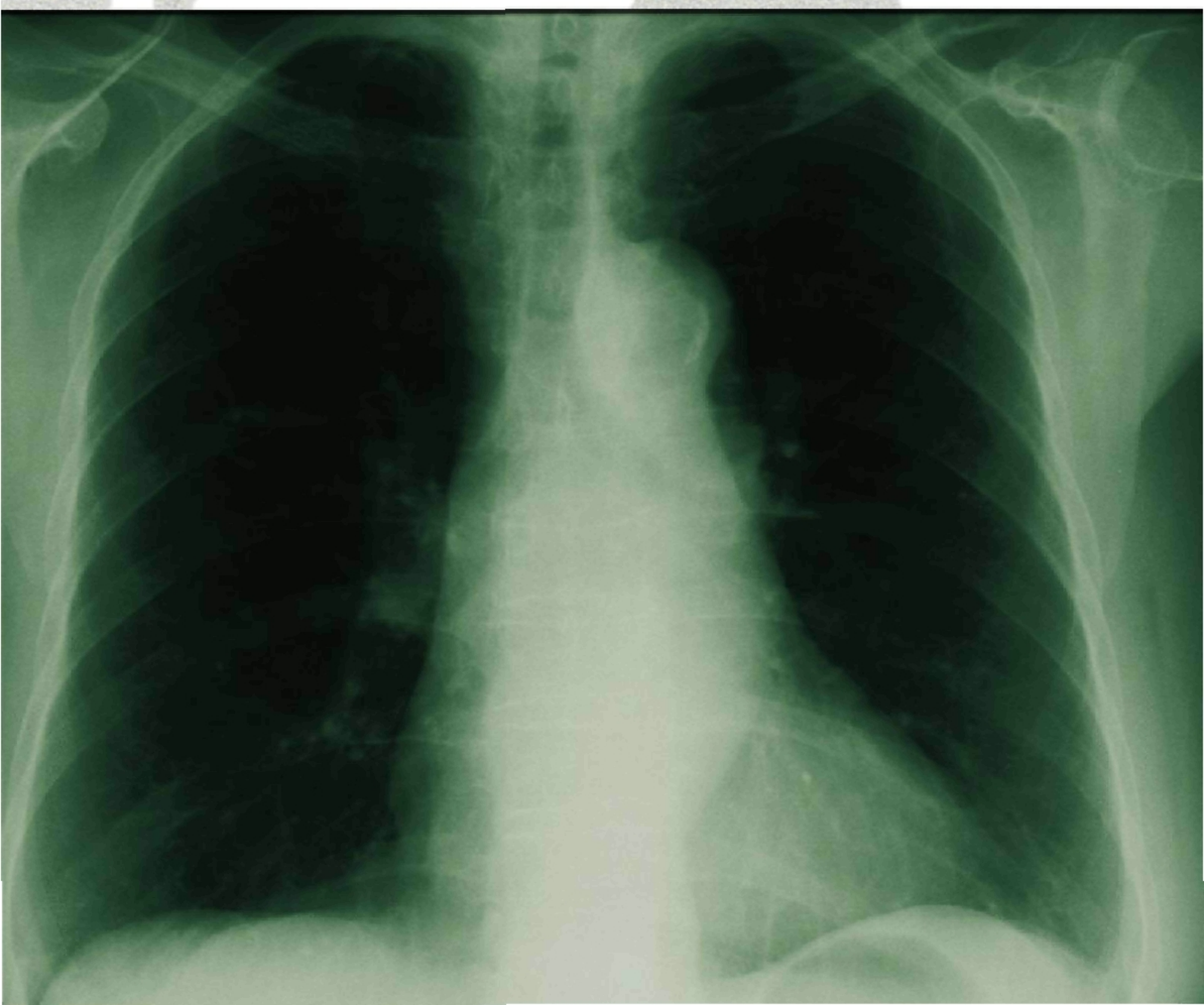
Respiratory Medicine

An Asian Perspective

Edited by
Mary IP
Moira CHAN-YEUNG
Wah Kit LAM
Nan Shan ZHONG



Respiratory Medicine

An Asian Perspective

Respiratory Medicine

An Asian Perspective

Edited by

Mary Ip, *MBBS(HK), MD(HK), FRCP, FRCPE, FRCPG, FHKCP, FHKAM*
Professor of Medicine, University Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong SAR, China

Moira Chan-Yeung, *MBBS(HK), FRCPC, FRCP*
Professor of Medicine, University Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong SAR, China

Wah Kit Lam, *MBBS(HK), MD(HK), FRCP, FRCPE, FRCPG, FRACP, FHKCP, FHKAM*
Professor of Medicine, University Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong SAR, China

Nan Shan Zhong, *MD, FHKCP*
Professor of Medicine, Director of Guangzhou Institute of Respiratory Medicine, Guangzhou Medical College, Guangzhou, China

