circulatory shock is essentially defined as a failure of the circulatory system to maintain adequate blood flow. As a result, delivery of oxygen to the tissues is impaired and the risk is of tissue ischemia leading to cellular dysfunction and organ failure. Classically, circulatory shock has been divided into four key types – hypovolemic, cardiogenic, obstructive, and distributive – according to its pathophysiological features [1]. However, although this provides a useful means of characterizing shock, many patients with shock will actually present aspects of several of the types of shock simultaneously.

Hypovolemic shock is the most common form of circulatory shock seen in surgical and trauma patients. Hypovolemic shock occurs following internal or external fluid losses and results in a depleted intravascular volume. The most obvious cause

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of fluid loss is acute hemorrhage, but severe vomiting or diarrhea, particularly in children and the elderly, can also be associated with hypovolemic shock. Patients with hypovolemic shock typically have a low cardiac output (due to reduced venous return), associated with decreased cardiac filling pressures and increased systemic vascular resistance (SVR).

Cardiogenic shock is the result of failure of the cardiac pump and is associated with particularly high mortality rates. Although most commonly the result of acute myocardial infarction with loss of large amounts of functioning myocardium, other causes include severe cardiac valvular disease, end-stage cardiomyopathy, and severe cardiac arrhythmia. Patients with cardiogenic shock typically have a low cardiac output, elevated cardiac filling pressures, and a high SVR.

Obstructive shock is the result of an obstruction to normal circulatory flow. The most common causes are massive pulmonary embolism, severe aortic coarctation, severe aortic stenosis, and cardiac tamponade. Patients with obstructive shock typically have a low cardiac output and high SVR.

Distributive shock is the most complex type of shock and is associated with an abnormal or uneven distribution of blood flow. The most common cause of distributive shock is sepsis, but other causes include anaphylactic shock and acute adrenal insufficiency. The patient with distributive shock typically has a normal or high cardiac output, reduced SVR (as vascular tone is reduced), and reduced cardiac filling pressures.

Monitoring in Patients with Shock

Monitoring of the patient with shock essentially involves measurement of global hemodynamic and oxygenation variables. Although shock is associated with impaired microcirculatory perfusion, techniques to monitor regional flow and oxygenation remain limited, although this is an area of keen ongoing study.

A large range of hemodynamic monitoring techniques is available and the choice for each patient will depend on the severity of the shock and the specific etiology. Electrocardiogram, blood pressure, and heart rate are the minimal routine parameters that must be monitored continuously in all patients with shock. Blood lactate levels provide a global indication of tissue hypoxia and should also be monitored.

Increasingly we are being encouraged to monitor our patients noninvasively, but in complex cases, invasive monitoring is still needed. Importantly, whichever technique or combination of techniques is used, hemodynamic monitoring can only be effective when the data it supplies are correctly interpreted and applied to the individual patient.

Non- (or Less-) Invasive Hemodynamic Monitoring

Concerns have been raised about the benefits, or lack thereof, of invasive hemodynamic monitoring systems, perhaps particularly those related to the pulmonary artery

catheter (PAC) [2], and considerable research has been conducted into finding and developing noninvasive alternatives.

Echocardiography

Echocardiography is widely used to evaluate the etiology of cardiac dysfunction, but can also be used to monitor cardiac output and ventricular volumes and to guide fluid and vasoactive drug therapy, especially with newer portable models. Various hemodynamic variables can be estimated using different echocardiography techniques, including cardiac output, pulmonary artery pressure, pulmonary artery occlusion pressure (PAOP), left atrial pressure, pulmonary vascular resistance, and transvalvular pressures [3]. However, echocardiography requires considerable operator training and skill and studies have demonstrated inconsistent results in terms of correlation with PAC thermodilution cardiac output [4]. Moreover, echocardiography can only provide intermittent, and not continuous, monitoring.

Bioimpedance

This noninvasive technique calculates cardiac output by measuring variations in impedance to flow of a high-frequency, low-magnitude alternating current across the thorax or the whole body. Bioimpedance can be unreliable in patients with pronounced aortic disease, significant edema or pleural effusion, increased positive end-expiratory pressure, or very high or small body weight [5]. Movement artifacts can also be problematic. While some studies have shown fair-to-moderate agreement between bioimpedance and thermodilution-derived cardiac output, others have not and further study is required before this experimental technique can be more widely recommended.

Partial CO_2 Rebreathing

In this technique, cardiac output is estimated by assessing changes in carbon dioxide (CO_2) elimination and end-tidal CO_2 in response to a brief re-breathing period. This technique is unreliable in patients with respiratory failure, and again, while several studies have reported good agreement between the partial CO_2 rebreathing technique and thermodilution cardiac output, others have not.

Invasive Hemodynamic Monitoring

Central Venous Line

Central venous lines are often inserted in critically ill patients as they provide access to the central venous circulation and can therefore aid in the delivery of fluids and

drugs. However, central venous lines can also be used to monitor the central venous pressure (CVP), which provides a measure of circulatory filling and cardiac preload, and central venous oxygen saturation ($ScvO_2$), which provides an indication of the adequacy of oxygen transport.

The important study by Rivers, et al. demonstrated improved outcomes in patients with sepsis managed by early goal-directed therapy in which one of the targets was an $ScvO_2$ >70% [6]. This study, combined with increased fears related to the use of PAC, led to increased interest in $ScvO_2$ monitoring. Several studies have demonstrated a good correlation between $ScvO_2$ and SvO_2, measured with a PAC, particularly when changes over time are considered [7,8]; if a PAC is not required for other reasons, $ScvO_2$ is, therefore, probably an adequate indicator of the adequacy of tissue oxygenation.

The central venous line may also be used to measure cardiac output if an arterial line is also sited. The pulse contour cardiac output (PiCCO) system monitors temperature changes in the arterial system after injection of a cold saline bolus intravenously and calculates cardiac output from analysis of the thermodilution curve. The lithium dilution cardiac output (LiDCOplus) calculates cardiac output from a concentration-time curve of the arterial lithium concentration after a small intravenous bolus injection of lithium. Other parameters can also be estimated, including pulse pressure variation and stroke volume variation, which can indicate fluid responsiveness. The cardiac output measured using these techniques has been validated against standard PAC thermodilution cardiac output, and they may be of use in patients who do not require a PAC for other reasons.

Pulmonary Artery Catheter (PAC)

The PAC has an inflatable balloon at its tip that allows it to move with the blood by flotation. Introduced intravenously, usually via the subclavian or internal jugular veins, the PAC progresses through the right atrium and ventricle to the pulmonary artery. The PAC was initially developed to measure the PAOP, with the balloon briefly inflated and carried by the flow of blood until it wedges in a branch of the pulmonary artery, occluding blood flow distal to this point. The pressure measured at this time thus represents the pressure that exists beyond the pulmonary capillaries, i.e., the pressure present in the left atrium which, in the absence of any abnormality of the mitral valve, is itself equal to the pressure in the left ventricle, thus providing an indication of left ventricular preload. The PAC can also provide measurement of right atrial pressure, right ventricular pressure, and pulmonary artery pressures, and when equipped with a thermistor can be used to calculate cardiac output by thermodilution. When equipped with several thermistors, almost continuous measurement of cardiac output can be obtained. As venous blood from all parts of the body is collected and mixed in the right heart chambers before passing through the pulmonary capillaries, the PAC can also be used to measure the SvO_2.

There has been considerable debate in recent years over the benefits and harms of PAC insertion in ICU patients. In a randomized controlled trial of patients with

severe symptomatic and recurrent heart failure, management guided by PAC-derived data was not superior to management guided by clinical assessment alone [9]. Several meta-analyses have similarly reported no global benefit of pulmonary artery catheterization in critically ill patients [2,10]. However, in patients who are hemodynamically unstable and in complex patients, PAC-derived data can provide a more complete and accurate evaluation of hemodynamic status and be of value in guiding therapy. Importantly, for PAC-derived data to be of use, physicians must be trained in its correct measurement, correct interpretation, and correct application [11].

Monitoring the Microcirculation

Monitoring global hemodynamic and oxygen-derived variables provides important information about global recovery, but little information about the state of local perfusion, which can remain impaired even after global parameters have apparently returned to normal [12]. Various techniques have been used to monitor changes in regional circulation and oxygenation during circulatory shock, but none has yet gained widespread acceptance in clinical practice. The gut is particularly sensitive to reductions in blood flow and has been a key focus for such techniques, notably with gastric tonometry, but the need for interruption of enteral feeding and concomitant use of H2-blockers with tonometry still limit its practical application in the ICU. Moreover, therapy guided by gastric intramucosal pH (pHi) was not shown to improve outcomes [13]. Sublingual capnometry and near-infrared spectroscopy are other indirect means of monitoring the microcirculation that have been investigated.

Direct techniques of visualizing the microcirculation have also been developed, including orthogonal polarization spectral (OPS) imaging and sidestream dark field (SDF) imaging. In addition, semiquantitative scores have been created to analyze the images seen with these techniques [14]. Using OPS imaging, De Backer, et al. reported frequent microvascular blood flow alterations in patients with cardiogenic shock and severe heart failure, which were more severe in patients who died [15]. Sakr, et al. reported that persistent microcirculatory changes were associated with organ failure and death in patients with septic shock [16]. Using the same technique, these authors have also reported the effects of various therapeutic agents, including blood transfusion, hydrocortisone, and drotrecogin alfa (activated) on the microcirculatory changes [17–19].

Management of Shock

There are two key factors to the management of any patient with shock: (1) correction of the underlying cause and (2) resuscitation to restore perfusion and oxygen balance.

Correction of the Cause

Clearly if the underlying cause is not corrected, resuscitation is unlikely to be successful. Detailed analysis of how to correct the cause of all the many possible causes of shock is beyond the remit of this chapter, but in general terms, in patients with hypovolemic shock due to hemorrhage, bleeding must be stopped. In patients with cardiogenic shock due to myocardial infarction, thrombolytic agents or percutaneous coronary intervention (PCI) are first-line strategies. In patients with obstructive shock due to tamponade, pericardial fluid should be drained, and in pulmonary embolus, thrombolysis or surgery may be used to remove the embolus. In septic shock, antibiotics must be administered early and any source of infection should be removed.

Resuscitation

Resuscitation should be based on the Ventilate, Infuse, Pump (VIP) rule developed by Weil and Shubin many years ago [20]:

Ventilate: As oxygen supply to the tissues is decreased during circulatory shock, oxygen should be given routinely to all patients with shock until blood gas results are available. Artificial mechanical ventilatory support should be started in any patient in whom mask ventilation is unlikely to be adequate.

Infuse: Fluid therapy aims to improve microvascular blood flow by increasing plasma volume, and increasing cardiac output by the Frank-Starling effect. The choice of fluid is probably less important than ensuring that adequate fluids are received and combinations of crystalloid and colloid are widely used in practice. Importantly, too much fluid can cause pulmonary or peripheral edema and a fluid challenge technique is the best method of determining a patient's ongoing need for fluids [21] (Table 13.1). Blood transfusion may be necessary, but recent studies support a more conservative approach to transfusion than in the past.

Pump: Vasopressors are usually required to restore arterial pressure in patients with shock and the choice of vasopressor may vary according to the underlying cause of the shock. For example, epinephrine is the drug of choice in anaphylactic shock and is also used in cardiac arrest, but due to its potentially detrimental effects on the regional circulation may not be the best choice in other types of shock. Dopamine and norepinephrine are the two vasopressor agents most commonly used in the treatment of shock and there are no consistent data suggesting that one is better than the other. Both drugs have potentially beneficial and detrimental effects and until further data are available comparing these two agents, both are recommended as first-line agents.

Inotropic agents are also often indicated in the presence of reduced myocardial contractility and dobutamine has become the agent of choice. Importantly, dobutamine should not routinely be used to increase DO_2 to supranormal levels as was popular in the late 1980s, but should be titrated on an individual basis to achieve acceptable oxygenation parameters.

Table 13.1 The four components of the fluid challenge [21]

1.	The type of fluid: The type of fluid that should be administered remains a matter of debate. No studies clearly demonstrate a benefit of one type over another so that the choice is largely based on availability and personal preference
2.	The rate of fluid administration: How much fluid is to be administered over how long a period should be defined before the fluid challenge, e.g., 500–1,000 mL of crystalloids or 300–500 mL of colloids over 30 min
3.	The target: The goal of fluid resuscitation may vary depending on the process underlying the need for a fluid challenge. Most commonly, the target will be to restore an adequate mean arterial pressure, but other targets could be restoration of urine output, or resolution of tachycardia
4.	The safety limits: Safety limits must be set to avoid potential complications of excess fluid administration, such as pulmonary edema. In practice, predefined values of the pulmonary artery occlusion pressure or the central venous pressure are used as safety limits

Other vasoactive drugs that may have a role in some patients with shock include vasopressin analogues, phosphodiesterase inhibitors, levosimendan, sodium nitroprusside, and nitrates.

Recommendations and Conclusions

Intensive care medicine is a specialty based on relatively little randomized controlled evidence and there are many remaining questions regarding the management of patients with acute circulatory shock. For example, what type of fluid should be given and how much? Which vasopressor agent is best? When should dobutamine be started and at what dose? Many studies are ongoing to try and provide answers to some of these questions. However, some general recommendations can still be made. Hemodynamic monitoring and appropriate therapy must be initiated early. The precise nature of the monitoring will depend on the severity and specific type of the shock. Noninvasive monitoring can provide information on a variety of hemodynamic parameters including blood pressure, heart rate, cardiac output, PAOP, right atrial pressure, and pulmonary artery pressures. Insertion of an arterial line and a central line are frequently necessary in patients with circulatory shock and can be used to assess CVP and $ScvO_2$. In patients with continuing hemodynamic instability who fail to respond to standard therapy, insertion of a PAC can provide additional, semicontinuous information on filling pressures and SvO_2. Hemodynamic support must be titrated to individual patients according to repeated clinical evaluation and global parameters of hemodynamic and oxygenation status. New techniques to monitor the microcirculation will become more widespread in the near future and will help guide resuscitation and ongoing therapy.

13

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Plasma Volume Expansion: The Current Controversy

14

C. Hartog, K. Reinhart

Introduction

Although rapid and adequate administration of fluid is largely accepted as a mainstay of resuscitation in the critically ill patient, there is still an ongoing debate on the merits of colloids against crystalloids as first line plasma expanders. The underlying biologic rationale calls for rapid restoration of fluid losses to maintain circulating blood volume and organ perfusion.

The main arguments in favor of colloids are that they restore hemodynamic parameters faster and with less volume load than crystalloids, remain in the intravascular space longer, and lead to less pulmonary and tissue edema. An increased volume load or positive fluid balance may favor tissue edema and decrease survival. However, recent studies in patients with capillary leak syndrome have shown that extravascular lung water or pulmonary SOFA score were not influenced by type of colloid or crystalloid fluid administered [1,2]. Moreover, colloids have beneficial effects on microcirculation and rheology, and exert potential anti-inflammatory effects. In comparison to albumin, synthetic colloids are less costly.

Crystalloid supporters argue that crystalloids are safe, do not interfere with coagulation beyond the effect of hemodilution, are not taken up and stored in the body, and are inexpensive to use.

Until recently, available information was based on comparison of fluids in terms of their physiological effect in small, under-powered studies with short observation periods. Meta-analyses based on these studies have consistently confirmed that crystalloids and colloids are equally effective plasma expanders [3]. The choice of an ideal plasma volume expander is often founded on personal belief as well as special-

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ty and location of practice, and use of these compounds varies considerably throughout the world, with starches predominating in Europe, particularly Germany and the Netherlands as well as in Canada, while albumin is preferred in the USA and Australia. Gelatin is favored more in the UK. In the USA, by request of the FDA gelatin was removed from the market due to coagulatory side effects, whereas tetrastarch (HES 130/0.4) was recently introduced to the market [4].

In the meanwhile, however, clinical trials with suitable design and power were undertaken to study the effect of crystalloids or colloids in critically ill patients and the results provide new insights, especially on the safety of these compounds in these patients.

Albumin

Albumin is a natural plasma protein which contributes strongly towards plasma oncotic pressure. Albumin has an excellent long-term safety record and serious adverse events reported from its use are rare [5]. A highly controversial meta-analysis which focused on albumin alone found an increased mortality risk in critically ill patients [6] and led to a steep decline in use of albumin. However, this was neither confirmed by subsequent meta-analyses nor randomized controlled trials. The large interventional Saline versus Albumin Fluid Evaluation (SAFE) study was the first adequately designed study to investigate the outcome of albumin administration in critically ill patients [7]. Nearly 7,000 patients were randomized to receive either 4% iso-osmotic albumin or normal saline for resuscitation according to clinical status and response to treatment. In addition, patients received maintenance fluids, specific replacement fluids, and enteral or parenteral nutrition and blood products as necessary. Patients in the two groups received similar volumes of non-study fluid during the first 4 days except for the albumin group, which received 71.0 ml more of packed red cells. All outcomes in both groups were comparable, in particular the lengths of stay, number of organ failures, duration of mechanical ventilation, or 28-day all-cause mortality [20.9% vs. 21.1%, the relative risk of death being 0.99; 95% confidence interval (CI), 0.91–1.09; $p = 0.87$].

The relative risk of death tended to be reduced in a subgroup of 603 patients with severe sepsis after resuscitation with albumin (30.7%) in comparison to saline (35.3%, $p = 0.06$ by the test for a common relative risk).

In a subgroup of patients with trauma, however, the relative risk of death during 28 days was higher in the albumin group (N = 1,186, 13.6% vs. 10.0%, 95% CI 0.99–1.86, $p = 0.06$). This was due to the greater number of patients with associated brain injury who died after random assignment to albumin as opposed to saline. A follow-up study of the enrolled patients with severe brain injury confirmed a significantly higher mortality at 24 months after treatment with albumin (N = 460, 33.2% vs. 20.4%, RR 1.88, 95% CI, 1.31–2.70; $p < 0.001$) [8].

In summary, 4% iso-osmotic albumin is safe to use in the intensive care unit (ICU), except in patients with traumatic brain injury, and may have some potential

benefit in patients with severe sepsis. Further trials are needed to determine the relevance of this observation.

Hydroxyethyl Starch

Hydroxyethyl starch (HES) is the most widely used synthetic colloid and has been on the market for many decades. Previous meta-analyses concluded that HES does not improve clinical outcome compared to either other colloids or crystalloids [3,9]. Only few clinical studies in ICU patients have focused on patient-related outcome measures, and most of them were carried out only recently [1,2,10–13]. These studies compared fluid therapy with HES against crystalloid and confirmed that HES administration does not confer a clinical benefit. Moreover, they provide evidence that HES administration in ICU patients carries the risk of severe adverse effects and shows dose-related toxicity with increased long-term mortality. Meanwhile, the use of HES in critically ill patients is highly controversial [14,15].

The recent Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis study (VISEP) was undertaken to test the hypothesis that HES resuscitation would lead to a better outcome in patients with severe sepsis [2]. This prospective multicenter study randomized 537 patients to either 10% HES 200/0.5 or modified Ringer's lactate to achieve a central venous pressure (CVP) >8 mmHg; in addition, patients received maintenance fluids, enteral or parenteral nutrition, and blood products. Twenty-eight-day mortality did not differ between the HES and the crystalloid group (26.7% vs. 24.1%, $p = 0.48$) but 90-day mortality tended to be higher in the HES group (41.0% vs. 33.9%, $p = 0.09$). Further analyses revealed that this was due to a substantial subgroup of patients (N = 100) who had received high doses of HES on at least 1 day (defined as >22 ml/kg body weight/day, 20 ml/kg/day being the dose limit recommended by the manufacturer). These patients also had received a cumulative dose of 136.0 ml/kg bodyweight and had an excessively high mortality rate of 57.9%, compared to the lower dose group with a median cumulative dose of 48.3 ml HES/kg and a mortality rate of 30.9%, $p < 0.001$.

Wills et al. conducted a single center, randomized, double-blind comparison of Ringer's lactate, 6% dextran 70, and 6% HES 200/0.5 for emergency resuscitation of children with Dengue shock syndrome stratified according to pulse pressure. The primary outcome measure was requirement for rescue colloid which was similar across treatment groups, the relative risk being 1.08 (95% CI 0.66–1.17; $p = 0.38$) for Ringer's compared with either colloid solution [11].

Hypervolemic hemodilution is a widely accepted therapy in patients with acute ischemia of the brain. In order to test its efficacy, a recent double-blind, placebo-controlled study randomized 200 patients within 6 h of a first ischemic stroke localized in the middle cerebral artery territory to 10% HES 200/0.5 or Ringer's lactate over a study period of 5 days. Primary outcome was clinical improvement within 7 days as measured by the Graded Neurologic Scale. An interim analysis showed that neurological recovery was similar between the groups at 7 days and 3 months and the study

was terminated early for futility [13]. The total dose of HES used was 2,500 ml within 5 days, which amounts to approximately 33 ml/kg cumulative dose in a 75 kg adult. Two subsequent small studies, which were undertaken with 10% and 6% HES 130/0.4 also failed to show a neurological outcome benefit over crystalloid [16,17].

Renal Impairment

There is now considerable evidence that HES can impair renal function in ICU patients, ranging from acute renal failure in prospective multicenter studies in septic patients [2,10] to chronic nephrotoxicity with secondary renal failure in liver transplant patients as long as 10 years after HES administration [18]. In patients with severe sepsis, administration of 6% HES 200/0.62 compared to 3% gelatin resulted in increased occurrence of renal impairment, defined as a twofold increase in serum creatinine from baseline or need for renal replacement therapy (N = 129; 42% vs. 23%, $p = 0.028$). The mean cumulative dose of HES was 31 ml/kg [10]. In the VISEP study, 10% HES 200/0.5 recipients had a higher risk of acute renal failure (34.9% vs. 22.8%, $p = 0.002$) and twofold days on renal replacement therapy (650 of 3,554 vs. 321 of 3,471 total days, or 18.3% vs. 9.2%). Renal impairment correlated with the cumulative dose of HES, but not of Ringer's lactate. Importantly, patients who always received HES doses below the manufacturer's daily dose limit still had a higher risk of renal failure than patients receiving crystalloid ($p = 0.04$) [2].

Safety of HES in critically ill patients has never yet been proven in adequately designed clinical studies. Studies called upon to rule out negative effects of HES solutions on renal function are flawed by inadequate comparators, e.g., other synthetic colloids like different HES solutions or gelatin, too-short observation periods, and inadequate endpoints for renal dysfunction [4, 19]. With observation periods of 5 days or less and creatinine serum levels as marker of renal dysfunction, neither the Schortgen [10] nor the VISEP study [2] would have revealed the higher incidence of renal failure after HES administration.

Similarly, findings from a recent European multicenter study which claimed that HES was not associated with increased renal replacement therapy are inconclusive because the study was purely observational and not designed to test the safety of HES. Patients received other colloid fluids and HES use was reported in a very low mean cumulative dose of less than 15 ml/kg [20]. Another recent comparison in cardiac surgical patients with 60-day follow-up concluded that HES 130/0.4 was as safe as 5% albumin; however, the cumulative dose during the 48-h study period was only approximately 33 ml/kg, which is less than one recommended daily dose of 50 ml/kg [21].

In 2007, use of tetrastarch (HES 130/0.4) in the USA was approved by the FDA for hypovolemia during or after surgery on the basis of noninferiority studies. The underlying clinical studies, which can be publicly assessed [4], show that comparator fluids were mainly other starches or gelatin. Estimation of safety was based on pooled results from studies in low risk patients excluding previous cardiac surgery; anemia; a history of heart, kidney, or liver disease; diabetes or severe infectious dis-

eases; history of coagulation disorders; known allergy to starch; BW >100 kg; pregnancy; and lactation. Mean observation period was 2 days and mean cumulative dose was 42 ml/kg, which is less than one daily allowed maximum dose of 50 ml/kg for this solution. There was no data on the safety of HES 130/0.4 in severe sepsis patients or ICU patients with pre-existing renal impairment or risk for renal dysfunction. Based on this evidence, HES 130/0.4 can only be safely recommended in small amounts and in patients with low risk [4]. Adverse effects on renal function have been noted in various clinical conditions and for all HES solutions [22,23]. Recently, persisting renal failure with osmotic nephrosis and interstitial foam cells was observed in a previously healthy patient with severe sepsis who had received fluid resuscitation with the most modern HES 130/0.4 in a cumulative dose of 81 ml/kg within 5 days [23].

The mechanism of renal failure is unclear. HES and dextran are taken up by the proximal tubular cells leading to swelling and subsequent lesions called osmotic nephrosis. The pathophysiology can be described as accumulation of proximal tubular lysosomes due to administration of exogenous solutes [24]. In the critically ill patient with hypovolemia or shock, such lesions may contribute to acute or chronic renal failure. Schortgen et al. have suggested that the use of hyperoncotic colloid solutions, i.e., starches, dextrans, and 20–25% albumin may be responsible for renal impairment [25].

Coagulopathy and Thrombocytopenia

HES interferes with clotting factors, thrombocytes, and prolongs bleeding time [26]. It may lead to potentially fatal bleeding in susceptible patients. A meta-analysis investigating perioperative blood loss in 653 cardiac surgical patients from 16 trials with albumin or HES exposure found that blood loss amounted to 789 ±487 mL in the HES group compared to 693 ±350 mL in the albumin group, the pooled standardized mean difference reaching statistical significance. Interestingly, increased bleeding was equally associated with HES solutions 200 or 450 kDa; and mean cumulative doses were 15.0 ml/kg and 8.9 ml/kg, respectively. Albumin moreover resulted in significantly less bleeding than HES in comparisons involving both volume expansion and addition of colloid to the priming fluid [27]. As a result, the FDA added a warning label on the package insert for hetastarch (HES 450 kDa), the only HES solution then on the US market, stating that this solution "is not recommended for use as a cardiac bypass pump prime, while the patient is on cardiopulmonary bypass, or in the immediate period after the pump has been discontinued because of the risk of increasing coagulation abnormalities and bleeding in patients whose coagulation status is already impaired." [28]. In France, HES 200/0.62 was withdrawn from the market after a pharmacovigilance study documented three cases of fatal cerebral hemorrhage among nine patients with subarachnoid hemorrhage and acquired von Willebrand's disease after HES exposure [29]. In patients with acute ischemic stroke or brain injury with cumulative HES doses of approximately 70, 87, and 253 ml/kg

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[16,17,30] raised safety concerns about increased incidence of intracranial bleeding [31,32]. Another group of patients at increased risk are patients with severe sepsis, where administration of 10% HES 200/0.5 compared to Ringer's reduced the platelet count (p <0.001) and was associated with transfusion of more units of packed red cells (p <0.001) [2].

Tissue Uptake and Storage

In critically ill patients with disturbed macro-und microcirculation, vascular leakage, and renal impairment, lysosomal uptake in the lysosomes of reticuloendothelial cells with subsequent tissue storage becomes a major route of elimination for HES molecules from plasma. HES thus may accumulate dose dependently in a variety of organs [33], particularly after repeated administration. Pruritus after HES is due to deposition in the skin, most probably in cutaneous nerve fibers [34] and can lead to protracted and long-lasting itching depending on the cumulative dose [35]. Pruritus is associated with all HES solutions, and was observed after hemodilution therapy with HES 130/0.4 to a higher degree than HES 200/0.5 [4]. Chronic administration can result in massive HES storage in macrophages, bone marrow, and liver cells with the aspect of a storage disease, manifesting as "foamy macrophage syndrome" or "acquired lysosomal storage disease" with liver failure and ascites [36, 37]. These patients had received cumulative HES doses in the range of 250 to 400 ml/kg or more for plasmapheresis or fluid therapy on the ICU.

Issue of Cumulative Dosage

It is becoming increasingly clear that HES-related toxicity is dose dependent and relates more closely to the overall cumulative rather than the maximum daily dose administered. In the VISEP study, need for renal replacement therapy increased almost linearly with cumulative doses of HES [2]. Awareness of cumulative dosage is still low. Manufacturers mostly recommend daily dose limits but do not mention cumulative dose thresholds. Cumulative doses are not routinely reported in HES trials, and large daily doses exceeding recommendations are not unusual in clinical studies or in daily clinical practice [30,38]. Use of HES should urgently be restricted to the cumulative doses which were found to be safe in clinical studies with adequate observation periods.

Dextran and Gelatin

Dextran and gelatin are synthetic colloids which share important characteristics with starches, namely their dose-related renal and coagulatory side effects [5,26] and their

inability to improve clinical outcomes compared to albumin or crystalloids [1,3,11,12,39].

Dextran is a polydispersed mixture of glucose polymers. It is associated with severe anaphylactoid reactions and has been increasingly replaced by gelatin or HES. Wills et al. compared 6% dextran 70 with Ringer's lactate for emergency resuscitation of children with Dengue shock syndrome and found that dextran use conferred no clinical benefit [11].

Gelatin is a bovine collagen derivative which was withdrawn from the US market as plasma volume expander in 1978 due to increased blood viscosity, reduced blood clotting, and prolonged bleeding time (http://www.fda.gov/ohrms/dockets/ 98fr/ 100898b.txt). Similarly, A well-conducted comparison between normal saline and gelatin for resuscitation in 60 children with septic shock showed that both performed equally in terms of hemodynamic stabilization. Both fluids were titrated to blood pressure, capillary filling time, or central venous pressure [39]. Gelatin impairs hemostasis during cardiac surgery as compared to albumin [40] and perioperative renal function in aortic aneurysm surgery compared to HES [41]. Anaphylactoid reactions are 4–6 times more common after gelatin than after HES or dextran (pooled incidence rate ratio in comparison to albumin 12.4; 95% CI 6.4–24.0) [5]. Gelatin has been found to result in a lower incidence of acute renal failure in severe sepsis in comparison to HES 200/0.62 [10], but comparisons to albumin or crystalloids in adult septic patients are lacking.

Crystalloids

Crystalloids contain water and electrolytes and are fluids without oncotic pressure, including normal or isotonic saline (0.9% NaCl), acetated or lactated Ringer's, or Hartmann's solution.

Hypertonic saline is still considered experimental in humans, except for the treatment of raised intracranial pressure and cerebral edema following traumatic brain injury [42]. Small volume resuscitation fluids are a combination of hypertonic crystalloid with a colloid, e.g., 7.5% sodium chloride and 6% dextran 70. A recent meta-analysis could not arrive at a conclusion about the efficacy of hypertonic crystalloids for lack of adequate data in patients with trauma, burns, or those undergoing surgery [43].

Saline-based fluids can lead to the development of hyperchloremic acidosis; this may not necessarily harm the patient. In surgical patients, volume therapy with normal saline required administration of bicarbonate, more total fluid, and more blood products than with Ringer's. This, however, had no direct effect on ICU or hospital stay and adverse events [44].

Crystalloids are devoid of allergic reactions or the side effects discussed above, are completely eliminated, and cheap to use. They have, however, been shunned for fear of pulmonary and tissue edema. Recent studies, however, have shown that the volume requirement for successful resuscitation is not as high as believed and considerable fluid loads did not lead to pulmonary edema. In septic patients, median res-

piratory SOFA score was 1.76 (interquartile range 1.00 to 2.71) in the Ringer's group and 1.80 (IQR 0.86–2.67) in the HES group ($p = 0.51$) [2]. Similarly, in a study comparing resuscitation fluids in 67 mechanically ventilated surgical patients with acute lung injury, determination of the 67Ga-transferrin pulmonary leak index and extravascular lung water showed no difference and oxygenation ratios improved in all groups. Pulmonary permeability and edema were not affected by different colloids or crystalloid administered for volume loading, despite the fact that significantly more saline than HES, albumin, or gelatin was used [12].

Differences in Hemodynamic Effects Between Crystalloids and Colloids

The current understanding and one of the arguments used in favor of colloids is that they expand the intravascular volume and increase myocardial preload faster than crystalloids [45]. However, larger studies and longer observation periods reveal that this effect is marginal and does not lead to improved clinical outcome in the ICU [2,7,11]. When septic patients with below target values of CVP, central venous oxygen saturation ($ScvO_2$), and mean arterial blood pressure (MAP) were resuscitated with HES or Ringer's, only CVP returned to target more quickly after HES ($p = 0.003$). $ScvO_2$ and MAP normalized equally fast with modified Ringer's lactate, and clinical outcomes were comparable [2]. Children with Dengue shock syndrome who received colloids achieved initial cardiovascular stability more rapidly and showed a faster reduction in median hematocrit values during the first 2 h (25, 22, and 9% reduction for dextran, gelatin, and Ringer's, respectively; $p < 0.001$). Subsequently, however, their hematocrit increased more than with Ringer's (5% increase for dextran or gelatin, 0% for Ringer's; $p < 0.001$). The authors explained this as a combination of fluid effects and vascular leak, such that colloids exerted a rapid effect followed by a rebound increase in vascular leak a few hours later. Overall time to final stabilization was not different between groups [11].

It is commonly believed that it requires 3–5 times more crystalloid than colloid volumes to raise the circulating intravascular fluid to a similar degree [46]. This concept was derived from small studies in surgical and septic patients with short observation periods. More recent studies reveal that considerably smaller volume ratios of colloid to crystalloid were needed in direct comparison for comparable clinical outcomes, ranging from 1 to 1.0 for HES or dextran [11], 1 to 1.2 for colloids [1], 1 to 1.4 for albumin [7], 1 to 1.4 for HES [2], 1 to 1.6 for gelatin [39], and 1 to 1.7 for colloids [12]. In summary, the evidence from these more recent studies strongly suggests that resuscitation with crystalloids in critically ill patients to the same hemodynamic goals does not require several-fold volumes and longer time to achieve than with colloids. The most likely reason may be that in critically ill patients with increased vascular leakage, colloids do not remain much longer in the vasculature than crystalloids.

Conclusions

Recent evidence confirms that the use of gelatin, dextran, or HES as plasma volume expanders in critically ill patients does not add a survival benefit in comparison to crystalloids. All synthetic colloids are associated with dose-related harmful effects, in particular coagulopathy and renal impairment. Moreover, HES is taken up and stored in various organs; this may be detrimental in ICU patients, in particular patients with sepsis. HES also raises safety concerns in patients with brain injury. Unfortunately, adverse effects were also observed with the most modern HES solution (HES 130/0.4, Voluven®).

While a potential benefit for albumin was shown in patients with severe sepsis which has to be confirmed in further clinical trials, albumin too is very likely to be harmful in patients with traumatic brain injury. Crystalloids are as effective as colloids but safer for resuscitation in critically ill patients. Longer observation periods show that the fluid requirement to achieve similar hemodynamic goals is not considerably higher for crystalloids than colloids and frequency of pulmonary edema is not increased.

Because synthetic colloids do not improve outcomes, but can cause considerable harm, the question arises whether they still have a place as plasma expanders in these high-risk patients. Notwithstanding, use of HES should urgently be restricted to the cumulative doses which were found to be safe in clinical studies with adequate observation periods.

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Predicting the Success of Defibrillation and Cardiopulmonary Resuscitation

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G. Ristagno

Introduction

Ventricular fibrillation (VF) remains the primary rhythm in many instances of sudden cardiac death, and defibrillation by electrical counter-shock represents the treatment of choice for this otherwise lethal arrhythmia. There is no doubt that the duration of VF remains one of the principal determinants for the likelihood of successful defibrillation. When the interval between the estimated onset of VF and the delivery of the first shock is less than 5 min, there is evidence that an immediate electrical shock would be successful [1]. When the duration of untreated VF exceeds 5 min, however, both human and animal studies demonstrate that initial CPR, with chest compression, prior to delivery of a defibrillation attempt, improves the likelihood of restoration of spontaneous circulation (ROSC) [2,3].

Despite major efforts to improve outcomes of cardiac arrest, including new technologies to guide rescuers through CPR maneuvers and new real-time approaches to assess the effectiveness and quality of such interventions, survival from cardiac arrest remains disappointing. For this reason, continued effort is directed toward evaluating new methods that might provide substantial information to the rescuers which would enable them to predict the success of defibrillation and CPR. Specifically, information is needed regarding the duration of the untreated cardiac arrest and the priority of intervention to be performed, namely defibrillation or chest compression.

Accordingly, the different approaches to assess the effectiveness of CPR and predict the success of defibrillation can be summarized in standard assessment of hemodynamics, or in methods based on electrocardiographic parameters measurement.

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Definition

Ventricular fibrillation is characterized by three time-sensitive electrophysiological phases, including (1) the electrical phase of 0–4 min, (2) the circulatory phase of 4–10 min, and (3) the metabolic phase of >10 min. During the electrical phase, immediate defibrillation is likely to be successful. As ischemia progresses, the success of attempted defibrillation diminishes without CPR. This phase is characterized by transition to slow VF wavelets during accumulation of ischemic metabolites in the myocardium. Type II VF often fails defibrillation attempts because of re-entry and recurrence of VF. In the metabolic phase, there is no likelihood of successful restoration of a perfusing rhythm [4]. During untreated VF, progressive and severe energy imbalance develops associated with increasing intramyocardial hypercarbic acidosis and depletion of high-energy phosphates. Early CPR, such as to restore coronary perfusion pressure (CPP) and myocardial blood flow, delays onset of ischemic myocardial injury leading to the well-known condition of "stone heart" and facilitates defibrillation [5].

Needs

The development of a noninvasive and real-time monitoring that allows prediction of whether or not a shock would achieve return of spontaneous circulation is of great importance in order to prioritize interventions, chest compression or defibrillation, such as to reduce the number of failed defibrillation attempts, the interruptions in CPR, and ultimately improve final outcome of cardiac arrest.

More than 50% of all patients initially resuscitated from cardiac arrest subsequently die before leaving the hospital and the majority of these deaths are due to impaired myocardial function [6–8]. The severity of postresuscitation myocardial dysfunction has been recognized to be related, in part, to the magnitude of the total electrical energy delivered with defibrillation [9]. Increases in the defibrillation energy were associated with decreased postresuscitation myocardial function [9,10]. The ability to predict defibrillation success may therefore minimize the damaging effects of repetitive and unnecessary electrical shocks.

Adverse outcomes also follow interruptions of precordial compression. Accordingly, uninterrupted chest compression would be expected to and, in fact, does produce better 24-h survival and neurological recovery [11]. Substantial interruptions of chest compressions have, instead, detrimental effects on the success of CPR [12], reducing the likelihood of success of defibrillation because of immediate declines of coronary perfusion [11,13]. Even minimal interruptions of only 4 sec cause decreases in aortic diastolic pressure and CPP, which require as many as seven chest compressions before achieving a return to maximal effect. In response thereto, new approaches, able to instruct the rescuers for the best timing for defibrillation, might further reduce interruptions of chest compression due to delivery of probably

unsuccessful defibrillation attempts by prompting the delivery of the electrical shock only when there is high likelihood of their success.

Standards for Predicting Success of Defibrillation and Return to Spontaneous Circulation

The evidence is certain that the quality of chest compressions is a major determinant of successful resuscitation. Established predictors of good quality CPR therefore can predict the success of defibrillation and thereby successful resuscitation. For this purpose, invasive hemodynamic measurements and especially coronary perfusion pressure [14–16], and end-tidal CO_2 ($EtCO_2$) are therefore employed [17,18].

Blood flows generated by chest compressions are dependent on the pressure gradient between the aortic and the venous pressures. CPP, defined as the difference between simultaneously measured minimal aortic pressure and right atrial pressure during compression diastole, is highly correlated with coronary blood flow during cardiac resuscitation and is currently recognized as the best single indicator of the likelihood of successful defibrillation and ROSC [16,19]. Based on both experimental and clinical observations, ROSC can be predicted when CPP is maintained above 15 mmHg during chest compressions [16]. Resuscitative strategies that increase CPP, including high quality chest compressions as well as the use of vasopressors, have therefore been supported and considered more effective in restore circulation.(Fig. 15.1).

Expired CO_2 is determined by the body's production of CO_2 and the relationship between minute ventilation and pulmonary perfusion. When the circulatory status is normal, pulmonary perfusion is in the physiologic ranges and $EtCO_2$ is determined

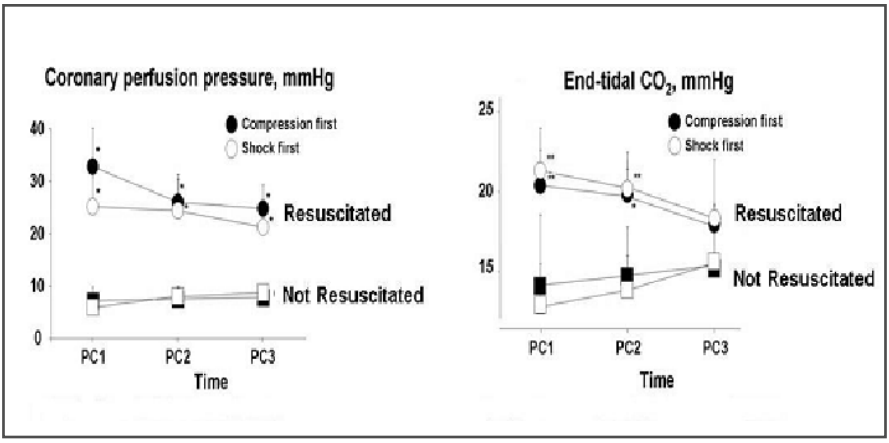

Fig. 15.1 Coronary Perfusion Pressure (CPP) and end-tidal CO2 (EtPCO2) during the first 3 min of precordial compressions (PC). CPP and EtPCO2 were significantly greater in resuscitated animals. * p <0.05, ** p <0.01 and † p <0.0001. Modified from [20]

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by minute ventilation. Under settings of cardiac arrest and CPR, cardiac output is usually less than one third of normal and therefore pulmonary flow and $EtCO_2$ is dramatically reduced. $EtCO_2$ is therefore an indirect measurement of pulmonary blood flow and cardiac output produced by chest compressions [17,18]. End-tidal CO_2 is highly correlated with CPP during CPR, and may therefore serve as a noninvasive surrogate for CPP and has emerged as another valuable tool for monitoring the effectiveness of chest compressions during CPR [17,18,20–22]. When $EtCO_2$ exceeds the threshold level of approximately 10–15 mmHg during CPR, greater likelihood of successful ROSC has been reported [23,24]. $EtCO_2$ values after 20 min of CPR have been recently recognized as even more reliable in predicting success of resuscitation [25].

Experimentally, in a porcine model of cardiac arrest and CPR, CPP and $EtCO_2$ above the threshold levels were the only predictors for successful resuscitation, independently from the priority of intervention, chest compression, or defibrillation [20]. Although the importance of blood pressures during CPR is clear, invasive measurements, including aortic and right atrial pressures are only available or feasible at the time of resuscitation in a very small minority of patients in critical care settings. The use of $EtCO_2$ measurements is also not widely available, especially because of the need of endotracheal intubation.

These restraints are in contrast, however, with the routine availability of the electrocardiogram (ECG) available in current external defibrillators. The attention, with the intent to identify a better predictor of defibrillation and ROSC, has been therefore focused on the analyses of electrocardiographic features of VF waveform. Filters and algorithms to reduce and eliminate ECG artifacts and noise due to chest compressions or ambient interferences have been developed. Among these, wavelet transform technique constitutes one of the most promising methods [26]. It allows for more reliable real-time ECG analyses to be used to predict defibrillation success and ultimately guide CPR interventions.

Analyses of ECG Features During Ventricular Fibrillation and CPR

We now recognize the importance of ECG signal analysis for predicting whether an electrical shock would successfully reverse VF. Real-time ECG analysis is therefore predictive of patient outcome. Moreover, the ECG analysis is dependent only upon the patient's condition at the time of treatment, with no need for knowledge of the response interval, which may be difficult to estimate [27]. The initial approaches to ECG analysis included measurements of VF amplitude [28], and then frequency [29].

Earlier investigations using ECG analysis focused on "amplitude or voltage" of VF wavelets as a predictor of the likelihood of successful defibrillation. VF voltage, or signal amplitude, is defined as the maximum peak-to-trough VF amplitude in a given time window of the ECG signal. Mean VF voltage is the average of VF voltage over the same time interval. It has been observed that VF amplitude declines over time, and greater amplitudes, especially after an interval of CPR, as shown in Figure 15.2, are

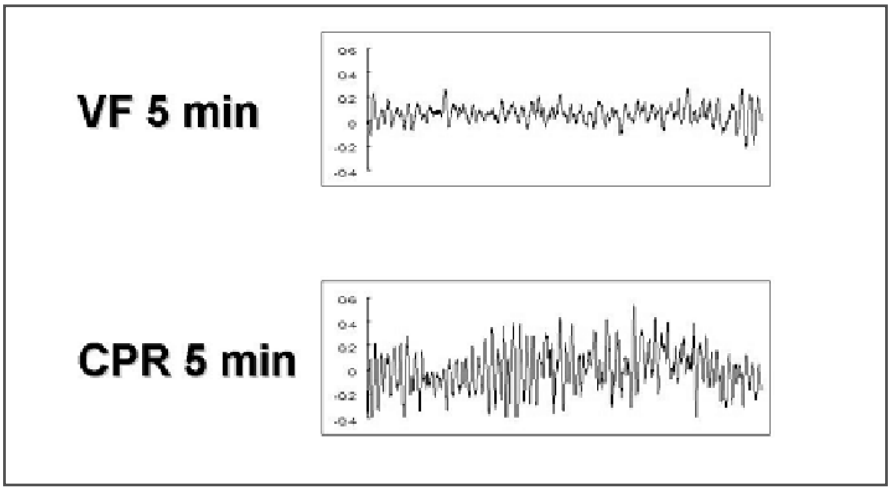

Fig. 15.2 Increases in VF amplitude after 5 min of CPR in comparison to untreated ventricular fibrillation

associated with correspondingly greater success of defibrillation [28,30–33]. This is because this ECG feature reflects myocardial blood flow and energy metabolism [28,32,33]. Based on the study of Weaver et al. [28], VF amplitude greater than 0.2 mV was recognized as a predictor of significantly greater likelihood of resuscitation.

Subsequently, other parameters were computed utilizing Fourier transformation analyses in a selected ECG interval. Specifically, VF median frequency, peak power frequency, edge frequency, and spectral flatness measure were introduced. The starting point for all these calculations is the "power spectrum," defined as the square of Fourier amplitudes. Brown et al. [29,34] specifically developed this technique that analyzed VF voltage and VF frequency such to obtain the so-called VF median frequency. Median frequency of VF served as a predictor of the success of electrical defibrillation [35,36]. Experimentally, a median frequency of more than 9.14 Hz had 100% sensitivity and 92% specificity in predicting the success of defibrillation. Frequency analysis of VF wavelets and, specifically, median frequency was also correlated with CPPs in animal models as well as human victims and therefore became the preferred ECG feature to be used as a predictor of outcome [35–38].

To improve sensitivity and specificity of the ECG predictors for defibrillation success and ROSC, more sophisticated methods of VF waveform analyses have recently been introduced and investigated, including wavelet decomposition, nonlinear dynamics methods, and a combination of different ECG parameter analyses. Since then, several new approaches have been proposed and their effectiveness proved in predicting defibrillation outcomes. One of these employed the $N(\alpha)$ histograms analysis, which was demonstrated to be superior to mean VF frequency analysis [39]. A combination of spectral features in the VF waveform was anticipated as a monitor of efficacy of interventions during CPR, evolving into a "probabili-

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ty of successful defibrillation" function [40]. This is a combination of two decorrelated spectral features based on a principal component analysis of an original feature set with information on centroid frequency, peak power frequency, spectral flatness, and energy. The function "probability of defibrillation success" discriminated between shocks followed by ROSC and No-ROSC. Methods employing entropy measure have also been shown to provide more optimal prediction of ROSC after electrical shock in human VF recordings [41], and methods of filtered ECG features from higher ECG subbands, instead of features derived from the main ECG spectrum, have improved accuracy of shock outcome prediction during CPR [42].

Our Approach: Amplitude Spectrum Area (AMSA)

The Amplitude Spectrum Area (AMSA) is another efficient ECG-derived defibrillation predictor in which mean amplitude and dominant frequency are combined. The amplitude spectrum is obtained by fast Fourier transform of the ECG scalar signal (Fig. 15.3), and is calculated from the resulting amplitude frequency spectrum according to the following equation:

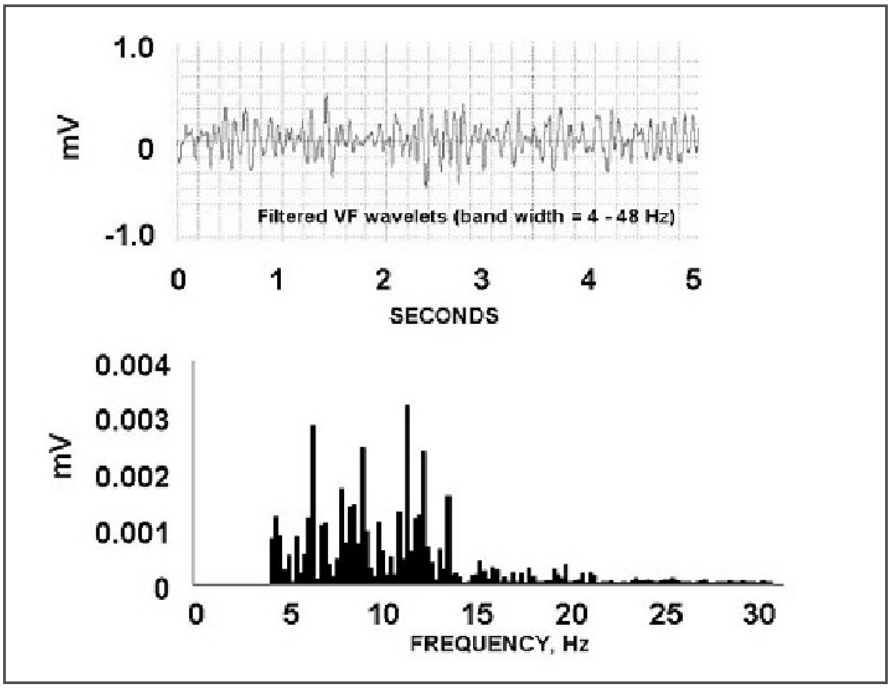

Fig. 15.3 A representative example of the amplitude frequency relationship and the area under the curve that defines the amplitude spectrum area (AMSA)

$$AMSA = \Sigma Ai \times Fi$$

where Ai is the amplitude at the ith frequency Fi.

In a porcine model of cardiac arrest and CPR, threshold values of AMSA for defibrillation success have been established and AMSA has confirmed its capability to optimize the timing of ventricular defibrillation [43]. It was, in fact, highly correlated with CPP levels during CPR and, similarly to CPP, significantly greater values were observed in animals that were resuscitated compared to those that were not [44]. Amplitude spectrum analysis demonstrated a negative predictive value for resuscitation of 96% and a positive predictive value of 78%. It is therefore apparent that AMSA represents a measurement that potentially fulfills the need for minimizing ineffective and detrimental defibrillation attempts during resuscitative maneuvers. The high negative predictive value, in particular, would minimize repetitive and ineffective electrical shocks during CPR. The progressive increases in AMSA observed before successful resuscitation further demonstrate that AMSA has the potential of providing an objective guide allowing for better quality control of CPR. Failure to increase AMSA values to near threshold levels prognosticates, instead, failure of defibrillation.

Subsequent validation studies have confirmed that AMSA has an impressively higher specificity and positive predictive value compared with the other predictors, maintaining sensitivity and negative predictive value comparable to the invasively assessed CPP. More importantly, AMSA is not invalidated by artifacts resulting from precordial compression, fulfilling the goal of a predictor that would allow for uninterrupted precordial compression during ECG analyses.

AMSA has also proved its validity as predictor for defibrillation outcomes in the clinical scenario [45,46]. Retrospective analysis of human ECG records, representing lead 2 equivalent recordings, confirmed the efficacy of this tool in predicting the likelihood that any one electrical shock would have restored a perfusing rhythm during CPR. AMSA values were significantly greater in successful defibrillation, compared to unsuccessful defibrillation (Table 15.1). A threshold value of AMSA of 12 mV-Hz was able to predict the success of each defibrillation attempt with sensitivity and specificity of more than 91%.

Table 15.1 Amplitude spectrum area and success of defibrillation (DF) attempts. Modified from [46]

	PR	NR
AMSA mV-Hz	16 ± 3.4	7.1 ± 2.6 *

PR, Return of a perfusing rhythm; *NR*, failure of return of a perfusing rhythm
* $p < 0.0001$

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New Approach to Predict Success of Defibrillation

In assessing the critical perfusion condition during and after resuscitation from cardiac arrest, both investigators and clinicians focused on pressure and blood flow through large vessels and cardiac output. CPR interventions and especially chest compression focused on increasing and maintaining optimal pressures such as to favor large vessel supplies to the heart, in order to prime the heart to successful defibrillation. With the advent of methods by which microvessels and especially capillaries could be visualized, it has become apparent that large vessel pressures and flows alone may not be predictive of the extent to which microvessels and therefore tissues are perfused. Yet, it is the microvessels and specifically the capillaries which serve as the ultimate exchange sites for vital metabolites. The availability of the Orthogonal Polarization Spectral, first, and now Sidestream Dark Field imaging techniques, allowed direct and real-time visualization of arterioles, venules, and capillaries and therefore provided a tool for assessing the effect of CPR interventions on the microcirculation [47]. Experimentally, we investigated changes in sublingual microcirculation during cardiac arrest and CPR. With the aid of the microcirculation imaging, we observed that microvascular blood flow in the sublingual mucosa was highly correlated with CPP during CPR. Like CPP, the magnitude of microcirculatory blood flow was indicative of the effectiveness of the resuscitation intervention and success of defibrillation attempt and outcome. In animals that were resuscitated, microvascular flow was significantly greater than that assessed in animals in which resuscitation attempts failed.

Tissue hypercarbia measurements might also represent a future tool to assess, noninvasively, hemodynamics generated by chest compressions and therefore predict success of CPR intervention. When oxygen delivery to the tissues is critically reduced during circulatory failure states, anaerobic metabolism is triggered with consequent hydrogen ion production. This excess of hydrogen ions is buffered by tissue bicarbonate such that CO_2 is generated. Buccal PCO_2 has therefore been confirmed as a useful guide to the diagnosis of circulatory shock, including cardiac arrest. It also provided rapid response for confirmation of the effectiveness of treatments. More recently, it has appeared as a useful tool to predict the duration of untreated cardiac arrest and thereby direct the rescuers to the best initial resuscitation maneuvers, chest compression or defibrillation [48].

Conclusions

CPP and $EtCO_2$ represent useful standard means for monitoring the effectiveness of chest compressions and to predict the success of CPR. These measurements, however, are not feasible in settings of out-of-hospital cardiac arrest. Investigators have therefore now focused their attention on the morphology of the VF waveform in order to predict the success of resuscitation. However, the challenge is to ensure high sen-

sitivity and specificity, especially during precordial compression, in order to identify the ideal moment to deliver the defibrillatory shock. A spectral analysis method such as AMSA is a simple parameter that can be easily obtained by a conventional surface ECG that is part of the routinely current practice of advanced cardiac life support. Experimentally, consistent evidence of the validity of AMSA has been proved in both animal and human data, with the advantage of being employed as a real-time indicator for effectiveness of chest compressions and prediction of the success of defibrillation. Future approaches might also integrate noninvasive measurements of blood flows produced by chest compression, including real-time measurements of sublingual microcirculation and tissue PCO_2 during CPR.

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Acute Renal Failure

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J. Besso, G. Blanco, R. Gonzalez

Introduction

The kidney is an organ that primarily regulates volume and composition of the internal fluid environment; its excretory function is incidental to their regulatory function. In renal failure, this regulatory function is impaired.

Definition

Acute renal failure (ARF) is defined as a fall in the glomerular filtration rate (GFR) and the accumulation of nitrogenous wastes products (e.g., urea, creatinine, and potassium) in the serum and also disturbances in fluid, electrolyte, and acid-base balance; this condition may be oliguric or nonoliguric.

The term acute renal failure is used when the fall in GFR occurs relatively rapidly, and the BUN and creatinine levels increase over the course of days to weeks. In chronic renal failure, the GFR falls much more slowly, over months to years. Acute renal failure is a complex syndrome that occurs in a wide variety of settings with clinical manifestations ranging from a minimal elevation in serum creatinine to anuric kidney failure. Although the majority of cases are the result of acute tubular necrosis, the same clinical manifestations follow many different etiologies, especially sepsis and nephrotoxin exposure [1]. Outcomes range from recovery to death and include the development of chronic kidney disease and progression to dialysis dependency. A wide variation in the definition of ARF has made it difficult to compare information across studies and population. ARF is based on high serum creati-

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nine, changes in urine output, or the need for dialysis [2]. Despite decades of experimental and clinical research, there has been little or no success in translating experimental therapy into clinical practice. Because of the use of creatinine-based definitions of ARF, the diagnosis of ARF has been made retrospectively and often by exclusion and usually without biopsy evidence. Consequently we know very little about the structural changes of early clinical ARF, including so-called prerenal ARF. However acute renal failure, more than any other ICU syndrome, has been defined different ways. Bellomo and collegues focused the importance of developing a consensus definition regarding acute or chronic renal failure [3]. The international Acute Kidney Injury Network (AKIN) proposed a change in nomenclature, and acute kidney injury (AKI) has become the preferred term to describe the syndrome of ARF, with "failure" related to patients who have AKI needing renal replacement therapy (RRT). An additional advance is a proposed grading of severity of AKI in 3 stages. This grading has been developed from an earlier 5-step grading captured in the acronym RIFLE (Risk, Injury, Failure, Loss and End stage) according to relative changes in the serum creatinine and urine output, which divided AKI into 3 severity-based categories (Risk, Injury and Failure) and 2 categories reflecting persistence (Loss and End-stage kidney disease). The new 3-step staging breaches the conceptual gap between "minor" and more severe elevations of creatinine but omits the 2 outcome categories of loss and end-stage kidney failure. Individuals who receive RRT are automatically graded as stage 3 [4].

Epidemiology

Acute renal failure is seldom a community-acquired disease but usually develops in hospitalized patients. It complicates 5% of all hospitalized patients [5]. Critically ill patients have the highest incidence of acute renal failure, more than 20%, and once they developed their mortality tend to increase five to sixth times more [6]. Renal failure is a common occurrence in the intensive care unit (ICU); it is frequently a part of a multitude of problems, which culminate in sepsis and multiple organ dysfunction/failure.

Etiology

The causes of ARF traditionally are divided into 3 categories: prerenal, postrenal, and acute tubular necrosis [7,8]. This simple clinical classification of ARF remains useful, because it provides a logical basis for the diagnosis and treatment. The most common causes of ARF are prerenal failure with approximately 35% of cases and acute tubular necrosis (ATN) with 50% of cases. Obstruction accounts for the minority of cases (Table 16.1) [10].

Pseudorenal failure is a clinical condition characterized by an increase of the BUN or creatinine without a decrease in the GFR (Table 16.2). One should always

Table 16.1 Causes of acute renal failure hospital versus ICU

	Hospital	ICU
Acute tubular necrosis	45%	78%
Prerenal	21%	17%
Postrenal	10%	5%
Renal vascular disorders	3%	
Glomerulonephritis	3%	
Acute interstitial nephritis	2%	

Table 16.2 Causes of pseudorenal failure

Increased BUN	Increased creatinine
GI bleeding	Rhabdomiolysis
Steroids	Trimethroprim, cimetidine
Hyperalimentation	Cefoxtin, acetone

consider these nonrenal factors as a potential explanation determining an increase of acute azotemia. Also, sometimes we may be in a situation where there is a decrease in the GFR with normal creatinine as in severe malnutrition or atrophic muscle disorders, or a decrease in GFR with normal BUN as in hepatic failure because of decreased urea synthesis.

Prerenal Azotemia

The reduction in GFR in prerenal failure is caused by abnormalities in glomerular perfusion. Prerenal ARF, by definition, is not associated with any intrinsic renal parenchymal disease and resolves rapidly when the underlying causes of renal hypoperfusion are corrected.

Although renal blood flow is reduced in prerenal failure, it remains adequate to provide enough oxygen and metabolic substrates to sustain the viability of the kidney. If prerenal ARF is not treated in a timely manner or is allowed to get progressively worse, ischemic injury to renal tubular cells ultimately occurs and precipitates ATN [9]. The pathophysiology and causes of prerenal azotemia is presented in Table 16.3. In the face of azotemia and oliguria, several markers are useful in order to differentiate prerenal azotemia versus ATN (Table 16.4). All those markers are useful in the absence of a prior diuretic administration, except for the fractional excretion of urea, which is not affected. It is also important to consider the causes of falsely high/low fractional excretion of sodium (Table 16.5). An abnormality of the routine urine analysis would suggest underlying acute or chronic renal disease. It is not unusual for the urinary sodium value to suggest a prerenal element, but the urine creatinine to suggest

Table 16.3 Pathophysiology and causes of prerenal azotemia

Absolute decrease ECV	Hemorrhage/GI/GU/Burns
Decreased "effective" ECV	CHF/cirrhosis/nephrosis
"Third Spaced" volume	Abdominal catastrophes

Table 16.4 Prerenal azotemia versus acute tubular necrosis (ATN)

	Prerenal	ATN
Bun: Cr Ratio	>20	<10
Urine Osm (mOsm/l)	>350	<300
U:P Osm	>1.5	<1.0
Urine Na (mEq/l)	<20	>30
FE. Na (%)	<1	>1
FE. Urea (%)	<35	>50

Table 16.5 Falsely high/low fractional excretion of sodium

Low	High
Rhabdomiolysis	Diuretics
Contrast nephropathy acute glomerulonephritis	Mannitol
Sepsis	Glucosuria
Congestive heart failure	Chronic azotemia
Cirrhosis	

renal dysfunction or vice versa. If even one of many parameters suggests a prerenal element, any potential prerenal factors should be identified and reversed.

Prerenal azotemia is confirmed if the urine output improves and the azotemia resolves with the administration of isotonic fluids or improvement in the underlying condition, e. g., heart failure.

Postrenal Azotemia

Postrenal azotemia is a diagnosis that should not be missed, and it is generally done by anatomic exclusion (Table 16.6). All patients with early oliguric ARF should have a urinary catheter and an ultrasound done early in the course, ; if the patient is known to have only one kidney it will be better to do a CT scan or a retrograde pyelography.

Table 16.6 Postrenal azotemia

Urethra	Stricture, stone, object
Prostate	Hypertrophy, tumor
Bladder	Neurogenic, tumor, clot
Ureter	Stone, tumor, clot
Retroperitoneum	Tumor, fibrosis

Acute Renal Failure

Although ATN is the most common cause of hospital-acquired ARF, one must consider the various intrinsic renal parenchymal or hemodynamic derangements responsible for ARF. These include diseases that primarily affect the glomerulus (glomerulonephritis), interstitium (interstitial nephritis), and blood vessels (vascular occlusion or vasculitis) (Table 16.7).

Table 16.7 Acute renal failure

- Glomerular disease
- Glomerulonephritis intrarenal hemodynamics
- Interstitial disease
- Vascular disease
- Tubular disease "ATN"

Fulminant glomerulonephritis due to bacterial endocarditis, staphylococcal septicemia, visceral abscesses, hepatitis B surface antigen, and Goodpasture syndrome, can be observed in a major intensive care unit. Once considered, these diagnoses are not difficult to make. The urinalysis will show dysmorphic red blood cells (those with multiple surface irregularities), red blood cell casts, and from moderate to heavy proteinuria. Hypertension is variably present. Blood cultures, serologic testing [antinuclear antibody, antineutrophilic cytoplasmic antibodies (ANCA), hepatitis B surface antigen, and antiglomerular basement membrane antibody], and a search for visceral abscess may be necessary. An early renal biopsy is usually helpful when acute glomerulonephritis causes ARF.

Alterations in glomerular hemodynamics are increasingly recognized as a cause of ARF. This situation includes afferent arteriolar vasoconstriction (hepatorenal syndrome) or efferent arteriolar vasodilation (angiotensin converting enzyme inhibitors). The latter is seen when renal blood flow is already compromised by diuretics, severe cardiac failure, or renal artery stenosis. In addition, less well-defined derangements in intrarenal hemodynamics are likely responsible for the ARF in sepsis, potent vasodilators, and the nonsteroidal anti-inflammatory drugs

(NSAIDs). In these cases, the urinary sediment is nonrelevant, and the renal biopsy, if performed, tend to be normal. Recovery of renal function is expected, provided the offending drug is removed or the underlying condition is corrected (Table 16.8).

Table 16.8 ARF due to glomerular hemodynamics

- Hepatorenal syndrome
- ACE inhibitors
- Sepsis
- NSAIDs

Acute interstitial nephritis is usually due to allergies to drugs such as penicillins, cephalosporins, sulfonamides, diuretics, and NSAIDs. Patients will present with fever, rash, arthralgias, eosinophilia, and eosinophiluria (excepting NSAIDs) [11]. Other less frequent causes are pyelonephritis, multiple myeloma, uric acid nephropathy, and occasionally infiltrative disorders, such as lymphoma, leukemia, and sarcoidosis. Oxalate nephropathy may complicate acute ethylene glycol ingestion. The urine sediment is usually nonrelevant, but crystalluria, pyuria, and white blood cell casts can be seen, even in the absence of infection.

Vascular disease is a frequently overlooked cause of ARF. Malignant hypertension usually accompanied by retinopathy, thrombocitopenia, and microangiopathy can cause ARF. Microangiopathy and thrombocitopenia also accompany hemolytic uremic syndrome or thrombotic thrombocytopenic purpura (TTP). Renal infarction due to trauma, arterial embolus, or thrombosis can cause ARF with fever, hematuria, acute flank pain, ileus, leucocytosis, and an increased LDH . level. This syndrome often mimics an acute abdomen. Renal atherosclerotic or cholesterol microemboli commonly occur following aortic manipulation (surgery or catheterization), besides ARF, gastrointestinal bleeding (due to microinfarction), livedo reticularis of the lower extremities, patchy areas of ischemic necrosis in the toes, hypocomplementemia, and eosinophilia are common. Finally, renal vasculitis often causes ARF. These syndromes are identified by their multisystem manifestations, very active urine sediment (hematuria, pyuria, red and white blood cell casts, and proteinuria), and in the cases of Wegener's and polyarteritis nodosa, the presence of ANCA in the serum (Tables 16.9–16.12).

Acute tubular necrosis is the most common cause of hospital and ICU-acquired ARF, which is broadly divided into toxic and ischemic causes (Table 16.13). Drugs that induce renal damage and mechanisms can be reviewed in Table 16.14. Among the more common toxins causing ATN are the aminoglycoside antibiotics. Risk factors for aminoglycoside nephrotoxicity include volume contraction, age, hypokalemia, concomitant use of other nephrotoxins, and a short-dosing interval. After an initial loading dose, the maintenance dose should be adjusted based on the patient's creatinine clearance. The routine use of peak and trough serum levels does not decrease the likelihood of ATN.

Table 16.9 Acute renal failure – vascular causes

• Hemolytic uremic syndrome/thrombotic thrombocytopenic purpura
• Renal vein thrombosis
• Renal artery embolism
• Vasculitis
• Cholesterol microemboli
• Malignant hypertension

Table 16.10 Renal artery embolism

Acute Azotemia	90%
Increased LDH	90%
Leucocitosis	90%
Microhematuria	80%
Proteinuria/pyuria	70%
Fever	70%
Flank abdominal pain	40%

Table 16.11 ARF. Cholesterol microemboli

• Eosinophilia/uria
• Intestinal ischemia/bleeding
• Livedo reticularis
• Myopathy
• Mononeuropathy

Table 16.12 ARF. Renal vasculitis

Syndromes	Diag	Therapy
Wegener's granulomatosis	ANCA	Cytox
Poliarteritis nodosa	ANCA	Cytox
Henoch Scholen purpura	Tissue Ig A	Pulse steroids
Cryoglobulinemia	Cryos, C3	Steroids? Interferon? Cytox?
Hypersensitivity Vasculitis	Skin Bx	Steroids

Table 16.13 Acute tubular necrosis

Toxic	Ischemic
Aminoglycoside	Shock
Contrast	Hemorrhage
Rhabdomyolysis	Sepsis
Platinum	Suprarenal clamp

Table 16.14 Drugs that induce renal damage

Class of drug	Damage
Diuretics, ACE, β-blockers	Decrease in renal perfusion
NSAID'S, contrast	Impaired intrarenal homodyne
Aminoglycoside, amphot	Tubular toxicity
β-Lactams, NSAIDs, furosemide, cimetidine	Allergic interstitial nephritis

Radiographic contrast agents may cause ARF in patients with pre-existing renal insufficiency, diabetes mellitus, poor left ventricular function, or when multiple diagnostic procedures are done in a 24-h period.

The volume of contrast used (>1. 5 ml/kg) appears directly related to nephrotoxicity. In patients at very high risk for contrast nephropathy, nonionic contrast may be slightly less nephrotoxic [12]. However, volume expanding these high-risk patients with intravenous crystalloids is a good prophylaxis [13]. Acetylcysteine appears to offer protection against contrast toxicity [14] though its use in very high-risk patients requires further study. Most cases of contrast nephrotoxicity are nonoliguric and resolve within a few days. Rarely, a patient will require dialysis.

Rhabdomyolysis is producing ARF at an increasing rate. Drugs (e.g., heroin, cocaine, and lovastatin) and major crush injuries have joined alcohol, seizures, and muscle compression as common causes. All have the potential of producing myoglobinuria and ARF, particularly if extracellular volume depletion or shock exists simultaneously. Hyperkalemia, hyperuricemia, hyperphosphatemia, and high levels of creatine-kinase, with low Bun/Cr ratio also result. Hypocalcemia occurs early; hypercalcemia appears during recovery [15]. Dark heme-positive urine without red blood cells is a major diagnostic clue. Prophylaxis against ATN depends on aggressive intravenous crystalloids administration. The addition of mannitol and bicarbonate (1/2 NS with 12.5 g/L of mannitol and 50 mEq/L of $NaHCO_3$/L at 250–500 ml/h) may be a useful adjunct.

Kidney ischemic insult occurs during prolonged hypotension, suprarenal aortic or renal artery occlusion (either with clot or clamp), and sepsis. The renal tubular cells are particularly susceptible to ischemic insults because their baseline balance

between oxygen supply and demand is tenuous [16]; thus, whenever systemic or intrarenal blood flow decreases slightly, ischemic insult to the tubular cell may occur. This imbalance of oxygen supply and demand may help to explain the beneficial effects attributed to loop diuretics in some studies; by inhibiting active chloride and sodium transport in the ascending limb of the loop, these agents decrease metabolic work and, therefore, oxygen requirements.

More than 50% of all cases of oliguric ARF in the hospital are due to sepsis. This condition appears related to a simultaneous decrease in systemic vascular resistance, reducing renal plasma flow and GFR. ARF occurs independently of systemic hypotension. Fever, leucocytosis, and overt signs of sepsis may be absent. A mild alteration in mental status or respiratory alkalosis may be the only clinical clue. Oliguria and or azotemia in this setting should be considered occult septicemia unless disproved. The mechanisms of ATN in sepsis are shown in Table 16.15

Table 16.15 Mechanisms of acute tubular necrosis in sepsis

SIRS/SEPSIS induce ATN	Ischemic renal injury + cytotoxic renal injury
Cytotoxic renal injury	Potential concomitant renal insults as nephrotoxic drugs, obstructive jaundice, rhabdomyolysis, contrast agent
Ischemic renal injury	Peripheral vasodilation: increased nitric oxide, prostacyclin, activation K-ATP channels
	Intrarenal vasoconstriction: endothelin, TX A2, LTC4, LTD4
	Microvascular injury: cytokines, activated leucocytes, PAF, intracapillary thrombosis

Sepsis and Renal Failure

The incidence of ARF is approximately 20–25% in patients suffering sepsis; with the condition of severe sepsis the incidence of ARF exceeds 50% [17,18]. The fundamental cause of ATN in sepsis, even in the absence of hypotension, is renal hypoperfusion and ischemic injury to proximal tubular cells. An important mechanism of renal hypoperfusion is the combined effect of arterial vasodilation and intrarenal vasoconstriction. Another mechanism is intrarenal microvascular injury caused by PMN- and complement-induced endothelial injury and intravascular thrombosis [19,20].

The intrarenal vasoconstriction associated with sepsis has been ascribed to the local release of endothelial-derived vasoconstrictors, including endothelin, thromboxane A2, and leukotrienes [21]. Renal hypoperfusion also increases renal susceptibility to superimposed nephrotoxic events, which are common in septic patients. Acute renal failure in sepsis is more often part of the multiorgan dysfunction syndrome (MODS) associated with sepsis. MODS is caused by diffuse microvascular injury, which leads to inadequate perfusion and hypoxia of the lung, heart, liver, and other organs.

Other Causes of Acute Renal Failure

Acute renal failure in pregnancy has declined markedly from years 1950 to 1990, from approximately 1/1,390 pregnancies to 1/20,000 pregnancies. It is generally associated with volume depletion (hyperemesis gravidarium, hemorrhage), pre-eclampsia or eclampsia (with a higher incidence of RCN), HELLP syndrome, acute fatty liver of pregnancy, and idiopathic postpartum renal failure.

Acute renal failure caused by nonsteroidal anti-inflammatory drugs is associated with the presence of certain risk factors such as true hypovolemia, cardiac failure, cirrhosis with ascites, and sepsis when the effective arterial blood volume is decreased; and with advanced age, chronic renal insufficiency, and diabetes when the effective arterial blood volume is normal.

Patients in ICU are at high risk for developing ATN [18]. These patients include post-operative and sepsis [22,23]. Postoperative ARF is associated with substantial increase in morbidity, length of stay in ICU and in hospital, and poor outcome (Table 16.16).

Other causes of acute renal failure in the ICU are consequences of osmotic nephropathy, i.e. with substances that are added as vehicles to drug formulations such as propylene glycol and sucrose. Other causes of osmotic nephropathy include mannitol, methanol, or ethylene glycol.

Table 16.16 Risk factors for acute tubular necrosis after surgery

Preoperatives variables	Chronic renal disease: creatinine >2mg/dl Advanced age Emergency surgery Cardiac dysfunction Diabetes mellitus Atherosclerotic vascular disease Obstructive jaundice
Type of surgery	Cardiac AAA repair Hepatobiliary
Postoperatives variables	Cardiac dysfunction Re-do surgery Number of transfusions Angiography within 24 h of surgery

Prevention of Acute Renal Failure

Because the risk and the mortality of ARF are high in critically ill patients [24,25], prevention is the better therapy. The most common risk factor is extracellular volume depletion. Volume expansion can minimize the risk of ARF from radiographic con-

trast agents, cisplatin, and NSAIDs. Mannitol appears to at least partially abrogate the ARF caused by rhabdomyolysis and cisplatin but not that caused by contrast agents. Limiting the dose and simultaneous exposure appears important in avoiding contrast, aminoglycoside, and cisplatin toxicity. Alkali may limit the nephrotoxicity of myoglobinuria and uric acid. Allopurinol should be used before chemotherapy, whenever tumor lysis is anticipated. Adjusting dosing interval for changes in Ccr is important to prevent aminoglycoside toxicity. Correcting hypokalemia and expanding ECV are also helpful. Positive end-expiratory pressure (PEEP), as well as high intrathoracic pressure associated with mechanical ventilator support, may compromise cardiac output and renal perfusion. If possible, PEEP should be minimized and ECV should be expanded in high-risk patients. There are animal data to suggest that high caloric nutrition may increase the risk of ARF. However, the benefits of nutritional support seem to far outweigh this risk. It appears to improve renal tubular cell regeneration and survival in patients, particularly those with several complications. Whenever possible, enteral nutrition is preferred.

Acute Renal Failure Oliguric Versus Nonoliguric

Converting oliguria to nonoliguria appears helpful. Nonoliguric patients have fewer complications, a decreased dialysis requirement, and in some studies improved survival [26] (Table 16.17). Conversion to a nonoliguria condition can often be accomplished by repleting intravascular volume (if deficient) and using high-dose loop diuretics (e.g., 200 mg i.v. of furosemide or continuous infusions at a rate of 10–40 mg/h). The diuretic may have the additional advantage of decreasing tubular cell metabolic activity, thus lessening the oxygen requirement. A renal vasodilatory dose of dopamine (0.5–2.0 μgr/Kg/min) is sometimes helpful in stimulating urine volume. However, in a recent placebo controlled trial in critically ill patients, low-dose dopamine failed to improve renal function [27]. Neither furosemide nor dopamine have any utility as prophylaxis prior to major surgery.

Table 16.17 Oliguric versus nonoliguric renal failure

	Oliguric	Nonoliguric
Hospital days	31	22
Dialysis	32 (84)	15 (28)
GI bleeding	15 (39)	10 (19)
Septicemia	16 (42)	11 (20)
Neuro changes	19 (50)	16 (30)
Deaths	19 (50)	14 (26)

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Standards of Care in Renal Failure

Unfortunately, there are no specific therapies for most causes of ARF. The management of patients with oliguria or anuria needs standardization of procedures such as:

- Assessment and correction of any respiratory or circulatory impairment
- Exclude obstruction of the urinary tract
- Establish underlying cause(s)
- Manage any life-threatening consequences of renal dysfunction
- Obtain a drug history and alter prescriptions appropriately
- Correct bleeding disorders
- Prevent and/or treat infection

Dialysis Modalities in the Intensive Care Unit

Intermittent hemodialysis has been the standard therapy for many years because it is efficient, widely available, and generally well tolerated. However hemodialysis is not without potential complications, bleeding (due to heparinization) and hypotension being the most severe. The bleeding can usually be avoided by using citrate as an alternative anticoagulant. Hypotension often can be modified by fluid removal (ultrafiltration). However, the hypotension of hemodialysis is, at least in part, due to the use of bioincompatible (cellulose) dialysis membranes. Complement activation and alterations in immune function are observed when hemodialysis is performed with these dialyzers. Recent studies have established that hypotension and complement activation can be reduced by the use of more compatible polysulfone, polyacrylonitrile, or polymethylmethacrylate dialysis membranes. Most importantly, survival is improved when ARF patients are dialyzed with these biocompatible membranes in some studies [28] while in others survival did not improve, but morbidity decreased. However, the use of biocompatible membranes is recommended for ARF patients requiring hemodialysis. Peritoneal dialysis requires no anticoagulation, and its slow continuous ultrafiltration rates are well suited to patients with baseline hypotension and/or poor cardiac output. However, its utility is limited after abdominal surgery and in severe catabolic patients because of relatively slow solute removal. Continuous extracorporeal techniques for solute and fluid removal are valuable in hemodynamically unstable patients, particularly those with multiple organ failure.

During the past decade, a number of advances have been made in the field of renal replacement therapy. Clinicians have gained a better appreciation of the need for early and aggressive management of patients with renal failure in the ICU [29].

Appropriate modality and decision making at the bedside requires an understanding of the clinical spectrum of renal failure in the ICU. Uncomplicated renal failure refers to an acute and transient decline in glomerular filtration rate without clinically apparent complications. Dialytic support often is not required in patients with

uncomplicated ARF or may be performed for a single indication, such as hyperkalemia. In complicated ARF, however, multiple metabolic and volume status perturbations are present; the patient is often oliguric, and the renal failure may be present in association with multiorgan dysfunction/failure. The threshold for initiation of dialysis and the choice of dialytic modality differ depending on the associated complications and comorbid conditions. Many nephrologists avoid dialysis initiation for as long as possible and the reasons are because dialysis procedure itself has associated risks (hypotension, arrythmias, vascular access) and the concern that dialysis may delay recovery of renal function [30]. This contention is supported by animal data in which hypotension resulted in recurrent renal ischemia and by human studies that showed a decline in the GFR during and after the intermittent hemodialysis session [31–33].

In the critically ill patient ARF usually does not occur in isolation from other organ system dysfunction and therefore providing dialysis can be viewed as a form of renal support for multiorgan dysfunction rather than renal replacement.

In the presence of oliguric renal failure, administration of a large volume of fluid to patients with MODS may lead to impaired oxygenation. In such a setting, early intervention with extracorporeal therapies for management of fluid balance may significantly impact the function of other organs, even in the absence of traditional indices of renal failure such as marked azotemia.

Renal Support Versus Renal Replacement

In renal support the purpose is to support other organs, ; the timing of intervention is based on individualized need; the indications for dialysis is broad and the dialysis dose is targeted for overall support. In contrast, the purpose of renal replacement therapy is to replace renal function; , the timing of intervention is based on the levels of biochemical markers; the indications of dialysis are narrow and the dialysis dose is extrapolated from end-stage renal disease.

Different modalities of renal replacement therapies and comparisons are represented in Tables 16.18, 16.19.

Table 16.18 Renal replacement therapy

Intermittent	Continuous
Hemodialysis (IHD)	Ultrafiltration (SCUF)
Ultrafiltration (IUF)	Peritoneal (CPD)
Peritoneal (IPD)	Hemofiltration (CAVH, CVVH)
Hemodialysis (CHD)	Hemodiafiltration (CA/CVVHDF)

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Table 16.19 Comparison of renal replacement therapies

	HD	PD	CVVH	CVVHDF
Solute	DIFF	DIFF	CONV	DIFF/CONV
Pore size	<5	5–20	>30	>30
C ur (ml/m) (L/D)	160 29	38 29	1826 32	20
Replace?	No	No	Yes	Yes

Continuous renal replacement therapy offer some advantages:

- Improve hemodynamic stability
- Allow an optimal fluid balance during gradual urea removal
- Permits a supply of virtually unlimited amounts of alimentation

The main disadvantages are:

- Patient immobilization
- Side effect from lactate-containing dialysate formulas
- Risk for hypophosphatemia, hypomagnesemia, and hypokalemia

Evidence-Based Selection of Dialysis Modality

Unfortunately, there is no consensus regarding the timing, duration, frequency, and amount of dialysis to be administered for patients with ARF in the ICU. In practice, the modality choice is dictated by the experience of the provider and the availability of various modalities, tailored to the needs of each patient. However, continuous renal replacement therapy is indicated for patients with hemodynamic instability associated with sepsis and multiorgan failure, patients in need of aggressive nutritional support, and in patients with oliguria and volume overload resistant to diuretics. In regards to the membrane of choice, biocompatible membranes seem to be associated with improved renal recovery [34–36] and specifically polyacrylonitrile membrane is more efficient in clearing certain cytokines such as tumor necrosis factor, and interleukin (IL)-1β and IL-6, when compared with a polysulfone or polyamide membrane. Nevertheless, human studies have shown the ability to remove cytokines during CCRT [37–40].

When considering dialysis modalities, it is important to remember that patients with ARF tend to have fluctuating body fluid composition and varying urea generation rates. Nevertheless, a number of factors are related to the dialysis dose delivered. Ronco et al. have shown that in patients treated with hemofiltration techniques, a filtration rate of 35 ml/h/kg was associated with improved 15-day survival [41,42].

According to intermittent versus continuous therapy, the data from retrospective

analyses conflict with some studies that show a survival advantage and other studies that show CCRT has no advantages over conventional dialysis. A review of multiple studies showed that no survival advantage was conferred with the use of continuous therapies [43]. Although there is no definitive evidence that CCRT is superior to intermittent hemodialysis, it may be inherently invalid to make such a broad comparison. It might be more appropriate to categorize patients into subgroups. Patients with heart failure may have different outcomes with CCRT than patients with sepsis or trauma. Similarly, patients with end-stage liver disease who do not have a transplant have a poor outcome irrespective of the treatment modality used.

There are also new emerging dialysis techniques developing as continuous coupled plasma filtration and adsorption for the management of SIRS and sepsis [40].

Recommendations

- Acute renal failure affects one fourth of intensive care unit patients and significantly increases morbidity and mortality, particularly in the setting of multiorgan failure and refractory hypotension.
- Early recognition and treatment of acute renal failure may limit progression of renal dysfunction and complications.
- Causes of acute renal failure in this setting are usually multifactorial, but often include decreased effective renal perfusion and exogenous or endogenous nephrotoxins.
- Use of continuous renal replacement therapy provides excellent metabolic control and is particularly useful for managing volume status in critically ill patients.
- Continuous renal replacement therapy is preferable to intermittent hemodialysis in hemodynamically unstable patients.
- Replacement fluid composition must be individualized for each patient and adjusted as needed.

Conclusions

Oliguria and renal dysfunction are common in critically ill patients. In most cases the kidney is an innocent bystander affected secondarily by the primary disease process. Circulation must be corrected before any other specific intervention is started. The cause of renal dysfunction must be determined and if possible treated. There are considerable differences in opinion and practice patterns regarding indications for dialysis in the intensive care unit setting. Renal replacement therapy should be started and tailored according to the degree of biochemical derangement and the patient's underlying condition. Most ICU patients die WITH acute renal failure, NOT FROM acute renal failure.

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Section VI
Respiratory System and Protective Ventilation

The Evolution of Imaging in Respiratory Dysfunction Failure

17

L. Gattinoni, E. Carlesso, F. Polli

Introduction

In this chapter we will illustrate the paradigmatic role that medical imaging has played in helping to define, understand, and treat a specific form of respiratory failure called acute respiratory distress syndrome (ARDS). ARDS is a life-threatening syndrome characterized by noncardiogenic (inflammatory) pulmonary edema causing mainly hypoxemic respiratory failure unresponsive to conventional therapy.