香港大學出版社
HONG KONG UNIVERSITY PRESS

Hong Kong University Press
14/F Hing Wai Centre
7 Tin Wan Praya Road
Aberdeen
Hong Kong

ISBN 962 209 693 X

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

www.hkupress.org
secure on-line ordering

Printed and bound by ColorPrint Production Ltd., Hong Kong, China

Contents

Foreword

Respiratory medicine, like other formally designated specialties and, in fact, like all disciplines within medicine at large, is changing at an exponential pace. Each year brings new advances and new surprises: ultra-sophisticated diagnostic methods; powerful new therapeutic remedies; results of clinical trials that show how best to treat specific disorders; and even never-before-heard-of diseases. Traditionally, every few years, compilations of new knowledge are packaged into textbooks or specialty monographs to provide a convenient source of authoritative and up-to-date information for practicing physicians, students and registrars in training, and seekers of reliable professional guidance. Textbooks, prepared by recognized experts in a particular field, have been a major way of collating and transmitting medical knowledge for hundreds of years. But when I saw the title of this book, *Respiratory Medicine: An Asian Perspective*, I wondered why go to the huge trouble and expense of creating a book focused on the problems in Asia? What is so special about Asian respiratory medicine that it warrants a separate publication? Then I read the text and found the answers.

Asia is a big place, the largest continent in the world by far. Nearly two thirds of the planet's inhabitants live in Asia's numerous countries under enormously varying circumstances. Some countries are rich, others are poor; some are huge, others are tiny; some are in tropical regions, the remainder in temperate zones; some are at sea level, others at high altitude; some have outstanding health care systems, others are much less well endowed. Nowhere else in the world are there such gigantic genetic, environmental, cultural, and socioeconomic differences that affect the kinds of respiratory diseases that arise in a given region and that influence the way the local residents react to them when they occur. These factors alone provide sufficient material for a textbook of respiratory medicine with an Asian perspective, but there is another reason: people don't stay put.

Within one week after it was carried from Guangzhou to Hong Kong, severe acute respiratory syndrome (SARS) spread to 11 countries in three different continents, by businesspersons and holiday travellers flying to various destinations. Every year, millions of people leave their homes, fleeing famine or wars, or desperately wanting to start a better life somewhere else. Emigration, legal and illegal, has distributed people and their indigenous diseases all over the world. One obvious example: more than half the newly diagnosed cases of tuberculosis in the United States and Canada and in several European countries occur in people who were born and raised in high-prevalence countries, including those in Asia, who took their tubercle bacilli with them when they emigrated.

Indeed, there are some uniquely Asian respiratory diseases, though in view of the mobility

of people just mentioned, it is not surprising that the conditions show up once in a while in other parts of the world. One such example is diffuse panbronchiolitis, which was discovered in Japan and has been reported in China and Korea. There are also several important pulmonary infections predominantly of Asian origin, including paragonimiasis, tropical pulmonary eosinophilia, and the complications of *Penicillium marneffei* and *Shistosoma japonicaum*. Southeast Asia has long been recognized as the crucible for successive epidemics of influenza and, of course, the outbreak of SARS in 2002 was traced to Guangdong province in southern China. Finally, there are the remarkable concentrations of cases of bronchogenic cancer in non-smoking women from mainland China, Hong Kong, and Taiwan, which seem related to the inhalation of carcinogenic toxins, perhaps in cooking oil vapors or smoky coal fumes.

In the chapters on asthma and chronic obstructive pulmonary disease, the authors comment on the striking differences in the prevalence of these diseases that have been reported both among and within different Asian countries. These are not only clinically relevant to the people and their physicians who live in these places, but they provide a special opportunity for investigators to track down the potential genetic and environmental factors that account for the differences. Many other such gaps in existing background scientific information are pointed out in the text.

Nothing is overlooked. These and many more subjects of topical and regional importance are fully discussed by internationally recognized experts. The chapters are comprehensive and thoroughly referenced, which will help those desiring more information. The book is of undoubted value to internists and pulmonary specialists practicing or training in Asia, but it will also be useful to doctors elsewhere who are looking for "an Asian perspective" when caring for their patients. The editors, who are among the unquestioned leaders in the burgeoning field of respiratory medicine, are to be congratulated for an accomplishment that will benefit physicians in all corners of the world.

John F. Murray, M.D., F.R.C.P
Professor Emeritus of Medicine
University of California San Francisco

Preface

The publication of this book *Respiratory Disease: An Asian Perspective* is most timely even though its inception has been several years earlier. The emergence of Severe Acute Respiratory Disease Syndrome (SARS) in 2003 and Avian flu in 2004 with the possibility of a pandemic has focused international attention on health care in Asia.

Respiratory specialists working in Asia have always noted that respiratory diseases in Asia are different in many aspects from other parts of the world. Unlike Western countries, the prevalence of cigarette smoking in Asian populations is rising, thus leading to increasing prevalence of chronic obstructive pulmonary disease and incidence of lung cancer. Densely populated urban areas predispose to infectious diseases that are spread by droplets or air-borne route such as the long-standing plague of tuberculosis. The close interface between human and animals in southern China has led to newly erupted viral outbreaks in recent years. Rapid changes in lifestyles in some countries have resulted in rising prevalence of obesity and obstructive sleep apnea. Urbanization and industrialization with air pollution pave the way for acute exacerbations of chronic obstructive pulmonary diseases. Changes in environmental factors are believed to account for the rising prevalence of asthma seen in many Asian countries. Furthermore, the standard of health care delivery for respiratory diseases varies widely in different parts of Asia. While advanced health care systems are in place in some cities, many regions still have limited access to health care.

Against this background, we felt that it would be useful and relevant to put together our collective knowledge and experience to share with those practicing in the region and also around the world. With population migration, diseases prevalent in Asia are no longer just confined to the continent; and with modern air travel, infectious respiratory disease, such as SARS, can reach other parts of the world within days.

In recent years, the ability to access information on relevant epidemiology and management in various parts of Asia is maturing, such that reasonably accurate data can be elaborated in this book. The insight and availability of such information are only possible from authors of this book, who have high professional standing in the respective community and have contributed their wealth of experience and knowledge.

Finally, we wish to express our gratitude to our respective families whose understanding and encouragement have made this book possible. We also wish to thank our colleagues and trainees whose insightful and stimulating questions have taught us not to be complacent. We wish to dedicate this book to young healthcare professionals working in Asia, on whom we pin our hopes for better health care in our communities in the future.

Mary Ip
Wah Kit Lam
Moira Chan Yeung
Nan Shan Zhong

February 2004

Contributors

Somchai Bovornkitti, MD, FRCP
Environmental Medicine Center
Mettapracharak Hospital (Wat Rai Khing)
Department of Medical Services
Ministry of Public Health
Thailand

Michael Brauer, ScD
Professor
School of Occupational and Environmental Hygiene
The University of British Columbia
Vancouver
British Columbia
Canada

Moira Chan-Yeung, MBBS, FRCPC, FRCP
Professor of Respiratory Medicine
Division of Respiratory & Critical Care Medicine
University Department of Medicine
Queen Mary Hospital
The University of Hong Kong
Hong Kong SAR
China

Suchai Charoenratanakul, MD, FCCP
Professor of Medicine
Department of Medicine
Siriraj Hospital
Mahidol University
Bangkok
Thailand

Rong Chang Chen, MD
Professor of Medicine
Guangzhou Institute of Respiratory Disease
Guangzhou Medical College
Guangzhou
China

Yuh Min Chen, MD, PhD, FCCP
Assistant Professor of Medicine
National Yang-Ming University
Attending Physician of Chest Department
Taipei Veterans General Hospital
Taipei
Taiwan

Shui Wah Chiu, MBBS, FRCS
Chief of Service
Cardiothoracic Surgical Unit
Grantham Hospital
Hong Kong SAR
China

C Peter Clarke, FRACS, FACS
Professor and Head
Thoracic Surgical Unit
Austin & Repatriation Medical Center
Australia

Teresita S de Guia, MD
Associate Clinical Professor
Department of Medicine and Surgery
University of Santo Tomas
Manila
Head, Division of Pulmonary & Critical Care Medicine
Philippine Heart Center
Quezon City
Philippines

Amita V Doshi, MD, FCCP
Associate Consultant
P.D. Hinduja Hospital & Research Centre
Mumbai
India

Donald Enarson, MD, FRCPC
Scientific Director
International Union Against Tuberculosis and Lung Disease
Paris
France

C G Guilleminault, MD, Biol. D
Professor and Director
Stanford Sleep Disorders Center
Stanford University Medical Center
Stanford, CA
USA

Wataru Hida, MD, PhD
Professor and Director
Health Administration Center
Department of Health Informatics on Pathophysiology
Tohoku University Graduate School of Information Science, Tohoku University
Japan

Mary Ip, MD, FRCP
Professor of Medicine
Division of Respiratory & Critical Care Medicine
University Department of Medicine
Queen Mary Hospital
The University of Hong Kong
Hong Kong SAR
China

S K Jindal, MD, FAMS, FNCCP, FCCP
Professor & Head
Department of Pulmonary Medicine
Postgraduate Institute of Medical Education and Research
Chandigarh
India

Charn Kiatboonsri, MD
Division of Pulmonary & Critical Care Medicine
Department of Medicine
Ramathibodi Hospital
Mahidol University
Bangkok
Thailand

Young Whan Kim, MD, PhD
Professor
Division of Pulmonary and Critical Care Medicine
Department of Internal Medicine
Seoul National University College of Medicine
Seoul
Korea