In 1967, Ashbaugh et al., when describing ARDS for the first time, wrote: "The clinical pattern, which we will refer to as respiratory-distress syndrome, includes severe dyspnoea, tachypnea, cyanosis that is refractory to oxygen therapy, loss of lung compliance, and diffuse alveolar infiltration seen on chest x-ray." [1] (Fig. 17.1), setting out the presence of bilateral infiltrates on a chest x-ray as one of the criteria for defining the syndrome. Since ARDS represents an unspecific response of the lung parenchyma to several pulmonary or extrapulmonary insults causing inflammatory edema, its imaging correlate is also unspecific. The chest x-rays film of a patient with ARDS would only display radiologic signs reflecting increased lung tissue density (caused by the widespread accumulation of edema [2]), such as diffuse ground glass opacification, possibly associated with patchy densities. Typically, the heart has a normal size and there are no indications of hemodynamic impairment, unless the patient has other diseases.

For almost 20 years, diagnostic imaging for patients with ARDS has been limited to chest x-rays. Such a technique made it possible both to evaluate the extent and distribution of lung opacities and to detect signs of barotrauma (e.g., pneumothorax,

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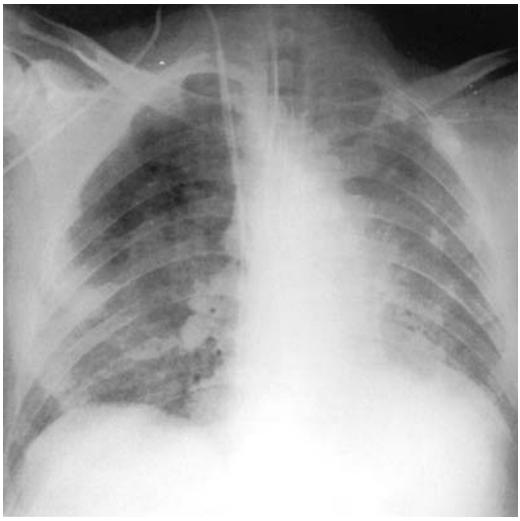

Fig. 17.1 Anteroposterior chest x-ray showing diffuse ground glass opacification, sparing the right upper lung. Published with permission from [18]

mediastinal or interstitial emphysema), a fairly common complication of mechanical ventilation in the 1980s [2,3]. However, already back in 1965, Fantoni and Damia [4] ran ahead of their times and could already evaluate the nature of x-rays densities (identification of atelectasis versus consolidation, i.e., lung recruitability) by performing conventional chest x-rays at different levels of end-expiratory airway pressure (0–15 cmH_2O). Unfortunately, their report in Italian was completely ignored and did not impact the scientific community. A similar fate befell the first report in German about the use of computed tomography (CT) in ARDS [5], which was only rediscovered a posteriori after Maunder et al. [6] and Gattinoni et al. [7] described, for the international literature, the CT findings in patients with ARDS.

In this chapter, we will examine two imaging techniques: conventional chest x-rays and CT scanning. To fully understand the potential of these techniques, it may be worthwhile to briefly summarize their physical and technical backgrounds. Other imaging techniques such as impedance tomography or CT-PET (positive emission tomography) – despite being promising – are still experimental and have not yet entered into clinical practice.

Chest X-rays

Physical and Technical Background

X-rays were discovered in 1895 by the German physicist Wilhelm Röntgen. Their nature is that of an electromagnetic radiation of extremely short wavelength (10^{-8} to 10^{-12} m) and high frequency (10^{16}–10^{20} Hz). X-rays are partially absorbed by the tis-

sues they traverse, with the result of being more attenuated when passing through dense tissues such as bone, and less attenuated when passing through softer tissues. Indeed, the basis of the formation of medical images is the different degree of attenuation of an x-ray beam by tissues of different density.

The equipment [8,9] for generating x-rays is regulated by voltage adjustment, milliamperage, and exposure time. Voltage adjustment controls the energy of the beam. The higher the difference in electrical potential, the more energetic the beam will be and the less impact will tissue density have on differential attenuation (i.e., images will have lower contrast). The milliamperage (mA) control and the exposure time affect the blackness of the film. Modern equipment is characterized by automatic exposure control. Adequate contrast of the image plays an important role in making it possible to detect the presence of abnormalities whose radiologic density may be only slightly different from that of surrounding normal tissues. A single optimal contrast level does not exist since different regions of the body are characterized by different patterns of tissue composition. In the chest, for example, tissues with radiologic density varying from that of bone to that of air may be found. In this case, images with low contrast (high kV, low mA) may be produced. In contrast, the breast is composed of different tissues, all with water-like density. High contrast images (low kV, high mA) are therefore necessary to study it correctly. It should be noted that for similar film densities a high kV technique results in lower radiation exposure for the patient.

The basic tool for recording radiographic images is usually a film-screen system where x-ray photons are converted into photons with wavelength close to that of the blue end of the visible light spectrum. This classic system, however, in recent years, seems to be becoming superseded by electronic recording in a digital format. Grids can be used to cope with the problem of scattered radiations generated by the interaction between photons and tissues (Compton effect).

Portable Chest X-rays

ICU patients are usually affected by complex medical problems, are invariably dependent on a variety of medical devices, and are frequently intubated. All these factors make their transport difficult. The use of portable chest x-rays complements, in most ICUs, the daily physical examination. Actually, in many hospitals, between one third and one half of the total number of chest x-rays performed are done in the ICU [10]. In this scenario, the portable chest x-ray remains one of the simplest examinations used at bedside to assess the cardiopulmonary status of ICU patients and the positions of catheters and lines. The accuracy and efficiency of portable chest radiography depends on the technique used and on the consistency of this technique. The previously described limitations coupled with the inability of ICU patients to cooperate and with the nature of the ICU environment render portable chest radiography one of the most challenging radiographic examinations. In an effort to improve the quality and interpretation of the images, the American College of Radiology promulgated practical guidelines for the performance of pediatric and adult portable chest radiographies [11]. The key to optimize the chest radiography is to minimize variations of all technical parameters. In

cooperative adults and older pediatrics patients, fully upright portable chest radiographs should be performed at a source-image distance of 102–182 cm, the optimal distance being the latter. Infants, younger children, and comatose and uncooperative patients may be imaged supine or semirecumbent with a 102-cm or greater distance. Radiographic exposure should be performed at peak inspiration and the radiograph should include the lung apices, the costophrenic angles, the upper airways, and the upper abdomen. In the adult, if no grid is used, kV should be between 70 and 100 to optimize penetration and limit the effects of scattered radiation. If a grid is used, kV greater than 100 may be employed. For pediatric patients lower kV may be used to optimize contrast. Mid-grey levels are used to properly display lung parenchyma. Exposure time should be as short as possible to reduce motion artifacts. Portable x-rays equipment should have exposure times ranging from 100 msec for adults to 30 msec for newborns and infants. Obviously, to compare chest x-rays performed on different occasions the degree of lung inflation, the distance between the machine and the chest, the kV, the mA, and the exposure time must ideally be the same. The literature indicates that findings (such as the amount of aerated and nonaerated lung tissue) obtained with portable chest x-rays (as performed in ICU) correlate sufficiently with data obtained with CT scanning, provided that a series of assumptions are met (such as a standardized technique for chest x-ray performance and a standardized semiquantitative film interpretation using a predefined scoring system for lung edema).

Clinical Use

The great advantages of chest x-rays are a low exposure to radiation and the possibility to perform the examination at the bedside. Conventional chest x-rays can adequately detect the position of catheters and lines [10] and identify pneumothorax or pneumomediastinum (with the exception of strictly anterior or posterior pneumothorax [12]). Chest x-rays, however, cannot discriminate whether opacities are bronco-pneumonia foci or areas of atelectasis [10]. The problem is addressed to by taking into consideration other clinical data besides the x-ray film. For years, ICU patients have received daily chest x-rays. Several reports, however, have shown that this practice is useless and has been currently abandoned in most ICUs [13–16]. We believe that chest x-rays are still useful for assessing position of devices but clinically insufficient to detect and to differentiate clinical events such as pneumonia, atelectasis, and lung recruitability. The gold standard for such purposes, as discussed below, is CT scanning.

CT Scan

Physical Background [17,18]

The CT scanner produces a digital image that consists of a square matrix of picture elements (pixels). Each pixel in the matrix represents a voxel (i.e., a volume element

of the tissue). What the CT scan measures is the linear attenuation coefficient (μ), which is the reduction of the radiation intensity (resulting from all types of interactions) upon passage through the matter. Traversing from one side of the patient to the other, the x-ray beam will be attenuated by all the voxels through which it passes. The intensity of the emerging x-ray is described by Lambert's law of absorption:

By measuring the emerging (I) and source (I0) intensity of the radiation, the CT scanner calculates the integral of the attenuation coefficient (μ) along the x-ray beam path. Through a different mathematical algorithm (usually a filtered back-projection) a given attenuation number is subsequently assigned to each voxel. The attenuation number depends on the energy of x-ray photons and on both density and the atomic number (Z) of the scanned material. For CT imaging, high kV (in the range 120–140 kV) and heavy beam filtration is used. These technical arrangements minimize x-ray interactions with matter, which are influenced by the Z of the material. Therefore, attenuation is primarily determined by the density of the tissue. After measuring all attenuation coefficients, the CT scanner converts the measured μ of the voxel to CT numbers. CT number is defined as CT = 1,000 * (μ - water) /μ water. The CT number of water is, therefore, zero. The factor 1,000 is used to magnify the small differences in attenuation coefficients of different tissues. Indeed, for practical purposes the CT number is a measure of density (i.e., the ratio of mass to volume). However, we must always remember that several factors may lead to under or overestimation of the attenuation coefficient within a given voxel [19,20].

CT Scanning and X-ray Exposure

While CT scans make up only 4% of all medical x-ray examinations, it is responsible for up to 40% of the collective radiation dose. The growth of CT scanning is dramatic: from 2.8 million CT exams in 1981 to 20 million CT exams in 1995. Consensus does not exist about the causal relationship between low level electromagnetic radiation and cancer. However, according to the data about the excess relative risk for cancer mortality in A-bomb survivors of all ages, followed-up for 40 years (1957–1990), the risk of developing fatal cancer per each dose of 10 mSv (milliSievert, the Sievert being a physical unit measuring effective absorbed dose) radiation – which is similar to the dose received during a CT exam – is 1/2,000).

Indeed, when CT scanning is indicated, great attention has to be paid to the technical protocol, so as to keep the exposure to x-rays as low as possible [21]. Specific exposure differences also depend on the specific acquisition technique used. To further comment on the issue, let us assume that a CT scan is required for a patient with ARDS. Two different approaches can be used: volumetric high-resolution scanning or single high-resolution slices acquired every 2 cm along the entire cranio-caudal axis of the lung. In the former case, if a 16-slice multidetector CT scanner is used (0.6-mm slice thickness, 140 kV, 250 mA and pitch 1.5) the volumetric approach implies an x-ray dose of 7.5 mSv, as compared to only 0.5 mSv with the single-slice approach. In this example, the advantages of a volumetric acquisition have to be compared with an approximately 15-fold increase in the x-ray dose delivered to the

patient. It is obvious that, for most patients, a single-slice technique should be employed.

Clinical Use

CT scanning has made substantial advances in the understanding of the pathophysiology of ARDS possible, and indirectly, has brought about a refinement of mechanical ventilation. Interestingly, despite the fact that CT scanning had been in use for more than a decade, it was only in the 1980s that two papers described the CT finding in patients with ARDS static conditions [6] and with application of different levels of positive end-expiratory pressures (PEEP) [7]. The most striking finding was that, unlike in conventional chest x-rays (diffuse bilateral opacity), large parts of the lungs appeared to be spared by the disease process. These "healthy regions" were mostly located in the nondependent lung regions (i.e., in the para-sternal areas when patients were lying in the supine position). A further advance in our understanding of ARDS occurred when a quantitative analysis was performed on the CT scan data [20]. Since ultimately the CT scanner measures the density within each voxel, an indirect measure of lung weight is possible, and an estimation (based on tissue density) of the amount of normally, poorly, and nonaerated tissue is also feasible. It must be noted that the classification of lung tissue (as seen with CT scanning) into normally, poorly, and nonaerated was absolutely arbitrary, although based on the observation of the frequency distribution of CT numbers in normal subjects. With a tool for quantifying the degree of aeration of lung tissue, the first attempts of investigating the structure-function relationship in the ARDS lung were made possible [22, 23]. It was found that, contrary to what had been believed for more than 20 years, the ARDS lung was not stiff but rather it was small. In fact, the low lung compliance observed in patients with ARDS was related to the small amount of normally-aerated tissue (Fig. 17.2). No relationship was found, instead, between reduced compliance and the amount of poorly- and nonaerated tissue [24]. The ARDS lung is small and not stiff and has, therefore, been compared to a "baby lung" [22,25]. In fact, in severe cases, the normally aerated tissue may be as poorly represented as 150–200g (as compared to 800–900 g found in normal individuals). The concept of the "baby lung" has greatly helped the conceptual refinement of the determinants of ventilator-induced lung injury. It became clear that a normal tidal volume delivered to a normal lung induces a normal tissue strain (e.g., 500 mL tidal volume delivered to a normal lung with an end-expiratory lung volume of 2.5 L, induces a normal strain of 0.2). The same "normal" tidal volume delivered to an ARDS lung (having much smaller end-expiratory volume) may induce greatly unphysiological tissue strains (up to 2 or even greater) [26]. This is one of the examples of the role that imaging has played in the understanding of the pathophysiology of ARDS and in determining therapeutical consequences.

After consistently documenting that, with patients in the supine position, the "baby lung" (i.e., the normally aerated portions of an ARDS lung) was apparently located in the upper lung regions, we started to use prone positioning, aiming to

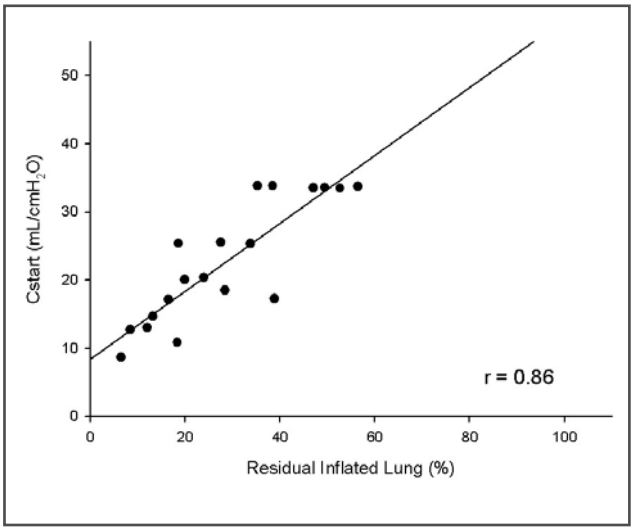

Fig. 17.2 Starting compliance (Cstart) as a function of Residual Inflated Lung expressed as percent of the expected normal lung volume. Published with permission from [24]

increase the "baby lung" perfusion and, consequently, oxygenation [27]. Indeed, oxygenation increased in most of the patients, sometimes by 150–200 mmHg. However, to our surprise, when we performed a CT scan with a patient in the prone position, we found that the "baby lung" moved from the anterior regions to the posterior regions (i.e., that densities redistributed when moving from the supine to the prone position so that they were always located towards the gravity-dependent lung regions) (Fig. 17.3) [28]. This observation marked the end of the model of "baby lung" as an

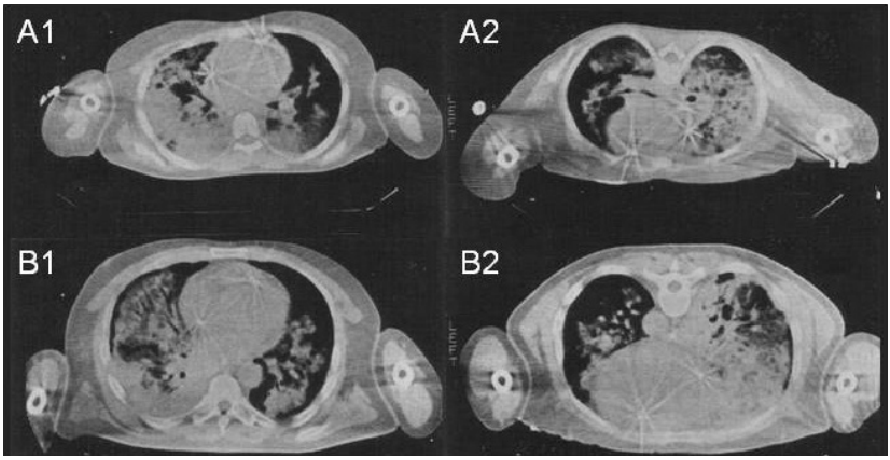

Fig. 17.3 CT scan images of two ARF patients in the supine (A1 and B1) and prone (A2 and B2) position. Published with permission from [28]

anatomical entity but was not in contrast with considering the "baby lung" a functional reality. To understand the phenomenon of lung density redistribution, we performed regional quantitative analyses with CT scanning [29]. Unexpectedly, we found that lung edema was uniformly distributed throughout the lung parenchyma. In fact, in each lung region (defined along the pulmonary vertical axis), the calculated weight of the tissue was 100% greater than in control subjects. This observation was the key to understanding the density redistribution observed when moving from the supine to the prone position. In fact, since the tissue mass is increased in all lung parenchyma, each slice of lung tissue (going from sternum to vertebrae) bears the increased lung weight of the slices above. Assuming that pressure in the lung can be transmitted as in a fluid, we could compute for each lung slice the "superimposed pressure" (Fig. 17.4) [29]. Typically, in the most dependent lung regions, the superimposed pressure to that region is 3–4 times the normal one (i.e., 12–15 cmH_2O versus 2–4 cmH_2O in control subjects). In other words, the lung collapses under its own weight. Obviously, in the prone position the superimposed pressure acts on the previously open anterior regions, which undergo collapse, while the posterior regions decollapse.

The computation and the observation of the behavior of the lung under the effects of the superimposed pressure has been the key to understanding the response to PEEP in ARDS. In a study in which we tested incremental effects of PEEP from 0 to 20 cmH_2O (by 5-cmH_2O steps), it was clearly demonstrated that at any given level, the lung could stay open (aerated) only if the applied PEEP was greater than the superimposed pressure at that level [30]. It must be understood, however, that the force counterbalancing the superimposed pressure is transpulmonary pressure (i.e., the difference between airway pressure and pleural pressure) and not airway pressure [26,31]. In mathematical terms the transpulmonary pressure necessary to exactly counteract the superimposed pressure (SP) may be expressed as:

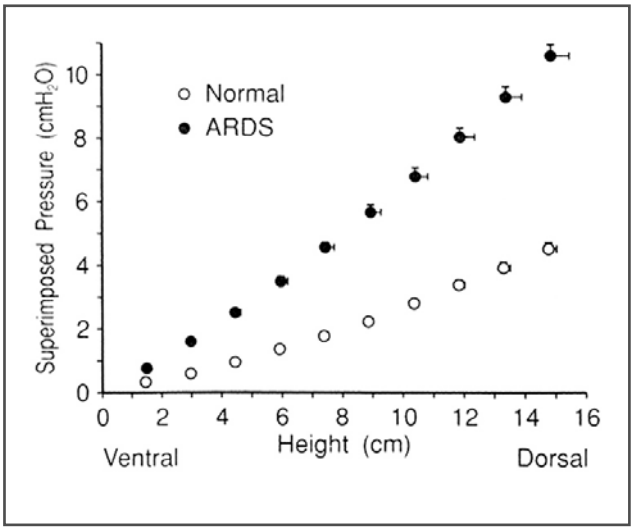

Fig. 17.4 The estimated superimposed pressure as a function of ventral-to-dorsal lung height in normal subjects (open circles, 24 lungs) and patients with ARDS (closed circles, 34 lungs). The data (mean ± SEM) of both normal patients with ARDS fits the general quadratic equation: SPL = a x hL + b x hL2. Published with permission from [29]

PEEP = SP * ETOT / EL

where ETOT and EL are the respiratory system and lung elastance.

This method of computing the PEEP level required for keeping the lung open by counterbalancing the superimposed pressure, although theoretically rigorous, has been never been tested or applied in clinical practice, since it requires both CT scanning with its quantitative analysis and the measurement of the esophageal pressure. None of these techniques are routinely performed in the ICUs around the world.

Finally, the CT scan has made it possible to describe more precisely the consequences of mechanical ventilation in terms of development of fibrosis within the baby lung, and the structure–function relationship within the ARDS lung as a function of time [18,32]. In early ARDS, the lung is basically edematous, its structure is well preserved and the intrinsic mechanical characteristics of the "baby lung" are approximately normal. In fact, in early ARDS patients, the stress–strain relationship [i.e., the slope between the applied transpulmonary pressure (stress) and the fractional change in lung volume (strain)] is indistinguishable from that of normal subjects [26]. Specific lung elastance/compliance are also similar between ARDS and normal subjects. However, if the disease leading to ARDS persists over time, dramatic structural changes (pronounced fibrosis and parenchymal lesions such as bullae or pseudocysts) occur within the lung, mainly in the dependent regions. Interestingly, bullae develop primarily in those lung regions where reiterative alveolar opening and closing phenomena (well documented in both experimental animals and patients) had mostly occurred (as demonstrated by CT scanning (Fig. 17.5) [32].

The last achievement that CT scanning has made possible is the assessment of lung recruitability. This is probably one of the most important because it may have direct clinical consequences [33]. As previously described, the primary mechanism of lung collapse during ARDS is increased superimposed pressure within the lung parenchyma due to the presence of edema. The clinical issue is to assess the amount of lung undergoing this process, which is the basis of the concept of "recruitability." In fact, the only regions of the lung which may be recruited by PEEP are the ones which are collapsed. Otherwise consolidated regions (i.e., filled with edema or solid material) cannot be reopened, no matter what the pressure applied. While the experimental ARDS models (primarily the oleic acid lavage models) are characterized by lung edema and huge recruitability, in human ARDS the picture is quite different. In fact, when we studied the first five patients in which the volume-pressure curve was

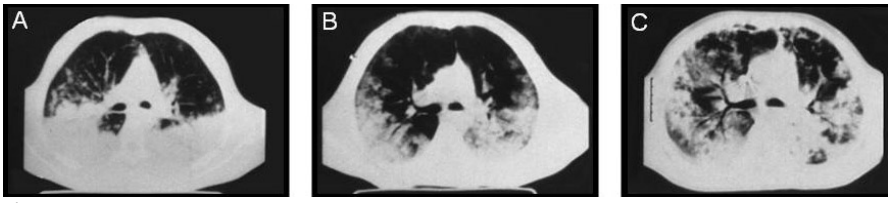

Fig. 17.5 CT scan slices taken at different ARDS stages: (A) early ARDS (1 week); (B) intermediate ARDS (2 weeks); (C) late ARDS (<3 weeks)

similar to the recruitment-pressure curve [34] (indicating that alveolar recruitment is a phenomenon occurring over a wide range of transpulmonary pressures), the actual recruitability was only 5% of the whole lung tissue. Therefore, we decided to investigate lung recruitability in a larger sample of patients with acute lung injury and ARDS [33]. The most striking finding was the huge variability of recruitability, which in patients with ARDS ranged from 0 to 80% of the lung tissue (Fig. 17.6). Interestingly, it was clear that recruitability was strictly linked to the amount of edema, giving further support to the model of the lung as a "sponge lung." This suggests that recruitment maneuvers and high PEEP should be reserved for patients with high recruitability. Otherwise, their only effect would be an unwanted overdistension of already open lung regions [35].

In our daily practice we use CT scanning as soon as possible in all the patients with ARDS to characterize their lung recruitability. CT scanning is currently the only way to quantify anatomical lung recruitment. To do so, it is necessary to perform a CT examination for at least two levels of airway pressure (e.g., 5 and 45 cmH_2O). The fraction of tissue which is nonaerated at 5 cmH_2O and regains aeration at 45 cmH_2O is the recruited tissue, which is then expressed as a fraction of the whole lung tissue (lung recruitability). The knowledge of lung recruitability allows a rational use of PEEP dur-

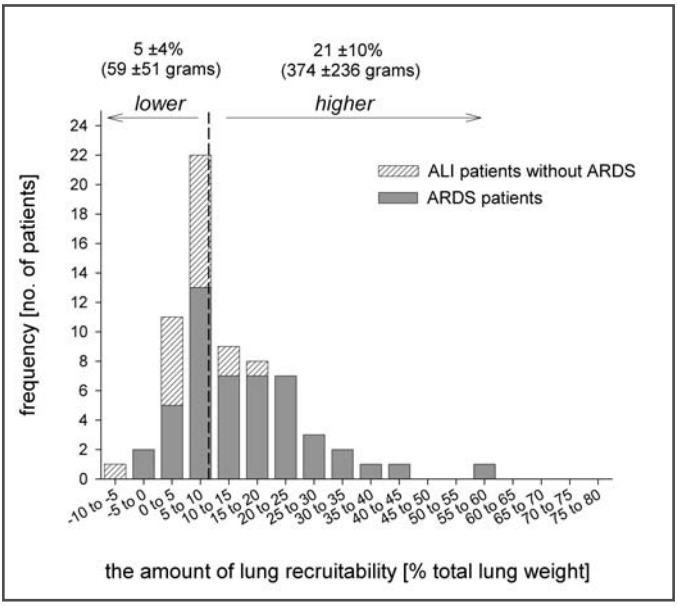

Fig. 17.6 The frequency distribution of 68 ALI/ARDS patients according to the percentage of potentially recruitable lung, expressed as the percentage of total lung weight. Acute lung injury without ARDS was defined by a PaO2/FiO2 of less than 300 but not less than 200, and ARDS was defined by a PaO2/FiO2 of less than 200. The percentage of potentially recruitable lung was defined as the proportion of lung tissue in which aeration is restored at airway pressures between 5 and 45 cm of water. Published with permission from [33]

ing the clinical management of an ARDS patient. Besides this strategic evaluation, we reserve CT scanning only for the situations in which it is strictly necessary (e.g., suspicion of a strictly anterior or posterior pneumothorax or the quantification of a prediaphragmatic area of atelectasis, not seen by conventional chest x-rays).

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ALI, ARDS, and Protective Lung Ventilation

18

R. Nanchal, E.J. Jimenez, F.E. Poalillo

Introduction

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are clinical syndromes characterized by acute onset of severe hypoxemia and diffuse bilateral pulmonary infiltrates in the absence of clinical evidence of left heart failure. The mainstay of treatment is supportive care with an emphasis on the delivery of mechanical ventilation. Often these syndromes are a part of a systemic critical illness, such as severe sepsis, polytrauma, or multiple organ failure with injury to the lung, either directly or indirectly. Increasingly, recognition of the genetic predisposition to lung injury has enhanced our understanding about these syndromes. Though therapeutic options are limited, evidence from prospective randomized trials over the last decade has provided insights into mechanical ventilation and fluid management strategies for these patients, which have improved mortality and decreased ventilator days.

Definitions and Diagnosis

First described by Ashbaugh and colleagues in 1967 [1], ARDS and ALI are characterized by the sudden onset (less than 7 days) of acute hypoxemic respiratory failure and diffuse pulmonary infiltrates that are not caused by hydrostatic pulmonary edema. In 1992 the American European Consensus Conference (AECC) developed a standardized definition for the syndromes based on the severity of hypoxemia [2]. In the absence of left atrial hypertension (pulmonary artery wedge pressure of <18

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mmHg, if measured) and presence of bilateral pulmonary infiltrates on a frontal chest radiograph, a ratio of the partial pressure of oxygen in arterial blood (PaO_2) to inspired fraction of oxygen (FIO_2) of less than 300 constitutes ALI, whereas a ratio of less than 200 constitutes ARDS. The causes of ALI/ARDS have been divided into direct and indirect injuries (Table 18.1) and although a host of clinical disorders can cause these injuries, outcomes are similar, in both categories, if underlying factors such as severity of illness and age are controlled [3,4].

Table 18.1 Examples of causes of direct and indirect ALI/ARDS

Direct lung injury	Indirect lung injury
Pneumonia	Severe sepsis (e.g., intra-abdominal sepsis, UTI)
Gastric aspiration	Massive transfusions
Pulmonary contusions	Prolonged shock
Alveolar hemorrhage	Pancreatitis
Fat embolism	Salicylate and other drug overdoses
Amniotic fluid embolism	
Near-drowning	
Smoke inhalation	

UTI, Urinary tract infection; *ALI*, acute lung injury; *ARDS*, acute respiratory distress syndrome

Though the AECC definitions have provided standardization and have been critical in identifying patients suitable for clinical trials, they are not without limitations. Interpretation of chest radiographs, even among experienced clinicians, is highly variable [5]; excluding cardiogenic pulmonary edema, even with a pulmonary artery catheter in place, can be problematic [6] and oxygenation can be altered by manipulating positive end expiratory pressure (PEEP). In a recent study using standard ventilator settings, over half of the patients initially classified as ARDS, no longer met criteria, after they were ventilated for 30 min using standardized PEEP [7]. Even when compared to autopsy findings, the clinical criteria for ARDS using AECC definitions demonstrated only moderate accuracy [8]. While the AECC definitions are the most widely used in clinical practice, other approaches to classifying lung injury such as the Lung Injury Score (LIS) exist [9].

The pathological correlate of ARDS/ALI is diffuse alveolar damage (DAD) [10]. DAD is a nonspecific response of the lung to a host of injurious events. The pathological diagnosis is rarely available due to the paucity of open lung biopsies obtained in clinical practice. Since a pathognomonic laboratory or radiological diagnostic has not been identified to confirm ARDS/ALI, important exceptions of rare diseases (e.g., acute eosinophilic pneumonia) that have specific treatments should always be kept in the differential. Patel and colleagues in a study of 57 patients who met ARDS criteria clinically, demonstrated that open lung biopsy could be performed safely, and frequently revealed an unsuspected diagnosis that led to a change in therapy [11].

Epidemiology and Outcomes

The reported incidence of ALI/ARDS varies between 1.5 to 78 cases per 100,000 persons according to the definitions used for the syndromes as well as geographical area studied. The most recent population-based cohort study was conducted in the USA and revealed a crude incidence of 78.9 per 100,000 person-years for ALI and 58.7 per 100,000 person-years for ARDS [12].

Many potential risk factors for ALI/ARDS have been reported in several studies over the years. It is abundantly clear that the clinical syndromes of ALI/ARDS represent a variety of heterogeneous diseases. The majority of the incidence has been found to be from pneumonia, sepsis syndrome, and trauma, respectively. Complex biological variables such as age, gender, body mass index (BMI), and race have emerged as potential risk factors for ALI/ARDS. Like most other diseases, the incidence and mortality from ALI/ARDS increases with advancing age [12]. Chronic alcoholics are at increased risk for developing ALI/ARDS whereas, interestingly enough, diabetics are less likely to do so [13,14]. African-American race and male gender are associated with increased death rates [15]. Mortality is greatest in those who have sepsis and is least in the trauma population [12]. The number of nonpulmonary organ dysfunctions, increased severity of illness, shock, and hepatic failure are all independent risk factors for increased mortality [16]. Of note is that the degree of hypoxemia is not an independent predictor of outcome [16]. An area of investigation that has been of extreme interest recently is the genetic epidemiology of ALI/ARDS. Multiple polymorphisms of genes that encode for various cytokines and other inflammatory mediators are being studied in an effort to gain insight into the reasons for the different phenotypic behaviors of patients with ALI/ARDS [17].

The most recent studies have reported mortality of ARDS between 29 and 40% [12,18]. We have continued to experience a decline in the overall mortality over time. The exact reasons for the declining mortality remain unclear but may have to do with better general care for critically ill patients as well as improved strategies of mechanical ventilation [18]. Most patients appear to die with ALI/ARDS, rather than from it. It is rare for patients to die from unsupportable hypoxemic respiratory failure [19]. It is rather the underlying disease process that caused ALI/ARDS that is the primary cause of mortality and, since sepsis is the most common cause for ALI/ARDS, most studies have reported sepsis-related multiple organ failure as the main reason for mortality [20].

Evolving data suggest that there is a significant burden of long-term neuromuscular, cognitive, and neuropsychological dysfunction in survivors of ALI/ARDS [21,22]. Pulmonary dysfunction in survivors largely resolves over time [21]; however, many have not returned to work or resumed their normal daily life even 1 year after the acute event [21]. Also, a number of patients will have significant cognitive decline [22]. Not only do these factors lead to a significant decline in the health-related quality of life for the survivors, but caregivers of these patients face significant challenges and may suffer from posttraumatic stress disorder (PTSD) [23].

Histopathology

Diffuse alveolar damage, which is the histopathological hallmark of ARDS/ALI, was first described in 1976 [24]. Injury to the alveolocapillary unit leads to an exudative protein-rich, predominantly neutrophilic fluid that accumulates first in the interstitium and then floods the alveoli. For didactic purposes, the progression of lung injury has been sequentially divided into the exudative, proliferative, and fibrotic phases. This division is arbitrary and recovery may occur without progression through all three phases. It is unclear why some survivors progress to the fibro-proliferative stage and some do not.

The exudative phase is characterized by a cytokine-induced inflammatory milieu, recruitment of neutrophils, increased oxidant stress, loss of surfactant, and destruction of type I pneumocytes. Characteristic hyaline membranes appear, which are the hallmark of DAD, and consist of fibrin and inflammatory debris. Alveoli are filled with this protein-rich, neutrophilic inflammatory exudate. During the fibro-proliferative phases, there is organization of the intraluminal exudates, type II pneumocyte proliferation, fibroblastic reaction, and collagen deposition. Involvement of the pulmonary vasculature is an important phenomenon and lesions that can range from in situ capillary thrombosis to vascular obliterative changes correlate with the stage of pulmonary parenchymal changes [25].

Pathophysiology

Leakage of protein-rich inflammatory fluid into the lung causes a compromise of gas diffusion, resulting in a ventilation-perfusion mismatch and shunt physiology, leading to a hypoxemic state that can be refractory to oxygen therapy. Loss of surfactant and collapse of the edematous lung under its own weight leads to widespread atelectasis and reduced thoracic compliance.

Capillary obliteration and regional overdistension lead to increased dead space. Hypoxic pulmonary vasoconstriction and destruction of the pulmonary vasculature lead to pulmonary arterial hypertension which, if sustained, may lead to right ventricular failure and circulatory collapse. These derangements greatly increase the work of breathing, and if left unsupported, hypoxemic and hypercapnic respiratory failure ensues.

Treatment

There is no specific treatment for ALI/ARDS. The mainstay of care is mainly supportive. Avoidance of iatrogenic injury is paramount. Specific strategies aimed at lung protective ventilation and fluid management have improved outcomes as

demonstrated by large clinical trials. The search for novel pharmacotherapies is the target of multiple ongoing research studies.

Supportive Care

Therapy should be aimed at the underlying cause of ALI/ARDS. Sepsis should be treated appropriately with fluid resuscitation and antibiotics. Care should be taken to provide prophylaxis to prevent gastrointestinal bleeding and deep venous thrombosis. Use of neuromuscular blockade and corticosteroids should be avoided or limited. Moderate glycemic control has been shown to reduce neuromuscular complications that are associated with prolonged mechanical ventilation and use of corticosteroids. Early enteral nutrition should be provided and the head of the bed should be raised to at least 30°. Protocols for targeted goal-directed sedation and weaning from mechanical ventilation should be utilized to lessen days on the ventilator.

Mechanical Ventilation

It has become abundantly clear from a plethora of animal data that mechanical ventilation itself can be injurious to the lung and cause pathophysiological changes that cannot be discerned from those of ALI/ARDS. This iatrogenic injury that occurs from mechanical ventilation has been termed ventilator induced lung injury (VILI) [26]. Initially, the goal of mechanical ventilation in ALI/ARDS was to normalize blood gases. High tidal volumes (10–15 ml/kg) and high inspiratory pressures were used to achieve this goal. CT scans of ARDS lungs provided much insight into the heterogeneous nature of lung injury and the realization that some areas were densely infiltrated (typically dependent portions), while others appeared normal or near normal [27]. Thus, the most compliant alveoli in the injured lung adjacent to tissue with markedly reduced aeration (baby lung) were significantly overdistended by the high tidal volume used. Once VILI occurs, its affects are not limited to the lungs, as there is spill-over of inflammatory mediators causing injury to distant organs. In this regard, injurious ventilation strategies may act as a motor for more diffuse multiple organ failure [28]. The facets of VILI have been described as volutrauma or alveolar distension injury, atelectrauma or injury due to shear stresses created by repeated opening and closing of collapsed alveoli, and biotrauma or biochemical injury from inflammatory mediator release.

Based on these observations, the first study to report an improvement in mortality using a low volume/low pressure strategy of mechanical ventilation was reported by Hickling in 1990. Hypercapnia with $PaCO_2$ levels up to 70 mmHg (Torr) were allowed in this study without any adverse consequences [29]. An era of research into protective strategies of mechanical ventilation in ARDS/ALI culminated with the NIH-sponsored Respiratory Management in Acute Lung Injury/ARDS (ARMA) trial [30]. Eight hundred sixty-one patients were enrolled across 10 institutions in a randomized fashion. Patients were randomized to either a ventilator protocol utilizing

tidal volumes of <6 ml/kg of predicted body weight (PBW) or 12 ml/kg of PBW. In addition, in the low tidal volume arm, the tidal volume could be reduced to 4 ml/kg if the inspiratory plateau pressure exceeded 30 cm H_2O. Thus, a combined pressure and volume limited approach was used for the low tidal volume arm. Conventional mechanical ventilation was provided to the 12 ml/kg arm. PBW was calculated based on sex and height. PEEP and FIO_2 were set according to a table to maintain oxygenation in both groups. Respiratory rate was adjusted (maximum of 35) to maintain a pH >7.3 and bicarbonate use was allowed if pH was <7.15 after adjustment of the respiratory frequency to 35. The final results demonstrated a mortality of 31% in the low tidal volume arm and 40% in those randomized to conventional mechanical ventilation (relative risk reduction of 22%) at 28 days. The patients in the lower tidal volume group also had a significantly greater number of ventilator-free days (p = 0.007), as well as, greater number of days free of nonpulmonary organ failure (p = 0.006). Plasma cytokine levels were also significantly lower in the low tidal volume group. Further analysis of the data revealed that patients randomly allocated to the low tidal volume strategy for every baseline quartile of plateau pressure had a lower mortality, thus providing a strong rationale for the use of low tidal volumes, even if the plateau pressure was low to start with. It is important to realize that patients randomized to the low tidal volume group had decreases in PaO_2/FIO_2 ratio, developed modest hypercarbia (permissive hypercapnia), and had increased respiratory rates. These physiological changes though seemingly adverse, did not have a negative impact on patient outcomes. This trial has generated substantial controversy and there still exists resistance to adoption of lung protective ventilation as the standard of care. Some of the criticisms of the ARMA trial include: that the control arm tidal volumes utilized were greater than utilized in practice, the potential deleterious effects of hypercarbia, a perceived need for more sedation and paralysis when using low tidal volumes, and the potential for development of auto-PEEP [31,32]. However, these criticisms have not been supported by evidence-based literature to date. In view of the overwhelming evidence supporting lung protective ventilation, a mechanical ventilation strategy using low tidal volumes (<6 cc/kg PBW) and limited pressures (inspiratory plateau pressure <30 cm H_2O) should be the standard of care for the majority of these cases. It is important to keep in mind that inspiratory plateau pressure is a surrogate measurement for transpulmonary pressure and this value may not be reliable in situations where the thoraco-abdominal compliance is significantly decreased. (e.g., intra-abdominal hypertension, abdominal compartment syndrome, paralytic ileus, enteric occlusions, marked chest wall edema or restrictive chest wall disease). In these cases, it may be necessary to obtain transesophageal pressures to titrate the ventilation strategy.

The Role of PEEP

The atelectrauma component of VILI is caused by repeated opening and closing of collapsed alveoli during a tidal breath. This creates large amounts of shearing forces and alveolar stress injury. The “open lung” approach calls for using higher levels of

PEEP to keep alveoli open and prevent their collapse at end expiration. The ARDSnet conducted a high PEEP versus low PEEP trial while maintaining low tidal volume ventilation [33]. This study did not show a mortality benefit between the groups, though oxygenation was improved in the high PEEP arm. PEEP has beneficial effects in terms of recruiting collapsed lung and reducing intrapulmonary shunt, but high levels can lead to adverse events such as hemodynamic compromise due to decreased venous return, elevation of end inspiratory pressures and increased dead space by overdistension of already recruited alveoli. In light of these factors use of the lowest PEEP/FIO_2 combination that produces acceptable oxygenation as used in the ARMA trial (Table 18.2) is recommended.

Table 18.2 Adjustment of PEEP using the FIO_2 required to keep PaO_2 between 55 and 80 mmHg; or SpO_2 between 88 and 95%. Adapted from [30]

FIO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.8	0.9	0.9	1.0	1.0	1.0	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	16	16	18	18	20	22	24

PEEP, Positive end-expiratory pressure; *FIO_2*, fraction of inspired oxygen; *PaO_2*, arterial partial pressure of oxygen; *SpO_2*, arterial oxyhemoglobin saturation measured by pulse-oximetry

Recruitment Maneuvers

The idea behind recruitment maneuvers rests on the concept of open lung approach. Collapsed alveoli require high pressures to reopen them. Once opened, a lower pressure is required to keep them open until a critical closing pressure is reached, after which a high recruiting or reopening pressure is required. Several approaches such as provision of high levels of PEEP (40 cm H_2O for 40 sec) or high levels of inspiratory pressure using pressure modes of ventilation for short periods of time (i.e., 2 min) can be used. Most studies using recruitment maneuvers demonstrate improved oxygenation parameters; unfortunately, no differences in terms of survival have been observed [34,35]. Further, the optimal timing, duration, or technique still remains unknown, as previously studied populations are largely heterogeneous.

Prone Positioning

Since its first description in the 1970s for improving oxygenation in respiratory failure, there have been several studies on prone positioning in ALI/ARDS. Physiological mechanisms postulated are: improvement in ventilation perfusion mismatch, recruitment of dependent lung areas, reduction in shunt, as well as less compression of the lungs by the heart. While most clinical studies have demonstrated an improvement in oxygenation for most patients, there are again no mortality benefits. While pronation cannot be recommended for routine ARDS treatment at this time, a recent meta-analysis suggests improved outcomes using this approach in patients

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with severe ARDS [36]. A large study by Gattinoni et al., completed in 2008, is expected to give substantial evidence in the near future. In a previous study, the association of improved CO_2 clearance with pronation has been observed as predictive of a better outcome in ARDS [37].

Alternate Modes of Mechanical Ventilation

The High Frequency Oscillatory Ventilation (HFOV) mode of ventilation delivers very small tidal volumes and has been proposed as the ideal mode for mechanical ventilation in ALI/ARDS. Unfortunately, none of the clinical trials have demonstrated a mortality benefit. The largest trial to date showed that patients randomized to HFOV had improved oxygenation and had a nonstatistically significant trend towards improved survival [38]. It should be kept in mind that the control group in this study was ventilated with large tidal volumes (8 ±2 cc/kg). The large OSCILLATE trial is currently underway, in an attempt to define the use of this modality outside of rescue strategies.

The Airway Pressure Release Ventilation (APRV) mode of mechanical ventilation uses two levels of continuous positive airway pressure. The majority of the time is spent at the higher pressure which promotes alveolar recruitment, with a release time to the lower pressure to supplement minute ventilation. The mode allows unrestricted spontaneous breathing at both levels of pressure, thus theoretically allowing for ventilation of dependent lung regions and recruitment of collapsed alveoli. Though there are physiological benefits, trials demonstrating end points such as mortality are lacking.

Other modalities of ventilation such as pressure control inverse ration ventilation (PC-IRV) and liquid ventilation, though available, have not shown any benefit in outcome as compared to conventional ventilation and are not recommended for routine use.

Fluid Management and Pulmonary Artery Catheter in ALI/ARDS

Recently a large randomized control trial comparing a liberal versus conservative fluid management strategy in patients with ALI/ARDS was published (Fluid and Catheter Treatment Trial of FACTT). Both strategies were tested in a factorial design that also tested the utility of a central venous catheter (CVC) versus a pulmonary artery catheter (PAC) [39,40]. Fluid and diuretic management was highly protocolized and all patients were managed with a lung protective strategy of mechanical ventilation. In terms of the catheters, the clinical outcomes were similar (CVC group 26.3% mortality vs. PAC group 27.4% mortality). In contrast, in the fluid management strategies, there were significantly improved outcomes in the fluid conservative group. Patients assigned to the fluid conservative group had significant more ventilator-free days than the fluid liberal group (14.6 ±0.5 vs. 12.1 ±0.5; p <0.001). The conservative fluid arm also had more ICU-free days (13.4 ±0.4 vs. 11.2 ±0.4;

p <0.0001). Although there was a 2.9% reduction in mortality at 60 days in the conservative fluid arm, this did not reach statistical significance. There were no differences in the two groups between the incidence and prevalence of shock, renal failure, or the need for renal replacement therapy. More importantly, diuretics in the study were only given to patients if they were out of shock for at least 12 h. Based on these findings, a fluid conservative strategy is recommended for management of patients with ALI/ARDS once they are hemodynamically stable. Careful attention should be paid to electrolyte balance when using aggressive diuresis. PAC for routine monitoring of patients with ALI/ARDS does not appear to add any significant management information and is not recommended.

Corticosteroids

Based on initial studies of corticosteroid use in patients with ARDS, the ARDSnet conducted a randomized placebo controlled trial using corticosteroids in patients with persistent ARDS, which was defined as meeting ARDS criteria and the need for persistent intubation and mechanical ventilation for at least 7 days and no more than 28 days [41]. Mortality was similar at 60 days in both the treatment and placebo arms. Though there was a benefit in terms of days on mechanical ventilation in the steroid arm, there was no benefit in terms of length of ICU stay. Moreover, more patients in the steroid arm were returned to mechanical ventilation presumably due to neuromuscular weakness. In subgroup analysis, patients who had ARDS for 14 days or more and were randomized to the steroid arm had a significantly higher mortality. Though complicated, the results of the trial led the authors to conclude that the routine use of corticosteroids was not justified in patients who had persistent ARDS.

Vasodilators

Many vasodilators, both nonselective and selective, such as nitroprusside, prostacyclin, and inhaled nitric oxide (INO), have been tested for ALI/ARDS. Most clinical data is with the use of INO and like many other therapies an improvement in oxygenation and pulmonary vascular resistance has been demonstrated without translating into any meaningful improved outcomes. Hence the use of INO and other vasodilators outside of rescue therapy cannot be recommended.

Extracorporeal Support

The initial trials of extracorporeal membrane oxygenation (ECMO) and CO_2 removal did not confer a survival advantage, though oxygenation and hypercarbia were markedly improved. The recently completed CESAR trial reportedly has shown a mortality difference in the ECMO arm, though the peer-reviewed publication is still awaited.

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Recommendations

1. ARDS/ALI are complex syndromes with a variety of causes and early diagnosis should be based on AECC criteria.
2. Mechanical ventilation and good supportive care are the cornerstones of treating patients with ALI/ARDS.
3. Lung protective strategies with low tidal volumes (<6 cc/kg PBW) should be employed during mechanical ventilation. Plateau pressure should be limited to less than 30 cm H_2O. Tidal volume may be reduced to 4 cc/kg in a step-wise fashion to achieve plateau pressure targets.
4. A fluid conservative strategy should be employed once patients are hemodynamically stable.
5. Until further trials become available, therapies such as HFOV, prone positioning, recruitment maneuvers, INO, and alternate modes of mechanical ventilation have been used in the context of rescue therapies for refractory hypoxemia, with no clear improvement in outcomes.
6. Routine use of corticosteroids and pulmonary artery catheters for the management of ALI/ARDS is discouraged.

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Section VII
Infections Surveillance, Prevention and Management

From Surveillance to Prevention

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Introduction

Healthcare-associated infections (HCAI) are preventable errors. In 1999 the Institute of Medicine (IOM) released its landmark report "To err is human." IOM estimated that as many as 100,000 patients died from medical errors in the USA, with a cost of over $50 billion/year [1]. The improvement of the quality of healthcare is a major concern for intensive care professionals because patients in the intensive care unit (ICU) are thought to be particularly at risk for errors due to the complexity of the patients, interdependence of the practitioners, and dependence on team functioning. Ensuring patients' safety during their hospital stay requires mechanisms to determine the incidence of adverse effects. Published reports estimate that 1.7 errors per patient per day occur in the ICU and 148,000 life-threatening errors would occur annually in teaching hospital ICUs in the USA [2].

Notification systems reveal that HCAI are key adverse effects in hospitals because of their frequency and impact [3,4]. ICUs account for 20–25% of reported HCAI. Critically ill patients present the highest incidence of nosocomial infections (NI) among hospitalized patients because they are the most susceptible patients with altered defensive barriers in an environment with many opportunities for cross-transmission and a selected ecosystem. ICU-acquired infections are generally related to the use of invasive devices such as mechanical ventilation (MV), central venous catheter (CVC), or urinary catheter (UC). Ventilator-associated pneumonia (VAP) is a common hospital-associated infection, occurring in between 10% and 20% of patients receiving MV for more than 48 h. Catheter related blood stream infection (CRBSI) is the second most important HCAI in the ICU. Both are associated with major morbidity and mortality and what is most important, up to 70% of them could be preventable.

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Definition

Surveillance and control systems are programs dedicated to collecting and analyzing data on the frequency of HCAI and their associated risk factors and pathogens. Effective surveillance involves counting cases and then calculating rates of various infections, analyzing this data, and then reporting that data in an appropriate way to personnel involved in patient care, to propose corrective measures and to evaluate them. The essential elements of surveillance are shown in Table 19.1.

Experts consider that several conditions are required for the success of reporting systems [3]. First of all, they should be not punitive to avoid the fear of the reporters for the consequences. Confidentiality: the identity of the patient, reporter, and institution shouldn't be revealed. Independence: the program should be independent with respect to authorities with power to punish. Expert evaluation: the report has to be analyzed by experts able to understand the clinical and underlying system causes. Timely: the feedback of the analysis of the report and the recommendations should be rapidly disseminated to those who need to know. System-oriented: recommendations for changes should focus on systems and processes rather than on individuals. Finally, the agencies receiving the information should be able to elaborate and disseminate recommendations and the participants agree to implement them.

Table 19.1 Essential elements for surveillance

Assess the population
Select the outcomes and processes to survey
Choose the surveillance methods for risk adjustment
Monitor for the outcome or process

Surveillance Programs

The first program of HCAI surveillance started in 1970 in the USA, following the requirements of the Joint Commission for Accreditation of Hospitals (JCAHQ). They use the definitions and guidelines issued by the Center for Disease Control and Prevention (CDC). The CDC National Nosocomial Infections Surveillance (NNIS) publishes national benchmark infection rates of hospitals for inter- and intra-hospital comparisons derived from data sent by participating centers [5,6]. These rates have been used as a reference for other surveillance systemsin some national or regional programs in Europe—France-Rea, KISS, and ENVIN-UCI, HELICS [7] or other continents, including limited-resources countries [8].

HCAI surveillance systems are based on prevalence and incidence studies [5,7,9,10]. Prevalence studies inform on infections present at the time of the study, not about infections already cured. They consume few resources, give a valuable snapshot of a particular moment, but are less accurate and tend to amplify infection rates and antibiotic resistance figures. The EPINE study [10] carried out in Spain

from 1990 includes the surveillance of all the hospital services, and the EPIC I and II, controlling only ICUs [9], are the most important prevalence studies till now. Incidence studies are time- and effort-consuming, but allow for an assessment of etiological forces with stronger evidence. This makes them the most used type of study to detect infections in high-risk units such as ICUs, and to evaluate their association with invasive procedures. Programs of the relevance of NNIS and HELICS use incidence methodology. The specific objectives of nosocomial infection surveillance in critically ill patients are shown in Table 19.2.

Exposure to devices can be calculated using unit-based or patient-based surveillance.

Unit-based surveillance is a simplified database assuming stratification by type of unit only. Denominators are collected per unit and consist of the number of patient days for patients staying in the ICU and/or number of patient days exposed to devices (MV, CVC, or UC). Numerators consist of data of patients with ICU-acquired infections. The main indicators are the site-specific incidence rates (e.g., number of ICU-acquired pneumonia episodes/1,000 patients days or 1,000 days of exposure to devices), pathogen-specific incidence rates (e.g., number of MRSA pneumonia infections per 100 patients or 1,000 patient days). It provides limited interunit comparability and is reasonably well suited for unit monitoring in time and for regional, national, and international trend follow-up. Limited comparisons are possible through stratification of the rates by ICU type and by the mean percentage of intubated patients in the ICU, an approximation of case mix severity. The simplicity and the low workload of unit-based surveillance favor continuous participation in order to obtain more extensive data to stabilize the NI indicators and the follow-up time trends.

In patient-based surveillance, device use data is collected individually for all patients, whether infected or not. Individual patient data on extrinsic and intrinsic risk factors is also collected. Surveillance being centered on patient characteristics and exposure allows the determination of device-adjusted infection rates, stratification of rates by patient type, and risk-adjusted inter-ICU comparisons for benchmarking purposes. However, it can overlook some of the unit characteristics influencing infection rates, such as staffing (patient to nurse ratio, skills, and turnover), architecture of the unit, case mix, or antimicrobial use [11].

Table 19.2 Objectives of nosocomial infection surveillance in critically ill patients

Assess the rates of device-related infections acquired in ICU
Identify the most frequent micro-organisms responsible for each surveyed infection
Monitor and assess multiresistance markers
Study of intrinsic risk factors frequency and exposure to extrinsic risk factors
Outbreak detection
Study of control measures
Evaluation of ICU-acquired infections' impact

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Infection Rates

Severity and underlying disease along with use of devices are the main risk factors to develop infections but differences in healthcare systems and budgets between countries may also affect nosocomial infection rates, e.g., budgets and healthcare policies influence education. Differences in the ICUs' populations explain in part why not all critically ill patients have the same risk to carry or to acquire infections. Trauma and some surgical patients (burns, neurosurgical) present the highest rates of ICU-acquired infections, particularly VAP. In the NNIS study, rates are expressed in device-adjusted NI rates stratified by more than 10 different types of units with a homogeneous case mix [6]. ICUs in Europe are mostly mixed (medical-surgical) and not as specialized as in the USA, so traditional NI rates including device-associated infection rates cannot sufficiently adjust for differences in case mix [12]. Therefore, advanced risk adjustment in Europe requires patient-based surveillance instead of CDC/NNIS unit-based surveillance.

It should be noted that the way of expressing the indicators of infections related to device use can lead to confusion. Rates per 100 patients or incidence densities per 1,000 stay days or per 1,000 days of device use are not equivalent. Nevertheless, incidence density per days of exposure to risk factors are the most helpful and allow intra-unit comparisons, but the risk of developing pneumonia of 100 patients ventilated for 1 day is not equivalent to the risk of 10 patients ventilated for 10 days.

Other factors explaining surveillance variability in the ICU are duration of surveillance and definitions of infections. Duration of surveillance is relevant in small ICUs with limited number of admissions, especially if the number of patients collected is less than 100; seasonality or presence of outbreaks can also modify rates. Differences in diagnosis can led to important variations in rates. VAP is the ICU-AI with the higher variability in microbiological diagnostic tests, not only between countries or areas, but between units too. In 2008, the CDC/NHSN launched the new definitions for surveillance of HCAI [13]. Pneumonia was categorized into 3 types: clinically defined pneumonia (PNU1), pneumonia with specific laboratory findings (PNU2), and pneumonia in immunocompromised patients (PNU3). Clinical diagnosis alone was considered not an acceptable criterium for healthcare-associated pneumonia. However, in PNU2, the accepted respiratory samples didn't include quantitative or nonquantitative cultures from possible lower respiratory tract as sputum or tracheal aspirate, which are the most commonly used diagnostic techniques in many ICUs. In the European surveillance, HELICS criteria for pneumonia definition includes 5 categories based on the microbiology diagnostic technique used, offering an option to compare similar pneumonia entities within and between networks [14]. The creation of 5 categories of PN according to the diagnosis criteria permits each practitioner to collect data according to his/her regular practice and to the coordination level to identify the diagnostic criteria used per country, region, and type of hospital (Table 19.3).

Table 19.3 Pneumonia definition in HELICS

Rx criteria	
Two or more serial chest X-rays or CT-scans with a suggestive image of pneumonia for patients with underlying cardiac or pulmonary disease	
In patients without underlying cardiac or pulmonary disease one definitive chest X-ray or CT-scan is sufficient and at least one of the following symptoms:	
Signs and symptoms	
Fever >38 °C with no other cause	
Leukopenia (<4,000 WBC/mm^3) or leucocytosis (≥12,000 WBC/mm^3)	
AND	
At least one of the following (or at least two if clinical pneumonia only = PN 4 and PN 5)	
New onset of purulent sputum, or change in character of sputum (color, odor, quantity, consistency)	
Cough or dyspnea or tachypnea	
Suggestive auscultation (rales or bronchial breath sounds), wheezing	
Worsening gas exchange (e.g., O_2 desaturation or increased oxygen requirements or increased ventilation demand)	
Microbiology	
Bacteriologic diagnostics	Code
Positive quantitative culture from minimally contaminated lower respiratory tract (LRT) specimen	PN 1*
Broncho-alveolar lavage (BAL) with a threshold of ≥10^4 CFU/ml or ≥5% of BAL obtained cells contain intracellular bacteria on direct microscopic exam Gram stain (classified in the diagnostic category BAL)	
Protected brush (PB Wimberley) with a threshold of ≥10^3 CFU/ml	
Distal protected aspirate (DPA) with a threshold of ≥ 10^3 CFU/ml	
Positive quantitative culture from possibly contaminated LRT specimen	PN 2*
Quantitative culture of LRT specimen (e.g., endotracheal aspirate) with a threshold of 10^6 CFU/ml	
Alternative microbiology methods:	PN 3
Positive blood culture not related to another source of infection	
Positive growth in culture of pleural fluid	
Pleural or pulmonary abscess with positive needle aspiration	
Histological pulmonary exam shows evidence of pneumonia	
Positive exams for pneumonia with virus or particular microorganism (*Legionella*, *Aspergillus*, mycobacteria, mycoplasma, *Pneumocystis jiroveci*)	
Positive detection of viral antigen or antibody from respiratory secretions (e.g., EIA, FAMA, shell vial assay, PCR)	
Positive direct exam or positive culture from bronchial secretions or tissue	
Seroconversion (ex: influenza viruses, *Legionella, Chlamydia*)	
Detection of antigens in urine (*Legionella)*	
Positive sputum culture or non-quantitative LRT specimen culture	PN 4
No positive microbiology	PN 5

* PN 1 and PN 2 criteria were validated without previous antimicrobial therapy.
** *CFU*, Colony Forming Units

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Needs

Surveillance programs allow detection of endemic and or outbreak situations, to evaluate the impact of ICU-acquired infections and the efficacy of control measures. The needs for surveillance are multiple, at local, national, and supranational levels. Locally, ICUs should use their data to guide local prevention strategies and other quality improvement efforts aimed at reducing infection rates, but also at implementing adapted local antibiotic guidelines. At a national level, the objectives will be to identify threats and establish national trends and risk factors, providing reference figures for risk-adjusted interhospital comparisons and benchmarking. If needed, training and support with follow-up of implementation guidelines should be offered by the public health authorities. At a supranational level (e.g., European Center for Diseases Control), surveillance is necessary for intercountry comparisons, to identify international threats and coordinate measures or implement recommendations.

There has been a global and rapid rise in the rate of resistance among bacterial pathogens recovered in ICUs. Multidrug-resistant pathogens are more frequently resistant to empiric antimicrobial regimens than are susceptible organisms, which leads to a delay in the institution of effective therapy with the result of, in some cases, increased mortality. The importance of knowing etiology and local resistance patterns has been illustrated by several studies. One report showed that the prevalence and types of resistant Gram-negative infections varied among ICUs and institutions. For example, in Barcelona, *P aeruginosa* accounted for 73 of 74 infections due to resistant pathogens, whereas at another ICU in Seville, *Acinetobacter* was the main culprit [15]. Another study showed that incidence and susceptibility of pathogenic bacteria can vary between ICUs within a single hospital. Statistically significant differences between surgical, trauma, and medical ICUs in susceptibility to various antibiotics were found for *Pseudomonas sp, Acinetobacter sp, Klebsiellla sp, S. aureus* or *Enterococcus sp.* Although *S. aureus* was the most common pathogen isolated, the incidence of recovered organisms in each unit also varied in a large teaching hospital [16]. Moreover, microorganism and their susceptibility patterns can vary through time in each individual ICU.

Standard of Care

Whatever the detection, registration, and reporting method, NI surveillance programs (NISP) are necessary to establish corrective measures. They are relevant only if they aim at improving care.

The standard of care should be interventions to promote progressive improvements in quality of care and also in efficiency. Resources required for surveillance staff and quality improvement teams should be provided by the administration, bearing in mind that adequate personnel requirements and isolation capacity are also essential.

Some legal aspects lead to differences in surveillance between countries. Whereas in certain countries the surveillance systems are optional, in others they are compulsory, or there are laws favoring their implementation. Mandatory surveillance carries costs that are not always understood by local governments [17,18]. Different political systems may have different ways of approaching the problem and consequently modify the surveillance results. Furthermore, hospitals participating voluntarily in surveillance networks are generally those most motivated to reduce their infection rates and therefore may have lower rates than hospitals with compulsory surveillance. Moreover, hospitals participating voluntarily may be penalized by publishing their infection rates, whereas nonparticipating ones, not being subject to surveillance network control, can benefit from not publishing their data. Another important issue is publicity in the media; if it is not voluntary [19], it can damage the image of the institution, or can be misinterpreted by those not familiar with the causes of differences among countries and hospitals. All of this could discourage hospitals from taking part in surveillance systems or even lead to modification of the results. Conversely, public reporting can positively influence infection prevention activities [20].

The information generated by the surveillance networks is of little use if the hospitals which participated in the data collection do not receive feedback quickly and it therefore cannot be used for infection control measures. There are surveillance networks which include in their programs the possibility for participating units to analyze their own data and obtain results in real time, such as the ENVIN-HELICS in Spain. The Spanish network also provides annual national information, facilitating comparison [7,21]. Although traditionally surveillance has been carried out by infection control staff, in recent years more and more intensive care staff (physicians and nurses) carry out this task with the result of greater involvement in the control measures to improve the situation in their units.

Quality Indicators (QI)

In many countries, public administrations have launched and favored the implementation of quality assessment and improvement program indicators including those related to ICU-acquired infection [22]. As previously mentioned, rates of NI varied widely in the different ICUs depending on the population, structure, and functionalism. A remarkable reduction of rates has been observed in recent years in the NNIS data, but this has not been confirmed in other areas including Europe. However, the figures published by individual ICUs in USA may be even greater than in developing countries [23], showing a huge variability in areas supposed to be more uniform.

To achieve Zero-NI should be the goal, but this is utopia for the majority of ICUs. Nevertheless, several rates are unacceptable. In Spain, the reference to define QI for ICU-acquired infections was obtained from the results of the previous 5 years of the national surveillance system. Indicators for antibiotic use were also included, those related to appropriateness of empirical treatment and later de-escalation [24]. Tables 19.4 and 19.5 show the Spanish QI references, and the figures of the last 3 years.

Table 19.4 Quality indicators for ICU-acquired infections in Spain

	2006	2007	2008	Reference
N of VAP/N days of MV × 1,000	14.6	14.5	14.9	<18
N of UI-UC/N days of UC × 1,000	5.11	4.69	4.73	<6
N of CRBSI/N of days of CVC × 1,000	5.05	4.65	4.89	<4
N patients with infection by MRSA × 100 admissions	0.60	0.31	0.29	<0.4

N, Number; *VAP*, ventilator-associated pneumonia

Table 19.5 Quality indicators for antibiotic use in Spain

	2006	2007	2008	Reference
N of ATB days/N days of stay in ICU × 100	109	114	117	<100
N of specific ATB/N of ATB for treatment × 100	24.3	23.1	23.7	>30
N of inappropriate ATB/N of empirical ATB × 100	14.1	12.0	14.7	<10
N of de-escalated ATB/N of empirical ATB × 100	5.7	7.0	8.9	>20
N of patients with SDD/N of pts ventilated more than 48 h × 100	5.4	6.6	5.2	>80
N of days with SDD (N of days of MV × 100	6.8	7.1	6.9	>50

N, Number; *ATB*, antibiotics; *SDD*, selective digestive decontamination; *MV*, mechanical ventilation

Preventive Strategies for Horizontal Transmission

Exogenous infections have the origin in inanimate reservoirs (ventilators, nebulizers, monitoring systems, surfaces, etc.) or in chronic carriers (sanitary workers or colonized patients) and can be transmitted during performance of basic hygiene and/or patient handling. Some preventive strategies are common to all NI, that is all those directed to the prevention of horizontal transmission of bacteria: hand and environmental hygiene; avoiding staff workload (especially for nurses); contact isolation of patient infected or colonized by resistant bacteria and surveillance of transferred patients who could be carrying resistant micro-organisms; reducing the length of stay in the ICU through the implementation of specific protocols for sedation and or weaning, enteral nutrition, etc., limits the exposition to risk factors for infection.

Hand hygiene: Although the concept of cleansing hands with an antiseptic agent emerged in the early 19th century, compliance with hand washing as basic intervention for prevention today is still a challenge. The topic chosen for the first Global Patient Safety Challenge (WHO) was healthcare-associated infection and over 2005–2006 was focused on the theme "Clean Care is Safer Care" [25]. In an ICU healthcare workers might have 30 opportunities per hour of patient care to disinfect

their hands with soap and water—that could take up half their time, so it's impractical. Alcohol-based hand rubs significantly reduce the number of germs on skin and are fast acting [26]. The alcohol dispensers are an improvement; they're convenient and can be used on the go.

Environmental hygiene: Failures in cleaning wards have been linked to MRSA and *Acinetobacter baumannii* acquisition in ICUs [27,28]. Currently, great emphasis is placed on environmental hygiene for the prevention of horizontal transmission of multiresistant bacteria. Some studies found that admission to an ICU room in which the previous occupant was a carrier of MRSA or vancomycin-resistant enterococci (VRE) increased the next patient's risk for MRSA or VRE acquisition by as much as 40%. The authors state that MRSA and VRE contamination risk could be lessened by an intervention that calls for immersing cleaning cloths in cleaning solution, an education campaign, and feedback regarding the removal of intentionally applied marks visible only under ultraviolet light [29].

The staff workload, especially for nurses, has shown an association with increased NI rates and acquisition of MRSA [30–32]. The expertise of staff is also important, and over holiday periods when the habitual staff are not available, a rise in NI and appearance of outbreaks is common. When overcrowding is added to understaffing, control of resistant bacteria is difficult due to poor hand hygiene compliance, greater number of contacts between healthcare workers and different patients, overburdening of screening and isolation programs and resultant staff burnout [33].

Contact isolation: isolation measures to limit the spread of an HCAI include several possibilities: healthcare workers using barrier precautions (gowns, gloves, masks) as physical barriers to transmission; putting patients into isolation wards (using or not single-bedded rooms); and "nurse cohorting," with or without designated nursing staff [34,35]. The addition of rapid screening with isolation of patients at risk for colonization on admission could have an incremental effect on reduction of transmission. In the Netherlands, the "search and destroy" policy has almost eliminated the presence of MRSA [36].

Antimicrobial stewardship should be included in control practices because of the growth of multiresistance in ICU and its impact on patient management and their outcome.

Basic process indicators in ICU include VAP and CRBSI. Prevention programs for these specific NI have been frequently implemented with varying results. Perhaps better risk prediction models can be developed to target prevention strategies to the patients at highest risk. Some questions about the best ways to prevent infections, the cost-effectiveness of different interventions, and which aspects of care "bundles" (a bundle is a set of interventions—usually 3 to 5—which when grouped and introduced together, promote better outcomes with a greater impact than if performed individually) are the most important, need to be answered. However, recent programs have been particularly successful for CRBSI and VAP [37–39].

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Evidence Based

The translation of research evidence into practice is one of the main concerns for ICU staff.

Surveillance and benchmarking contributes to control. The impact of intensive HCAI surveillance and control programs in the SENIC study led to a global reduction of 33%, the highest (35%) for bloodstream infections and surgical site infections and the lowest (28%) for pneumonia and lower respiratory tract infections [5]. More recently, hospital-acquired infections in ICUs have gradually declined from 1998 to 2003 in US hospitals, according to NNISS reports. The Healthy People 2010 target for central line-associated bloodstream infection among ICU patients (4.8 infections per 1,000 days' use) is close to being met. In Europe, trends in cumulative incidence of surgical site infections from 2004 to 2006 showed a reduction in several countries [40].

The decline in rates is a response in part to a culture change in several aspects. Different guideline and bundle recommendations have been published by scientific societies, healthcare institutions, and groups of experts [41,42], although in general, guidelines require local adaptation for implementation in specific ICUs. In many settings, principles of patient safety, quality improvement, and performance improvement have been incorporated into HAI prevention. The Institute for Healthcare Improvement (IHI) created an initiative aimed at saving 100,000 lives and reducing VAP incidence in critical care [43]. The IHI is one of the main drivers of the bundle concept. Care bundles aim to ensure that patients receive recommended treatments on a consistent basis. It is advised that each aspect be well defined and based on evidence from at least 1 systematic review of multiple, well-designed, randomized controlled trials.

Important interventions such as education, checklists, standardized orders, competency assessments, and monitoring tools have played a role. What is more important, reduction in NI has become more multidisciplinary and team based, including administrative support and accountability, present at the moment in many institutions.

Keystone Intensive Care Unit Project

One of the most successful programs of prevention using bundles has been the Keystone Intensive Care Unit Project, an intervention to decrease CR-BSI [37]. The goal of this project was to improve patient safety in ICUs in Michigan, and the analysis was focused on an intervention to reduce the rate of CRBSI. Evidence-based activities included the 5 interventions that had the strongest evidence and the lowest barriers to implementation: handwashing, using full barrier precautions during the insertion of central venous catheters, cleaning the skin with chlorhexidine, avoiding the femoral site if possible, and removing unnecessary catheters.

A Comprehensive Unit-Based Safety Program (CUSP) for improving safety culture, including communication and teamwork was implemented to translate evidence into practice, identify local barriers, measure baseline performance, and ensure that

all patients receive the evidence care, using the "4Es" model: Engage, Educate, Execute and Evaluate. This model targeted senior leaders, ICU directors, and staff. Team leaders (at least one nurse and one physician) were instructed in the science of safety and in the interventions and then disseminated this information among their colleagues. Clinicians were educated about practices to control infection and harm resulting from catheter-related bloodstream infections, a central-line cart with necessary supplies was created, a checklist was used to ensure adherence to infection-control practices, providers were stopped (in nonemergency situations) if these practices were not being followed, the removal of catheters was discussed at daily rounds, and the teams received feedback regarding the number and rates of catheter-related bloodstream infection at monthly and quarterly meetings, respectively. A total of 108 ICUs agreed to participate in the study, and 103 reported data. The median rate of catheter-related bloodstream infection per 1,000 catheter-days decreased from 2.7 infections at baseline to 0 at 3 months after implementation of the study intervention ($P< or =0.002$), and the mean rate per 1,000 catheter-days decreased from 7.7 at baseline to 1.4 at 16–18 months of follow-up ($P<0.002$).

The IHI Ventilator Bundle

As in the Michigan project, The IHI ventilator bundle is the basis for focused team care, enhancing the use of protocols and guidelines to bring about optimal patient outcomes [43].

The Ventilator Bundle contains four components: elevation of the head of the bed to 30–45°, daily "sedation vacation" and daily assessment of readiness to extubate, peptic ulcer disease prophylaxis, and deep venous thrombosis prophylaxis. Some interventions such as DVT prophylaxis and peptic ulcer prophylaxis improve the outcome of ventilated patients, but do not affect the VAP rate.

The best way to prevent VAP is to avoid intubation or reduce the length of time. Implementing noninvasive ventilation whenever possible, and daily spontaneous awakening and breathing trials have been associated with early liberation from mechanical ventilation and VAP reduction [45–47]. To reduce the gastroesophageal reflux and subsequent aspiration, the semirecumbent patient position is recommended as an A-I measure in ICU intubated patients [48]. However, other authors [49] have found many difficulties in implementing the targeted backrest elevation of 45° for semirecumbent positioning (not achieved 85% of the time). The obtained difference in position (28° vs. 10°) did not prevent the development of VAP.

The IHI recognizes that other methods to reduce VAP, such as oral care and hygiene, chlorhexidine in the posterior pharynx, gut decontamination, specialized endotracheal tubes (continuous aspiration of subglottic secretions, silver-coated) are also important preventives strategies [41,42,51]. Some ICUs have considered their inclusion, in particular revised Ventilator Bundles more specifically aimed at VAP prevention.

One of the most successful maneuvers to decrease VAP is the use of selective digestive tract decontamination, SDD [50]. Because of concern about selection of antibiotic-resistant organisms, the routine use of SDD and selective oropharyngeal

decontamination (SOD) remains controversial, and neither approach is recommended in international guidelines. In a recent multicenter crossover trial carried out in 13 ICUs in Netherlands, three regimens (SDD, SOD, and standard care) were administered to all eligible patients over the course of 6 months, enrolling about 2,000 patients in each of the three trial arms [51]. In a random-effects logistic-regression model with pertinent factors used as covariates, the odds ratios for death during the first 28 days were 0.83 (95% confidence interval, 0.72–0.97) and 0.86 (95% CI, 0.74–0.99) for the SDD and SOD groups, respectively, compared with the standard-care group. Absolute reductions in mortality rates at day 28 were 3.5% for the SDD group and 2.9% for the SOD group, compared with 27.5% for the standard-care group.

Recommendations

Nosocomial infection prevention is one of the prominent fields for quality improvement in the ICU. Guideline production and dissemination do not necessarily result in the widespread adoption of best-evidence clinical care. Education alone had no significant effect on practice, but neither did financial incentives.

Recently the Society of Critical Care Medicine has published a "how-to" guide focused on critical care, summarizing key concepts and outlining a practical approach to development, implementation, evaluation, and maintenance of an interdisciplinary quality improvement program in the ICU [52]. The step-wise approach includes 12 points:

1. Motivation, teamwork, and leadership.
2. Prioritize and choose a project.
3. Prepare for the project.
4. Perform an environmental scan.
5. Create a data collection system.
6. Introduce strategies to change behavior.
7. Evaluating and sustaining an ICU.
8. Quality improvement program.
9. Sustain data collection.
10. Modify behavior change strategies.
11. Sustain interdisciplinary leadership and collaboration in the ICU.
12. Sustain support from hospital administration and take advantage of the application of this methodology for infection control.

Conclusions

To consider NI as a preventable error is the first step towards eradication. Surveillance systems are necessary to effectively measure NI problems and the rea-

sons why they develop, as well as implementing interventions to address known risks.

The main role of patient safety reporting systems, including surveillance programs, is to enhance patient safety by learning from failures of the healthcare system; reporting must be safe and is only of value if it leads to a constructive response as recommendations for changes in processes and systems of healthcare; the analysis, learning, and dissemination of conclusions and agreements requires expertise and human and financial resources. The agencies or institutions receiving reports should disseminate the information, making recommendations for changes and developing solutions.

The application of local, national, or international campaigns to reduce infection errors such as CRBSI prevention or handwashing, needs active surveillance systems to evaluate such interventions. Regular surveillance and training together with adequate resources allocation, will allow us to minimize rates and achieve the goal of near zero NI.

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Antibiotic Policy in Critically Ill Patients 20

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Introduction

Antimicrobials are pharmaceutical drugs very frequently prescribed in the intensive care unit (ICU) setting. In the last decade, there is a growing body of evidence showing that early and appropriate use of antimicrobials has a short-term favorable impact on the course of critically ill patients [1–4], whereas in the long-term, antimicrobials facilitate the appearance of emerging flora and changes in resistance patterns of pathogens that form part of the hospital ecosystem [5–6]. Over the years, a number of guidelines and strategies have been proposed to improve and optimize the use of antimicrobials in ICU patients, which have been collectively named "antibiotic policy."

To develop effective recommendations for antibiotic policy, it is necessary to achieve the active participation of all health personnel of the hospital, not only of those devoted to control and surveillance of nosocomial infections, but also of those involved in the prevention and/or treatment of hospital-acquired infections. In some ICUs, there are intensivists who spend part of their time in the control, surveillance, treatment, and prophylaxis of nosocomial infections, as well as in the regulation of antibiotic use, which has stimulated the consolidation of antibiotic policies in these high-risk areas. In collaboration with specialists of other disciplines (microbiology, pharmacy, clinical pharmacology, preventive medicine), they are responsible for designing the most appropriate therapeutic strategies for each individual ICU.

This article presents the general recommendations for the use of antimicrobials in critically ill patients (Table 20.1), together with strategies proposed in recent years to optimize the use of these agents and to reduce morbidity associated with the inappropriate administration of antibiotics. These guidelines form the basis of any antibiotic policy in the ICU setting.

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Table 20.1 Use of antibiotics in critically ill patients: the 10 recommendations

1. To use antimicrobials only in the presence of clinical and/or microbiological suspicion of infection
2. To obtain samples from infected tissue(s) before starting antibiotic treatment
3. To select empirical antibiotics according to consensuated therapeutic protocols
4. To obtain a rapid response from the Laboratory of Microbiology
5. To select a recommended antimicrobial treatment when the causative pathogen is known
6. To monitor the efficacy of antimicrobial treatment
7. To be alert for the appearance of adverse effects and/or emergence of multiresistant bacterial flora
8. To limit the duration of antibiotic treatment according to the clinical and/or microbiological response
9. An intensivist should be in charge of the antibiotic policy in the ICU
10. To ensure coresponsibility with all health care personnel for adequate adherence to recommendations

General Guidelines for the Use of Antimicrobial Agents in Critically Ill Patients: The 10 Recommendations

First Recommendation: Use of Antimicrobials Only in the Presence of Clinical and/or Microbiological Suspicion of Infection

Antimicrobial agents should only be prescribed in the presence of a clinically and/or microbiologically-suspected infection. In critically ill patients, however, it may be difficult to ascertain the initial clinical expression of sepsis (infection) or systemic inflammatory response due to other noninfectious causes (e.g., traumatism, polyarthritis, pancreatitis, hemorrhage) [7,8]. In addition, recovery of microorganisms from samples containing endogenous flora (e.g., sputum, bronchial aspirates, stools, skin) or low virulence pathogens (coagulase-negative *Staphylococcus*, *Corynebacterium spp*.) from blood or respiratory samples obtained through invasive techniques (e.g., catheter, protected specimen brush, bronchoalveolar lavage) should not justify the initiation of antimicrobial therapy. In all cases, both microbiological findings and the patient's clinical condition should be considered.

In mechanically-ventilated patients, work-up studies including fiberoptic bronchoscopy and chest CT scans should be performed when an infection of the lower respiratory tract is suspected on clinical grounds by the presence of purulent sputum, fever, and leukocytosis in the absence of radiographic evidence of infiltration. In cases of fever of unknown origin and in the absence of severe systemic response, replacement and/or withdrawal of catheters may be sufficient to solve the infectious process. The administration of antibiotics without waiting for the clinical response to catheter withdrawal is one of the reasons for an increased consumption of glycopeptides in the ICUs.

A large percentage of ICU patients are given antimicrobials prophylactically. In these circumstances, antimicrobial agents should be administered according to hospital protocols and for a short period of time. Different studies have shown the efficacy of nonabsorbable antibiotics to prevent late-onset endogenous infections in patients on mechanical ventilation [9–13] or the use of systemic antibiotics to prevent early-onset respiratory infections in unconscious patients requiring intubation [14]. Despite extensive evidence, the use of local antibiotics has not become a generalized practice and is usually restricted to high-risk patients (e.g., liver or lung transplant recipients, critical traumatisms, or complex surgery) [15–17]. In patients with acute severe pancreatitis in which antimicrobials have been usually recommended to prevent the appearance of infectious complications [18], recent studies have shown the lack of effectiveness of this approach [19].

Second Recommendation: To Obtain Samples from Infected Tissue(s) Before Starting Antibiotic Treatment

In critical patients, the use of antibiotics without obtaining infected tissue and/or blood samples is not justified. The isolation of pathogens allows confirmation of infection in those clinical conditions in which diagnostic uncertainties may be present, such as in cases of bacteremia, pneumonia, or urinary tract infection. Therefore, beginning antimicrobial use should be preceded by recovery of appropriate samples from each site using invasive or surgical techniques if necessary. In some cases in which the use of safe procedures for sample collection (e.g., if the aid of other specialists is required) is not possible, less safe samples must be obtained, such as bronchial secretions (simple bronchial aspirates), abdominal secretions (drainage, fistulas, or external/surgical wounds), and oropharynx, nasal, and/or rectal exudates. The use of invasive "blind" techniques (telescopic catheter, bronchoalveolar lavage) has proved to be useful in the diagnosis of respiratory infections [20,21].

When infections are suspected in patients already treated with antibiotics, samples should be immediately obtained to prevent the appearance of resistance without waiting for the efficacy of the agents currently administered. In these cases, sampling should be performed prior to the administration of the next dose of the drug at the time of minimum plasma drug concentration.

Third Recommendation: To Select Empirical Antibiotics According to Consensuated Therapeutic Protocols

The empirical antibiotics used in the majority of infectious processes diagnosed in critical patients should be those included in the therapeutic protocols previously established for each individual ICU. Infections in which it would be advisable to develop treatment protocols for empirical administration of antimicrobials are detailed in Table 20.2.

Table 20.2 Infections for which it is advisable to have available specific therapeutic protocols

1. Severe community-acquired infection
2. Acute meningitis
3. Encephalitis
4. Sepsis of urinary origin
5. Secondary peritonitis
6. Hospital-acquired pneumonia
7. Catheter-related urinary tract infection
8. Postsurgical meningitis
9. Postsurgical peritonitis
10. Catheter-related infection
11. Severe sepsis in the absence of an infection focus

In this respect, protocols should include specific recommendations for the use of antimicrobials as first- and second-choice agents or rescue treatment and according to different characteristics of the patients (e.g., renal failure, allergy to beta-lactam antibiotics, pregnancy), indicating the most appropriate agent, dose, and route of administration for the most common pathogens present in each geographical area, hospital, or ICU setting. In all critically ill patients, the intravenous route should be used to ensure high plasma and tissue drug concentrations as soon as possible. Recommended dosages associated with optimal plasma concentrations should be followed, with necessary adjustments according to the renal function of the individual patient. All specialists in the hospital involved in the prevention and treatment of infections, such as microbiologists, pharmacists, clinical pharmacologists, intensivists, and specialists in infectious diseases and preventive medicine should participate in the development of therapeutic protocols, although an expert intensivist in infectious diseases should be responsible for the implementation and control of compliance with the protocol. On the other hand, periodic information on the predominant pathogens in significant samples together with data on the results of antibiotic susceptibility testing permits the adjustment of empirical therapy protocols to the particular epidemiological characteristics of each area. Collaboration with the staff of the service of microbiology is crucial to update the protocols periodically.

Fourth Recommendation: To Obtain a Rapid Response from the Laboratory of Microbiology

Knowledge of the agents responsible for a specific infection and/or sensitivity, permits and facilitates use of antibiotics in a controlled manner, avoiding the persistence of broad-spectrum empirical treatments for many days or even until the end of treat-

ment. Therefore, it is necessary to optimize the processes of (a) transfer of samples to the laboratory and (b) provision and dissemination of the information.

Sample handling must follow previously established guidelines, which include extraction/procurement of each sample, means of transportation, and minimum arrival times at the laboratory for processing [22]. Lack of adherence to any of these steps may increase the risk of contamination and in situ multiplication of microorganisms, affecting both the quality of results and quantification of pathogens present in the samples. In recent years, the use of molecular-based diagnostic techniques (e.g., real-time quantitative PCR) [23–25] in the routine daily practice of the laboratories of clinical microbiology has been crucial to make an early etiological diagnosis of infection and to be able to use the most appropriate antimicrobial agents without delay.

The information obtained in the laboratory of microbiology, including the results of simple techniques (e.g., Gram stain) should be immediately known by the attending physician. Communication of results by e-mail reduces the response time but this system is not available in all hospitals. A telephone call to inform on the most relevant results, such as isolation of multiresistant pathogens (identified as multiresistant markers) is a simple, rapid, and efficient procedure. In some hospitals, intensive care physicians in charge of surveillance of nosocomial infections participate in daily meetings with the microbiology staff, which facilitate the information exchange and the knowledge of changes in the resistance patterns of endogenous flora in their ICUs.