Yoshimochi Kurokawa, MD, PhD
Associate Professor
Division of Advanced Surgical Science and Technology
Department of Surgery
Graduate School of Medicine, Tohoku University
Japan

Hajime Kurosawa, MD, PhD
Associate Professor
Department of Internal Medicine and Rehabilitation Science
Graduate School of Medicine, Tohoku University
Japan

Wah Kit Lam, MD, FRCP, FRACP
Professor of Medicine
Chief of Division of Respiratory & Critical Care Medicine
University Department of Medicine
Queen Mary Hospital
The University of Hong Kong
Hong Kong SAR
China

Mei Lin Liao, MD
Chief of Shanghai Lung Cancer Clinical Medical Center
Shanghai Chest Hospitalp
Shanghai 2nd Medical University
Shanghai
China

Hui Ping Liu, MD, FACS
Professor and Chief
Division of Cardiothoracic Surgery
Chang Gung Memorial Hospital
Taipei
Taiwan

Tze Pin Ng, MD, FRCP
Department of Psychological Medicine
The National University of Singapore
Singapore

Clara Gaik Cheng Ooi, MBBCh, MRCP, FRCR
Associate Professor of Radiology
University Department of Diagnostic Radiology
Queen Mary Hospital
The University of Hong Kong
Hong Kong SAR
China

Reury-Perng Perng, MD, PhD
Clinical Professor of Medicine
National Yang-Ming University and Taipei Medical University
Head of Chest Department
Taipei Veterans General Hospital
Taipei
Taiwan

Joseph S M Pieris, MBBS, DPhil, FRCPath
Professor
Department of Microbiology
The University of Hong Kong
University Pathology Building
Hong Kong SAR
China

Chaicharn Pothirat, MD
Associate Professor
Chief of Division of Pulmonary and Critical Care
Department of Internal Medicine
Chiangmai University
Chiangmai
Thailand

Percival Punzal, MD
Program Director
Section of Pulmonary Rehabilitation
Division of Pulmonary & Critical Care Medicine
Philippine Heart Center
Quezon City
Philippines

Pantpis Sakornpant, MD
Cardiothoracic Surgeon
Rajvithi Hospital
Bangkok
Thailand

Yukihiko Sugiyama, MD, PhD
Head, Division of Pulmonary Medicine
Department of Medicine
Jichi Medical School
Minamikawachi-machi
Japan

Cheuk Ming Tam, MBBS, FRCP
Consultant
The Hong Kong Government Tuberculosis & Chest Service
Department of Health
Hong Kong SAR
China

Wan Cheng Tan, MD, FRCP
Professor of Medicine
Department of Medicine
National University of Singapore
Singapore

Kenneth Tsang, MD, FRCP
Associate Professor
Division of Respiratory and Critical Care Medicine
University Department of Medicine
Queen Mary Hospital
The University of Hong Kong
Hong Kong SAR
China

Zarir F Udwadia, MD, FRCP
Consultant Physician
P. D. Hinduja Hospital & Research Centre
Mumbai
India

V K Vijayan
Director
V.P. Chest Institute
University of Delhi
Delhi
India

Gary W K Wong, MD, FRCPC
Assoicate Professor
Department of Pediatrics
The Chinese University of Hong Kong
Prince of Wales Hospital
Hong Kong SAR
China

Pan Chyr Yang, MD, PhD
Professor and Chairman
Department of Internal Medicine
National Taiwan University College of Medicine
Taipei
Taiwan

Wing Wai Yew, MBBS, FRCP (Edin)
Chief of Service
Tuberculosis and Chest Unit
Grantham Hospital
Hong Kong SAR
China

Anthony P C Yim, MD, FRCS, FACS
Professor of Surgery
Chief of Cardiothoracic Surgery
The Chinese University of Hong Kong
Prince of Wales Hospital
Hong Kong SAR
China

Kwok Yung Yuen, MD, FRCS, FRCPath
Professor of Infectious Diseases
Department of Microbiology
Queen Mary Hospital
The University of Hong Kong
Hong Kong SAR
China

Li Xing Zhang, MD
Professor of Tuberculosis Control
Beijing Research Institute for Tuberculosis Control
Beijing
China

Jin Ping Zheng, MD
Associated Professor of Medicine
Head of Laboratory Department
Guangzhou Institute of Respiratory Disease
Guangzhou Medical College
Guangzhou
China

Nan Shan Zhong, MD, FHKCP
Professor of Medicine
Director of Guangzhou Institute of Respiratory Disease
Guangzhou Medical College
Guangzhou
China