Fifth Recommendation: To Select a Recommended Antimicrobial Treatment when the Causative Pathogen Is Known

Data provided by the microbiology laboratory is essential for the use of an antibiotic regimen recommended in the therapeutic protocol. Isolation of one or more microorganisms in safe samples allows adjustments to the initial treatment. Whenever possible, antibiotics with proved efficacy, the safest spectrum of activity, and the most convenient cost-benefit relationship should be selected. In the majority of infections in which the causative pathogen has been isolated, treatment with a single antimicrobial agent (monotherapy) should be used. In cases in which early appearance of resistance is possible or if high percentage of treatment failures with monotherapy has been reported, the use of two or more antimicrobials is recommended [26]. When two or more pathogens have been recovered, the contribution of each pathogen (causative, colonization, contamination) to the patient's infection should be evaluated. Patients with infections of polymicrobial etiology should be given the minimum number of agents ensuring broad-spectrum coverage [27,28].

Sixth Recommendation: To Monitor the Efficacy of Antimicrobial Treatment

The use of antimicrobials should never be a routine act but should be accompanied by a set of active measures to monitor their efficacy. The first evaluation of therapeutic response should be at 72 h after starting empirical treatment. The appearance of

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new signs of infection or worsening of the initial clinical manifestations should lead us to suspect that the antibiotics being administered are not appropriate for treating the pathogens responsible for the infection. In this case, blood and infected tissue samples should be taken again and more potent rescue regimens of a broader spectrum of activity to cover potentially multiresistant pathogens should be administered. In contrast, when an improvement of the initial symptomatology is observed, treatment should be continued until isolation of the causative pathogens and awareness of their susceptibility patterns, so that proper adjustments can be made. In those cases in which the antimicrobial treatment is appropriate according to susceptibility testing and the patient's clinical course is unfavorable, it is necessary to ensure that the antibiotics being administered have good penetration in the infected tissue, that the dosage is correct, and that the antibiotic is given at the proper intervals to guarantee an adequate pK/pD relationship [27,28]. Results of clinical and microbiological response should be assessed at the end of treatment and at follow-up between 7 and 60 days after cessation of therapy depending on the type of infection.

Seventh Recommendation: To Be Alert for the Appearance of Adverse Effects and/or Emergence of Multiresistant Bacterial Flora

Each class of antimicrobial agents has been associated with specific adverse effects. Many adverse effects are common to more than one antibiotic family; moreover, adverse events may be reinforced by the use of other concomitant drugs, so that, in many patients, it is difficult to attribute a particular adverse effect to a single medication.

Some of the most frequent adverse effects, such as nephrotoxicity, ototoxicity, or selection of mutant resistant strains are related to plasma concentrations of inadequate antibiotics [29,30]. Critically ill patients, especially those with complicated surgical procedures, extensive burns and decompensated heart failure frequently present an important increase in body mass distribution, affecting plasma and/or tissue drug concentrations. Hemodynamic instability and renal failure also affect renal drug elimination. These characteristics modify the pharmacokinetic profile of antibiotics and may account for the large individual differences in plasma drug levels when the same dose is administered. For this reason, it is advisable to monitor plasma drug concentrations, particularly when the therapeutic margin is small (drugs that can easily be under- or overdosed), such as aminoglycosides and vancomycin. The introduction of pharmacokinetic model programs designed to monitor plasma drug concentrations allows adjustment of doses to maximize clinical efficacy and minimize the occurrence of adverse effects [31].

The consumption of antimicrobial agents in the ICU favors the development of multiresistant pathogens, the presence of which may be associated with treatment failure in individual patients and the need to modify antibiotic policies [32–35]. Surveillance studies in high-risk patients based on recovery of samples at the infection foci and mucous membranes (oropharynx, tracheal aspirates, stools) are useful to assess the emergence of multiresistant bacterial pathogens.

Eighth Recommendation: To Limit the Duration of Antibiotic Treatment According to the Clinical and/or Microbiological Response

There are no general rules regarding the duration of antibiotic courses in critically ill patients. Duration of treatment mainly depends on the clinical and microbiological response, etiology of infection, and patient's characteristics (immunosuppression, prosthetic devices, intravascular lines, etc.). Most infections in the critically ill patient require the administration of antimicrobials during the time required for the most important clinical signs and symptoms to disappear, such as fever, leucocytosis, hemodynamic instability, intolerance to glucose, and pulmonary shunt. Antimicrobial treatment can be discontinued between 48 and 72 h after control of these symptoms. The duration of treatment in immunocompetent patients with sepsis caused by Gram-negative bacteria varies from 8 to 14 days. In patients with infections caused by multiresistant pathogens and evidence of recurrence due to *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, or *Enterobacter spp*. bacteremia producing broad-spectrum beta-lactamases, the administration of antimicrobials should be prolonged for at least 2 weeks [36]. However, persistence of pathogens in the airways of patients with tracheostomy and/or prolonged mechanical ventilation, in the absence of clinical signs of infection should not be a reason for prolonging treatment. One-week treatment is usually sufficient in catheter-related urinary tract infections caused by Gram-negative bacilli and Gram-positive cocci. When the presence of infection is excluded by the favorable patients' clinical course and microbiological data, antibiotic treatment should be withdrawn.

Ninth Recommendation: An Intensivist Should Be in Charge of the Antibiotic Policy in the ICU

The role of an intensivist specialized in the field of antibiotic therapy has been the cornerstone in the development and implementation of antibiotic policies in the ICU. The following aspects are related to the tasks involved in the control of antibiotic therapy:

1. To gather information provided by the hospital surveillance systems of nosocomial infection and to disseminate these data. In cooperation with other hospital staff, the intensivist in charge of the antibiotic policy should actively participate in surveillance studies of hospital-acquired infections (prevalence and/or incidence). In addition, he/she should be responsible for the follow-up of ICU patients. Information collected in the ICU should be also regularly transmitted not only to the ICU staff, but also to the infection committee of the hospital as well as to the medical director and the hospital manager.
2. To maintain a fluid relationship with the staff of the clinical microbiology and hospital pharmacy departments, and whenever possible participation in the clinical microbiology departments meetings in which the most significant pathogens isolated in the hospital are discussed, would be highly desirable. On the other hand, in collaboration with this department, the ICU epidemiological map is

established, which provides updated information of infection rates and secular trends of multiresistance markers and sensitivity patterns of the most common pathogens. In addition, in collaboration with the hospital pharmacy department, the use of antibiotics regarding indications, dosage, and duration of treatment should be controlled. Therefore, the intensivist in charge of the antibiotic policy informs both departments about patients at risk in the ICU and reciprocally receives the most important data generated in these departments as quickly as possible.

3. To develop therapeutic and preventive ICU protocols for the most frequent infections. Therefore, he/she will present therapeutic and/or preventive protocols available in the hospital to the ICU staff, together with protocols specifically developed for the ICU setting (e.g., prevention of pneumonia in mechanically-ventilated patients, catheter-related infections, etc.). Whenever possible a working group should be organized, including other ICU staff (nurses, technicians) with the aim of collaborating in the collection of data, implementation of the different protocols, and periodic assessment of nursing procedures.

Tenth Recommendation: To Ensure Coresponsibility with All Health Care Personnel for Adequate Adherence to Recommendations

Fulfillment of antibiotic policy guidelines is the responsibility of all ICU staff. The establishment of periodic meetings in which indicators of antibiotic consumption are presented, together with infection rates and data on sensitivity patterns of the most frequent pathogens allows updating antibiotic policy protocols and ensures coresponsibility of intensivists and good adherence to the recommendations. Audits are also useful to assess the level of compliance with guidelines included in the antibiotic policy.

General Strategies of Antibiotic Use in Critical Patients

With the aim of optimizing antibiotic use in the environment of critical patients, various strategies have been proposed. Prominent among these are: de-escalation therapy, antibiotic cycling, pre-emptive therapy, and the application of pharmacokinetic/pharmacodynamic parameters (pK/pD) for regulating dosage.

De-Escalation Therapy

De-escalation therapy consists of initially administering a broad empirical treatment to cover the pathogens most frequently associated with the infection to be treated, including multiresistant pathogens. This is followed by swift adjustment of the antibiotic treatment, once the etiology is known [37]. The adjustment must be carried

out between the second and third day after establishing the initial antibiotic treatment. The application of this technique has principally been evaluated in critical patients with nosocomial pneumonia or septic shock [38–41].

The aim of this strategy is to obtain lower morbidity-mortality rates, by attaining the appropriate empirical treatment and limiting the appearance of resistant bacteremia through reduced antibiotic pressure. Unfortunately, none of the studies carried out up till now have been able to establish these objectives [38–41]. Likewise, the application of this strategy requires that certain basic conditions be fulfilled, which are not available in all ICUs. These are: (a) knowledge of the epidemiological map of the hospital ecosystem, including the sensitivity patterns of most frequent bacteria, (b) a fast response to microbiological analysis, and (c) adherence to recommended adjustment of the initial empirical treatment, according to secure microbiological data.

Antibiotic Cycling

Antibiotic cycling consists of periodic substitution of one class of antibiotics for another, or for a combination of antibiotics which have a similar activity spectrum, but do not share the same resistance mechanism. During each period or cycle, of a few weeks' or months' duration, only antibiotics corresponding to that cycle may be used. The appearance of resistance can be reduced by substituting the antibiotic before resistance occurs and preserving it for reintroduction in the hospital at a later date.

This strategy, whose origin dates back to the 1980s [43], has been proposed in recent years to prevent the development of multiresistant pathogens in the environment of critical patients. Studies carried out so far have had contradictory results, although the numerous differences between them do not permit comparisons to be established [44–48]. The methodological limitations of many of the studies and the impossibility of controlling other variables which could influence results (admittance of patients with multiresistant pathogens, adherence to cycling norms) hinders evaluation of this strategy [49–51].

Pre-Emptive Therapy

Pre-emptive therapy consists of administering antimicrobials in certain patients, before the appearance of clinical signs of infection. This concept was developed in hematological patients through seriological tests, which allow diagnosis to be performed before the appearance of clinical signs [52]. Application to critical patients depends on identification of those at risk of infections associated with high mortality, such as invasive candidemias or candidiasis. The development of different scores [53,54] has permitted these patients to be identified, although, for the present, there is no study establishing reduced mortality through the use of this strategy in ICUs.

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PK/PD Parameters

In traditional infection treatment with antibiotics, the determination of plasma levels in antibiotics with a narrow therapeutic margin is recommended in cases where therapeutic concentrations are close to toxic. This situation occurs, mainly, in the case of aminoglycosides and vancomycin [55]. However, in recent years, the clinical importance of different pharmacodynamic relationships formed between antibiotic plasma concentrations and minimum bacteria inhibiting concentration (MIC) has been established. This is also true of the relationship between maximum plasma concentration (Cmax) and MIC, the area below the curve, (AUC) the MIC, and the time of plasma concentration above the MIC [56]. The attainment of specific quotients of different indicators has been associated with greater antibiotic efficacy, (increased bactericidal strength and lysis of bacteria) along with a reduction in the appearance of multiresistant strains [57–60]. In critical patients admitted to ICUs the determination of antibiotic plasma levels is specifically indicated by the presence of different factors that modify the pharmaco-kinetic behavior of these drugs and justify the wide interindividual variability in serum levels obtained when similar doses are administered. Unfortunately, there are no studies establishing the efficiency of this strategy to reduce mortality in critical patients and there are multiple technical problems in the majority of hospitals for their application in daily practice [61].

Conclusions

The antibiotic policy applied to critical patients must be based on adherence to a set of basic norms on the use of antibiotics. Strategies proposed in recent years to optimize efficacy and minimize adverse effects should be applied cautiously, with constant evaluation of results obtained and adjustment to the needs of each individual ICU. Educational programs for clinicians on basic antibiotic use and de-escalated therapy, based on the results of microbiological cultures, are the best option for success in the control of antibiotic resistance.

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The Physiopathology of Antimicrobial Resistance on the Intensive Care

21

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Introduction

Nowadays a major clinical problem facing the intensive care team is antimicrobial resistance [1]. We believe that the focus of studies should be directed to the clinical aspects of the antimicrobial resistance problem as opposed to concentrating upon molecular-biological mechanisms of antimicrobial resistance. The ecological fundamental that while flora remains normal, resistance is unlikely to emerge is not acknowledged in the resistance debate.

Normal vs. Abnormal Flora

The abnormal carrier state is defined as the persistent presence in throat and/or gut of "abnormal" micro-organisms [2]. These are micro-organisms irrespective of their sensitivity pattern that are not persistently present in healthy individuals. The group of "abnormal" flora includes aerobic Gram-negative bacilli (AGNB) other than the individual's own indigenous *Escherichia coli* (*E. coli*), such as *Klebsiella*, *Enterobacter*, *Citrobacter*, *Proteus*, *Morganella*, *Serratia*, *Acinetobacter*, and *Pseudomonas* species, whether they are sensitive or not to the commonly used antimicrobials. "Abnormal" flora also includes nonalbicans *Candida* species, such as *Candida glabrata* and *Candida tropicalis*. Thirdly "normal" bacteria such as *E. coli*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* resistant to the commonly used antimicrobials belong to the "abnormal" flora group, e.g., extended spectrum beta-lactamase (ESBL) producing *E. coli*, methicillin-resistant *S. aureus*

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(MRSA), penicillin-resistant *S. pneumoniae*. Finally, *Candida albicans* resistant to fluconazole is an "abnormal" micro-organism.

Normal Flora

The adult human gut is home to more than 1,000 million bacteria, which dwarves the number of somatic and germ cells in the entire human organism [3]. There are an estimated 500–1,000 species of bacteria present in our gut [4]. Only healthy people carry normal flora in throat and gut [5]. Normal flora comprises mainly of anaerobic bacteria requiring a low oxygen tension. These indigenous micro-organisms are present in high concentration, 10^8 anaerobes per ml of saliva and 10^{12} per g of feces. Aerobic micro-organisms grow easily in the presence of oxygen and are also present in the human body. However, their concentrations are 10^4 lower than the anaerobic concentrations. Everybody carries their own indigenous *E. coli*, in a concentration of 10^3–10^6/g of feces. *E. coli* is sensitive to the commonly used antimicrobials. One third of healthy people carry *S. aureus* sensitive to methicillin (MSSA). About 30% of healthy adults are carriers of *Candida albicans* sensitive to the antifungal fluconazole, and about 70% carry *S. pneumoniae* sensitive to penicillin.

Abnormal Flora

Only diseased individuals carry abnormal flora. Although it has been demonstrated that patients with severe systemic inflammatory response syndrome (SIRS) have lower anaerobic bacteria and higher aerobic potentially pathogenic micro-organisms (PPM) in their gut, less is known about how critical illness affects the quality of the indigenous anaerobic flora [6]. More is known about the impact of illness severity on aerobic flora.

Four Stages in Resistance

The difference between carriage and overgrowth needs to be appreciated. Carriage is the persistent presence of PPM in any concentration in throat and/or gut, while overgrowth implies carriage in high concentrations, i.e., $\geq 10^5$ colony forming units of PPM per ml of saliva and/or g of feces. There are several stages in the development of the carriage of antimicrobial resistant micro-organisms [7].

Firstly, it has only been recently learned that illness severity is the most important independent risk factor for the carriage of abnormal, often resistant, micro-organisms [8–11]. Healthy individuals have innate mechanisms that clear abnormal micro-organisms [12–16]. Unhealthy individuals carry abnormal micro-organisms in the throat and gut and, where present, skin lesions. The predominant site of carriage of abnormal micro-organisms is the gut.

Secondly, for carriage of abnormal flora to occur, the patient must have been exposed to the abnormal micro-organisms. Patients may either carry abnormal flora on admission (import) into the intensive care unit (ICU) [17], or the flora may have been normal on admission and the abnormal micro-organisms are acquired following transmission of hands of caretakers during treatment in the ICU (acquisition) [8].

Thirdly, following exposure, ill patients may develop carriage, i.e., persistent presence in the throat and/or gut. Healthy individuals do not become sustained carriers of abnormal flora [8–16].

Finally, abnormal carriage inevitably leads to overgrowth of abnormal flora in the critically ill patients [1]. Drugs including opiates, histamine2 (H2)-receptor antagonists, and antimicrobials promote overgrowth in reducing peristalsis [18], increasing the gastric pH >4 [19,20], and via the suppression of the normal indigenous mainly anaerobic flora [21] required to control abnormal flora, respectively.

Digestive tract (gut) overgrowth, defined as $\geq 10^5$ colony forming units of abnormal micro-organisms per g of feces, represents a serious problem in the ICU for three reasons:

1. Overgrowth guarantees increased spontaneous mutation leading to polyclonality and antibiotic resistance in the critically ill [22].
2. Overgrowth is required for the endogenous super-colonization/infection of the individual patient [23].
3. Overgrowth promotes dissemination throughout the unit via the contaminated hands of the caretakers [24].

Approximately one third of patients requiring treatment in ICU import resistant micro-organisms in their admission flora, about one third acquire resistant micro-organisms following transmission via hands of caretakers, and the last third develop de novo resistance due to mutation following overgrowth.

Four features, disease severity, exposure, carriage, and subsequent overgrowth, are the reasons why the ICU is the epicenter of the resistance problem [6]. Of the four factors involved in resistance, only two are modifiable, i.e., carriage and overgrowth.

Surveillance samples of throat and rectum have recently been recognized as the most sensitive sampling sites for the detection of multiresistant micro-organisms including MRSA [17,25].

Traditional Approach to Antimicrobial Resistance

The traditional approach is based on two pillars, restriction of parenteral antibiotics and control of transmission of resistant micro-organisms using isolation and handwashing.

Restriction of Solely Parenteral Antimicrobials

There is evidence relating antimicrobial usage to emerging resistance [26]. Generally, carriage in the throat and gut, and colonization of internal organs by PPM,

are not treated. Only infection is treated (parenterally) to limit the use of systemic antibiotics. Despite widespread attempts to limit the use of systemic antibiotics, over 70% of all patients who stay over 3 days in the intensive care unit (ICU) will receive them [27]. There are two approaches to controlling antibiotic usage. These include increasing the specificity of the diagnosis of pneumonia, which causes 30% of all infections, by invasive techniques, and scheduled changes of antibiotic classes.

The "pneumonia" rate is halved using invasive strategies compared with noninvasive methods [28]. Two randomized trials have demonstrated that diagnosing pneumonia less frequently in this fashion is not associated with a reduction in mortality [29,30]. A French randomized trial of 413 patients compared 204 patients managed invasively with protected brush specimens with 209 patients managed noninvasively with tracheal aspirates [29]. They failed to show any survival benefit at 28 days (30.9% vs. 28.8%, $p = 0.10$) using restrictive antibiotic prescribing policies. A Spanish randomized trial of 77 patients, comparing an invasive (n = 37) with a noninvasive (n = 39) diagnostic approach, found that the 30-day outcome of pneumonia was not influenced (38% vs. 46%, $p = 0.46$) by the techniques used for microbial investigation [30]. Additionally, both trials evaluated the emergence of antimicrobial resistance as a secondary endpoint. In the French trial the proportions of resistant isolates obtained from lower airway secretions were similar in both invasive (61.3%) and noninvasive (59.8%) groups, despite significantly less use of antibiotics in the invasive group. The Spanish trial reported identical high isolation rates of 58.3% of resistant bacteria, MRSA and *P. aeruginosa* in both groups.

Strategies that recommend manipulating in-hospital antibiotic use have been suggested, in order to reduce possible emergence of resistance in critically ill patients. One such strategy is to schedule a rotation of antibiotics. This strategy entails a regimented preference for a specific antibiotic in a given environment over a fixed period, after which preference is switched to an alternative agent with a similar spectrum of activity. The assumption underlying this strategy is that the exposure to each antibiotic in the schedule is sufficiently short to preclude the emergence of significant populations of micro-organisms resistant to any one of them.

The evidence to support this recommendation is sparse and the data are conflicting [31,32]. In a cardiac ICU, 6 months of ceftazidime administration was followed by 6 months of ciprofloxacin administration and a comparison was made [31]. Although not true cycling (the prior regimen was not reused, therefore the effect of a full cycle was not tested), this study suggested that scheduled changes in classes of antibiotics may reduce infection with resistant AGNB. There was a significant reduction in the incidence of pneumonia due to resistant AGNB (4% vs. 0.9% p = 0.013). The nonrandomized design is a fundamental flaw confirmed by the difference in the etiology of the causative agents. During ceftazidime treatment there was an outbreak of intrinsically resistant Serratia (7 pneumonias); additionally, there were five viral and three Aspergillus pneumonias, i.e., 15 of 41 pneumonias were inappropriately treated by ceftazidime. During ciprofloxacin treatment there were 22 pneumonias in total, only one of which was viral. The difference in pneumonia is no longer significant when comparing the appropriately treated pneumonias, i.e., 26 and 21.

In a neonatal ICU, a monthly rotation of gentamicin, piperacillin-tazobactam, and

ceftazidime was compared with unrestricted antibiotic use between two geographically separated teams (rotation vs. control team) [32]. In total, 10.7% of infants on the rotation team versus 7.7% on the control team carried resistant AGNB in the throat and gut. There was no difference in the incidence of infections, morbidity, and mortality.

Proponents and antagonists of antibiotic cycling agree that there are many difficult and complex methodological issues surrounding the use of antibiotic cycling.

Factors potentially determining the effectiveness of antibiotic cycling include endemic rates of carriage with particular AGNB and their mechanisms of antibiotic resistance, the transmission dynamics of particular AGNB in a specific unit, the population dynamics of the unit staff, the composition and duration of the antibiotic regimens, compliance with antibiotic cycling, and concurrent infection control practices to limit transmission of resistant AGNB. There is limited information on which to base decisions of how long each antibiotic regimen should be used and how many regimens should be cycled.

Control of Transmission of Resistant Micro-Organisms via Hands of Caretakers

The endpoint of traditional infection control is the control of infection due to the control of transmission of resistant micro-organisms via hands of caretakers. The two main maneuvers are isolation [33] and handwashing [34]. A recent two-center prospective crossover study from the UK demonstrated that placing patients who are treated in ICU and who carry MRSA or who are infected by MRSA in single rooms or cohorting them in a multibed bay when a single room was not available, had no effect on transmission of MRSA when combined with what the investigators term "standard" [33] precautions for all patients treated on ICU.

The experts tried to explain this negative study by the poor adherence to hand hygiene, the handwashing compliance rate was 21% in the study [35]. A recent systematic review of handwashing suggests that handwashing does not abolish but only reduces transmission of potential pathogens by lowering the contamination level of hands [34].

The policy of sole use of parenteral antimicrobials has failed to control resistance. Generally, resistance to a new antibiotic emerges within 2 years of general use [36,37]. We believe that this experience is due to the common denominator of ignoring the gut in all four maneuvers of restricted antibiotic use, cycling of antibiotics, isolation, and handwashing. The major source of the gut is left intact allowing resistant mutants to emerge and to cause superinfections and subsequent outbreaks.

The Selective Decontamination of the Digestive Tract (SDD) Approach

Selective digestive decontamination (SDD) aims to convert the abnormal carrier state in overgrowth concentrations into normal carriage, therefore preventing the emergence of antimicrobial resistance [38].

The many years, over 20, of clinical SDD research yielding 56 randomized controlled trials (RCTs) demonstrated an intriguing finding that SDD does not increase the problem of antimicrobial resistance but reduces the problem [39].

Two [40,41] of the 56 RCTs, report an increase in resistance. Interestingly, the endpoint was the number of resistant isolates, not patients, in these two RCTs.

Three RCTs evaluated the impact of SDD on the number of patients who carried antibiotic resistant AGNB [42–44]. A Klebsiella pneumoniae producing ESBL was endemic in a French hospital [42]: carriage and infection rates were 19.6% and 9%, respectively. Once enteral antimicrobials were added to the parenteral, there was a significant reduction in both carriage and infection (19.6% vs. 1%; 9% vs. 0%) [42]. A Dutch monocenter RCT including 1,000 patients reports that carriage of AGNB resistant to imipenem, ceftazidime, ciprofloxacin, tobramycin, and polymyxins occurred in 16% of patients receiving parenteral and enteral antimicrobials, compared to 26% of control patients receiving only parenteral antibiotics with a relative risk of 0.6 (95% CI 0.5–0.8) [43].

The largest multicenter RCT to date, also from the Netherlands, includes 6,000 patients, and the proportion of patients with Gram-negative bacteria in rectal swabs that were not susceptible to the marker antibiotics was lower with SDD than with standard care or selective oropharyngeal decontamination (SOD), a modified SDD protocol without the gut component. For example, carriage of multiresistant *P. aeruginosa* was 0.4% in SDD vs. 0.8% in SOD and 1.3% in the group receiving standard care (p <0.005) [44].

There are four long-term studies (≥2 years) evaluating the impact of polymyxin/tobramycin on resistance amongst AGNB [45–48].

The resistance data of the long-term studies confirm the RCT findings that rates of carriage and infection due to resistant AGNB in patients receiving enteral and parenteral antimicrobials are not increased but actually lowered compared with patients receiving solely parenteral antimicrobials.

Most patients who require long-term treatment on ICU have overgrowth of abnormal flora defined as 10^5 AGNB per ml of saliva and/or per g of feces.

Gut overgrowth guarantees increased spontaneous mutation, leading to polyclonality and antimicrobial resistance [22]. As parenteral antimicrobials generally fail to eradicate the abnormal carrier state in overgrowth concentrations, the enteral antimicrobials polymyxin/tobramycin aiming at converting the abnormal carrier state into normal carriage, are the essential component of SDD, because they eradicate carriage and overgrowth of AGNB including resistant mutants, maintaining the usefulness of parenteral antimicrobials.

SDD using enteral polymyxin/tobramycin with or without vancomycin, prevents acquisition and de novo development in eradicating abnormal flora of resistant bacteria present in the admission flora.

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Infections in ICU: An Ongoing Challenge 22

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Introduction

During the late 1970s most intensivists acknowledged that the pathogenesis of the majority of infections in the intensive care unit (ICU) was endogenous. However, there were no supporting data.

Chris Stoutenbeek introduced surveillance cultures into ICU medicine in 1980, after meeting Steven Schimpff, the champion of surveillance cultures. Stoutenbeek implemented throat and rectal swabs to monitor carriage of potential pathogens causing lower airway and bloodstream infections, respectively. The first results showed that 85% of all ICU infections are endogenous, i.e., preceded by oropharyngeal and/or rectal carriage. Surveillance cultures obtained at admission and twice weekly afterwards allowed the distinction between primary carriage of potential pathogens (imported in the admission flora) and secondary (super-) carriage of potential pathogens acquired during treatment in ICU. In conjunction with diagnostic cultures, 55% of ICU infections are primary endogenous, 30% secondary endogenous, and 15% exogenous, i.e., without previous carriage.

Stoutenbeek was the first to recognize that these three types of ICU infection each require a different prophylactic maneuver. Parenteral antimicrobials are required to control primary endogenous infections, enteral antimicrobials to prevent secondary endogenous infections, and topical antimicrobials to control exogenous infections. Selective decontamination of the digestive tract (SDD) is a prophylactic maneuver using parenteral, enteral, and topical antimicrobials aiming at a reduction of the three types of infection and at a reduction in mortality. Surveillance cultures are the fourth and integral component of the full SDD strategy.

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Introduction

The main aim of definitions is uniformity, in any discipline. In particular, intensivists have shown increasing interest in the terminology used [1]. Although no definition will be perfect in complex diseases such as sepsis, standardization of denitions is thought to be pivotal to ensure uniformity in clinical assessment and in enrolment in multicenter clinical trials. A review of the recent literature on prevention of infection in the ICU reveals a lack of terminology [2]. Remarkably, in the field of clinical microbiology and infectious diseases, there is an urgent need for definitions in order to guarantee consistency. Therefore, the adoption of eleven concise definitions is proposed [3].

Normal flora exists when the surveillance samples yield indigenous aerobic and anaerobic flora. Some people carry "normal" potential pathogens: *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Escherichia coli, Staphylococcus aureus,* and *Candida albicans*.

Abnormal flora exists when aerobic Gram-negative bacilli (AGNB) including *Klebsiella, Enterobacter, Citrobacter, Proteus, Morganella, Serratia, Acinetobacter, Pseudomonas* species and/or methicillin-resistant *Staphylococcus aureus* (MRSA) are persistently present in surveillance samples.

Primary endogenous infection is due to "normal" and/or "abnormal" micro-organisms present in the admission flora.

Secondary endogenous infection is due to "abnormal" bacteria not present in the admission flora but acquired later in the ICU. The "abnormal" bacteria are first acquired, followed by carriage and overgrowth. Colonization and then infection may occur.

Exogenous infection is caused by "abnormal" bacteria introduced directly into the patient; omitting the stage of carriage, to a site where colonization and then infection occurs.

Parenteral antimicrobials used in an SDD regimen are administered at admission to an ICU and for the subsequent 4 days to control primary endogenous infection. Cefotaxime has often been used in high doses as it eradicates carriage of "normal" bacteria via saliva, bile, and mucus.

Enteral antimicrobials are applied in the throat as a paste or gel and in the gut as a suspension at admission and throughout treatment in the ICU to control secondary endogenous infection. Polymyxin/tobramycin (with or without vancomycin) is the classical combination.

Topical antimicrobials are applied on the tracheostoma as a paste or gel at admission and throughout treatment in the ICU to control exogenous infection. Generally, 2% polymyxin/tobramycin is applied topically.

Surveillance cultures are defined as throat and rectal swabs aiming at the detection of the "abnormal" carrier state; regularly obtained (e.g., Monday and Thursday) as they are the most sensitive samples to detect resistance.

Selective decontamination of the digestive tract is a prophylactic protocol using parenteral and enteral antimicrobials aiming to prevent endogenous infection and

reduce mortality [3]. Endemicity of exogenous infections requires topical antimicrobials; the integral component of SDD is regular surveillance samples.

Consensus or widespread agreement does not make sense [4].

Approximately 20 years ago, the first European consensus conference was held in Paris in December, 1991 [5]. Interestingly, the opening lecture also dealt with definitions [6]. However, even more interesting is the observation that the selected definitions have not changed, apart from one, i.e., consensus. This observation implies that people have not changed over 20 years, as they selectively read and believe their own opinions, a phenomenon called "primacy of opinion over evidence."

Consensus has been successfully employed by experts to bypass evidence-based medicine (EBM) [4]. Consensus was used to condemn SDD as an expensive prophylactic method without survival benefit at the first European consensus conference [5]. More recently, the Surviving Sepsis Campaign needed consensus to exclude SDD [7], and the original Canadian EBM promoters are not immune from becoming experts [8]. These few examples illustrate that consensus does not make sense.

Time vs. Carrier State Classification of Pneumonia

Two different approaches for classifying pneumonia were introduced in the 1980s. Stoutenbeek et al. classified pneumonia using the concept of carriage [9] and Langer et al. assessed time [10] to categorize pneumonia in 1984 and 1986, respectively.

The carrier state concept distinguishes among three different types of pneumonia: primary endogenous pneumonia due to potential pathogens, both "normal" and "abnormal," present in the admission flora. Primary endogenous pneumonia generally occurs within the first week of treatment in the ICU and the frequency is about 55% (Table 22.1). Secondary endogenous pneumonia is caused by abnormal potential pathogens not present in the admission flora but acquired in the ICU. One third of ICU pneumonias are secondary endogenous and usually develop after a week. Thirdly, the exogenous pneumonia is due to abnormal ICU bacteria not carried at all, but immediately introduced into the lower airways, bypassing carriage. This type of pneumonia is common in tracheotomized patients. About 15% of all ICU pneumonias are exogenous, and can occur at any time during ICU treatment.

Pneumonia which occurs early during the ICU treatment is addressed as "early-onset pneumonia" [10]. However, it is unknown what is the best cut off to separate "early" from "late" onset pneumonia. The cut off of 4 days has been used by several authors [11,12]; others have used 5 [13] or even 7 [14] days. Silvestri et al. intensively studied both classification schemes in the 1990s, and demonstrated that monitoring carriage of potential pathogens is a more realistic approach for classifying pneumonia developing in the ICU [15–17]. He also showed that a time cut off of 9 days was more reliable to identify pneumonia due to ICU-associated bacteria rather than 4 days [15]. These results were consistent with similar experiences from the UK, Spain, and Italy [18–22].

Stoutenbeek realized that each of the three types of pneumonia based on the sur-

veillance culture approach requires different prophylactic interventions [9]. Parenteral antimicrobial agents control primary endogenous pneumonia, enteral antimicrobials prevent secondary endogenous pneumonia, and a high level of hygiene combined with topical antimicrobials can control exogenous pneumonia (Table 22.1). The full protocol of SDD including parenteral and enteral antimicrobials, hygiene and topical antimicrobials aims at the control of primary endogenous, secondary endogenous, and exoge-

Tabella 22.1 Classification of infections occurring ICU

Infection	PPM	Timing	Frequency	Maneuver
Prim endog	6 "normal" 9 "abnormal"	<1 week	55%	Parenteral antimicrobials
Sec endog	9 "abnormal"	>1 week	30%	Enteral antimicrobials
Exogenous	9 "abnormal"	Anytime during ICU treatment	15%	Hygiene and topical antimicrobials

PPM, potentially pathogenic micro-organisms; *Prim endog*, primary endogenous; *Sec endog*, secondary endogenous
6 "normal" PPM are: *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Candida albicans, Staphylococcus aureus, Escherichia coli*
9 "abnormal" PPM are: *Klebsiella, Proteus, Morganella, Enterobacter, Citrobacter, Serratia, Acinetobacter, Pseudomonas* species and methicillin-resistant *Staphylococcus aureus* (MRSA)

nous pneumonia, and at the reduction in mortality. SDD based on carriage classification has consistently been proven to control pneumonia [23] and mortality [8], while Martin Langer, in his randomized controlled trial (RCT) of 1,319 patients in 23 ICUs, failed to show any benefit in terms of pneumonia and mortality [24]. The endpoint of the Italian RCT was the prevention of early-onset pneumonia, using solely parenteral antimicrobials, and patients eligible for the study were divided into three groups which received either cefoxitin (2 g IV for 3 doses/8 h), penicillin G (2 million U IV for 4 doses/6 h), or no antibiotic (control group). In the overall population, the incidence of early-onset pneumonia was 6.1% in the prophylaxis recipients versus 7.2% in the control group. No statistically different rates of pneumonia or death were found among the groups. Stoutenbeek wrote immediately to Martin Langer stating the reasons he thought the RCT based on time classification was negative [25]. He wrote the "…systemic antibiotic prophylaxis only prevents primary endogenous infections, at the price of selection of resistant strains and subsequent secondary endogenous infections." His views, expressed about 20 years ago, have recently been confirmed in a Dutch RCT showing that the full SDD protocol using parenteral and enteral antimicrobials actually reduces antimicrobial resistance [26,27]. The largest multicenter RCT to date includes 6,000 patients and the proportion of patients with AGNB in rectal swabs that

were not susceptible to the marker antibiotics was lower with SDD than with standard care or selective oropharyngeal decontamination (SOD), a modified SDD protocol without the gut component. For example, carriage of multiresistant *P. aeruginosa* was 0.4% in SDD versus 0.8% in SOD and 13% in the group receiving standard care ($p<0.05$).

Nonantibiotic Measures to Prevent Pneumonia

Interestingly, the time classification has recently enjoyed a come-back [28]. Craven, in a recent editorial, suggested the use of subglottic drainage to control early-onset pneumonia, although parenteral agents are still required to control lower airway infections due to respiratory pathogens present in the admission flora, and silver-coated tubes to control late onset pneumonia. We find the Craven proposal puzzling, as neither subglottic drainage nor silver-coated tubes have been associated with a survival benefit [29], while therapy with parenteral antimicrobial agents without enteral antimicrobial agents promote the emergence of resistance [27].

Similarly, Dallas and Kollef in their most recent editorial on pneumonia prevention [30] recommend silver-coated endotracheal tubes as an alternative which has been shown to significantly reduce the incidence of ventilator-associated pneumonia (VAP) in a large randomized trial that included patients in a variety of ICU settings [31]. This strategy is also easier to employ and has a lower risk of promoting antimicrobial resistance. However, the RCT has important limitations. First, the author did not report whether the cuff pressure of the endotracheal tube was controlled during the study and which type of ventilation was used. The cuff pressure should be regularly and carefully measured during ventilation in order to minimize the mucosal damage and to maintain as much as possible a clinical seal preventing aspiration of oropharyngeal secretions containing bacteria in overgrowth [32]. Moreover, positive expiratory pressure has been recently shown to delay the leakage of fluid around the cuff [32]. Second, coagulase-negative staphylococci, enterococci, and yeasts were included among the micro-organisms causing VAP. In general, the first two bacteria do not cause VAP, and the role of *Candida* in VAP isunder debate. The exclusion of those episodes may have changed the results as in the study the difference in VAP rates was marginally significant in the intention-to-treat analysis. Third, the effect of silver ions on oropharyngeal colonization was not reported. The knowledge of colonization of the oropharynx allows the distinction between endogenous and exogenous infections. The silver-coated tube showed its greatest effect during the first 10 days of mechanical ventilation, thus mainly on micro-organisms present in the patient's admission flora, i.e., it controls primary endogenous VAP. The inactivation of silver ions by proteins, saliva, mucosal cells, and leukocytes may explain why the silver-coated tubes failed to control secondary endogenous VAP occurring late during ICU stay. Additionally, exogenous VAP, in which micro-organisms are introduced directly into the lower airways due to poor hygiene, bypassing the oropharynx, may be an inherent limitation of the silver-coated tubes. Finally, there was no impact of silver-coated endotracheal tubes on survival.

The accumulation of oropharyngeal secretions above the cuff of the endotracheal tube is thought to increase the risk of aspiration of secretions and pneumonia. Removal of these pooled secretions through suctioning of the subglottic region may reduce the risk of developing VAP. There are two meta-analyses of only RCTs assessing the effectiveness of subglottic secretion drainage in preventing VAP and in reducing mortality [33,34]. In the meta-analysis by Dezfulian [33], which included five RCTs, secretion drainage appeared effective in preventing early-onset VAP. No impact on mortality was demonstrated. In another recent meta-analysis by Silvestri et al. [34], ten RCTs of subglottic secretion drainage were included [35–44]: in five the suction was continuous [36–38, 40, 44], and in two it was intermittent [35, 42]. In the remaining trials the method of suctioning was not reported [39, 41, 43]. Data on pneumonia during mechanical ventilation were available in 9 RCTs including 1,953 patients (984 tests, 969 controls). There were 90 patients developing VAP in test and 164 patients in the controls, demonstrating a 57% reduction of VAP due to subglottic drainage (OR 0.43, 95% CI 0.32–0.58; p<0.001) (Fig. 22.1). Mortality was evaluated in 7 RCTs including 1,846 patients (924 tests, 922 controls). There were 133 deaths in the test group and 141 in the control group. Subglottic secretion drainage did not significantly reduce mortality (OR 0.93, 95% CI 0.71–1.21; p=0.57) (Fig. 22.2). The microbiological data were reported by a small number of RCTs. Subglottic secretion drainage mainly

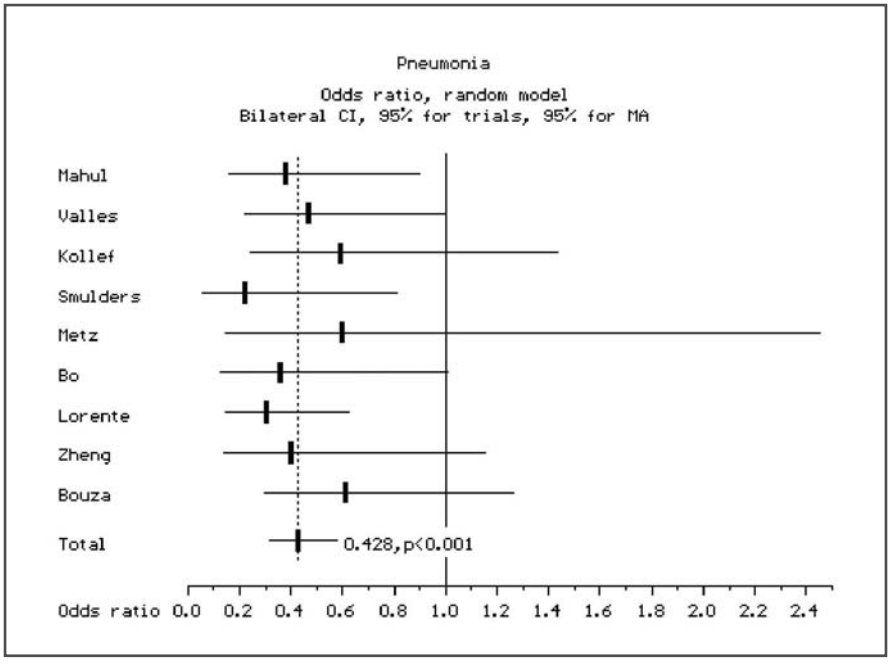

Fig. 22.1 Meta-analysis of aggregate data of the impact of subglottic secretion drainage on pneumonia

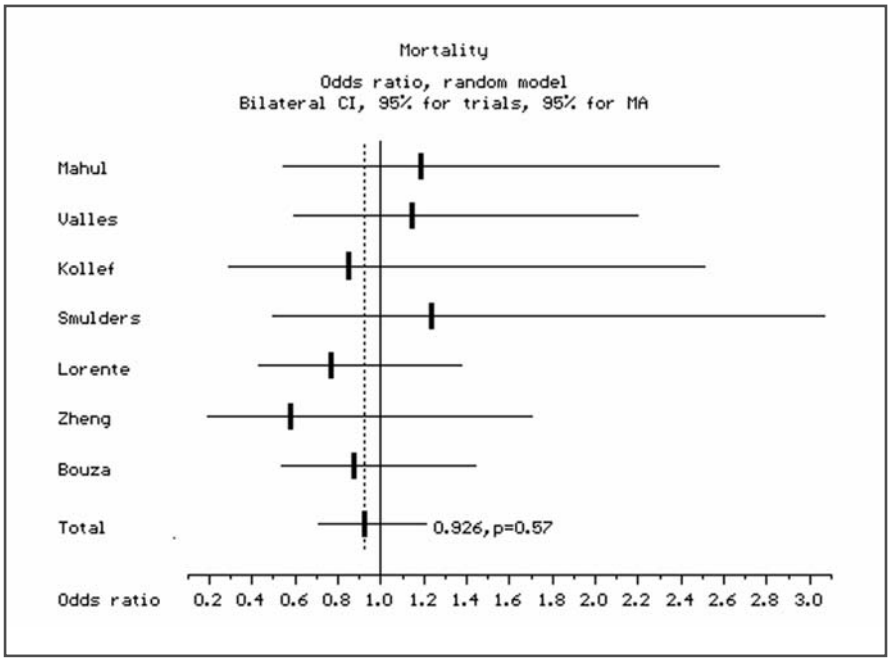

Fig. 22.2 Meta-analysis of aggregate data of the impact of subglottic secretion drainage on mortality

impacted VAP due to normal flora, such as *S. aureus* and *H. influenzae*, causing primary endogenous pneumonia which develops "early" during ICU stay. In contrast, there was no impact on abnormal flora, such as *P. aeruginos* and other aerobic Gram-negative bacilli, causing secondary endogenous VAP, which develops "late" during ICU stay. In summary, subglottic secretion drainage appears effective in preventing early-onset pneumonia due to normal flora with no significant impact on survival. More studies are needed to assess the impact of the maneuver on late-onset VAP, although exogenous infections are an inherent limitation of the maneuver.

Semirecumbent position has been claimed by several authors and influential scientific societies as a method to prevent VAP [45–47]. This was based on experimental studies with radioactive-labeled enteral feeding, suggesting that endotracheal aspiration of gastric content occurred more frequently in patients positioned supinely rather than semirecumbently at 45°. However, clinical data supporting that statement are not robust. Three RCTs on semirecumbent position [48–50] and three meta-analyses have been published [8,51,52] providing data on overall 337 patients (168 test, 169 control). When the appropriate statistical method was used due to heterogeneity, i.e., the random effect model, semirecumbency did not significantly reduce the odds of both microbiological and clinically suspected VAP, and mortality was also not statistically reduced.

Moreover, in the Spanish study [48] the overall benefit of the preventative method was due to a 50% incidence of clinically suspected VAP in patients treated horizontally and receiving enteral nutrition, and in the Dutch study [49] the target backrest elevation at 45° was not achieved for 85% of the study time. This may reduce the robustness of the studies. In summary, although semirecumbency demonstrated a trend toward a reduction of VAP and mortality, this was not significant, and no conclusions can be drawn for clinical practice.

Recently, topical application of antiseptics, such as chlorhexidine or povidone-iodine, to the oral mucosa for the prevention of VAP has been studied in RCTs with opposite results [53–64]. To our knowledge, five meta-analyses of oral antiseptics have been published [8,65–68]. The majority of meta-analyses concluded that oral antiseptics seem to be effective in reducing VAP. However, the results of RCTs of oral antiseptics and meta-analyses should be interpreted with caution. Two thirds (928 test, 940 controls) of the population included in the last meta-analysis [8] were cardiac surgery patients enrolled in three RCTs [53,55,60]. These patients received no more than 2 days of mechanical ventilation. The identical problem was encountered in the Tantipong study in mixed population where more than 50% of patients were ventilated for less than 48 h [63,69]. Therefore, these four studies should not be included in a meta-analysis with the end-point of VAP. Moreover, the different definition of lower respiratory tract infections and the different dosages and applications of antiseptics (e.g., chlorhexidine vs. povidone iodine, 0.12% vs. 2% chlorhexidine, use of solution, spray, gel, or paste) may have influenced the results. In summary, it seems that oral antiseptics may be effective in preventing lover respiratory tract infection only in patients who receive mechanical ventilation up to 48 h [68]. Whether oral antiseptics are useful to prevent late-onset VAP requires further investigation. Again, oral antiseptics did not significantly reduce mortality.

There is not sufficient evidence to recommend any of the discussed nonantibiotic measures to prevent VAP. Prevention strategies both antibiotic and nonantibiotic should block the endogenous mainly oropulmonary route. As microaspiration cannot be fully prevented by manipulating critically ill patients, prevention protocols should aim at the elimination of potential pathogens from the oropharynx. However, it should be realized that exogenous infections are substantial in ICU patients and require additional preventative measures [70].

Conclusions

1. Definitions are crucial to ensure uniformity in clinical assessment and enrolment in clinical trials.
2. Maneuvers based on the carriage classification of pneumonia rather than on time improve survival.
3. Nonantibiotic measures cannot be recommended to prevent VAP using EBM methodology of survival benefit; SDD is the only EBM maneuver with grade 1A recommendation.

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Selective Decontamination of the Digestive Tract (SDD). Twenty-five Years of European Experience

23

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Introduction

The key to infection control in the intensive care unit (ICU) is to appreciate that three different types of infection, due to a limited range of potentially pathogenic micro-organisms (PPMs), six "normal" and nine "abnormal," require a different prophylactic maneuver. Primary endogenous infections can only be controlled by the immediate administration of parenteral antibiotics, and secondary endogenous infections by the application of enteral antimicrobials in throat and gut. A high level of hygiene and topical antimicrobials are required to control exogenous infections despite being less frequent [1–3] (Table 23.1).

Table 23.1 Classification of infections occurring on intensive care unit

Infection	PPMss	Timing	Frequency	Maneuver
Primary endogenous	6 "normal" 9 "abnormal"	<1 week	55%	Parenteral antimicrobials
Secondary endogenous	9 "abnormal"	>1 week	30%	Enteral antimicrobials
Exogenous	9 "abnormal"	Anytime during ICU treatment	15%	Hygiene and topical antimicrobials

PPM, Potentially pathogenic micro-organisms
"Normal" PPMs are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Candida albicans*, *Staphylococcus aureus*, *Escherichia coli*
"Abnormal" PPMs are *Klebsiella*, *Proteus*, *Morganella*, *Enterobacter*, *Citrobacter*, *Serratia*, *Acinetobacter*, *Pseudomonas* species and methicillin-resistant *Staphylococcus aureus*

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Definition

Selective decontamination of the digestive tract (SDD) using parenteral and enteral antimicrobials, hygiene and surveillance cultures is a prophylactic protocol aiming at the control of primary and secondary endogenous and exogenous infections due to the 15 PPMs and at the reduction in mortality [1]. Regular surveillance cultures of throat and rectum are an essential component of the SDD strategy, and constitute the fourth element of the full four-component strategy of SDD described by Chris Stoutenbeek in 1984 [1].

Efficacy

SDD has been assessed in 59 randomized controlled trials (RCTs) and eight meta-analyses of only RCTs [4–11]. SDD using parenteral and enteral antimicrobials consistently demonstrated reduced pneumonia in four meta-analyses [4–6,10] with the endpoint of pneumonia (Table 23.2). The parenteral component, normally cefotaxime, effectively controls primary endogenous pneumonias due to the "normal" respiratory pathogens *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*, whereas the enteral antimicrobials polymyxin and

Table 23.2 Efficacy of selective decontamination of the digestive tract assessed in eight meta-analyses of only RCTs

Author	Number of RCTs	Sample size	Lower airway infection OR (95% CI)	Bloodstream infection OR (95% CI)	Mortality OR (95% CI)
Vandenbroucke-Grauls [4]	6	491	0.12 (0.08–0.19)	NR	0.92 (0.45–1.84)
D'Amico [5]	33	5,727	0.35 (0.29–0.41	NR	0.80 (0.69–0.93)
Liberati [6]	36	6,922	0.35 (0.29–0.41)	NR	0.78 (0.68–0.89)
Safdar [7]	4	259	NR	NR	0.82 (0.22–2.45)
Silvestri [8]	42	6,075			
- yeasts			NR	0.89 (0.16–4.95)	NR
Silvestri [9]	51	8,065	NR	0.63 (0.46–0.87)	0.74 (0.61–0.91)
Silvestri [10]	54	9,473			
- Gram negative			0.07 (0.04–0.13)	0.36 (0.22–0.60)	NR
- Gram positive			0.52 (0.34–0.78)	1.03 (0.75–1.41)	NR
Silvestri [11]	21	4,902	NR	NR	0.71 (0.61–0.82)

RCTs, Randomized controlled trials; *OR*, odds ratio; *CI*, confidence interval; *NR*, not reported

tobramycin (with or without vancomycin) reduces secondary endogenous pneumonias due to "abnormal" bacteria including aerobic Gram-negative bacilli (AGNB) and methicillin-resistant *Staphylococcus aureus* (MRSA).

Bloodstream infection was the endpoint of three meta-analyses [8–10]. SDD using parenteral and enteral antimicrobials significantly reduces overall blood stream infections, those due to Gram-negative bacteria, without affecting bloodstream infections due to Gram-positive bacteria. SDD including an enteral polyene, either amphotericin B or nystatin, also reduced fungaemia, albeit not significantly mainly due to the low event rates in test and control groups [8].

Mortality was also the outcome measure in six of the eight meta-analyses [4–7,9–11]. There was a consistent survival benefit in all meta-analyses that assessed the full four-component SDD protocol, providing the sample size was large enough [5,6,9,11]. The meta-analyses of Vandenbroucke-Grauls [4] and Safdar [7] showed an impact on mortality which was not significant due to the small sample size.

Safety

The 20-plus years of clinical SDD research demonstrated an intriguing finding that SDD does not increase the problem of resistance but rather reduces it [12]. Two of the 59 RCTs [13,14] report an increase in resistance. Interestingly, the endpoint was the number of resistant isolates rather than the number of patients with resistant isolates in these two RCTs.

Three RCTs evaluated the impact of SDD on the number of patients who carried antibiotic resistant AGNB [15–17]. A *Klebsiella pneumoniae* producing extended spectrum beta-lactamase (ESBL) was endemic in a French hospital [15]: carriage and infection rates were 19.6 and 9%, respectively. Once enteral antimicrobials were added to the parenteral there was significant reduction in both carriage and infection (19.6% vs. 1%; 9% vs. 0%). A Dutch monocenter RCT including 1,000 patients reports that carriage of AGNB resistant to imipenem, ceftazidime, ciprofloxacin, tobramycin, and polymyxins occurred in 16% of patients receiving parenteral and enteral antimicrobials, compared to 26% of control patients receiving only parenteral antibiotics with a relative risk of 0.6 (95% confidence interval 0.5–0.8) [16]. The largest multicenter RCT to date, also from the Netherlands [17], includes 6,000 patients and the proportion of patients with AGNB in rectal swabs that were not susceptible to the marker antibiotics was lower with SDD than with standard care or selective oropharyngeal decontamination (SOD), a modified SDD protocol without the gut component. For example, carriage of multiresistant *P. aeruginosa* was 0.4% in SDD vs. 0.8% in SOD and 1.3 in the group receiving standard care ($p < 0.05$).

There are four long-term studies (≥2 years) evaluating the impact of polymyxin/tobramycin on resistance amongst AGNB [18–21] (Table 23.3). The resistance data of the long-term studies confirm the RCT findings that rates of carriage and infection due to resistant AGNB in patients receiving enteral and parenteral antimicrobials are not increased but are actually lower compared with patients

Table 23.3 Long term studies (≥2 years) of enteral antimicrobials polymyxin/tobramycin on resistance amongst aerobic Gram-negative bacilli

Author	Study		Patients		% patients with carriage (surv) and/or infection (diag) due to resistant AGNB
	Type	Period	Type	Number	
Stoutenbeek [18]	Prospective observational	2 years	Trauma	164	4% of patients carried *E.coli* resistant to tobramycin, *Acinetobacter* resistant to tobramycin, *Pseudomonas* resistant to tobramycin
Leone [19]	Retrospective case-control	6 years	Mechanically ventilated	720	No difference between test and control
Sarginson [20]	Prospective observational	4 years	Children ≥4 days of ventilation	1241	4% of children were infected with resistant bacteria including MRSA
Heininger [21]	Prospective observational	5 years	Mechanical ventilation >2 days	1913	0.05% of patients infected with *E. coli* resistant to tobramycin

Surv, Surveillance samples; *diagn*, diagnostic samples

receiving solely parenteral antimicrobials. Most patients who require long-term treatment on ICU have overgrowth of abnormal flora, defined as 105 AGNB per ml of saliva and/or g of feces. Gut overgrowth guarantees increased spontaneous mutation, leading to polyclonality and antimicrobial resistance [22]. As the parenteral antimicrobials generally fail to eradicate the abnormal carrier state in overgrowth concentrations, the enteral antimicrobials polymyxin/tobramycin aiming at converting the abnormal carrier state into normal carriage, are the essential component of SDD because they eradicate carriage and overgrowth of AGNB, including resistant mutants, maintaining the usefulness of parenteral antimicrobials.

Vancomycin-resistant enterococci (VRE) and MRSA are intrinsically resistant to the parenteral and enteral antimicrobials of the SDD protocol. Nine RCTs assessed the impact of SDD on carriage and infection due to these two Gram-positive bacteria, two on VRE [23,24] and seven on MRSA [14,25–29,30]. VRE carriage and infection were the primary endpoints of SDD RCTs in two American ICUs with endemic VRE [23,24]. There was no difference between test and control groups. There are seven RCTs conducted in ICUs where MRSA was endemic at the time of the trial [14,25–30]; they report a trend towards higher MRSA carriage and infection rates in patients receiving SDD. The addition of enteral vancomycin to the classical SDD is required to control MRSA in ICUs with endemic MRSA [31]. Neither Staphylococcus aureus with intermediate sensitivity to vancomycin (VISA) nor VRE emerged in any of the six RCTs using enteral vancomycin [32–37]. Three studies using long-term SDD with vancomycin (≥2 years) failed to report the emergence of VISA or VRE [38–40] (Table 23.4). Similarly, MRSA overgrowth is invariably pres-

Table 23.4 Long-term studies (≥2 years) of enteral vancomycin on resistance amongst *Staphylococcus aureus* and enterococci: *Staphylococcus aureus* with intermediate sensitivity to vancomycin and vancomycin-resistant enterococci

Author	Study		Patients		% patients with carriage (surv) and/or infection (diagn) due to VISA and/or VRE
	Type	Period	Type	Number	
de la Cal [38]	Prospective observational	4 years	Medical/ Surgical >3 days of mechanical ventilation	799	13/799 (5%) carried VRE
Cerda [39]	Prospective observational	4 years	Burns	375	No emergence of VRE or VISA in either surv or diagn
Viviani [40]	Prospective observational	2 years	Mechanical ventilation >3days	265	No emergence of VRE or VISA in either surv or diagn

Surv, Surveillance samples; *diagn*, diagnostic samples; *VISA*, vancomycin-intermediate *Staphylococcus aureus*; *VRE*, vancomycin resistant enterococci.

ent in the critically ill in case of MRSA endemicity and guarantees the presence of VISA strains following the parenteral use of vancomycin [41]. The addition of enteral vancomycin associated with fecal vancomycin levels of up to 3,000 μg/mL prevents or eradicates, if already present, the VISA mutants [42].

A similar scenario applies to carriage and overgrowth of abnormal VRE and the intravenous administration of antimicrobials such as linezolid, resulting in the emergence of linezolid resistant VRE mutants [43]. As far as we are aware, there are no studies that assessed the efficacy of enteral vancomycin in preventing and eradicating carriage and overgrowth of VRE [44,45].

Costs

Costs at €6/day [17,46,47], can hardly be an issue for an ICU intervention that reduces pneumonia, septicemia, and mortality by 65, 27, and 29%, respectively, without antimicrobial resistance emerging in unselected critically ill patients.

SDD: The Only EBM Maneuver with Grade 1A Recommendation

It is remarkable that in the 21st century, after 60 years of intensive care medicine, ICU maneuvers are only now being properly assessed with the endpoint of mortality. There are five maneuvers that have been shown to reduce mortality in RCTs: ventilation with low tidal volumes for acute lung injury and the acute respiratory distress syndrome [48], recombinant human activated protein C for severe sepsis [49], intensive insulin therapy [50], low doses of steroid in patients with septic shock [51], and SDD [16,17,37] (Table 23.5). Table 23.5 reports the levels of evidence obtained using

Table 23.5 Intensive care unit interventions that reduce mortality

Intervention	Relative risk (95% CI)	Absolute mortality reduction % (95% CI)	NNT	Grade of recommendation*
Low tidal volume [48]	0.78 (0.65–0.93)	8.8 (2.4–15.3)	11	1B
Activated protein C [49]	0.80 (0.69–0.94)	6.1 (1.9–10.4)	16	2B
Intensive insulin [50]	0.44 (0.36–0.81)	3.7 (1.3–6.1)	27	2C
Steroids [51]	0.90 (0.74–1.09)	6.4 (-4.8–17.6)	16	2C
SDD [16]†	0.65 (0.49–0.85)	8.1 (3.1–13.0)	12	1A

CI, Confidence interval; *SDD*, selective decontamination of the digestive tract; *NNT*, number needed to treat; * Grades of recommendation are retrieved from reference [53] except for SDD; † Two randomized controlled trials reported a significant reduction in intensive care unit mortality with odds ratio of 0.81 (95% CI 0.69–0.94) [17], and relative risk of 0.51 (95% CI 0.29–0.87) [37]

the Grade system [52,53], which classifies the quality of evidence as high (grade A), moderate (grade B), low (grade C) or very low (grade D). RCTs begin as high quality evidence but may be downgraded due to limitations in implementation, inconsistency or imprecision of the results, indirectness of this evidence, and possible reporting bias [53]. An example of this is tight glucose control (A down to C): the original Belgian RCT [50] has never been supported and the data confirmed in subsequent studies [54–57]. Additionally, a recent tight glucose control meta-analysis is negative [58].

The Grade system classifies recommendations as strong (grade 1) or weak (grade 2). The grade of strong or weak is considered of greater clinical importance than a difference in letter level of quality of evidence. A strong recommendation in favor of an intervention reflects that the desirable effects of adherence to a recommendation (beneficial health outcomes, less burden on staff and patients, and cost savings) will clearly outweigh the undesirable effects (harms, more burden, and greater costs).

All RCTs of SDD, whether mono- [16] or multicenter [17,37], that assessed the full four-component SDD protocol consistently demonstrated a significant survival benefit providing the sample size was large enough. Similarly, all meta-analyses that assessed the full SDD protocol and with a large enough sample size showed a consistent survival benefit [5,6,9,11]. The mortality data show an intriguing observation that trial design determines the magnitude of the survival benefit [11]. The relative reduction in the odds ratio for mortality was 41% when all patients receive the full SDD protocol [16], 29% when half the patients receive the prophylaxis [11], and 17% when less than half of the population are treated with SDD [17]. In the trial of the unit-wide application of SDD [16], the SDD protocol virtually eliminated transmission of potential pathogens via hands of caretakers and hence exogenous infections in decontaminated patients. The survival benefit is diluted by mixing decontaminated and nondecontaminated patients in the same unit. This is the case in the RCT design, wherein the patients receiving and not receiving SDD are treated within the same unit [11]. Patients receiving SDD protect control patients from transmission, acquisition, carriage, and subsequent infection, whereas the patients receiving SDD remain at risk of acquiring potential pathogens and subsequent exogenous infections, resulting in a reduction in the true effect of SDD. The most recent multicenter RCT in 6,000 patients with a 17% relative reduction – albeit statistically significant – clearly underlines the issue of diluting the SDD effect by increasing the number of nondecontaminated patients treated in the same unit with patients receiving SDD [17].

Practical Guidelines: How To Do SDD

All patients who are admitted to the ICU for minimally 2 days require the immediate administration of parenteral cefotaxime in high doses, for 4 days, to control mortality due to “early” primary endogenous infections caused by the “normal” potential pathogens such as *S. pneumoniae* and *S. aureus* (Table 23.6). The enteral antimicro-

Table 23.6 The full four-component protocol of selective decontamination of the digestive tract

Target PPMs and antimicrobials	Total daily dose (4 times daily)		
	<5years	5–12 years	>12 years
1. Parenteral antimicrobials: "normal" PPMs			
Cefotaxime (mg)	150/Kg	200/Kg	4000
2. Enteral antimicrobials: "abnormal" PPMs			
A. Oropharynx			
1. AGNB: polymyxin E with tobramycin	2 g of 2% paste or gel		
2. Yeasts: amphotericin B or nystatin	2 g of 2% paste or gel		
3. MRSA: Vancomycin	2 g of 4% paste or gel		
B. Gut			
1. AGNB: polymyxin E (mg)	100	200	400
with tobramycin (mg)	80	160	320
2. Yeasts: amphotericin B (mg)	500	1,000	2,000
or nystatin units	$2x10^6$	$4x10^6$	$8x10^6$
3. MRSA: vancomycin (mg)	20–40/Kg	20–40/Kg	500–2,000
3. Hygiene with topical antimicrobials			
4. Surveillance swabs of throat and rectum on admission, Monday, Thursday			

PPMs, Potentially pathogenic microorganisms; *AGNB*, aerobic Gram-negative bacilli; *MRSA*, methicillin-resistant *Staphylococcus aureus*; the total daily dose has to be divided into 4 doses

bials are given throughout the treatment in ICUs to control mortality associated with "late" secondary endogenous infections. A paste or gel is applied into the lower cheeks to prevent and, if already present, eradicate oral carriage of "abnormal" PPM, i.e., to decontaminate the oropharynx. A suspension is administered via the naso-gastric tube to decontaminate stomach and gut. Polymyxin and tobramycin are used to control "abnormal" carriage of AGNB, in particular Pseudomonas aeruginosa. Enteral vancomycin is added to polymyxin/tobramycin, in case of MRSA endemicity. Tobramycin is replaced by paromomycin in case of endemicity of AGNB-producing ESBL. In case of *Serratia* endemicity, both polymyxin and tobramycin are replaced by paromomycin. Enteral amphotericin B or nystatin is used to control yeast overgrowth. The third component is hygiene combined with topical antimicrobials to control "exogenous" infections of the lower airways. And finally, regular surveillance cultures of throat and rectum are obtained to monitor efficacy and safety of the enteral antimicrobials [59].

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Antifungal Management

24

S. Rinaldi, A.R. De Gaudio

Introduction

During the last 2 decades, an increased frequency of severe life-threatening infections caused by yeasts has been reported in critical ICU patients [1]. The two main factors contributing to yeast infections are: the disregulation of immune system and the alteration of microbial flora secondary to extensive use of broad-spectrum antibiotics. Critically ill patients exhibit a complex change in immune function characterized by deactivation of macrophages and altered cellular response with shift from Th1 to Th2 response [1,2]. Many other factors impairing the immune function during critical illness include hyperglycemia and the use of corticosteroids [2]. In particular, corticosteroids have profound effects on the distribution and function of neutrophils, monocytes, and lymphocytes and they directly stimulate the growth of some yeasts like *Aspergillus fumigatus* that have sterol binding proteins [2]. In ICU the two main fungal species involved in severe invasive infections are *Candida spp.* and *Aspergillus spp*., while *Cryptococcus spp*. remains a significant pathogen only in patients with severe immunodepression like those affected by HIV [1]. Invasive candidiasis affects around 2% of ICU patients in the USA, causing around 10% of ICU-acquired bloodstream infections and representing the third commonest bloodstream pathogen [1]. However, the epidemiology of candidemia depends upon geographic region, ICU type, and case mix. The crude mortality associated with candidemia ranges between 40 and 70%, depending on the severity of the underlying disease, while attributable mortality estimates vary between 20 to 50% from retrospective studies and 5–7% from prospective clinical trials [3]. In Europe the epidemiology is similar [4]; Candida is the seventh most common nosocomial pathogen

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in German ICUs [5]; in UK the hospital-wide incidence of candidemia is around 3 per 100,000 bed days, and half of all cases occur in ICUs [6]. However, the incidence of candida infection varies between different types of ICUs. For example among surgical ICUs, those caring for abdominal surgical or immunosuppressed patients have a higher incidence of invasive candidiasis than general medical ICUs.

Regarding the incidence of invasive aspergillosis in ICUs, data remain scarce and variable [7]. An incidence of 5.8% has been reported in critical ICU patients without typical risk factors such as hematological malignancies and exogenous immunosuppression. The mortality rate associated with invasive pulmonary aspergillosis exceeds 50% with retrospective studies reporting a mean in-hospital mortality of 80% even despite antifungal therapy [7].

Because of the substantial morbidity, mortality, and economic cost of invasive fungal infection, their appropriate management seems to be an important challenge for intensivists.

Definition of the Topic

Antifungal management in ICU should include:
- Identification of risk factors for fungal infection
- Appropriate diagnosis
- Selection of an efficacious therapeutic strategy

Identification of Risk Factors

Recognized risk factors for fungal infection in ICU may be reconducted to the two cited pathogenetic conditions (immune disregulation and perturbation of the normal microbial flora) underlying the shift from yeast colonization to yeast infection [1,3] (Table 24.1).

In 2006 Leon et al [8] obtained a score for deciding early antifungal treatment when invasive candida infection is suspected in nonneutropenic critically ill patients. They identified three predictors of proven candida infection: precedent surgery, multifocal Candida colonization, and surgery.

More recently, a clinical prediction rule for the early diagnosis of invasive candidiasis in the ICU [9] used a combination of the following factors: any systemic antibiotic or presence of central venous catheter and at least two other risk factors, including total parenteral nutrition, major surgery, pancreatitis, any use of steroids, and use of immunosuppressive agents. This prediction rule had good specificity (90%), but poor sensibility (34%), therefore, it seems to be helpful just to rule out invasive candidiasis.

Although the real clinical utility deriving from these risk scores remains to be established in prospective clinical studies, the recognition of an increased risk for fungal infection in a critical ICU patient should activate proper diagnostic and therapeutic strategies.

Table 24.1 Risk factors for invasive fungal infections. Adapted from [1,3]

• Prolonged treatment with multiple broad-spectrum antimicrobials
• Presence of central venous catheters
• Total parenteral nutrition
• Abdominal surgery
• Loss of integrity of skin and mucosal barriers
• Acute renal failure
• Hemodialysis
• Treatment with immunosuppressive agents
• Prolonged ICU stay
• Reacutization of chronic obstructive pulmonary disease
• Diabetes mellitus
• Acute liver failure
• Advanced liver cirrhosis
• Chronic renal failure
• Near drowning

Diagnosis of Candida Invasive Infections in ICU

Candida usually colonizes the oropharynx (63%), urine (25%), gut (11%), and the lumen of medical devices (urinary catheters and wound drains). The risk of colonization increases with the duration of the ICU stay, the use of urinary catheter, and the use of broad-spectrum antibiotics [10]. Colonization is the first step of infection and the gastrointestinal tract; the skin and the urogenital tract are the main portals of entry for candida infections [10]. Diagnosis of Candida invasive infection include clinical examination, cultural tests, radiological signs, and serological and molecular tests (Table 24.2).

Clinical examination in invasive candida infections usually reveals nonspecific signs and symptoms suggesting the presence of infection and sometimes indicating

Table 24.2 Diagnosis of invasive candidiasis

• Clinical examination
• Cultural examination (colonization index)
• Radiological signs
• Serological tests: mannan galactomannan; β 1,3 D-glucan
• DNA testing

the site of infection. Such symptoms may be blunted by the immune disregulation often associated with invasive candida infections with a consequent delay in the initiation of additional diagnostic examinations.

Regarding cultural examinations, blood cultures have low sensitivity (<50%) and usually become positive late [11], while invasive tissue sampling is often problematic in critically ill ICU patients. In 1994 Pittet et al [10] introduced the colonization index (CI) to predict candida infection. CI was calculated by dividing the number of colonized sites by the number of cultured sites (upper respiratory or stomach samples, urine and wound swabs). CI resulted significantly higher in patients who developed invasive candidiasis than in control individuals with a negative predictive value for candidemia of 100%, but with a low positive predictive value (66%) [10]. Although quantitative cultural examination could improve the performance of CI, the cost effectiveness of screening all patients is relatively low [3]. Therefore cultural examination should be reserved for patients with risk factors for candida infection. Once they have been performed, it is advisable to record and speciate all Candida from clinical samples of ICU patients in order to aid empirical antifungal treatment if it becomes clinically necessary [3].

Regarding radiological signs, they may be used for pulmonary candida infections appearing as diffuse confluent patchy consolidations. However, radiological signs are observed late in the course of infection and therefore they are not useful for early diagnosis [3].

Tests able to detect circulating fungal metabolites, antigens, antibodies, and fungal DNA were developed as early sensitive and specific diagnostic tools for candida infection. Serological tests search for components of the fungal cell wall (mannan, galactomannan, and β-(1,3)-D-glucan), or antibodies directed against these antigens (antimannan) in blood or other body fluids [12]. Measurements of mannan and/or antimannan seem to lead to earlier diagnosis of candida infection when compared with blood cultures [13]. Sensitivity and specificity were 40 and 98% for mannan and 53 and 94% for antimannan antibodies, and 80–90% when combining the two tests [13]. Studies conducted with β-(1,3)-D-glucan assays have yielded sensitivities ranging from 69 to 97%, and specificities ranging from 87 to 100% [14]. Therefore β -(1,3)-D-glucan tests can help to rule out invasive candidiasis. Molecular diagnostic tests for detection of Candida DNA in either blood or tissues have been described [15]. Albeit promising, relatively few data have been published on the performance of the detection of fungal DNA in high-risk critically ill patients. Fungal endogenous endophthalmitis is one of the most common complications following candidemia with an incidence of 9–15% in ICU patients, therefore fundoscopy is recommended in all candidemia patients.

Diagnosis of Invasive Pulmonary Aspergillosis in ICU

The diagnosis of invasive pulmonary aspergillosis in critical patients is difficult because signs and symptoms are nonspecific, with a delay in additional diagnostic

examinations that should be triggered by the combination of persistent or rapid developing infiltrative abnormalities on thoracic imaging and/or a persistent pulmonary infection despite broad spectrum antibiotics accompanied by one or more risk factors for fungal infection [2]. Besides clinical examination, diagnosis of invasive pulmonary aspergillosis may include histopathological and microbiological examination, radiological findings, and serological tests (Table 24.3).

Histopathological evidence of invasive pulmonary aspergillosis is the diagnostic gold standard due to a very high tropism for blood vessels [16], but it requires invasive procedures particularly dangerous for critically ill patients.

Microbiological examination is performed by means of direct microscopy and culture of sputum or broncho-alveolar lavage fluid (BALF). Isolation of *Aspergillus spp*. in the respiratory tract may represent: evidence of current disease, colonization, or a marker for the future development of invasive disease. Colonization is frequent in case of cultures of *Aspergillus* in respiratory secretions of immunocompetent hosts, whereas they are associated with invasive disease in the immuno-compromised host with a positive predictive value of 80–90% but with a poor sensitivity [17]. Direct microscopic examination of sputum or BAL improves the sensitivity of microbiological examination [18] and it enables the discrimination between septate (e.g., *Aspergillus*, *Fusarium*, and *Scedosporium*) and nonseptate (e.g., *Mucorales*) molds often not susceptible to voriconazole. The extra value of a positive culture is that growing of the fungus enables identification and susceptibility testing to antifungal drugs.

Regarding radiological findings, chest computerized tomography (CT) has proved to be an important tool for the diagnosis of pulmonary aspergillosis, even in the absence of evident lesions on a conventional chest X-ray. Radiological findings might include nodules with rapid growth and cavitations. A “halo sign” (a pulmonary mass surrounded by a zone of lower attenuation with ground-glass opacification produced by adjacent hemorrhage) and/or the “air crescent sign” (crescentic radiolucencies around a nodular area of consolidation) may be present [19]. The halo sign together with the air crescent sign have good sensitivity and specificity [19]. Due to the high tropism for blood vessels, pulmonary aspergillosis may be complicated by localizations in the central nervous system, therefore CT scanning or magnetic resonance imaging (MRI) of the brain should be considered [2].

Table 24.3 Diagnosis of invasive pulmonary aspergillosis

• Clinical examination
• Histopathological examination
• Cultural examination
• Radiological signs (halo sign, air crescent sign on CT scan)
• Serological tests: galactomannan; β 1,3 D-glucan
• DNA testing

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Regarding serological and molecular tests, they have been developed in the last decade, focusing on the detection of components of Aspergillus, such as the galactomannan antigen, 1,3-β-glucan, and the detection of Aspergillus DNA by PCR [2]. The specificity of the galactomannan assay is around 85%, with a variable sensitivity between 29 and 100%. Circulating galactomannan could be detected even 8de by a combination of radiographic findings and Aspergillus isolation [2]. When searched in BALF the sensitivity of galactomannan assay ranges from 85 to 100%. The use of an assay to detect serum 1,3-β-glucan derived from fungal cell walls is a useful diagnostic adjunct for invasive fungal infection [20], even if false-positive tests have been found in patients after hemodialysis, cardiopulmonary bypass surgery, high-dose immunoglobulin treatment, after exposure to glucan-containing gauze, and in bacterial infections [21]. Amplification of nucleic acid by PCR technology for the diagnosis of invasive pulmonary aspergillosis is being increasingly studied. It can be applied to serum and BAL specimens. Experience is limited to patients with hematological malignancies where this method reached a sensitivity of 92.3% and a specificity of 94.6% [22].

The interpretation of serological and molecular tests must move from the clinical picture of the patient.

Antifungal Agents

Antifungal agents include three main classes of drugs: polyenes, echinocandins, and triazoles.

Polyenes act by binding irreversibly to the ergosterol of the fungal membrane. Amphotericin B deoxycholate has been the first antifungal drug clinically used; it has a broad spectrum against *Candida spp*., *Aspergillus spp*., *Cryptococcus spp*., *Histoplasma spp*., and *Coccidioides spp*. Side effects include hepatic and renal toxicity, fever, decreased platelet count, anemia, seizures, and skin rash. Lipid formulations (colloidal dispersion, lipid complex, and liposomal) have been developed in order to significantly reduce such side effects that limited the use of amphotericin B deoxycholate especially in the critical patient prone to hepatic and renal failure [23]. Several studies comparing the efficacy of amphotericin B deoxycholate with that of lipid formulations for the treatment of patients with invasive candidiasis suggested that lipid formulations of amphotericin B are as efficacious as conventional amphotericin B [24]. However, high costs and the existence of alternative antifungal therapies reserve lipid formulations for second-line therapy in patients with refractory invasive fungal infections.

Triazoles include the first generation triazole fluconazole and the second generation triazoles voriconazole, itraconazole, and posaconazole [23]. Triazoles share the same mechanism of action represented by the inhibition of 14α sterol demethylation, a key reaction in the ergosterol synthesis that involves the cytochrome P450 of yeasts.

Fluconazole is active against *Candida spp*., *Aspergillus spp*., *Cryptococcus spp*.,

and *Histoplasma spp*. Side effects of fluconazole are represented by headache, dizziness, itch, vomit, and diarrhea. In critical patients with candidemia, fluconazole (400 mg/day) was found to be as efficacious as and better tolerated than amphotericin B deoxycholate (0.5–0.6 mg/kg per day) [24]. Fluconazole remains one of the most commonly used antifungal agents for the treatment of candida infections even if innate (*C. krusei*) or emerging (especially *C. glabrata* and *C. guilliermondi*); resistance to azoles among nonalbicans *Candida spp*. has been noted in various regions of the world [25]. Therefore the use of fluconazole as empirical therapy for yeast bloodstream infections in critically ill patients before species identification and results of antifungal susceptibility testing are known should be based on local epidemiologic data. The efficacy of high doses (800–1,200 mg) of fluconazole for treatment of less susceptible *Candida* strains remains controversial. Voriconazole is active against *Candida spp*., *Fusarium spp*., and *Scedosporium spp*. Side effects include: cardiac, hepatic (5–15%), renal and ocular toxicity (20–40%), and Stevens Johnson syndrome. In patients with invasive candida infections, voriconazole (6 mg/kg per day after a 12 mg/kg loading dose on day 1) was shown to be as effective as and safer than amphotericin B deoxycholate [26]. Monitoring of circulating voriconazole concentrations to target values between 2 and 6 mg/l is suggested during acute invasive infections because the efficacy of voriconazole may be influenced by great variability in blood levels caused by nonlinear pharmacokinetics, polymorphism of cytochrome CYP2C19, and hepatic dysfunction. Intravenous voriconazole is contraindicated in moderate-to-severe renal impairment (i.e., creatinine clearance <50 ml/min) given the potential toxicity from accumulation of the i.v. solvent vehicle, sulphobutylether β cyclodextrin sodium.

Itraconazole and posaconazole are new azoles with a broad spectrum of antifungal activity against *Candida spp*., *Aspergillus spp*., and other emerging molds, including *Fusarium spp*. and zygomycetes [27,28]. Data regarding the use of these antifungal agents in critically ill patients with invasive fungal infections are lacking. The potential risk for development of cross-resistance should limit the use of these new azoles.

Echinocandins are a new class of antifungal agents sharing as mechanism of action the inhibition of beta 1-3 D glucan synthesis, an essential component of the fungal cell wall. This class includes: caspofungin, micafungin, and anidulafungin [23]. They are active against *Aspergillus spp*. and *Candida spp*., even if candida parapsilosis in vitro has shown high MICs [23]. No cross-resistance with azoles has yet been reported. Side effects are rare and include: abnormal liver function tests, phlebitis, histamine-like reactions. Echinocandins penetrates poorly the blood–brain and blood–ocular barrier, therefore they are not effective for CNS infections or fungal endophthalmitis [29]. Caspofungin has been the first echinocandin used in invasive mycoses, including candidiasis. It has proved to be as effective as amphotericin B deoxycholate or fluconazole [30]. In a multicenter trial conducted in patients with invasive candidiasis, caspofungin (50 mg/day after a 70 mg loading dose) was as efficacious as and less toxic than amphotericin B deoxycholate [30]. Recent reports have described the emergence of resistance to caspofungin in patients with esophagitis, candidemia, and endocarditis [3]. Micafungin and anidulafungin seem to have the

same clinical efficacy and safety profile of caspofungin. Anidulafungin is eliminated only via chemical degradation, therefore it could be preferred in case of liver or renal failure.

Recommendations for Management of Invasive Candida Infection

Appropriate management of invasive candida infection should focus on two key aspects: the timing and the choice of antifungal therapy.

Regarding the timing, there is abundant evidence supporting the notion that delayed initiation of antifungal therapy in invasive candidiasis is associated with worse clinical outcomes. A significant mortality benefit was demonstrated for patients commencing antifungal therapy within 12–24 h of the drawing of the first (ultimately) positive blood culture [31,32]. In order to optimize the timing of antifungal therapy, new markers of infection are required to overcome the delays and relative insensitivity associated with traditional blood culture techniques [23]. Modern blood culture systems still require around 24–48 h of incubation from inoculation to signal positive for yeasts and longer for species identification. However, the rapid identification and differentiation of *C. albicans* from *C. glabrata* can be achieved within 3 h using a commercial nucleic acid fluorescent in situ hybridization technique [23]. Serological and molecular methods, with all their above reported limits, may further reduce the time necessary for the diagnosis of invasive candida infections. The delay associated with microbiological diagnosis suggested early antifungal intervention strategies, classified as prophylaxis, pre-emptive, or empiric therapies [23].

Antifungal prophylaxis with fluconazole is associated with a reduction in invasive candidiasis by around 50% [33]. However, unless targeted to high-risk patients, antifungal prophylaxis remains an inefficient strategy. Therefore, several risk-predictive models have been developed integrating many of the well-established risk factors for invasive candidiasis [8,9].

Pre-emptive therapy is defined as an intervention based upon biological markers of infection risk [23]. Such biological markers may be a Candida colonization index of at least 0.4, and elevated levels of beta 1-3 D glucan [23]. The use of Candida colonization index to guide preemptive fluconazole therapy seems to reduce ICU-acquired invasive candidiasis, but it requires repeated surveillance cultures from five body sites and this may not be broadly practical or cost effective. However, the association between colonization at particular anatomical sites, particularly the urine, and invasive candidiasis may allow refinement of the body sites to be sampled [34].

Empiric antifungal therapy, consisting of the use of an antifungal drug in the clinical suspicion of fungal infection (i.e., antibiotic-refractory fever) when cultural samples have been taken but results are still pending, is relatively common in the ICU and it has been reported to be cost effective [35]. However, in patients at low risk of infection, culture-directed antifungal therapy is preferred over an empiric approach [23].

Considering the choice of antifungal therapy, it should be guided by the available information on the causative Candida regarding species and susceptibility as derived from antibiogram [1]. Empiric therapy should derive from local epidemiologic studies. The emergence of nonalbicans *Candida spp*. with reduced susceptibility to fluconazole, as increasing causes of invasive candidiasis in ICU has been a major driver of echinocandin use [36]. However, this epidemiological trend has not been uniformly reported, and the major determinants of the *Candida spp*. distribution remain undefined, even if azole use is likely to be a major contributor [36]. Although *C. krusei* is intrinsically resistant to fluconazole, *C. glabrata*, which is the second or third commonest cause of invasive candidiasis among ICU patients, generally displays dose-dependent susceptibility to fluconazole.

Concluding, fluconazole may be used for the empirical treatment of candidemia in patients without multiorgan failure or severe sepsis, while an echinocandin is preferred if the patient is hemodynamically unstable or if the patient is known to be colonized with a fluconazole-resistant

strain. Patients treated for invasive candida infection should repeat blood cultures every 5–7 days to monitor breakthrough infections and response. Most uncomplicated candidemia cases are treated for 14 days from the last negative blood culture and resolution of symptoms [37].

Recommendations for Management of Invasive Aspergillus Infection

Antifungal therapy should be promptly started with the clinical suspicion of invasive pulmonary aspergillosis while cultural examination is still pending using an empirical approach because any delay in antifungal therapy initiation has been associated with a worse outcome [2]. Among the triazoles, voriconazole is increasingly recommended as initial empiric therapy for invasive pulmonary aspergillosis [38]. Voriconazole seems to provide higher response rates and better survival than amphotericin B in the treatment of "probable or proven" pulmonary aspergillosis with fewer drug-related adverse events [39]. Itraconazole has activity against Aspergillus, but its clinical utility in critically ill patients is limited by drug interactions and toxicity as well as low bioavailability of the oral suspensions. Furthermore, strains of *A. fumigatus* resistant to itraconazole have already been described. Posaconazole is a promising new triazole with broadspectrum antifungal profile and has shown activity for salvage treatment of invasive pulmonary aspergillosis in patients refractory to conventional therapy.

The echinocandins have in vivo activity against *Candida spp*. and *Aspergillus spp*. Caspofungin has been successfully used in patients with "proven or probable" invasive pulmonary aspergillosis who had treatment failure with liposomal amphotericin B, itraconazole or voriconazole, or who were intolerant to these antifungal drugs.

No conclusive evidence supports the superiority of extended-spectrum triazoles in respect to echinocandins or polyenes for monotherapy of invasive pulmonary

aspergillosis in ICU patients.

In any case, the efficacy of antifungal therapy for invasive pulmonary aspergillosis, whatever antifungal drug is used, is poor with more than 50% of all patients experiencing failure of first-line therapies. Therefore empirical administration of combination antifungal regiments for proven or probable pulmonary aspergillosis may be an important strategy to improve outcome. Combination therapy has been associated with a widened spectrum and potency of drug reactivity, more rapid antifungal effect, synergy, and a reduced risk of antifungal resistance [40]. In any case, the real clinical benefits of combination antifungal therapy with respect to monotherapy remains controversial, therefore combination therapy should be reserved for particular clinical conditions such as refractory disease or breakthrough infections [40].

Conclusions

Invasive fungal infections are increasingly frequent in ICU patients and they are associated with high mortality. Individuation of risk factors is important to guide the clinical suspicion toward a fungal infection and to start appropriate diagnostic and therapeutic management. New serologic and molecular diagnostic methods could shorten the time required for the diagnosis of fungal infection and then for the initiation of treatment. Recently new antifungal agents entered the clinical practice with promising results when used in a timely fashion and at correct dosage. They should be used with caution due to the risk of resistance and should be reserved for selected cases.

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Section VIII
Sepsis, Organ Dysfunction and the Bundles

Sepsis: Clinical Approach, Evidence-Based at the Bedside

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Introduction

Sepsis is a common disease in intensive care medicine representing almost one third of patient admissions. Its incidence has substantially increased over the past decades and overall mortality has declined during this period of time. It was reported that sepsis incidence increased from 82.7 to 240.4 per 100,000 population between 1979–2000. At the same time, sepsis global mortality decreased from 27.8 to 17.9% [1–3]. However, the absolute number of deaths significantly increased from 21.9 to 43.9 per 100,000 population. Male gender, some chronic diseases like diabetes, immunosuppressive states, human immunodeficiency virus infections, and malignancies are factors that increase the risk for sepsis. Some particular conditions like progressive number of organ dysfunctions, in-hospital-acquired infections and increasing age are associated with higher risk of death [1,4]. On the other hand, septic shock mortality only diminished from 61.6 to 53.1% [5]. This slight decline in mortality observed during recent decades could be attributable to improvements in supportive care and/or avoidance of iatrogenic complications. For example, the instrumentation of early goal resuscitation protocols not aiming at supranormal targets for cardiac output and oxygen delivery, and the use of lung protective strategies could explain at least in part this favorable change. Other strategies directed to treat the pathophysiological mechanisms involved in the septic process like recombinant human-activated protein-C (rhAPC), have also contributed to improve survival. However, mortality remains unacceptably high and further improvement in sepsis management is needed. Novel therapeutic approaches are under investigation and will probably be incorporated in the clinical practice in the near future.

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Since 2002 the Surviving Sepsis Campaign was introduced with the initial goal of increasing clinicians' awareness about severe sepsis mortality and to improve outcome in this patient population. It was pursued to generate a change in the standard of care that could finally result in a significant mortality reduction. A consensus committee from several international organizations was created and evidence-based guidelines were elaborated [6]. Despite the fact that most of these recommendations were not supported by high levels of evidence, they represented the international consensus on the best available standards of care for the management of sepsis. These guidelines were recently updated and continue to be the core of the Surviving Sepsis Campaign [7]. The clinical practice needs clear and concise recommendations based on the best available level of evidence.

Definitions

Sepsis is defined as the host response to infection. In other terms, it is the clinical syndrome that results from the inflammatory response to infection. In the clinical setting, sepsis is diagnosed when an evident or suspected infection courses with a systemic response called the systemic inflammatory response syndrome (SIRS). According to the 1991 North American Consensus Conference, SIRS was defined by the presence of at least two of the following signs: body temperature >38ºC or <36ºC, heart rate >90 beats/min, respiratory rate >20 breaths/min (or $PaCO_2$ <30 torr), and/or white blood cells count >12,000 or <3,000/mm^3 [8]. However, these signs are too sensitive and nonspecific for sepsis and could occur in many other different situations not related to infection. In an attempt to better reflect the systemic response to infection, the clinical manifestations described by Bone et al. were expanded by the 2001 Consensus Conference [9]. Other possible signs, symptoms, and laboratory findings were summarized (Table 25.1). Again, most of them are also nonspecific for sepsis. It is well known that infection and sepsis are sometimes difficult to confirm.

In an attempt to improve diagnostic capabilities, some biological markers were developed. Procalcitonin (PCT) and C-reactive protein (C-RP) have been proposed but it is considered that there is still no ideal biological marker for sepsis diagnosis [10,11]. None of the mentioned biomarkers are absolutely specific, meaning that diagnosis or prognosis cannot be made solely on this basis.

An infection probability score (IPS) was also proposed to be calculated from several variables: body temperature, heart rate, respiratory rate, white blood cells count, C-reactive protein, and sequential organ failure assessment score (SOFA). The potential role of such an index was recently evaluated [12].

Some concepts and definitions remained unchanged after the last consensus conferences and should be emphasized. The following terms are widely accepted.

Infection is the pathologic process caused by the invasion of normally sterile tissues, fluids, or cavities by pathogenic microorganisms.

Sepsis is the clinical syndrome defined by the presence of infection and a systemic inflammatory response syndrome.

Table 25.1 Clinical manifestations of sepsis

General signs and symptoms
Fever or hypothermia
Tachypnea/respiratory alkalosis
Tissue edema (positive fluid balance)
Generalized hematological/inflammatory reactions
White blood cells increased (sometimes leukopenia)
Increased inflammatory biological markers:
Plasma C-reactive protein greater than 2 SD above normal.
Plasma procalcitonin greater than 2 SD above normal
Hemodynamic and metabolic alterations
Arterial hypotension
Tachycardia
Increased cardiac output
Low systemic vascular resistances
High S_vO_2 >70%
Cardiac index >3.5 L/min/m^2
Decreased skin perfusion
Decreased urine output
Increased lactatemia >2 mmol/L
Decreased capillary refill
Decreased base deficit
Multiple organ dysfunction
Acute lung injury
Altered mental status
Acute renal Injury.
Hyperglycemia in the absence of diabetes
Thrombocytopenia (<100,000/μL)/disseminated intravascular coagulation
Liver dysfunction. Hyperbilirubinemia >4 mg/dL
Ileus. Intolerance to feeding

Severe sepsis relates to the presence of sepsis and one or more related organ dysfunctions.

Septic shock should be diagnosed when severe sepsis courses with acute circulatory failure. Cardiovascular compromise becomes evident when arterial hypotension remains after adequate fluid infusion or there is need for vasopressor therapy. Systemic hypotension is defined when arterial systolic pressure remains <90 mm Hg, mean arterial pressure <60 mm Hg, or there is a decrease in blood pressure >40 mm Hg from previous values.

Pathophysiology of Sepsis

Different processes could occur during severe sepsis and septic shock at the same time. Hypovolemia, maldistribution of blood flow within or between organs, vasoreg-

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ulatory-perfusion abnormalities, peripheral microcirculatory failure, and myocardial dysfunction are major hemodynamic disturbances observed during sepsis. Hemodynamic parameters could course with normal or decreased mean arterial pressure while cardiac output may vary from low to higher than normal. The hemodynamic values change in response to volume replacement and the severity of myocardial dysfunction. Systemic tissue hypoxia occurs when cardiovascular failure and low cardiac output dominates the clinical presentation. The presence of low mean arterial and central venous pressures, and decreased central venous oxygen saturation when confirmed, should cause immediate therapeutic interventions. Efforts should be made to correct systemic hemodynamic abnormalities in order to avoid the development of global tissue hypoxia.

However, cytokine release from the inflammatory reaction or prolonged tissue hypoxia is followed by severe microcirculatory abnormalities that become a central protagonist of organ dysfunction/failure [13]. The main significance of microvascular dysfunction has been studied during sepsis and major changes like decrease of both capillary density and microvascular blood flow were documented in vivo by video microscopy [14]. Thus, peripheral gas exchange becomes impaired and tissue dysoxia ensues. These abnormalities also occur despite normal or even supranormal hemodynamic variables. In terms of peripheral oxygen metabolism, severe heterogeneity of oxygen distribution within the tissues is characteristic during septic shock. Under- and overperfuse areas coexist within the same tissue resulting in an inhomogeneous tissue oxygen partial pressure distribution (P_tO_2). In these conditions, metabolic demands are not met by microvascular oxygen delivery, making peripheral shunting and tissue dysoxia the cause of organ failure.

However, metabolic abnormalities also occur at the cellular level. Mitochondria dysfunction is secondary to oxidative and nitrative stress initiated by the inflammatory reaction. Energetic failure develops and less high energy compounds are available for cellular function. This situation was referred to as cytopathic hypoxia and leads to multiple organ failure and death. Mitochondria dysfunction and decreased ATP production was documented during the course of sepsis in experimental and clinical situations. Efforts should be made to preserve mitochondrial functioning and improve the cellular energetic state [15–17].

Diagnosis and Clinical Evaluation

Early and accurate recognition of the signs and symptoms of sepsis is mandatory after patient admission. Risk factors like age, gender, race, immunocompromised states, presence of invasive instrumentation maneuvers, or any other condition that could represent a via for bacterial colonization. Clinical presentation and laboratory findings are essential. Fever is the hallmark of infection, but hypothermia is also possible in some patients. Other nonspecific signs like tachycardia, tachypnea, and hypotension should also be documented. When looking for the source of infection a careful physical examination should be complemented with x-rays images, CT scans,

ultrasound, etc. Finally, it is necessary to investigate the presence and severity of organ dysfunction. In the vast majority of the cases this information is easily collected and diagnosis becomes straightforward. However, this is not always the case. It is important to realize that the septic patient is always at risk of death and some clinical signs may be indicative of disease severity. Clinical demonstration of acute respiratory and/or circulatory failure, or any other organ dysfunction are indicative of the aggressive host response to the septic insult [8,9].

Since organ failure is an integral part of severe sepsis, a brief summary of major organ dysfunctions will follow.

Acute Lung Injury/Acute Respiratory Distress Syndrome (ALI/ARDS)

Pulmonary or extrapulmonary ALI is present in about 60–70% of severe sepsis. It is defined by pulmonary infiltrates in the chest x-ray and the absence of left ventricular failure (pulmonary wedge pressure <18 mm Hg). Pulmonary gas exchange is impaired showing a PaO_2/FIO_2 ratio under 300 for ALI or below 200 for ARDS. Most of the time, the severity of ALI/ARDS determines mechanical ventilation. While mechanical ventilation will restore pulmonary gas exchange and decrease systemic metabolic demands, detrimental effects should be avoided by a rational application of protective ventilatory strategies.

Central Nervous System Dysfunction, Septic Encephalopathy

When the focus of infection is located outside the central nervous system (CNS), the neurologic compromise could be attributable to septic encephalopathy. Some other conditions may add secondary effects such as hypoxemia, metabolic and electrolytical disorders, and cerebral hypoperfusion during shock states. Symptoms may vary from agitation, confusion, delirium, and coma. No focal neurologic deficits are present but myoclonias and seizures are possible [18]. Severe CNS derangement requires airway protection and ventilatory support.

Liver Dysfunction

Liver dysfunction is characterized by some degree of hepatomegalia and total bilirubin plasma levels >2 mg/dL. Higher conjugate bilirubin concentration is characteristic and increased gamma glutamil transferase is frequently observed. Moderate levels of aminotransferases generally <200 UI can also be found.

Coagulation and Hematologic Disorders

Decreased red blood cells without bleeding evidence and platelets <100,000/mm^3 are frequent findings. Coagulation cascade has been widely studied. Sepsis enhances

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coagulation and impairs fibrinolysis. Endogenous-activated protein C that prevents microvascular thrombosis is decreased during sepsis. When small and medium microvessels become occluded, the disrupted microcirculation generates tissue dysoxia. Given the context of severe sepsis, rhAPC could contribute to ameliorate coagulation disorders [19].

Acute Renal Injury

Renal dysfunction could course with normal or decreased urine output. Increase in creatinine level >0.3 mg/dL from previous values or a percentage increase >50%, or a reduction in urine output (oliguria <0.5 ml/kg/h for more than 6 h) defines acute renal injury and is associated with poor outcome.

Hemodynamic Failure, Septic Shock

Arterial hypotension unresponsive to volume expansion defines septic shock. Variable degrees of hemodynamic dysfunction may vary from hypodynamic to hyperdynamic shock. Mortality increases according to the presence of shock, and metabolic markers like arterial lactate are useful to characterize disease severity and the response to treatment [8]. Despite the fact that lactate concentration depends on the balance between tissue production and metabolism, a plasma level >4 mmol/L should be considered as indicative of circulatory failure.

Gastrointestinal Tract

Some other organ compromise could also be part of the multiple organ dysfunction syndrome. Splanchnic ischemia and intramucosal acidosis ensue early during the course of sepsis. Clinical expression includes changes in smooth muscle function like ileum or diarrhea. Gastrointestinal bleeding because of stress ulcer or acute gastritis may also be a manifestation of sepsis. Gastric intramucosal pH monitoring was used to identify and guide resuscitation therapy. Increased levels of intraluminal pCO_2 are associated with tissue ischemia and mucosal acidosis.

Neuromuscular Dysfunction

Skeletal muscles are also affected by inflammatory mediators and reactive oxygen species. There is simultaneous decrease in protein synthesis and proteolysis. In conjunction, these factors explain decreased muscular force. Respiratory muscles are involved and respiratory pump failure may aggravate or precipitate an acute respiratory failure.

Multiple organ dysfunction is part of the severe sepsis syndrome. Poor prognosis

is related to increased number of organ failures. Technical resources for the management of organ dysfunction have improved in recent years and consume a substantial part of the therapeutic effort. Most of the described dysfunctions are reversible as long as the infectious disease becomes controlled. However, the additive effects of the different failures may initiate a series of independent processes that may aggravate the patient status and be the cause of death. Prognostic scores are helpful to predict mortality and some organ failure scores were proposed to evaluate severity and to follow the evolution of septic patients. The Multiple Organ Dysfunction Score (MODS) and the Sequential Organ Failure Assessment (SOFA) are frequently used for this purpose [20,21].

To identify the source of infection and the microbial agent is crucial during sepsis. Microbiological investigation is mandatory and adequate antibiotic therapy must be initiated as early as possible [7]. Most of the time the diagnosis results from a correct anamnesis and clinical examination. Suspicion of sepsis must be followed by complete bacteriological cultures, taking samples from blood and other possible foci of infection. Some other special exams should not be deferred and may add complementary information. Positive blood cultures are only confirmed in about 50% of the cases [22]. No bacterial etiology is identified in 20–30% of septic patients. Almost 45% of the initial antibiotic selection should be changed or adjusted after blood cultures are informed. Decreased mortality is related to prompt bacteriological identification [23]. Despite the fact that infection is generally caused by bacterial agents, virus and fungal agents are possible, especially in immunocompromised patients. Epidemiological data coming from each ICU or hospital could be helpful when hospital-acquired infections are under study. Infection is a frequent complication in polytrauma and in the critically ill patient who was subject to invasive procedures. Increased life expectancy and special situations like organ transplant create further opportunities for microbial invasion and sepsis development.

As mentioned before, biochemical markers of infection could be helpful in particular situations where diagnosis is not straightforward. Procalcitonin (PCT), C-Reactive Protein (CRP), and some interleukins like Interleukin-6 (Il-6) have been proposed to contribute to diagnosis. However, further evidence is needed before these biomarkers are incorporated in the clinical practice. Actually, some authors have considered PCT as a good indicator for severe sepsis and septic shock [24,25]. Research on new biomarkers continues with the aim of early detection of patients at risk of severe sepsis [26].

Evidence-Based Clinical Management of Severe Sepsis

The current management of severe sepsis and septic shock aims to control infection, achieve hemodynamic stabilization, modulate the immune response, and provide metabolic and organ support. Evidence-based medicine has become the cornerstone of medical practice but it is difficult to apply in patients with sepsis. The SSC is a global initiative that involves several international organizations with the common

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objective of elaborating evidence-based guidelines and recommendations for the management of severe sepsis and septic shock. Lack of high-level evidence coming from large RCT is a severe limitation in sepsis. To accomplish these goals, experts determined that improving patient care was a possible task and could lead to a significant decrease in mortality. Despite the fact that only a few of the Guidelines were supported by high levels of evidence, it was agreed that they represent the best available evidence for the management of the septic patient. During the last consensus conference a grade system was agreed upon by the participants. Guidelines were classified from A to D based on the levels of evidence; however, at the same time a strong or weak recommendation was introduced by the panel of experts [7]. The International Guidelines of the Surviving Sepsis Campaign will be briefly discussed below.

Initial Resuscitation

This group of measurements should be accomplished within the first 6 h of patient admission. This could probably happen in the emergency department before ICU admission. Early identification and comprehensive resuscitation of septic patients will have a significant impact on outcome. The first 6 "golden hours" constitute a critical opportunity for the patient [27,28]. Resuscitation should be started immediately when hypotension or elevated serum lactate (>4 mmol/L) are detected and treatment should not be delayed until ICU admission. Initial resuscitation not only includes hemodynamic stabilization but also simultaneous administration of empiric antimicrobial drugs and actions directed toward the control of infection [7].

Hemodynamic Resuscitation

Early resuscitation is initially based on aggressive volume expansion. It could be administered via a peripheral vascular access while a central venous line and central venous pressure (CVP) measurement are instrumented somewhat later within the initial hours. When fluid therapy does not restore arterial blood pressure or lactate remains elevated, administration of vasopressors becomes mandatory. The resuscitation goals are based on easily obtainable physiologic variables. Treatment targets CVP pressures between 8 and 12 mm Hg, mean arterial pressure ≥65 mm Hg, urine output ≥0.5 mL/kg/h, and superior cava vein oxygen saturation ≥70% or mixed venous oxygen saturation ≥65% [7,29].

Fluid Therapy

No difference between crystalloids and colloids fluid was demonstrated [30]. However, it is mentioned that resuscitation with crystalloids is less expensive but

requires more fluid to achieve the same end points and may result in more edema formation. Fluid challenges of 1,000 mL of crystalloids or 300–500 mL of colloids over 30 min are recommended, but larger volumes or infusion rates could be required [7].

Vasopressors

When resuscitation goals are not rapidly achieved vasopressor therapy must be started. There is no high-quality primary evidence to recommend norepinephrine over dopamine. However, norepinephrine could be more effective in reversing hypotension in patients with septic shock. The selected vasopressor, either norepinephrine or dopamine, should be titrated until MAP ≥65 mm Hg. Epinephrine is another alternative vasoactive agent when blood pressure is poorly responsive to norepinephrine or dopamine. Low-dose dopamine should not be used for renal protection [31]. In patients requiring vasopressors, an arterial catheter and continuous arterial pressure monitoring must be instrumented.

Inotropic Therapy and Packed Red Blood Cells

If central venous oxygen saturation remains <70% further fluid infusion and/or packed red blood cells transfusion should be considered. Hematocrit ≥30% is desirable to assure systemic oxygen delivery. Increase in cardiac index by the effect of dobutamine infusion to a maximum 20 μg/kg/min is recommended. Dobutamine is the first line inotrope for patients with measured or suspected low cardiac output and adequate or high left ventricular filling pressures. A combination of inotropes/vasopressors, such as norepinephrine and dobutamine, is recommended if cardiac output is not directly measured [7].

Antibiotic Therapy

Antibiotics should be administered during the first hour of the initial resuscitation. The time taken to initiate effective antimicrobial therapy is one of the strongest predictors of outcome in septic shock [32]. Initial antimicrobial selection should be wide enough to cover likely pathogens. There is evidence that failure to initiate appropriate antimicrobial therapy within this period of time correlates with increased mortality [33].

Source Identification and Control

Source control includes an appropriate diagnosis of the specific site of infection within the first 6 h. Surgical procedures aimed at abscess draining, debridement of

infected necrotic tissue, or removal of potentially infected devices should be instrumented without delay [7]. These practices are believed to be important for infection control but no randomized trials support them [34].

Maintenance Therapy

Most of the measurements initiated in the previous stage will continue during the following hours. At the same time, some other therapeutic interventions could be started earlier, during the initial resuscitation phase.

Steroids

Two big trials of patients with vasopressor-unresponsive septic shock showed a significant and faster resolution of shock when steroid therapy was associated [35,36]. Thus, low-dose intravenous hydrocortisone (≤300 mg/day) should be considered for adult septic patients when hypotension is poorly responsive to fluid resuscitation and vasopressors. On the other hand, an adrenocorticotrophic hormone (ACTH) stimulation test is not recommended. Steroid therapy must be weaned once vasopressors are no longer required [7].

Mechanical Ventilation of Sepsis-Induced ALI/ARDS

The importance of lung-protective strategies for patients with ALI/ARDS is supported by clinical trials and has been widely accepted [37]. Low tidal volume (6 mL/kg) and upper limit plateau pressure ≤30 cm H_2O are desirable in patients with ALI/ARDS. This respiratory pattern may result in $PaCO_2$ increase above normal or permissive hypercapnia. A prone position should be considered when potentially injurious levels of FIO_2 or plateau pressure cannot be controlled. Titration of positive end expiratory pressure (PEEP) should be made according to bedside measurements in an attempt to reach optimal levels of respiratory system compliance [7].

Glucose Control

Several randomized, observational clinical trials showed reductions in ICU mortality when intensive insulin therapy was utilized [38,39]. A large randomized trial recently showed that intense glucose control increased mortality. These authors found that a blood glucose target <180 mg/dL resulted in lower mortality than a target between 81 to 108 mg/dL. Higher episodes of hypoglycemia were reported in the tight glucose control group [40]. Based on this report, intense insulin therapy is questionable. However, the SSC recommendation is to maintain blood glucose levels below 150 mg/dL [7].

Recombinant Human-Activated Protein C (rhAPC)

Recent studies reported nonsignificant mortality reduction after rhAPC administration in patients with a low risk of death or in the pediatric population. Furthermore, rhAPC administration is associated with increased risk of bleeding. The evidence concerning rhAPC use in adults is primarily based on two RCTs: the PROWESS and the ADDRESS (stopped early for futility) [41,42]. Additional information comes from an open-label observational study, the ENHANCE that suggested that early administration of rhAPC was associated with better outcomes [43]. As a result, the latest recommendation of the SSC is to consider rhAPC only for adult patients at high risk of death (APACHE II ≥25 or multiple organ failure). During patient selection, possible contraindications for rhAPC administration should be discharged.

Blood Product Administration

Red blood cell transfusion should be administered when haemoglobin decreases below 7.0 g/dL. A hemoglobin target between 7.0 to 9.0 g/dL in adult septic patients is recommended. Do not use fresh frozen plasma to correct laboratory clotting abnormalities unless there is bleeding evidence or planned invasive procedures. Administer platelet concentrates when platelet counts are $<5{,}000/mm^3$ regardless of bleeding. Platelet counts between 5,000 to $30{,}000/mm^3$ do not call for platelet administration unless there is a significant risk of bleeding [7].

Other Measures

- Sedation and analgesia in sepsis. It is recommended to use sedation protocols with daily interruption/lightening to produce awakening [7].
- Renal replacement therapy. Current evidence is insufficient to draw strong conclusions regarding the best replacement therapy method for ARI in septic patients [44,45]. It is not clear whether high doses of renal replacement may influence patient outcome [46]. Intermittent hemodialysis and continuous veno-venous hemodiafiltration (CVVH) are considered equivalent for septic patients. However, CVVH and sustained low-efficiency dialysis will probably offer a safer and easier management in hemodynamically unstable patients.
- Bicarbonate therapy. Sodium bicarbonate infusion must not be used for the purpose of improving hemodynamics or reducing vasopressor requirements when treating hypoperfusion-induced lactic acidemia with a pH ≥7.15 [7].
- Deep vein thrombosis prophylaxis. Use either low-dose unfractioned heparin (UFH) or low-molecular weight heparin (LMWH), unless contraindicated. Use a mechanical prophylactic device when heparin is contraindicated [7].
- Stress ulcer prophylaxis. Stress ulcer prophylaxis based on H2 blockers or proton pump inhibitors could be used for septic patients [7].
- Nutritional support. It is very important to initiate early nutritional support in

critically ill patients. Enteral nutrition is generally safer and more effective than total parenteral nutrition. Immunonutrition needs to be further studied before clear recommendations can be made.

As mentioned before, these guidelines were based on the best available evidence. Ongoing and future studies will provide further valuable information and changes in these recommendations will become necessary. The use of these guidelines is not easy in clinical practice. It was an objective of the SSC to facilitate the instrumentation of these recommendations [47]. In the last phase of the SSC the concept of sepsis bundles was introduced. This idea aimed to create a series of simple recommendations easily applicable as packages of measurements for the clinical setting [48]. Conceptually, a bundle is a group of interventions that when implemented together will result in better outcomes. The bundles were developed in conjunction with the Institutes for Health Care Improvement (IHCI). Different tools were created to assist clinicians at the bedside. These clinical tools and databases are available on the SSC web page. Treatment of severe sepsis can be organized into two groups of interventions known as the initial resuscitation bundle (initial 6 h) and the management bundle (24 h bundle) [49]. Table 25.2 summarizes this particular approach. Some recent works have studied bundles compliance and new favorable results on outcomes are coming. It has been shown that bundles compliance is associated with a reduction in ICU mortality and length of stay [50,51].

Table 25.2 Sepsis bundles

Sepsis resuscitation bundle (initial 6 h)
1. Serum lactate measured
2. Blood cultures obtained before antibiotic administration
3. Broad spectrum antibiotics administered within 3 h for ED or 1 h for ICU admission
4. If hypotension and/or lactate >4 mmol/L
Deliver minimum of 20 mL/kg crystalloid or colloid equivalent
Apply vasopressors for hypotension not responding to fluid resuscitation
5. If persistent hypotension and/or lactate >4 mmol/L
Achieve central venous pressure >8 mm Hg
Achieve central venous oxygen saturation >70%
Sepsis management bundle (24 h bundle)
1. Low dose steroids in septic shock
2. Drotrecogin alfa activated administered in accordance with ICU policy
3. Glucose control <150 mg/dL
4. Inspiratory plateau pressures <30 cm H_2O in mechanically ventilated patients

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Intra-Abdominal Infections: Diagnostic and Surgical Strategies

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G. Sganga, V. Cozza

Introduction

Intra-abdominal infections (IAIs) are defined as an inflammatory response of the peritoneum to micro-organisms and their toxins, which results in purulent exudate in the abdominal cavity [1–5]. They have two major manifestations: generalized peritonitis and IA abscess. Peritonitis remains a potentially fatal disease and still represents a challenge for surgeons [3]. Although greater understanding of the pathophysiology of IAIs, improvement in critical care, and timely surgical and/or radiological intervention have reduced the mortality associated with severe peritonitis, the rate remains unacceptably high, ranging from 3% in localized abscess to 10% in localized peritonitis, 32% in diffuse suppurative peritonitis, and 70–80% in complicated mixed infections [1–5]. In an effort to improve the results of treatment of severe IAIs, especially of those resulting from anastomotic leakage or perforation of the gastrointestinal tract (GIT), new surgical techniques have been introduced.

Definition and Classification

Many attempts have been made to classify peritonitis in general, and secondary peritonitis in particular, together which include a large variety of different pathological conditions ranging in severity from a local problem to a devastating disease. A simplified version is reported in Table 26.1. This differentiates the relatively rare forms of primary peritonitis (which usually respond to medical treatment) and tertiary peritonitis (which does not respond to any treatment) from the commonly occurring sec-

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Table 26.1 Classification of IAIs

Primary peritonitis
Diffuse bacterial peritonitis in absence of GIT disruption
Spontaneous peritonitis in children
Spontaneous peritonitis in adults
Peritonitis in patients receiving continuous peritoneal dialysis
Tuberculous and other granulomatous peritonitis
Secondary peritonitis
Localized or diffuse peritonitis originating from a defect in GIT
Acute perforation peritonitis (GIT perforation, intestinal ischemia, pelviperitonitis, and other forms)
Postoperative peritonitis (anastomotic leak, accidental perforation, and devascularization)
Post-traumatic peritonitis (after both blunt and penetrating abdominal trauma)
Tertiary peritonitis
Late peritonitis-like syndrome due to disturbance in the immune response of the patient
Peritonitis without evidence of pathogens
Peritonitis with fungi
Peritonitis with low-grade pathogenetic bacteria

ondary peritonitis that mandates surgical intervention and antibiotic therapy [2].

IAIs include the following pathological conditions:

1. Infections of single organs (cholecystitis, appendicitis, diverticulitis, cholangitis, pancreatitis, salpingitis, etc.), which can be or not be complicated by peritonitis even in the absence of perforation.
2. Peritonitis, classified as primary, secondary or tertiary.
3. Intra-abdominal abscesses classified on the basis of their location and anatomic configuration.

The term "complicated intra-abdominal infections" (C-IAI) is used to indicate those infections which, originating in an organ cavity, extend into the peritoneal space and form an abscess or peritonitis. Resolution of this type of infection requires both surgical treatment and percutaneous drainage as well as systemic antibiotic therapy [6]. They are divided into two types: *community c-IAIs,* which can be mild or serious; or *hospital c-IAIs,* which usually occur as postoperative infections.

The nature of severe IAIs makes it difficult to precisely define the disease, to assess its severity, and to evaluate and compare therapeutic progress. Both the anatomical source of infection, and to a greater degree, the physiological compromise it inflicts, affect the outcome of IAI.

Microbiology of IAIs

Primary peritonitis is a monomicrobial, aerobic infection [2] caused by *Streptococcus pneumoniae*. The underlying risk factor most frequently encountered

is the presence of cirrhosis and ascites. Bacteriological cultures grow *Escherichia coli*, while anaerobes are rare, and their presence, or a mixed flora, suggests secondary peritonitis [2]. The latter represents a polymicrobial infection (average of four isolates per patient, with the most frequent combination being *E. coli* and *Bacteroides fragilis*) after a spontaneous or traumatic breach in a viscous containing micro-organism, or due to postoperative breakdown of GIT anastomosis [7, 8].

The quantity and variety of micro-organisms increase progressively the more the lesion is in a distal part of the gastrointestinal tract: the proximal anatomical regions (the stomach and duodenum are usually sterile) usually contain aerobic coliform flora with a small anaerobic component (<104 CFU). In the more distal regions (for example, the colon), the intestine contains a higher concentration of bacteria (1,012 obligatory anaerobes and 108 facultative anaerobes in 1 g of feces). After colon perforation, the peritoneal cavity can be invaded by more than 400 different bacterial species, but only some of these are directly responsible for infectious processes. Prolonged hospital stay, especially in ICU, repeated surgery and administration of systemic or intraluminal antibiotic treatment may drastically modify the patients' ecology, resulting in colonization of the proximal GIT with abnormal micro-organisms (fungi, Gram-negative bacteria of low pathogenicity), that may be found in tertiary peritonitis [9], in critically ill patients, in ICU infections, and in multiple organ failure (MOF) [2].

Inflammatory Response in Peritonitis

The outcome of peritonitis depends on the results of a struggle between the systemic and local defenses of the patient (SIRS, Systemic Inflammatory Response Syndrome) on one hand, and the nature, volume, and duration of bacterial contamination on the other. The exact events that follow the invasion of the peritoneal cavity with bacteria and adjuvants of infection (blood, bile, barium sulfate), and, subsequently, its translymphatic spread, have been clearly defined in recent studies [1–4,10,11]. The micro-organisms and their products stimulate the host's cellular defenses to activate several inflammatory mediators, which are responsible for the sepsis. Bacterial peritonitis appears to induce an intense compartmentalized inflammatory process [10]. A key element is cytokines (proinflammatory: tumor necrosis factor, interleukin-1, and interleukin-8; and anti-inflammatory: interleukin-6 and interleukin-10), host-produced, pleomorphic immunoregulatory peptides [10,11]. A trigger, such as a microbial toxin, stimulates the production of tumor necrosis factor and interleukin-1, which in turn promote endothelial cell-leukocyte adhesion, release of proteases and arachidonate metabolites, and activation of clotting. Interleukin-1 and tumor necrosis factor are synergistic and share many biological effects, and their inhibition improves organ function and survival. Interleukin-8 may have an especially important role in perpetuating tissue inflammation. Interleukin-6 and interleukin-10, which are perhaps counterregulatory, inhibit the generation of tumor necrosis factor, augment the action of acute-phase reactants and immunoglobulins, and inhibit T-lymphocyte and macrophage function [11]. Cytokines are measurable in the sys-

temic circulation and in peritoneal exudates, and the magnitude of the phenomena is negatively correlated with outcome [2,3]. Most peritoneal cytokines probably derive from macrophages exposed to bacterial endotoxin [12]. Recent findings suggest that female sex hormones play a critical role in maintaining the immune response after trauma-hemorrhage by suppressing the production of tumor necrosis factor-β and preventing the increased mortality from subsequent sepsis [12]. Other potential sources are direct translocation of cytokines through the GIT barrier or production by traumatized tissues [13]. Timely therapeutic intervention is crucial to abort the ensuing, self-perpetuating SIRS, sequential MOF, and death [2,10–12].

Diagnosis

Clinical Diagnosis

Clinical diagnosis of intra-abdominal sepsis is usually assisted by the presence of systemic signs of inflammation (such as fever, neutrophil leukocytosis) and by local abdominal symptoms (defense, rigidity and respiratory hypomobility, absence of peristalsis, paralytic ileum), possibly with the assistance of some diagnostic imaging techniques [abdominal x-ray, ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI)]. The typical presentation of secondary peritonitis is spontaneous acute abdominal pain, exacerbated by breathing and movement, accompanied by abdominal distension, fever, nausea or vomiting, and irregular intestine. The diffused pain is suggestive of generalized peritonitis, while localized pain is more indicative of a process involving an organ or its immediate environment. Diagnosis is often difficult, especially in old or immunocompromised patients, because the clinical presentation is less precise, or in those with altered state of conscience or sedated for mechanical ventilation [14]. Acute abdominal complications are considered infrequent events in the ICU, although they are characterized by serious prognosis when they do appear. The absence of clinical signs and typical symptoms, with consequent delay in diagnosis and treatment, has assigned to IAIs the role of “silent offender” [15,16]. Occult IAI can also manifest itself as renal dysfunction or elevated bilirubin and transaminases. Blood culture is often negative and the absence of bacteremia in a surgery patient with fever increases the probability of IAI. Polymicrobial or anaerobic bacteremia also suggests the presence of an intraperitoneal infection. Differential diagnosis of unexpected difficulty in breathing or supraventricular arrhythmia occurring 3–4 days after abdominal surgery must include suture dehiscence or other intra-abdominal infectious pathology, and their diagnosis should be excluded through appropriate imaging techniques [17]. Biohumoral data are generally not very specific and do not permit diagnosis but can contribute to suspected clinical diagnosis of IAI [18]. In trauma or surgery patients who have undergone operations for secondary peritonitis of community origin, the evolution of an IAI following surgery can manifest itself with general worsening of the patient’s clinical condition. This may be due to the appearance of intra- or extra-

abdominal complications or to the development of organ (single or multiple) insufficiency as a consequence of early serious damage due to peritonitis [19].

Diagnostic Imaging Techniques

Radiographic imaging is the definitive diagnostic tool for patients with suspected IAI and can usually identify the problem prior to any planned intervention. White abdomen usually indicates the presence of gas in the peritoneum, an intestinal obstruction, or signs of intestinal ischemia. Studies with contrast medium, using hydrosoluble agents, can reveal a fold break. Contrast fluid in a drain or fistula can help to delineate the anatomy of a complex infection and help verify the adequacy of abscess drainage. Ultrasound and especially CT scan play a principal role in the diagnosis and therapeutic strategy. Ultrasound has the advantage of being easily available, can be carried out on the patient in bed and repeated as often as necessary because of its innocuous effect on the patient. Ultrasound permits investigation of the entire abdominal-pelvic cavity, revealing even mild intraperitoneal effusion (<500 ml), detection of the distribution of the peritoneal cavity or part of it (localized effusion), thus assisting in hypothesizing about the nature of the effusion based on its possible homogeneous aspects, and finally can help guide fine needle percutaneous aspiration [20]. Abdominal CT is the reference method for evaluating the abdomen in critically ill patients [21]. Most of the causes of secondary peritonitis can be diagnosed promptly by using CT with intravenous iodinated contrast fluid and opacification of the digestive tube (using hydrosoluble contrast medium injected orally or rectally) Although CT is an invaluable diagnostic instrument, it usually involves moving a potentially unstable patient from one ward to another. Furthermore, the iodinated contrast medium can worsen renal function. Renal insufficiency and paralytic ileum are both contraindications for CT so the risks must be taken into account when deciding whether to carry out this diagnostic technique. One alternative in a very unstable patient is diagnostic peritoneal lavage, which consists of injecting 1–2 l (20 ml/kg) of saline solution through a catheter into the peritoneum. This can put into evidence the presence of bacteria, leukocytes, bile, enteral content, or blood in cases of acute intestinal ischemia [24]. Scintigraphy has a very limited role in the diagnosis of IAI in critically ill patients because it is not specific enough and cannot provide an accurate enough image to guide drainage [22,23]. Magnetic resonance imaging (MRI) has very high diagnostic accuracy in evaluating acute intra-abdominal abscess [24].

Management

Standards of Care

Source control is defined as any and all physical measures necessary to eradicate a focus of infection, as well as influence factors that maintain infection, promoting

microbial growth or impairing host antimicrobial defenses [7,25].

Primary peritonitis is essentially a disease that is managed with antibiotics and not surgery [26]. There is no reliable evidence that cefotaxime is the treatment of choice for spontaneous bacterial peritonitis, although many authors have suggested this. Furthermore, results indicate that 4 g/day cefotaxime may be as effective as 8 g/day cefotaxime in terms of reduction in mortality and resolution of symptoms, and that treatment for 10 days is no more effective than treatment for 5 days. Goals of management of secondary peritonitis are summarized in Table 26.2. Several studies have identified *E. coli* and *B. fragilis* as the main target organisms for antibiotic therapy [2,27]. The current practice of early empirical administration of antibiotics targeted against these bacteria is well established. However, issues concerning the choice and timing of drugs, the need for surgical cultures, and the duration of postoperative administration are controversial. Despite several published options, antibiotic therapy for secondary peritonitis is simple. The emerging concepts suggest that less, in terms of number of drugs and duration of treatment, is better [2]. Furthermore, recent studies suggest that monotherapy with a single broad-spectrum antibiotic that includes full activity against *E. coli* may be equal or superior to polytherapy with multiple drug combinations [27–30]. The surgical strategy depends on the source of the infection [31,32], the degree of peritoneal contamination, the clinical condition of the patient, and the concomitant disease. Moreover, early goal-directed therapy provides significant benefits with respect to outcome in patients

Table 26.2 Principles for the management of peritonitis and indications for staged abdominal repair

1.	Supportive measures
	To combat hypovolemia and shock and maintain adequate tissue oxygenation
	To treat bacteria not eliminated by surgery with antibiotics
	To support failing organ systems
	To provide adequate nutrition
2.	Operative treatment
	Repair and/or control the source of infection
	Evacuate bacterial inoculum, pus, and adjuvants
	Treat abdominal compartment syndrome
	Prevent or treat persistent and recurrent infection or verify both repair and purge
3.	Staged abdominal repair
	Critical patient condition, due to hemodynamic instability, precluding definitive repair
	Excessive peritoneal edema (abdominal compartment syndrome, pulmonary, cardiac, renal, or hepatic dysfunction, decreased visceral perfusion) preventing abdominal closure without under tension
	IA pressure >15 mmHg
	Massive abdominal wall loss
	Impossible to eliminate or to control the source of infection
	Incomplete debridement of necrotic tissue
	Uncertainty of viability of remaining bowel
	Uncontrolled bleeding (the need for packing)

with severe sepsis and MOF [33]. Ideally, a severe IAI should be cured with a single surgical procedure; unfortunately, infection often persists or recurs. Traditionally, severe peritonitis has been treated by performing a midline laparotomy to identify and eliminate the source of infection. In certain instances, complete control of the infective focus is not feasible during the first operation [2]. While elimination of the focus and reduction of contamination are accepted as conditions of successful treatment, surgical procedures differ for the treatment of residual infection. The following major approaches have been developed: (1) continuous peritoneal lavage, (2) planned relaparotomy, and (3) open treatment by laparostomy. Continuous peritoneal lavage takes the whole concept of lavage to an extreme, the hypothesis being that continual IA irrigation will enhance the removal of bacteria and their products, and improve the time to resolution [34]. Various forms of peritoneal lavage are routinely used in management of patients with peritonitis. There is little evidence that supports this approach in either the clinical or scientific literature; moreover, it has been documented that lavage damages mesothelial cells, dilutes agents that are involved in peritoneal defense, and may spread previously contained infection. In cases of IAI a single operation may not be sufficient to achieve source control, thus necessitating re-exploration [5]. The planned relaparotomy approach involves reoperations at fixed intervals, irrespective of the clinical condition of the patient, to prevent development of further septic fluid collections, thereby precluding their systemic effects. Adverse effects of planned relaparotomies are frequent and include damage to abdominal wall structures and IA viscera. Open management facilitates frequent re-exploration and, by treating the entire peritoneal cavity as one large infected collection, continuous exposure for maximal drainage. Furthermore, it serves to reduce the high IA pressure caused by peritoneal edema associated with fluid resuscitation and inflammation, thus obviating the deleterious systemic consequences of the abdominal compartment syndrome [35]. GIT fistulas and abdominal wall defects have plagued simple open management; these complications should be minimized by introduction of temporary abdominal closure devices, such as artificial mesh-zipper techniques. Tertiary peritonitis develops late in the postoperative course, presents clinically as sepsis, and is associated with a sterile peritoneal cavity or particular microbiology. Further antimicrobial administration and surgical interventions may contribute to peritoneal superinfection with yeasts and other low level pathogens [2]. The low virulence of these organisms, which represent a marker of tertiary peritonitis and not its cause, reflects the global immunodepression of the affected patients.

Management of IA Abscess

Abscesses represent a relatively successful outcome of peritonitis. They may be visceral or nonvisceral, extra- or intraperitoneal. Nonvisceral abscesses arise after resolution of diffuse peritonitis in which a localized area of suppuration persists, or after a GIT perforation that is effectively localized by peritoneal defenses. Percutaneous, ultrasound, or CT-guided drainage is the method of choice for single abscess. Although retrospective studies attribute no lesser mortality or morbidity rates to per-

cutaneous drainage versus surgical drainage [36], the former represents a minimally invasive procedure that can spare the patient the unpleasantness of another open abdominal operation . Moreover, a recent study has shown that percutaneous catheter drainage should be considered as the initial therapy for patients with culture-positive peripancreatic fluid collections [37].

Conclusions

In conclusion any physical measures ("source control") able to eradicate the focus of infection, to prevent on-going contamination and ultimately to restore optimal anatomy and function are essential for increasing the survival rate, especially in the critically ill patient in ICU.

Drainage, debridement, and the definitive surgical management are the usual consecutive steps to be carried out, but in many circumstances the procedure has to be tailored to the single patient.

Successful source control and antibiotic management is associated with resolution of clinical features of systemic inflammation and reversal of organ dysfunction. Progression or failure of resolution of organ dysfunction suggests persistence of the disease and the need for further intervention.

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Surviving Sepsis Campaign and Bundles 27

J.-L. Vincent

Introduction

The Surviving Sepsis Campaign (SSC), an initiative of the European Society of Intensive Care Medicine (ESICM), the International Sepsis Forum (ISF), and the Society of Critical Care Medicine (SCCM), was developed in 2002 in a global effort to improve the management, diagnosis, and treatment of sepsis. The three planned phases of the SSC reached a conclusion in December 2008, but the ideas created continue to impact on the daily management of the patient with severe sepsis.

The Surviving Sepsis Campaign

The ultimate aim of the SSC was to decrease global mortality from sepsis by 25% by the year 2009. To achieve this, a three-phase campaign was envisaged, sponsored by an unrestricted educational grant from Baxter, Edwards Lifescience, and Eli Lilly and Company.

Phase I of the Surviving Sepsis Campaign

The first phase of the Surviving Sepsis Campaign involved the introduction of the campaign at several major international critical care conferences, starting with the ESICM meeting in Barcelona, Spain in October 2002. The so-called Barcelona Declaration was a six-point action plan comprising the following elements (www.survivingsepsis.org):

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- Awareness: increase awareness of healthcare professionals, governments, funding agencies, and the public to the high frequency and mortality of sepsis.
- Diagnosis: improve the early and accurate diagnosis of sepsis by developing a clear and clinically relevant definition of sepsis.
- Treatment: increase the use of appropriate treatments and interventions.
- Education: encourage the education of all healthcare professionals who manage sepsis patients by providing leadership, support, and information about all aspects of sepsis management.
- Counseling: provide a framework for improving and accelerating access to post-ICU care and counseling for sepsis patients.
- Referral: recognize the need for clear referral guidelines that are accepted and adopted at a local level in all countries by initiating the development of global guidelines.

Phase II of the Surviving Sepsis Campaign

The second phase of the SSC concentrated on the development of guidelines for the management of patients with severe sepsis or septic shock. Using a modified Delphi methodology, evidence-based guidelines were developed by a group of about 50 international critical care and infectious disease experts in the diagnosis and management of infection and sepsis. All aspects of management of the patient with severe sepsis were covered, ranging from initial resuscitation to consideration of limitation of life support, and the recommendations were published jointly by Intensive Care Medicine [1] and Critical Care Medicine [2] in 2004. Revised guidelines were published in 2008 [3,4], developed by 55 ICU experts and supported by 16 scientific societies [5]. In contrast to the earlier guidelines, there was no industry funding. The revised guidelines also used a different system to evaluate the evidence, the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology [6], by which each recommendation was graded according to the quality of evidence [from high (A) to very low (D)] and the strength of the recommendation (1 for strong and 2 for weak). The system allows essential interventions which have not been tested in randomized controlled trials, but have an accepted desirable risk/benefit ratio, like antibiotic therapy or fluid administration for example, to be awarded a strong recommendation.

Importantly, the guidelines were developed as an aid for physicians to direct rather than command management. As new data become available, guidelines will need to be updated and adapted accordingly.

Phase III of the Surviving Sepsis Campaign

The third phase of the SSC was focused on translating the guidelines into clinical practice and assessing how effective they were in improving outcomes. For this purpose, the Surviving Sepsis Campaign developed a partnership with the Institute for

Healthcare Improvement (IHI) to develop sepsis bundles, groups of guideline-based interventions that, when executed together, result in better outcomes than when implemented individually (http://www.ihi.org/IHI/Topics/CriticalCare/Sepsis).

Two sepsis bundles for patients with severe sepsis or septic shock were developed (Table 27.1):

1. The Severe Sepsis Resuscitation Bundle includes seven tasks that must be accomplished within the first 6 h of presentation.
2. The Sepsis Management Bundle lists four management goals that must be completed within 24 h of presentation.

The bundles developed by the IHI are designed as templates from which it is recommended that individual ICUs should develop protocols customized to their local environment and structure. ICUs were encouraged to perform a Plan-Do-Study-Act (PDSA) cycle in which the bundles were adapted to local set-up, applied, and their effects assessed. The aim then was that if successful and after further adaptation if necessary, they could be applied to larger units locally and further afield. As ICUs around the world started to adopt the bundle concept, tools for bundle application, data gathering, process analysis, successful protocol formation, etc. were gathered and made available on the IHI website. More than 160 sites in 18 countries have provided data on how application of SSC-based changes and use of bundles has impacted on care of patients with severe sepsis. Although the full data are not yet published, results show that implementation of the sepsis bundles was associated with a modest reduction in mortality rates (presented by Dr M Levy at the Society of Critical Care Medicine 38th Critical Care Congress, Nashville, Feb 2009).

Table 27.1 The sepsis "bundles" (from http://www.ihi.org/IHI/Topics/CriticalCare/Sepsis)

Sepsis resuscitation bundle (6-h bundle):

1. Measure serum lactate
2. Obtain blood cultures prior to antibiotic administration
3. Administer broad-spectrum antibiotics within 3 h from time of presentation for ED admissions and 1 h for non-ED ICU admissions
4. In the event of hypotension and/or lactate >4 mmol/L (36 mg/dl):
   a. Deliver an initial minimum of 20 ml/kg of crystalloid (or colloid equivalent)
   b. Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure >65 mmHg
5. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate >4 mmol/L (36 mg/dl):
   a. Achieve central venous pressure (CVP) of ≥8 mmHg
   b. Achieve central venous oxygen saturation ($ScvO_2$) of ≥70% (or mixed venous oxygen saturation, SvO_2 ≥65%)

Sepsis management bundle (24-h bundle):

1. Administer low-dose steroids for septic shock in accordance with a standardized ICU policy
2. Administer drotrecogin alfa (activated) in accordance with a standardized ICU policy
3. Maintain blood glucose control > lower limit of normal, but <150 mg/dl (8.3 mmol/L)
4. Maintain inspiratory plateau pressures <30 cm H_2O for mechanically ventilated patients

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In a study in two hospitals in the UK, Gao et al. [7], showed that compliance with the 6-h sepsis bundle was associated with a more than twofold decrease in hospital mortality (49% vs. 23%) and compliance with the 24-h bundle showed a trend to reduced mortality; however, compliance with both the bundles was not very high (52% for the 6-h bundle and 30% for the 24-h bundle). In a single center study in the USA, Micek et al. reported that implementation of a standardized order set for the management of septic shock in the emergency department, which was based on the SSC recommendations and focused on hemodynamic resuscitation and antimicrobial treatment, was associated with more rigorous fluid resuscitation, greater administration of appropriate initial antibiotic treatment, a lower 28-day mortality, and reduced costs [8, 9]. Similarly, Nguyen et al. reported that implementation of a severe sepsis bundle in the emergency department setting was feasible and was associated with decreased in-hospital mortality [10]. However, a recent audit in a UK emergency department reported only 19% compliance with the sepsis resuscitation bundle [11] suggesting that there remains considerable ground for improving awareness. In a before and after design in 59 Spanish medical-surgical ICUs, Ferrer et al. [12] reported that a national educational effort to promote bundles of care for severe sepsis and septic shock was associated with improved guideline compliance and lower hospital mortality (44.0% vs. 39.7%; $p = 0.04$). However, compliance rates were still low, and the improvement in compliance with the resuscitation bundle lapsed by 1 year. Finally, in a prospective observational study in our ICU, we noted that compliance with the 6-h bundle was obtained in 72% of patients and with the 24-h bundle in 67% (30/44) of eligible patients [13]. Patients in the 6-h compliant group had a lower mortality rate (16% vs. 41%, $p = 0.04$) and a shorter length of ICU stay than patients in the noncompliant group. The mortality rate and duration of ICU stay were the same in the 24-h compliant and noncompliant groups, but patients who complied with the 24-h sepsis bundle after only 12 h had a lower mortality rate (10% vs. 39%, $p = 0.036$), and a shorter length of stay than those in whom compliance was achieved in the 24-h period, suggesting that earlier implementation of the 24-h management bundle (by 12 h instead of 24 h) could result in better outcomes.

Needs and Limitations

Severe sepsis is the leading cause of death in noncoronary intensive care units (ICUs), associated with mortality rates of 30–50% [14]. As people live longer and more patients survive conditions they would previously have died from and receive long-term immunosuppressive therapies, the number of cases of sepsis will increase at an estimated 1.5% per year [15]. Sepsis already imposes a considerable burden on healthcare costs, accounting for 40% of total ICU expenditure; annual costs of sepsis have been estimated at some $16.7 billion in the USA [15] and 6.2–8.3 billion euros across Europe [16].

Clearly strategies are urgently needed to improve outcomes and, in the absence of a single curative drug, implementing packages of best practice care may be one way of achieving this, perhaps particularly in hospitals/units where standards of care are

not already optimal. However, where patient management is already good, creating fixed protocols based on suggested bundles of care may not necessarily be the best way of improving outcomes. First, many uncertainties remain across the field of intensive care medicine, and in sepsis in particular. For example, which intravenous fluids should be used during resuscitation and in what quantity? Which vasoactive drugs should be employed and to which endpoints should they be titrated? Bundles also need to be carefully adapted as new evidence comes to light. For example, although the pivotal study by Annane et al. [17] showed an increased survival rate in patients with septic shock who received steroid therapy, the more recent European Corticus study failed to confirm these findings [18], but studied a less severely ill population, leaving unanswered the question of whether there is still a place for steroids in severely ill patients with septic shock unresponsive to fluid resuscitation. Similarly, although a tight approach to blood glucose, targeting levels 80–110 mg/dl, was shown to be associated with reduced mortality rates in a single center study [19], multicenter studies failed to confirm these findings [20,21], but there is still support for targeting a moderate glucose of about 150 mg/dl.

Second, an important limitation of the bundle approach is the time factor. There is now considerable evidence that early diagnosis and initiation of appropriate therapy is crucial in patients with sepsis: early goal-directed resuscitation [22], early effective antibiotics [23], and early initiation of drotrecogin alfa (activated) [24], have all been associated with improved outcomes. The sepsis bundles are separated according to a somewhat artificial time limit, which may create a false sense of security. Rather than encouraging us to complete a bundle within 6 or 24 h, it may be better to encourage completion of each facet "as soon as possible." Our recent study suggested that outcomes could have been improved if the sepsis management bundle had been completed within 12 h rather than the recommended 24 h [13].

Conclusions and Recommendations

The multinational Surviving Sepsis Campaign provided a base for strategies to improve sepsis awareness and to standardize care processes. It provided informed, evidence-based guidance for clinicians caring for patients with severe sepsis or septic shock. The development of sepsis bundles and related protocols has introduced some degree of uniformity to the process of caring for a patient with severe sepsis. Importantly, these bundles were not developed as rigid sets of orders, but as guides to best practice. They must be adapted to local policy and may be most beneficial when viewed as a list of key interventions to be completed as soon as possible in any patient with a diagnosis of severe sepsis. In addition, as the results of new trials become available, they need to be incorporated into guidelines (and bundles) as rapidly as possible to ensure that patients continue to be treated with the very latest best standard of care. Although the SSC has now drawn to a close it is important that we, as individual physicians, maintain the momentum created by this campaign as we strive to improve outcomes from this common and destructive disease process.

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Section IX
Trauma

The Trauma: Focus on Triage

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F. Plani

Introduction

Triage is a term used to describe the process of categorizing multiple victims or mass casualty patients into different treatment and evacuation categories [1,2].

Its main goals are to:

(i) Prevent avoidable deaths

(ii) Ensure proper initial medical treatment within a minimal time frame

(iii) Avoid misusing assets on hopeless cases

Triage should be applied whenever the number of patients exceeds the capabilities of the available resources. This does not occur commonly in civilian circumstances in the developed world, where help can be summoned from afar, but is practiced routinely in resource-poor countries.

Universally, therefore, it is mainly associated with the decision making required for the management of victims of multiple casualties incidents (MCI) and mass casualties, and in battlefield situations.

In modern times, furthermore, the term "triage" has acquired two different meaning as well, namely:

1. Civilian Field Triage: The identification of the most appropriate scene management, destination, and form of transport of any major trauma victim within the context of a Trauma System [3].
2. Emergency Department Triage: The process of determining the appropriate priority and period for all patients in an emergency department [4–6].

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Triage in Mass Casualty Incidents, War, and Disasters

Treatment Priorities in Mass Casualty Incidents

Triage has been intimately associated with the management of battlefield casualties since Napoleonic times and the name is indeed derived from the French "trier," meaning "To sort."

Dominique-Jean Larrey, Surgeon-in-Chief of the Napoleonic armies, first described it in 1797, in the following terms: "Those who are dangerously wounded should receive the first attention, without regard to rank or distinction. They who are injured in a less degree may wait until their brethren-in-arms, who are badly mutilated, have been operated and dressed…"

Dr. Larrey was also the first surgeon to treat battlefield casualties, from Egypt to Waterloo, near the site of injury, In 1797, he also devised a system of casualty evacuation which he called the "Ambulance Volante," made up of a doctor, a quartermaster, a drummer boy, 24 infantrymen, and necessary supplies, in order to follow through with the triaged patients [7].

Triage in War and Disasters

The aim of triage is to provide "The greatest good for the greatest number," since resources will often be exceeded [8,9] and the normal standard of care interventions cannot be completed for each patient.

Triage is a dynamic process, with reclassification of status possible after the transport and definitive treatment of the victim has occurred [10,11].

One of the first priorities is to rapidly identify the 10–20% of survivors in need of immediate care, some of whom are not obviously evident, such as blast lungs and pulmonary and myocardial contusions, internal injuries, spinal injuries, and head injuries.

During mass casualty incidents (MCI), triage officers must quickly determine which victims need immediate medical treatment and which can wait; which victims require emergency surgery and which are not endangered.

Wartime triage differs from all forms of peacetime triage in two aspects:

Evacuation: This is often multidirectional in peacetime and usually only unidirectional in war.

Standard Operating Procedures (SOP): The triage officer must comply with them, and be aware of the availability of resources and changing battlefield conditions.

Transfers, however, may be possible to military high echelon referral hospitals within most established military health services, and principles similar to civilian field triage may then apply.

Reverse Triage

The prioritization of patients with a good-to-reasonable chance tosurvive, rather than treating the most seriously injured ones first, constitutes "Reverse Triage." It was described in the American Civil War where the emphasis was on patients requiring early amputations. Gunshot wound injuries to the abdomen were automatically neglected because of very high mortality irrespective of treatment.

Even nowadays, in war, an important consideration of triage is in returning a casualty to the battlefront [8], and therefore the more easily transported and salvaged may be treated first.

Reverse triage is less commonly employed in peacetime conditions, where extra help can be more easily obtained, except for in overwhelming disasters.

Prehospital Triage

Even before the arrival of the Emergency Medical Services, the initial triage must be performed by the first officials on scene, usually police officers or firefighters.

Out-of-Hospital Triage Principles

The first responders on the site should perform the initial triage, and unless relieved by more experienced personnel, should provide oversight of the entire situation [12].

The first rescuers at a scene will follow a standard procedure, starting with safety first, of:

- Self
- Scene
- Survivor

Then they should assess the scene using the acronym "ETHANE" [7]:

- E Exact location of incident
- T Type of incident (rail, chemical, road)
- H Hazards, potential or actual
- A Access direction of approach
- N Number of casualties and their severity/type
- E Emergency services (present on scene and required)

The first Emergency Physician (Most European countries) or paramedic (North America, UK, Australasia, South Africa) arriving at the scene should organize the overall rescue procedure and establish:

- Operational areas (Assembly, Triage, Treatment, Transport zones)
- "Exclusion zones" if indicated (HAZMAT, bomb blasts, etc.)

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Treatment Priorities in Multiple Casualty Incidents (MCI)

During the initial triage, patients are assigned a "treatment priority.">Initially, there are only two main categories: those who can wait for treatment and those who cannot [2]; these two groups can initially be identified by utilizing "walking" as the first criterion.

Further immediate evaluation allows for triaging into four or five categories. This is dependent on the categorization of the "expectant" or" delayed" group as a separate group, or into the "immediate" group in multiple patient scenes or into the "dead" group in mass casualty disasters.

A number of triage systems have been developed in order to provide a common language to all rescuers involved in the treatment of multiple casualties, from first responders to the hospital.

The best-known are the systems taught in the North American-based START (Simple Triage and Rapid Treatment) system and the UK/Australasian-based MIMMS (Major Incident Medical Management and Support) system [1,7,13].

They both rely on color coding of casualties and a rapid assessment of physiological parameters to triage victims into four categories.

"Triage Sieve"

This is MIMMS First Triage: the initial actions by all rescuers are as follows: Check for open airway, presence and rate of breathing, and circulation based on pulse rate and capillary refill time, and attach a color code card according to the findings.

In START, abnormal findings are as follows: breathing >30, absence of radial pulse or slow capillary refill, altered mental status (follow simple commands or not), leading to the mnemonic: "RPM 30, 2, can do."

These simple parameters allow the application of the four color-coded categories method [14–16] as follows:

Red has the highest priority. The victim has a life-threatening situation and requires immediate medical treatment at the scene and/or immediate evacuation, but has been assessed as having a good prognosis.

Yellow is the second priority. It is a casualty who is seriously injured but with vital functions and, presently, stable. The victim requires medical treatment, but has a very good outcome prognosis.

Green are all walking the victims, with or without injuries. They may still deteriorate, but the very fact a victim is walking makes them a green category.

Black are the dead (sometimes the color is white or dark blue), and they have to be certified as such by a relevant official [17,18].

Expectant Category: Patients who still have signs of life, but are expected to die with the resources available. These casualties are triaged to an "expectant" area, survival being expected to be less than 24 h. However, if additional resources become available, they may be reclassified up to red, or downgraded to black if resources

remain inadequate.

The purpose of the first scene assessment, through the MIMMS-Sieve or the START method therefore, allows the allocation of different color cards to the different groups of patients.

The immediate and urgent patients can be identified and receive appropriate treatment, which starts with the casualty-clearing station, thence the ambulance-loading point, and then the appropriate hospitals.

From "Triage Sieve" to "Triage Sort:" The Triage Revised Trauma Score

As soon as the categories are identified and brought together, a Triage "SORT" is carried out, based on the Triage Revised Trauma Score (TRTS).

This is again based on a more detailed physiological evaluation, and utilizes Glasgow Coma Scale (GCS), Respiratory Rate, and Systolic Blood Pressure [19].

In practical terms, the assessment must determine if victims' requirement for surgery is:

- Red: Immediate
- Yellow: Within 2–4 h
- Green: Beyond 4 h

The advantage of the Triage Revised Trauma Score is that it is quick, reproducible, and an extension of the Triage Sieve. However, it does not take into account the nature of the injury at all, and therefore cannot be used to decide whether a patient should be referred to a specialist center or not. It is therefore supplemented by as much relevant anatomical information as can be obtained at the time, leading to a provisional diagnosis and decision making on the resources needed for the patients.

It is essential to undergo training in order to practice MIMMS or START Triage, and remain current through refresher courses, since triage decisions are likely to raise questions, due to the rigidity of the sieve and sort system, and the need to triage aggressively [1,2,13].

Special Triage Situations

Pediatrics

Injured children are often triaged to a higher triage category, often because of communication and emotional reasons. Children respond better and sometimes worse to injury, but the basic triage principles and procedures are nevertheless the same as for adults [20].

The pediatric version of START triage is called "Jump-START" [21], and it allows for modifications in children, in terms of higher respiratory rates, presence of pulses, and assessing the mental status by using the AVPU score (Alert, Verbal, Painful, Unresponsive).

Bomb Blasts

Many mass casualty situations, both military and civilian, result in complex and often hidden injuries, both blunt and penetrating. Bomb blasts in particular often combine the effects of blunt, penetrating, and burn trauma.

Mass Disasters

Environmental problems and progressive destruction of the resources one is used to rely on are often a problem in mass disasters, and will affect triage decision making [1,2,22].

HAZMAT Events

Any hazardous materials (HAZMAT) event requires the establishment of "exclusion zones" [23–28].

Decontaminated zones must be uphill, upwind, and upstream from the contaminated zone.

Triage usually must be performed outside of the hot and warm zones, while treatment is performed almost exclusively in the cold zone.

Nuclear Incidents

Triage for radiation incidents is complicated because only highly exposed victims will be initially symptomatic while the vast majority of the irradiated and contaminated are initially asymptomatic.

Triage therefore should rely more on descriptive facts and expected effects and measured reactivity than on obvious symptoms.

Thus, known distance from the source, exposure, and radiation count will be of greater significance, even in asymptomatic patients [1]. Far greater distances will be needed to determine safe zones, and longer periods of observation will be needed for victims.

Biological Agents Disasters

The triage of biological agents is in a way similar: victims are often asymptomatic for days or weeks, and long periods of observation may be needed.

Chemical Agent Release

Two specific triage precautions must be observed during response to chemical agent (CA) release incidents:

1. Protection of the rescuers, although the realization that a chemical incident has happened may be difficult at first, and
2. Victim exposure: like in nuclear events, symptoms can be delayed, and the victims may not directly link them to the exposure.

Limitations and Pitfalls of Triage

Rescue and extrication in entrapment take priority overtriage, which can only be carried out later [29–31].

Subsequent to triage, the availability of rapid transport methods such as helicopter or just greater or decreased availability of ambulance transport can change the survivability of casualties radically.

Cultural sensitivities and familiarity with having to deal with limited resources routinely also play a role of how triage is carried out, especially when it comes to assessment of salvageability.

Recognition of fatigue and the need of adequate briefing and debriefing after situations requiring triage also ensure accuracy and recovery.

Civilian Field Triage

In 1976, The Committee on Trauma of the American College of Surgeons started publishing documents on the requirements of trauma centers within trauma systems, including directions for the appropriate transportation of injured patients [32,33].

From these recommendations, Field Triage Decision Schemes have been published by the American College of Surgeons since 1986, the latest having been released in 2006 [34].

These recommendations are based on the successive steps of physiological, anatomical, mechanism of injury, and other criteria.

Nowadays, at any incident scene, the Emergency Medical Services (EMS) providers determine the severity of injury, initiate medical management, and identify the most appropriate facility to transport the patient to through a process called "civilian field triage."

This radical change has been particularly obvious in North Americ and to a greater or lesser extent, in the South African and Australasian set up, and is performed by paramedics. In case of multiple casualties, however, scene command centers with physicians may be established [45,46].

Physicians are present at the scene in most European countries. Patients had previously been transported to the nearest facilities regardless of the capability of that hospital [32]. This is still the case in many parts of the world outside North America and parts of Australasia and South Africa.

It is generally accepted that the risk for death of a severely injured person is 25%

lower if the patient receives care at a Level I trauma center [3,47]. However, since not all patients require the services of a Level I trauma center, less injured patients should be preferentially transported to other hospitals [48].

Determining the most appropriate facility for a given patient's injury is a complex process that also involves the patient's clinical situation, patient and family member preferences, state laws or regulations that might affect destination choices (e.g., mandating transport to the closest facility), and hospital trauma center and EMS system capability and capacity.

Trauma Centers

The Level I trauma center has the greatest resources and personnel, is usually a teaching hospital, with leadership in education and research.

The Level II center offers similar resources to a Level I facility, minus the emphasis on research and training, and is in fact the center likely to treat most patients with major trauma.

The Level III center is capable of assessment, resuscitation, and emergency surgery, prior to transfer to a higher center if required.

The Level IV center is a hospital with 24-h medical cover that can provide some stabilization in the emergency room prior to mandatory transfer of trauma patients [46].

Preliminary Consideration

Civilian scene triage must take the following factors into account:

- Location, traffic, weather
- Specific capabilities of the different hospitals in the area
- Need to go to the nearest center irrespective of severity in specific cases
- Which level of trauma center, and which mode of transport

The Triage Decision Scheme provides a systematic approach on how to determine what immediate interventions need to be carried out, and the disposition of the patient.

Step One: Physiologic Criteria

Any of the following findings should prompt transfer to a trauma center:

- Glasgow Coma Scale of <14
- Systolic Blood Pressure (SBP) of <90 mmHg
- Respiratory Rate of <10 or >29 breaths per minute (<20 in infant aged <1 year)

The rationale for this comes from, among others, two large studies indicating that there was decreased mortality if patients with abnormal physiological parameters, particularly GCS and respiratory rate, were transported to a Level 1 trauma center [49].

Abnormal radial pulse and abnormal Best Motor Response (M) or Best Verbal Response (V) of GCS indicate a probability of emergency intervention of 88%; Respiratory rate >25 is a predictor of serious injury; when everything else is normal, GCS can help in reducing under- and overtriage [50].

Anatomic criteria should be taken into account next even if the above physiologic parameters are not abnormal.

Step Two: Anatomic Criteria

Sometimes reliance on physiological abnormalities alone can lead to undertriage, as a study from South Carolina evidenced. In that study physiologic parameters had a Positive Predictive Value of only 42% for Serious Injury with an Injury Severity Score (ISS) >15 [51,52].

The recommended anatomic abnormalities indicating transport to a trauma center are as follows:

- Penetrating injuries to head, neck, torso, and extremities proximal to elbow and knee
- Flail chest
- Two or more proximal long-bone fractures
- Crushed, degloved, or mangled extremity
- Amputation proximal to wrist and ankle
- Pelvic fractures
- Open or depressed skull fracture
- Paralysis

The reason anatomical scores play a secondary role in patient assessment is because the ISS cannot be used for prehospital triage.

Anatomic criteria however may be of relevance if the EMS response is particularly rapid, before physiological derangements become apparent, and with penetrating trauma. A precordial injury or a partial decapitation are going to determine the need for a trauma center even before any physiological parameters are considered [53–55].

The combination of physiologic and anatomic criteria alone, however, may still not be sufficient. In a large series from New York State, the most important parameters to predict major operative interventions were physiological and anatomical criteria alone in 57% of cases; however 43% of patients who needed major operative interventions would not have been triaged without mechanism and other criteria [56].

Step Three: Mechanism-of-Injury Criteria

Primary reliance on mechanism of injury to triage patients to trauma centers would lead to a very high overtriage [57,58]; on the other hand, over 20% of patients with major injuries did not have a significant mechanism in a large study from Victoria, Australia [59].

On this basis, mechanism of injury should be a third step in the triage to a trau-

ma center, and should comprise the following conditions:

- Falls.
  Adults: fall >6 meters; children aged <15 years: fall >3 meters or two to three times child's height
- High-risk auto crash
  Intrusion: >30 cms; to the occupant site; or >50 to any site
  Ejection (partial or complete)
  Death in same passenger compartment
  Vehicle telemetry data consistent with high risk of injury
- Car versus pedestrian/bicyclist thrown, run over, or with significant (>30 kph) impact
- Motorcycle crash >30 kph

Step Four: Special Considerations Criteria

In some cases, even if none of the above situations apply, the EMS or prehospital medical personnel may feel there are good reasons to take a patient to a trauma center [33,60–63].

Presently, these are the following:

- Age >55 years and <15 years
- Anticoagulation and bleeding disorders
- Burns
  Without other trauma mechanism: triage to burn facility
  With trauma mechanism: triage to trauma center
- Time-sensitive extremity injury
- End-stage renal disease requiring dialysis
- Pregnancy >20 weeks
- EMS provider judgment

Undertriage and Overtriage.

Flexibility with assessment is to be expected in the prehospital setting, but undertriage, or the underestimation of the patients injuries and needs, should be at most 5%.

Up to 30–50% of overtriage in patients taken to trauma centers is acceptable in daily practice, but should be less than 10% in MCI and disasters where overtriage adversely affects the care given to seriously injured patients.

Because of the inevitable "triage errors," the system must be "error tolerant," by having multiple triage stations and having medical officers allocated also to the nonurgent groups, in order to identify deterioration promptly.

Undertriage is more frequent with older persons (Up to 18% vs. 8% in young and middle aged in a large study) and persons with brain injuries: blunt trauma in old people often covert [64–66].

On the other hand, there is a prevalence of overtriage of younger patients [67].

Hospital Triage

Mass Casualty Incidents

In cases of mass casualties incidents (MCI), the in-hospital triage is part of the hospital's disaster plan. It is applied at the receiving hospital and is performed by emergency department (ED) physicians or nurses [62,63].

Like Triage carried out at the scene, its main goal is to treat the right patient at the right time by the right practitioners, and avoid preventable mortality and morbidity while avoiding wasting resources on unrecoverable cases.

Greater emphasis is placed on the direct effect of prioritization, such as which patients go to the operating theatre first, which patients go to the intensive care unit first, and so on.

It must be an "error-tolerant" system, in that while there must be a unidirectional flow of casualties, ongoing assessment of patients must allow for a smooth reclassification as patients deteriorate or improve.

The first hospital triage area should be in front of the ED, and specific documentation highlighting the reasons for the choice of triage, and the changes from the allocated prehospital category must be completed [68,69].

Similarly to what happens at a major incident scene, if the hospital is overwhelmed and starts receiving all the casualties, that hospital becomes a "Triage Hospital," or " Ground Zero Hospital," and should only distribute casualties to all the other hospitals rather than try to combine treatment and triage under the same roof.

At the same time, and especially if no other hospitals can receive the desired number of patients, the hospital can try to increase capacity by creating alternate site surge capacity: tent-covered parking lots or field hospitals, and utilization of predetermined areas within the hospital.

Common pitfalls in hospital triage generally center on inadequate training and education, disaster plans found to be unworkable, uncertain command structures, and inadequate communications and security.

Medical care delivery is often inadequate if emphasis has been placed on surge capacity and not on surge capability, although in terms of absolute numbers, the number of beds needed in a disaster is normally underestimated while the number of doctors is often overestimated.

A common strategy to best utilize human resources and minimize bed overutilization is to have a small team for each stretcher to assess, treat, and quickly send the patient to the next level of care, and be ready for the next patient.

In particular circumstances, such as in bomb blasts, it can be predicted that most casualties with an ISS <25 will go to ICU and those with ISS >25 will go straight to the operating theatre and most will require mechanical ventilation.

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Resource-Limited Hospital Triage

Field Surgical Hospitals for the Weapon Wounded of the International Committee of the Red Cross (ICRC) in most cases have to cater for all admissions during humanitarian crises and war while utilizing only available resources [70]. These do not include artificial ventilation and advanced diagnostic and therapeutic modalities.

The only immediate treatment is surgical, and the triage of patients is dependent on how soon patients need surgery.

Victims are to be classified by the most experienced person, who may or may not be the ICRC surgeon, into the following categories based on their need for urgent surgery:

- Red: Serious, requiring immediate surgery, within 4 h, and have a good chance of recovery, often abdominal and thoracic injuries
- Yellow: Serious, but able to wait for surgery for more than 4 h if necessary, while temporizing methods are applied; these are often fractures and head injuries
- Green: Ambulatory treatment only is required: simple closed fractures, lacerations that can be treated under local anesthesia.
- Black: Dead or presenting with such severe wounds, exceeding the capacity and capability of a field hospital, that only expectant and supportive treatment should be given.

In most cases, this means that any patient requiring ventilation or inotropic support would be classified as black within the resources of an ICRC field hospital.

Triage in the Emergency Department

Triage is an essential function in Emergency Departments (ED), both for trauma and nontrauma conditions, where many patients may present simultaneously. It is carried out on arrival by a specifically trained and experienced registered nurse. Specific maximum times are allocated according to the need for time-critical intervention, not necessarily order of severity.

Victims of trauma should be allocated a triage category according to their objective clinical urgency. As with other clinical situations, this will include consideration of high-risk history as well as brief physical assessment (general appearance ± physiological observations).

Various hospital triage algorithms exist worldwide, [71], none of which have been formally validated, leaving more or less leeway for individual nursing assessment.

In Australia, the Australian Triage Scale allocates a number of descriptors and periods to its categories as follows:

ATS 1: Immediate threat to life or deterioration: Immediate

ATS 2: Imminently life threatening: 10 min

ATS 3: Potentially life threatening: 30 min

ATS 4: Potentially serious or situational urgency: 60 min

ATS 5: Less urgent: 120 min

The most urgent clinical feature identified determines the ATS category and once a high-risk feature is identified, a response equal to the urgency of that feature should be initiated.

The triage assessment should generally take no more than 2–5 min. Vital signs are only measured at triage if required to estimate urgency, and if time permits. This scheme covers all patients visiting emergency departments.

The following are examples of trauma conditions in the various triage categories.

Australian Triage Scale Category 1 Trauma

- Immediate risk to airway – impending arrest
- Respiratory rate <10/min
- Extreme respiratory distress
- BP <80 (adult) or severely shocked child/infant
- Unresponsive or responds to pain only (GCS <9)

Australian Triage Scale Category 2 Trauma

- Airway risk – severe stridor or severe respiratory distress
- Circulatory compromise, severe blood loss, hypotension
- Very severe pain – any cause
- Drowsy, decreased responsiveness any cause (GCS <13)
- Major multitrauma (requiring rapid organized team response)
- Severe localized trauma – major fracture, amputation

Australian Triage Scale Category 3 Trauma

- Moderately severe blood loss
- Moderate shortness of breath SAO_2 90–95%
- Head injury with short loss of consciousness (LOC) – now alert
- Moderately severe pain – any cause
- Moderate limb injury – deformity, severe laceration, crush
- Limb – altered sensation, acutely absent pulse
- Trauma – high-risk history with no other high-risk features

Australian Triage Scale Category 4 Trauma

- Mild hemorrhage
- Chest injury without rib pain or respiratory distress
- Minor head injury, no LOC

- Moderate pain, some risk features
  Minor limb trauma – sprained ankle, possible fracture, uncomplicated laceration

Australian Triage Scale Category 5 Trauma

- Minor wounds – small abrasions, minor lacerations (not requiring sutures)

Conclusions

In conclusion, the concept of triaging casualties according to their chance of survival is as viable now as when it was first developed in 1797. The allocation of casualties to color-coded groups is universal, despite some national and regional variations.

Courses such as the Major Incident Medical Management and Support (MIMMS) can ensure that a common language and philosophy is understood by all levels of responders.

Wars and disasters still stretch resources to the point that triage remains the only way of ensuring the best possible chance of survival for the greatest number of people.

In-hospital triage in multiple patient incidents is a continuation of what happens prehospital, while routine hospital triage in the emergency department aims to match staff and resources with the needs of all patients in a controlled fashion.

In the routine prehospital civilian context, field triage has been developed as the best way of saving as many trauma victims as possible, irrespective of their location, by broadening the sphere of available resources within a trauma system.

Indeed, trauma systems and trauma centers save lives [69,72]. The Decision Scheme is an essential component of the trauma system, guiding EMS providers in transporting injured patients to the most appropriate facility, ensuring proper treatment, and thus reducing death and disability.

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Damage Control in Surgery

29

D. Demetriades, K. Inaba, P. Talving

Introduction

Damage control surgery is considered by many surgeons as one of the most significant advances in the last 2 decades in the care of trauma or other surgical patients with severe hemorrhage, which cannot easily be controlled by other techniques. In the recent wars in Iraq and Afghanistan this approach has been used extensively and has been credited with saving many lives [1]. The present chapter reviews the history, indications, techniques, controversies, complications, and outcomes for damage control procedures.

Definition

Damage control is defined as the temporary control of bleeding or other injuries, in patients in poor physiological condition or in situations with very difficult surgical exposures. The definitive surgical repair or reconstruction is performed semi-electively after physiological stabilization of the patient and in an optimal environment. Damage control procedures were initially performed in abdominal operations but have been expanded to a wide range of trauma and nontrauma procedures in the neck, chest, soft tissues, peripheral vascular injuries, orthopedic injuries, and gynecological operations.

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History

The first documented damage control procedure was performed by Halsted in 1908 and involved intrahepatic packing control of severe bleeding from a major liver injury. The procedure remained ignored for many decades until the late 1970s when it was rediscovered and used as perihepatic, retroperitoneal, or pelvic packing for bleeding. It was given a major boost in 1993 [2] and gained widespread popularity in the 2000s. It has now become a standard technique in trauma and acute surgery involving the abdomen, the pelvis, chest, neck, neurotrauma, and long bones [3–5].

Incidence

The earlier indications for damage control were fairly strict and the technique was used in 2–5% of laparotomies for trauma. However, more recent studies reported a much higher incidence, with an average of 10% of patients undergoing laparotomy for trauma. In a recent prospective study of 900 laparotomies for traumatic injuries, 93 patients (10%) were managed with damage control techniques [6]. More specifically, in a review of 394 laparotomies for trauma in a modern level I trauma center, about 14% of laparotomies for blunt trauma, 13% of laparotomies for gunshot wounds, and 2% of laparotomies for stab wounds, were managed with damage control techniques. The use of damage control increases with the injury severity. About 25% of trauma laparotomies with injury severity score (ISS) >25 are managed with damage control. The reasons for the increased utilization of this approach include the higher numbers of trauma patients reaching the hospital alive because of shorter prehospital times (scoop and run) and increased awareness by surgeons about the benefits of damage control.

Indications and Timing for Damage Control

Damage control procedures should be considered in the following situations: (a) in patients "in extremis;" (b) in difficult surgical exposures of the bleeding area; (c) in suboptimal environments with limited resources, such as in combat fields or rural hospitals; and (d) when the surgeon is inexperienced with the required techniques.

(a) Patients "in extremis." This condition describes patients with exhausted physiological reserves, who are in imminent danger of irreversible shock and death. The patient in extremis is characterized by severe hypothermia, coagulopathy and metabolic acidosis.
   - Hypothermia in trauma is a common problem and affects up to two thirds of severe trauma patients. Most studies consider it as an ominous predictor of survival [7–9]. While hypothermia might be helpful in some elective operations

and might be protective to the brain, it has major adverse effects on thecardiovascular, respiratory, gastrointestinal, endocrine, and coagulation systems. Bleeding is the most common cause of death of potentially salvageabletrauma patients and hypothermia plays an important part in aggravating coagulopathy. Hypothermia related coagulopathy is caused by dysfunction of theclotting factors, platelets and fibrinolytic activity. At ≤34°C there is a clinically significant impairment of the coagulation system [10–12]. There aremany methods to prevent or correct hypothermia: Use of warm intravenousfluids, increase of the room temperature, use of warming devices, removal ofwet clothes, and cover exposed intestine with wet and warm packs. In caseswith an open chest or abdominal cavity there is an excellent opportunity forrapid rewarming with copious irrigation (8–10 liters) with hot normal saline.

- Metabolic acidosis complicates most multitrauma patients and has an adverse effect on the cardiac function and effective coagulation. At a pH of 7.1 there is significant inhibition of thrombin and fibrinogen generation and platelet-dysfunction [13, 14]. Such a low pH seems to have a worse effect on coagulation than hypothermia [13].
- Coagulopathy is a common cause of intraoperative or early postoperative death in patients with severe bleeding. There are numerous factors which con tribute to the development of this ominous complication, including severe head trauma, hypothermia, metabolic acidosis, multiple transfusions of old blood, and transfusion of large amounts of crystalloid solutions. Bleeding due to coagulopathy is impossible to control with conventional surgical techniques such as ligation or application of local hemostatic agents. Persistent attempts to control this bleeding with these techniques are futile and result in further deterioration and death.
- Damage control should be considered in the presence of the above conditions in order to stop and reverse the rapid physiological deterioration. On the basis of the available experimental and clinical studies it has been suggested that damage control should be initiated in the presence of hypothermia (<35°C), metabolic acidosis (pH<7.2, base deficit <-15 mmol/L in patients <55 years of age or <-6 mmol/L in patients >55 years of age or serum lactate >5 mmol/L), or coagulopathy (prothrombin time and/or partial thromboplas tin time >50% of normal).

(b) Bleeding from a complex injury can challenge the skills of even the most experienced surgeon and can result in rapid deterioration of the condition of the patient by aggravating hypothermia, acidosis, and coagulopathy. Attempts to achieve definitive repair of the injuries are usually futile and accelerate the patient's death. Examples of such injuries include severe liver or pancreaticoduodenal trauma, some types of retroperitoneal bleeding, and many vascular injuries. These conditions are excellent indications for damage control surgery, which involves temporary control of the bleeding by tight packing with gauze or shunting of an injured artery.

(c) Suboptimal environments turn even fairly moderate severity procedures into complex operations with high mortality. Limited resources, such as lack of a

well-stocked blood bank or inadequate equipment, should be considered as strong indications for damage control and transfer of the patient to a higher-level facility. Typical scenarios of such environments include battlefield or small rural hospitals.

(d) The experience of the operating surgeon with specific procedures is critical for the timely and appropriate definitive control of severe bleeding or completion of complex organ resections, such as major liver or pancreaticoduodenal resections. A surgeon with good judgment will institute damage control and ask for more specialized care by another team or at another facility.

In summary, a surgeon should consider early damage control, before the patient reaches an "extremis" condition. The indications for damage control should be individualized, taking into account the type of injury or surgery; the physiological condition, age, and comorbidities of the patient; the hospital facilities; and the experience of the surgical team. There is evidence that early damage control improves survival [15].

Stages of Damage Control Surgery

Damage control surgery is a three-stage approach:

Stage 1

The first step involves temporary control of bleeding by compression and/or packing with surgical gauze. A fast but careful evaluation is then performed to assess the extent and severity of injuries. The next step is to achieve definitive bleeding control with fairly easy surgical techniques, such as ligation or simple repairs of vascular injuries and suturing or removal of bleeding organs. Bleeding which is difficult to control by conventional surgical techniques should be managed by tight packing. At this stage, the surgeon in consultation with the anesthesiology team should evaluate the general condition of the patient (vital signs, physiological parameters such as temperature, pH, and coagulation status, and comorbid conditions) and decide about continuing the operation for definitive repair of the injuries or terminating the procedure. The termination of the procedure should be performed in an orderly fashion, making sure that no significant injuries are missed and that the packing effectively controls the hemorrhage. Under no circumstances should the operation be terminated if packing does not effectively control the bleeding. In these cases the packing should be removed, the area inspected again for any bleeders which can be ligated, and then the area is repacked. Missing associated significant injuries during a hasty exploration is not uncommon [15] and should be avoided because it increases mortality and serious complications.

In damage control laparotomies the abdominal wall should never be closed primarily because of the high risk for abdominal compartment syndrome [16,17]. Temporary abdominal closure can safely be achieved with a sterilized plastic sheet or any of the commercially available vacuum-assisted devices (Fig. 29.1).