Part I Airway Diseases

1 Asthma Epidemiology

Gary W K Wong and Moira Chan-Yeung

Introduction

Asthma has become one of the most common chronic disorders in the Western world. However, the a etiology and pathogenesis of asthma are still not clearly understood. There is considerable concern over the increase of asthma and related atopic disorders over the past three decades (1). Compared to the West, the prevalence of asthma in the Asia region has been reported to be lower (2). Epidemiological studies performed in the region also suggested possible increasing prevalence of asthma and related atopic disorders (3–6), but the lack of precise definitions of asthma makes reliable comparison of reported prevalence of asthma from different regions very difficult. During the 1990's, there have been a number of large multi-centered epidemiological studies of asthma in children and adults (7,8). The aims of these studies were to describe the global variations of asthma and to evaluate the possible risk factors for asthma. The European Community Respiratory Health Survey (ECRHS) studied the geographic variation in asthma and allergies among the adult population from 22 countries. The International Study of Asthma and Allergies in Childhood (ISAAC) investigated the global variations of asthma and atopic disorders in children utilizing questionnaire survey, skin-prick testing and assessment of bronchial hyperresponsiveness (BHR) (9–12). Many countries in the Asian region have participated in the ISAAC. These epidemiological studies have revealed important information on the prevalence and burden of asthma in Asia and have also provided a framework to investigate the possible determinants of asthma that might explain the global variations and trend of asthma prevalence. Because of the diverse racial, socioeconomic and environmental background in Asia, epidemiological studies in the region can explore the potential roles of various genetic and lifestyle factors in the pathogenesis of asthma. This chapter reviews the existing data on asthma epidemiology especially those from the Asian region and summarizes the existing knowledge regarding the role of various risk factors in the development of asthma.

Asthma Epidemiology

Methodology used to study asthma prevalence

The major problem that hindered progress in the epidemiology of asthma has been the lack of a universally accepted definition of asthma. Although there have been numerous studies on the prevalence of asthma performed in different regions of the world, the lack of standardization of the study methodology made meaningful comparisons between countries extremely difficult

or impossible Most epidemiological studies used symptom questionnaires to distinguish asthmatics from non-asthmatics from a population sample The patients or their parents' responses are likely to be affected by their understanding of asthma symptomatology Studies in children are further complicated by the fact that there are different phenotypes of wheezing disorders with different a etiologies and pathogenesis (13) Identification of asthma in the elderly is also frequently confounded by similar symptoms due to cardiac failure or chronic obstructive pulmonary disease and normal age related decline in pulmonary function (14,15) The choice of diagnostic labels by doctors in the community is also likely to influence the results Studies of 4 European cities by Burney et al (16) have shown that only half of the subjects with symptoms compatible with asthma responded that they had asthma Studies that utilized "physicians diagnosis of asthma" to estimate the prevalence of asthma usually underestimate the prevalence of disease "Wheeze" is the most widely recognized symptom of asthma and different standardized questionnaire usually ask for the presence and the frequency of this symptom (8,9) However, in some languages such as German and Chinese, there is no equivalent term for "wheeze" such that the questionnaire may underestimate the true prevalence of wheezing (16) Furthermore, validation of the survey instrument is difficult because there is no "gold standard" for the defining asthma (17)

The ISSAC study attempted to circumvent the linguistic problem of the written questionnaire by the addition of a video questionnaire, which shows children and adolescents with different asthma symptoms and asks the subjects whether they have similar symptoms and the frequencies of such symptoms Other investigators included additional "objective" markers of asthma to define asthma phenotype BHR has been considered to be one of the best objective measures of asthma (17), but there is a continuing debate of whether measurement of BHR would have greater validity than symptom questionnaires alone (17–19) For epidemiological studies, the value of measuring BHR lies in its relatively high specificity and low sensitivity when compared with other clinical markers of asthma (18) However, due to the poor agreement between BHR and clinical asthma, it has been suggested that symptoms and BHR should be analyzed separately (17) The high response rate and larger sample size obtainable with symptom questionnaires are of definite advantages over BHR testing (19) The interpretation of any epidemiological study of asthma must take into account the case definition of asthma as well as the methodology used in data collection

To confirm the validity of the ISAAC questionnaire in the assessment of asthma prevalence, there have been several validation studies performed in children to assess the accuracy of the ISAAC written and video questionnaires in predicting asthma associated BHR (20,21) In Chinese children, a comparative study of the ISAAC video questionnaire with written questionnaire for estimating BHR has also been performed (22) The sensitivity and specificity for a positive response to the video questionnaire on the question of wheeze in the past 12 months were 0 56 and 0 86 respectively in predicting BHR while having a physician diagnostic label of asthma had the highest sensitivity (0 88) and specificity (0 90) in predicting BHR Furthermore, the ISAAC questionnaire has also been validated to be reliable in predicting BHR to hypertonic saline in a population of mixed ethnic background including Asian and European origins (20) Therefore, the ISAAC questionnaire appears to be a valid tool for the assessment of asthma prevalence and symptoms of asthma in children