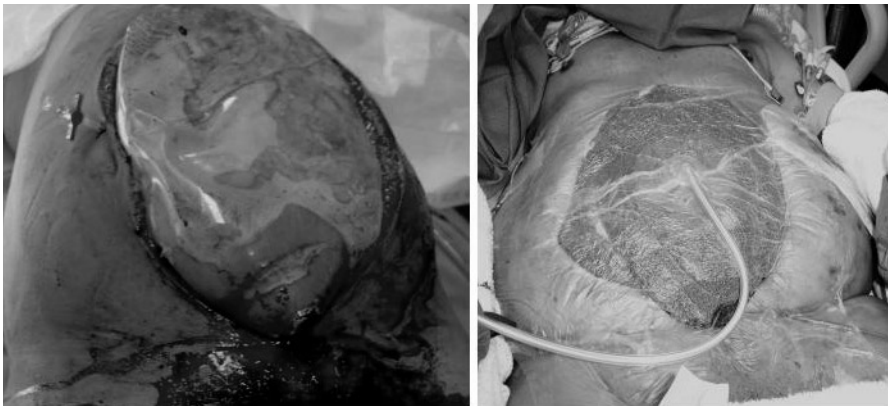

Fig. 29.1 Stage 1 of temporary abdominal wall closure with plastic sheet (*left*) or a vacuum-assisted dressing (*right*)

Stage 2

After completion of the damage control phase, the patient is transferred to the intensive care unit for resuscitation and stabilization. Some patients might benefit from angio-intervention and embolization of bleeders, especially from the liver or complex pelvic fractures. In these cases the resuscitation should be continued in the radiology suite by intensive care unit nurses and physicians. This move of the intensive care unit to the radiology suite is an essential component of angio-intervention in these critically ill patients. The second stage of damage control involves resuscitation and correction of the hypothermia, acidosis, and coagulopathy. The goals for resuscitation are shown in Table 29.1. This stage usually lasts for 24–48 h, but sometimes it might last longer because of severe cardiorespiratory failure. If during resuscitation there is evidence of severe active bleeding, such as hemodynamic instability, or continuous bleeding from the drains, the patient should be returned urgently to the operating room for re-exploration and repacking.

Tabella 29.1 Stage two of damage control – goals for resuscitation in the intensive care unit

Temperature >36°C
Hemodynamically stability
Correction of base deficit, normal lactic acid
Correction of coagulopathy
Prothrombin time <15 sec
Partial thromboplastin time <36 sec
Platelet count >50,000

Stage 3

The third stage of damage control takes place semi-electively, usually 24–48 h after the initial operation, when the patient returns to the operating room for removal of the packs and definitive repair of any injuries.

Damage Control in Specific Injuries

Neck

The most common indication for damage control in neck trauma or surgery is severe bleeding from difficult-to-access vascular injuries, such as the internal carotid artery near the base of the skull or vertebral artery injury in the bony vertebral canal. In these cases, tight packing or insertion of a balloon catheter often controls bleeding [18]. In some cases with penetrating trauma to the common or internal carotid artery, insertion of a temporary shunt secures continuous perfusion of the brain until stabilization of the patient and definitive repair of the vessel at a later stage.

Chest

Damage control is rarely indicated in chest trauma because of the inability to pack the lung. In cases with persistent bleeding from the lung, a nonanatomical resection provides the fastest and most effective way to control the hemorrhage. The most common condition which can benefit from tight packing and damage control is continuous bleeding from an open fracture of thoracic spine, usually due to a gunshot wound.

Abdomen

Abdominal trauma is the most common indication for damage control procedures. Deep suturing of the liver with tight packing is the most effective way to control bleeding from severe liver injuries, especially in the hands of surgeons with limited experience in hepatic resections. Balloon catheter tamponade combined with perihepatic packing may be effective in controlling bleeding from a deep tract in the liver after penetrating trauma [19,20]. Angio-embolization after perihepatic packing can be an excellent adjunct in damage control (Fig. 29.2). Diffuse retroperitoneal bleeding is the second most common indication for abdominal damage control. Bleeding from torn and retracted lumbar vessels or from an open lumbar spine fracture is very difficult to control by conventional surgical techniques and packing is the most effective way to manage these cases. Complex pancreaticoduodenal injuries, especially after penetrating trauma, are often associated with major vascular injuries and severe

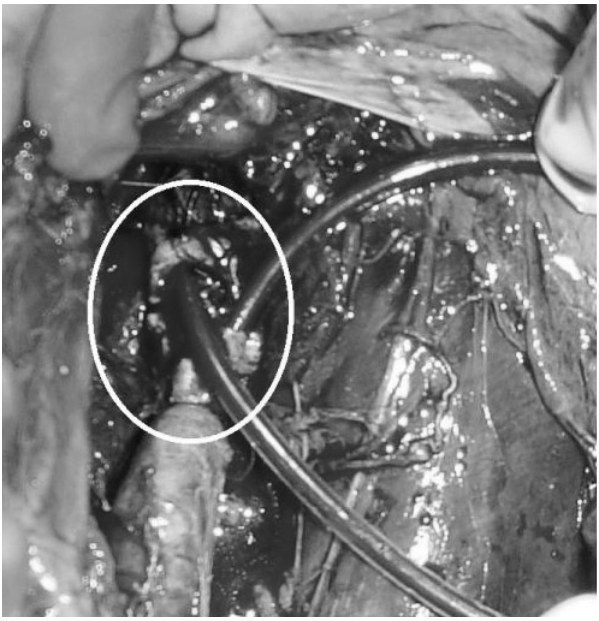

Fig. 29.2 Angio-embolization may be an important adjunct to damage control. Embolization of active liver bleeding after perihepatic packing for damage control

hemodynamic instability. In these circumstances a damage control procedure with packing and intestinal spillage control is the most appropriate approach. Definitive major resections and reconstruction may be performed semi-effectively after stabilization of the patient.

Vessels

Damage control for vascular injuries may be achieved by ligation of noncritical vessels or by temporary shunting. As a general rule, the vast majority of veins can safely be ligated without serious consequences. The only exceptions are the ligation of the superior vena cava, which is not compatible with life and ligation of the suprarenal inferior vena cava, which usually results in renal failure. Also ligation of the right renal vein results in the loss of the kidney.

Major arterial injuries which cannot be ligated may be managed with temporary shunting using any appropriate size tubing (Fig. 29.3). Definitive arterial reconstruction is performed semi-electively.

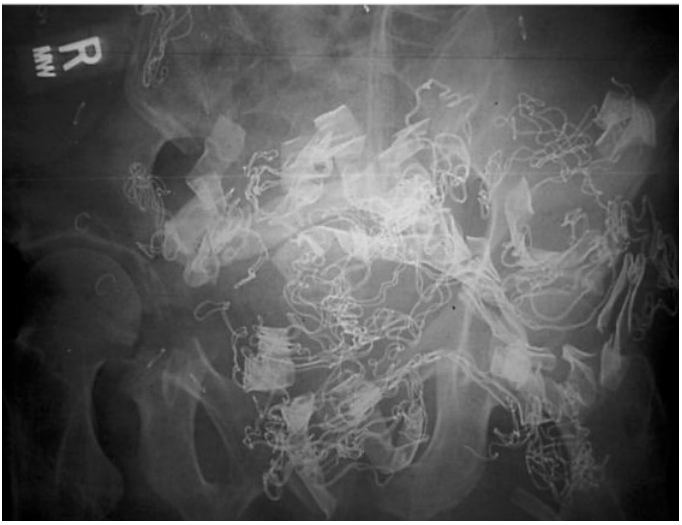

Fig. 29.3 Temporary tube stenting of a gunshot wound to the iliac artery as part of damage control

Orthopedic Injuries

The damage control concept has been expanded for complex orthopedic injuries, usually pelvic or long bone fractures. Bleeding from severe pelvic fractures can be life threatening. Angio-embolization is the most appropriate intervention, provided the patient is fairly stable. In the presence of major hemodynamic instability, damage control surgery with external pelvic fixation and pelvic packing, with or without bilateral internal iliac artery ligation, may be life saving [21] (Fig. 29.4).

Pitfalls of Damage Control

1. Pitfall: Delaying damage control until the patient becomes "in extremis."
   Correct response: Consider early damage control, on the basis of the type and severity of injury, the physiological condition, age and comorbid conditions of the patient and the experience of the surgeon and the medical center. "Packing" in desperation is unlikely to save the patient.
2. Pitfall: "Bail out" of the operating room even if the packing does not effectively control the bleeding.
   Correct response: If the packing does not control the bleeding do not leave the operating room. Remove the packing, look for surgical bleeders, repack the area.
3. Pitfall: Perform damage control in a hasty and disorganized manner.
   Correct response: The procedure should be done in an organized and controlled manner, ensuring that no surgical bleeding or other serious injuries are missed.

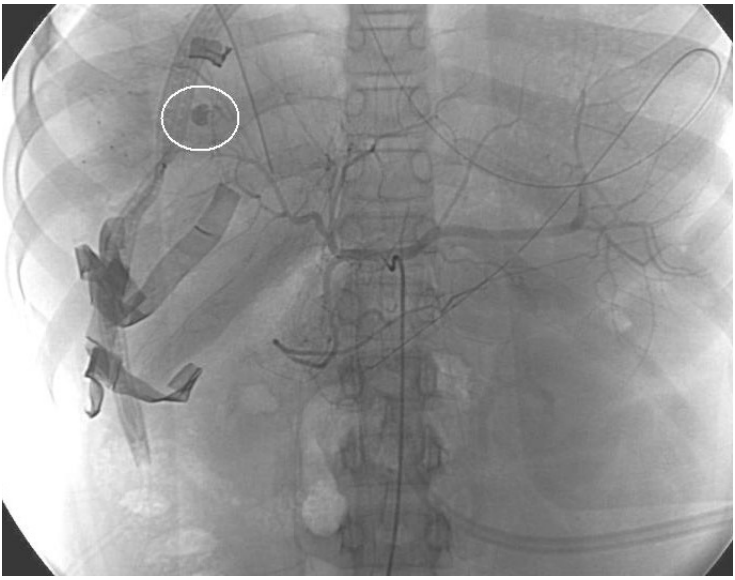

Fig. 29.4 Extensive pelvic packing for severe bleeding due to a complex pelvic fracture

4. Pitfall: Routine stapling off or ligation of an injured hollow viscus in the abdomen.
   Correct response: Try to repair the bowel whenever is possible. Stapling off or ligating the bowel creates a closed loop which aggravates bowel dilation and proximal bowel ischemia or even necrosis.
5. Pitfall: Failure to return to the operating room if the patient still bleeds during the resuscitation in the intensive care unit, in the second stage of damage control.
   Correct response: Continuous bleeding in the ICU without any evidence of improvement despite aggressive blood product resuscitation is an indication to return to the operating room for re-exploration. Often there is a surgical bleeding or repacking may be more effective.
6. Pitfall: Terminate an operation in the chest or abdomen as part of damage control in order to correct hypothermia.
   Correct response: An open body cavity provides an excellent opportunity to rewarm a hypothermic patient. Copious irrigation with hot fluids corrects hypothermia quickly and effectively.
7. Pitfall: Close the fascia or skin of a laparotomy after damage control in the abdomen.
   Correct response: Never close the fascia or skin following damage control; laparotomy is associated with a high incidence of abdominal compartment syndrome. Temporary abdominal wall closure with a prosthetic material is the appropriate approach.

Conclusions

Damage control in surgery, especially in trauma, has revolutionized the management of patients "in extremis" due to severe hemorrhage and has saved more lives than any other surgical technique in the last 2 decades. The procedure should be considered early, before the physiological decompensation of the patient. The decision for damage control should be made on the basis of the type and severity of injury, the physiological condition, age and comorbid conditions of the patient and the experience of the surgical team. It should be done in a controlled and organized manner, making sure that no surgical bleeding or other significant injuries are missed. Angio-intervention may be an excellent adjunct therapeutic modality in appropriate cases.

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Section X
Limited Resource, Disaster

Emergency Mass Critical Care

30

E.J. Jimenez

Introduction

At any moment regular television programming could be interrupted with news of the emergence of a new strain of infective agent, a major industrial accident, or a terrorist event. Many devastating events are widespread and naturally occurring, like hurricanes, in which we have ample warning time to enact preparation plans; while others, like earthquakes, volcanoes, or tsunamis may kill or injure thousands before the news reports hit the airwaves. Industrial accidents and terrorist events are usually sudden and occur without any warning. Any of these events may have a local or regional effect; some may even have a global impact [1]. Regardless of the cause, after such an event, large amounts of the populace will be seeking medical care, whether from their primary care providers, public health departments, or local hospitals.

As healthcare professionals it is our duty to be prepared for any of the above, to be able to provide the best possible care to our communities. This requires an awareness of the vulnerabilities of one's region, as well as on-going global surveillance. Development of a response plan is requisite for any hospital to have a significant expectation to be able to respond in a meaningful way to a sudden disaster that leaves large amounts of the population seeking emergency medical care. Preparedness plans include performing hazard-vulnerability analysis (HVA), coordinating of response plans with all potentially involved entities, reviewing results of routine drilling, and revising the plan based on results of practice. In order to prepare and plan accordingly for different possible scenarios that may overwhelm routine operations, it is essential to identify available resources, specifically people,

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materials, and physical locations – often referred to as; staff, stuff, and space [2].

Within this chapter we will focus our attention on the most important considerations for managing patient care within the hospital with an emphasis on critical care in response to a mass casualty incident (MCI), as we plan to expect the unexpected.

Definition

Disaster preparedness medicine focuses on preparation, response, surge, administration of resources, and recovery from events that generate demands that overwhelm the local medical community's capacity to deliver care.

Emergency mass critical care (EMCC) [3] is defined as the organization of critical care delivery when presented with situations manifested by increased – and for the most part – unexpected demand or surge. This results in a shortage of specialized staff, medical equipment, supplies, and available patient care areas. This lack of resources could actually limit the number of patients that can be treated while maintaining accepted standard of care interventions. When faced with an overwhelming demand for care that far outstrips the resources, in order to increase the chances of survival for the largest number of patients, only essential processes may be maintained during an MCI.

Considerations

Historically, disaster preparedness has concentrated on the management of multiple trauma casualties, generated by accidents, weather events, civil disturbances, or armed conflicts [4,5]. In these situations, the most severely injured frequently die on-scene, often before the arrival of first responders. Those that initially survive and are able to be transferred to hospitals usually have nonlife-threatening injuries during the initial period. However, many of the survivors may have prolonged hospitalizations and require critical care services due to the development of severe sepsis, acute lung injury (ALI), acute respiratory distress syndrome (ARDS) [6], or multiple organ dysfunction syndrome (MODS) [7–10]. This pattern forces us to realize that our disaster preparedness must include a focus on caring for the critically ill for a period of time well beyond the initial insult.

Critical care, in particular the provision of mechanical ventilation and hemodynamic support, becomes the mainstay of treatment when highly contagious or lethal biological agents are encountered, as in a pandemic influenza or a biological terrorist attack. It is also crucial when dealing with severe, life-threatening exposures to chemicals [11] or radiological agents that result in acute respiratory compromise and other severe organ dysfunctions.

In most instances, the ability to expand critical care capacity at any given time is limited. Hospital critical care units are often fully occupied, or do not have enough

staff to be at capacity, whether due to shortage or economic strategy. For this reason, when presented with an unexpected, large-volume surge in demand, the hospital census, and in particular lack of available critical care beds, can become a limiting factor for survival [12,13]. It is important to keep in mind that in these situations, the duration of surge demands on emergency departments may be several hours, while the critical care support required may last from days to weeks after the initial incident [14].

Throughout the world, public health departments and civil defense, antiterrorist, and military agencies have developed scenarios that focus on predicting the potential numbers of casualties. The USA's Center for Disease Control (CDC) has made software available for public access [15] (e.g., Flu Surge) that can help estimate the potential surge of different patients geographically. The majority of plausible events result in overwhelming numbers of critically ill patients who without critical care available to them will not survive [12].

Hospitals should have a pre-established organizational structure to be activated in emergency situations. In the USA and many other areas of the world, the Hospital Incident Command System (HICS) [16], initially developed in California, has been used for this purpose (see Fig. 30.1).

Planning and drills must contemplate a wide range of situations, with different degrees of social and institutional disruption. Basic plans should include response to an isolated or local event with an intact support infrastructure. Complex planning should anticipate response to a widespread disaster with loss of institutional and commercial facilities in an entire community or region. It is important to specifically determine anticipated needs and plans when large-scale events often disrupt access to external supply lines for both the hospital and the entire community.

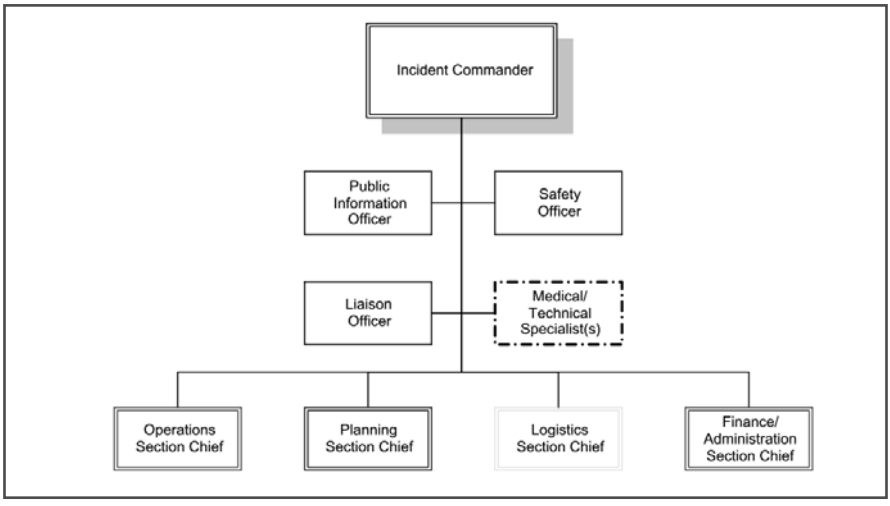

Fig. 30.1 Hospital Incident Command System (HICS) – Basic management structure. Distribution of authority and responsibility for primary management functions within HICS.

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Risk

Geographical, social, economic, and political factors are essential considerations when defining the risks for a given location. Completing an HVA tool, like the one suggested by Kaiser Permanente [17] or by the Joint Commission of the United States [18], can be useful in defining priorities. The HVA tool considers three major areas: Probability, Risk (or Impact), and Preparedness, and is presented in Appendix 1. The HVA should be based on an "all hazards approach," establishing an initial list of all possible disasters, regardless of their likelihood, geographic impact, or potential outcome. This list can be divided into typical categories that include natural, technological, and human events. The list will later be prioritized, taking into consideration the probability of occurrence, overall impact, current level of preparedness, and time requirements.

The probability of occurrence can be derived from historical records, statistics, and expert opinions. The impact of various events should also be evaluated as many can be ameliorated by sufficient back-up systems, i.e., generators for the loss of electrical power.

Some communities have specific seasonal disasters like hurricanes, tornadoes, floods, or wildfires. The dependence on technology and continued integrity of supply lines must be considered as well. The tool uses the qualitative terms of high, medium, low, or no probability of occurrence.

The potential risk or impact must be analyzed to include a variety of factors, listed as follows in order of importance:

- Threat to human life
- Threat to health and safety
- Property damage
- Systems failure
- Economic loss
- Loss of community trust/goodwill
- Legal ramifications

The HVA tool gives the highest score individually to the threat to human life, followed by the threat to health and safety. The remaining elements from the table: property damage, systems failure, economic loss, loss of community trust, and legal ramifications are all considered together when determining the level of risk.

An organization's preparedness plan(s) developed to manage any given disaster should also involve the input of community agencies, as healthcare facilities will not be responding to an emergency by themselves.

The coordination with the local emergency medical system and other hospitals is necessary, as planning for patient disposition should be determined before any event occurs. Police and fire departments are also very important, as security may need to be augmented. All plans need to be tested and studied in order to detect potential flaws. In the USA, the Joint Commission [19] requires for accreditation a minimum of 4 drills per year, two of them as tabletop exercises and the others with full simulation of casualties and hospital flows.

Once the HVA tool is completed, the factors are multiplied to give an overall total score for each hazard. i.e., a hazard with no probability of occurrence for a given organization is scored as zero, and will automatically result in a zero for the total score. This tool may help in a more objective prioritization of preparedness planning.

When preparing plans derived from the HVA keep in mind that there is no perfect plan to address every potential threat and all plans will need to be developed with a degree of flexibility to adjust, while still preserving a core structure. Also, there may be significant social issues affecting staffing as healthcare workers (HCWs) and support staff may not be able to come to work due to: community compromise, lack of transportation, illness of dependents or self, fear, closed schools, lack of basic utilities or food; they have essentially gone into a "family survival" mode. Planning should also address how to support the HCWs to facilitate them coming to work and also having their basic needs met.

Needs

It is of utmost importance to develop an EMCC Committee at your hospital, with representatives from all departments that will be involved in the response. The initial task of this committee is to complete an evaluation, with a "staff, stuff, and space" approach. Detailed inventories of equipment and their functional state, supply levels and their distribution should be completed and reviewed carefully. Hospitals should plan to maintain enough supplies and foodstuffs to be able to function for at least 10 days without any deliveries, to be prepared for an adequate response to a large-scale event that disrupts usual supply routes or community infrastructure. Coordination with external agencies may provide assistance in an organized regional response with better resource utilization, back-up systems, and "shared" costs when building inventories of equipment and supplies.

With the input of building engineers, floor plans should be analyzed to identify areas that could be potentially converted to Intensive Care Unit (ICU) wards, or isolation wards with improvised seals to generate negative pressure areas, via portable units or by reversal of ventilation systems. Personnel contact information and rosters should be maintained and updated regularly to ensure current contact information is available. Creative planning may include provision for child care or temporary schooling if there is discontinuation of community services (i.e., closed schools), to enable HCWs to work and have their basic needs met.

Recommendations

The following is a summary of recommendations for preparing a Disaster Preparedness plan and delivery of EMCC, based on the most recent publications from the American College of Chest Physicians Task Force [2] and the Fundamentals

of Disaster Management (FDM) [20] course of the Society of Critical Care Medicine, with emphasis in the Staff, Stuff, and Space orientation:

Staff

1. In any circumstance, and specially when facing a disaster, it is of utmost importance to maintain or, when necessary, enhance the protective measures of all HCW. Failure to do so may leave the institution in a situation with an excessive demand for resources and limited HCWs. The lack of available HCWs may be due to disease, injury, or fear of acquiring disease and exposing families and close contacts. Therefore, it is paramount that the HCW is reassured that their level of personal protective equipment (PPE) is more than adequate and that continuous surveillance, screening, and quality compliance programs have been implemented across the facility for their protection.
2. Staffing plans require careful consideration, as due to direct and indirect situations, their actual number may be lower than during routine operations, as the hospital faces an increased demand. Some key points include:
   - Decision making and patient management should be performed by the most experienced physicians, nurses, and ancillary personnel available, and within their scope of work.
   - Physicians and nurses without significant critical care experience may be reassigned to ICU areas following a tiered staffing organization (Fig. 30.2). Adequate ratios of supervision must be maintained with experienced personnel, utilizing clear guidelines and protocols. Previous basic training with courses like Fundamental Critical Care Support course (FCCS) [21] and FDM would facilitate this model.
3. Rationing of critical care should only be considered after all efforts at augmentation have been exceeded. The province of Ontario, Canada, after their experience during the Severe Acute Respiratory Syndrome (SARS) epidemic, developed a critical care/ventilator triage protocol based on the Sequential Organ Failure Assessment score (SOFA) [22] to be used in case of a pandemic, in view of the potential limitation in the number of ventilators. All decisions should follow well-defined, objective protocols using this score or similar approaches. All patients should receive basic care, including comfort and palliative support in extreme situations, even when the standard of care cannot be maintained.
4. Biological threats [24,25]:
   - Hospitals are high-risk areas for secondary spread of contagious diseases.
   - Hospitals should implement high-level PPE whenever an infectious agent is suspected, and adjust the level of protection, once the contagion is identified.
   - Agents transmitted by droplet may require higher precautions (i.e., airborne), when patients are subjected to high risk for aerosolization procedures or devices; these may include:
     - Noninvasive ventilators

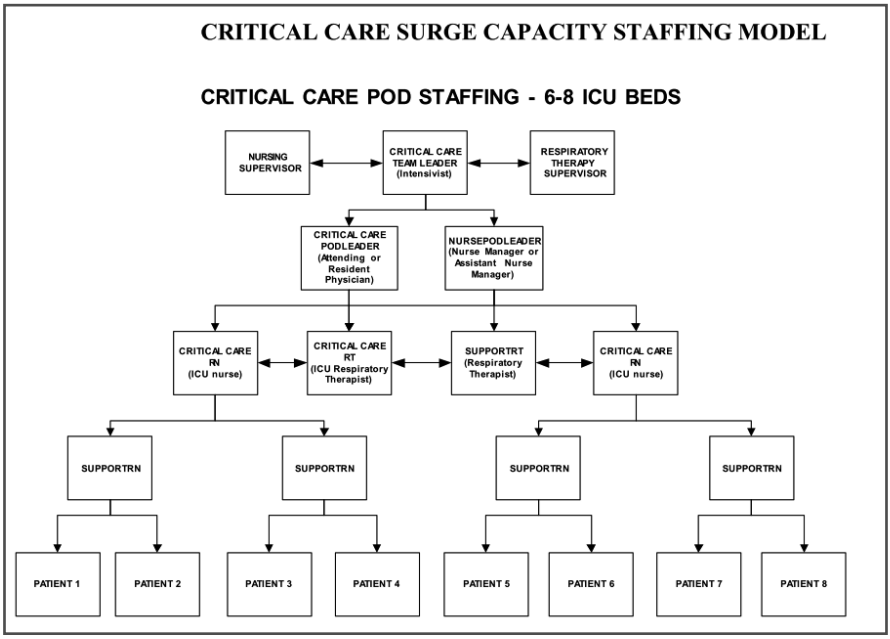

Fig. 30.2 Emergency Mass Critical Care – Example of Tiered Staffing Organization

- Endotracheal intubation
- Airway suctioning with an open circuit
- Bronchoscopy
- High flow oxygen masks
- Administration of nebulizers (i.e., bronchodilators)
- Chest tube insertion

5. Some of the CDC recommendations to don and doff PPE have been linked to an increased risk of contamination [26–28]. A summary of basic recommendations follows with modifications:
   - Strict hand hygiene and sanitation measures remain the primary interventions in decreasing the potential for transmission.
   - The PPE for routine care (no aerosolization procedures are expected) [23,24]:
     - Two layers of light, disposable, impervious gowns
     - Two layers of patient care gloves, taped longitudinally to facilitate removal as one piece with gown
     - Appropriate eye protection (regular eye glasses don't offer adequate protection)
     - N-95 mask (minimum grade)
     - Disposable surgical cap
     - Shoe covers (optional) or preferably, a nonporous, synthetic material shoe, that can be easily disinfected.
   - The highest level of airborne protection requires the use of a Powered Air Purifier Respirator (PAPR) (Fig. 30.3).

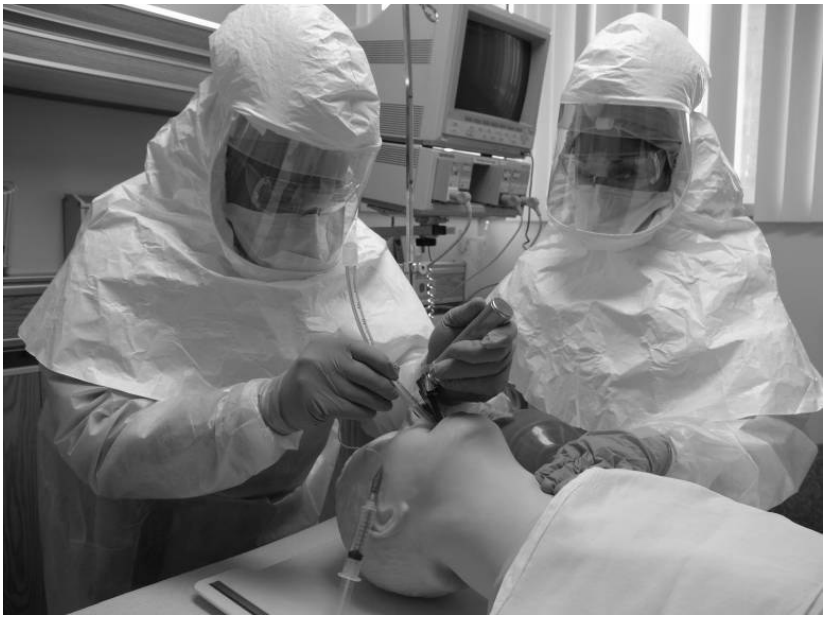

Fig. 30.3 PPE for high risk of aerosolization procedures – The team is using double layers and a PAPR for ICU use, during an intubation training session.

- PAPR for ICU use only protects against biological particles and cannot be used for decontamination procedures at the hospital's entrance, as they DO NOT offer protection for volatile chemicals. The infection control plan should clearly delineate criteria for isolation, quarantine, prophylaxis, and treatment.

6. Hospitals should prerecord instructions for personnel on a specific hotline, so they can better prepare themselves and their families for their interactions with the situation.

Stuff

7. In disaster situations, the EMCC should strive to still provide the following evidence-based, effective interventions [3]:
   - Mechanical ventilation
   - IV fluid resuscitation
   - Vasopressors
   - Antidotes and/or antimicrobials administration for specific diseases
   - Sedation and analgesia
   - Basic ICU measures:
     - Stress ulcer prophylaxis
     - Deep venous thrombosis prophylaxis

- Elevation of the head of bed to 30°
- Turning the patient routinely
- Oral care

• Renal replacement therapy
• Enteral nutrition

8. Mechanical ventilators utilized for surge response, should have the following characteristics [3,6,19]:
   • Capable of supporting pediatric and adult patients with conventional modes and deliver a PEEP of up to 20 cm H_2O
   • Have an internal compressor device that allows them to function without an external compressed air source and low-flow oxygen
   • Have alarms for: low minute volume, apnea, circuit disconnect, low gas source, low battery, and high peak airway pressures
   • Battery power for at least 4–6 h
   • Have high-efficiency filtering devices for exhaled gases, to prevent aerosolization of secretions into the environment, when dealing with a potential contagion
9. Pharmacy regulations should include clear tables and algorithms including dosing for all ages, adjustment for patients with renal and/or liver insufficiencies, substitutions, authorized prescribers, restrictions and, if authorized by health authorities, guidelines for medication shelf life extension.

Space

10. Facility protection is another crucial aspect of the response, including possible contaminations of physical spaces or systems (i.e., air handlers, water, food). Secured access may be the most important safety program during an incident, including perimeter definition and its maintenance with attention to strategic areas such as switchboards, medical gas depots, generators, and pharmacy. Enhanced security will help the facility maintain independence, as the facility may become the target of desperate community members if all other institutions in the locale have failed.
11. The plan should consider ideally a surge of up to 3 times the normal ICU census and 10-day self-sustainability [3].
12. The plan should have a graded response based on the potential size of the demand, from multiple casualty events to catastrophic situations, with clear delineation of interinstitutional coordination and participations.
13. Transfer agreements should be obtained with regional and extraregional facilities (Joint Commission requirement in the USA) [18] in situations where the hospital integrity and/or functionality are compromised.
14. The designation of resources should follow a prioritization scheme based on severity, available expertise at the site, and institutional surge capacity. The person performing TRIAGE should be experienced and follow objective guidelines with classification criteria and facilitate patient flow to predesignated surge areas

depending on level of support required and number of casualties.

15. Physical space used for delivery of EMCC should have the infrastructure to support expected critical interventions, such as mechanical ventilation (which requires a supply of medical gases), monitoring, and emergency generator-supported electricity. Areas of expansion may include elective procedure recovery wards in outpatient surgical centers, pre- and postangiography or cardiac catheterization units, and endoscopy suites.

Other suitable areas include mobile (i.e., tents or trailers) ICU facilities, and even veterinary hospitals. Many plans purposefully avoid delivering prolonged care in postanesthesia care units (crucial for the utilization of the operating rooms) and the ED, in order to maintain the functionality of these to departments as much as possible. Should more critical care space be required, consideration should be given to expand, sequentially, to intermediate or step-down care units, telemetry units, and eventually hospital wards. Other nonmedical facilities should be avoided, as they require significant repurposing for EMCC. They should be considered only in extreme circumstances on a temporary basis, when there has been a significant impairment of the hospital infrastructure.

General

16. Every hospital with critical care capabilities should have a plan to provide EMCC. This plan should be coordinated with local, regional, and national initiatives and entities.
17. The internal organization diagram for the implementation of the emergency plan should follow the HICS recommendations, including an Incident Commander and four sections: Operations, Planning, Logistics, and Finance (Fig. 30.1).
18. Hospitals should prerecord instructions on well-publicized hotline numbers, so the public at large, incoming patients and other inquirers can obtain guidance in accessing the facility or other information.
19. A web page can assist in posting information about unidentified patients or the deceased, as well as to provide instructions for HCW.
20. Coordination with local media (TV, radio, newspapers) to provide the public with instructions on how to access care in the community, as some health-care facilities may be designated to a specific type of ailment or severity. For example, hospital A may be designated the receiver for the event patients, while hospital B is accepting routine emergency care (i.e., a broken leg, dog bites, etc.)

Conclusions

Response to any MCI or disaster should be proportional to the event and objective and follow pre-established guidelines. Following an organizational structure similar to that of HICS, the plan should be implemented and carried out by the most experi-

enced personnel available (i.e., physicians, nurses administrators, facility engineers). If the amount of patients overwhelms the system to the point that critical care support needs to be rationed, clear, objective TRIAGE guidelines should be used and applied consistently [29]. These guidelines should be developed with ample consideration of the associated ethical, moral, and legal aspects addressing the potential inability to provide complex, aggressive care to all during an extreme EMCC implementation. Hospitals, physician, nurses, and legislators must work together to develop the necessary regulations and laws for their implementation.

"Previous preparation prevents poor performance." Any plan should be tested routinely with drills utilizing local and regional or national resources; it should be assessed, modified accordingly, and then retested in a continuous cycle. Only a complete and wide-spread understanding of the required response by all key participants will increase the probability of decreasing the potentially deleterious effects of an event. All preparations should have started yesterday.

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Natural Disaster

31

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Introduction

At 14:28 on May 12, 2008, an earthquake of 8.0 on the Richter Scale and a maximum intensity of 11 on Modified Mercalli Intensity Scale struck Wenchuan County in Szechuan Province in southwest China. As the most deadly and the strongest earthquake in China since the 1976 Tangshan earthquake, it led to 69,227 deaths, 375,783 injuries, and 17,923 people being reported missing [1].

This catastrophe represents only one example of the global suffering associated with natural disasters during the past decade. Apart from the Wenchuan Earthquake, Indian Ocean Tsunamis (2004), Hurricane Katrina (2005), and Kashmir Earthquake (2005) are also well known for the significant devastating effects on human life, which have rewritten the history of destructive natural disasters.

In response to all kinds of disasters, healthcare providers including critical care professionals are among those who arrive at the scene at the very beginning, help to rescue victims from the rubble, resuscitate the victims at the scene with limited resources, and evacuate the injured to nearby healthcare facilities, as well as treat the patients both physically and psychologically even years after the disasters. Therefore, preparedness is a prerequisite to attempts at nullifying the disaster's potential effects on human life and suffering.

In this article, we will briefly review the effect of major natural disasters, the challenge to disaster relief teams, and potential resolutions.

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Definition, Classification, and Epidemiology

Natural disaster is, as defined by Center for Research on the Epidemiology of Disasters (CRED), "a situation or event which overwhelms local capacity, necessitating a request to a national or international level for external assistance; an unforeseen and often sudden event that causes great damage, destruction and human suffering" (Table 31.1) [2]. However, the definition of "large-scale disaster" or "mass-casualty scenario" is variable [3].

In the past decade, the world has witnessed a steady increase in the reported natural disasters. In 2007, 414 natural disasters were reported, with 16,847 deaths, more than 211 million victims and over US $74.9 billion economic damages (Table 31.2).

Common natural disasters include, but are not limited to, earthquakes, volcanoes, floods, and storms, which are classified into 5 subgroups, which in turn cover 12 disaster types (Table 31.1) [2].

As we all know, floods are the most common natural disasters that affect developed and developing countries [4]. In the year of 2007 when no "mega disasters" were reported, both hydrological (mainly floods) and meteorological (mainly storms) disasters were the major contributors to the number of occurrences, mortality and/or casualties, and economic damages, which accounted for 80.7, 95.6, and 72.1% respectively of all the reported occurrences, people affected, and damages (Table 31.2).

Although an average of 120–130 countries are hit by any kind of natural disasters each year, the human impact remains extremely concentrated in a few countries, including China. For example, nine countries account for over 80% of earthquake fatalities (China, Japan, Pakistan, Chile, Russia, Turkey, Peru, Iran, and Italy) [5]. In 2007, the Chinese government reported the second highest number of disaster events (n = 20, after the USA), the third highest disaster mortality rate (n = 1,161, after

Table 31.1 Classification of natural disasters

Classification		Example
Biological		Epidemics Insect infestations Animal attacks
Geophysical		Earthquakes Volcanoes Dry mass movements
Hydrometerological	Climatological	Droughts Extreme temperatures Wildfires
	Hydrological	Floods Wet mass movements
	Meterological	Storms

Table 31.2 Natural disasters in 2007: occurrence, number of victims and damages. Data from [2]

Disaster	Occurrence	No. of Victims	Damages*	Comment
Geophysical	26	1,251,187	16,312	Earthquakes (20), volcanic eruptions (6)
Climatological	54	8,052,520	4,597.45	Extreme temperature events (25), wildfires (18), droughts (11)
Hydrological	229	177,932,428	24,517.07	Floods (219), wet mass movements (10)
Meteorological	105	23,980,280	29,558.74	Tropical cyclone disasters (64)
Total	414	211,216,415	74,985.26	

*in 2007 US $ Million

Bangladesh and India), the most people affected (n = 120,117,437), and the fourth highest economic damages (US $8,004,698, after Japan, UK, and the USA) in the world [2].

Moreover, China also suffers from other kinds of natural disasters [6, 7], including the well-known epidemics of severe acute respiratory syndrome (SARS) in 2003, which inevitably resulted in significant morbidity and mortality (Table 31.3). Even so, there is evidence that injury-related fatalities in China remain an important but largely under-recognized public health problem [8].

Injuries and Illness Related to Disasters

The epidemiology of disaster-related injuries and illness remains to be elucidated. However, it is self-explanatory that they are significantly associated with the type of natural disaster. Better understanding of the mechanism of disaster-related injuries will, no doubt, help to better predict the expected patient population after the disaster, which may result in better preparedness (both psychologically and materially) and, in turn, lead to early identification of high-risk patients, better medical care for the victims, and possibly better outcomes.

Partial or complete collapse of buildings during the earthquake is the major reason for most cases of trauma. It is estimated that 75% of earthquake-related fatalities are caused by the collapse of buildings that were not earthquake resistant, were built with inadequate materials, or were poorly constructed [5]. Although all kinds of injuries could be encountered by disaster medical responders, crush injuries and crush syndromes are the most common entities [5,9].

Zhang and his colleagues summarized a total of 1,723 patients admitted to three general hospitals in Szechuan, China within the initial 5 days after Wenchuan Earthquake [10]. They found that the most common injuries included the injuries of

Table 31.3 Natural disasters by type since 2003 in China

Event	Category	Time	Location	Victims	Deaths
SARS epidemics [6]	Biological	March–June, 2003	24 provinces	5,327	349
Streptococcus suis epidemics in human [7]	Biological	June–August, 2005	12 cities in Szechuan Province	204	38
Floods [2]	Hydrological	June–July, 2007	31 provinces	105,004,535	535
Wenchuan Earthquake* [1]	Geophysical	May, 2008	Wenchuan, Szechuan Province	45,546,065	69,227

SARS, Severe acute respiratory syndrome
*A total of 375,783 injuries and 17,923 missing were also reported

lower extremities (i.e., the knee, lower legs, ankle and foot) (36%), followed by head injuries (18%), and the injuries of upper extremities (i.e., shoulder and upper arm, elbow and forearm, wrist and hand) (13%), and multiple trauma (10%). Approximately 9% of adult admissions were above the age of 75.

A case-control study in West China Hospital, Szechuan Province reported that, in all 180 patients enrolled, extremity fracture (n = 89), trunk fracture (n = 62), thoracic injury (n = 26), severe traumatic brain injury (n = 17), and abdominal injury (n = 13) were the most common injuries. Complications included infection (n = 47), acute renal failure (n = 13), multiple system organ failure (n = 13), and crush syndrome (n = 8). In addition, amputation was performed in 14 patients [11].

Sever et al. summarized data from major earthquakes from 1988 to 2005, and concluded that the 9 earthquakes resulted in more than 217,000 deaths, more than 1,900 patients with crush syndrome, and more than 1,200 patients were treated with dialysis [9]. Based on the above statistics, we could deduce that there might be more than 760 patients with crush syndrome, and more than 480 patients to be treated with dialysis during Wenchuan Earthquake, which was described by the nephrologists as "renal disaster" [9,12].

It has been estimated that as many as 25% of hospitalized victims of earthquakes appear to be at risk for acute renal failure [9]. However, many factors may affect the prevalence of crush syndrome and/or acute renal failure after earthquakes, such as rescue ability [13], the time of disaster onset [14], the materials of the buildings (concrete vs. masonry vs. adobe) [15,16], and the severity and rapidity of building collapse [17]. For example, it was reported that the incidence of acute renal failure secondary to crush syndrome after the September 11, 2001, terrorist attack in New York City, was extremely low (only one case), in spite of more than 3,000 deaths. This was explained by the rapid collapse of the buildings, resulting in very few injured survivors [17]. Although this is not a natural disaster, it might have some implications for the disasters with similar mechanisms in the future.

On the contrary, floods and tsunamis may only cause few severe injuries. Most injuries are mild to moderate, such as extremity fractures, lacerations, and sprains [4]. Crush syndrome is rare seen, if any. For example, no cases of acute renal failure were reported, and the number of serious injuries was much lower than many emergency medical teams expected after the Southeast Asian tsunami in 2004, most likely because all victims who were crushed subsequently drowned [4,9].

Following Hurricane Andrew in 1992, a National Disaster Medical System (NDMS) Special Operations Response Team saw a total of 1,203 adult and 336 pediatric patients [18]. Only five injuries were directly caused by the hurricane; 285 injuries were sustained during the cleanup. After Tropical Storm Allison in Texas in 2001, D'Amore et al. reported that among 1,036 cases over 11 days, 507 were "general medicine," and 232 were "trauma," and only 16 operations were performed [19].

This is also true for Hurricane Katrina. Among 2,299 patients with complete medical records who were cared for in the Katrina Clinic run by the University of Mississippi Medical Center, 43% were triaged to the pharmacy unit only, 55% were triaged to the medical unit, and 2% received dental care [20]. Hypertension/cardiovascular diseases, diabetes, and new psychiatric conditions accounted for the three

most common medical problems, i.e., 56.9% of all visits [4], while cardiovascular medications accounted for 30.8% of all 4,902 onsite recorded prescriptions in the Katrina Clinic [20].

In addition, because of the mechanism of soft tissue and bone injuries as well as the exposure to potentially contaminated flood waters and crowded living conditions, infection is a significant risk. Necrotizing fasciitis and aspiration pneumonias (also called "tsunami lung") are not uncommon in individuals who were exposed to the deluge [21]. Moreover, tetanus, cholera, malaria, dengue fever, and tuberculosis have also been reported after floods and/or tsunamis [4].

All these data indicate that common illnesses are still most common, therefore, most of the care after floods and/or tsunamis is routine and provided to those whose source of care is destroyed or not accessible after the disasters [4].

Early identification of patient group at risk for death or complications may be helpful. Demographic characteristics associated with increased risk for death and injury among earthquake victims are extremes of age (over 60 years, or between 5 and 9 years of age), and chronic illness. Entrapment, the occupant's location within a building, the occupant's behavior during the earthquake, and time until rescue are factors impacting mortality and morbidity [5].

Wen et al. reported the result of a hospital-based case-control study including all 36 deaths in West China Hospital until October 11, 2008, and 144 controls matching for sex and age [11]. A conditional logistic regression analysis demonstrated that severe traumatic brain injury [odds ratio (OR) 253.3, 95% confidence interval (CI) 8.9 to 7208.6], multiple system organ failure (MSOF) (OR 87.8, 95% CI 3.9–1928.3), major underlying diseases (OR 14.9, 95% CI 1.9–119.0), and infection (OR 13.7, 95%CI 1.8–103.7) were independent risk factors associated with earthquake-related patient deaths. Moreover, case fatalities significantly increased with the number of risk factors.

As mentioned earlier, acute kidney injury (AKI) is the second most common cause of disaster-related death following traumatic injury [22]. Najafi and colleagues analyzed data from 1,441 hospitalized victims following the Bam Earthquake in 2003. A total of 94 patients (6.5%) developed AKI. Two decision rules were proposed to predict the development of AKI in earthquake victims. In the first decision rule, multivariate regression analysis had identified serum creatinine level on day 1 (≥177 μmol/L), lactate dehydrogenase (LDH) (≥2,000 IU/L) and serum uric acid levels (≥357 μmol/L) as the independent predictors for the development of AKI, with a sensitivity of 100% and specificity of 96.1%. The second rule was a formula for predicting serum creatinine level on day 3: {[0.45 x creatinine phosphokinase (IU/L)] + [2.5 x LDH (IU/L)] + [2,700 x potassium (mEq/L)] + [2,000 x uric acid (mg/dL)] - 14,000}/10,000. This formula had a sensitivity of 96.6% and a specificity of 95.7% [23].

Among 499 evacuees residing in American Red Cross shelters in Louisiana 2 weeks after landfall of Hurricane Katrina, more than one third (34.5%) arrived at the shelter with symptoms warranting immediate medical intervention, including dehydration (12.0%), dyspnea (11.5%), injury (9.4%), and chest pain (9.7%). Risk factors associated with presenting to shelters with acute symptoms included concurrent chronic disease with medication (OR 2.60, 95% CI 1.98–3.43), concurrent disease

and lacking medication (OR 2.22, 95% CI 1.36–3.63), and lacking health insurance (OR 1.83, 95% CI 1.10–3.02) [24].

All the above statistical models represent the great effort to early triage and manage the high-risk patient groups, with the use of only routine laboratory data readily available even with limited resources at the rescue scene [22].

Response to Natural Disasters: Focus on Critical Care Professionals

Similar to the ABCs of trauma care, disaster medical response includes basic elements common to all disasters. The mass casualty response to natural disasters (including earthquakes) is composed of the four essential elements of disaster medical response: (1) search and rescue; (2) triage and initial stabilization; (3) definitive medical care; and (4) evacuation [4].

Traditionally, critical care professionals are rarely involved in the initial phase of medical response to disasters, i.e., the search and rescue phase of victims. However, from our experience in SARS epidemics, *Streptococcus suis* epidemics in human, avian influenza, and Wenchuan Earthquake, the public were extremely anxious due to the vulnerability of the general population, high communicability of the disease, and high case fatality. As a result, intensivists were often convened by the healthcare authorities to be involved in patient management very early.

Since some important life-saving measures should be started on site before the patient is transported to medical facilities (e.g., aggressive fluid therapy to prevent crush-related acute renal failure), there is a critical need to educate both medical professionals and the paramedics about the expected disease entities and general principles of patient management [22].

All kinds of natural disasters often leave behind them significant infrastructure damages, with widespread power, transportation, water supply, telephone, and mobile phone outages lasting from days to more than 2 weeks [20,23,25], as in Hurricane Katrina on August 29, 2005. More important, hospitals in the immediate area may be nonfunctional, and further damages are possible due to aftershocks. Under these circumstances, the triage of mass casualties differs in many important ways from traditional triage in the hospital settings: the wide and scattered distribution of victims, the limited medical resources, the unpredictable time interval before available standard care, and difficulty of early evacuation [26].

A consensus statement by the Society of Critical Care Medicine Ethics Committee arbitrarily required that anyone deemed to have, with treatment, at least a 50% chance of survival should receive medical care [27]. However, for practical purposes, the on-site triage should be based on very simple rules, as outlined by Schultz and colleagues [26]. Does the patient begin to breathe spontaneously only after relief of upper airway obstruction? Is the patient tachypneic (defined as respiratory rate ≥30 breaths per minute)? Is radial pulse absent due to uncontrolled bleeding? Is there any sign that the patient could not follow commands? An answer of "Yes" to any of the above four questions indicates that the patient requires immedi-

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ate care, while an answer of "No" to the last three questions means that delayed care might be more appropriate. Cardiopulmonary resuscitation is generally not recommended in mass-casualty.

Appropriate triage is often followed by immediate resuscitation at the rescue scene, especially for victims under the rubble after an earthquake. One of the most important missions of the disaster relief team is to determine the functional status of local hospitals [9]. However, as mentioned above, hospitals in the affected area of a disaster either are heavily damaged or must be evacuated because of the possibility of collapse from aftershock in the case of an earthquake. At this time, a well-equipped and self-sustainable mobile hospital will be highly effective [28], but it is almost impossible in developing countries, including China. The concept of "portable" critical care borrowed from the US military service might be more realistic [29,30], although modifications according to available expertise and resources are necessary.

Definitive medical care at the rescue scene is not only very difficult, but also bears the difficulty of continuous logistic support, as the basic requirements such as self-sustainability for 72 h [4], and communications could not be met in most of the cases. Consequently, the decision of victim evacuation from affected areas is mandatory [9].

Quick and efficient evacuation of disaster victims often results in overwhelming patient inflow into hospitals in unaffected areas. It has been reported that in a mass-casualty earthquake, the greatest demand for patient care occurs during the first 24–48 h after the disaster [31]. For example, after the 1988 earthquake in Armenia, more than 97% of the 902 patients who eventually required hospitalization were admitted in the first 6 days after the temblor [32].

After the earthquake in Northridge, Los Angeles County in 1994, eight of 91 acute care hospitals (9%) were evacuated. Six hospitals evacuated 818 patients within 24 h, and the other two hospitals performed late evacuation due to structural damage [33]. Four out of these eight hospitals were ultimately condemned. Interestingly, another study by the same authors found that the peak ground acceleration, rather than the distance from the epicenter, is a superior indicator of the risk for hospital damage and evacuation. The result suggested that, when evacuating patients from affected areas, peak ground acceleration data should be obtained to guide disaster response [34].

Nevertheless, evacuation is not always so rapid. The Wenchuan Earthquake occurred in a rural and mountainous region in western Szechuan Province, about 80 km west-northwest of Chengdu [11]. Due to the widespread collapse of country roads, the transfer of thousands of severely injured victims were delayed, so that many were admitted to West China Hospital (WCH) up to 7 days after the earthquake. WCH is the largest state-level and general teaching hospital in the earthquake-affected area, with a total of 4,300 beds, including 135 ICU beds. After the earthquake, WCH treated 2,728 cases (872 in the emergency department, and 1,856 hospitalized) from the disaster area, but only less than 20% were transferred to WCH within 72 h after the earthquake [11].

The lag time before ICU admission was more significant. Out of the 142 ICU

admissions in WCH, only 3 cases were admitted within 72 h (Fig. 31.1). The number of earthquake victims remaining in the ICU did not reach a plateau until 3 weeks after the earthquake. As usual, the severity of these critically ill patients could be demonstrated by a mean APACHE II score of 20, as well as the intensity of supportive treatment (Fig. 31.2). During ICU stay, 42 patients developed Multiple Organ Dysfunction Syndrome (MODS). Among these patients with MODS, mechanical ventilation (n = 34, mean 9.2 days), vasopressors (n = 29, mean 5.2 days), and continuous renal replacement therapy (n = 19, mean 4.3 days) were the mainstay of supportive treatment.

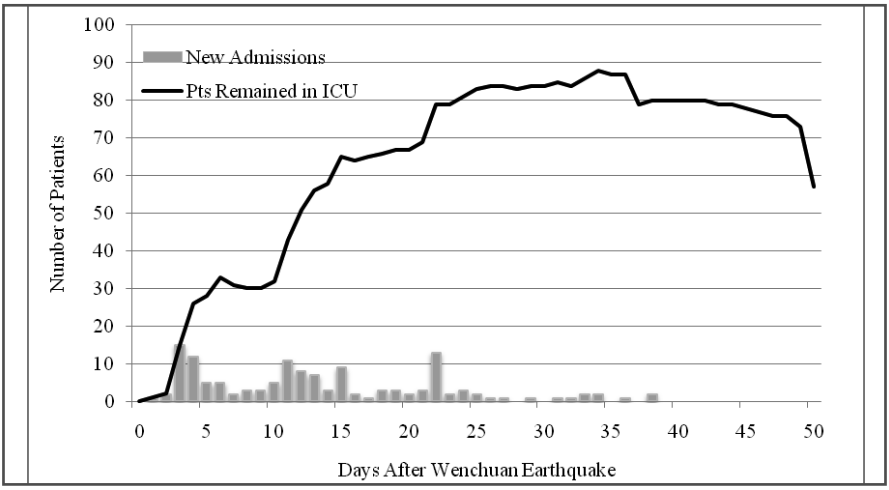

Fig. 31.1 Intensive care admission of victims of Wenchuan Earthquake in West China Hospital

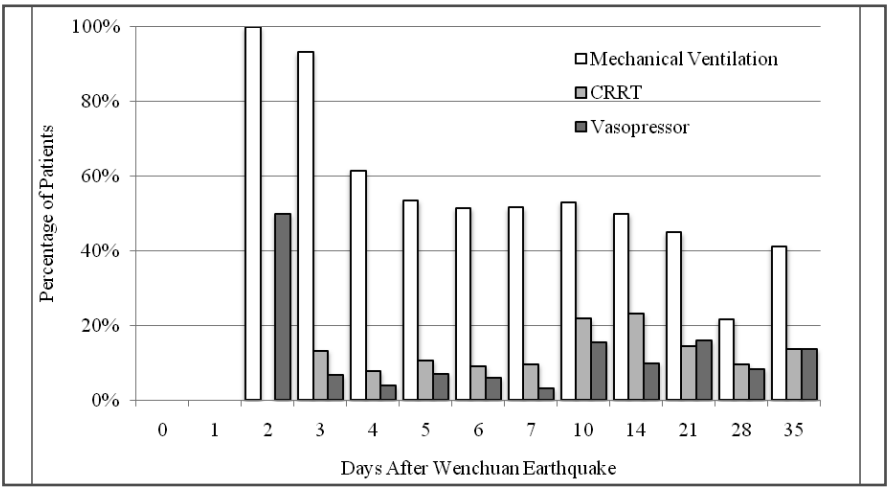

Fig. 31.2 Supportive treatment in victims of Wenchuan Earthquake during ICU stay

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All these facts indicate that critical care professionals in unaffected areas must be prepared with adequate resources to cope with a heavy clinical workload for quite a long period of time. First, there is always a need to expand ICU during mass casualty.

The Task Force for Mass Critical Care strongly recommended that "hospitals with ICUs should plan and prepare to provide emergency mass critical care every day of the response for a total critically ill patients census at least triple usual ICU capacity" [35]. However, for a variety of rationales, these critically ill patients may receive sophisticated and advanced modalities of care outside of a usual ICU setting, and often without the benefit of advanced physiologic and other monitoring that is routinely available in the ICU [29].

Anticipating the evolving medical needs (including drugs and equipment) of disaster victims may be very difficult but crucial in determining the extent of national and international help needed, despite the fact that medical supplies in response to a disaster are not always usable [9,20].

Lack of human resources is another important issue. Local medical personnel might be unavailable because of injury, transportation difficulties, the need to care for family members, and psychological stress [20]. It is very likely that critical care professionals from elsewhere will be ready to help, but such an influx may also have drawbacks. Unfamiliarity with anticipated disease entity, colleagues, working environment, and common practice may increase the workload and decrease the efficiency of both local teams and deployed support teams. Our solution during the Wenchuan Earthquake was to assign individual members of deployed support teams into the seven original teams in ICU of WCH.

The responsibility of "the foreign aid" was to assist the team leader running morning and afternoon rounds, to decide treatment plan for individual patients with the residents, to participate in case discussion and consultation with other specialties, to perform invasive procedures, as well as to provide education of knowledge and skills to the residents. However, a rapid response team might be a better example, in conjunction with noncritical care professionals as an effective strategy to extend ICU capabilities during a disaster [20].

Lastly, the professional task force may also play a key role in the management of the disaster. The Renal Disaster Relief Task Force (RDRTF) was established by the International Society of Nephrology (ISN) after the Armenian earthquake in 1988. The RDRTF is involved in material support, logistic support, and in sending medical personnel to help local staff in the disaster region. The RDRTF reportedly functioned well at earthquakes in Turkey in 1999, Iran in 2003, and Kashmir in 2005 [22]. Based on the above and other experiences, it is very important to set up a national critical care disaster relief team, whose capabilities were depicted by Farmer and his colleagues as follows [29]:

1. Be rapidly deployable (on-site within 12–24 h).
2. Provide "self-contained," comprehensive critical care capabilities for medical and postsurgical patients.
3. Be able to care for acute disorders or the decompensation of predetermined chronic medical conditions (chronic critical illness).
4. Be fully functional in a hospital, in an austere prehospital setting, or in an aircraft.

Conclusions

Natural disasters occur frequently worldwide, and often result in significant mortality and morbidity, as well as economic damage. Knowledge of the mechanisms of disaster-related injuries and illness is a prerequisite of an effective plan for medical response to mass-casualty disasters. The responsibility of critical care professionals during natural disasters is highly variable, and multifaceted. The coordination and integration of all available healthcare resources by critical care professionals may help improve medical care to the disaster victims.

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The Needs of Children in Natural or Manmade Disasters

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A.C. Argent, N. "Tex" Kissoon

Introduction

Disasters have been described as "events of sufficient scale, asset depletion, or numbers of victims to overwhelm medical resources" [1] or as "a serious disruption of the functioning of a community or a society causing widespread human, material, economic or environmental losses that exceed the ability of the affected community or society to cope using its own resources" [2]. Importantly, that definition goes on to state: "A disaster is a function of the risk process. It results from the combination of hazards, conditions of vulnerability and insufficient capacity or measures to reduce the potential negative consequences of risk."

Disasters may occur in many forms (Table 32.1); in different settings and levels of complexity; with variable amounts of warning and very different consequences for people. The number of natural disasters have increased in the last century and doubled within the last 30 years, with many more people affected. During the same period the proportion of disasters that are manmade has increased from 16.5% in the 1970s to 42% in the 1990s (not including "complex emergencies") [3]. As the density of population across the world increases (related both to population growth and increasing urbanization) it is likely that the frequency and impact of disasters will continue to increase. Climate change (with associated extreme weather conditions; change in regional weather and associated change in distribution of pathogens and vectors) is likely to exacerbate this trend.

Increasingly, plans are being put in place to cope with disasters [2]. Sadly, many of the most devastating disasters in recent times have taken place in poorer countries

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Table 32.1 Disasters and their causes

Causes	
Human	Mass shooting Terrorism War Genocide Building collapses Dam collapses (may be precipitated by severe weather conditions or earthquakes) causing flooding Fires Chemical, biological, radiological and nuclear contamination may occur both deliberately and accidentally
Infective processes	Pandemic infections (such as SARS and influenza, etc.)
Natural	Bush fires Wildfires
Extreme weather	Floods Blizzards Heat waves Hurricanes Tornadoes Cyclones Droughts and famines
Earth related	Earthquakes Volcanic eruptions Tsunamis
Geographical	Mud slides Gas eruptions Avalanches

with limited resources to plan for or recover from disasters. [4]. On the other hand, the international capacity to assist in these settings has substantially improved [2].

Children are at particular risk in nearly all forms of disasters; this is reflected in the excess pediatric mortality in events such as earthquakes and tsunamis. They are at risk for a multiplicity of reasons including: physiology and anatomy (Table 32.2); behavioral stages, organization of schools and educational facilities, pre-existing problems such as technological dependence or illness, and adult behavior. Their vulnerability is compounded by the limited capacity of most health systems to deal with increased numbers of children in need of acute care [5]. Moreover, while acute needs are important, longer-term public health problems are frequently far greater in magnitude and potential impact on health. As an example, in the recent earthquake in April 2009 in Italy, approximately 295 people were killed, 1,000 were injured, but

Table 32.2 Special needs of children

Anatomy and physiology	Consequences	Implications
Cardiovascular physiology		
Low blood volumes and limited cardiac reserve	More liable to: consequences of vomiting and diarrhea (either infective or chemical) Consequences of limited water availability	Need for oral rehydration resources
	More susceptible to dehydration and have limited reserve	Increased need for intravenous access and therapy
	Very limited reserve for blood loss	Need for rapid control of hemorrhage
Respiratory physiology		
High oxygen consumption	More vulnerable to airborne toxins (sarin or chlorine) or pathogens such as anthrax (in context of chemical or biological attack)	More services may be required. May need different gas masks and filters
Limited oxygen reserve High respiratory rate Breath gas at lower levels because of being smaller		
	Many toxic gases are heavier than air, so children are more exposed than adults In nuclear contamination, radioactive material may be at lower levels	Increased need for environmental ventilation and monitoring
	Higher susceptibility to CO poisoning	Increased care with heating and power sources after incident
Skin		
High surface area and permeability (particularly infants <6 months of age)	High absorbance of toxins (chemical and radioactive) that are absorbed via skin	Special needs for pediatric decontamination
Rapid heat loss	Rapid heat loss	Increased needs for warming and environmental control

Cont. ↓

Table 32.2 *Cont.*

Anatomy and physiology	Consequences	Implications
Relatively poor keratinization	More liable to abrasion, burns (thermal and chemical)	
Musculoskeletal Limited strength and speed	Limited capacity to escape from danger and harm	
Softer bone structure	Increased damage from falling masonry, etc. Different injuries to adults	Significant needs for pediatric orthopedic services. Equipment required for stabilization and treatment of fracture may be different
Nutrition Extremely limited nutritional resources (particularly in small infants)	Children cannot cope for long without food and water intake	Systems required to provide appropriate food supplements for children rapidly
Different nutritional needs to adults Require assistance with feeding		
Pharmacology Routes of administration of medication	Smaller children are not able to take tablets	Medication (e.g., required in nuclear event) must be available in form that can be taken in appropriate dosage by children
Susceptibility to toxins	Children may be more susceptible than adults to short-term toxins (e.g., organophosphates) as well as radioactivity	Increased attention to protection from toxins

Cont. ↓

Developmental and psychosocial issues Age and individual dependant	Limited capacity for self care in the aftermath of a disaster	Resources required for basic care and not just medical care
Children are often grouped in areas away from parents (schools, etc.) guardians	Small children may not be able to provide information about identity and place of origin	Systems must be in place to identify children and ensure that they are kept together with family or
	Psychological consequences of disaster will depend on age and development stage	Appropriate structures required to provide psychological and social support over a period of time
Remain vulnerable to dangers in the environment including abusive adults	May investigate dangerous items or areas as part of curiosity and ignorance	Need to address environmental safety post incident Protect from abusive adults
Infection control	Children will have limited immunization	In mass relocalization situations infectious disease interventions are required to prevent development of epidemics (including immunization programs)
Children with special needs	Dependency on technology which may be affected by the disaster	Range from nebulizers to ventilators

55,000 people were left homeless (http://earthquake.usgs.gov/eqcenter/eqarchives/significant/sig_2009.php). While there was a surge in demand for acute medical services, additional resources are required to meet the specific needs of children including: prevention of infectious diseases; creating safe environments; dealing with the psychosocial aftermath of the events, and recreating appropriate educational and training facilities.

Not only are children caught up in general disasters, but they are sometimes specifically involved in tragedies that affected institutions where large numbers of children were grouped together in schools (as happened in China in 2008). Some mass casualty events have even been specifically targeted at children. As reviewed by Rassin et al. [6] there have been a number of attacks that have specifically targeted schools and nursery schools across the world, resulting in significant mortality and morbidity among children at those institutions.

Although many disaster plans make provision for the care of vulnerable sectors of the population, relatively few plans are specifically geared for the needs of children and particularly for children across the full range of developmental stages. Unless those needs are specifically addressed in the planning for and organization of disaster relief, it is inevitable that children will suffer unnecessary harm.

The Particular Needs of Children

Some of the reasons for the vulnerability of children in disasters are outlined in Table 32.2. Children are vulnerable at virtually all phases of disasters, and it is important to highlight both their specific needs and the skills and resources that are required to fulfill those needs at various stages [7].

Death and Injury

In the acute phase of physical disasters such as tsunamis and earthquakes, children have been particularly vulnerable to death and injury. With limited strength and capacity to flee and/or find shelter from danger, mortality has been particularly high in young children in these events [8]. In a survey of mortality in the Aceh province of Indonesia following the 2005 tsunami, the age-specific mortality in the age-group of children 0–9 years was 19.8%, which was higher than all other age groups other than >70-year-olds. [8]. In eastern coastal areas of Sri Lanka, the mortality among children (during the same tsunami) aged less than 5 years was 31.8%, vs. 23.7% for children aged 5–9 years and 7.4% for adults aged 20–29 years ($p<0.001$) [9]. At a Red Cross Field Hospital in Kashmir in 2005, 145 (45.9%) of patients attending for emergency care were under the age of 14 [10].

In the 1985 gas explosion disaster in Bhopal children were particularly affected by gas inhalation, aggravated by the tendency of many toxic gases to gravitate to ground level. Children were also less able to use clothes or other methods to limit

their inhalation of toxic gases [11].

The pattern of injury suffered by children in physical disasters has also differed from those of adults. Commenting on their experience in Pakistan, Laverick et al. [12] noted that children often presented with scalp injuries and Le Fort facial fractures as if they had been looking up when the masonry began to fall on them, instead of protecting themselves by lying face down (as the adults did).

The care of children in acute disasters may be considerably complicated when parents have been killed or injured, or when children have been separated from their parents. Apart from the psychological trauma of separation, consent for procedures and ongoing care is also problematic [13].

Even after the acute phase of a disaster children remain more at risk for injury in the "damaged environment." Following Hurricane Katrina one team commented on the higher rates of injury for children saying: "The most common injuries in children were lacerations and punctures caused by debris. Several children were bitten by animals, many of which were stray pets with unknown rabies status. Many of the wounds were infected, likely because clean water and antibacterial ointment were unavailable. Cellulitis resulting from insect bites was also particularly common in children." [14].

Disasters Involving Chemical or Radioactive Contamination

Children may be particularly susceptible to injury from disasters involving chemical or radioactive contamination (Table 32.2). While rapid decontamination is ideal, decontamination of small children may pose challenges both to healthcare workers and to the children [15] and there are no existing tested and proven guidelines [16]. Children are also at higher risk of hypothermia (Table 32.2) and small children will require considerable assistance in the process of decontamination. As children may be accompanied by their parents, pediatric facilities should ideally have the resources to decontaminate accompanying parents [15].

Guidelines for chemical and radioactive material decontamination are available in many centers [17,18]; although some protocols have been suggested [16], there is a need for altered protocols that reflect pediatric needs [19]. Unfortunately, few centers are adequately equipped to decontaminate large groups of children in terms of facilities; appropriate washing environments to ensure adequate privacy, temperature control for small children, and adequate numbers of trained and equipped staff to decontaminate large numbers of small children [17]. This is particularly true in the developing world where industrial chemical accidents are probably more likely.

Infection

In general, children and especially infants are more susceptible to infection than adults. Thus children may be afflicted as part of a widespread infective process (possible influenza epidemic) but they may also develop infections in the environment that develops subsequent to a disaster. Ligon [20] and Watson have recently reviewed

Table 32.3 Phases in a disaster

Phase	Issues	Essential activities	Organization required
Planning	Recognition of the risk for disaster and the events which are more likely in that setting		Particular organization of children's services Organization of schools and children's institutions
Warning	Communication of situation to affected people	Safe evacuation of people	Transportation required for groups of children
		Maintenance of law and order in evacuated areas	Management of accommodation, with emphasis on ensuring safe accommodation for children . Communication systems to put children in contact with parents
Initial impact	The immediate consequences of the event with large numbers of injured people, people at risk of ongoing injury, limited resources available to intervene	Rescue, resuscitation, stabilization, and emergency care (for both physical injuries and psychiatric problems)	Needs assessment Establishment of control centers Establishing communication systems Management of "surge in pediatric medical services"
Secondary phase	Dealing with ongoing load of medical requirements.	Provision of "normal resources" such as clean water, power, warmth, shelter, etc. to large groups of people	Ongoing needs assessment
	Starting to stabilize the physical environment	Management of displaced people and animals Management of dead bodies (if at all possible attention should be paid to enabling private rather than mass burial)	Bringing available resources to the appropriate areas Provision of appropriate food for children of different ages

Cont. ↓

Table 31.3 *Cont.*

		Stabilization and securing of environment (unstable land, masonry, exposed electrical cables, gas leaks, water leaks) Provide ongoing medical care Establishment of law and order	
Subsequent phase with	Large groups of displaced people and problems of infection control and nutrition	Prevention of communicable disease (clean water provision, sewerage and waste disposal systems, immunization) Provision of food	Maintenance of supply chains Establishment of more sustained systems to stabilize the affected area Immunization programs for children
Rehabilitation phases	Dealing with the long-term consequences of the disaster in that community (much of the psychiatric and rehabilitation data in this section)	Economic redevelopment Social redevelopment Repair of infrastructure	Decisions regarding viability of restoration or alternative plans

the infectious diseases that may be problematic following disasters. Often the environment following a disaster may be highly contaminated (toxins, sewerage, dead bodies, etc.) with limited access to clean water and frequent overcrowding of survivors. In that context infections spread via hands are particularly frequent unless particular attention is paid to hand washing. Many survivors may have wounds, which again have risk of being contaminated, either during the incident or soon thereafter. Meticulous cleaning of wounds and debridement of devitalized and infected tissue is particularly important. This may be difficult to achieve with limited pediatric services.

Respiratory infections may be more frequent in conditions following disasters. Children may be particularly vulnerable to viral infections, and also to infections such as tuberculosis when crowding exists. Every effort must be made to ensure that patients with known tuberculosis receive ongoing therapy, and if possible are kept away from children.

Gastrointestinal infections (including hepatitis) are a particular problem in the context of limited water and sewerage disposal facilities. Children are particularly vulnerable to gastro-enteritis and attention must be paid to prevention and arranging oral rehydration facilities to resuscitate and treat children. Outbreaks of infections such as cholera [21], rotavirus [22,23], tetanus [24,25], malaria [26–28], typhoid [29], shigellosis, novovirus, leptospirosis, and others have all been documented following natural disasters [20].

Other pathogens that have been involved in outbreaks of disease include viruses including dengue [27], and malaria [26–28]. Rabies may be a problem in some parts of the world.

It is important to note that when people are grouped together into a high population density, a much higher level of immunization is required to prevent the development of epidemics [30]. Following the 2007 tsunami, spread of measles was documented in a population that had had 1 dose of vaccine following the tsunami [31].

Clearly early involvement of public health experts in the management of disaster aftermath is vitally important. A manual has been produced by the WHO to provide guidance for health care workers who may be called on to provide care for children in humanitarian disasters.

One of the issues that is often seen as a priority following disasters is the disposal of dead bodies. In fact these are not a major infection hazard, and it is likely that it would be better to try and allow families every opportunity to mourn and bury their dead, rather than to use mass graves [20].

Urgent and rapid epidemiological assessments by teams with pediatric expertise may be useful in disease prevention and treatment following disasters.

There is limited data available on the effect of respiratory viral pandemics on children [32]. However, experience from the SARS outbreak in Toronto in 2004 highlighted the need for extensive planning for infection control measures before the outbreak of an epidemic and management of epidemics involving children using a family-based approach [33]. Children are particularly vulnerable to adverse effects of isolation, and this may be a significant problem in management of other outbreaks [33]. In the case of SARS there seemed to be limited spread of the infection from

children to adults [34] but that may not be so in other pandemics. Schools and institutions for children may be also an important source of cross-infection in communities exposed to pandemic infections.

Environmental Dangers Exposure Following Disaster

Following disasters there may be an increased exposure to many toxins. Carbon monoxide poisoning has occurred on many occasions because of the means used to provide power and warmth [35].

Following Hurricane Katrina in the USA >200,000 people were rendered homeless and many were given temporary accommodation in mobile homes. Many of those homes were found to be contaminated with formaldehyde, and the management of related symptoms was complicated by the fact that the healthcare structure surrounding those in displaced housing was inadequate [36].

In many settings the post-disaster environment may have many dangers such as unstable masonry, exposed power and gas lines, contaminated soils and environments, etc. Children with their capacity for exploration and limited knowledge of potential dangers may be at substantial risk, particularly if adult supervision is compromised (as will usually be the case post disaster).

Effect of Conflicts

There is relatively little data available that compares the rates of mortality following conflicts with baseline data. Guha-Sapir and Gijsbert reviewed data from 37 available datasets, and showed that there were considerable differences in mortality rates for children following conflicts [37]. In most cases the rates or death increased sharply, although there were other situations in which mortality rates dropped, largely related to populations who were displaced as a result of the conflicts.

Complex Disasters

In mass displacements (usually as a consequence of war or civil strife) children under 5 have often had the highest mortality. In these situations "Complex emergencies" defined as "relatively acute situations affecting large civilian populations, usually involving a combination of war or civil strife, food shortages and population displacement, resulting in significant excess mortality" [38] may occur. Essentially these disasters combine many of the individual components of issues described above.

During the 1980s the mortality of children aged 1–14 in areas such as northern Ethiopia (in 1985) and Southern Sudan (1988) were extremely high [38]. In the 1990s crude death rates in refugees in some parts of Africa were 5–25 times higher than the crude death rates of the nondisplaced (with rates of up to 80 times described

[39], and the rates were highest in children under 5 years of age [40]) leading Toole et al. to state that "Children under the age of 5 regularly bear the brunt of the death toll associated with complex emergencies" [41]. Likewise in 1996, 54% of all the deaths among refugees from Rwanda and Burundi who fled to eastern Zaire were under the age of 5 [42]. A recent publication [43,44] has reviewed much of the data. One of the problems quoted is that much data is in "gray data" which is not readily available to the greater audience.

Children are also affected by the patterns of adult mortality. In many settings such as the Indonesia tsunami three women died for each man [45], and as most child care is provided by women, their children would have been adversely affected.

Fortunately much has been learned about the management of complex disasters [46], and there is hope that future events will provide better care for children. The issues of relief work in complex disasters are extremely complex and challenging to all concerned.

Psychological Concerns

There is a large body of evidence documenting the psychological problems of children who have been exposed to disaster situations [47–49] which has been recently reviewed [50–53].

Specific and focused care is required from the time of the disaster onwards to ameliorate the long-term psychological problems for children affected by disasters [54]. Particular attention needs to be focused on the family [55].

Penrose et al. have recently highlighted the importance of involving children in the process of planning for disaster, as well in the recovery phases following events. Children can offer useful knowledge and information, and it is deeply in their interests to feel part of the processes that surround actual and potential disasters. "The children consulted have clear ideas about the information, knowledge, and skills that they and their communities need to be better prepared for future disasters; all we have to do is listen." [56]. The same authors have raised many issues surrounding children's rights in disasters and ways in which they can be addressed [56].

It is also important to bear in mind that dealing with child victims of disasters or mass casualty events can be extremely demanding and emotionally devastating for healthcare and rescue workers [57,58]. Specific steps must be taken to provide support to these people both during and after the events.

Resources for Care of Children in Disasters

In any disaster, there may be direct (e.g., injury related to the earthquake), or indirect consequences (e.g., subsequent epidemics) which may be physical or psychosocial in nature [30] (or both).

Not only are children more likely to suffer injury in physical disasters, the facil-

ities available for their care are likely to be more limited than would be the case for adults. The special needs of injured children include: a range of equipment sizes; personnel with special expertise in dealing with children; increased nursing requirements post intervention, etc.

Particular insight into the needs of children and the availability of specific pediatric resources will be required by any team coordinating both planning for and response to any disaster in which significant numbers of children are involved [1,14,59,60].

Facilities

Even within well-resourced areas children's services in general have extremely limited capacity to deal with a surge and there are limited alternatives [61]. Recent reviews considered options for surge management for adult patients, but did not include children [62–64]. Although up to 45% of the population in developing countries may be pediatric, there are usually far fewer pediatric services than there are adult services.

In the USA about 37% of hospitals have both emergency departments and separate hospital wards with specific facilities for children, while 10% do not admit children [65,66]. Only 5.5% had all the equipment recommended for emergency care for children, while about 50% had 85% of the equipment suggested in the 2001 guidelines [67]. Thus capacity to accommodate a large surge of pediatric patients may be limited, even in countries as well-resourced as the USA.

Kanter and Moran [68] have reviewed the adequacy of pediatric beds in New York City for mass casualty purposes. The current bed numbers could accommodate approximately 250 children per 1 million population assuming no surge in current demand and that all beds were available. Even if there were reductions in the intensity of care to allow 20% more admissions, it would not be possible to accommodate more than 300 children per million population and more than 63 children per million in PICU even if the standards of care were altered to allow quadruple the usual throughput. Disaster situations involving 500 children per million and with 30% requiring intensive care would almost always exceed PICU capacity. To further compound the situation 55% of all PICU capacity was located in four hospitals. The WHO has recently launched a campaign aimed at ensuring that health facilities remain safe during and after disasters "Health facilities are only truly safe from disasters when they are accessible and functioning, at maximum capacity, immediately after a hazard strikes." (http://www.who.int/hac/techguidance/safehospitals/en/index.html) (Safe hospitals document) and this is of particular relevance to pediatric facilities.

There is frequently a "surge" in demand for injury care shortly after the onset of the disaster. At a teaching hospital in Sri Lanka for instance there was a 50% increase in admissions on the day of the 2005 tsunami (with 89% injuries). The rate of admissions for injury remained high for the next week [69]. However, the ongoing need for additional care may be high, particularly in the setting of burns (or other injuries

requiring multiple surgical procedures or investigations) or children requiring intensive care. Thus the surge may be sustained, and is always superimposed on existing service requirements.

Fortunately, there are few reports of disasters overwhelming the capacity of children's hospitals. However during the Hurricane Katrina disaster in New Orleans, it was necessary to move significant numbers of critically ill children and neonates away from affected areas to other hospitals. Patients requiring transportation included those affected directly by the hurricane, but also those who were in neonatal and pediatric wards and critical care areas at the time of the event [70]. This may be much more challenging or even impossible in other contexts.

It may be necessary to provide accommodation for parents and caretakers at the health facility where the children are being cared for. This may be particularly important when the surrounding environment is significantly affected by the disaster [71].

Following the early phase of a disaster shortage of healthcare facilities for children (if facilities have been damaged during the acute incident) may remain a significant problem for a long period unless there is focused rehabilitation of pediatric services. Even provision of accommodation and health care for relatively well (but displaced) children may be a problem [59].

Equipment

The equipment required for the care of children (and particularly small children and infants) is different from that required for adults. In a study of preparedness of pediatric disaster assistance teams, Mace and Bern reviewed the availability of pediatric resources. Pediatric equipment was missing as follows: airway, 16%; intravenous lines, 37%; cervical collars, 38%; medicines, 38%; Broselow tape, 46%; backboards, 62%. Pediatric patients were included in disaster drills 63% of the time [72]. A review of emergency departments in the USA again showed significant deficiencies in availability of pediatric equipment [65].

Recommendations to ensure the availability of pediatric equipment include appropriate stocking of pediatric emergency departments [67], some stockpiling in pediatric practice offices [1], or the collection of pediatric equipment in international relief equipment collections.

The majority of injuries requiring early treatment will be orthopedic and hence there is a major need for orthopedic devices which may be short supply, particularly in the countries affected [73]. This was also expressed by Laverick et al. with regard to their experience following the Pakistani earthquake [12]. Experience has shown that there may be many spinal cord injuries [74,75] after earthquakes.

Provision of Food and Pharmaceutical Supplies

Children have different food and pharmaceutical requirements than adults. For small infants, breast feeding remains the most important source of nutrition and should be

encouraged if at all possible. A study from Pondicherry following the 2005 tsunami showed that breastfed infants who were given formula feeds had a threefold higher incidence of diarrhea [76].

Noji et al. [77] have commented on the challenges of providing appropriate medication, immunization resources, and nutritional support for children following disasters. Extensive recommendations relating to these problems are available from the WHO [2].

Personnel and Organizational Structures

Pediatric expertise is required at many stages of the management of a disaster involving significant numbers of children [60,78]. This ranges from triage systems at the point of first contact with the injured children, through emergency and intensive care services, to ongoing medical and rehabilitative care. Expertise is also required at different levels in the organization of relief efforts from management of the casualties, management of evacuation and transportation, allocation of resources, and management of overall relief organization.

Personnel

The number of people within rescue and health care services who are trained and experienced in the care of children may be extremely limited. Mace and Bern [72] reviewed the capacity of disaster medical assistance teams in the USA to respond to pediatric emergencies and found major deficiencies in the training curriculum with pediatric topics such as trauma, disaster triage, burns, pain management, and mental health missing in 33, 36, 42, 42, and 45% of the time, respectively.

Data from emergency units in Israel showed that the staff were significantly less well prepared to cope with pediatric mass casualties than with adults [6].

There is a need to involve pediatric trained personnel in the disaster management process [14] at all levels. However, those personnel are unlikely to be of significant assistance unless they have gone through some training [79] as the skills required in an acute disaster are very different to normal pediatric practice.

Processes

Management of large groups of patients requires multiple levels and command structures.

At the point of first patient contact, and subsequently in the hospital services, there is a need for triage systems. Triage systems used for adults may overestimate the severity of injury of children [60], and not be a problem when small numbers of children are involved. However, when large numbers of children are affected it is important that pediatric triage systems be used. A number of systems have been

devised including the Pediatric Triage Tape, Simple Triage and Rapid Treatment (START), JumpSTART, and Careflight systems. JumpSTART was the only system available to 32% of disaster medical assistance teams in the USA [72]. However, when application of the systems was assessed in a South African emergency department the Careflight system had the highest specificity and sensitivity with similar performance from the Pediatric Triage Tape. The JumpSTART and START systems did not function well [80].

Weiner et al. [14], within the context of disaster relief for Hurricane Katrina, have clearly described the role that pediatric subspecialty teams within the national disaster management system can play. The teams that were deployed had been trained specifically prior to that event, and had prepared for the possibility of a hurricane affecting New Orleans.

Pediatric Planning for Disasters

A recent survey of emergency medical systems in the USA showed that although 72.9% of agencies had mass casualty plans in place, only 13.3% reported having specific pediatric mass casualty plans [81].

Planning for the needs of children is complicated by a number of factors. Children are not a homogeneous group of people. Children of different ages and developmental stages have very different needs (infant foods vs. adult nutrition), capacity to respond to situations (adolescents vs. infants), vulnerability to infection (infants vs. adolescents), needs for parental care, etc. There are also children with specific needs, and in the richer parts of the world there is an ever-growing population of children who are dependant on technology such as home ventilators.

Some disasters are completely unexpected, and detailed planning to deal with such events is impossible. However, many disasters are predictable and with increasing access to geological, meteorological, and other data across the world, many regions will have increased capacity to consider and plan for disasters. While it may be impossible to make adequate plans for events such as the Kashmir earthquake in 2005 in which some 86,000 people were killed and 80,000 injured [82,83], there are many other disasters for which appropriate planning can and should be made. In many cases children are included under the category of "vulnerable people," and specific plans are not made to deal with the needs of children. Improving pediatric emergency care needs should be at the forefront of every disaster planner's agenda [19].

Appropriate disaster planning should include: measures to reduce the injury during possible disasters, organization of emergency and pre-hospital services to deal with emergencies, plans for utilization of health services and utilities such as hospitals and intensive care units, and contingency plans to provide accommodation and resources to support both the rescue efforts and the ongoing needs of displaced people

In the 2008 Sichuan earthquake, which is reported to have killed some 90,000 people, the Chinese government has reported that 5,335 children died when school buildings collapsed on them (http://www.timesonline.co.uk/tol/news/world/asia/article6239476.ece accessed 2nd June 2009). Appropriate building standards for institu-

tions in areas at risk for seismic events could reduce death toll, even though it could be argued that the devastation was related to the force of that particular earthquake.

In 2007 Rassin et al. [6] found that in Israel, despite well-developed plans for mass casualty events, there were "no epidemiologic data concerning children affected by MCEs in Israel and no unique recommendations to enable the Ministry of Health to prepare for coping with such pediatric casualties." Shirm et al. [81] have completed a recent survey of emergency departments across the USA showing that about 50% have not met with schools or child care agencies to discuss the care of children in the event of a mass casualty.

The role of adults who are in charge of children such as teachers, nurses, and caregivers should be defined. Particular responsibilities of organizations that care for large groups of children whose needs will differ depending on the age group and the particular characteristics of the children at that institution – e.g., special schools and hospitals – should beaddressed. In addition, plans should be developed to deal with children whose caregivers are missing. A crucial part of pediatric planning for disasters is comprehensive involvement of the communities that may be affected [84].

Disaster planning can take place at many different levels within the community, both national and international. To some extent the level of planning is also affected by the relative size of the likely disaster.

Planning of disaster management processes and structures should incorporate schools and educational facilities. Incorporation of pediatric health services in planning may include the utilization of both public and private resources and the designation of some adult hospitals as alternative centers for pediatric care.

Planning is constrained by the resources available, and if health care resources are already inadequate or are functioning at the limits of capacity, then it may not be possible to plan for large disasters in any meaningful way. It is in this scenario that the international community may have a role in developing resources with which to assist in the amelioration of disasters across the world.

With regard to organization of responses to emergencies, a common theme is that there needs to be centralized control centers that monitor and keep processes in action. A deep concern is that the people and systems that are put in this position are fully competent to deal with children's issues. These concerns arise from the recognition of the following:

1. It is often relatively easy to get resources (often the wrong ones) in the short term, but much more difficult over a longer period of time.
2. The need to get the correct resources, and not what the people in other countries want to give.
3. The need to work out how to deal with "excess resources" and make sure that these are not actually sources of development of ongoing crime and corruption.

Training Courses

Olness et al. [85] have described their experience of establishing and running training courses for health professionals in management of children's needs in disasters

and emergencies. The training course is based on the extensive experience of faculty who have worked in emergencies across the world on many occasions. Some of the topics to be covered in the course include: definition and overview of disasters; the international humanitarian disaster response system; rapid epidemiological assessment; triage; malnutrition; renal emergencies for children in disasters; water, shelter, and sanitation; logistics and resource management; personal preparedness; infectious diseases and immunization; and the psychosocial issues for children who suffer disasters.

However there is considerable evidence of major deficiencies in the training programs for staff who may be required to care for pediatric mass casualties [72].

The AAP (all the websites related to disasters) the WHO (website-based materials), and other organizations have put significant emphasis on involvement of families in preparation for disasters [1].

Ethics Related to Children in Disasters

A number of authors have considered the principles of resource allocation in the context of mass disasters [86–88]. One of the underlying problems from a critical care perspective is that many intensive care systems are currently operating at 98% of capacity [88]. There is also data suggesting that the capacity to upscale intensive care facilities for adults (even with a gradual onset disaster) would be maximum at 30%. It is likely that the potential to increase pediatric intensive care beds to cope with mass casualties may be substantially less that that.

Essentially it is likely that in most countries of the world there would be limited capacity within the health systems to deal with a significant surge in demand for acute services for children. In most developing countries there is simply no capacity at present to deal with the current demand, and in both situations we will have to work out how to provide the best possible care to the affected children.

While some general principles appear to be recognized for the triage of adult patients [86,88–97], there is very little published material on the allocation of scarce resources for children in the context of mass casualties or disasters [80,98]. The tenets of the accountability for reasonableness [99–102] may be useful in working through this process.

As it is simply not tenable for clinicians involved in disaster care to make these decisions on their own, there is an urgent need for communities across the world to consider and discuss the possible approaches to allocation of scarce clinical resources in disasters in their region. This may be relatively straightforward within countries, but becomes extremely problematic in the context of disasters in countries where foreign healthcare workers are brought in as part of the response to the emergency.

Dealing with the Long-term Consequences

The long-term consequences of disasters may affect every level of society; however, there is a specific need to address the health care needs of people who have either been displaced or severely affected by the disaster. In many cases healthcare services will be curtailed in the disaster and these need to be rebuilt and redeveloped in a configuration that is appropriate to the new context. In addition, development of those services must take into the account the health consequences of the disaster which may operate over a range of time scales. Particular attention may need to be paid to the ongoing development of mental health services.

In the Bhopal gas tragedy in 1985, it was estimated that the death toll 1 week after the event was approximately 2,500, by the end of 1989 the mortality was estimated to be 3,598, and by the end of 1994 the numbers were approximately 6,000. By 2001 it was estimated that disaster-related deaths may have been between 15,000 and 20,000 [11]. Thus the systems required for health effects may need long-term commitment.

Conclusions

In summary, planning must address the unique needs of children (immediate and long-term) the context of the likely disaster, and the resources available. Planning should involve clinicians, health planners, the public, and children. Protocols and processes should be devised a priori and should be transparent, taking into consideration the ethical principles of fairness and equitable care.

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Suggested resources

CDC http://www.bt.cdc.gov/disasters/

Children and disasters. Website related to the American Academy of Pediatrics. http://www.aap.org/disasters/index.cfm (accessed 2nd June 2009)

Federal emergency management agency website for children. http://www.fema.gov/kids/ (accessed 2nd June 2009)

http://www.health.state.ny.us/facilities/hospital/emergency_preparedness/guideline_for_hospitals/section_14/psychosocial.htm (accessed 2nd June 2009)

Safe Hospitals Bibliography http://safehospitals.info/index.php?option=com_newsfeeds&task=view&feedid=11&Itemid=198 (accessed 3rd June 2009)

The Youngest victims: disaster preparedness to meet children's needs. http://www.aap.org/disasters/pdf/Youngest-Victims-Final.pdf (accessed 2nd June 2009)

WHO Health Action in Crises http://www.who.int/hac/en/ (accessed 3rd June 2009)

Section XI
Special Clinical Conditions

The Neuroendocrine Response to Sepsis 33

D. Annane

Introduction

Acute response to LPS includes the release of a number of proinflammatory mediators that reach the brain in areas free of blood-brain barrier, or via specific transport systems. The hypothalamic-pituitary axis is also activated via neural routes. Then, infection is characterized by high circulating levels of adrenocorticotrope hormone (ACTH), and cortisol which remain in plateau as long as the stressful condition is maintained. Circulating vasopressin levels follow a biphasic response with high concentrations, followed by relative vasopressin insufficiency in about one third of cases. Early response to sepsis is characterized by decreased serum T3 and increased rT3 levels. Serum T4 levels decrease within 24 to 48 h, and thyroid-stimulating (TSH) levels remain normal, and have no more circadian rhythm. Prolonged sepsis is associated with centrally induced hypothyroidism. In the initial response to sepsis, growth hormone levels are high with attenuated oscillatory activity and low insulin-like growth factor (IGF)-1 levels. Later on, growth hormone (GH) secretion shows a reduced pulsatil fraction, and correlates with low circulating levels of IGF-1. Exposure to endotoxin caused prompt increase in circulating adrenaline and noradrenaline concentrations. Catecholamines have a very short half-life and are metabolized through captation, enzymatic inactivation, or renal excretion. Plasma catecholamines levels remain elevated in plateau up to few months after recovery. Insulin levels rapidly increased following LPS as a result of both increased secretion and tissue resistance. The clinical consequences of the stress system activation include behavioral changes, cardiovascular, metabolic and immune adaptations. The use of exogenous hormones in critical illness has become a standard of care.

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Hypotension can be corrected by administration of catecholamines, and these drugs are routinely administered in the intensive care unit (ICU). Vasopressin can help improve cardiovascular function in vasodilatory shock. There is enough evidence supporting the benefit of corticosteroids or insulin critical illness morbidity, and their benefit on survival remains controversial.

During critical illness, the stressors are multiple and include emotional and physical stress resulting both from an acute aggression such as trauma or infection and various therapeutic or diagnostic interventions such as surgery, arterial or venous catheterization, laryngeal intubation and mechanical ventilation, and drugs. It is also paramount to recognize that stress is sustained at a certain level of intensity for several days with additive and unpredictable surges. Thus, the host has to adapt his response to counteract a prolonged stress while still remaining able to adjust to the unpredictable surges of stress. Therefore, it is needless to say that the integrity and flexibility of host response to these stressors is essential to survive critical illness.

It is now recognized that the "stress system" has two main components: the corticotropin-releasing hormone/vasopressin neurons of the hypothalamus and the Locus Coeruleus noradrenaline/autonomic neurons of the brain stem [1]. We will summarize recent knowledge on how immune molecules such as interleukin or nitric oxide signal the brain to generate both neurological and hormonal responses aimed at turning down the immune system when the inflammatory response is no longer needed to fight off an infection for example.

Physiology of the Endocrine Response

Two pathways are used by the organism for interorgan communication, the central nervous system and its peripherals arms, and the endocrine system [1]. Nowadays, in the vertebrates the endocrine organs include anterior and posterior pituitary, ovary and testis, adrenal cortex and medulla, thyroids and parathyroids, islets of Langerhans in the pancreas, and various parts of the intestinal mucosa. The pineal and thymus can also be considered as endocrine organs. In addition, other organs may have some endocrine properties. For example, the kidney secretes renin and angiotensin; the heart secretes natriuretic factors. The main known hormones are listed in Table 33.1. Basically hormones are divided into steroids (cholesterol derived proteins), peptides, and amines (Table 33.1).

Physiological Control of the Endocrine System

There is probably no uniform mechanism for the regulation of hormone activity. For example, there is no evidence that parathormone is released upon nervous stimulation or action of a specific trophic hormone, in contrast to the thyroid, adrenals, and gonads. We will focus on the main hormones involved in response to stress, i.e.,

Table 33.1. List of hormones

Hormones	Organ	Carrier in blood streal	Target tissues	Main actions
Insulin	Pancreas: α cells of the islets of Langerhans	Free	Liver, muscle, fat	Decrease blood glucose level Decreased gluconeogenesis, proteinolysis, lipolysis Increased fatty acid and glycogen synthesis
Glucagon	Pancreas: α cells of the islets of Langerhans	Free	Liver	Increase blood glucose level by increasing glycogenolysis and gluconeogenesis
Somatostatin	Hypothalamus cells and Δ cells of pancreas, intestine, stomach	Free	Pancreas	Suppress gastro intestinal hormones secretion Inhibits insulin and glucagon secretion Inhibits GH and TSH release
Thrombopoietin	Liver, kidney, striated muscle, stromal cells of the bone marrow	Free	Bone marrow	Regulates the differentiation of megakaryocytes and platelets
Angiotensinogen	Liver	Free	Plasma	Release of aldosterone Vasoconstriction
Insulin Growth Factor	Liver	IGF-binding proteins	Muscle, cartilage, bone, liver, kidney, nerves, skin and lungs	Regulate cell proliferation and apoptosis
Triiodothyronine (T3)	Thyroid	Thyroxine-binding globulin (TBG 70%)	Whole body	General increase in metabolic rate Promote growth

Cont. →

Table 33.1 *Cont.*

Hormones	Organ	Carrier in blood streal	Target tissues	Main actions
		Thyroxine-binding prealbumin (TBPA 10-15%) Albumin (15-20%)		Metabolic effects: stimulates carbohydrate metabolism, fat metabolism ; decreases cholsterol, phospholipids and triglycerides plasma levels
Thyroxine (T4)	Thyroid			Prohormone for the active T3
Calcitonin		Free	Intestines, bone, kidney, central nervous system	Reduces blood calcium levels Vitamine D regulation and bone mineral metabolism Satiety
Adrenocorticotropin hormone (ACTH)	Anterior pituitary	Free	Adrenal cortex	Production of glucorticoids and mineralcorticoids
Luteinizing hormone (LH)		Free	In females, granulosa cells and theca cells In males, leydig cells of the testis	*Reproduction:* • In females, it triggers ovulation and maintains luteal function during the first two weeks of menstruation • In males, it increases testosterone production
Follicle stimulating hormone FSH		Free	In females, graafian cells In males, Sertoli cells of the testes	*Reproduction:* • In females, it initiates follicular growth

				• In males, it enhances androgen-binding protein and acts in the spermatogenesis
Thyroid-stimulating hormone (TSH)		Free	Thyroid gland	Secretion of thyroxine (T4) and triiodothyronine (T3)
Growth hormone (GH)		Free	Liver, chondrocytes, and whole body	Anabolic hormone: promotes lipolysis, increases protein synthesis, reduces liver uptake of glucose Height growth in childhood Increases calcium retention and increases bone mineralization Stimulates the immune system
Prolactin		Free	Mammary glands	Stimulates lactation
Oxytocin	Posterior pituitary	Free	Brain , mammary gland, myometrium, endometrium, kidney, heart	*Peripheral actions:* • Letdown reflex in lactating • Uterine contraction • Reduces diurese and stimulates sodium excretion • Embryonal development of heart *Brain actions:* • Sexual arousal • Social behavior • Maternal behavior • Increases trust and reduces fear

Cont. →

Table 33.1 *Cont.*

Hormones	Organ	Carrier in blood streal	Target tissues	Main actions
Antidiuretic hormone (ADH)	Posterior pituitary	Free	Vessels, liver, pituitary gland, kidney, brain	*Peripheral actions:* • V1a: vasoconstriction, gluconeo genesis, platelet aggregation and release of factor VIII and von Willebrand factor • V1b: ACTH secretion • V2: water reabsorption in the collecting ducts *Brain actions:* • Memory formation • Response to stress
Cortisol	Adrenal cortex	Corticosteroid-binding globulin (CBG 90%) Albumin Free (about 4%)	Liver, vessels, immune system, hippocampus…	*Metabolic properties:* • Enhances hepatic gluconeogenesis and glycogenolysis • Induces peripheric insuline resistance • Induces free-faty acids and amino-acids release *Cardiovascular properties:* • Maintenance of vascular tone • Maintenance of endothelial and vascular permeability Anti-inflammatory and immuno-suppressive actions

Aldosterone		Free	Collecting dusts of the kidney	Reabsorption of sodium and excretion of potassium H+ secretion
Estrogens	Ovary, placenta	Free	Uterus, coagulation system, liver, gastrointestinal tract	Promote the development of female secondary sex characteristics Regulation of the menstrual cycle Thickening of the endometrium Others: lipid metabolism, protein synthesis, fluid balance
Progesterone		Free	Endometrium, vaginal epithelium, brain, smooth muscle, immune system, thyroid, skeleton	Reproduction Neurosteroid: involved in myelinization, synaptic functioning
Testosterone	Testes of males and ovaries of females	Sex hormone binding globulin (SHBG)	In males	*Anabolic effects:* • Growth of muscle mass • Increased bone density and maturation *Virilizing effects:* • Maturation of sex organs • Development of male secondary sex characteristics
Parathormone	Parathyroid	Free	Skeleton, gastrointestinal tract, kidney	Increases blood calcium concentration in three ways: • Enhancing calcium release from the bones • Enhancing calcium reabsorption from renal tubules

Cont. →

Table 33.1 *Cont.*

Hormones	Organ	Carrier in blood streal	Target tissues	Main actions
				• Enhancing clacium absorption in the intestine
Human chorionic gonadotrophin HCG	Placenta	Free	Uterus	Maintains the corpus luteum and progesterone production during pregnancy
Atrial natriuretic peptide (ANP)/ Brain natriuretic peptide (BNP)	Atrial myocytes of the heart	Free	Kidney, vessels, adrenal, adipose tissue	Reduction in blood volume, central venous pressure, cardiac output, arterial blood pressure Increases renal sodium secretion and excretion Increases lipolysis
Melatonin	Pineal gland, retina, gastro intestinal tract	Free	Brain	Circadian rythms Antioxidant Immune system: increases T cell response
Renin	Kidney	Free	Plasma	Activates the Renin-Angiotensin-Aldosterone system by cleaving angiotensinogen to angiotensin 1
Calcitriol	Kidney	Free	Intestinal epithelium	Increases calcium absorption from the gastrointestinal tract

steroids, catecholamines, and vasopressin. There are two main mechanisms of regulation of the endocrine activity: feedback loops and neural control. Experiments in which peripheral glands are disconnected from the pituitary showed full cessation of gonad function whereas the thyroid and adrenal cortex continues to secrete hormones at a lower level depicting their intrinsic activity. Similarly, the anterior pituitary has an intrinsic activity specific to thyroid and adrenal cortex function.

The feedback mechanisms allow circulating hormones from the target organs as well as from the anterior hypophysis to down- or upregulate the release of hypothalamic molecules. The feedback loop involves also central nervous structures such as the hippocampus. This self-balancing system stabilizes the endocrine activity under resting conditions but is insufficient in case of enhanced endocrine activity [1]. Then, the hypothalamus plays a key role in the regulation of these hormones. First, it is directly connected to the neurohypophysis and the adrenal medulla. Second, it modulates the anterior pituitary function by releasing, in synchronous pulses (roughly hourly), stimulatory or inhibitory hormones in the hypophysial portal vessels of the pituitary stalk. Stimulatory peptides include corticotropin-releasing hormone (CRH), LH-releasing hormone (LHRH), FSH-releasing factor (FSHRF), GH-releasing factor (GHRH), prolactin (PRL) stimulating factor and thyrotropin-releasing hormone (TRH). Other peptides are inhibiting factors like GH-inhibiting hormone (somatostatin) and PRL-inhibiting hormone. Vasopressin, natriuretic peptides, and catecholamines also influence the pituitary function. The effect of CRH on ACTH release by the pituitary is permissive and vasopressin acts in synergy with CRH. There are tight interconnections between CRH-synthesizing neurons from the parvocellular nuclei and the Locus Coeruleus in the brain stem [1]. Thereby, noradrenaline, CRH, and vasopressin can stimulate each other. Through collateral fibers, ultra-short negative feedback loops allow permanent adaptation of the synergy between the two systems. Finally, CRH, vasopressin, and noradrenaline are on the stimulatory control of the serotoninergic, cholinergic, and histaminergic systems and are inhibited by the gamma amino butyric acid, benzodiazepine, and opioids systems [1].

Potential Mechanisms of Regulation of the Endocrine Activity During Critical Illness

Critical illness is a condition involving multiple stressors of both emotional and physical types. The unpredictable nature, duration, and intensity of these stressors render the host response more problematic. Acute inflammatory responses to LPS include the release of a number of mediators such as tumor necrosis (TNF) alpha, interleukin (IL)-1, IL-6, IL-8, nitric oxide, macrophage migration inhibiting factors (MIF), and high mobility group box (HMGB)-1 [2]. These mediators reach the hypophysial portal capillaries in the median eminence via the anterior hypophysial arteries. Cytokines can diffuse into the pituitary as these areas are free of blood-brain barrier [3]. Then, they are carried to the hypothalamus and the brain areas lacking a blood-brain barrier (circumventricular organs), or via specific transport systems [3].

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In addition to the blood-borne cytokines, glial cells can produce a number of cytokines such as IL-1, IL-2, and IL-6 [4]. Interestingly, i.p. injection of LPS induces IL-1b followed by inducible NO synthase (iNOS) mRNA within 2 h, peaking in 4–6 h and then returning to basal values by 24 h [3]. The induction of IL-1b and iNOS occurred in this study in the meninges, areas lacking a blood-brain barrier, and also in the parvocellular nuclei and the arcuate nucleus, which contain the hypothalamic-releasing and inhibiting hormone producing neurons. Thus, it is likely that delayed overexpression of NO through iNOS activation prolongs the synthesis of hypothalamic hormones induced by LPS [3]. In addition, cytokines via activation of GABAergic neurons block NO-induced LHRH but not FSH release, inhibit GHRH release, and stimulate somatostatin and prolactin release [3].

Various afferent neurons of the peripheral system sense the threat at the inflammatory sites and stimulate the noradrenergic system and the hypothalamus [1]. Activation of vagal afferent fibers by LPS results in activation of the Locus Coeruleus which neurons have projections that synapse on cholinergic interneurons in the parvocellular nucleus [1]. It has been shown that CRH is released upon acetylcholine stimulation of muscarinic receptor, and that this effect is prevented by non-specific NO antagonists [5].

Endocrine Activity During Critical Illness

Infection, LPS challenge, major surgery, trauma, or burns elicit very similar patterns of pituitary hormone secretion. Plasma ACTH and prolactin increase within a few minutes following the insult and are associated with a rapid inhibition of LH and TSH but not FSH secretion. Growth hormone secretion is also stimulated in humans.

Hypothalamic Pituitary Adrenal Axis

Acute stress induced an immediate increase in the amplitude of hypothalamic hormones pulses, mainly CRH and vasopressin, resulting in increased amplitude and frequency of ACTH and cortisol pulses, and the loss of the circadian rhythm [1]. The common feature is characterized by high circulating levels of ACTH and cortisol, which remain in plateau as long as the stressful condition is maintained. However, circulating levels of cortisol depend on both synthesis and clearance and do not strictly reflect the HPA axis function. Thus, they vary from <5 μg/dl to more than 100 μg/dl [6].

Vasopressin

Circulating vasopressin levels are regulated through various stimuli including changes in blood volume or blood pressure and plasma osmolality, cytokines, and other mediators. In sepsis, vasopressin levels in plasma may follow a biphasic

response with initially high concentrations, followed by a decline in concentrations down to the limits of normal range within 72 h with relative vasopressin insufficiency as a consequence of NO-induced neuronal loss [7].

The Hypothalamic-Pituitary Thyroid Axis

Low T3–T4 syndrome has been described for more than 20 years in fasting conditions and in a wide variety of diseases (e.g., sepsis, surgery, myocardial infarction, transplantation, heart, renal, hepatic failure, cancers, malnutrition, inflammatory diseases) and is also called euthyroid-sick syndrome or nonthyroidal-illness syndrome (NTIS) [8]. In the early phase of stress, there is a decrease in serum tri-iodothyronine (T3) level, an increase in rT3 level, then serum thyroxine (T4) levels decrease within 24 to 48 h, and TSH levels remain within normal range and show no more circadian rhythm. Underlying mechanisms include (1) decreased conversion of T4 and T3 in extrathyroid tissues due to inhibition of the hepatic 5'-monodeiodination, (2) presence of transport protein inhibitors preventing T4 fixation on the protein, (3) dysfunction of the thyrotrophic negative feedback, (4) cytokines (IL-1, IL-6, TNFα, IFNγ) induced inhibition of the thyrotrophic centers activity and/or affected the expression of thyroid hormones nuclear receptors, and (5) other inhibitory substances such as dopamine. Prolonged critical illness is associated with centrally induced hypothyroidism as suggested by restoration of T3 and T4 pulses by exogenous TRH infusion.

Growth Hormone

The acute phase of critical illness is characterized by high growth hormone levels with attenuated oscillatory activity associated with low levels of IGF-1 [9]. Serum concentrations of GH effectors IGF-1 are low during this phase, suggesting resistance to GH as a result of decreased expression of GH receptor. Subsequently, direct lipolysis and anti-insulin effects of GH might be enhanced, liberating metabolic substrates such as free fatty acids and glucose to vital organs, while costly metabolism mediated by IGF-1 is postponed. In prolonged critical illness, the pattern of GH secretion shows a reduced pulsatile fraction that correlated with low circulating levels of IGF-1.

Adrenal Medulla Hormones

It is well known that under resting condition very few amounts of adrenaline and noradrenaline are released from the adrenal medulla (i.e., less than 50 ng/kg/min in the dog). Therefore, removing the adrenal medulla allows an animal to survive the intervention indefinitely. However, exposure to stressors caused prompt increase in circulating adrenaline and noradrenaline concentrations by 2–3 logs, an effect that was prevented by removal of the adrenal medulla. Adrenaline is stored in medulla

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vesicles. Noradrenaline is present in the subcellular granules of the sympathetic nervous endings. Catecholamines have a very short half-life (10–20 sec for adrenaline) and are metabolized through captation, enzymatic inactivation (methylation in metadrenaline or normetadrenaline in liver or kidney, oxidative deamination by monoamine oxidase), or renal excretion. The hormonal regulation depends on cortisol, which is necessary for the enzymatic degradation of catecholamines synthesis. The nervous regulation involves cholinergic preganglionic parasympathetic pathways via splanchnic nerves. Like cortisol, catecholamines levels in plasma can remain elevated in plateau as long as the stress is maintained and even up to few months after recovery.

Insulin

Insulin is involved in glucose metabolism through (1) mobilization of store of glucose transport molecules in target cells, such as muscle and fat tissue, (2) activation of hepatic glucokinase gene transcription, and (3) activation of glycogen synthetase and inhibition of glycogen phosphorylase [10]. Other actions of insulin include growth stimulation, cellular differentiation, intracellular traffic, increase of lipogenesis, glycogenesis, and protein synthesis. These effects result from insulin fixation to a ubiquitous membrane receptor belonging to the tyrosine kinase family including insulin-like growth factor receptor (IGF-1) and insulin receptor-related receptor (IRR). Insulin levels in plasma are rapidly increased following an acute stress as a result of both increased secretion and tissue resistance. Insulin suppresses and antagonizes the effects of TNF, macrophage migration inhibitory factor (MIF) and superoxide anions, and decreases the synthesis of the acute phase reactants. Moreover, insulin modulates leptin and other adipokines release from fat cells.

Clinical Consequences of Endocrine Activity in Critical Illness

The main objective of the neuroendocrine response to critical illness is “fight and flight.” Then, the immediate manifestation of the activation for the endocrine system, mainly the sympato-adrenal hormones, include alertness; insomnia; hyperactivity; pupillary dilation; reception of hairs; sweating; salivary secretion; tachycardia; rise in blood pressure with dilation of skeletal muscles, blood vessels, and coronary arteries; bronchiolar dilation and polypnea; skin vasoconstriction; mobilization of glucose from liver and hyperglycemia; increased oxygen capacity of the blood via spleen constriction and mobilization of blood red cells; and shortening of coagulation time. However, in practice, fighting is the only option, and the appropriateness of the neuroendocrine activity to the intensity and duration of the stress is the determinant of host survival and recovery. The clinical consequences of the stress system activation roughly include behavioral changes, and cardiovascular, metabolic, and immune adaptations.

Behavioral Changes

In animals, infections are associated with anorexia and body weight loss, hypersomnia, psychomotor retardation, fatigue, and impaired cognitive abilities. Similar behavioral changes are consistently reported in humans after cytokine or LPS challenge. The socalled depression due to a general medical condition is likely mediated through release of peripheral and brain cytokines [11]. Then, when glucocorticoids and catecholamines responses are insufficient, the critically ill patients will develop brain dysfunction that can result in coma.

Cardiovascular Changes

The cardiovascular adaptation is mainly driven by the sympatho-adrenal hormones even though thyroid hormones and vasopressin contribute respectively to cardiac adaptation and blood volume and vasomotor tone regulation. Corticosteroids exert important actions of the various elements of the cardiovascular system including the capillaries, the arterioles, and the myocardium. The underlying mechanisms are not fully understood and may involve direct mobilization of intracellular calcium, enzymatic metabolism of adrenaline, increased binding affinity of adrenaline for its receptor or facilitation of the intracellular signalization that follows the coupling of adrenaline to its receptor. Whenever the hypothalamic-pituitary adrenal axis or the noradrenergic responses are inappropriate, critically ill patients will develop cardiovascular dysfunction. Indeed, septic shock patients with adrenal insufficiency, as defined by a delta cortisol of 9 μg/dl or less, have more pronounced hypotension than those with presumed normal function, and are more likely to develop refractory shock and to die [6]. Adrenal insufficiency is at best recognized at the bedside of critically ill patients by either low baseline cortisol levels (<10 μg/dl) or cortisol increment after 250 μg of corticotropin of <9 μg/dl [6]. Failure of the noradrenergic system will also result in cardiovascular dysfunction during critical illness. Sepsis is associated with decreased noradrenergic activity that preceded cardiovascular dysfunction [12]. The decrease of the pulsatile activity of the HPA axis and the noradrenergic system result in regularity within the circulatory and respiratory function becoming unable to adjust to stressful conditions, loss in interorgan communications with multiple organ dysfunction, and death [13]. Finally, inappropriately low vasopressin levels contribute to the vasodilatory shock [14].

Metabolic Changes

The net result from the activation of the endocrine system is hyperglycemia. Tissues that are insulin-dependent cannot uptake glucose, which is then available for insulin-independent tissues like the brain or inflammatory cells. The main reason for critical-illness-associated insulin resistance is cytokines-induced impairment in GLUT-4 metabolism [15]. Hyperglycemia has been shown to increase mortality in critical ill-

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ness [16]. The mechanisms underlying glucose toxicity for the cells are still unknown and may include an overloading of the insulin-independent cells like neurons. Subsequent to low ATP levels in the cells, the excess of intracellular glucose cannot enter the Krebs cycle and result in the generation of free radicals and peroxynitrites, which in turn block complex IV of the mitochondria. Then, by killing the mitochondria of insulin-independent cells, hyperglycemia may facilitate acquisition of superinfection, damage the central and peripheral nervous systems and the liver, and eventually result in multiple-organ-dysfunction-related death [16]. Excess in the catabolic hormones, cortisol, adrenaline, and glucagon will also elicit an imbalance between the muscle protein breakdown rate and the rate of muscle protein synthesis, resulting in a net catabolism of muscle protein, which may contribute to critical-illness-induced muscle weakness and affect long-term prognosis.

Immune Changes

The changes in the immune function again are mainly related to the sympatho-adrenal hormones even though insulin and vasopressin can also influence immunity. Glucocorticoids suppress most, if not all, T-cell derived cytokines, and change the Th1/Th2 balance toward excess Th2 cells [1]. They do not affect IL-10 synthesis by monocytes, and they upregulate lymphocytes-derived IL-10. They also inhibit the synthesis of many other inflammatory mediators such as cyclo-oxygenase and inducible NOS, and down regulate cell surfaces markers such as endotoxin receptor and adhesion molecules. Finally, they enhance the occurrence of apoptosis of thymocytes, mature T-lymphocytes, eosinophils, epithelial cells and precursors of dermal/interstitial dendritic cells, but delay apoptosis of neutrophils [1]. Catecholamines also drive a Th2 shift in both antigen presenting cells and Th1 cells via beta adrenergic receptors. While the stress hormones, glucocorticoids, and catecholamines induced systemically a shift of the Th1/Th2 balance in favor of Th2 cells, catecholamines also promote locally at the level of inflamed tissues the synthesis of proinflammatory mediators via alpha adrenergic receptors. Then, critical-illness-associated impaired HPA axis shifted the Th1/Th2 balance to release proinflammatory mediators in the circulation and broadly in body tissues.

Modulating the Endocrine System During Critical Illness

The use of exogenous hormones in the context of critical illness has become a standard of care. Indeed hypotension can be corrected by administration of catecholamines. Even though there is no randomized controlled trial of adrenaline, noradrenaline or dopamine versus a placebo or no treatment, these drugs are routinely administered in critically ill patients with cardiovascular dysfunction. Adrenaline and noradrenaline are equally effective in restoring cardiovascular homeostasis during shock [17]. Vasopressin may also restore hemodynamic stability in critical illness [14]. However, the survival benefit from catecholamines or vasopressin remains uncertain.

There is enough evidence supporting the benefit of corticosteroids on hemodynamic and systemic inflammation and supporting that survival benefit is dose dependent [2,6]. The use of corticosteroids in patients with septic shock continues to be controversial despite two recent, large, well-performed studies [18,19]. The two studies evaluated different patient populations and came to opposite conclusions. Similarities between the two studies included steroids' beneficial effects on time-to-shock reversal, no evidence for increased risk of neuromuscular weakness, and hyperglycemia. Differences between the two studies include for Annane et al. [18] and Sprung et al. [19] respectively: entry window (8 vs. 72 h; SBP <90 mmHg; >1 h vs. <1 h); additional treatment (fludrocortisone vs. no fludrocortisone); treatment duration (7 vs. 11 days); weaning (none vs. present); SAPS II scores (59 vs. 49); non-responders to corticotropin (77% vs. 47%); differences in steroids effects according to the response to corticotropin (yes vs. no); increased risk of superinfection (no vs. yes); and study occurred after practice guidelines published recommending steroids (no vs. yes). Currently, patients with vasopressor dependent shock should be treated with hydrocortisone.

Recently, intensive treatment with insulin targeting blood glucose of 4.4–6 mmol/L was shown to significantly improve morbidity and mortality in both surgical [20] and medical [21] patients. The benefit is mainly observed in the chronic phase of critical illness (after 72 h) and may be related to protection of cells from glucose toxicity rather than from direct anti-inflammatory effects of insulin. However, two recent multicenter studies did not find any benefit for a tight glucose control with intensive insulin therapy in patients with severe sepsis [22,23]. One may suggest that the very early increase in blood glucose mainly relates to stress hormones and should not be counteracted, whereas later hyperglycemia relates to cytokines-induced insulin resistance and should be treated.

Other attempts to manipulate the endocrine system during critical illness have included thyroid hormones replacement therapy or growth hormone therapy and have been less successful.

Conclusions

The neuroendocrine response to critical illness is paramount for host survival and recovery. The sympatho-adrenal hormones are key actors in maintaining homeostasis. When the neuroendocrine response to an acute stress is appropriate both in time and in intensity then critical illness does not develop and recovery is easy. Otherwise, syndrome of multiple organ failure develops. By contrast, if the host response is too excessive, persistent changes in behavior and mood, in metabolic state and in immune function cause increased susceptibility to superinfection, risk for chronic muscle fatigue, and posttraumatic stress disorders. Whether the neuroendocrine system can be manipulated to be adjusted to the inflammatory process remains a controversial issue.

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Blood Transfusion and Its Components 34

E. Celis-Rodriguez, K. Reinhart, Y. Sakr

Introduction

Transfusion of blood products in the critical care setting is a common practice that has been performed for many years. Since the 19th century, when James Blundell reported the clinical application of the treatment of hemorrhage for the first time in the Lancet [1], blood transfusion has been the cornerstone in the treatment of severe hemorrhage, not only as a means of improving oxygen transport capacity, but also to maintain homeostasis and reduce mortality rates [1]. The 10/30 rule was the standard of care for decades [2], but the first report of this appeared in the 1940s, when Lundy et al. [3] stated that "It is a clever idea to provide blood before surgery," referring to patients whose hemoglobin levels were between 8 and 10 g/dL. With the more restrictive use of blood transfusion since the 1980s, there have been attempts to define specific indications for transfusion, minimal hemoglobin levels for critically ill patients, and the benefits and potential risks of transfusion [4].

Recent publications have proposed targeting lower hemoglobin levels (7 g/dL) to reduce complications related to transfusion of blood products, such as transfusion-related infections, immunosuppression, transfusion-related acute lung injury (TRALI), hemolytic reactions and fever reactions, in addition to its effects on mortality.

The use of blood derivates, such as fresh frozen plasma (FFP), cryoprecipitates and platelets for the treatment of bleeding is yet to be defined with accuracy. Despite the large amounts of FFP being transfused every year all over the world, there is clinical and laboratory evidence that this may not always be appropriate. In the future, the application of genomic tests to evaluate hemostatic function will make it possi-

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ble to spot genetic polymorphism, and hence improve diagnosis and provide more accurate treatments [1].

Anemia in Critically Ill Patients

Anemia is common in critically ill patients, and is usually diagnosed after measuring the concentration of hemoglobin (Hb) and the hematocrit (Hct), which reveals the ratio between the existing red blood cells and the plasma volume [5]. Anemia is defined as a concentration of Hb which is below the expected value, taking into account age, gender, pregnancy, and some environmental factors, including altitude above sea level [6] which leads to a reduction in the erythrocyte mass and hence in a lower ability to carry oxygen. The World Health Organization (WHO) has defined anemia as an Hb concentration less than 13 g/dL (Hct <39 %) in adult males, and less than 12 g/dL (Hct <36%) in adult, nonpregnant females [6]. The condition of critically ill patients can worsen in the presence of anemia; however, aggressive treatment of anemia in these patients may be as harmful as no treatment [7].

The incidence of anemia in patients admitted to the intensive care unit (ICU) varies depending on the population studied, and on the severity of the disease and on coexisting comorbidities. The ABC trial [8] reported an average Hb value of 11.3 (g/dL) at ICU admission; 63% of the patients had an Hb level lower than 12 g/dL on admission and in 29% it was less than 10 g/dL. In the CRIT trial [9], nearly two thirds of the 4,892 patients tested had Hb levels less than 12 g/dL on admission to the ICU.

Anemia in critically ill patients is multifactorial and is hematologically similar to chronic anemia, but often patients experience acute onset anemia [7]. Some of the causes (Table 34.1) can be modified, which may facilitate prevention strategies, such as making the collection of blood samples more efficient in order to reduce losses, guiding fluid replacement therapy to avoid extreme hemodilution, and the supply of iron.

Nguyen et al. [10] reported that during a patient's stay in the ICU, the Hb concentration decreases by up to 0.66 g/dL per day during the first 3 days and then it continues to decrease at a rate of 0.12 g/dL per day. Similar findings have been reported in large observational studies [8,9].

The biochemical characteristics of anemia in critically ill patients include a low serum iron concentration, a low binding affinity for iron, a low ratio between serum iron and total iron, increased ferritin levels, reduced transferrin, low transferrin saturation with normal concentration of receptors for soluble ferritin, normal or high percentages of hypochromic red cells, and a normal or slightly increased concentration of erythropoietin [7,11].

During inflammation, normal erythrogenesis is inhibited, which contributes to critical illness anemia by a similar mechanism to that described by Weiss et al. for chronic inflammatory conditions [12]. In addition, high circulating levels of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1, C-reactive protein (CRP), and interferon (IFN) α, β, and γ, decreased production

Table 34.1 Etiology of anemia in critical illness. Modified from [7]

Blood loss
Phlebotomy
Active bleeding: trauma, surgery, GI bleeding
Diminished erythropoiesis
Myelosuppressive drugs or toxins
Nutritional deficiencies: iron, folate vitamin B12
Bone marrow diseases
Deficiency of erythropoietin
Renal failure
Inflammation or infection/anemia of chronic anemia
TNF-α, IL-6, IL-1, C-reactive protein
Increased red blood cell destruction
Certain drugs
Certain toxins
Certain diseases

of erythropoietin, deficient erythropoiesis, increased free radicals, and a reduction in the average life of erythrocytes are also responsible for the appearance of anemia in less than a week [7,12].

When Should Critically Ill Patients Be Transfused?

Different studies have attempted to determine at which Hb threshold a critically ill patient should be transfused. In the past few years, we have observed that the results obtained in these studies have positively influenced daily medical practice. One of the recent changes was in the guidelines published by the Surviving Sepsis Campaign in 2008, in which they recommend that adult patients suffering from severe sepsis whose tissue hypoperfusion has been resolved after the acute resuscitation period, and who have no prior record of ischemic heart disease, severe hypoxemia, acute hemorrhage, cyanotic heart disease or lactic acidosis should only receive a blood transfusion when the Hb concentration is less than 7.0 g/dL, in order to keep the Hb level between 7.0 and 9.0 g/dL (Grade 1B recommendation) [13].

Although the optimal Hb level for patients with serious sepsis has not yet been established, the TRICC study [14], a randomized, controlled trial including 838 critically ill patients suggested that Hb levels between 7.0 to 9.0 g/dL, as compared with Hb levels between 10.0 and 12.0 g/dL, were not associated with increased mortality rates in adults. These findings support the suggestion that transfusions must be performed only when Hb levels are less than 7.0 g/dL. The exceptions identified in this study include chronic ischemic heart disease and acute coronary syndrome, in which the critical Hb level should be near 9.0 g/dL.

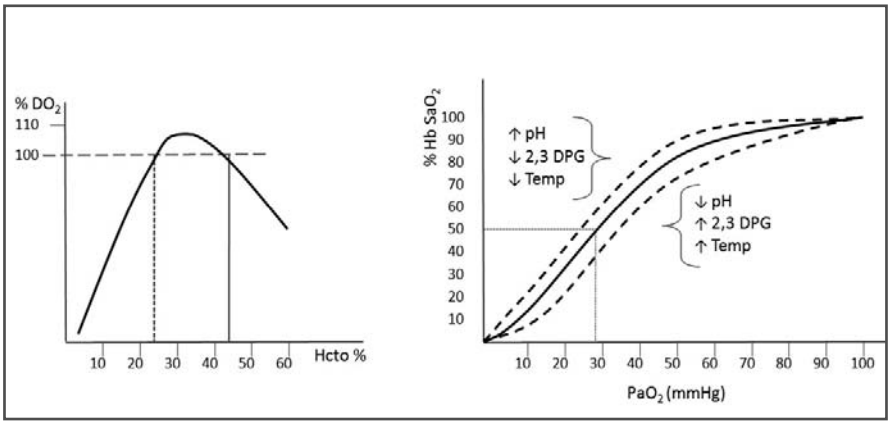

Fig. 34.1 Struttura molecolare dell'acido zoledronico

A restrictive approach to transfusion should be considered on an individual basis, based on comorbidities and on physiological knowledge of the different phases of oxygen delivery (DO_2), as proposed by Laks et al. in 1972 [15] and Messmer in 1981 [16]. These groups referred to hemodynamic changes as consequences of the acute normovolemic hemodilution technique [16]. In the oxygenation phase, in which the union of oxygen to Hb depends on affinity, transportation, and delivery are not altered. The p50 changed only when the Hct levels were close to 10%, while DO_2 increased up to 106% when the Hct levels ranged between 27.5% and 30% (Fig. 34.1) [15,16].

Tissue DO_2 is altered in inflammatory processes because of changes in the structure of erythrocytes, resulting from the reduction of glycophorins in the cell membrane, which leads to a more spherical shape and a reduction in the capacity to be deformed. This in turn results in altered blood rheology, and a reduction in the concentration of intracell 2,3-DPG, conditions which alter the capture and delivery of oxygen at a tissue level [3,17].

Blood Transfusion in Patients Receiving Mechanical Ventilation

Some studies have evaluated the impact of transfusion on prognosis in patients receiving mechanical ventilation. It has been suggested that blood transfusion might improve DO_2 to compensate for the high demand for oxygen as mechanical ventilation is withdrawn [18]. A study published by Hébert et al. compared the duration of ventilatory support and the rate of weaning success in 730 patients. One group received a restrictive transfusion strategy, and the other a liberal transfusion strategy. It was not possible to conclude that the liberal transfusion of red blood cells reduced the length of time during which patients required mechanical ventilation [18].

Levy et al. [19] performed a retrospective analysis of the database of the CRIT study, including 4,892 patients. The reasons for performing transfusions on patients receiving mechanical ventilation and on patients not receiving mechanical ventilation were compared. Nearly 60% of the included patients were receiving mechanical ventilation and had significantly higher APACHE II scores (p <0.0001). Patients receiving mechanical ventilation received more red blood cell units (Hb 8.7 g/dL on average) than patients with no mechanical ventilation (Hb 8.2 g/dL on average). Mortality rates were higher in the mechanical ventilation group (17.2 vs. 4.5%, p <0.001), as was the length of time they stayed in the ICU and the hospital.

Transfusion in Patients With Ischemic Heart Disease

A large number of recent publications support the idea that anemic patients with underlying ischemic heart disease have poorer outcomes, as measured by several variables, than ischemic heart patients with higher Hb concentrations, defining anemia as any Hb concentration below 13 g/dL.

Hébert et al. [20], in a multicenter, randomized, controlled trial including 838 patients, found that patients with heart disease and higher Hb levels had lower mortality rates as compared with those with lower Hb levels. A study by Zeidman et al. [21] compared ischemic heart disease patients with and without anemia. Anemic patients experienced more arrhythmias and congestive heart failure and had higher mortality rates than nonanemic patients. Similar findings have been reported by others in patients with acute coronary syndrome, heart attack with or without ST-segment elevation, recurring ischemic events, and elderly patients younger than 70 with ischemic heart disease [22–25].

However, although the association between anemia and a negative prognosis in these patients is supported by evidence, the existing literature also shows that transfusions do not seem to be routinely prescribed [26].

The Benefits and Risks of Transfusions

In normal physiological conditions, DO_2 depends on the metabolic oxygen consumption (VO_2). If DO_2 is considerably reduced, so is VO_2, leading to a critical condition called oxygen debt or anaerobic threshold. Transfusions are performed in order to resolve this situation, mainly occurring as the result of acute blood loss through hemorrhage, by increasing the erythrocyte cell mass and the blood volume. Transfusions are also used in clinical practice in order to increase DO_2, thus alleviating symptoms associated with anemia, such as fatigue, mental confusion, and adynamia, especially in elderly patients. If untreated, serious anemia may lead to anaerobiosis or tissue ischemia. However, the transfusion of red blood cells has not proved to be an efficient way of treating this situation [27,28].

The effects of transfusions on microvascular perfusion are not well defined. In anemic preterm infants, transfusion was associated with a significant increase in functional capillary density, as assessed by an orthogonal polarization spectral (OPS) probe applied to the skin of the upper arm [29]. Functional capillary density increased already 2 h after transfusion and increased further after 24 h, indicating improved microvascular perfusion; there were no changes in clinical variables such as heart rate or blood pressure. In adult ICU patients with sepsis, we recently used OPS to investigate the effects of RBC transfusion on sublingual microvascular perfusion [30]. Microvascular perfusion was not significantly altered by the transfusion of 1–2 units of leukocyte-reduced blood. There was, however, considerable interindividual variability. The change in capillary perfusion after transfusion correlated with baseline capillary perfusion, with baseline capillary perfusion being significantly lower in patients who increased their capillary perfusion following transfusion compared to those who did not. However, hemodynamic and global oxygen transport variables were similar in the two groups. Thus, the microcirculation in septic patients who already have microcirculatory changes may improve with transfusion. Similar observations have been made in anemic patients with traumatic brain injury. Leal-Noval et al. [31] observed that RBC transfusions had a variable effect on brain oxygenation. Interestingly, cerebral oxygenation improved only in patients with altered cerebral oxygenation at baseline. Although microcirculatory blood flow was not directly measured in this study, it was estimated by a surrogate measurement (near infra-red spectroscopy).

The transfusion of red blood cells may lead to well-known adverse effects, such as the transmission of viral infectious diseases [hepatitis A, B, C, human immunodeficiency virus (HIV)], bacterial and parasite infections (Chagas' disease, malaria), and infections caused by prions. Noninfectious complications include volume overload, fever, anaphylactic, allergic or hemolytic reactions, TRALI, multiple organ failure, and a longer hospital stay [32–34]. In a study including 2,085 patients, Taylor et al. [34] reported a higher rate of nosocomial infections in patients who had received transfusions than in those who had not (14.3% vs. 5.8%). The exact mechanism by which transfusions are related to higher morbidity and mortality rates and higher infection rates is not well defined. It is believed that immunomodulation and the transfusion of old erythrocytes could be likely causes [33–40] (Table 34.2).

Blood Transfusion and Mortality

Different studies have reported an increase in mortality rates in critically ill patients who have received red blood cell transfusions during their stay in hospital [8,9]. Results from the ABC trial, which included 3,534 critically ill patients, revealed a 28-day mortality rate of 22.7% in patients receiving transfusions, compared to 17.1% in patients who did not receive a transfusion (p <0.02), showing that receiving a transfusion increased the risk of death by a factor of 1.4 [8]. The CRIT trial yielded similar results [9]. A recently published population-based cohort study by Kamper-

Table 34.2 Incidence of adverse effects associated with transfusions

Side effect	Incidence per unit of RBC transfused	Reference
Infectious		
Viral infections		[34]
Hepatitis A	1:2,000,000	[32]
Hepatitis B	1:31,000 to 1:81,000	
Hepatitis C	1:1,935,000 to 1:3,100,000	
HIV	1:2,135,000 to 1:4,700,000	
HTLVI/II	1:1,900,000	
Bacterial contamination	1:14,000 to 1:28,000	
Parasitic infection	1:4,000,000	
Prion disease	Rare	
Noninfectious		
Febrile nonhemolytic reaction	1:500	
Urticarial reaction	1:50 to 1:100	
Anaphylactic reaction	1:23,000	
Hemolytic transfusion reaction	1:1,900	
Transfusion-related acute lung injury (TRALI)	1:1,300 to 1:5,000	[41]
Post-transfusion purpura	1:1,430,000	

Jørgensen et al. carried out in Sweden and Norway [38] on a total of 1,118,261 transfusions reported that the standardized mortality rate in the 3 months following the transfusion was 17.6 times higher compared with the general population; from 1 to 4 years after the first transfusion, the standardized mortality rate was 2.1 times higher, and 17 years later it was still 1.3 times higher.

However, the SOAP study, which analyzed data from 3,147 patients in 198 European ICUs in May 2002 reported that, unlike the ABC [8] and CRIT [9] studies, transfusion was not linked to an increase in mortality rates in a multivariate analysis. Although the ABC and SOAP studies shared similar design and analyses, a plausible explanation for this important difference in results was the increased use of leukocyte-free blood at the time of the SOAP study [36]. Leukocyte reduction is used to minimize the presence of white cells by means of centrifugation or filtration. Using this technique, it is possible to reduce the presence of leukocytes up to 99% and it has been effective in reducing the number of cell-associated viruses, such as cytomegalovirus, herpes virus, and Epstein-Barr virus. Leukoreduction may also reduce the transmission of parasites and prions, and the incidence of transfusion-related fever reactions and TRALI [38–40].

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The Use of Fresh Frozen Plasma

Several million units of FFP are transfused every day (>4 million in England and the USA), and use of FFP has increased significantly in recent years. For example, in the USA in 1979, one unit of FFP was transfused compared to 6.6 units of red blood cells. In 2001, the ratio was one unit of FFP to 3.6 units of red blood cells [1,42]. This is possibly due to the fact that the number of invasive procedures is increasing and surgeons attempt to maintain available laboratory tests (PT, PTT, and INR) within normal ranges in order to prevent complications associated with bleeding [1].

However, recent literature shows that the international normalized ratio (INR) and the activated partial thromboplastin time (aPTT) fail to predict which patients will suffer from bleeding as a result of an invasive procedure, and hence they should not be used to make decisions related to prophylactic procedures or transfusions [1]. These tests were not developed for this purpose, but rather to explore hemostatic defects in patients already identified as suffering from coagulopathy. They fail to measure global hemostasis and cannot identify some coagulation defects; most importantly, they wrongly suggest the presence of defects which do not exist [1,43]. The belief that transfusion of FFP may correct mild to moderate coagulation defects is unfounded, as is the idea that the INR predicts bleeding, and that FFP corrects the INR in this type of patient. In the future, genomic applications will help to improve diagnosis and hence treatment [1]. Until then, the recommendation is to use FFP in patients with massive hemorrhage or abundant bleeding with prolonged PT and aPTT (>1.5 times normal). The recommended initial dose is 10–15 ml/kg. Larger doses may be required depending on the diagnosis and the clinical situation [42].

Platelets

There is no scientific basis for defining a minimal platelet count as 20,000/μL. There is a real danger of massive bleeding when the number of platelets is below 5,000 to 10,000/μL and there is a risk of intracranial hemorrhage when the numbers are below 1,000/μL. Patients with chronic autoimmune thrombocytopenia may tolerate values between 5,000 to 10,000/μL for years and transfusion is not necessary in such patients, especially when their condition is stable [42].

However, in severely traumatized patients with massive hemorrhage, it is recommended that the number of platelets be kept above 50,000/μL and when there is associated cranial trauma, it is suggested that the platelet count be kept greater than 100,000/μL. One possible explanation for this recommendation is that in these situations, patients have increased fibrin degradation products, disseminated intravascular coagulation (DIC), or hyperfibrinolysis, which interferes with platelet function and hence, a larger number of platelets could be beneficial. Evidence supporting this concept is, however, weak [42].

When transfusing platelets, the suggested dose is 4–8 platelet concentrates or 1 unit of plateletpheresis [43]. It is important to carry out a platelet count 15 min after

transfusion. A poor platelet count may indicate the presence of HLA antibodies. A good count after 15 min but low after 24 h may reveal consumption related to fever, sepsis, drug toxicity, etc. [43].

Cryoprecipitates

Cryoprecipitates are useful to achieve a rapid increase in the fibrinogen levels in patients with DIC or in massive transfusion with hemodilution and active bleeding. They are the third line of action in the treatment of von Willebrand's disease type 1, and the second line of treatment for other types of von Willebrand's disease. In trauma patients, evidence supporting cryoprecipitate use is very limited [42,43]. In cirrhotic patients during liver transplant, when low fibrinogen levels are often found, cryoprecipitates are very useful.

Conclusions

It seems appropriate not to transfuse red blood cells to patients tolerating Hb levels of 7 g/dL (Hct 27%) when there is an adequate VO_2/DO_2 ratio. Imbalance in oxygen transport becomes evident when clinical signs of tissue hypoperfusion and lactic acidosis appear.

It also seems to be clear that the transfusion of packed red blood cells can bring about serious complications as discussed above, which can increase the number of days in the ICU and in hospital and also morbidity and mortality.

The above recommendation seems not to apply to patients with cardiac decompensation, elderly patients, and some neurological patients for whom hemoglobin levels of 10 g/dL are more appropriate minimum values. It is possible that leukocyte reduction provides some answers to some of the problems associated with transfusions, especially for patients not tolerating low hemoglobin or hematocrit concentrations.

Further studies are required to provide solid evidence and make clear and precise recommendations to help us define more accurately the clinical use of blood derivates, such as FFP, platelets and cryoprecipitate, and to reduce the use of these blood products in cases where they are not indicated.

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Pain Management in Neonates and Children

35

M. Astuto

Introduction

Until about 10 years ago, newborns and children were considered to be relatively unable to feel pain, and that even if they could they would not remember it [1]. Recently, more studies have shown that children, including newborns, do feel stress and perceive noxious stimuli as painful. By measuring heart rate, oxygen saturation, mean arterial pressure, and behavioral response [2], it has been shown that newborns respond to painful stimuli, similar to adults. Therefore, we have to implement pain measurement for all children who are potentially in pain, and improved research and education on the causes, prevention, and short-term and long-term effects of pain and analgesia: these are priorities. Currently diagnostic and surgical procedures are required for the survival of critically ill newborn babies, and the possible pain generated by such procedures has been a source of concern. However, in normal practice a specific analgesic or anesthetic treatment is used only for the problematic infants undergoing painful procedures, normally most infants are given a nonspecific analgesia and some infants nothing or only one dose of analgesics [3].

Pain Assessment

The fact that pain is a subjective experience means that anybody with problems communicating will have more difficulty conveying not only that they are in pain but also the site, nature, and severity of the pain.

Pain assessment is the key to effective pain management and optimal pain man-

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agement requires competent pain assessment, which can be particularly difficult to perform in neonates, infants, and children. Although a wide variety of communication disorders may occur at any age, in pediatrics the developmentally appropriate difficulty with communication of normal infants and young children is the commonest cause of difficulties with pain assessment. Clinical judgment alone is often used in neonates, whereas simple assessment tools are useful in older children.

There are many methods that can be used to help the clinician in arriving at an assessment, either by assisting the patient's expression such as a visual analog scale (VAS), faces pain rating scale (Wong-Baker or Bieri scale) or by formally scoring various observable clinical factors such as heart and respiratory rates, mobility, blood pressure, oxygen saturation, vagal tone, palmar sweating, and plasma cortisol or catecholamine concentrations. Behavioral indicators include changes in facial expressions, body movements, and crying, but these may be absent in some neonates who are neurologically impaired or pharmacologically paralyzed.

In small children the family may assist assessment by describing the patient's previous behavior in response to pain.

However, children as young as 18 months can indicate their pain and give a location, although they cannot specify pain intensity before about 3 years of age. At the age 3 years, they can give a gross indication: "no pain," "a little pain" or "a lot of pain." However, their reports are not always reliable and in these very young patients the best indicator is often the parents' impression. If young children (from 4 to 8 years) have normal development, self-reports of pain using assessment tools designed for young children can be reliable. A simple numeric scale using age-appropriate language may be helpful at the upper end of this age range. The most commonly used assessment tools are listed in Table 35.1.

Although appearing more scientific, these methods have advantages and disadvantages, and are not inherently better than a clinical assessment by an experienced care giver with a personal relationship with the patient (and the patient's family). Clinically, the goal of a quantitative assessment of pain need only be to categorize the pain as absent, mild, moderate, or severe. The charting, preferably with other routine observations, of whatever pain assessment is used is important for continuity of patient care and overall assessment.

Pain assessment in neonates who cannot describe their pain is a difficult problem. Various "objective pain scores" (OPS) have been suggested, usually involving summation of points allocated for various observable behaviors and physiological measurements. These provide some standardization and guidance about what to look for when assessing a child.

When pain is prolonged, striking changes occur in the infant's physiologic and behavioral indicators. During episodes of prolonged pain, neonates enter a ste of passivity with few, if any, body movements; an expressionless face; decreased heart rate and respiratory variability; and decreased oxygen consumption, all suggestive of a marked conservation of energy. Prolonged or repeated pain also increases the response elicited by future painful stimuli (hyperalgesia) and even by usually nonpainful stimuli (allodynia).

Although long-term effects are less easy to prove, pain has been associated with

Table 35.1 The most commonly used assessment tool

Gestational age tested	Assessment tool	Physiologic indicators	Behavioral indicators	Scoring adjusts for gestational age
Term and preterm neonates	BPSN: Bernese Pain Scale for Neonates	Heart rate, respiratory rate, blood pressure, oxygen saturation No	Facial expression, body posture, movements, vigilance	No
25–36 wk (preterm infants)	EDIN: Echelle de la Douleur Inconfort Nouveau-Ne' (Neonatal Pain and Discomfort Scale)	None	Facial activity, body movements, quality of sleep, quality of contact with nurses, consolability	No
28–40 week	PIPP: Premature Infant Pain Profile	Heart rate, oxygen saturation	Brow bulge, eyes squeeze shut, nasolabial furrow	Yes
	NIPS: Neonatal Infant Pain Scale	Respiratory patterns	Facial expression, cry, movements of arms and legs, state arousal	No
32–36 wk	CRIES: Crying, Requires Oxygen Saturation, Increased Vital Signs, Expression, Sleeplessness	Heart rate, oxygen saturation	Crying, facial expression, sleeplessness	No
0–100 d of age and adjusts score on the basis of gestational age	N-PASS: Neonatal Pain Agitation and Sedation Scale	Heart rate, respiratory rate, blood pressure, oxygen saturation	Crying, irritability, behavior state, extremities tone	Yes
Preterm and term neonates,	NFCS: Neonatal Facing	None	Facial muscle group	No

Table 35.1 *Cont.*

Gestational age tested	Assessment tool	Physiologic indicators	Behavioral indicators	Scoring adjusts for gestational age
infants at 4 mo of age	Coding System		movement	
Neonates	PAT: Pain Assessment Tool	Respirations, heart rate, oxygen saturation, blood pressure	Posture, tone, sleep pattern, expression, color, cry	No
	SUN: Scale for Use in Newborns	Central nervous system state, breathing, heart rate, mean blood pressure	Movement, tone, face	No
Neonates	PAT: Pain Assessment Tool	Respirations, heart rate, saturation, blood pressure	Posture, tone, sleep pattern, expression color, cry	No
	SUN: Scale for Use in Newborns	Central nervous system heart rate, mean blood pressure	Movement. tone, face	No
2 months to 7 years	FLACC (Face Legs Arms Cry Consolability Scale)	None	Facial expression, legs movements, activity, cry, consolability	No
4 years and over	Wong & Baker (Faces Pain Rating Scale)	None	Facial expression	No
4 years and over	VAS (visual analogic scale)	None	None	No

numerous adverse long-term outcomes including altered pain perception of immunizations after an anesthetized circumcision [4], abnormal cortisol responses to stress in later infancy [5], and altered pain responses in childhood.

In summary, there would appear to be considerable data supporting the view that pain offers the sick infant few advantages, and that its treatment improves both the short-term and long-term outcome. These factors emphasize that from an ethical position we should not allow infants to suffer avoidable severe pain.

Pain Management

Nonpharmacological Pain Management

A number of nonpharmacological strategies can be used to minimize the effects of pain in the newborn, infant, and children (Table 35.2).

An integrated approach to pain management that includes nonpharmacological modalities may have a significant impact on both the degree of pain perception by a newborn, as well as upon the requirement for pharmacologically mediated analgesia.

Armstrong et al. [6] showed the role of play preparation to pediatric anesthesia. Play therapy can be an effective method for providing tangible information about the surgical experience and simultaneously decreasing the child's fantasies and fears about the surgery. For Bowmer [7] play is a simple way of helping the child to deal with the painful hospital world, and to master situations that might otherwise be overwhelming. The results are rewarding in terms of happier, less anxious children, parents, and medical staff.

Table 35.2 Nonpharmacological strategies in neonatal pain management

Comforting
Feeding
Oral sucrose
Refrigerant sprays
Reduction of environmental noxious stimuli

Drug Treatment of Pain in Neonates and Children

When choosing pain treatment for neonates and children, the following considerations should be kept in mind because the dose requirements for analgesic agents vary throughout postnatal development. Pharmacokinetic variables change rapidly after birth and will be influenced by:

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- Organ maturation (e.g., renal tubular function and change in glomerular filtration rate). Before this, the clearance of drugs may be delayed, necessitating an increase in dosing intervals.
- Body composition (e.g., total body water is approximately 85% in preterm neonates, 75% in term neonates, and 60% by 5 months of age). Because of the increase in total body water concentration in neonates, water-soluble drugs have a larger volume of distribution.
- Changes in protein concentration and binding (affecting the volume of distribution). Neonates have less plasma protein binding, resulting in increased free drug concentration.
- Changes in drug elimination pathways. The principal method of metabolism for analgesics drugs is the conjugation in the liver. Neonates, having an immature cytocrome P450 system, will conjugate drugs slowly.

In preterm neonates, postconception age and not just postnatal age requires consideration in pharmacokinetic models. Understanding age-related changes in pharmacokinetics has allowed refinements of dose recommendations for acetaminophen and i.v. morphine in preterm and term neonates and infants. There is a poor correlation between pain score and plasma concentration that may be related to discrepancies between plasma and effect-site concentrations or large interindividual variability in kinetics. This emphasizes the need for regular assessment and titration of doses against response in the clinical setting. Further details of analgesic use in neonates can be found in reviews and practice guidelines [8].

In addition to changes in pharmacokinetics, postnatal age can influence the pharmacodynamic profile of analgesic drugs, but this can be difficult to investigate clinically.

Data from preclinical investigations can inform and improve the design of clinical studies by providing additional information regarding the following:

- Analgesic efficacy. Evaluation of dose-related effects at a range of postnatal ages in the rat pup has provided data about the efficacy and sensitivity to side effects for a number of systemic and regionally administered analgesics, including local anesthetics, opioids, NSAIDs, and α^2-adrenergic agonists.
- Changes in receptor expression and distribution. Developmental alterations in opioid receptor distribution are likely to contribute to the age-related differences in dose requirements observed in clinical studies. During the first postnatal week, functional opioid receptors are expressed by both small (C-fiber) and large (A-fiber) cell bodies in the root ganglia, but by postnatal day (P) the adult pattern of expression in predominantly small diameter neurons is seen. In the spinal cord, mu opioid receptor binding sites are initially spread diffusely through the dorsal horn, with a peak in overall binding at P7, reducing by P21 and becoming more localized to the superficial dorsal horn.
- Changes in transmitter function. The neurotransmitter noradrenaline has a trophic role in the developing nervous system, and α^2-adrenergic receptors are highly expressed in the brainstem during the early postnatal period. These changes may underlie the increased susceptibility to centrally mediated sedatives and cardiovascular effects of the α^2-agonistm dexmedetomidine seen in younger rat pups.

- Developmental toxicity. The nervous system may be susceptible to unexpected age-related effects, as shown by recent data linking general anesthetics, including ketamine, with apoptosis (programmed cell death) in the developing brain. This occurs in the absence of hypoxia, hypoglycemia, or reduction in cerebral blood flow. Additionally, this effect is limited to specific susceptible developmental periods (which differ across species), is dose-related, is worse when combined with GABA agonists and NMDA antagonists are given, and can produce long-term structural and functional consequences. The significance of these findings has been debated but further clinical research is warranted.

Systemic Analgesic Drugs

Paracetamol is widely used for antipyresis and analgesia. Paracetamol acts by inhibiting cyclo-oxygenase and is thought to have an analgesic effect on NMDA receptors in the spinal cord. The drug-dynamics of paracetamol analgesia has not been adequately described in humans and the therapeutic range for analgesia is not well established. Little or no analgesia is obtained below plasma levels of 10 mcg ml^{-1}. Pediatric studies using paracetamol 10 mg kg^{-1} orally have shown no more analgesic effect than placebo in children undergoing myringotomy [9]. Anderson et al. [10] described 100 children, scheduled for tonsillectomy, 40 mg kg^{-1} of paracetamol receiving the dose by oral or rectal route. Fifty minutes later plasma concentration was measured and related with analgesia. Anderson found an increasing number of patients with satisfactory analgesia as plasma concentrations increased and a ceiling effect at 25–30 mcg ml^{-1}. The peak analgesic effect of paracetamol is obtained 1 h after peak plasma concentration. A relationship between plasma and cerebrospinal fluid (CSF) paracetamol concentrations seems to be evident. Therefore, the central analgesia effect is ascribed to the ability of paracetamol to cross the blood barrier in high concentrations [11].

Both rectal and oral routes of administration are commonly used in children. A maximum daily dose of 90 mg/kg/day is widely accepted as safe [12]; 60 mg/kg/day is recommended in neonates [13].

However, the dosing regimen that best maintains therapeutic levels has not been fully ascertained yet. Commonly, it is indicated as a dose of 10–15 mg kg^{-1} every 4 h orally and 15–20 mg kg^{-1} every 4 h rectally.

The hepatic glucuronide process in neonates is immature and they are likely to develop the reactive intermediate causing hepatocellular damage, despite a comparatively low level of the cytochrome P450 system. However, the constant rate for the sulphation metabolic pathway is higher in neonates than in adults and it is the most important route of metabolism. Anderson concluded that a rectal loading dose of 40 mg kg^{-1} followed by 30 mg kg^{-1} every 12 h or an oral loading dose of 30 mg kg^{-1} followed by 20 mg kg^{-1} every 8 h will achieve concentrations of 10–20 mg L^{-1} [14]. However, high doses of paracetamol have to be used to be effective and the problem of cumulative toxicity with repeated dosing has not been addressed yet in neonates. Therefore, Morton [15] concluded that caution is required when using the current maximum dosage for a period longer than 72 h.

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Nonsteroidal anti-inflammatory drugs (NSAIDs). The main benefits of NSAIDs in minor, moderate, and severe pain derive from an opioid-sparing effect. They can be introduced in a multimodal approach to enhance the quality of analgesia by combining drugs with central and peripheral effects. However, the clinical use of NSAIDs in the perioperative period should be limited due to the risk of homeostasis derangement caused by the inhibition in the production of thromboxane-A2 and the consequent decrease in platelet function. The effect of NSAIDs on clinical bleeding tendency is difficult to quantify and generally homeostasis remains below the upper limits found in healthy patients.

Diclofenac. Intraoperative use of rectal diclofenac (1 mg kg^{-1}) in 1–10-year-old children has been proven to provide a lower postoperative analgesia if compared to 1 ml kg^{-1} of caudal bupivacaine 0.25%, but a better pain control in the late recovery phase [16].

Ketorolac is an NSAID effective in most patients for postoperative pain relief. It has been used through the intravenous (0.5 mg kg^{-1}) or intramuscular (1 mg kg^{-1}) route; ketorolac has been demonstrated to significantly reduce opioid requirements and to shorten its time of permanence with no evidence of increased bleeding [17].

Opioids (morphine, fentanyl, sufentanyl) are the most commonly prescribed analgesics and are potent and effective in the treatment of moderate to severe pain. Opioids can be used safely in children with appropriate monitoring, dosing, and administration techniques. Pediatric dosing of analgesic drugs is presented in Table 35.3.

Patient-controlled analgesia (PCA) and nurse or parent controlled analgesia (NCA) are opioid delivery systems that allow the patient to administer a preset amount of opioids at preselected intervals.

PCA may be used in children as young as 5–6 years of age; children have control over their own analgesia, which has considerable psychological benefits. Kerschlbaum et al. [18] reported that the range of patients receiving opioids can be increased with NCA. Recent studies have focused on the prevention of side effects, such as postoperative nausea and vomiting during PCA morphine [19–22]. Routine prophylactic antiemetic treatment seems to be advisable during pediatric PCA. Tramèr et al. [19] showed evidence that droperidol is effective in preventing postoperative nausea and vomiting (PONV) in adult PCA, although the use of droperidol in children is to be cleared [20] as other antiemetic agents may be a more appropriate choice. Tropisetron, a long-acting 5-hydroxytryptamine-3 receptor antagonist, has been shown to reduce vomiting during PCA in children [21].

Busoni et al. [22] showed that dexamethasone reduces the incidence of vomiting when administered intravenously in children for common pediatric operations and this protective effect should be studied to prevent nausea during use of PCA. During adult PCA, ketamine reduced incidence of PONV [23]. This approach has not been examined yet in children. Tolerance and respiratory depression are other important side effects of opioids. Ketamine may be safe in adults to reduce tolerance [24] and respiratory depression during adult opioid administration [25]. These findings indicate that the inclusion of small doses of ketamine in balanced analgesia might be an interesting field for future pediatric pain research. In brief: opioids are effective but cause side effects; a multimodal approach to analgesia works better and offers the chance to lower the doses thus weaning faster from them.

Table 35.3 Pediatric dosing of analgesic drugs

Pediatric dosing of drugs	Dose	Epidural dose	Notes
Acetaminophen	10–15 mg·Kg^{-1} q4h	mg·Kg^{-1}	Can be given PO or PR max daily dose is 100
Naproxen	5 mg·Kg-$^{-1}$ q12h		Available as oral liquid
Ketorolac	0.5 mg·Kg^{-1} q6h		Should not be used for more than 5 d
Ibuprofen	4–10 mg·Kg^{-1} q6–8h		Available as oral suspension
Morphine	0.3 mg·Kg^{-1} q3–4h PO	0.02–0.05 mg·Kg-$^{-1}$	0.05–1 mg·Kg^{-1} q3–4h parenteral
Codeine	0.5–1 mg·Kg^{-1} q3–4h PO		
Fentanyl	15–20 μg·Kg^{-1} "lollipop"	1–2 μg·Kg^{-1}	0.5–1 μg·Kg^{-1} parenteral
Hydromorphone	0.05–0.1 mg·Kg^{-1} q3–4h		Only PO
Bupivacaine 125%	<5 Kg 0.8 mg·Kg^{-1} 5–15 Kg 0.5 mg·Kg^{-1} 16–35 Kg0.4 mg·Kg^{-1}	0.2 mg·Kg^{-1}·h^{-1}	Children 0.3–0.4mg·Kg^{-1}·h^{-1}
Ropivacaine 0.1%	<5 Kg 1 mg·Kg^{-1} 5–15 Kg 0.5 mg·Kg^{-1} 16–35 Kg 0.5 mg·Kg^{-1}	0.2 mg· Kg^{-1}·h^{-1}	Children 0.3–0.4 mg·Kg^{-1}·h^{-1}
Levobupivacaine 0.125%	<5 Kg 1 mg·Kg^{-1} 5–15 Kg 0.5 mg·Kg^{-1} 16–35 Kg 0.3 mg·Kg^{-1}	0.2 mg·Kg^{-1}·h^{-1} mg·Kg^{-1}·h^{-1}	Children 0.3–0.4

Epidural Analgesic Drugs

Regional and local anesthetic techniques are often used in children and provide the advantages of prolonged analgesia extending into the postoperative period and reduced distress and opioid requirement. The techniques are generally safe because infants and young children appear to be relatively resistant to the hemodynamic and respiratory effects of epidural anesthesia. The safe use of local anesthetic drugs in neonates requires appropriate training, resuscitation facilities, and an understanding of the differences between the pharmacologies of these drugs in neonates compared

with children and adults (Table 35.3).

Ropivacaine is a widely used local anesthetic with a wider margin of safety for pediatric patients. Ropivacaine 0.2% appears to be optimal in terms of producing adequate analgesia with an acceptable motor blockade; the use of ropivacaine 0.3% was associated with a higher incidence of motor block and minimal improvement in postoperative pain relief if compared with 0.2% [26]. Higher concentrations of ropivacaine (0.3%) have been demonstrated to provide less motor blockade if compared with equal volumes and concentrations of bupivacaine [27]. When a longer duration is needed, with no motor block, clonidine, 2 mg kg^{-1}, or preservative-free ketamine, 0.5 mg kg^{-1}, will prolong analgesia [25–26]. However, the main interest is for the safe profile of ropivacaine. It has been used successfully in children, infants, and neonates in continuous infusion through lumbar epidural catheter, although pharmacokinetic data are limited to these over 3 months old [27].

Levobupivacaine is a new local anesthetic. It is a single-isomer formulation [S(-)-enantiomer of bupivacaine] supposed to have less toxicity in comparison with the racemic formulae. Studies in human volunteers confirm a minor arrhythmogenic and less negative inotropic effect, if compared with bupivacaine [28]. Studies in the pediatric population have been performed, using levobupivacaine for peripheric and central blocks. Levobupivacaine reduced the rescue analgesia administration providing effective analgesia and less intense motor block compared with bupivacaine [29]. Therefore, the reduced toxicity of bupivacaine gives a wider safety margin in daily clinical practice both for single and continuous infusion in pediatric patients. Recent studies in children showed that caudal levobupivacaine and ropivacaine have a similar potency [30].

Opioids given epidurally providing analgesia that is effective and relatively free of side effects because much smaller doses are used. Epidural opioids are avoided or used with caution in infants and children at risk. As a general principle an epidural dose is 1/10th of IV [31,32] (Table 35.3).

Pain During Medical Procedures

Chronic diseases imply a long-term therapy with diagnostic and therapeutic procedures which are often painful and invasive. Putting the child in such conditions as to limit the traumatic effects of these procedures is a crucial component of the therapy plan. The fact that intrusive procedures are experienced by children as absolutely traumatic and painful events is well documented. Even though the pain connected to the procedures represents a short-term experience, an intense level of fear and anxiety accompanies it. For example, some researchers [33,34] have realized that children with cancer perceive bone marrow aspiration (BMA), biopsy, and lumbar puncture (LP) as being extremely painful. For the treatment of procedural pain in pediatrics it is worth following some basic principles listed in Table 35.4.

The techniques used to control procedural pain are mainly of the medical and nonmedical kind [35]. Treatment must be customized for every child, that is to say, the best technique for pain control should be detected, according to the child's needs

Table 35.4 Recommendations for pain management during medical procedures

Supply child and parents with adequate information and psycho-emotional support.
Ensure the most accurate treatment of pain and anxiety from the first procedure to reduce symptoms of anticipatory anxiety.
Make sure that the staff in charge of the procedures has an adequate knowledge of the child's behavior and of the medical treatments of acute pain and anxiety.
Use appropriate monitoring and reanimation equipment in the room where the procedure is carried out, once sedation is given.
Make sure that the operator carrying out the pediatric procedure is manually skilled.
Evaluate the child behavior in order to assess the effectiveness of the treatment of pain and anxiety.
Recreate an environment as pleasant as possible in the place used for the treatments.

and personal characteristics.

An essential part of pain treatment is the measurement of the pain itself, by means of specific instruments adapted to the age of the child. Along with pain measurement, sedation should be measured in order to verify the effectiveness of the method used to control pain and to monitor possible collateral effects.

Nonmedical Techniques

Nonmedical interventions for pain control are psychological techniques, which achieve very good results in those children who must undergo various procedures. These pain control techniques are easily learned. Distraction, muscular relaxation, and guided imagination are easy-to-learn techniques and can be used with children, even from a very early age. The aim is to divert the child's attention from the physical component of the pain connected to the painful procedure [36,37].

Armstrong et al. [38] demonstrated the role played by the preparation of children to anesthesia. The therapy "game" can be an effective method of giving appropriate information on the surgical operation and at the same time of relieving the fear connected to it. For Bowmer [39] games are a simple method of helping children to moderate their fear when they are in the hospital. The results are remarkable and involve the child, who appears quieter and less anxious, as well as parents and medical staff. However, it must be pointed out that nonmedical techniques are a supplement to the medical approach. Each technique calls for a previous knowledge of child and parents; it is also important that each child chooses the technique he/she prefers and makes it his/her own (Table 35.5).

Tabella 35.5 Nonmedical techniques based on child's age

Age	Techniques
0–2 years	Physical contact with the child: touching, stroking, and rocking. Listen to music, toys above the cradle.
2–4 years	Play with puppets, tell stories, read books, breathing and bubbles, magic glove.
4–6 years	Breathing, story-telling, playing with puppets, speaking about favorite places, watching television, magic glove, visualization, involvement.
6–11 years	Music, breathing, counting, speaking about favorite places, watching TV, visualization, switch game.
11–13 years	Music, breathing, visualization, switch game.

Medical Techniques

The medical treatment for procedural pain must guarantee both sedation and an effective analgesia [40]. Our medical approach is: local anesthesia, conscious sedation, deep sedation, general anesthesia. Local anesthesia should never be forgotten whether using medical or nonmedical techniques. In children, we cannot mark out a line between deep sedation and anesthesia: speaking of general anesthesia would definitely be more appropriate. The "first painful procedures" represent a fundamental diagnostic and therapeutic moment for a tumor-affected child. Therefore, general anesthesia should possibly be performed inside the ward in the presence of parents, if they can stand it and wish to assist the child during induction maneuvers.

Conscious sedation can be used in the posttreatment phases, when the child has become familiar with the procedures. After the first few times children and their families start to "get acquainted with the illness;" they know doctors, nurses and other hospital workers. By means of adequate information and the support of a psychologist we offer them the opportunity to choose whether they want to "sleep" or to use some "magic" technique (nonmedical techniques) for lumbar puncture; for bone marrow aspiration conscious or deep sedation should be preferred. Local anesthesia and nonmedical techniques must be used for intravenous cannulation and blood tests (Table 35.6).

Pain in Pediatric Intensive Care

Provision of optimum comfort control to a critically ill child in the Pediatric Intensive Care Unit (PICU) requires a great degree of skill and planning and should be a prime concern for all practicing pediatricians. Failure to provide adequate sedation and analgesia to control the stress response has been seen to be associated with increased complications and mortality [41]. Anxiolysis and pain control are a duty

Table 35.6 Drugs and antagonists used for conscious sedation in children

Drug	Dose (mg/kg)	Onset (min)	Indication
Midazolam	OR, IR: 0.5–0.75 IN, SL: 0.2–0.5 IV: 0.2 INF: 1–10 μg/kg/min	2–3	Short procedures Prolonged MV
Propofol	IV: Loading dose: 2–3 INF: 1–4 mg/kg/h	1–2	Short procedures Short MV
Ketamine	IM: 3–5IV: Loading dose: 1–3 INF: 0.7–3 mg/kg/h	0.5–1	Short procedures Intubation in acute severe asthma
Thiopental	IV: Loading dose: 3–5 INF: 1–5 mg/kg/h	Immediate	Intubation in ICH
Dexmedetomidine	IV: Loading dose: 1 μg/kg INF: 0.2–0.75 μg/kg/h	2–5	Short MV

for physicians and must be treated very carefully in PICUs, although it is very difficult to assess them: in critically ill children sedatives and/or analgesic medications are routinely provided and titrated to obtain a satisfactory level of sedation, but different evaluation scores are needed to discriminate between light or inadequate and deep or excessive sedation, especially when the clinical examination is unavailable. The ideal approach should be an administration of sedative and hypnotic: sedatives are necessary to reduce the anxiety and agitation that result from the admission to a "hostile" environment and from medical procedures; analgesics are used to treat pain secondary to surgical interventions and/or invasive methods, besides the pain inflicted by the disease itself. Moreover, the combined use of analgesics and sedatives allows patients to adapt to mechanical ventilation through the hypnotic effects of these drugs, respiratory depression, and cough reflex [42].

Therefore, it is essential to provide the right drug for the problem at the right time in the right dosage. However, the incorrect use of sedatives and analgesics may have negative effects, causing a prolonged necessity for ventilatory support, increasing mortality and morbidity, and lengthening the PICU stay. The use of protocols that facilitate the selection of appropriate drugs and their adequate administration and careful monitoring can improve the quality of sedation and analgesia and prevent their adverse effects. There is a wide availability of sedative and analgesic drugs that can be used in critically ill children, and each one of them has advantages and disadvantages. Nevertheless, no analgesic or sedative meets all the criteria of an ideal drug: rapid onset of action, short half-life, metabolization and elimination by organs that are less susceptible to failure (liver and kidney), minimum secondary effects without hemodynamic or respiratory involvement, no interaction with their drugs,

and availability of a specific antidote. There is a paucity of reviews and practical guidelines for the use of sedatives, analgesics, and muscle relaxants in critically ill children [43,44], and most recommendations are based on experience with adult patients [45]. It is usual to associate a benzodiazepin with an opioid, more often Midazolam and Morphine or Fentanyl, or Remifentanyl. A recent survey of sedation assessment and management in Australian and New Zealand pediatric intensive care showed only half of the units had guidelines for sedation management, and most units did not use validated pediatric scales to assist staff in assessing patient sedation and pain levels [46].

Sedative Drugs

Sedation is necessary in many PICU children, especially in those who need ventilatory support. There are a wide variety of drugs with different indications, but there is no sedative that will be excellent in all situations. Table 35.7 summarizes the basic characteristics of the most important drugs. The selection of the drug depends on several factors, such as age, disease, and organ dysfunction/failure.

Analgesic Drugs

As occurs with sedation, there is no such thing as an all-purpose analgesic, and the selection of drugs depends on numerous factors. Opioid derivatives and nonsteroidal anti-inflammatory drugs are the most widely used analgesics in critically ill patients. Opioids are the drugs of choice for mechanically ventilated patients, especially if combined with benzodiazepines, since they have shown a synergistic effect that allows reducing the dose of both medications. Morphine and fentanyl are widely used in continuous infusion, but remifentanil and tramadol have been increasingly used as well [47]. Table 35.8 summarizes the characteristics of the most commonly used drugs.

Analgesic and Sedative Drugs

Dexmedetomidine in intravenous infusion has a sedative and analgesic effect due to their action on alpha-2 receptors, minimizing the need for opioids. It may be very useful in the immediate postoperative period, facilitating early extubation. The use of dexmedetomidine was initially considered as a sedative to be used in mechanically ventilated adults, but now its use in children is also documented. Although dexmedetomidine has been primarily investigated for its sedative effect, it apparently has analgesic effects that are appropriate for cases where opioids are needed, therefore allowing for a lower opioid use [48] (Table 35.7).

Table 35.7 Characteristics of some sedatives used in children

Drugs	Dose	Side effects	Antagonists
Midazolam: benzodiazepine			
Short-term action	OR: 0.3–0.5 mg/kg; 30–45 min before procedure; max: 20 mg	Respiratory depression, apnea, amnesia, altered vision	Flumazenil: 0.2 mg/dose every min; max cumulative dosage = 1 mg
Onset: 2–3 min			
Fentanyl			
Opioid	IV: 1–2 mcg/kg/dose	Respiratory depression, apnea, convulsions, chest rigidity (more frequent after high doses or rapid infusion)	Naloxone: 5–10 mcg/kg/dose
Onset: 1–2 min			Max.: 0.2 mg
Morphine			
Opioid	IV: 0.05–0.1 mg/kg	Sedation, sleepiness, respiratory depression, itching, nausea, vomiting	Naloxone: 5–10 mcg/kg/dose
Onset: 20 min			Max.: 0.2 mg
Propofol			
Anesthetic	IV: 1–4 mg/kg followed by 75–100 mcg/kg/min	Pain upon injection, involuntary movements, hypotension, apnea (more frequent in case of high doses or rapid infusion)	None
Onset: Immediate	IV: 1–4 mg/kg followed by 75–100 mcg/kg/min		

Nonpharmacological Treatment

Several nonpharmacological interventions can improve the routine of children in the PICU, reducing their anxiety, improving their sleep-wake cycles, and minimizing the necessity for sedative and analgesic drugs. Music therapy has proven efficient in overcoming anxiety and increasing relaxation of critically ill patients of any age, including preterm infants [49]. Other effective measures include noise control in the PICU, control of lighting to maintain the day and night pattern and the sleep-wake cycle, massage, and communication, if the patient's age and health status allow [50,51].

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Table 35.8 Characteristics of some drugs used in critically ill children

Drug	Dose (mg/kg)	Onset (min)	Indication	Notes
Morphine	IV: 0.1–0.2 mg/kg/4–6 h INF: 10–40 μg/kg/h	20	Sedation and analgesia in MV Acute or chronic pain	Pulmonary edema Lower dose in renal or liver failure Releases histamine Nausea and vomiting
Fentanyl	IV: 1–3 μg/kg INF: 1–10 μg/kg/h	1–2	Short painful procedures	Prolonged clearance Thoracic rigidity after quick admini stration
Remifentanyl	IV: 1 μg/kg INF: analgesic: 0.5–6 μg/kg/h Sedation 6–12 μg/kg/h	1	Sedation and ana gesia in MV Immediate postope rative period	Immediate clearance Better hemodyna mic tolerance Thoracic rigidity after quick admini stration
Tramadol	IV: 1–2 mg/kg/4–6 h INF: 0.2–0.4 mg/kg/h	10	Acute pain	Good hemodynamic tolerance Less respiratory depression
Ketorolac	OR: 2 mg/kg/day every 6–8 h IV, IM/kg/6 h mg/kg/6 h	30	Moderate to severe pain	Anti-inflammatory drug Gastrointestinal bleeding Nephrotoxicity
Paracetamol	IV: 10–15 mg/kg/6 h	30	Moderate pain	Hyperthermia Central action Hepatotoxicity

Monitoring of Sedation and Analgesia

The challenges of sedation in critically ill children include avoidance of oversedation and its accompanying risks of cardiovascular depression, worsened withdrawal syndromes, and prolonged duration of mechanical ventilation. The monitoring of sedation level is key to avoiding undersedation, which causes suffering to the patient, and oversedation, which delays extubation.