Prevalence of asthma

Prior to the 1990s, most of the epidemiological data in Asia were collected in a non-standardized fashion with different types of written questionnaire The majority of the data are in children and few studies were in the adult population Table 1 summarizes the available data of asthma prevalence in Asia As shown, there is wide variation in the prevalence rates across different geographical locations Interestingly, the prevalence of asthma in the Chinese population from Hong Kong was much higher than that in Guangzhou, a Chinese city only 200 km north of Hong Kong The results of the ECRHS and ISAAC surveys clearly documented the dramatic

Table 1. Prevalence of Asthma in Asian Countries as Documented by Studies Using Different Methodologies

Country/Location	*Year of Survey*	*Age in years (range or mean±SD)*	*Asthma ever*
China			
Guangzhou	1988–1989	11–17	2.4%
San Bu	1992	16.4±1.8	1.6%
Hong Kong	1989	16–28	4.8%
	1992	7–15	7–10%
	1994	17–33	7.2%
Indonesia	1981	7–15	2.3%
Malaysia	1990	7–12	13.8%
Philippines	1991	<15	3.9%
Singapore	1967	4–17	3–5.5%
	1987	6–19	13.7%
	1991	20–74	4.3–4.7%
Taiwan	1994	7–15	19.7%
Thailand	1987	6–12	4.3%

Data summarized from references 2–6,21–24

variations of prevalence of asthma symptoms across different countries and racial background. The ECRHS investigated representative samples of 20–44 years old from 22 countries, predominantly in Western Europe and showed an eight-fold variation in the prevalence of wheeze among the participating countries. The highest prevalence rates were found among the English speaking countries such as British Isles, New Zealand, and Australia while lower rates in the Mediterranean region and Eastern Europe (23). The prevalence of wheeze in the past 12 months ranged from the lowest of 4.1% in India to the highest of 32.0% in Ireland.

The ISAAC is the largest epidemiological study of asthma. ISAAC Phase One was carried out between 1994–1995 and it used standardized core questionnaires to assess the prevalence and severity of asthma in representative samples of school children of two age groups (6–7 and 13–14 years) from centres in many regions of the world (7,9). A total of more than 130,000 children from 20 centres from 8 countries in Asia have participated in the Phase One of ISAAC. These countries include China, Indonesia, Japan, Malaysia, Philippines, Singapore, South Korea and Thailand. In line with the results of the ECRHS results, the prevalence of asthma in 13–14 year-old varies widely across different regions, highest of 32.2% in the UK and the lowest of 1.6% in Alcola, India. Figure 1 shows that the twelve-month prevalence of self-reported asthma symptoms of 13–14 year-old in Asian countries were lower than those in the UK and Australia (7). The wide variations in asthma prevalence within the Asia region were confirmed. Table 2 shows the prevalence of wheeze in the past 12 months in the 13–14 year-old children as documented by the written and video questionnaires. The mean prevalence rates of wheeze in the past 12 months in the Asian region were only 8.0% and 5.3% as documented by the written and video questionnaires respectively. In general, the more affluent countries such as Singapore, Japan, and Hong Kong have higher prevalence rates. However, the prevalence rates from Japan (10.2%) and Hong Kong (10.1%) assessed by the video questionnaire were still lower

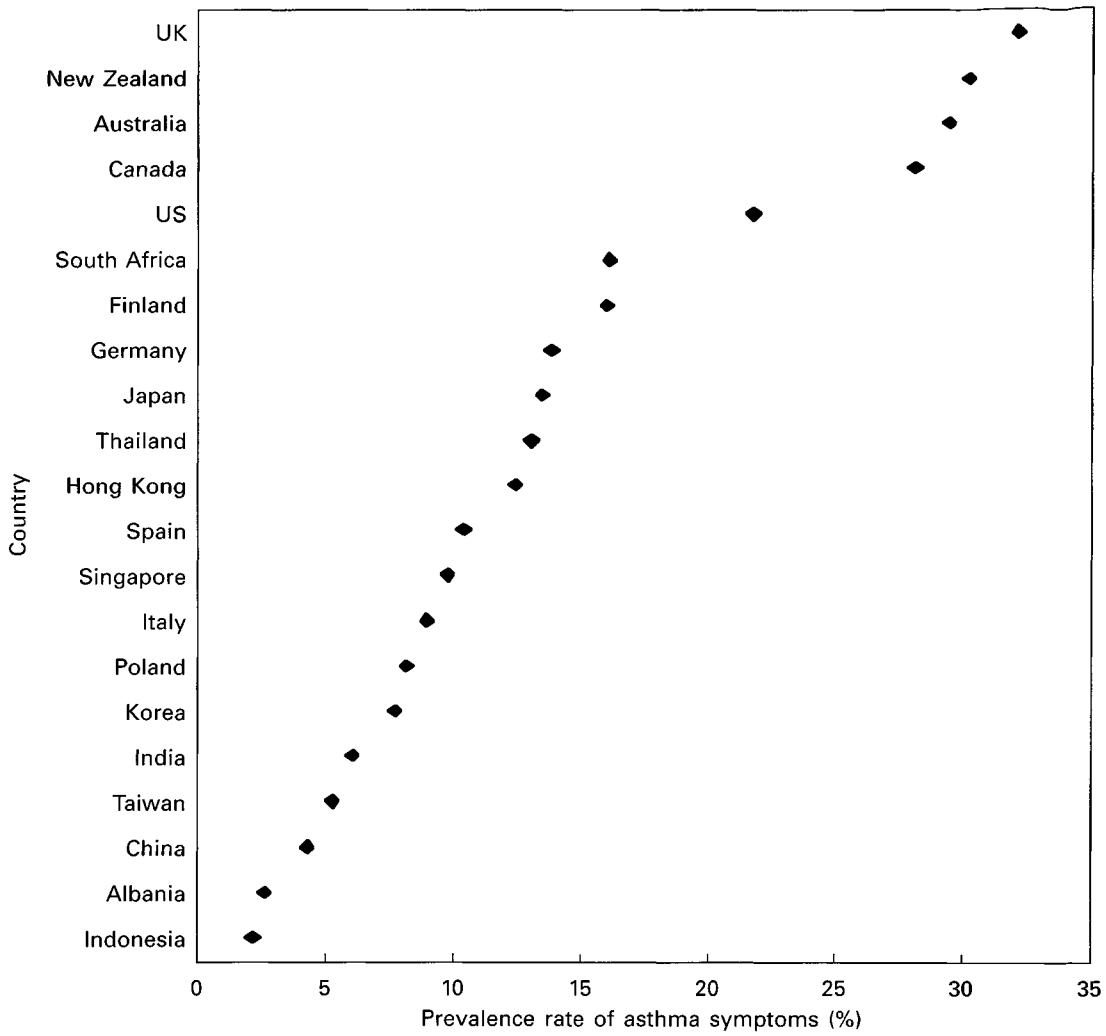


Figure 1. Twelve-month prevalence of self-reported asthma symptoms from written questionnaires: ISAAC Phase I results in 13–14 year-old subjects

than the reported rates from Australia (17.6%) and New Zealand (18.4%). Table 3 shows the prevalence of asthma symptoms in the 6–7 year old children from Asian countries. The variations in the prevalence rates of asthma symptoms in this age group mirrored those found in older age groups. There was a statistically significant correlation ($r = 0.71$, $P < 0.0001$) between the prevalence rates of wheezing in the past 12 months in the two age groups that took part in the Phase One ISAAC study from 90 centres around the world (7).

The marked variation in the prevalence of asthma as shown by the ISAAC study most likely reflects true differences among the various regions. Comparison of the results of the ISAAC and ECRHS study demonstrated a strong correlation of the two sets of prevalence data (24). The marked global variation in asthma prevalence, therefore, appears to be true but the exact reasons for the variation remain unclear.

Table 2. 12-Month Prevalence of Asthma Symptoms in 13–14 Year Old Children from the Asia Region in Comparison with Western Europe and Oceania: ISAAC Phase One results

Location	*Written questionnaire*			*Video questionnaire*		
	Wheeze	*Wheeze disturbs sleep*	*Severe wheeze limiting speech*	*Wheeze*	*Wheeze disturbs sleep*	*Severe wheeze*
China						
Mainland	4.2	0.3	0.7	2.0	0.6	1.2
Hong Kong	12.4	0.5	2.4	10.1	3.8	6.9
Indonesia	2.1	0.8	0.9	1.3	0.6	0.8
Japan	13.4	0.6	2.1	10.2	3.7	5.3
Malaysia	9.6	0.8	1.8	5.9	2.5	3.6
Philippines	12.3	2.0	4.1	9.6	3.9	4.9
Singapore	9.7	1.3	2.4	9.9	3.2	5.0
South Korea	7.7	0.2	2.7	3.7	0.5	1.9
Taiwan	5.2	0.4	0.8	4.6	1.8	2.8
Thailand	13.0	1.1	3.5	6.9	2.1	3.8
Regional (Asia)	**8.0**	**0.6**	**1.8**	**5.3**	**1.8**	**3.1**
Western Europe	16.7	1.7	4.2	6.7	3.7	3.7
Oceania*	29.9	3.1	8.1	18.1	11.4	12.0

*Oceania includes Australia and New Zealand

Table 3. Asthma Symptoms (Written Questionnaire) of 6–7 Year Old Children in the Asia Region: ISAAC Phase One Results

Location	*12-Month Prevalence*				
	Wheeze	*Wheeze disturbs sleep*	*Exercise wheeze*	*Nocturnal cough*	*Ever had asthma*
Hong Kong	9.1	0.3	6.9	21.7	7.7
Indonesia	4.1	0.7	3.1	9.1	6.6
Japan	17.3	1.2	5.3	9.5	18.2
Malaysia	6.1	0.5	4.3	16.2	10.4
Philippines	11.3	1.4	6.7	30.6	16.4
Singapore	15.7	1.8	8.2	15.0	18.5
South Korea	13.3	0.5	4.4	17.4	8.5
Taiwan	9.6	0.8	6.0	17.0	12.7
Thailand	11.0	0.9	5.1	22.8	9.3
Regional	9.6	0.7	5.0	17.6	10.7