Clinical scores are the most common tools for monitoring the levels of sedation. The Ramsay and Comfort scores are the most widely used tools for determining the level of sedation in pediatrics patients. The Ramsay score (Table 35.9) has not been validated in children, and it is not useful in relaxed patients. In addition, it uses auditory and painful stimuli to evaluate responses, which increases its subjectivity. The Comfort score (Table 35.10) was designed for mechanically ventilated children and does not require the use of any stimulus for evaluation. However, these scores are limited, since they are subjective, their assessment is intermittent, and they sometimes give more importance to pain sensitivity than to the sedation level. Moreover, their usefulness is limited in deep levels of sedation and in patients with muscle relaxation.

In addition, it is more time-consuming and complex; it assesses both objective and subjective parameters; it includes variables such as heart rate and blood pressure, which change in critically ill patients as a result of several other factors, and it has not been validated in children with muscle relaxation. Ista has described a simplified Comfort score with the same value as the original score, in which physiological variables were eliminated [52].

Over the last few years, several methods have been developed that allow objective assessment of the level of consciousness by analyzing electroencephalographic findings, such as the bispectral index (BIS), auditory evoked potentials of intermediate latency, and analysis of electroencephalographic (EEG) spectra [53]. The BIS monitor has been well validated in the pediatric anesthesiology literature and shows potential for use in the PICU. The assessment of pain in the PICU is much more difficult, especially in mechanically ventilated sedated patients. Quite often, it is not possible to make a distinction between pain and anxiety, and both should be treated simultaneously. To assess pain, different scales have to be used for each stage of childhood (Table 35.1).

Table 35.9 Ramsay Sedation Scale

1. Patient is anxious and agitated or restless, or both
2. Patient is cooperative, oriented, and tranquil
3. Patient responds to commands only
4. Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5. Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6. Patient exhibits no response

Table 35.10 Comfort scale

Variable	1	2	3	4	5
Alertness	Deeply asleep	Lightly asleep	Drowsy	Fully awake and alert	Hyperalert
Calmness/agitation	Calm	Slightly anxious	Anxious	Very anxious	Panicky
Respiratory response	No coughing and no spontaneous respiration respiration	Spontaneous respiration with little or no response to ventilation	Occasional cough or resistance to ventilator	Actively breathes against ventilator or coughs regularly	Fights ventilator, coughing or choking
Physical movement	No movement	Occasional, slight movement	Frequent, slight movement limited	Vigorous movement movement to extremities	Vigorous movement including torso and head
Mean arterial blood pressure	Blood pressure below baseline	Blood pressure consistently at baseline	Infrequent elevations of 15% or more	Frequent elevation of 15% or more above baseline	Sustained elevation of 15% or more
Heart rate	Heart rate baseline	Heart rate consistently at baseline	Infrequent elevations of 15% or more baseline	Frequent elevations of 15% or more above	Sustained elevation of 15% or more above
Muscle tone	Muscle totally relaxed, no muscle tone	Reduced muscle tone	Normal muscle tone	Increased muscle tone and flexion of fingers and toes	Extreme muscle rigidity
Facial tension	Facial muscles totally relaxed	Facial muscle tone normal, no facial muscle tension evident	Tension evident in some facial muscles	Tension evident throughout facial grimacing	Facial muscles contorted

Conclusions

Significant advances in the assessment and management of pain in children are supported by an increase in the availability and accessibility of evidence-based data. There will probably never be an ideal analgesic, but sufficient information is available to enable adequate relief of pain using both pharmacological and nonpharmacological approaches. The provision of adequate analgesia in neonates with severe pain requires intensive monitoring. The humanitarian goal of relieving the infant's pain remains paramount.

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Obstetrics at High Risk

36

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Introduction and Definition

The Confidential Enquiry into Maternal and Child Health 2003–2005 is the 7th triennial report into maternal deaths in the UK. The anesthesia chapter from Saving Mothers' Lives, concerning maternal mortality due to anesthesia, is the 18th in a series of reports within the Confidential Enquires into Maternal and Child Health and reviews the causes of maternal deaths in the UK making recommendations for improvements in care [1].

Maternal deaths in The Confidential Enquiry are classified into Direct, Indirect, Coincidental, and Late Group. Direct maternal deaths are those resulting from conditions or complications or their management which are unique to pregnancy, occurring during the antenatal, intrapartum, or postpartum period. Indirect maternal deaths are those resulting from previously existing disease or disease that develops during pregnancy, not due to direct obstetric causes, but which were aggravated by physiologic effects of pregnancy. Coincidental is defined as the death of a woman while pregnant or within 42 days of the end of her pregnancy, irrespective of cause. Late maternal death, defined as the death of a woman from Direct or Indirect causes more than 42 days but less than one completed year after the end of the pregnancy [2].

The Confidential Enquiries Report considered all the deaths in pregnant women or those who died within 42 days of giving birth between the years 2003 and 2005 inclusive in the UK. Two hundred ninety-five women died from conditions directly (132) or indirectly (163) related to pregnancy, out of more than two million births, giving a maternal mortality rate of 13.95 per 100,000 pregnancies [3]. This is a slight increase from the last Report due to an increase in direct deaths, but is not statistically significant. Although the overall maternal death rate from indirect causes is still

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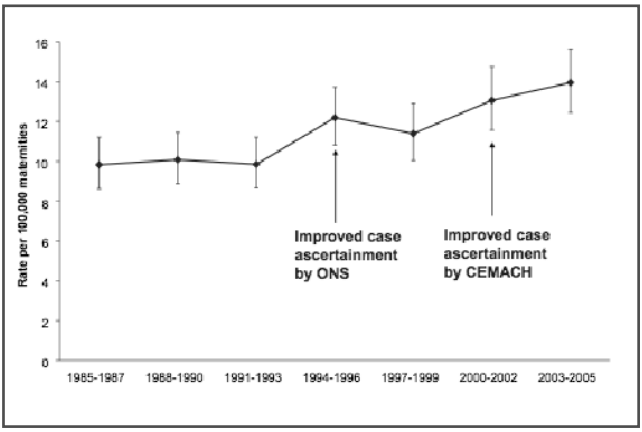

Fig. 36.1 Overall maternal mortality rate (deaths from Direct and Indirect causes combined) per 100,000 maternities; United Kingdom: 1985–2005

higher than for deaths from direct causes, the gap between them is narrower (Fig. 36.1).

The possible reasons for the lack of decline of the overall mortality rate are multifactorial: the mean age of motherhood is increasing, overweight or obesity, smoking, substance abuse, lifestyles, influx of economic migrants, and between 2001 and 2005 an increase in fertility from 1.63 to 1.84. The commonest cause of direct death was again thromboembolism, the rates for which remain largely unchanged since 1997–1999.

Cardiac disease was the most common cause of indirect death, as well as for maternal deaths overall; this reflects the growing incidence of acquired heart disease in younger women related to poor diets, smoking, alcohol, and obesity. More than half of all the women who died from direct or indirect causes were either overweight or obese. More than 15% of all women who died from direct or indirect causes were morbidly or super morbidly obese [4] (Tables 36.1, 36.2).

As in the last report, among anesthetic deaths, 100% are classed as avoidable. Indirect death rates are now more numerous than direct death rates. The major single cause of maternal death was cardiac disease, which accounted for 48 out of the 163 indirect deaths. This large number reflects the increasing importance of indirect deaths, as it may be compared with thromboembolic conditions, which were the cause of 41 of the 132 direct deaths. The largest group is those deaths caused by myocardial infarction or ischemic heart disease, which totaled 16. Age was a factor in these deaths, with a median age of 35 for these women, although other "lifestyle factors" such as smoking and obesity were also blamed. The recent increase in indirect mortality reflects an increase in cardiac mortality; cardiac disease is now the second most common cause of maternal death after psychiatric causes and is more common than the most frequent direct cause of maternal death, thromboembolism. Other examples of indirect deaths include deaths from epilepsy, diabetes, cerebral hemorrhage, and HIV infection. Despite another decrease in this triennium, venous thromboembolism is still the leading direct cause of maternal death in the UK. Hemorrhage is a critical problem and the mortality rate per million maternities has more than doubled since the last triennium (Table 36.3).

Table 36.1 Numbers of maternal deaths from Direct and Indirect causes by BMI and percentages overweight or obese; United Kingdom: 2003–2005

	BMI						Total with BMI 25	Total n. with known BMI	Not stated or recorded
	Less than 20	20-24	25-29	30-34	35-39	40-60			
	n	n	n	n	n	n	n (%)	n (%)	
Direct									
Thromboembolism	3	8	6	6	2	6	20 (65)	31 (100)	10
Pre-clampsia / eclampsia	1	8	6	0	1	2	9 (50)	18 (100)	1
Haemorrhage	2	6	2	3	2	0	7 (47)	15 (100)	2
AFE	2	6	4	0	2	0	6 (43)	14 (100)	3
Early pregnancy	0	4	0	1	1	0	2 (33)	6 (100)	8
Sepsis	1	2	5	2	0	1	8 (73)	11 (100)	7
Anaesthetic	0	2	0	0	1	1	2 (50)	4 (100)	2
All Direct	9	36	23	12	9	10	54 (55)	99 (100)	33
Indirect									
Cardiac	4	9	14	6	4	5	29 (69)	42 (100)	6
Other Indirect	8	35	12	10	4	1	27 (39)	70 (100)	17
Psychiatric	3	4	4	0	0	2	6 (46)	13 (100)	5
Malignancies	2	2	2	0	0	1	3 (43)	7 (100)	3
All/indirect	17	50	32	16	8	9	65 (49)	132 (100)	31
All	26	86	55	28	17	19	119 (52)	231 (100)	64

Table 36.2 Risks related to obesity in pregnancy for the mother and for the baby

For the mother
Increascd risks include
- Maternal death or severe morbidity
- Cardiac disease
- Spontaneous first trimester and rccurrent miscarriage
- Pro-eclampsia
- Gestational diabetes
- Thromboembolism
- Post caesarean wound infection
- lnfection from other causes
- Post partum haemorrhage
- Low breast feeding rates

For the beby
Increascd risks include
- Stillbirth and neonatal death
- Congenital anormalities
- Prematurity

Table 36.3 Numbers and rates per 100,000 maternities of maternal deaths reported to the Enquiry by cause; United Kingdom:1985–2005

Cause of death	1985 1987	1988 1990	1991 1993	1994 1996	1997 1999	2000 2002	2003 2005	1985 1987	1988 1990	1991 1993	1994 1996	1997 1999	2000- 2002	2003 2005
	Numbers							Rates per 100.000 maternities						
Direct deaths														
Thrombosis and thromboembolism	32	33	35	48	35	30	41	1.41	1.40	1.51	2.18	1.65	1.50	1.94
Pre-eclampsia and eclampsia	27	27	20	20	16	14	18	1.19	1.14	0.86	0.91	0.75	0.70	0.85
Hemorrhage	10	22	15	12	7	17	14	0.44	0.93	0.65	0.55	0.33	0.65	0.66
Amniotic fluid embolism	9	11	10	17	8	5	17	0.40	0.47	0.43	0.77	0.38	0.25	0.80
Early pregnancy deaths	16	24	17	15	17	15	14	0.71	1.02	0.73	0.68	0.80	0.75	0.66
Ectopic	11	15	9	12	13	11	10	0.48	0.64	0.39	0.55	0.61	0.55	0.47
Spontaneous miscarriage	4	6	3	2	2	1	1	0.18	0.25	0.13	0.09	0.09	0.05	0.05
Legal termination	1	3	5	1	2	3	2	0.04	0.13	0.22	0.05	0.09	0.15	0.09
Other	0	0	2	0	0	0	1	0.00	0.00	0.09	0.00	0.00	0.00	0.14
Genital tract sepsis	9	17	15	16	18	13	16	0.40	0.72	0.65	0.73	0.85	0.65	0.85
Other direct	27	17	14	7	7	8	4	1.19	0.72	0.60	0.32	0.33	0.40	0.19
Genital tract trauma	6	3	4	5	2	1	3	0.26	0.13	0.17	0.23	0.09	0.05	0.14
Fatty liver	6	5	2	2	4	3	1	0.26	0.21	0.09	0.09	0.19	0.15	0.05
Other causes	156	9	8	0	1	4	0	0.66	0.38	0.35	0.00	0.05	0.20	0.00
Anesthetic	6	4	8	1	3	6	6	0.26	0.17	0.35	0.05	0.14	0.30	0.28
All direct	**139**	**145**	**128**	**134**	**106**	**106**	**132**	**6.13**	**6.14**	**5.53**	**610**	**4.99**	**5.31**	**6.24**
Indirect														
Cardiac	23	18	37	39	35	44	48	1.01	0.76	1.60	1.77	1.65	2.20	2.27
Psychiatric	-	-	-	9	15	16	18	-	-	-	0.41	0.71	0.60	0.85
Others	62	75	63	86	75	90	87	2.73	3.18	2.72	3.91	3.53	4.51	4.12
Malignancies	-	-	-	-	11	5	10	-	-	-	-	0.52	0.25	0.47
All indirect	**84**	**93**	**100**	**134**	**136**	**155**	**163**	**3.70**	**3.94**	**4.32**	**6.10**	**6.40**	**7.76**	**7.71**
Coincidental	**26**	**39**	**46**	**36**	**29**	**36**	**55**	**1.15**	**1.65**	**1.99**	**1.64**	**1.37**	**1.80**	**2.60**
Late														
Direct	-	13	10	4	7	4	11							
Indirect	-	10	23	32	39	45	71							

Worldwide maternal mortality is the health index that shows the greatest disparity between developed and limited resources countries. Maternal deaths in developed countries continue to decline, maternal mortality statistics are essentially similar in the USA and UK [5]. However, the situation is completely different in countries with limited resources, where maternal mortality exceeds 0.5 million each year. More than 99% of all maternal deaths occur in that community where simple clinical interventions could reduce significantly the mortality rate in the mother and the child. One of the Millennium Developmental Goals is the reduction of maternal mortality by three quarters by the year 2015 [6].

Thromboemolic Disease

Pregnant women and, in particular, those with a history of thromboembolic disease are at high risk during pregnancy. The reported incidence of deep vein thrombosis (DVT) and nonfatal pulmonary embolism varies considerably because of the peculiar diagnostic difficulties in pregnancy. Real time ultrasound scanning combined with Doppler studies, being noninvasive, are the first line diagnostic techniques for DVT in pregnancy [7]. The following are the recommendations of the College of Obstetricians and Gynecologists :

- Pregnant patients with a history of isolated venous thrombosis directly related to a transient, highly thrombogenic event (orthopedic trauma, complicated surgery) in whom an underlying thrombophilia has been excluded may be offered heparin prophylaxis or no prophylaxis during the antepartum period. However, they should be counseled that their risk of thromboembolism is likely to be higher than the normal population. Prophylactic warfarin should be offered for 6 weeks postpartum.
- Pregnant patients with a history of idiopathic thrombosis, thrombosis related to pregnancy or oral contraceptive use, or a history of thrombosis accompanied by an underlying thrombophilia other than homozygous for the factor V Leiden mutation, heterozygous for both the factor V Leiden and the prothrombin G20210A mutation, or antithrombin-III (AT-III) deficiency should be offered antepartum and postpartum low-dose heparin prophylaxis.
- Patients without a history of thrombosis but who have an underlying thrombophilia and have a strong family history of thrombosis also are candidates for antepartum and postpartum prophylaxis. At the minimum, postpartum prophylaxis should be offered.
- Pregnant patients with a history of life-threatening thrombosis, with recent thrombosis, with recurrent thrombosis, receiving chronic anticoagulation, or patients with thrombosis found to be AT-III deficient, homozygous for the factor V Leiden mutation or prothrombin G20210A mutation, heterozygous for both the factor V Leiden and the prothrombin G20210A mutation should be given adjusted-dose heparin every 8 h to maintain the activated partial thromboplastin time (APTT) at least 1.5 times control throughout the dosing interval. Low-molecular-

weight heparin (LMWH) administered twice daily also is an alternative.

- Patients at risk for thrombosis should receive warfarin postpartum for 6 weeks to achieve an international normalized ratio (INR) of approximately 2.0 to 3.0. Heparin should be given immediately postpartum with warfarin for at least 5 days until the INR is therapeutic.
- Patients with antiphospholipid syndrome and a history of thrombosis require adjusted-dose prophylactic anticoagulation.
- Patients who are candidates for either prophylactic or therapeutic heparin may be given enoxaparin or dalteparin during pregnancy. However, because of the lack of data regarding adequate dosing during pregnancy, antifactor Xa levels may be monitored [8–12]. The safety of epidural anesthesia with twice daily dosing of LMWH is of concern and should be withheld until 24 h after the last injection [13]. Epidural anesthesia appears to be safe in women taking unfractionated low-dose heparin if the APTT is normal. The major concerns with heparin use during pregnancy are not fetal but maternal and include heparin-induced osteoporosis and heparin-induced thrombocytopenia (HIT) [14]. Bleeding is also an issue. Warfarin derivatives cross the placenta. A skeletal embryopathy resulting in stippled epiphyses and nasal and limb hypoplasia can occur when warfarin is given between 6 and 12 weeks of gestation. Midtrimester exposure may result in optic atrophy, microcephaly, and developmental delay. Bleeding can occur in the fetus at any time, resulting in a high fetal loss rate.

Hypertensive Disease

Hypertensive disease of pregnancy is one of the most common direct causes of maternal death in the developed world [15]. The largest single cause of death among women with pre-eclampsia and eclampsia in the UK is intracranial hemorrhage, reflecting a failure of effective antihypertensive therapy. HELLP syndrome associated with pre-eclampsia is another cause of death [16]. Gestational hypertension occurs after 20 weeks gestation and returns to normal within 3 months of delivery. It has none of the other features of pre-eclampsia. Eclampsia indicates the occurrence of seizures in a parturient who may have no underlying pathology. Pre-eclampsia is a complex multisystem disorder that may sometimes precede eclampsia. There are several definitions of pre-eclampsia, but they generally involve hypertension occurring after 20 weeks with the involvement of at least one other organ system, for instance headache or epigastric pain. Hypertension in pregnancy is defined as a systolic pressure of >140 mmHg and/or a diastolic pressure of >90 mmHg.

Pathophysiology

Hypertension affects 10% of all pregnancies and pre-eclampsia complicates approximately 2–8% in the UK. It also occurs more frequently in a woman who has previ-

ously suffered from pre-eclampsia. Other risk factors include diabetes, obesity, advanced age, nulliparity, and a family history of pre-eclampsia. The presence of antiphospholipid antibodies and other autoimmune and chronic disease increase the likelihood of pre-eclampsia. PET is a multisystem disorder of endothelial dysfunction, characterized by widespread increased capillary permeability and generalized vasoconstricted hypovolemic circulation with a lower cardiac output. However, the hemodynamic findings in pre-eclampsia are complex and vary widely between studies. Circulating catecholamines and administered vaso-active drugs may cause exaggerated responses. A high index of suspicion must be maintained even when the classic signs and symptoms are mild. Patients with pre-eclampsia are at risk of developing pulmonary edema. Early in the disease process the hypercoagulable state of normal pregnancy may be enhanced. Later on, both platelet activation and consumption are increased which can lead to significant thrombocytopenia (platelet count <100,000 mm3) in approximately 15% of women with severe pre-eclampsia. DIC occurs in 7% of cases of severe pre-eclampsia. Renal tubular function deteriorates relatively early in pre-eclampsia. The proteinuria of severe pre-eclampsia occurs later and reflects an ischemic insult to the glomerulus. Normal individuals have an upper limit of proteinuria of about 100 mg/day which is exceeded up to 500 mg/day. Most patients who develop oliguria respond to optimization of the intravascular volume status. Abnormal liver function tests are frequently found in pre-eclampsia [17]. More rarely, epigastric pain may be a symptom of tension on the capsule of the liver caused by edema or intrahepatic hemorrhage. HELLP syndrome is the well-recognized association of Hemolysis, Elevated Liver enzymes and Low Platelets. The neurological changes associated with severe pre-eclampsia include headaches, visual disturbances, and hyperreflexia [18]. This may culminate with seizures (eclampsia) due to cerebral vasospasm and reduced blood flow [19].

Treatment

Treatment is focused on control of blood pressure, correction of intravascular volume and symptomatic organ support, and prevention of complications. Delivery remains the only curative treatment for pre-eclampsia, although the disease process may not resolve immediately. Commonly used oral antihypertensives include methyl dopa, a centrally acting alpha-2 agonist; labetalol; and beta blocker nifedipine, a calcium channel blocker. Hydralazine or labetalol are commonly used for acute control of a rising diastolic pressure or resistant. It is now accepted that magnesium sulphate ($MgSO_4$) is the anticonvulsant of choice in preventing and treating eclamptic fits. Magnesium sulphate is usually administered as a slow intravenous bolus of 4–6 g and then as an infusion of 1–2 g per hour to keep the serum Mg in the therapeutic range. Treatment of overdose is supportive in the first instance and also includes intravenous calcium (e.g., calcium gluconate 1 g). Magnesium therapy is often continued for at least 24 h post partum [20]. Clinical indicators of magnesium toxicity include the absence of tendon reflexes and decreased respiratory rate. ECG changes occur (P–Q interval prolonged, QRS complex widened) which may progress to conduction defects and cardiac arrest. The risks increase in the presence

of oliguria since magnesium depends on the kidneys for excretion. Assessment of the coagulation status of the blood is essential before regional anesthesia, particularly in severe pre-eclampsia. Thrombocytopenia correlates with the severity of pre-eclampsia but there is no absolute level of platelet count that accurately predicts the occurrence of bleeding associated with regional anesthesia. If the platelet count is less than 80,000 mm3 then further assessment of the coagulation status is justified. The results of the PT, APTT, and perhaps thrombo-elastography can be compared with the normal range for pregnant patients. When caesarean section is required the relative risks of general and regional anesthesia cases must be assessed on an individual basis. Regional anesthesia is usually considered safer [21]. The added risks associated with general anesthesia include airway difficulties due to edema (often aggravated by tracheal intubation), and the pressor response to laryngoscopy and extubation. If a working epidural is already present this should be extended for surgery. Spinal anesthesia is currently controversial in PET—the anticipated potential risks of pulmonary edema, profound cardiovascular instability, possibly from a fall in cardiac output, and the consequent recourse to intravenous fluids and vasoconstrictors, suggest it is not a technique to be recommended in PET.

However, limited data supporting the use of spinal anesthesia in pre-eclampsia do exist, although information from a larger number of patients, preferably in randomized prospective trials, is urgently required. Sequential CSE (low-dose spinal then epidural top-ups) may prove useful. Fulminant PET (and the risk of an eclamptic seizure occurring during surgery) is considered a contraindication to regional block by some authors, but many anesthetists would still choose a regional technique where possible. Even following an eclamptic convulsion, providing the patient has recovered airway reflexes, is cooperative, and has been commenced on appropriate therapy (i.e., including magnesium sulphate), a regional technique may be considered preferable to general anesthesia. When general anesthesia is chosen, care should be taken to reduce the pressor response to laryngoscopy. Several techniques have been described to abolish this, but none are completely reliable. A bolus of $MgSO_4$ may be the most effective technique, although newer agents such as esmolol and remifentanil may find a role with further experience. Extubation may be particularly hazardous due to aggravation of airway edema leading to acute upper airway obstruction, and fulminant patients with marked edema or airway compromise should be sent to the ICU for postoperative ventilation and stabilization. Whether a regional or general anesthetic technique is used for caesarean section, adequate recovery facilities are mandatory, and patients need high dependency nursing for at least 24 h.

Specific Heart Diseases in Pregnancy

The parturient with heart disease, whether congenital or acquired, represents a challenge even for the experienced anesthesiologist [22,23]. The main goal in the management of these patients is to prevent further derangement of cardiac function during labor in a heart, which is already stressed by the “physiological” changes of pregnancy with the potential to precipitate heart failure. This can be accomplished by effective anxiolysis, analgesia, and anesthesia. Ultimately, the aim of any anesthetic intervention is to ensure the well-being of both the mother and the fetus. Accurate cardiovascular monitoring during labor

and in the puerperium is essential in the management of all parturients with heart disease. Monitoring of ECG, BP (preferably invasive), and Sa02 is mandatory in patients with severe disease [24].

Mitral Stenosis

This condition is usually the result of rheumatic heart disease. The main hemodynamic features are pulmonary congestion and reduced left ventricular diastolic filling. Epidural analgesia for labor has been successfully used in these patients and has been shown to have little influence (and sometimes beneficial effects) on the hemodynamic picture. Pulmonary artery pressure monitoring (Swan-Ganz catheter) is strongly recommended by some authors in patients with moderate-to-severe mitral stenosis. Many authors recommend epidural block as the technique of choice in providing anesthesia for caesarean section in these patients. Great care is needed in the administration of the block and its cephalad spread should be restricted at T5 level.

Mitral Regurgitation

In these patients an increase in systemic vascular resistance should be prevented. Epidural block is the technique of choice for analgesia in labor as well as for anesthesia for caesarean delivery.

Aortic Stenosis

The key to the anesthetic management of these parturients is the maintenance of both preload and afterload. Coronary perfusion is crucially dependent on the maintenance of diastolic pressure and time, and cardiac output is relatively fixed. Analgesia for labor is best provided by parenteral narcotics as well as by inhalation of nitrous oxide and oxygen. For the second stage of labor, pudendal nerve block can be used. Good analgesia has also been provided by intrathecal narcotics. The choice between regional or general anesthesia as the technique of choice for caesarean section is hotly debated, but as long as care is taken with instituting the block regional anesthesia may be more advantageous.

Aortic Regurgitation

These patients tolerate the circulatory overload produced by pregnancy very well and most techniques of analgesia and anesthesia have been used successfully. A decrease in left ventricular afterload (such as occurs with neuraxial blockade) can lead to an improvement in cardiac function by reduction of the regurgitant fraction.

Congenital Heart Disease

Among women with congenital heart disease, Eisennmenger's syndrome and primary pulmonary hypertension carry particularly high risk of death in pregnancy [25].

Eisenmenger's Syndrome

These patients present with pulmonary hypertension with right-to-left or left-to-right shunt at aortopulmonary, ventricular, or atrial level. A decrease in the ratio of systemic to pulmonary vascular resistance results in increasing cyanosis. In these patients pregnancy and delivery are associated with a high mortality rate. Epidural blockade using low concentrations of local anesthetic has been used to produce satisfactory analgesia in labor or combined spinal epidural technique [26]. For caesarean section the anesthetic technique of choice is general anesthesia using drugs that do not depress cardiovascular function.

Coarctation of the Aorta

The main cardiovascular consequence of coarctation is a chronically-increased left ventricular afterload that causes hypertrophy of the left ventricle. Epidural blockade, as well as intrathecal morphine, have both been successfully used to provide analgesia in labor. General anesthesia is preferred for caesarean section.

Cardiomyopathy

On the basis of anatomical and functional features cardiomyopathies can be classified as either dilated or hypertrophic. There is little information regarding the anesthetic management of patients with a cardiomyopathy in labor. In principle, depression of myocardial function should be avoided in those patients with a dilated cardiomyopathy, but mild afterload reduction may be of benefit. In those patients suffering from a hypertrophic cardiomyopathy, preload should be well maintained to avoid systolic cavity-obliteration and beta-agonists (whether used for tocolysis or cardiovascular reasons) should be avoided. Peri-partum Cardiomyopathy (PPCM) is a relatively rare disease estimated to occur in 1 in 3,000–4,000 pregnancies [27].

Criteria for diagnosis include:

1. Development of cardiac failure in the last trimester of pregnancy or within 5 months of delivery.
2. Absence of a determinable etiology for the cardiac failure.
3. Absence of demonstrable heart disease prior to the last month of pregnancy.

The diagnosis therefore, is largely one of exclusion as the disease has no pathognomic features. The etiology of PPCM remains poorly understood with theories generally centered upon viral infection triggering autoimmune mechanisms in suscepti-

ble individuals [28].

Considerations for regional anesthesia in these patients are similar to those with other causes of heart failure. With regard to anesthesia for caesarean section, general anesthetic techniques involve either cardiodepressant drugs such as thiopentone and the inhalational anesthetic agents, or high-dose narcotic techniques, which, while they maintain hemodynamic stability, may necessitate postoperative ventilation for both mother and infant.

Epidural anesthesia or combined spinal epidural (CSE) offer several advantages in addition to avoid these problems [29]. Anesthesia may be induced in a gradual and controlled manner and minimal change in hemodynamic parameters can be achieved if a pulmonary artery catheter is used to guide fluid and inotrope requirements. Small bolus doses or an incremental infusion of bupivacaine 0.1% with fentanyl 2 mcg/ml is suitable for these purposes. In addition, major neuraxial blockade may actually improve myocardial performance by reducing the afterload on the left ventricle without impairing contractility, although not all authors agree.

Drug Abuse

The prevalence of recreational drug abuse among young women, including in pregnancy, has increased markedly over the past 2 decades. Drug abuse is a significant social problem that can lead to serious obstetric complications [incidence of premature delivery, abrupto placentae, breech presentation, and intrauterine growth retardation (IUGR) were significantly greater in the drug-dependent women], some of which may be confused with pregnancy-related disease states. Drug abuse in pregnancy poses significant health risks to mother and fetus (low birth weight infants, intrauterine growth restriction, neonatal abstinence syndrome (NAS), and sudden infant death syndrome (SIDS). Abrupt withdrawal of opiates in pregnancy is also potentially dangerous because of stillbirth and preterm labor.

The diverse clinical manifestations of drug abuse combined with physiologic changes of pregnancy and pathophysiology of coexisting pregnancy-specific disease may led to life-threatening complications and significantly impact the management of obstetrical anesthesia. Substance abuse poses a number of challenges with respect to the management of pain and the conduct of anesthesia in the peripartum period. In the absence of uniform anesthetic guidelines for pregnant patients with a history of drug abuse the decision regarding the administration of peripartum analgesia or anesthesia should be individualized and conducted on a case-by-case basis [30]. These high-risk pregnancies require multidisciplinary care to optimize the outcomes for both mother and baby. Management of these pregnancies should be based on guidelines on clinical management regarding drug misuse and dependence and should involve a multidisciplinary approach and team [addiction psychiatrist, obstetrician, general practitioner (Gp), social service childcare, anesthetist, neonatologist, and midwives]. About 50% of infants develop neonatal abstinence syndrome, and to avoid this syndrome a substitution treatment with methadone, buprenorphine, or dihydrocodeine is suggested [31]. Cocaine, marijuana, amphetamines, and hero-

in remain the drugs commonly used for recreational purposes in pregnancy.

In the last Confidential Enquire into maternal deaths, the women who died from any cause, including those unrelated to pregnancy: 11% had problems with substance abuse, 60% of whom were registered addicts.

An overdose of drugs of abuse was responsible for the deaths of twenty-two women, three of which occurred during pregnancy and three shortly after birth. These six cases are counted as Indirect maternal deaths as the circumstances surrounding the pregnancy and death meant the assessors could not rule out an intentional overdose. The others deaths were most probably accidental and occurred later after childbirth. Substance misuse was either directly or indirectly associated with the deaths of 57 women [32]. Twelve of these women were alcohol dependent and 45 were illicit drug dependent. Most of the drug-dependent women were using heroin, but a large number were also misusing amphetamines, cocaine, benzodiazepines, and alcohol. Six of the women who died from suicide were known substance misusers, five of whom used intravenous heroin. Four died by hanging and two died from an overdose of paracetamol, one in pregnancy and one later after delivery.

Twenty-two substance misusing women died after a drug overdose, one of which was due to alcohol toxicity. Eight more women who were alcohol dependent and a further fifteen who were drug dependent died from medical causes directly or indirectly associated with their substance misuse.

A further two alcohol-dependent women died in house fires while intoxicated and five drug-dependent women were either murdered or died in a road traffic accident as a consequence of their drug use. This highlights the high-risk nature of pregnancies in women who abuse substances; and the care of these women during pregnancy and the postnatal period presents a challenge to maternity care, drug treatment, and social services.

ICU Management

The occurrence of critical illness against a background of an additional patient (the fetus) and significant anatomical, physiological, and biochemical changes with altered cardiorespiratory, immunological, and metabolic function complicates the management of obstetric patients.

General Principles

The indication for admission, the presence of maternal comorbidities, fetal viability, and fetal condition need to be evaluated on admission. The multidisciplinary management team should include obstetric input. Maternal well-being takes precedence and the timing of delivery is guided by the risk–benefit assessment of prematurity versus maternal gains from delivery. Management principles should take into account that pregnancy is characterized by a hyperdynamic circulation, an elevated cardiac output, tachycardia, a diminished systemic vascular resistance, a diminished reserve

to withstand hypoxia, a hypercoagulable state, and an increased predisposition to cholestasis. From a fetal perspective adequate placental perfusion and oxygen delivery is required.

The performance of procedures and drug prescriptions should consider deleterious fetal effects, if any. Further the dose and frequency of renally excreted drugs need to be modified to accommodate the increase in glomerular filtration rate and maternal volume of distribution. As the uteroplacental circulation lacks an autoregulatory ability, maternal hemodynamic decompensation results in the rapid onset of fetal hypoxia and fetal acidemia. Thus effective maternal resuscitation is the cornerstone in optimizing fetal well-being. The focus should be on restoring and preserving the maternal airway, breathing, and circulation. The goal is to ensure that tissue perfusion and adequate oxygen delivery is achieved by adequate resuscitation. The general principles of management are similar to the nonobstetric patients. Specific issues are highlighted below.

Specific Issues

Mechanical ventilation is associated with barotrauma, volutrauma, and atelectrauma. The ARDS network study supports the use of a lung-protective ventilation strategy in general ICU patients [33]. Fetal oxygenation decreases with a maternal saturation of <90% which corresponds to a maternal PaO_2 of 65 mmHg. It is therefore recommended that the maternal PaO_2 be maintained at 60–70 mmHg with the lowest possible FiO_2 (fraction of inspired oxygen). Transplacental transfer of CO_2 depends on a PCO_2 difference of approximately 10 mmHg between the fetal and maternal umbilical veins. Maternal hypercapnia results in fetal respiratory acidosis. This reduces the ability of fetal hemoglobin to bind oxygen. Thus permissive hypercapnia is considered with caution in pregnancy. The use of bicarbonate is not currently recommended. The maternal pCO_2 should be maintained below 45 mmHg and the pH above 7.30. In patients with Adult Respiratory Distress Syndrome (ARDS) one should aim for a PaO_2 of 60–70 mmHg, FiO_2 <0.6, and a saturation >90%. The higher ventilatory requirements of pregnancy may not permit the use of low tidal volumes advocated for ARDS. The use of positive end-expiratory pressure averts atelectasis and can improve alveolar unit recruitment. Recruitment measures have not been evaluated in pregnancy. There is also no data on the effect of proning position on maternal or fetal perfusion. A left lateral tilt should be achieved to prevent supine hypotension.

Fluids and Inotrops

Patients typically have a depleted intravascular volume and therefore require large volumes of fluid to ensure adequate microvascular blood flow and adequate cardiac output during resuscitation. The pregnancy-related reduction in colloid oncotic pres-

sure and the occurrence of "leaky capillaries" in critical illness predispose the patient to pulmonary edema. Central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) reflect back pressure to the right atrium and pulmonary artery, respectively. Neither is predictive of preload responsiveness or cardiac performance, particularly in the face of altered ventricular compliance. Left ventricle end diastolic volume is reported to be a better indicator of preload, but it is not easily measured. Despite the limitations of the CVP, it remains the most widely used tool to guide fluid therapy. The reality is that it is practical and what we have readily available. The important point is to utilize serial measurements and bear its limitations in mind. Superior and more widely available tools to ascertain preload are urgently required. Until then, pressure measurements and clinical acumen need to be relied upon. Usually only half of the hemodynamically unstable patients in an ICU are fluid responsive (that is they will increase their cardiac output following fluid therapy). This is explained by the configuration of the Frank-Starling curve, which relates stroke volume and cardiac preload. Beyond the ascending limb, the Starling curve reaches a plateau and further fluid administration can be detrimental by leading to right ventricular overload and/or pulmonary edema. Thus one needs to identify fluid responders. Intravascular volume assessment by evaluating static variables (CVP, PAOP) is unreliable. As there is no linear relationship between intravascular volume and filling pressures, the intravascular volume may be insufficient or excessive over a wide range of right heart pressures [34].

Current recommendations pertaining to assessment of volume responsiveness include the following:

Preload assessment alone cannot be used to predict fluid responsiveness; low values of CVP, PAOP, right atrial pressure and ventricular volumes should lead to immediate fluid resuscitation with careful monitoring. A fluid challenge or passive leg-raising test is recommended. Other dynamic measures (pulse pressure variation, aortic flow changes, systolic pressure variation, collapse of vena cava, and respiratory systolic variation test) are not routinely recommended in shock states. Cardiac output monitoring or echocardiography assessment is recommended if there is clinical evidence of ventricular failure and persistent shock despite adequate fluid resuscitation. In ARDS, a fluid restrictive strategy has been demonstrated to improve lung function, increase ventilator-free days, and reduce ICU stay. Crystalloids and colloids are equally efficacious. The SAFE Study demonstrated no significant difference in outcome (28-day mortality) with the use of either agent.

Fluid prescription needs to be individualized. Subgroup analysis of the SAFE Study revealed in severe sepsis a trend in mortality reduction with the use of albumen compared to normal saline (Relative Risk 0.87, p=0.09). This may have been a chance effect and needs further investigation. There is a paucity of randomized controlled trials pertaining to synthetic colloids and they have not been demonstrated to improve patient outcome. Further, they are expensive and there exist safety concerns (effect on coagulation, renal function, and anaphylaxis in particular) [35]. The cardiac output, mean arterial pressure and systemic vascular resistance will influence inotrope prescription. The effect on organ perfusion and uteroplacental blood flow also needs to be considered.

Sepsis

Early recognition and aggressive strategies to eradicate the source of sepsis is of paramount importance in the treatment of sepsis. Broad spectrum antibiotic therapy should be initiated as early as possible. In the antenatal patient beta-lactam antibiotics, aminoglycosides, and macrolides are generally safe from a fetal perspective. Chloramphenicol and tetracyclines should be avoided.

The Surviving Sepsis Campaign guidelines on the management of severe sepsis and septic shock address various issues including the use of early goal-directed therapy, corticosteroids, activated protein C, and glycemic control [36]. Current management recommendations include the following:

- Early initiation of resuscitation.
- Use of crystalloids or colloids.
- Target a mean arterial pressure of >65 mmHg, CVP of 8–12 mmHg, urine output >0.5 ml/kg/hr.
- Suggested endpoints of fluid resuscitation: lactate <1, Svo_2 >65%, $Scvo_2$>70%, adequate cardiac output.

The associated venodilatation and concurrent capillary leak necessitates aggressive fluid resuscitation during the first 24 h of therapy. The fluid input (which can approach 6–10 L of crystalloids or 2–4 L of colloid) will invariably exceed output during this period.

Delivery of Fetus

Fetal surveillance is recommended for viable pregnancies. The timing of delivery is individualized based on the maternal and fetal condition. Fetal delivery has, however, not been shown to improve maternal physiology or outcome in patients with respiratory compromise.

Cardiopulmonary Resuscitation

Cardiopulmonary arrest is uncommon but challenging. An airway must be established immediately in the face of diminished respiratory reserve and increased oxygen consumption. The patient should be positioned in the left lateral decubitus position at an angle of 30° to ensure effective chest compressions and to avert vena cava obstruction. Fetal monitoring electrodes need to be removed prior to maternal defibrillation. Drugs are prescribed as per standard protocols. The use of hypothermia has not been evaluated in pregnant patients.

Perimortem Caesarean Section

This should be considered 4 min following the initiation of CPR if spontaneous circulation has not been established. The rationale is to relieve uterine compression and permit effective chest compressions in pregnancies greater than 20 weeks gestation. In pregnancies between 20 and 24 weeks it is utilized for maternal survival and in viable pregnancies (>24 weeks gestation) for maternal and fetal survival. Effecting delivery within 5 min of the cardiac arrest has been demonstrated to improve maternal and fetal survival [37].

Conclusions

Worldwide maternal mortality is the health index that shows greatest disparity between countries with limited resources and developed countries. Maternal deaths in developed countries continue to decline, maternal mortality statistics are essentially similar in the USA and UK [3]. However, the situation is different in developing countries, where maternal mortality exceeds 0.5 million every year. More than 99% of all maternal deaths occur in developing countries; many of the deaths in developing countries could be avoided by improving the availability of simple clinical interventions.

The Millennium Developmental Goals include the reduction of maternal mortality by three quarters by the year 2015 [2]. High-risk pregnancies require multidisciplinary and multiprofessional intervention to optimize the outcomes for both mother and baby.

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Intensive Care in the Elderly

37

C. Foot, M. Fisher

Introduction

The ageing demographic in developing countries provides an unprecedented challenge for practitioners of Intensive Care Medicine (ICM). Over 10 years ago Callahan stated: "The future goal of medicine in the care of the aged should be that of improving the quality of their lives, not seeking ways to extend their lives. In its long standing ambition to forestall death, medicine has, in the care of the aged, reached its last frontier" [1].

The major needs in the management of the geriatric patient in intensive care are to provide treatments which are appropriate and produce outcomes which are acceptable to the patient and are affordable by the society in which the patient lives. This paper addresses the current issues and obstacles relating to the meeting of these needs. After review of some key concepts inherent to the term elderly, the needs of older patients are quantified and a typology of their health problems is provided. A global review of the state-of-the-art regarding ICU outcomes for older patients follows. Finally, recommendations for the future are explored.

Definitions

A recent dialogue has suggested that the term elderly should not be used in the medical literature, stating that the preferred respectful term should be older or senior person [2]. Inherent to this recommendation is the premise that older people are susceptible to discrimination (including healthcare provision) based on their age.

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The chronological ages of 60, or 65, have been used to arbitrarily classify commencement of old age [3]. Unlike the onset of puberty, this designation is not physiologically based but a consequence of the debates regarding the "retirement age" or "pension age" that played out between the late 1800s to mid-1900s [4]. The medical literature commonly refers to old patients as those aged 70–79 or very old if 80 years or older.

Patients of advancing years are a heterogeneous group ranging from the well older person whose healthcare needs are focused on disease prevention, to the frail, dependent individual [5]. Described collectively by decade (e.g., Octogenarian for those aged 80–89) or by generation (e.g., Greatest or Silent), various attributes have been assigned; respect for discipline and authority, a belief in the value of paying their dues and from their work days, comfort with a system of privilege based on seniority [6].

The concept of active ageing is a relatively new one used to describe "the process of optimizing opportunities for physical, social, and mental well-being throughout the life course in order to extend healthy life expectancy" [7].

Western societies have been described as perceiving older people as having low value and placing a high economic burden on society [8]. Despite these comments intergenerational commitment to caring and valuing older family members persist in developed countries [9].

"Geriatrics is the physician discipline that focuses exclusively on health care for older persons. Its mission is to improve the health, functioning, and well-being of older persons and, when this is not possible or is not the patient's preference, to provide palliative care that is consistent with the patient's wishes" [10].

This is a rapidly growing specialty that in actuality is practiced by most doctors, from GPs to Intensivist. The emphasis of geriatrics is on the assessment and evaluation of individuals in terms of physical and mental function, rather than age per se. The concept of physiological age acknowledges the differences in organ reserve and functional ability within individuals of a similar chronological age, and yet remains poorly defined.

Changes in human anatomy, physiology, pathophysiology, and pharmacology are well described. Some of the principal issues are outlined in Table 37.1. These changes make older patients more likely to die when faced with critical illness, take longer to get better, and to develop more complications.

Negative attitudes towards older patients continue to be described. Recently an Emergency Medicine Residency Program described how its new Geriatric Curriculum improved knowledge, as well as shifted the attitudes towards caring for geriatric patients from negative, to neutral or positive [13]. There is a paucity of literature that has examined the precise origins of these feelings. One group identified that medical students' initial exposure to older adults is to frail, functionally dependent patients burdened by a multiplicity of comorbid illnesses, including cognitive impairment. The risk is that profound negative attitudes are developed early as a result of these encounters, leading to enduring generalizations that are not applicable to the majority of adults over 65 [14].

The concept of ageism abounds in the dialogue on older patients. Butler [15]

Table 37.1 Changes of ageing (adapted from [11,12])

System	Morphologic changes	Functional changes
Cardiac	Decreased myocyte number, increased myocyte size and LV wall thickness	Decreased intrinsic contractility
	Decreased conduction fiber density and sinus node cell number	Increased myocardial stiffness, filling pressures, LA pressure and size with diastolic dysfunction
	Reduced fatty acid and increased myocardial glucose utilization	Decreased conduction velocity
	Thickening of mitral and aortic valve leaflets and annulus	Decreased coronary flow reserve
		Decreased beta-adrenoceptor modulation of inotropy and chronotropy
		Decreased arrhythmia threshold
		Increased myocardial oxygen consumption
Vascular	Increase in diameter and stiffness of large elastic arteries	Decreased vasodilatation due to beta-adrenoreceptors, endothelium, flow dependent and ANP dependent mechanisms
	Increased medial and intimal thickness	Decreased NO production and effect
	Increase in elastolytic and collagenolytic activity	Net vasoconstriction
Respiratory	Costal cartilage calcification Decreased intervertebral disc space and increased kyphosis	Decreased chest wall compliance
	Reduced respiratory muscle strength and stamina	Increased residual volume and FRC
	Decreased lung elastic recoil and decreased diffusing capacity	Closing volume approaches and overtakes FRC. Decreased expiratory flow rates and volumes
	Reduced mucous clearance	Decreased response to hypoxia and hypercarbia
		Increased sleep disorders
Renal	Loss of cortical area and glomerular mass	From the age of 40–50 loss of approximately 1ml/min/yr of GFR
	Interstitial fibrosis	Loss of ability to regulate electrolyte, glucose, and water balance
	Reduced glomerular basement membrane permeability from changes in structure	Loss of renin-angiotensin-aldosterone regulation
		Reduced ADH responsiveness and nocturnal polyuria

Cont. ↓

Table 37.1 *Cont.*

System	Morphologic changes	Functional changes
		Artificially preserved serum creatinine as concurrent loss of muscle mass
		Impaired vitamin D metabolism with reduced urinary calcium secretion
Gastrointestinal	Decreased gut motility, secretion and absorption	Decreased saliva with impaired oral lubrication. Impaired swallow initiation
	Loss of 40% muscle mass	Delayed transit with increased dysphagia, reflux and constipation
	Decreased caloric requirement	Increased risk of aspiration and malabsorption
		Decreased mucosal drug absorption
		Increased susceptibility to peptic ulceration
		Impaired healing and immune function
Hepatic	Decreased liver size and volume	Decreased drug metabolism especially by the cytochrome enzyme system
	Reduced liver blood flow by 40%	Reduced nitrogen clearance and urea synthesis
		Reduced bile acid synthesis with increased total serum bilirubin and reduced conjugated fraction
Central nervous	Cerebral atrophy	Lower intracranial pressure
		Susceptibility to subdural hematomas
Musculoskeletal	Osteoporotic bones	Susceptibility to fractures
	Loss of elastin and collagen from tissues	Increased tissue fragility
	Increased body fat % with reduced water %	Higher Vd of lipophilic drugs and increased concentration of water soluble drugs
Immune	Decline and dysregulation of cellular and humoral processes	Susceptibility to infections
		Increased cancers and autoantibody mediated diseases

described it as: "…a process of systematic stereotyping of, and discrimination against people because they are old…old people are categorized as senile, rigid in thought and manner, old fashioned in morality and skills…ageism allows the younger generations to see older people as different from themselves; thus they subtly cease to identify with their elders as human beings."

Despite these connotations there remains a certain reverence towards older people, particularly those who survive beyond the average lifespan.

The well-known concept of dying of old age has also been challenged. It has been hypothesized that this term arose because atypical and/or asymptomatic presentations in the elderly were mistaken for no cause of death [16]. Autopsy studies have subsequently revealed a list of causative conditions headed by ischemic heart disease and pneumonia [16]. A heightening of expectations on doctors and a reduced acceptance of death has also evolved. For example, pneumonia is no longer considered as the old man's friend.

Needs

Like many countries, the Australian population is ageing as a result of unprecedented improvements in healthcare. Over the last 5 decades life expectancy at birth has increased by over 20 years in developing countries and almost 10 years in industrialized regions [1]. The proportion of citizens aged 65 and over is projected to double from the current estimate of around 15 to 30% by 2051. There are predicted to be over 1,000 million people in this age group worldwide within the next 20 years [7].

As death from cancer and heart disease falls in developed countries the impact of degenerative diseases, particularly dementia, assume greater importance. A typology of disease in old age that may facilitate future healthcare planning has been postulated [18]. This model may be developed further to assist in categorization of the diverse ways that older patients may come to require intensive care management. A fifth category has also been added that encompasses conditions that may present at any age (Table 37.2).

In practice, patients commonly have diseases from more than one category that adds to their management complexity. Elements of the first category also add to the risks of managing conditions in all other groups. For example, in trauma, the presence of osteoporosis may extend the time needed for bones to heal or make adequate treatment of fractures impossible. Skin may be very much more susceptible to damage both from the direct trauma of removing electrodes or dressings, and the development of pressure necrosis [19].

Complex comorbidities increase the difficulty both in managing geriatric patients, and the likelihood of a good outcome. It is not uncommon to admit patients to hospital, who are chronically on in excess of six drugs, and many of these, such as beta-blockers, Clopidogrel, and Warfarin have been shown to be associated with increased complications in the elderly. Dementia makes ICU an even more frightening place and predisposes the patient to behavioral difficulties.

Table 37.2 Typology of disease in older patients requiring intensive care

Category	Description	Example of conditions	Examples of associated ICU needs
1	Physiological changes which are only possibly a disease	Osteoporosis	Fractures requiring postoperative care after surgical fixation; ventilatory support after rib fractures
2	Age related diseases with a long latency period	Atherosclerosis and end organ ischemic sequelae	Complications of ischemic heart disease, cerebrovascular, renovascular and peripheral vascular disease
3	Diseases with different physiologic processes because of reduced homeostatic regulation and repair mechanisms	Pneumonia, increased influenza, and pneumococcal susceptibility	Respiratory failure and severe sepsis requiring ventilatory and hemodynamic support
4	Diseases arising from long-term accumulated exposure to risks	Cancers	Postoperative support after major surgical intervention; ventilatory or hemodynamic support after chemotherapy
5	Processes that may arise at any age	Unnatural events	Management of traumatic injuries—accidents or self-harming episodes

Implications for the Healthcare System and ICM

Intensive Care is not practiced in isolation. Increased numbers of patients needing preventative care as well as disease management necessitate increased health-based services of all kinds, from residential and primary care to hospital-based services including critical care and rehabilitation teams. Required resources are of all kinds, including committed skilled human capital as well as increased building works and consumables (medications and equipment).

Given the rising number of older patients with complex healthcare needs it is not surprising that the pressure on ICU beds is increasing. In 2004 Angus stated that: "One in five Americans die using ICU services. The doubling of persons over the age of 65 yrs by 2030 will require a system-wide expansion in ICU care for dying patients unless the healthcare system pursues rationing, more effective advanced care planning, and augmented capacity to care for dying patients in other settings" [20].

The reality of the need to urgently plan for the critical care needs of the ageing population is well made in this statement. The existing outcome data regarding the older patient in ICU does not support this notion that intensive care for the older patient is solely end of life care and will be discussed in the next section.

Standards of Care

ICU staff, patients and their families are increasingly focused on delivering care that delivers quality of life benefits and not just improvements in 28-day mortality.

Intensive Care Outcomes for Older Patients

Over the last decade papers reporting excellent ICU outcomes (as measured by survival and/or quality of life) can be found for older patients with a range of admission diagnoses and organ failures. Significant disagreement prevails about whether age itself is an important predictor of outcome from ICU. Despite this, these papers have been sufficiently powerful to lead to a conclusion by Levin and Sprung in a commentary about ICU triage that: "Age has been considered as a basis for triage: however, the lack of difference in survival rates or functional outcome in the elderly suggests that this is not appropriate" [21].

It has been cautioned, however, that these studies may be overestimates of the true benefits to individuals, as these patients are likely to have been subject to a selection bias; only those perceived to have a high chance of surviving ICU are admitted [22].

Regardless of these concerns, studies of the ICU admission practices of ICU doctors suggest that age is not a principal criterion influencing their decision-making. The prognosis of the underlying acute disease, chronic conditions and the patients' wishes were ranked most highly in a recent survey [23]. Similarly, the factors influencing end-of-life decision making in intensive care were found to predominantly

relate to the patients' condition and response to therapies rather than to age [24].

This apparent lack of ageism amongst intensivists is further reflected in the fact that the mean age of patients admitted to the ICU has been increasing. A recent French study found that over the past decade the mean age has increased by approximately 6 months per year in ICU patients [17]. An NHS cross-sectional study found that although there was an unmet need for ICU beds for critically ill patients, there was no relationship between these unmet needs and the age of the patient [25]. In Australia, the number of intensive care days provided to patients over 70 has been increasing by 14% per annum [26].

It is beyond the scope of this paper to review the detailed literature on outcomes but a number of important conclusions are apparent from recent high quality coverages of the debate:

1. There is actually insufficient high-quality literature on which to define evidence-based recommendations for ICU admission of elderly patients [17].
2. Current prognostic models for ICU patients have not been specifically developed or validated in the elderly, particularly those over 80 years and these are urgently needed [22].
3. Health-related quality of life and functional status outcomes in the elderly should be the focus of future studies [27].

Recommendations

A number of recommendations are summarized in Table 37.3.

Table 37.3 Principal recommendations

Intensive care medicine
• Prioritize quality ICU research that will provide the evidence-basis for triage decisions for older patients—use a range of meaningful metrics
• Educate society regarding what is/isn't achievable in ICUs
• Determine the preferences of patients regarding their end-of-life care
• Work with other specialties on developing their evidence regarding outcomes of care and nonageist tools for measuring physiologic reserve and risk
• Rationalize chronic therapies and reduce polypharmacy
• Investigate strategies for early mobilization in ICU
• Educate future healthcare professionals on what is achievable and appropriate for older patients
Society
• Ongoing governmental scenario planning with public engagement regarding economic capabilities, health care opportunity costs and implications for what health care can be expected

Society

Microeconomic theory provides a useful framework for any recommendation regarding how to approach the provision of ICM to older patients.

At the heart of the issue are the simple concepts of demand and supply. For well over 20 years the medical literature has been dotted with warnings such as: "The problem of severely constrained resources is likely to become more acute, given new medical technology and the high costs of medical care … it will ultimately be essential for this society to come to grips with life and death issues in a manner to which it is not accustomed" [28].

Supply of the necessary budgets to purchase healthcare resources has never been more threatened. At the time of writing of this article the global financial crisis is continuing to evolve. The world's leading economies of the USA, Eurozone, and Japan are already in recession as well as at least a dozen more industrialized countries. Predating this recent predicament is the pensions crisis. Attempts to assist societies to prepare for the insufficient resources being reserved for retirement income is being seriously threatened by the collapse of global markets and share prices that have reduced superannuation balances.

Developments in microeconomics have resulted in tools that facilitate direct comparisons of costs and outcomes of different therapies. Studies involving hypothetical patients are attempting to define prevailing value systems that could inform rationing. Tools such as time trade off analysis and the standard gamble enable a perception about the value of good health to be ascertained from individuals.

Simple egalitarian comparisons of intervention-associated Quality Adjusted Life years (QALYs) between patients of different ages are being increasingly utilized. Health technology assessment, including cost-effectiveness evaluation is developing as a cost-containment strategy restraining implementation of new therapies. Organizations such as the National Institute for Clinical Excellence (NICE) in the UK use factors such as cost per QALY to compare, then accept or reject new therapies.

This approach has been criticized, on the grounds that QALYs consistently benefit younger people. This is because the remaining predicted lifespan of individuals decreases with age. In contrast, anti-ageist theorists favor older patients as being more deserving of care, as in the name of fairness they have lived longer and contributed more to society. The fair innings argument states that older patients are less deserving as they have already lived their lives. A UK study measuring well people's preferences regarding ageism in health found that participants were broadly in favor of giving priority to younger over older people based on feelings about productivity and the fair innings argument [29]. Whether there coexists an underlying pejorative attitude to older patients that is also in operation is unclear.

It is recognized that perceptions regarding appropriateness of certain therapies may differ between well people in hypothetical situations than when personally faced with a threat to their health. Lloyd and colleagues [30] studied attitudes towards ICU care among adult inpatients with chronic illness and an estimated 50% 6-month mortality and another group of patients over 80 with an acute illness. They found that

there was a wide variation in preferences for aggressive care that appeared unrelated to individual's age or prehospital quality of life. The most important factor appeared to be predicted future quality of life with the prevailing opinion being that extended therapies such as mechanical ventilation would only be acceptable if their prognosis was improved.

Attempts to develop a society-wide approach to rationing is complicated by the fact that attitudes will vary for individuals with their health status, illness experience, and over time. Consensus derived from hypothetical attitudes of well people is likely to change when they or their loved ones become unwell and have a shifted paradigm. It is also recognized that adaptation to a new circumstance or health status takes time. These issues limit the capacity for meaningful open societal dialogue. It is not difficult to see how rationing decisions have remained with the medical profession under a veil of ignorance, the term coined by Goold [31] to describe the situation that is occurring because: "Our pluralist, liberal society has no consensus on a conception of distributive justice".

Intensive Care Medicine

Triage decisions are being made by intensivists daily with a current emphasis on respecting patients' wishes (autonomy), expressed themselves or through surrogate decision makers if they are incapacitated. Notwithstanding the fact that patient-designated and next-of-kin surrogates incorrectly predict patients' end-of-life preferences in a third of cases [32], the paucity of strong evidence regarding outcomes of older patients admitted to ICU suggests the current state of play is actually more like the blind leading the blind.

The good news is that the situation is changing. Initiatives such as the ELPICUS study, an empirical, prospective, observational multicenter European study to examine triage decisions and their consequences for the elderly, are underway. From such data objective, standardized triage admission and discharge instruments will be available for prospective, multicenter investigation. Long-term outcome studies evaluating the quality of life of ICU survivors are ongoing and the healthcare profession is embracing health economic theories and increasingly sophisticated methods of evaluating care.

Society, and the microeconomists will be unable to develop a robust healthcare rationing policy on their own. The key to solving the issues of scarce resources, at least regarding ICU care, will only be found by measuring what can be achieved. It is with evidence from high quality research defining the outcomes and associated costs of our care that true societal-based discussion can progress.

The concept of cost must be expanded beyond fiscal components to include the negative effects of ICU management on patients and their families during and after their stay and well into the rehabilitation phase. Issues such as Post Traumatic Stress Disorder (PTSD) in ICU patients and/or their families must be factored into the

risk–benefit equation. A true understanding of the benefits and demands of ICU stay need to be characterized not only for elderly patients but also for all those admitted under our care.

We will need to look outside the walls of our units and join forces with our colleagues. ICM is not practiced in isolation. They too need to develop outcome data that is meaningful for informing societal rationing discussions. They too are under scrutiny and have been accused of ageism. A lack of prescribing of statins for hypercholesterolemia is a high profile example. On one hand authors such as Jacobson [33] believe the evidence for statins in the elderly is sufficiently strong that withholding them is ageist. In contrast evidence is mounting to indicate that the effect of total plasma-cholesterol on the risk of incident coronary heart disease decreases with age. The Copenhagen City Heart study [34] recently found that in people aged 70–80 years only plasma-cholesterol >8 mmol/L conferred increased relative risk and recommended that approaches to cholesterol-lowering therapy in older patients is reconsidered. It is likely that other therapies could be stopped, treatment regimens altered, and polypharmacy should be avoided in elderly patients.

From an ICU perspective rationalization of anticoagulant prescribing to older patients needs to be a high priority as complications that lead to, complicate, and prolong ICU admission are common. There is increasing recognition that intense anticoagulation for disorders such as atrial fibrillation may be a high-risk, low-benefit strategy for octogenarians [35]. Older patients experiencing traumatic brain injuries on clopidogrel have increased long-term disability and fatal consequences when compared with patients who are not on these drugs or on other anticoagulants [36]. Older patients who experience orthopedic injuries, commonly with falls, have known delays to surgery and increased transfusion requirements and length of hospital stay [37].

One of the major goals of the specialty of geriatrics is to keep patients mobile and return the patients to full mobility and function at the earliest opportunity. The dangers of going to bed, first described by Richard Asher in the 1940s [38] are well known. Critical illness is not conducive to the early mobilization of elderly patients but this does not mean it should not be attempted. Potential benefits for all patients exist and approaches have been described that warrant urgent consideration [39].

Some of the greatest progress in avoiding inappropriate ICU admission is occurring in the community where active efforts are helping to define the preferences of patients pre-emptively, regarding their end-of-life care. In our local region, the South-Eastern Area Health Project has led to a reduction in admission to local hospitals of nursing home residents [40].

We must embrace tools that assist our assessment of risk, independent of chronologic age. Investigations such as Cardiopulmonary Exercise (CPX) testing are useful nonageist measures of physiologic reserve, although the utility is limited to patients being electively referred to the ICU after surgery. Most importantly we must educate a new generation of ICU specialists who will benefit from more precise information to guide their triage decisions.

Conclusions

While our research progresses, Governments and healthcare providers are locked in scenario planning to evaluate different policy contingencies to manage the needs of ageing populations. Just as rational measures were being formulated the rules have changed. For example, extending working years and increasing immigration have previously been solutions for revenue creation from increased worker taxation that may no longer be viable if unemployment is the new immediate principal enemy.

The global financial crisis is creating a perfect storm for a major worldwide health funding disaster and new solutions are yet to be found. The opportunity costs of providing intensive care will need to be deliberated as infrastructure, education, defense, and the environment compete with other forms of healthcare for the budget. Engaging clinicians and improving efficiency of care are likely to be more important than ever before. Penny pinching achieved through the cutting of skilled nursing staff from wards will only add to the pressure on high dependency and intensive care services and we must fight to prevent this.

These are daunting priorities and everyone's problem. Medical, ethical, economic, and political collaboration is urgently needed… but later today and tomorrow we will have to go on doing the best that we can. Respect and dignity are fortunately low-cost items!

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Severe Malaria in the ICU

38

S.V. Prayag, A.R. Jahagirdar

Introduction

The term malaria (from the Italian mala "bad" and aria "air") was used by the Italians to describe the cause of intermittent fevers associated with exposure to marsh air or miasma. The word was introduced to English by Horace Walpole, who wrote in 1740 about a "horrid thing called mal'aria that comes to Rome every summer and kills one." The term malaria, without the apostrophe, evolved into the name of the disease only in the 20th century. Up to that point the various intermittent fevers had been called jungle fever, marsh fever, paludal fever, or swamp fever.

In 1902, Ronald Ross was awarded the Nobel Prize for Medicine "for his work on malaria, by which he has shown how it enters the organism and thereby has laid the foundation for successful research on this disease and methods of combating it".

Magnitude of the Problem

The annual global case load of the disease is around 500 million in a year with approximately 1–3 million deaths [1]. Malaria has traditionally been a problem of the poor and tropical nations due to several factors such as hot, humid climate, the low socio-economic state, possible genetic factors, and lack of adequate control measures. Malaria is not a uniform disease. It depends on several factors such as epidemiological setting, age, sex, gender, immunity, and socioeconomic conditions.

Major trends in the last two decades point to a worsening situation if effective measures are not taken. These trends include:

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- Increase in epidemic malaria
- Increasing drug resistance in *P. falciparum*
- Upward trends in mortality
- Emergence of *P. vivax* malaria where it was eradicated
- Emergence of imported malaria in travelers

In the present situation of increasing global travel and immigration, the problem of malaria threatens to be global. The incidence in travelers is around 25,000 cases annually of which 10,000 are reported and 1% (150) are fatal [1]. Malaria has become the most commonly imported tropical disease in the UK with 1,500–2,000 cases reported annually and 10–20 deaths [2]. In areas of stable transmission or high transmission such as subSaharan Africa, young children are the most affected. In areas of unstable transmission such as southeast Asia and Latin America, adults present with severe forms of disease due to lack of immunity [3].

Parasitology

As is well known, the disease is transmitted by the bite of a mosquito. Of the four malarial species the most severe form of malaria is caused by plasmodium falciparum, which is associated with organ dysfunction and death. Other species, *P. vivax*, *P. ovale*, and *P. malarie* lead to a febrile illness, which rarely causes death [4,5]. Most of the cases of death and severe organ failure due to malaria are a result of plasmodium falciparum infection.

Pathophysiology

Severe malaria in humans and animals is initiated by interactions between malaria-infected cells, host blood cells (including monocytes, T cells, and platelets) and endothelial cells of the microcirculation.

The parasite avoids splenic sequestration and destruction of infected red blood cells (RBCs). This occurs by the formation of knobs on the RBC membrane [6,7]. These knobs appear to attach to specific receptors such as ICAM-1 on the endothelium of capillaries in the brain, chondroitin sulfate in the placenta, and CD36 in other organs [8,9]. The infected RBCs also attach to uninfected RBCs by a process called rosetting. The attachment to the endothelium of the capillaries and the resetting causes the blockage of capillaries and venules and leads to end-organ dysfunction.

Adhesion to vascular cells, and possible vascular obstruction in severe human disease involves interaction between host receptors and parasite-derived proteins, such as the variant antigen plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1). In most instances downstream immune-mediated inflammatory processes appear more central than parasite accumulation to the development of clinical features of severe malaria [10].

The resultant endothelial damage, intravascular hemolysis, and parasitic proteins stimulate the release of cytokines and tumor necrosis factor [11]. Besides this, altered prostaglandin metabolism, intravascular coagulation, platelet adherence, and depletion of antithrombotic proteins such as protein C and antithrombin III as in bacterial sepsis contribute to the microcirculatory changes and organ dysfunction seen in severe malaria [12]. The brain is the most common organ to be involved in severe malaria. Up to 45% of cerebral capillaries may be occluded at postmortem examination because the receptors to which infected RBCs adhere are maximally expressed on cerebral capillary endothelium [13,14].

Patients with severe falciparum malaria show extensive microvascular obstruction that is proportional to the severity of the disease. This finding underscores the prominent role that microvascular obstruction plays in the pathophysiology of severe malaria and illustrates the fundamental difference between the microvascular pathophysiology of malaria and that of bacterial sepsis [15]. From this finding in the microcirculation, it appears that loss of functional capillaries rather than tissue hypoxia is a major lethal event in severe malaria [16].

Clinical Features of Severe Malaria

The diagnosis of malaria requires high index of suspicion. History of travel to endemic areas and blood and blood products transmission is highly relevant.

Even in countries where it is highly prevalent, a geographical and travel history for possible exposure is important. Malaria may mimic many other diseases prevalent in the tropics such as bacterial meningitis, viral encephalitis, typhoid fever, hepatitis, hemorrhagic fevers, leptospirosis, septicemia, and influenza. In pregnant women, malaria needs to be distinguished from infections arising from the uterus. In children, convulsions need to be distinguished from febrile seizures.

The patient with severe falciparum malaria may present to the intensive care unit with one or more features of end organ damage such as altered sensorium, severe anemia, oliguria/anuria, shock, respiratory distress, hypoglycemia, jaundice, and bleeding. Prognosis largely depends upon the number of organ systems involved with mortality as high as 40–50% if more than two organs are involved [17].

Cerebral malaria presents as encephalopathy without any focal signs. Cerebral sinus thrombosis with venous infarcts can also be found. Cerebral malaria is the most severe form of disease, having a high mortality of 30% [17].

Acute tubular necrosis presents as oliguria/anuria which may need renal replacement therapy. Intravascular hemolysis can lead to hemoglobinuria contributing to the renal failure.

Adult respiratory distress syndrome (ARDS) due to noncardiogenic pulmonary edema usually occurs after the other vital organs are involved or even may be recovering. Its occurrence as the single manifestation of otherwise uncomplicated malaria is also known [18].

Hemolysis, cholestasis, and hepatocellular dysfunction can lead to hyperbilirubinemia. The hepatic dysfunction is usually not severe but rarely can contribute to the development of hypoglycemia, coagulopathy, and hepatic encephalopathy.

Some patients, particularly semi-immunes, develop massive intravascular hemolysis and hemoglobinuria (blackwater fever) as a complication of falciparum malaria especially when given quinine. The mechanism remains unknown. Blackwater fever does not in itself indicate severe renal impairment but reflects the presence of massive hemolysis. In some cases it may be associated with an underlying hemolytic tendency (e.g., glucose-6-phosphate dehydrogenase deficiency). When associated with renal impairment the prognosis is far worse [19].

Features of shock along with diarrhea called algid malaria can be present [20]. Patients with algid malaria are more prone to primary bacteremia due to breakdown of the gastrointestinal mucosal barrier and resultant bacterial translocation [17].

Secondary bacterial sepsis can complicate malaria further. Severe sepsis can be profound, may occur early in the disease, and may lead to shock and multiorgan failure needing organ support and intensive care management. Septicemia can be due to bacterial pneumonia, urinary tract infection, or meningitis. Common organisms include pneumococci, salmonella, escherichia coli, and other gram-negative organisms. Secondary viral infection with herpes simplex and invasive aspergillus have been reported [21].

Evidence from a study show that multiple organs are affected in severe malaria. The mortality is relatively low when a single organ is affected. This is even true for cerebral malaria but the mortality rises steeply as the number of involved organs increases [17].

Some significant differences have been noted between children and adults presenting with severe malaria [22].

Laboratory Diagnosis

In the majority of the patients presenting to the intensive care unit, the examination of thick and thin Giemsa-stained blood films will reveal malarial parasites. Thick films are more useful in detecting low-density parasitemia. The parasitic index – the measure of parasitic density – aids in guiding the severity of disease and the response to treatment. If malarial parasites are not visible on the initial films, the examination should be repeated at 12- to 24-h intervals. The prognostic value of the parasitic count may be improved considerably by assessing the stage of the parasitic development in the blood film. In general, if more than 50% of the parasites are at the ring stage then prognosis is relatively good. If more than 20% are mature forms such as trophozoites or schizonts then the prognosis is relatively poor. Besides, if more than 5% of the neutrophils contain malarial pigment on the peripheral film, the prognosis worsens especially so in patients with low parasitic index. In an international trial, almost 70% of 1,050 severe malaria patients had a peripheral parasite count of less than 5%, and the mortality in this population was 18% [23]. Emphasis on a “low” parasite count, rather than disease manifestations, may offer the clinician false reassurance or lead to an underestimation of the contribution of the malaria infection to a patient’s symptoms [23].

Although there is an association between the peripheral parasite count and patient outcome, it is a relatively weak one. Other clinical and laboratory variables have stronger prognostic value, particularly acidosis and pulmonary and renal disease [24]. Anemia is normocytic and may be "severe" (hemoglobin <4 g/dl) due to the significant amount of hemolysis. In fact, a sudden drop in hemoglobin in the absence of any bleeding (indicating hemolysis) alerts a good clinician to the possibility of malaria in a febrile patient. Studies have shown the HbS carrier state was found to be negatively associated with all major forms of severe falciparum malaria, the negative associations of the carrier states of HbC, and appeared to be limited to cerebral malaria and severe anemia, respectively [25].

Thrombocytopenia (<100,000 platelets/μl) is usually present, and peripheral leukocytosis is found in patients with the most severe disease. Apart from the disseminated intravascular coagulation (DIC), thrombocytopenia that complicates some malarial infection is immunologically mediated; IgG binds to the platelet bound malaria antigen through the Fab portion of the immunoglobulin molecule [26]. Although absence of thrombocytopenia is uncommon in malaria, its presence is not a distinguishing feature between the two types; *P. vivax* and *P. falciparum*. Thrombocytopenia less than 20,000/microl can occur in *P. vivax* malaria although statistically more common with *P. falciparum* malaria. This finding can have therapeutic implications in the context of avoiding unnecessary platelet transfusions with the relatively more benign course in *P. vivax* malaria [27].

Hypoglycemia is a common feature, especially with hepatic dysfunction and the use of quinine as a therapeutic agent. The elevation of serum creatinine, bilirubin, and enzymes such as aminotransferases and 5'-nucleotidase, may be found. Levels of liver enzymes are much lower than in acute viral hepatitis. Severely ill patients are commonly acidotic, with low capillary plasma pH and bicarbonate concentrations. Concentrations of lactic acid in the blood and cerebrospinal fluid are often high in both adults and children in proportion to the severity of the disease. In a prospective study, nonlactate unmeasured plasma anions were found to be the greatest quantitative contributor to the metabolic acidosis of severe malaria [28]. The strong ion gap was a significant independent prognostic factor for hospital mortality [28]. Fluid and electrolyte disturbances (sodium, potassium, chloride, calcium, and phosphate) are variable.

High levels of procalcitonin have been reported in malaria [29]. This contributes to the difficulty in differentiating between a bacterial cause of sepsis and malaria in patients who do not have a positive blood smear. In patients proven to have malaria, this contributes to the difficulty in ruling out an associated bacterial sepsis.

Newer Methods

Immunochromatographic Tests

Various test kits are available to detect antigens derived from malaria parasites. Such immunologic ("immunochromatographic") tests most often use a dipstick or cassette

format, and provide results in 2–15 min. These "Rapid Diagnostic Tests" (RDTs) offer a useful alternative to microscopy in situations where reliable microscopic diagnosis is not available. Current RDTs are based on the detection of histidine rich protein 2 (HPR2), which is specific for falciparum species, panspecific or species-specific parasite lactate dehydrogenase, or other panspecific antigens such as aldolase. They provide rapid results, require less trained professionals, and ensure reinforcement of diagnosis. Published sensitivities of RDTs for P. falciparum are comparable to good field light microscopy (>90% at 100–500 parasites/μlit of blood) [3]. Malaria RDTs are currently used in some clinical settings and programs. However, before malaria RDTs can be widely adopted, several issues remain to be addressed, including improving their accuracy, lowering their cost, and ensuring their adequate performance under adverse field conditions [3].

Immunodiagnosis and PCR-based Methods

Detection of antibodies to parasites is not specific, sensitive, rapid, or cost effective. DNA-based polymerase chain reactions (PCR) are highly sensitive and useful for detecting mixed infections, particularly at low parasitic densities [3].

Severe Malaria – Intensive Care Management

General Supportive Measures

The supportive measures are similar to initial management in sepsis. Careful monitoring of the vital signs and all organ system functions including sensorium is done in an intensive care unit.

Adequate hydration of the patient needs special attention in the initial resuscitation. Optimal fluid administration should be guided by central venous pressure, if necessary, as fluid overload may lead to worsening of the pulmonary edema. Similarly, if the dehydration caused due to vomiting and fever is not corrected, it may result in acidosis and prerenal azotemia. The role of Early Goal-Directed therapy in the initial resuscitation has not been substantiated by specific data; however, there is no physiological rationale for treating it differently than any other form of severe sepsis. Appropriate organ support such as mechanical ventilation, renal replacement therapy, blood and blood products, and control of raised intracranial pressure should be provided. Metabolic derangements such as hypoglycemia, hyperpyrexia, and acidosis should be aggressively controlled. Seizure episodes need appropriate anticonvulsants. There is no role for phenobarbital for the control of seizures in malaria. Similarly, dexamethasone for raised intracranial pressure is not recommended [30]. Broad-spectrum antibiotics should be initiated if bacterial sepsis is suspected.

Specific Antimalarial Therapy

In the presence of a high index of suspicion or when the diagnosis of severe malaria is certain, treatment should be immediately instituted as if it were a chloroquine-resistant malaria. The primary aim in treatment of severe malaria is prevention of mortality and any life-threatening complications. Mortality from untreated severe malaria approaches 100%. Death from severe malaria can occur within hours of hospitalization; hence, it is essential to achieve therapeutic drug levels as early as possible [3].

Several antimalarial agents are available for use such as quinine, artemisinin derivatives, mefloquine, doxycycline, clindamycin, and chloroquine. But *P. falciparum* has acquired resistance to almost all drugs especially in endemic areas of southeast Asia. Parenteral chloroquine is no longer recommended for the treatment of severe malaria because of its widespread resistance. Intramuscular sulfadoxine-pyrimethamine is also not recommended as treatment of severe malaria. The WHO guidelines recommend the use of either cinchona alkaloids or artemisinin derivatives for the treatment of severe malaria [3]. The first artemisinin to be studied in large clinical trials of severe malaria was artemether. Large randomized comparisons of intramuscular artemether and quinine in Gambian children [31] and Vietnamese adults [32] and a meta-analysis of individual data from 1,919 patients in 11 trials of parenteral therapy [33] identified no significant difference in efficacy between these agents. However, in the meta-analysis, the subgroup of adults had lower mortality when treated with artemether. A large, randomized comparison of intravenous artesunate and quinine in 1,461 patients in Asia showed a significant survival benefit with artesunate. Mortality was 22% with quinine, as compared with 15% with artesunate, a risk reduction of 34.7% [23]. A systematic review of five randomized trials comparing the efficacy of intravenous quinine with that of artesunate and one additional trial of intramuscular artesunate demonstrated the superiority of artesunate, with significant reductions in the risk of death, incidence of hypoglycemia, and parasite clearance time, as compared with quinine [34]. Based on these observations, it is now recommended that artesunate should become the treatment of choice for severe falciparum malaria in adults [23].

A key advantage of the artemisinin compounds is rapid action against all the erythrocytic stages of the parasites including transmissible gametocytes resulting in rapid clinical benefit, decreased transmission of malaria, and limited drug resistance to artemisinins. Because of their short half-lives a standard 3-day course is commonly followed by parasite recrudescence and relapse of the disease. The intravenous course, therefore, should be followed by oral artemisinin-based combination therapy (artesunate–amodiaquine, artemether–lumefantrine) [35]. Of the available artemisinin derivatives, artesunate is preferred due to its water solubility and availability of intravenous form for administration. Artemether is oil based and intramuscular absorption is erratic in severe malaria. Intravenous artesunate is given as 2.4 mg/kg body weight at time of admission to be followed at 12 h and 24 h and then once daily to compete a schedule for 7 days once the patient starts taking orally. No dose adjustment is necessary in organ dysfunction [3]. Toxic effects have been reported less frequently with the

artemisinins than with other antimalarial agents. The most common toxic effects that have been identified are nausea, vomiting, anorexia, and dizziness; other rarely noted toxic effects are neutropenia, hemolysis, anemia, elevated liver enzymes, and severe allergic reactions. Neurotoxicity is the greatest concern regarding artemisinins as shown in several animal studies. Fat-soluble artemisinins are shown to be more toxic than water-soluble artesunate. A case report of ataxia in humans is documented, as is hearing loss shown in a case control study [35].

Limited data are available on the use of intravenous artesunate for severe malaria during pregnancy [23].

While it is available in many developing countries, artesunate has not yet been approved by the US Food and Drug Administration (FDA) for routine use in the USA [3]. However, on June 21, 2007, the FDA approved an investigational new drug (IND) protocol entitled Intravenous Artesunate for Treatment of Severe Malaria in the United States [36]. Intravenous artesunate is unlicensed in the EU. Assistance in obtaining artesunate may be sought from specialist tropical medicine centers [2].

Cinchona derivatives have been established as the treatment of several malaria long before clinical trials. They act principally on the mature trophozoite forms of *P. falciparum*. The WHO guidelines recommend a loading dose of quinine salt of 20 mg/kg body weight to establish effective blood levels at the end of 4 h unless the patient has received 40 mg/kg body weight quinine in the previous 48 h or has received a loading dose of mefloquine in the previous 12 h. There is a reduction in the apparent volume of distribution and clearance in proportion to the severity of malaria. Hence, reductions in the initial loading dose are not recommended in the presence of renal failure. Only if the clinical condition does not improve after 48 h, should the dose be reduced by one third. No dose adjustment is required if a patient is undergoing hemofiltration or hemodialysis. The recommended daily dose is 30 mg/kg body weight salt in three divided doses at 8-h intervals. Quinine may be erratically absorbed if given intramuscularly and may lead to abscess formation; hence, the recommended route of administration is intravenous. Rapid intravenous injections can lead to hypotension and cardiac arrest. Hence, rate controlled infusions (<5 mg/kg/h) are preferred with strict hemodynamic and electrocardiographic monitoring.

Toxicity includes cinchonism, severe hypersensitivity reactions, massive hemolysis with hemoglobinuria, and renal failure (blackwater fever). In severe malaria, hypoglycemia due to hyperinsulinemia needs vigilant monitoring of blood sugar levels. The more harmful adverse side effect is the cardiotoxicity, more seen with quinidine. Widening of QRS complex leading to prolongation of QT interval can lead to ventricular arrhythmias. Hence coadministration with other agents causing QT prolongation (i.e., flecainamide, amiodarone, terfenadine, halofantrine, mefloquine) should be avoided.

Once the patient starts tolerating oral medications the same treatment schedule can be given orally up to 7 days. In nonpregnant adults, doxycycline is added for 7 days over and above quinine. Mefloquine should be avoided in cerebral malaria due to neuropsychiatric side effects.

The current WHO treatment guidelines note that quinidine is more toxic than quinine and should only be used if no other effective parenteral drugs are available [3].

Exchange Transfusions

The rationales for the use of exchange transfusions in severe malaria are:

- Removing infected blood cells and reducing parasitic burden
- Rapidly reducing antigen load, parasite-derived toxins, and mediators produced by host
- Replacing rigid unparasitized erythrocytes with more deformable ones and alleviating microvascular obstruction

A meta-analysis comparing eight studies and involving 279 patients with severe malaria suggested a lack of survival benefit for patients treated with adjunct exchange transfusion [37]. However, there were significant problems with the comparability of treatment groups in the studies reviewed. Furthermore, the possible benefit of adjunct exchange transfusion for patients with at least partial immunity to malaria and/or among patients in different geographic regions needs to be explored. Well-equipped and well-staffed intensive care facilities with safe blood supplies are essential for exchange transfusions. Until an adequately designed, randomized, controlled clinical trial is conducted, adjunct exchange transfusion cannot be recommended for the routine treatment of severe falciparum malaria [37]. Erythrocytapheresis seems a reasonable option to exchange transfusions as it is safer and avoids the hemodynamic compromise and electrolyte disturbances seen during exchange transfusions. The CDC recommends exchange transfusions for patients with high parasitemia >10%, cerebral malaria, nonvolume overload pulmonary edema, or renal failure [38].

Activated Protein C

Drotrecogin alpha (activated protein C) is an important modulator of coagulation and inflammation associated with sepsis. Falciparum malaria may cause extensive disruption and excessive activation of the coagulation cascade, including significant reductions in the levels of protein C. This can be the rationale for the use of activated protein C in severe malaria with organ dysfunction.

Activated protein C can also be considered for the secondary bacterial sepsis complicating malaria, though definitive differentiation between the two can be difficult at times.

Although the use of drotrecogin alpha in malaria is not supported by enough evidence, several case reports have been cited in the literature. It has been used in ten patients with tropical diseases complicated by severe organ failure in an Indian ICU [39]. In spite of risk associated with thrombocytopenia and coagulopathy with bleeding in malaria, the use of dotrecogin alpha did not lead to bleeding complications in patients in this study [39]. In another published case report, the compelling evidence for the use of drotrecogin alpha was multiorgan failure, high risk of death, possibility of associated bacterial sepsis, and high APACHE score [40].

Other Measures

Various adjunctive treatments appear in the literature that are either unproven or are harmful in the treatment of severe malaria and are not currently recommended. They include phenobarbitol for prophylaxis of seizures, dexamethasone for treatment of cerebral malaria, heparin for treatment of thrombocytopenia and/or fibrinogenemia, iron chelators that aim to reduce parasite clearance time, pentoxifylline for inhibition of tumor necrosis factor synthesis, and dichloroacetate for treating metabolic acidosis [38].

Malaria and Pregnancy

Pregnant women particularly in the 2nd and 3rd trimester are more susceptible to develop severe malaria. Maternal mortality is around 50% [3]. The clinical manifestations may vary according to the state of immunity in pregnancy. Nonimmune pregnant women are at an increased risk of abortions, stillbirth, and premature delivery. They are more likely to have complications such as cerebral malaria, hypoglycemia, and pulmonary edema. Partially immune pregnant women are prone to severe anemia but other manifestations of severe malaria are unusual. Severe malaria in pregnancy has to be treated in an intensive care unit. Threatened abortion/maternal or fetal distress may need intervention such as cesarean section at times. As per the current WHO Guidelines [3], artesunate or artemether is preferred over quinine as the later causes severe hypoglycemia in the second and third trimester. In the first trimester, the risk of hypoglycemia associated with quinine is lower, and the uncertainties about the safety of the artemisinin derivatives are greater. Quinine may be used [3,41].

Prognostic Indicators

Many studies have looked at the prognosis of patients with severe malaria. Poor outcome has been associated with one of the following observations/measures [42,43]:

- Deep coma
- Convulsions
- Shock
- Anuria
- Hypoglycemia <45–50 mg/dl
- Lactate >5 mmol/L
- Creatinine >3.0 mg/dl
- Platelets <50,000/mm3
- PCV <15%
- Bilirubin >3.0 mg/dl, AST and ALT >3× normal
- Parasitemia >100,000/microlitre in nonimmune individuals

It is obvious that severe organ dysfunction will result in poorer outcomes in these patients.

Challenges for the Future

Widespread research has been done to understand the basic pathophysiology of the effect of the invasion by the malarial parasite on the various organ systems of the body. Mechanisms have been considered for the cause of organ dysfunction in severe malaria. The adherence of the parasitized erythrocytes to the endothelial lining of the major organs causes microvascular obstruction. Extensive microvascular obstruction in proportion to disease severity differentiates the pathophysiologic mechanism from severe sepsis. However, of particular interest is the role of the immune-mediated inflammatory host responses that appear to play a major role apart from the microvascular obstruction. Some evidence does point to a lesser severity of organ dysfunction due to malaria, in contrast to sepsis, due to bacterial infections [17].

With expected international funding, deaths from falciparum malaria in tropical Africa can soon be reduced by as much as 90%, even in countries such as Nigeria and the Democratic Republic of Congo, where political conditions or government instability have posed challenges to other public health efforts. A rapid, region-wide reduction in mortality "is a very likely scenario – it will happen in the next 3 to 5 years" [44].

In order to reduce the high mortality associated with severe malaria, we need to understand the disease process and treat malaria more effectively in the ICU. We need to answer a number of questions appropriately:

- Can we detect malaria earlier with better and cost-effective diagnostic tools?
- Does microcirculation and host response hold the key to future therapeutic advances?
- Can we prevent the drug resistance against the currently useful antimalarial drugs?
- Can we manipulate the microcirculation for better outcomes?
- Is there a role for activated protein C, especially in view of its effects on microcirculation?

Addressing these issues quickly may save more lives in the future.

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End-of-Life in the ICU

39

J.-L. Vincent

Introduction

The intensive care unit (ICU) is generally considered as part of the hospital where patients are treated during an acute severe illness or after acute major injury. However, the ICU is also a common place of death with 1 in 5 Americans dying during or just after an ICU admission [1]. Advances in modern medicine have altered the dying process such that many deaths in hospital, and particularly in the ICU [2–5], are preceded by an end-of-life decision, a decision to withdraw or withhold life-supporting therapy. There is no specific definition of "end-of-life," but it is generally considered to be the period during which it is recognized that a patient has a terminal process and that further treatment will offer no benefit, and to be the transition period from cure to comfort [6]. The decisions surrounding end-of-life on the ICU are often complex because they are affected not only by medical factors, but also by multiple personal aspects, including individual preferences, religion, and cultural influences. The influence of family and friends in such decisions can also be considerable. Some recommendations for end-of-life care have been published in the USA [7] and by several national medical societies, but there remains considerable variability in the approach to end-of-life care and decision making at an international, national, and even local level.

Definitions

Ethical Principles

In considering medical ethics in general, there are four key principles, which can

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provide a useful framework when focusing on the various concepts surrounding end-of-life care:

1. *Beneficence* involves acting in a way that ensures that treatment will benefit the patient. However, what constitutes "benefit" can be controversial with different physicians sometimes reaching different conclusions. Moreover, a physician's view of what may benefit a patient may not be the same as the patient's view or that of his/her family, and the principle of beneficence may conflict with the principle of autonomy.
2. *Nonmaleficence* is an obligation to inflict no harm. Here again what constitutes "harm" can be difficult to define as many effective medical treatments have harmful, or potentially harmful, adverse effects. In such cases, the principle of nonmaleficence must be balanced against the principle of beneficence. In end-of-life decisions, for example, allowing a patient to die may be seen as causing harm, but death can sometimes be a "benefit" or at least the better option for the patient.
3. *Autonomy* acknowledges the right of a well-informed and competent individual to make their own decision about personal matters; in end-of-life care this essentially recognizes that patients should be able to choose their own management plan based on their values and beliefs. Importantly, a patient may opt for an approach that differs from the advised course of care, and this should be respected. However, if a patient requests a treatment that the clinician does not think is in his/her best interests, the principle of autonomy may come into conflict with other ethical considerations, such as nonmaleficence, and the respective weights of the various principles need to be considered and balanced. In the ICU, this principle is often further complicated by the fact that patients are often unable to make an informed decision for themselves as a result of their illness, sedation, etc. The role of surrogate decision makers then comes into play.
4. *Distributive justice* relates to fairness in the distribution of healthcare, so that all patients receive the care to which they are entitled. However, limited resources can restrict this ethical principle, and distributive justice must include assessment not only of what the patient is entitled to but of how that may affect other patients and society as a whole. Continuing life-sustaining treatment in a patient with absolutely no hope of survival is against the ethic principle of distributive justice-because it uses resources that could be better employed in an individual who is more likely to recover.

Withdrawing/Withholding of Life-Sustaining Therapy

Most western ethicists consider that there is no ethical difference between withholding, whereby a patient is refused further medical therapy that is not indicated and will not benefit that patient, and withdrawing, whereby a patient has medical therapy that is of no benefit removed. In both cases, the immediate result of the decision will be the same; for example, if we take as an example mechanical ventilation, whether a decision is made to stop mechanical ventilation (withdraw) or not to start mechanical ventilation (withhold), the ultimate result just after the decision has been made is

the same, i.e., no mechanical ventilation. Moreover, in the situation where a patient no longer has any chance of survival, withdrawing and withholding similarly respect all four ethical principles. They respect beneficence and nonmaleficence because although it may be difficult to call death a benefit, in this situation it is more beneficial than futile, and potentially harmful or uncomfortable, life-sustaining interventions. They respect the principle of distributive justice because continuing "futile" therapy demands time, cost, and energy that could be otherwise reserved for patients more likely to benefit. And they can even be said to respect the principle of autonomy because generally one assumes that no one wants to prolong organ function when there is no hope of meaningful recovery. Another important reason why withholding and withdrawing should be seen as equivalent ethical decisions is that if withdrawing is not allowed, physicians may hesitate to give patients the benefit of a therapeutic trial for fear that once started they would be obliged to continue and then fail the principle of nonmaleficence. Indeed, withdrawing may be preferable to withholding because it ensures that patients are given every possible chance, particularly in cases where the prognosis is not clear [8]. Such patients can be offered a therapeutic or ICU trial with a predefined time limit at which point treatment would be stopped if there had been no improvement. Nevertheless, withdrawing therapy is often more difficult to apply than withholding it; once a decision has been made to start a therapy, withdrawing it can be seen as "giving up" on the patient.

In ICU nonsurvivors, studies from individual countries have reported various rates of withdrawing/withholding: Some examples include 59% in Hong Kong [9], 53% in France [10], 45% in Lebanon [11], 41% in Sweden [12], 35% in Spain [13], and 34% in India [14]. Although it is difficult to compare rates across these studies due to differences in populations and study designs, they give some idea of the considerable variations among countries. In an analysis of the recent SAPS 3 database, which included data on 14,488 patients from 282 ICUs in seven different geographical regions, 36% of deaths occurred after an end-of-life decision, ranging from 26% in Central and South America to 48% in Central and Western Europe [5]. In the Ethicus study conducted in 37 ICUs in 17 European countries [4], withdrawal of therapy was reported as more common in northern European countries (Denmark, Finland, Ireland, Netherlands, Sweden, UK) than in countries of southern Europe (Greece, Israel, Italy, Portugal, Spain and Turkey; 47 vs. 18%, $p < 0.001$). There are many reasons for these international differences but clearly religious and cultural background is a key factor. Further analysis of the Ethicus data showed that withholding occurred more often than withdrawing if the physician was Jewish (81%), Greek Orthodox (78%), or Moslem (63%), while withdrawing occurred more often for physicians who were Catholic (53%), Protestant (49%), or had no religious affiliation (47%) [15].

Therapeutic Limitation vs. Administration of Drugs to Hasten Death

van der Heide et al. [2] studied end-of-life decisions in six European countries (Belgium, Denmark, Italy, Holland, Sweden, and Switzerland) by sending a questionnaire to doctors who had signed a sample of 20,480 death certificates. In all coun-

tries, doctors reported having given drugs with the intention of speeding death, with a frequency ranging from 1–3.4%. Results from the Ethicus study [4] suggested that as many as 6.5% of ICU deaths were associated with active shortening of the dying process. This is a difficult ethical issue. Some would argue that since the patient is dying anyway, administering drugs to speed that process and limit suffering is acceptable. Others would consider that this approach is unethical and even tantamount to murder. Importantly, the intention of the physician must be clear and focused on relieving suffering not on killing [7].

Decision-Making in End-of-Life Care

An important issue in end-of-life decision making is who should be responsible for or involved in that decision? Clearly the physician must be involved, but what about other members of the ICU team, what about the patient's family and friends? Here too, there are considerable international and national variations. Guidelines on end-of-life practice emphasize the importance of involving the patient (where possible) and the family [7], yet frequently relatives are not consulted. Traditionally in Europe there has been a paternalistic approach to decision-making. In Spain, the patient's family was not involved in the decision making process in 28% of cases [13], while in France, 56–83% of families were not involved [10,16]. In Italy, Giannini et al. [17] reported that 82% of withdrawal/withhold decisions were made by the medical team, with the involvement of nurses in just 13%; 19% of physicians said the close family were never involved in such decisions, and 56% would never involve the patient even if competent. In a questionnaire study involving 1,961 intensivists from 21 countries worldwide, Yaguchi et al. [18] reported that, for a hypothetical patient with no family, 62% of physicians from Northern and Central Europe said they would involve nurses in end-of-life discussions compared with only 32% of physicians in Southern Europe, 38% in Brazil, 39% in Japan, and 29% in the USA ($p < 0.001$ for all comparisons).

End-of life decisions need, wherever possible, to be made by consensus of all involved including physician(s), nurse(s), patient (or surrogate) and family members. In many situations where good communication is established early and time is taken to carefully explain the concepts and options, agreement will be reached without conflict. However, studies have shown that families are often not satisfied with the end-of-life care provided, frequently as a result of inadequate communication [19]. Conflict between physicians and relatives is not infrequent [19] and good communication can limit the likelihood of this arising and help resolve conflict should it occur. Several articles have dealt with methods of improving communication in the ICU, in general [20], and more specifically during end-of-life care [21]. Some suggested approaches are listed in Table 39.1. In analysis of recordings of end-of-life discussions, Curtis et al. [21] reported that in 30% of conferences there were missed opportunities for the physician to provide support or information to the family, mostly related to missed cues for listening and responding. McDonagh et al. similarly

Table 39.1 Ten strategies for improving communication at the end-of-life in the ICU

• Make the first step in approaching the subject with patient and relatives – don't wait for them to ask you
• Introduce yourself, including your position
• Dress and act appropriately and use simple, jargon-free language
• Allow enough time and allot a specific place for discussion
• Include other team members in discussions
• Be genuine, honest, and truthful, avoiding excessive optimism
• Be willing to admit that you don't have all the answers
• Explain the processes of withholding and withdrawing and stress that withholding/withdrawing life-sustaining therapy does not equate with withholding/withdrawing care
• Take time to listen
• Encourage questions and take time to answer

reported that allowing families more time to express themselves was associated with greater feelings of satisfaction [22]. Various other approaches have been used to improve the satisfaction of relatives with end-of-life care. In a recent randomized controlled study, Lautrette and colleagues [23] assigned family members of 126 patients dying in 22 French ICUs to a standard end-of-life conference or to a proactive end-of-life conference, with more time for families to talk, and a bereavement brochure. The families who received the proactive conference and brochure had a significantly lower incidence of anxiety, depression, and posttraumatic stress disorder 90 days after the death of their relative. Ultimately, the decision to withhold/withdraw life-sustaining therapy is a medical one, and must be made by the physician, but providing adequate time for informed discussion with staff and family members is important in ensuring that the dying process proceeds without conflict. Where there is conflict, ethics consultations with experienced teams may be beneficial [24].

Conclusions

The majority of deaths in the ICU are now preceded by a decision to withdraw or withhold therapy. Issues surrounding end-of-life decisions are now much more openly discussed and more widely studied. There are considerable variations in such decisions in different countries largely reflecting different religious and cultural heritages. Individuals also differ in their attitudes and wishes regarding end-of-life care and these differences must be understood and respected. A compassionate approach at the end-of-life with good communication with the patient, family, and other staff members can make the dying process easier for all involved.

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Section XII
Environment and Clinical Research

Designing Safe Intensive Care Units of the Future

40

P. Barach, M. Potter Forbes, I. Forbes

Historical Background

Hospitals, clinics, and other health buildings occupy a unique place in our sensibilities. They are safe havens for the care and treatment of the sick, but they are also dynamic, challenging, and risky environments marked by high levels of stress and fragmentation in the continuity of care. Complexity is manifest in patient and treatment protocols, in the interdisciplinary coordination and hand-offs between providers, the interdependence of humans and technology, the large volumes of information required for decision making, and the residual uncertainty associated with these decisions. It is widely acknowledged that the physical environment has a significant impact on health and safety. However, innovation in the design of Intensive Care Units (ICUs) has not been done with the goal of enhancing patient safety or improving the quality of care, as these aspects were presumed to be implicit in the clinical practice of the facility.

The ICUs of the past were developed to care for postoperative patients, those on ventilators from poliomyelitis, and those injured in battle. Often these patients were unconscious and not aware of their immediate surroundings. We now have a wider variety of patients and the future will result in more critically ill patients seeking our care. The patients will come from the extremes of age. Technology will continue to provide us with more information about our patients. Instant feedback will be available to guide our therapy. ICU caregivers will need one hand to fill out the ever-growing mountains of forms required for reimbursement, another hand to work on the computer that controls every aspect of the patient's care, and another hand to actually, on rare occasions, touch the patient.

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Critical care medicine attempts to salvage individuals injured beyond all possibility of natural, nontechnologically assisted repair and healing. The hallmark of the intensive care unit (ICU) patient is injury or illness so profound that the ability to self-maintain homeostasis or sustain other vital functions such as gas exchange, circulation, digestion, host defense, and excretion of waste products has been lost.

Patient Safety and National Health Policy Drivers of ICU Care

Reducing mishaps from medical management is central to efforts to improve quality and lower costs in health care. Nearly 100,000 patients are estimated to die preventable deaths annually in hospitals in the USA, with many more incurring injuries at an annual cost of $9 billion. This annual toll exceeds the combined number of deaths and injuries from motor and air crashes, suicides, falls, poisonings, and drownings. Yet it is estimated that adverse events are underreported by 50–96% annually. An environment fostering a rich reporting culture must be created to capture accurate and detailed data about nuances of care.

The Institute Of Medicine (IOM) report made a series of recommendations designed to:

- Esblish a national focus to create leadership, research, tools, and protocols to enhance the knowledge base about safety.
- Identify and learn from errors through immediate and strong mandatory reporting efforts, as well as encouragement of voluntary efforts, with the aim of making sure the system continues to be made safer for patients.
- Raise standards and expectations for improvements in safety through the actions of oversight organizations, group purchasers, and professional groups.
- Create safety systems inside health care organizations through the implementation of safe practices at the delivery level.

The IOM report concluded that a reduction in avoidable medical errors of 50% over the next 5 years was achievable and should be the minimum target for national action. A hallmark of the report was its emphasis on subjects not normally considered under the quality umbrella: human factors, interdisciplinary teamwork, cultures of safety, and complex issues associated with mandatory and voluntary reporting of events of patient harm and near misses. Outcomes in a complex work environment depend on the integration of individual, team, technical, and organizational factors. A continuum of cascade effects exists from apparently trivial incidents to near misses and full-blown adverse events. Consequently, the same patterns of causes of failure and their relations precede both adverse events and near misses. Only the presence or absence of recovery mechanisms determines the actual outcome.

The report quickly led to a presidential mandate to all federal agencies dealing with health care to prepare an action plan for improving patient safety. Many stakeholders in health care have begun to work together to resolve the moral, scientific, legal, and practical dilemmas of medical mishaps.

Current Critical Care Crisis

The rapid and enormous technological strides were facilitated by unfettered and unregulated application of innovation to medicine. In areas of endeavor where the cost of failure is deemed acceptable, advance is both rapid and sustained. Nowhere is this more evident than in the areas of computing, software development, industrial data acquisition and process control, and consumer electronics. These areas consistently attract the best and brightest minds because of the lack of regulation, rapid transit of technology from idea stage to developed product, and the prospect of large financial reward for success. Technological advances in areas unrelated to critical care medicine will increasingly allow for monitoring and control of diverse physiological parameters. Continuous monitoring of blood and parenchymal gases, pH, electrolytes, lactate, and other meolites, as well virtually all aspects of respiratory function, are either currently in clinical use or soon will be. Real-time sensor arrays capable of continuous monitoring of circulating hormone and cytokine levels already exist in the laboratory and will likely become clinically available in the next decade.

Continuous monitoring of a wide range of other physiological parameters has long been routine: core temperature, mean arterial pressure (MAP), central venous pressure (CVP), cardiac output (CO), systemic vascular resistance (SVR), central venous oxygen saturation (SVO 2), intracranial pressure (ICP), cerebral cortical perfusion, and intra-abdominal pressure via a transducer placed in the urinary bladder. Continuous measurement of gastric tonometry and pH are both approved technologies, although little used at this time. The immediately foreseeable future presents the possibility for the continuous monitoring of vascular and tissue drug levels or of any molecule, native or synthetic, which is of clinical interest.

As of the year 2007, critical care medicine consumed 4.2% of US healthcare costs and 0.9% of the US gross domestic product, and over 20% of the acute care hospital costs. While there are data that indicate the cost effectiveness of critical care medicine is comparable to that achieved in other areas of medicine, there is no doubt that critical care medicine is a bad bargain and an extravagance when compared to the value returned for dollars invested in basic public health infrastructure. Yet, critical care medicine is unarguably a necessity for those individuals in need of it.

Most patients who utilize critical care medicine in the West do not pay for it on fee-for-service basis. Rather, government-administered healthcare programs or large bureaucratic insurance companies pay the tab and determine what kinds of technology are worthwhile. The pressure to demonstrate the cost-benefit of critical care is exacerbated by the expected increase in demand associated with the ageing of the baby boomer generation and the ever-escalating cost of technology implementation. Access to, and expansion of, critical care medicine is increasingly under pressure to improve outcomes and demonstrate the value of future investment in expensive technologies.

There is evidence of improved patient outcomes and costs savings with dedicated intensivist models but this is confounded by the workforce crisis with shortages of 20% in intensivists and ICU-trained nursing staff. This crisis is forcing a model of

austerity which will require a redesign of current critical care practice. This will require better organization and design of the ICU to improve workflow efficiency including better present and remote technologies and the use of robotics and telemedicine such as the VISCU model.

The priority placed on improving patient safety and the overall quality of health services has significant implications for medical education of ICU professionals. Strong federal policy recommendations have addressed improving provider education and training for information and systems management, teamwork, and building cultures of safety and excellence. In the Australian state of New South Wales, the Garling Inquiry recommended a number of strategies for clinical practice improvement and continuing safety education of clinicians, including the introduction of an Institute for Health Innovation. Although other risk management strategies must be implemented at the systems-design level, a number of these solutions (such as protocols for new technologies and the development of care pathways) explicitly and implicitly depend on improvements in medical education, training, assessment, and feedback for their ultimate effectiveness.

Traditional ICU Design Approach

The evidence is overwhelming. The healthcare environment – where care is actually provided and received – has substantial effects on patient health and safety, care effectiveness, staff efficiency, and morale. The USA spends approximately 16% of its Gross National Product on healthcare, much of which is provided in hospitals. Quite extraordinarily, we are in the midst of the largest hospital building booms in US history, with over 500 facilities being planned, designed, or constructed. This program will have a $200 billion impact. We have a unique opportunity to shape them by creating clear evidence-based, scientific guidelines, which will assure that they are built for safety and effectiveness of care.

Yet, despite this enormous expenditure and the available technological resources, today's hospital care frequently runs afoul of the cardinal rule of medicine – "above all else, do no harm." The physical environment in which that complexity exists has a significant impact on health and safety; however, enhancing patient safety or improving quality have not been overtly integrated into planning processes and the design of hospital buildings.

The present ICU designs do not address fundamental elements of the patient experience: lack of control, insecurity, lack of privacy, disorientation, lack of sleep and rest, family absence, and an overarching sense of dehumanization. There is a growing sense that although we are able to address the physiological needs of life support, a significant portion of ICU veterans, perhaps as many as 50%, suffer permanent physical and psychological damage that reduces their quality of life.

Facility concerns with older ICU designs include lack of space, poor access and way finding to the ICU, ongoing problems with transfer to and from the ICU, incompatible life support systems, staff shortages – all leading to operational cost inefficiencies. New

design needs to adopt a microsystem organizational model that puts the patient and family at the center of the design process. And we need a much stronger evidence base for ICU design (Fig. 40.1).

The traditional ICU design process starts when architects are given functional program objectives which are then translated into specific space requirements. Those are followed by creation of departmental adjacency diagrams. Importantly from the architect's point of view, the key design issues can only be resolved if the operational issues are understood. Too little involvement by clinical staff in the preparation of the functional program will result in poor adjacencies and hindrance to the staff flows. After those steps, room-by-room adjacencies are developed and then a detailed design of each room is completed. The room-by-room design, together with other building requirements, are described in drawings and specifications that define how individuals, equipment, and technology will function together. Equipment and technology planning generally occurs in the later stages of the design process in the USA, although in other jurisdictions preparation of detailed room data sheets will proceed construction documentation phase. The British and Australians in particular have detailed building standards and health building guidelines which are meant to be evidence based. Nevertheless, the standards have little to do with addressing the organizational components of patient safety issues. And in the USA, the building standards do little to address patient safety opportunities.

Fig. 40.1 A traditional NICU with wall-mounted bed head units so all the electrical leads and gas lines trail across to the bed, restricting movement around the bed and creating a number of hazards. There is no natural light. There are no private spaces. There is no provision for family. The interiors are cold and technical in ambience

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Considerable research has gone into engineering service designs for ICUs in recent years and cover issues about air filtration, air volumes, numbers of outlets and power points; all well understood. But typically, no detailed discussion of patient safety takes place, creating the probability that latent conditions which exist in current settings and which contribute to active failures (adverse events, sentinel events, and near misses) will be repeated. Human factors and ergonomics, and the interface and impact of equipment, technology, and facilities are also not often explored in the design process.

Global performance, in terms of outcome, risk management, and safety, is influenced by local interactions and synchronization of system components (e.g., providers, patients, technologies, information systems, material resources, and physical and temporal constraints). As a result, adverse events and unintended consequences are impossible to understand in terms of simple rational rules. To date, reductionist approaches towards ICU design have failed to adequately control risk or reduce the number of adverse events. Conditions in which providers work, such as fatigue from 24-hour duty rotations or double shifts, high workloads, confusing labels, look-alike names, poor handwriting, and poorly designed equipment and health care buildings, can lead to errors. These are open or ill-posed problems that are best understood through controlled observations, cases study, and modeling, with insights drawn from other complex adaptive systems such as emerging economies and dynamic social systems.

New Innovations in Design of Healthcare Facilities

Despite the recent discussions in the architectural literature regarding design of "patient-centered" health care facilities, little assessment has been conducted involving the impact of the built environment on patient outcomes. Studies have focused primarily on the effects of light, color, views, and noise, yet there are many more considerations in facility planning that can influence the safety and quality of care. Most fundamentally, these concern understanding the preferred model of care and the workflow practices between members of the work unit, or team. Specific aspects include: the path and frequency of patient movement, patient visibility to staff, patient room configuration, details of design, and standardization.

High turnover of nurses and other staff has also been blamed on the hospital work environments. Crowded, noisy, poorly thought-out nursing stations add to stress, reduce efficiency, and increase the risk of medical errors. Nosocomial infections are strongly related to air quality, ventilation, presence and arrangement of hand-washing stations, room occupancy, and surface finishes. Poor lighting/day-lighting is linked to depression, medication errors, and order entry errors; and room arrangement, surface finishes, and lighting are linked to patient falls. In short, hospitals are not designed to foster creative and collaborative teamwork that are the foundations of providing safe and effective care.

The opportunity to build a new ICU facility emerges infrequently; indeed, most are in a continuous cycle of remodeling and expanding existing facilities to meet to changing demands. The challenge is to incorporate patient safety concerns as another con-

straint to be addressed in hospital design. In planning for the new ICU facility, the hospital design process has been approached with a blank sheet of paper, an appreciation of the evidence that there is ample opportunity to improve hospital patient safety, and the belief that improving hospital facility design will not only increase patient safety directly but also indirectly promote a safety-oriented organizational culture. The new foundation for understanding the occurrence of human errors considers that healthcare providers make mistakes because the systems, tasks, and processes they work in are poorly designed (Fig. 40.2).

New ICUs will need to be designed to accommodate (Figs. 40.3, 40.4):

- Larger private rooms (from 150 sq feet to 200 sq foot)
- Acute adaptable design with universal bed system, reducing patient transfers, reducing LOS, falls, disconnects, and medical errors
- Windows in each room to enhance neurological orientation and prevent sundown symptoms
- Headwall versus pendant-mounted systems improving access to head and airway and less obstruction of floor space
- Standardized protocols for device and software integration with universal connectivity of all life support systems
- Standardized electronic medical records with easy sharing with other hospital units as well as other ICUs
- Decentralized nursing station
- Nature views and warmer colors of interior design
- No overhead paging and attention to the acoustic environment
- Fully controlled sound and light by patient/family
- Active engagement of family with family-centered rounds, improved waiting rooms, and overnight stays in patient rooms

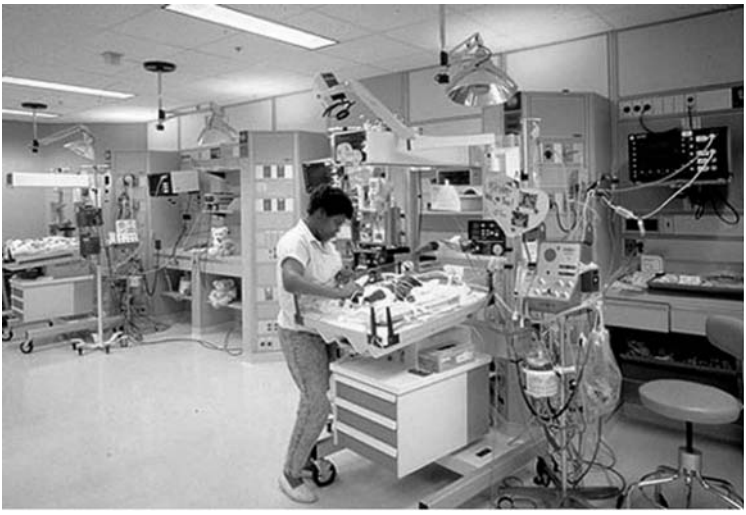

Fig. 40.2 A contemporary space with pendant-mounted services, natural light, windows to the corridor, wooden paneling to soften the space

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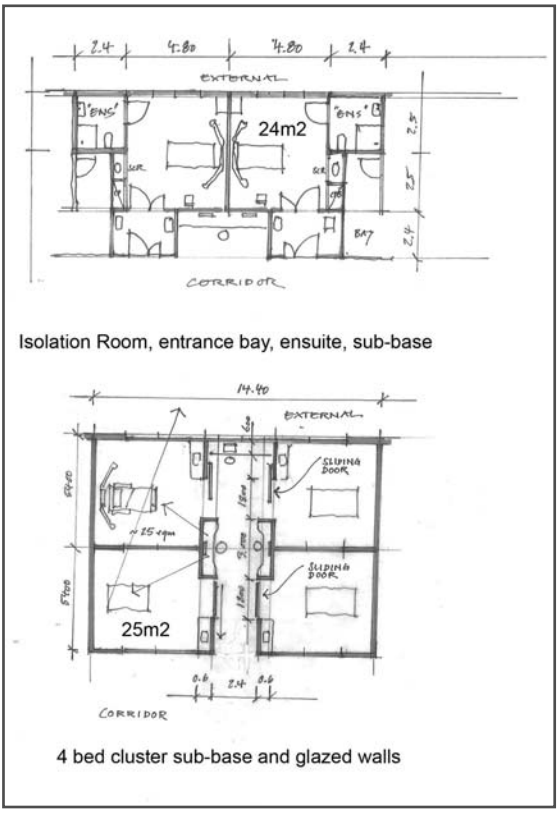

Fig. 40.3 Plan for a contemporary ICU

- Rest rooms and fatigue management policies and places for staff and trainees
- Point of care testing

Patient Safety Research Roadmap in the ICU (Table 40.1)

Noise

The Problem

The research literature on noise in healthcare environments is large, running to at least 140 studies. Hospitals and ICUs are much too noisy, with dB levels far exceeding WHO guideline values. Hospitals are excessively noisy because noise sources are unnecessarily numerous and loud, and many environmental surface are hard and sound-reflecting, causing noise to echo and propagate over large areas. Long reverberation times (e.g., 0.8–1.0 sec for sound to decay 60 dB) are commonly measured in healthcare spaces with hard sound-reflecting surfaces.

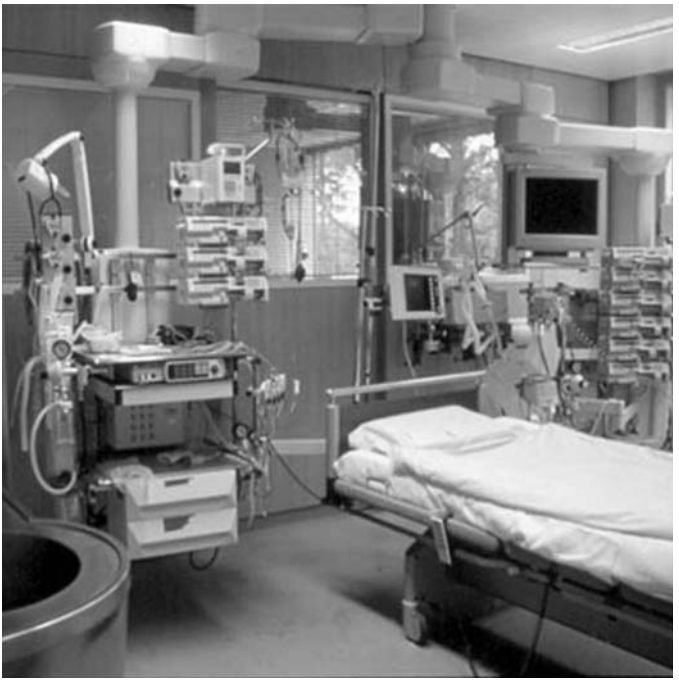

Fig. 40.4 Detail of the two- and four-bed clusters – the two-bed clusters are intended for isolation cases. All bedrooms get natural light and can be darkened with Venetian blinds in double-glazed windows to ensure cleanable surfaces for infection control. There are two main corridor systems, a front of house in which public and relatives come to a reception point available 24 hours and back of house in which beds and staff link to emergency and operating rooms with secure access. Families have retreat spaces within the unit for when staff carry out a procedure or when they need respite. A major staff base has visibility through glazed walls for vision at night and sub-bases are located close to all patient bed areas during the day. Staff are kept within conversation distance to increase communication and support. ICU operates as one unit and CCU as another but are contiguous for access to support spaces and for future expansion as all patient rooms are the same. All but one room has positive air pressure; negative pressure is needed for infectious cases. Staff have no control over flow direction to maintain the integrity of the system

Research Has Found

Several laboratory studies involving nonhealthcare participants have shown that cognitive tasks or activities involving high load in working memory, such as sustained attention to multiple cues or complex analysis, are directly sensitive to noise and performance suffers. Performance on short duration tasks is not consistently impaired by noise when there is incentive or pressure to maintain accuracy. Maintaining accuracy, however, comes at the cost of increased effort as evidenced by heightened physiological mobilization (e.g., cardiovascular activity) and fatigue.

There is also considerable evidence from laboratory research and studies in non-health contexts (schools, for example) that poor acoustic conditions characterized by background noise and especially by longer in contrast to shorter reverberation times

Tabella 40.1 Physical environmental conditions critical for consideration in the ICU environment

Infection control
Selection of surface materials
Handwashing station provision
Space for maintenance of sterile technique
Ventilation design – filtration, air flow, temperature, humidity
Patient identification
Lighting intensity and quality
Sound/noise – design for aural quality
Human factors
Vibration
Noise and acoustic quality
Layout of room for placement and movement of surgical systems, robots, imaging, etc.
Staff workflow
Access to supplies and emergency services
Room environment control design
Staff accommodation
Minimize stress
Transfer
Physical – provision for patient transfer system
Information – environment for accurate, undistracted communication
Utility systems
Design for ease of maintenance and indication of failure
Clarity of controls, displays, and indicators
Standardization of systems (important in other areas as well)
Systems coordination
Design of systems to eliminate confusing alarms and indicators
Testing of systems in simulated surgeries to discover shortcomings

reduce speech intelligibility and sharply heighten comprehension errors. A longer reverberation time indicates that the decay of a sound is comparatively slow (more echo), causing blending and overlapping of sounds that erode speech intelligibility and recognition accuracy.

There is evidence that a bad acoustic environment during acute illness may have detrimental physiological effects on rehabilitation. In one study, patients admitted for acute myocardial infarction or angina pectoris, had much greater pulse amplitude and a higher incidence of incidence of rehospitalization when exposed to a bad acoustic environment (sound reflecting tiles).

What Can Be Done

There are highly effective design strategies available for quieting healthcare buildings, including: providing single-bed rooms, installing high performance sound-absorbing ceiling tiles that reduce reverberation and diminish propagation, and eliminating noise sources (for example, replacing overhead paging with a noiseless system).

Research Needs Around Safety-Relevant Gaps in Noise Research

There is little rigorous research on the relationship between noise in healthcare settings and staff fatigue. Busy and preoccupied staff must maintain exacting performance and accuracy over long periods despite often high levels of uncontrollable noise. Further, there is a conspicuous lack of research concerning the possible detrimental effects of noise on performance and errors by physicians and clinical staff engaged in tasks involving high load in working memory.

There is a clear and pressing need for research to ascertain whether poor acoustic conditions are linked to increased speech recognition mistakes among clinical teams, and may thereby worsen patient safety in treatment settings such as emergency departments.

Design to Reduce Medication and Data Entry Errors

The Problem

Medications are pervasive in ICUs and error rates related to systems for prescribing, dispensing, and administering medications are known to be high. A small number of rigorous studies have identified latent conditions tied to the physical environment that can influence medication error rates.

Research Has Found

This limited amount of research indicates the following:

Medication dispensing errors decline steeply when distractions or interruptions, such as telephone calls, are reduced or eliminated. Other human factors and human performance research in nonhealth settings indicates that data entry errors likewise decline when distractions or interruptions are eliminated.

Studies of pharmacists have found that dispensing errors can be lowered by providing appropriate work surface lighting levels (1,500 lux) and placing light fixtures to reduce glare, so that the higher levels of illumination can be used with task lighting. (Lighting design involves more than determining light levels.) Low illumination levels (200–500 lux) are often found in healthcare spaces and may be too low to support high accuracy in medication dispensing or paper-based reading and data entry tasks. In this regard much research has shown that persons past the age of 40 usual-

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ly require higher on-task illumination for accurate work. The aging of the US nursing work force (average age: 47.5 years) implies that work surface illumination levels of 1,500–2,000 lux might be needed to help lessen errors in dispensing medications and performing paper-based reading and writing tasks.

Research Needs Around Safety Relevant Gaps in Noise Research

1. The worse-case environment from the standpoint of latent conditions that foster errors is one that may actually exist on many patient floors. This would be a dispensing or other work space with low illumination adjacent to a busy or noisy central nurse station or hallway that generates distractions and interruptions. Errors might be lessened by providing a dispensing space that is separated from work areas where staff cluster, that minimizes distraction and interruptions, and which has adjustable task lighting to enable bright illumination as needed. Research is necessary to evaluate this and other hypotheses for designing medication dispensing and work spaces that improve safety by eliminating latent conditions that foster errors.
2. There is an urgent need for research to investigate the possible effects on error rates when entering data and performing other tasks at bedside (or in patient rooms) versus decentralized and centralized nursing/charting stations. On the basis of human factors considerations, it might be contended that bedside data entry could worsen errors when there are distractions and questions from patients and family. Are errors reduced when nursing units are designed with hallway charting stations where clinicians enter data or perform tasks without distraction? Is information acquired by clinicians at bedside retained fully in working memory when they leave the room and walk to a nearby charting station? The absence of sound research on these and other questions is worrisome given that large investments in electronic technology and nursing unit architecture often are tailored to support either bedside (in room) or charting station data entry.

Design Measures to Reduce Healthcare Associate Infections (HCAI) in the ICU

The Problem

A large body of scientific evidence (more than 145 studies) shows that the built environment influences HCAI rates, especially for airborne and contact-spread infections. Airborne infections are linked to bacteria, fungi, and other pathogens that are small enough to become suspended in the air.

Research Has Found

- Much research has shown that hospital air quality and ventilation (air changes per hour, type of filter, direction of airflow, and air pressure) decisively affect concen-

tration levels of airborne pathogens and thereby strongly influence infection rates. The American Society for Healthcare Engineering (ASHE) produced a Green Guide in 2002 and is involved in the new LEED-Healthcare rating tool which is due out shortly and covers all aspects of air changes, filtration, waste, etc.

- The literature suggests a clear pattern for infection rates to be lower when there is very good air quality. For example, bone marrow transplant recipients, burn patients, and other high-acuity or immunocompromised patient groups have lower incidence of infection and often reduced mortality when housed in single-bed rooms with HEPA-filtered air or laminar airflow.
- New research derived from Environmentally Sustainable Design (ESD) show the benefits of 100% fresh air when used with displacement air system and chilled beams instead of fully air-conditioned environments.
- Single-bed patient rooms, compared to multi-bed rooms, are far superior with respect to reducing airborne transmission through air quality measures such as filtration, negative room pressure to prevent a patient with an aerial-spread infection from infecting others, or creating positive pressure to protect an immunocompromised individual from airborne pathogens in nearby spaces.
- More than a score of studies have identified hospital construction and renovation activities as sources of airborne infection outbreaks due to dust or particulate generation. Effective prevention or control measures during construction include portable HEPA filters, installing barriers between patient care and construction areas, sealing patient windows, and creating negative air pressure in construction areas relative to patient care spaces.
- Although airborne infections are a serious safety issue, most infections are now spread via contact transmission. Many environmental surfaces and features become contaminated in rooms with infected patients (e.g., computer keyboards, bed privacy curtains, overbed tables). These and other contaminated features act as reservoirs for pathogens that increase cross-infection risk. There is considerable evidence implicating unwashed staff hands as a key source of contact transmission. A great deal of research has shown that staff handwashing rates usually are low, and this represents a major patient safety problem. Handwashing compliance rates in the range of 15% to 30% are typical; rates above 40% to 50% are the exception.
- Research suggests that single-bed rooms, compared to multi-bed rooms, help to lessen risk of infections acquired by contact. Multi-bed rooms, compared to singles, are more difficult to decontaminate thoroughly after a patient leaves the unit, and therefore worsen the problem of multiple environmental surfaces acting as pathogen reservoirs that can potentially spread infection.
- Patients in single-bed rooms, unlike multi-bed rooms, are protected from contact with roommates who are admitted with undiagnosed infection that flourishes in the hospital setting. Proactive assignment to single rooms is needed, for example, to separate newly admitted patients for the 2–3 days required to obtain diagnostic test results for dormant infections such as MRSA.

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Research Needs Around Safety-Relevant Gaps in HCAI Research

While many of the technical components of patient safety, for example, electrical standards, fire safety walls, and air quality are covered by innumerable standards, the psycho-social aspects and operations for individual staff are not; for example, handwashing works but clinicians fail to wash hands. The internal architecture of a hospital needs to encourage this activity. Given the tremendous morbidity, mortality, and cost associated with high rates of HCAI, research is urgently needed to identify more effective ways for producing substantial and sustained increases in handwashing.

Costly and intensive programs to increase handwashing through education have produced disappointing or, at best, mixed results. Some education programs have succeeded in raising handwashing compliance but the increases usually are transient, lasting only 2–3 weeks. Findings from a few studies are encouraging in the sense they raise the possibility that certain design measures, including providing numerous conveniently located alcohol gel hand rub dispensers and sinks, may produce sustained increases in handwashing.

There is a clear need for studies that include controlled prospective experiments that systematically vary the number and location of hand-cleaning dispensers or stations. Research also is plainly needed to define accessible and appropriate locations for gel dispensers and sinks in an evidence-based manner – that is, on the basis of empirical analysis of staff visual fields, movement paths, and work processes.

The neglect of human factors and research methods is a glaring and unfortunate weakness of handwashing research and, more generally, of the infection control literature. We recommend that research to address this should be carried out by teams that include human factors specialists and environmental psychologists. This research direction warrants very high priority.

Design Measures to Reduce Falls in the ICU

The Problem

Research identifying effective ways to reduce falls is of great importance because patients who fall incur physical injuries, psychological duress, and have longer hospital stays. It is estimated that the total cost of fall injuries in healthcare buildings runs to billions of dollars annually. Scores of studies have addressed the causes and risk factors related to patient falls in hospitals and other types of healthcare buildings. It is disappointing there is not yet convincing evidence tying any single or specific environmental intervention (e.g., improved lighting, secure carpeting) with reliable reductions in falls.

Current Research Has Found

- Most falls occur in the patient bedroom, followed by the bathroom, especially when patients get out of bed unassisted, for example, when walking to the toilet.

- Many bedroom falls occur at the edge of patient beds, or en route to or from the toilet through space lacking a handrail. There is considerable evidence that bedrails are ineffective for reducing falls and may actually increase the severity of fall injuries from beds.
- Design faults identified as contributing to falls in bedrooms and bathroom include slippery floors, inappropriate door openings (often too narrow), poor placement of rails and accessories, and incorrect toilet and furniture heights.
- Falls in the elderly can be associated with cognitive impairment due to the mixture of an unfamiliar environment, stress, changed medication, and postoperative disorientation. Although there is no persuasive evidence that any single environmental measure reliably reduces falls, a few studies have found that multifaceted fall-prevention programs can lessen patient falls (identifying high-risk patients in combination with multiple environmental interventions and care process adjustments).

Research Needs Around Safety-Relevant Gaps in Falls Prevention Research

- One of the major factors in falls is the inability of staff to see patients due to the separation from single-bed rooms and the location of central staff bases as well as support spaces in relation to the view of beds or toilets. Satisfactorily resolving conflicting design issues of access, visibility, and available staff numbers requires specific research. To increase observation and improve assistance for patients and thereby reduce fall injury, Methodist Hospital in Indianapolis changed its coronary critical care floor from a unit with centralized nurse stations and two-bed rooms to one with localized nurse stations designed for high visual access to patients, and large single-bed rooms furnished to support ongoing family presence. Comparison of data from 2 years prior and 3 years after the new unit opened showed that falls declined by two-thirds. Additional studies are needed to confirm and understand the effectiveness of this quite promising approach.
- Innovatively designed patient rooms are beginning to appear that place the door to the toilet on the same wall as the bed headwall, thereby shortening the distance substantially that a patient must cover when moving from the bed to the toilet. Importantly, headwall placement of the toilet entrance makes it possible to provide continuous wall-mounted handrail support from the bed to the toilet. It is possible that such room designs may reduce falls, and rigorous research is needed to test this hypothesis.
- Technology and devices are available for detecting patient motion or movements, including when they attempt to get out of bed. Some of this technology is intended for incorporation into the architecture of patient rooms. As an example, St. Joseph's Hospital in West Bend, Wisconsin was built with infrared motion detectors in the walls of patient rooms. If a patient attempts to get up at night, the detectors gradually turn on lighting in the room and toilet and notify nurses to assist or observe the individual. Studies are needed to evaluate the effectiveness of such systems and alarms in preventing falls.

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Reducing Patient Transfers

The Problem

There is increasing evidence that intrahospital transfers worsen patient safety and markedly increase costs. Transfers (hand-offs) increase medical errors, including medication errors, heighten risk for cross-infection, cause manual lifting injuries to staff, and can trigger serious clinical complications including, for example, arrhythmia, hemorrhage (dislodgement of arterial catheter), and cardiac arrest.

Apart from patient transport, other reasons why transfers increase errors and erode safety include changes in staff caring for a patient, communication discontinuities, loss of information, changes in systems and computers, and delays or interruptions in patients receiving medications and care. If transfers generate errors and other threats to safety, it follows that safety should be enhanced if care processes and physical environments are reorganized and redesigned to eliminate many transfers and temper the negative effects of those that remain.

Research Needs Around Safety-Relevant Gaps in Handoff Research

- More studies are needed to achieve a better understanding of safety threats and costs associated with transports of specific categories of patients between different types of units and treatment areas. This knowledge could inform a rethinking of architectural adjacencies based on safety considerations. The knowledge would also be extremely important for estimating safety gains and costs savings that could be realized by reorganizing care processes and redesigning physical environments in ways that reduce transfers.
- A most promising approach for reducing transports involves an acuity-adaptable care process/staff model in combination with single-bed rooms having gas outlets and other equipment that permit the room to flex up or down in acuity according to the condition of the patients. Research by Hendrich and colleagues found that such a unit for coronary patients reduced transfers by 90% and medication errors were correspondingly lowered by 70%. It is important that the acuity-adaptable care model be extended to other categories of patients and evaluated by rigorous research.

Conclusions

The health care system has only recently begun to approach patient safety in a more systematic way. A major tension that characterizes this process is the attempt to achieve a balance between learning and control in complex systems with technical, social, and organizational components. Efforts to improve learning in the ICU are marked by better information flow, discovery, flexibility in thinking, embracing of

failures as learning opportunities, and core incentives to promote voluntary participation of all stakeholders in the process. Organizational accidents have multiple causes involving many people operating at different levels, which translate to failures at the point of service (e.g., a physician ordering a drug to which a patient is allergic; patient falls due to use of over-smoothed surface materials). Based on this idea, exceptional design of ICUs will provide an environment of patient safety as well as a safety-oriented organizational culture for staff. It will require a constant focus on safety by ICU leadership, physicians, and staff and will only be accomplished through a continuous cycle of evaluation and improvement of the facility, equipment, technology, and processes.

ICUs of the future will need to be bigger, costlier, and more advanced, but integrated more closely into the hospital flow. Better outcomes will require a more humane and therapeutic environment. This will lead to better patient satisfaction and better outcomes.

Suggested Reading

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How to Plan and Design a Clinical Research Project

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A.A. Zin, A. Gullo W.A. Zin

Introduction

Scientific research is in fact the systematic process of collecting and analyzing data in order to increase the available knowledge on a specific field of interest. To start with it is mandatory that a protocol be established and understood by all personnel involved in the research. This protocol must be approved by an Institutional Review Board (IRB) before the research starts off. The research protocol is a formal written document specifying the study design and the manner in which it will be conducted. It is the blueprint of the study and serves as a guideline throughout the implementation and analysis phases. It details procedures to be followed yielding valid results. The research protocol fulfils scientific, ethical, and organizational requirements so that the study may be conducted efficiently and according to the plan, thus standardizing the procedures for research personnel to follow. The purpose of the study and the setting will determine which professionals will be consulted about the development of the research protocol. Subject area experts, epidemiologists, and/or statisticians can be included.

The protocol document is the blueprint for all those working on the research project. It should be well organized to facilitate the finding of relevant information. The title page includes the study title, protocol number, study site, principal investigator name/affiliation, study sponsor, and final or draft date. All documents and forms relevant to the implementation of the study must be attached in the appendices, including schedules for assessments, informed consent form approved by the IRB, and study procedural requirements (source documentation, case report forms, data collection and storage methods, study monitoring, study medication accounta-

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bility, conditions for modifying or terminating the study, disclosure of data/publication and conflict of interest), and product information about drugs or devices (clinical trials). The essential components of a research protocol consist of: research question, background information and relevance, aim and objective(s), design, subjects, variables, statistical issues, analysis approach, and ethical considerations.

Research Question

A question, problem, or hypothesis should originate one's research. In all fields there are so many unanswered questions; it is just a matter of asking oneself: "Why?" "What is the meaning of this?" "What has caused that?" Accidents may happen, of course, but researchers will never start data collection expecting that these data will show them the way to follow. The problem establishes the origin of formal research.

There are in fact several sources of ideas for developing research questions: (a) they usually arise from the investigator's previous studies, as well as from other professionals' in the same field. For this purpose it is of paramount importance that the investigator follows very attentively the literature in the respective area of interest; (b) scientific meetings where recent studies are presented offer an excellent opportunity to informally meet leading scientists and discuss with them new ideas and projects. It should be stressed that very frequently scientific associations emerge from a coffee break conversation, and, furthermore, researchers are very keen to collaborate; (c) a skeptical approach towards accepted ideas can trigger excellent research questions; (d) new technologies often generate new insights and doubts about known clinical issues, which, in turn can generate new standards; (e) careful observation of patients and of the natural history of the disease can result in a fecund source of research questions; (f) although frequently underestimated, teaching represents an excellent starting point for research. Ideas for studies frequently arise during the preparation of presentations, as well as during debates with questioning students.

Background Information and Relevance

Usually background information triggers the research question. In a protocol the background information will support the research question by exposing the knowledge gap that will be fulfilled by the investigation. Hence, the researcher must be extensively aware of the current accumulated knowledge in the intended investigation area.

Aim and Objective(s)

A clear and unambiguous statement of the aim of the research is imperative. One must start up a project knowing exactly what is intended. "What is the goal?" repre-

sents the question to be answered at this step of the project.

The aim states the intention or purpose of a chosen area of research. On the other hand, the objective specifies a given way to achieve the aim. It is not uncommon to have more than one objective to satisfy the aim of the research. Thus, the aim and objectives are interrelated. The aim reflects the final goal of the research, and the objective describes how that goal is going to be achieved. Finally, objectives must fulfill the requisites of the aim.

Design

The research question guides the choice of the best study design to obtain a valid answer. No approach is better than the others and each research question requires a judgment about which design represents the most efficient way to obtain a satisfactory answer. The research question is sharpened in an iterative process, supported by an analysis of the current literature and conversations with experts. It is then refined into a hypothesis, which should be clear, observable, and measurable.

Initially when investigating new phenomena observational study designs are used. The investigator is observing the phenomena of interest. Descriptive study designs are used to gather general information such as age, habits, diseases, symptoms, and so on. Analysis of the results of descriptive studies serve as a basis for the development of new research questions and hypotheses that can be tested using analytical designs such as case-control or cohort studies. Here measures of association between characteristics of interest are determined, for example, smoking and lung cancer. To firmly establish a relationship of cause and effect, the investigator is no longer just an observer but plans an experiment (Fig. 41.1) such as therapeutic trials. The gold standard of study designs for establishing a cause/effect is an intervention study, for example, clinical trials (Fig. 41.1).

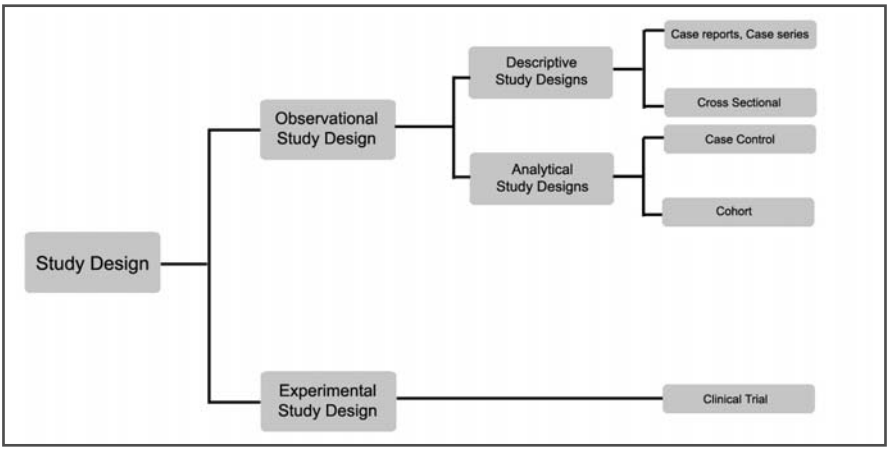

Fig. 41.1 Study designs

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One should describe the study in one sentence that includes the type of study design, population, intervention (if existent), primary outcomes, and length of follow up. Study design description may include the terms prospective or retrospective. Although sometimes confusing, the terms usually refer to the occasion of the events being studied. If they happened in the past and one is reviewing medical charts or medical databases, then the study is retrospective. If data about the events of interest are collected as they occur, the term prospective applies. Prospective studies are sturdier designs, as the investigator can eliminate errors related to coding of diseases and incomplete information and apply strict criteria for defining conditions across different study sites.

The choice of design is influenced not only by the research question, but by feasibility factors as well. The main feasibility factors are the time frame one has to conduct the study, the level of funding, the type of data required, and the resources available. Prospective studies like cohorts and clinical trials are more time consuming and expensive. Multisite studies add another level of complexity for implementation.

Most clinical studies involve comparison of groups and can be broadly divided into two categories: observational and experimental.

Observational

Observational studies collect information on events that are happening or have happened, over which one has no control. Data can be collected from populations or from individuals. There are some observational studies where the outcome of interest is described with no reference to exposure (descriptive studies), while others consider a possible association of outcome of interest and exposure (analytical studies).

The basic strategy designs used in clinical research can be broadly categorized according to whether these investigations focus on describing the distributions of disease or elucidating its determinants. Descriptive studies are concerned with the distribution of disease, which populations are affected, in what geographic location, and how the frequency of occurrence varies over time. Such information can provide clues leading to the formulation of a hypothesis that is consistent with existing knowledge of disease occurrence. Analytic studies focus on the determinants of a disease by testing the hypotheses formulated from descriptive studies.

Descriptive Studies

A descriptive study reports the general characteristics of the distribution of a disease, mainly related to person, place, and time. Information such as age, sex, race, marital status, occupation, medication use, consumption of foods, geographic distribution of a disease, and seasonal patterns in disease onset are examples of the kind of data that can be collected. They can be done quickly and easily as such information is usually available. Descriptive studies have usually provided reliable information about the possible determinants of a disease. However, due to limitations of design, this kind

of study is useful to formulate an hypothesis that can be tested later on using an analytic design.

Descriptive data addresses some questions:

1. "Who is getting the disease?"
2. "Where are the rates of disease highest and lowest?"
3. "When does the disease occur commonly or rarely?" and "Is the frequency of disease at present different from the corresponding frequency in the past?"

There are three main types of descriptive studies: case reports, case series, and cross-sectional studies.

Case Reports and Case Series. The case report is the most basic type of descriptive study of individuals. It is usually used to describe a new or unusual condition or circumstance and is often the first reported indication of a problem. Case series is a collection of individual case reports in a short period of time. One important limitation of case reports is its dependence on the experience of one person. Case reports and case series are limited to carefully describing a problem and suggesting potential hypotheses to be tested in future studies.

Case reports are among the most common types of studies published in medical journals. They document unusual medical occurrences and may represent the first clues in the identification of a new disease or adverse effect of exposures.

Cross-Sectional Surveys. In cross-sectional studies exposure and disease status are assessed at the same time in a defined population. The presence or absence of both the exposure and the disease are determined at the same time point. Because both exposure and disease are determined at the same time, it is impossible to determine, in most cases, which came first. Therefore, cross-sectional studies can suggest associations between an exposure and a disease but cannot prove causality. Cross-sectional studies are relatively simple to conduct, cheap, and take a short time. For these reasons, they are frequently used for planning purposes. In general, they are used to estimate the prevalence of common conditions of reasonably long duration or to determine the distribution of continuous variables within a population.

Analytic Studies

Analytic study designs are used for testing the hypotheses formulated by descriptive studies. These studies enable comparison among groups, determining whether the risk of disease is greater in individuals exposed or not exposed to a known risk factor.

In an observational analytic study, the researcher does not interfere with the natural course of events. In interventional studies, the researcher allocates the exposure at random in a sample of sufficiently large size, following the groups for the development, or not, of the outcome of interest.

There are two main types of observational analytic studies: case-control and cohort.

Case-Control Studies. A case-control study is designed to help to determine if an exposure is associated with the outcome of interest. The first step is to identify a group of cases, i.e., individuals with the outcome of interest (a disease) and a group

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of controls (individuals without the illness). Then it looks backward to find differences in exposure variables that may explain why the cases got the disease and the controls did not. The proportion of people exposed to a suspected risk factor is then measured in the two groups and compared. If the proportion of individuals exposed to the factor is higher in the case group than in controls, then the exposure might be a risk factor for the disease. If it is lower, it might be a protective factor.

The case-control design can also be used to look at other outcomes among those subjects that already have a disease. For instance, obesity can be identified as a risk factor for diabetes; however, other risk factors such as aging and sedentary life-style could be possible outcomes.

Case-control studies provide descriptive information on the characteristics of the cases and an estimate of the strength of the association between each risk factor and the presence or absence of the disease. Case-control design cannot be used to estimate the incidence or prevalence of a disease because the investigator chooses the sample size of cases and controls, which does not represent the real proportion of sick people in the population. The more important weakness of case-control studies is their susceptibility to bias, but there are strategies to deal with the diverse kinds of bias.

Considering diseases that are either rare or have long latent periods between exposure and disease, case-controls are much more efficient than any other design. Indeed in many instances they constitute the only suitable alternative.

Advantages of case-control studies

1. Quick and cheap
2. Only feasible method for very rare disorders or those with long time gap between exposure and outcome
3. Can investigate a wide range of risk factors
4. Fewer subjects needed than in cross-sectional studies
5. Consistency of measurement techniques maintained
6. Generate hypotheses about the causes of disease

Disadvantages of case-control studies

1. Bias in determining exposure (recall bias, interviewer bias, missing data, lack of standardization of prerecorded data, measures affected by disease onset, use of nonnewly diagnosed cases)
2. Bias in choosing controls (inappropriate source, overmatching)
3. Problems in sorting out sequence of events (because retrospective)
4. No estimate of absolute risk
5. Only one outcome (disease)
6. Not suitable for investigating a rare risk factor (unless it is the only cause of disease)
7. Cannot estimate disease incidence or prevalence

Cohort Studies. In a cohort study a group of individuals is followed up over a period of time, looking at the development of some outcome. Therefore, an exposed and an unexposed group to a potential cause of disease are followed up over time and the incidence of disease in one group is compared with the incidence in the other. The exposure can be a personal characteristic, behavior, or exposure to anything, e.g.,

radiation. At the time exposure status is defined, all subjects must be free of the disease under investigation. All participants are then followed up to assess the occurrence of the outcome (Table 41.1).

Table 41.1 Schematic representation of a cohort study

	Disease +	Disease –	Total
Exposed	a	B	a+b
Nonexposed	c	D	c+d

Cohort studies are useful to evaluate disease etiology, prognosis (natural history of disease) and incidence of a disease, as all subjects in both groups (exposed and nonexposed) are free of disease at the beginning of the study. Incidence can be calculated as follows:

No. of new cases of disease (in a time period) / Population size = Incidence rate

A cohort study design can be used to investigate research issues such as when it is not ethical to carry out a randomized controlled trial to determine the outcome of a treatment. Experiments in the organization and delivery of health services are also ideal for the cohort design, for example, the relationship between volumes of procedures carried out in a hospital and outcomes such as complication rates or mortality.

There are three study design features that are pivotal in the outcome of an appraisal of cohort studies. The first one is the recruitment of subjects, which has to be evaluated for its completeness. It can be useful to ask about the subjects not recruited. Also assess the possibility of a selection bias before entry point. For example, the more severe cases may be referred elsewhere. Secondly, the criteria to evaluate outcomes of care must be valid or validated; for example, hospital mortality may vary due to variations in length of stay and therefore is not a valid measure. A validated measure would be 30-day mortality. Third, when analyzing the results make sure that some measure of control for comorbidities is taken into account, as this can systematically bias the results.

Cohort studies may be prospective or retrospective. These terms refer to the temporal relationship between the initiation of the study and the occurrence of the disease outcomes being studied. In the prospective model the groups of exposed and unexposed individuals have been assembled but the disease has not occurred yet. The researcher must follow the patients up for a certain period to ascertain the outcome of interest. In the retrospective design the investigation begins at a point in time after both exposure and outcome have already occurred. A cohort study is ambidirectional when data are collected both retrospectively and prospectively in the same cohort. This type is applicable for exposures having both short-term and long-term effects.

Retrospective studies can be conducted more quickly and cheaply than prospective studies. Hence, retrospective studies are more suitable in investigating diseases

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with long latency periods, which would require many years for significant results to be achieved. However, it depends on availability of previously recorded data on exposure. Sometimes this can result in incomplete and incomparable data for all study subjects, such as when information on possible confounders (i.e., smoke, diet, coffee intake) is not recorded.

In prospective studies the investigator can assess information on exposure and potential confounders directly from study subjects.

A cohort study offers the possibility of examining a range of outcomes, which will depend on the chosen method of measurement. Whatever the procedure, it is crucial for the validity of the study that the method of ascertainment be identical for those exposed and those unexposed.

It is important to consider the possibility of bias, chance, and confounding as an alternative explanation for the results of a cohort study. Misclassification of exposure and/or disease may increase the similarity between exposed and nonexposed groups. Hence, any possible association will be underestimated. A major problem in cohort studies is the bias introduced by losses during follow-up, which would greatly affect the validity of the results. The longer the follow-up period, the more difficult it will be to achieve complete data collection as more subjects are likely to move and change jobs. A drop out of 10–15% is usually acceptable. The only way of eliminating this effect is prevention to minimize losses.

Not all eligible subjects to participate in a study agree to do so. Nonparticipants may differ from participants in various ways, such as smoking habits, diet, and health care. The results may be valid for the studied population but cannot be generalized.

Advantages of cohort studies:

1. Ethically safe
2. Subjects can be matched
3. Timing and directionality of events can be established
4. Rare exposures can be examined by appropriate selection of study cohorts
5. Multiple outcomes can be studied for any one exposure
6. Incidence of disease can be measured in the exposed and nonexposed groups
7. If prospective, minimize bias in the ascertainment of exposure
8. Eligibility criteria and outcome assessments can be standardized
9. Easier and cheaper to manage than a randomized controlled trial

Disadvantages of cohort studies:

1. Controls may be difficult to identify
2. Exposure may be linked to a hidden confounder
3. Blinding is difficult
4. Randomization not present
5. For rare disease large sample sizes or long follow-up is necessary
6. Very expensive and time consuming particularly if follow-up is long and outcome is rare
7. If retrospective, requires the availability of adequate records
8. Validity of results can be affected by losses of follow-up
9. Changes over time in exposure status and diagnostic criteria can affect the classification of individuals according to exposure and disease status

Experimental Studies: Clinical Trial

In experimental studies the researcher plans an intervention and observes the outcomes. The process of studying the effects of an intervention has evolved tremendously in the last century.

In medical research the clinical trial is the experimental study design of choice for studying the effects of therapies. A clinical trial is a carefully, ethically planned experiment. Amongst clinical trials the most representative design is the double blind randomized controlled trial, considered the gold standard in the scientific community for determining a causal effect. Double blind means researchers and subjects are not aware of which intervention the subjects received; randomized means the researchers have no influence in choosing which subjects received the experimental or control intervention, and controlled means there is a control group. This design is used to assess the efficacy of an intervention. This intervention can be a drug therapy/device (e.g., risk of myocardial infarction associated with antihypertensive drug therapy), a method of clinical or surgical management (e.g., management of patients with venous leg ulcers), or an evaluation of health services organization (e.g., acute stroke intervention: special stroke unit vs. general medical ward).

The comparison of the effects between the equivalent experimental group (receiving the active intervention) and the control group (receiving the placebo or standard care) is an essential element of study design towards making an assertion of cause and effect of an intervention.

The control group can receive different types of "control" intervention. For example, when studying the effects of new drugs, the control intervention is usually a placebo. Placebo is defined as being very similar to the intervention except for the active ingredient, for example, in appearance and taste. The control intervention may also be standard of care, for example, when studying the effects of a new drug for diseases with established therapy.

It is vital in the study design that the control group be treated in the same way as the intervention group in every aspect related to their care. For example, thought needs to be given to use of adjunct therapy, involvement of other healthcare providers such as physiotherapists, number of tests, and so forth. Subjects can make changes in their life-style, unrelated to the intervention, in a manner that affects the outcome. This is described as the Hawthorne effect. If there are important differences between the control group characteristics and the intervention group characteristics, the validity of the results may be reduced.

Randomization refers to the way one selects from one's study sample who will receive the active intervention and the control intervention. The goal of randomization is to maximize the probability that groups receiving different interventions will be comparable. When an adequate randomization procedure is used, the assignment of subjects to the intervention is determined by chance alone, i.e., the potential for bias in allocation to study groups is removed. Study groups tend to be comparable with respect to all known confounding variables as well as other unsuspected confounders. However, there is no guarantee that differences will not arise by chance between the two groups. A larger sample size reduces the risk of differences between groups.

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The randomization method should provide true random allocation. Computer-generated random numbers and tables of random numbers are the most commonly used methods of randomization. Alternate allocation and allocation by birth date or medical record number are not true randomization procedures. Central randomization procedures are preferable to local randomization; i.e., randomization is carried out by a statistician or a researcher not involved in the recruitment and follow-up of subjects.

When the researcher is unaware of which intervention group the subject will be allocated to there is concealment of allocation. This should remove any possibility of manipulation of subject allocation in the field. Concealment of allocation strengthens the randomization process. It is usually achieved by using sequentially numbered, sealed, opaque envelopes.

If there is a need to balance the number of subjects in different strata of subject characteristics a blocking procedure can be used when randomizing the sample. Subjects are first classified with respect to variables that will affect the outcome (e.g., age, sex, severity of disease) and then randomized. The two most important elements in eliminating bias in clinical trials are randomization and blinding.

Blinding refers to defining who does NOT have knowledge of which intervention subjects are receiving. In a clinical trial subjects, investigators and statisticians can be blinded to the intervention received by each study group. When subjects and investigators know the intervention being given, the trial is referred to as having an open label design. The aim of blinding is to avoid bias both in the study execution and in the interpretation of the results.

Investigators, clinicians, and subjects are prone to change their behavior if they know who is receiving which treatment. Blinding avoids the effect of this change of behavior in the results. Blinding is especially important when knowledge of the treatment received may influence the outcomes. Subjective outcomes, for example pain, are especially prone to be influenced by the knowledge of the treatment received. Hard outcomes like death or recurrence of a disease are not affected as much.

Ethical and practicability issues need to be taken into consideration when deciding the level of blinding in a clinical trial. Increasing the level of blindness brings higher costs, increased complexities, and longer timelines for trials. Double blind is the most common type of blinding used in clinical trials.

Advantages of the clinical trial design are that blinding and randomization allow for the unbiased distribution of unknown confounders between study groups and this strengthens the validity of the results. The disadvantages of the clinical trial design include the ethical constraints when designing the study, the high cost both in financial terms and in time, and a risk of volunteer bias in selection of subjects.

Trials for approval of new therapies are usually described by sequential phases of experimentation:

1. Preclinical: studies in cell cultures and animals.
2. Phase I: unblinded, uncontrolled experiments in human volunteers to evaluate safety.
3. Phase II: small-scale randomized blinded trials to test the effect of a range of doses on side effects and clinical outcomes.
4. Phase III: relatively large randomized blinded trials to test the effect of therapy on clinical outcomes. Once a treatment has been shown to be reasonably effica-

cious, it is necessary to compare it with the standard treatment for the same condition in a larger study.
5. Phase IV: postmarketing surveillance. After a treatment has been approved large trials or observational studies are conducted to assess the rate of important side effects and evaluate additional therapeutic use.

Subject

One key objective of research is to be able to make inferences from the results of a study to a more general population. Target population is defined as the group from which the study sample will be selected. The characteristics of the target population for the study determine the extent to which the study conclusions can be generalized to a wider population. Subject eligibility criteria ought to be clearly defined by establishing inclusion and exclusion criteria. Characteristics frequently taken into consideration include: age, sex, function of major body systems, mental status, previous health conditions, and/or previous drug treatment. The inclusion and exclusion criteria may affect the generalizability of the results.

The broader the inclusion criteria the easier it is to find study subjects and the results can be generalized to a wider population. Subjects unlikely to comply with study procedures and who have a higher risk for adverse therapy reactions should be excluded.

To select the target population the condition of interest should be clearly established. Are there validated definitions? Are there issues relating to staging the severity of illness that need to be clearly described? Consider the natural history of the condition of interest and the existence of validated prognostic markers to support the effect of intervention on the outcome variables.

Once the target population is ascertained, the ways to screen and recruit patients need to be clearly defined. Then, the screening procedure to select potential subjects must be settled. Where will the information about potential subjects be gathered? Will patients be screened or will charts be reviewed? What information will be collected?

The recruitment procedure is decided with two main goals in mind: (a) to recruit a sample that appropriately represents the target population; and (b) to recruit enough subjects to meet the sample size requirements. The inability to enroll enough subjects is a frequent problem in clinical research. The accessible population, from which the study sample is recruited, should contain more probable subjects than required in the study sample. Contingency plans should be foreseen if recruitment efforts fail in the initial effort.

Patients who refuse to participate can be systematically different (by gender, severity of illness, or other factors) from those who agree to enter the study. An account of subject refusals is of paramount importance in order to compare those who consented and those who did not. A low response rate of recruited subjects influences the ability to generalize the results to a wider population.

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Variables

Any measured aspect of a subject (e.g., gender, breathing frequency) is called a variable. Qualitative variables (also known as categorical or nominal) are not numerical, denoting different categories, rather than actual measurements of some quantity (e.g., sex, marital status, diarrhea, and so on). On the other hand, quantitative variables can take any numerical value along a continuous scale of measurement (continuous variables, e.g., temperature, arterial blood pressure, breathing frequency) or may vary by finite specific steps (discrete variables).

The precise distinction between outcome and exposure variables will determine the appropriate data displays and statistical approaches to be used. The focus of the study constitutes the outcome variable (for instance, disease, death, or a state of health). In particular the identification of factors or exposures (those which are included in the hypothesis) that may influence the size or the occurrence of the outcome variable, as well as other exposures that may influence the outcome (confounders), is mandatory.

A confounder is an alternative explanation for the outcome. In order to be a confounder, a factor has to be associated with the exposure being investigated and independently associated with the risk of developing the outcome of interest (Fig. 41.2). A factor can be an outcome in one study and an exposure in another.

The first step in a research study is to define the hypothesis that will be tested. This should be done in a way that makes clear what are the primary outcome(s), exposure(s), and potential confounders. Then, the most appropriate design will be chosen. In designing a study to determine if there is an association between exposure (risk factor) and an outcome (a disease), one should anticipate the potential alternative explanations that might be responsible for such an association. Awareness of the existence of a confounding factor is essential in clinical studies and many study designs are built around the control of confounding.

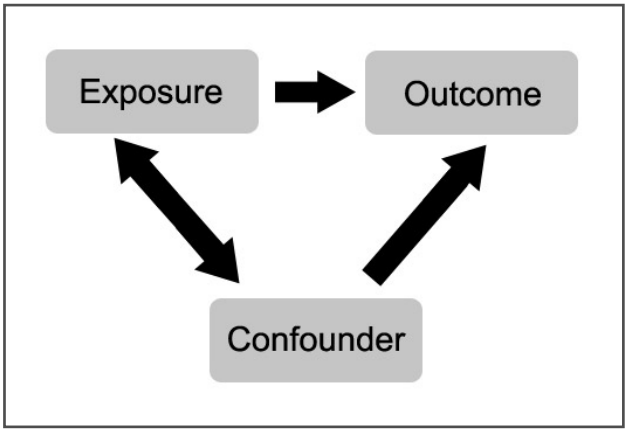

Fig. 41.2 Relationships among exposure, outcome, and confounding variables

Accuracy and precision are measurement characteristics. Precision relates to the method obtaining the same or very similar results after repeated measures. Precision is affected by observer variability (e.g., skill in using an instrument when measuring blood pressure), subject variability (for instance, mood when responding to a questionnaire), and instrument variability (for example, hearing screening tests affected by background noise). Actions to enhance precision include standardizing the measurement methods, training the observers, refining instruments, automating the instruments, and repeating the measurements. Accuracy is defined by how close the measurement is to the "true" value. Systematic error is reflected by less accuracy, for example, when a noncalibrated scale is used. Assess the accuracy of an instrument by using a "gold standard" or by comparing it with a technique that has had its accuracy accepted. Strategies for enhancing accuracy include standardizing the measurement methods, training the observers, refining the instruments, automating the instruments, developing measures that subjects are not aware of, blinding, and calibrating the instrument.

Statistical Issues

Populations and Samples

It is not feasible to examine or study every single individual of a population of interest. Hence a representative sample of n individuals drawn from this population is chosen. The proportion of a specific genetic trace or disease can be calculated from a random sample drawn from the entire population.

In reality, different random samples will provide slightly different estimates of the true population proportion. It follows that any sample estimate is subject to sampling error. As an example, let us assume that a sample of 60 individuals revealed that 14 were smokers, so that the proportion of smokers was 23%. However, as a result of sampling error it is unlikely that the proportion of smokers in the town equals exactly 23%. Hence, how far from 23% is it likely to be?

Suppose that all possible samples of 60 individuals in the town were studied, and the sample proportion p was computed. As aforementioned, the value of p will change from sample to sample. If all values of p were plotted, a sampling distribution of p would result. Most samples estimates would be located around the true (population) proportion π, whereas some would lie away from this true value. The degree of spread would reflect how precise the sample proportion π would be. A wide distribution would mean that a great deal of sampling error was present, so that p could lie far away from π, and vice versa.

The spread of a sampling distribution can be measured by the standard error (SEp), which indicates how precisely the sample value p estimates the true value π, and is given by:

$$SE(p) = \sqrt{[p(1 - p) / n]}$$

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As a conclusion, if the sample size is increased, the standard error will fall and the sampling distribution will become narrower. Additionally, it is possible to demonstrate mathematically that 95% of all sample estimates will fall within two standard errors of π; 2.5% will fall more than two SEs below π, and 2.5% will lie beyond 2 SEs above π.

The initial sample of 60 individuals may have come from any part of the above distribution, but there is a 95% chance that the observed proportion *p* lays within ±2 SEs of the true value π. In other words, it can be said with 95% confidence that the true proportion *p* is between:

$$p \pm [2 \cdot \mathrm{SE}(p)]$$

This interval is called a 95% confidence interval (or 95% confidence limits). The confidence interval is in fact a range of values that is likely to encompass the true population value, but there is no absolute certainty that it will. The confidence interval gives the precision of the sample estimate of a parameter. The size of the sample determines the precision of the estimate; the bigger the sample, the more precise the sample estimate is likely to be.

If one intends to be more confident that the interval includes the correct value, the 99% confidence interval can be computed. For this purpose 2.58 substitutes for 2 in the above formula, resulting:

$$\mathrm{p} \pm [2.58 \cdot \mathrm{SE(p)}]$$

It should be stressed that for the above considerations one should have taken a randomly selected sample of individuals from the population of interest, which was thoroughly defined beforehand. In other words, every single individual in the population has an equal chance of being in the observed sample.

When measuring the degree of association between two variables, its confidence interval can be used to determine whether the observed association could be due to chance. If it overlaps the null value (no association), it is equivalent to a nonsignificant result. If it excludes the null value, the result is statistically significant.

Hypothesis Testing

Statistical significance testing is a method that attempts to quantify the chance of obtaining the observed results if no true difference between groups or association between factors actually exists in the whole population.

A researcher conducting a study should have a theory in mind. For example, low tidal volume is better than high tidal volume in the treatment of acute respiratory distress syndrome (ARDS). This theory is called the study hypothesis. The null hypothesis states that the treatments are equally effective. If the null hypothesis were true, then for all patients with ARDS low and high tidal volumes would have the same responses. The alternative hypothesis states that the results of the treatments are different.

Once the null hypothesis is defined, the main question is: If the null hypothesis were true, what are the chances of getting the observed difference? For instance, in the ARDS trial, what is the probability of getting a treatment difference as large as (or larger than) 45% vs. 15%? This probability is determined by applying an appropriate statistical test.

Values of p exceeding 0.1 are generally considered large enough to accept the null hypothesis, i.e., there is insufficient evidence of a true difference. It is widely accepted that $p < 0.05$ indicates that there is substantial evidence that the null hypothesis is untrue. This arbitrary cut-off value has been used to definitively decide between significant and nonsignificant. Instead, one should report the true p value and discuss the results accordingly.

In summary, when dealing with statistical significance testing the investigators should always keep the following sequence in mind: (a) state study hypothesis, (b) formulate null hypothesis, (c) collect the data, (d) apply statistical significance test, and (e) reject or fail to reject the null hypothesis.

The Significance Test

The probability (p) that a result could have arisen if the null hypothesis were true must be calculated for every significance test. If the p value is less than the significance level, the hypothesis is rejected. One should bear in mind that the significance level should be stated before the test is applied, i.e., the cut-off value for p to declare a statistically significant result must be known beforehand ($p < 0.05$ and $p < 0.01$ are often used).

Type I and Type II Errors, Sample Size and Power of the Study

Table 41.2 depicts the main elements of the decision process. The columns correspond to the reality: is the null hypothesis true or false? The rows represent the decision taken: is the null hypothesis (H0) to be accepted or rejected?

Table 41.2 The main elements of the decision process. The columns correspond to the reality: is the null hypothesis true or false? The rows represent the decision taken: is the null hypothesis (H0) to be accepted or rejected?

		Reality Null hypothesis true	Null hypothesis false
Decision	Do not reject H_0	Correct decision	β or type II error
	Reject H_0 (significant result)	α or type I error	Correct decision

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If H0 holds true and a nonsignificant result is obtained, the correct decision has been reached. If the null hypothesis is true and a significant result is achieved, the decision to reject H0 is incorrect, yielding a type I or α (alpha) error, i.e., the probability of rejecting the null hypothesis when it is true. The significance level of the test must be revised.

If the null hypothesis is false, and H0 is not rejected, a β or type II error takes place. The chances of occurrence of type II errors depend on the true value of the population mean. The actual size of the β probability depends on the overlap between the sampling distributions of the mean under: (a) the null hypothesis, and (b) a specific alternative hypothesis for which the type II error is to be calculated. Type II errors can be reduced by: (a) decreasing the significance level to a value greater than 5% (this will increase α) and (b) diminishing the spread of the sampling distribution of the mean, thus reducing the overlap between the null and alternative hypotheses distribution curves. In other words, type II error can be reduced by increasing the sample size (preferred method).

The sample size should be calculated by someone familiar with statistical methods rather than relying on clinical experience or judgment. When the sample size is too small, it is impossible to distinguish between real and spurious results. Once the appropriate sample size has been calculated, an extra percentage should be added to it to allow for dropouts or withdrawals. As a general rule, a loss of up to 10–15% of subjects is acceptable and should not bias the result unless there is a strong confounder present. The requirements needed to calculate a sample size are: (a) significance level, (b) the accepted chance to make a type II error, (c) the size of what would be considered an important result, and (d) an estimate of the population variability.

The power, or sensitivity, of a test (1- β) is the probability of detecting the difference that is looked for when it is present. The power depends on: (a) the significance level, (b) the size of the effect or difference to be detected, (c) the underlying population variability, and (d) the sample size. It is desirable to have a high power or probability of detecting a difference between treatments to justify the efforts and ethical issues involved in conducting an experiment. The power of a significance test increases as the true size of the effect augments. Both sample size and power computations are used to determine the parameters for an intended experiment, before it is actually carried out. Power or sample sizes can be determined for: (a) paired and unpaired t tests, (b) one-way analysis of variance, (c) *z* test comparison of proportions, (d) chi-square analysis of contingency tables, and (e) correlation coefficients.

If the power to detect a true difference is established at 80%, then there is a 20% chance that this real difference could be missed. Generally, power levels of 80, 90, or 95% are used, and it is accepted that the size of the type II error should be around four times that of the two-sided significance level chosen. It thus follows that 80% power and 5% significance is the most common combination in the determination of the sample size, whereas 95% power is linked with 1% significance.

Analysis Approach

Planning the Analysis

The analysis strategy to evaluate primary and secondary outcome variables is defined in the study protocol. Describe the types of variables collected for outcomes and statistical tests planned. The handling of specific situations should be described in advance. For example, will there be a subgroup analysis? An interim analysis is a planned analysis conducted at a predetermined time in the study. The strategy used for this analysis is defined in the protocol. In clinical trials an interim analysis is conducted to (a) assess trends in incidence of adverse events and (b) assess efficacy results. Ethical issues and cost are the main justifications for planning interim analyses. In drug development trials an independent monitoring group apart from the investigators conducts the interim analysis.

Conducting the Analysis

Statistical analysis of the data collected provides information about the strength of the association between exposure variables and outcome variables. It supports the answer to the primary outcomes.

Descriptive statistical analyses are used to summarize the data using noncomparative techniques such as frequency distributions (proportions), description of averages (mean, mode, and/or median), and description of the spread of the values (standard deviation and standard error). Assess assumption for statistical tests, i.e., if the data has a normal distribution or not. Compare baseline characteristics searching for differences that may impact the outcome, like demographic characteristics and prognostic factors.

Analytic statistical analyses are used to test the primary outcomes (hypotheses) and secondary outcomes. Variables are compared to evaluate the pattern and strength of relationships. The adequate statistical test depends on a variety of factors (e.g., presence of normal distribution, between/within subjects variation, repeated measures, and so forth) and circumstances (e.g., time line) surrounding data. Consult a statistician to plan the appropriate analysis methods in advance, including subgroup analysis. The analysis plan is dynamic and additional analysis may be planned before looking at the data.

Hypotheses can be proven wrong, but they can never be proven correct because the investigator cannot test all the existing subjects with the condition of interest. Consider all the specific factors that may have influenced or biased the data and/or the interpretation reached.

Interpretation begins after the study is completed; the data is collected, edited, and entered into a database; appropriate statistical tests have been performed to analyze the data; and the statistical report providing a permanent and detailed record of

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the study is compiled. This report allows other investigators to repeat the study using identical design and audit of the results.

Analyses of data are primarily statistical exercises, whereas interpretation of data is an exercise in discerning the clinical meaning of the data evaluated. The researcher is primarily concerned with drawing conclusions to report in publications. The goals of interpreting research data include establishing meaning of the data collected with an emphasis on clinical significance, reporting the results of the original objectives of the study by comparing them with results from previous studies, developing hypothesis for future studies, and gaining insight into interpretations of the condition of interest.

When interpreting the analyses results one should look for factors that may bias the data or affect their interpretation. These include characteristics of the study design, subject enrolled, the condition being evaluated, the study intervention, the investigator and staff, and the trial environment. Statistical significance, on its own, does not provide information about whether a result is clinically important. When considering clinical significance evaluate the relevance of chosen outcomes, the size of the effect observed, the risk/benefit and also cost/benefit.

Ethical Considerations

Three basic ethical principles guide research with human participants: respect for human subjects (autonomy), beneficence (do good), and justice (exclusion). Ethical considerations are important throughout the study: establishment of the research question, decision on the study design, implementation of study protocol, analysis, interpretation, and publication of the results. There are also concerns relating to individual study subjects and to scientific novelty and integrity.

Once a research question has been established and a study protocol developed, the research protocol ought to be reviewed by an independent committee (the Institutional Review Board (IRB) to assess whether any ethical principles have been violated. The IRB is a multidisciplinary committee, whose objectives are to protect patients' rights and to assure that ethical standards are met by the study protocol. They review the protocol and any subsequent amendments, expressing their approval (or disapproval) and recommendations. However, the IRB does not check if the proposed study procedures are being adequately followed. Sponsors and researchers have full responsibility to conduct research in accordance with the guidelines recommended.

IRBs are established in hospitals and educational institutions carrying out medical research. National policies provide the guidelines for the IRB. For multicenter studies, the study protocol has to be approved by all involved IRBs. The investigator should be aware of the IRB requirements for protocol approval in order to avoid multiple corrections and delay of the study.

The IRB determines if an Informed Consent Form (ICF) is needed and approves (or disapproves) its content. Informed consent should be obtained from all subjects

entering the study, or their next of kin, and should be retained for future audit. The ICF must provide appropriate and adequate information on the study protocol, benefits and risk of harm, clarify that the subject is able to withdraw from the study at any time without suffering consequences, and explain the protection of confidentiality. The ICF must be written in nontechnical language so that the subject can clearly understand the potential risks and benefits of entering the study and consciously decide whether to participate in it.

The IRB must approve the compensation of subjects. To avoid undue inducement participants should be compensated for actual expenses and time. The sponsors, however, must provide compensation, regardless of legal liability, if the subject suffers deterioration in health or well being caused by participation in the study.

Once the IRB approves the study protocol and the ICF, the research study can be initiated, not before. Ethical considerations are relevant to all individuals and groups involved in the study, the investigator research team, and the sponsor.

In certain circumstances early study discontinuation is ethically required, for example, when research staff fails to comply with study procedures or an interim analysis may indicate an increase in harmful effects in the group receiving an experimental intervention. By the same token, if beneficial effects are disclosed in the interim analysis, ethical concerns are raised for patients not receiving the intervention.

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Subject Index