Secular trends of asthma prevalence

There have been many studies showing an increasing prevalence of asthma in Western countries (25,26). However, many of these studies utilized only questionnaire surveys. Increased community awareness of asthma and related atopic disorders are likely to contribute to the increase in disease prevalence documented by these questionnaire surveys. To improve the validity of the questionnaire survey, some investigators include the additional assessment of more "objective" markers of asthma such as the measurement of total IgE and specific IgE, skin-prick test, and measurement of BHR (27–29). Burr et al carried out 2 surveys using the same questionnaire along with exercise provocation test in schoolchildren from England in 1973 and 1988. They confirmed that the prevalence rates of asthma and bronchial hyperresponsiveness have doubled over the study time period (30). Peat et al studied 8–10 year old children in 2 Australian towns over the years 1982–1992. The prevalence of wheeze in the previous 12 months has increased by two-folds while the prevalence of BHR has also increased by 1.4 to 2 folds (27). Interestingly, von Mutius et al (29) performed two surveys in former East Germany including questionnaire assessment, skin-prick test and measurement of BHR in 9–11 year old children. The prevalence rates of symptoms of hay fever and atopic sensitization have increased by 2 and 1.5 folds, but there was no significant change in the prevalence of asthma or BHR.

Within the Asian region, similar increasing trends of asthma prevalence were observed in a number of studies (3–6). A survey of schoolchildren aged 12–18 years performed in 1992 in Hong Kong revealed that the prevalence of asthma and wheeze in the past year were 3.7% and 6.6% (31). In 1995–1996, the prevalence of asthma and wheeze have increased to 11.2% and 12.4% in 13–14 year old children as shown by Phase One ISAAC study. Nishima studied children using the same Japanese translation of the American Thoracic Society (ATS) questionnaire and found that asthma prevalence has increased from 3.5% in 1982 to 4.6% in 1992 (3). Similarly in Taiwan, two studies using the same methodology revealed that the prevalence of childhood asthma has increased from 1.3% in 1974 to 5.07% in 1985 (4). The magnitude of increase was particularly striking in more affluent countries in the region such as Singapore where prevalence rates of asthma have increased from 5.5% in 1967 to 13.7% and 20.7% in 1987 and 1996 respectively (6). Although all these surveys suggested an increasing trend, none of them included any "objective measure" to support their results (Table 4).

Another way of assessing the possible changing trend of asthma is to investigate the same ethnic group living in different environment. There have been several large comparative studies in the Chinese population (31–33). Leung and Ho (31) performed a study of asthma and allergies in Chinese children aged 12–18 years recruited from three locations (Hong Kong, San Bu and Kota Kinabalu) and found the prevalence of asthma and allergies to be highest in children recruited from Hong Kong. In line with this early study, data from Chinese centers participating in the ISAAC Phase One survey showed that the prevalence of wheeze was 2 to 4 times higher in schoolchildren from Hong Kong compared with the centers from Mainland China (7). The ISAAC Phase Two protocol included "objective" markers of atopic disorder such as skin-prick test and bronchial challenge test. A total of over 10,000 schoolchildren from three Chinese cities (Hong Kong, Beijing, and Guangzhou) participated in this survey (33). The prevalence rates of wheeze and atopic sensitization remained highest in Hong Kong. Interestingly, the rate of allergic sensitization was significantly higher in Guangzhou (30.8%) than in Beijing (23.9%) but the prevalence of asthma symptoms was similar in these 2 cities.

A comparative study of the prevalence of asthma in subjects with different ethnic backgrounds living in Singapore has also been performed by Ng et al (34) on a total of 2868 adults aged 20 to 74 years. Lifetime physician diagnosis of asthma was found to be highest in Indians (6.6%), intermediate in Malaysians (6.0%), and lowest in Chinese (3.0%). These data highlighted the importance of genetic factors in the development of asthma. Furthermore, recent studies of asthma in farming communities showed that asthma and allergies are less common in such rural environments (35–37). Chan-Yeung et al (38) have performed a study of asthma among adults

Table 4. Secular Trend of Asthma Prevalence in Asian Countries

Location	*Year*	*Age (years)*	*Asthma ever*	*Wheeze ever*
Hong Kong	1989	8–10	7.4–7.7%	8.3–10.9%
	1992	12–16	6.6%	7.8%
	1995	13–14	11%	20%
Indonesia	1981	7–15	2.3%	–
	1998	13–14	1.6%	–
	1998	6–7	6.6%	–
Malaysia	1990	7–12	8.7%	–
	2000	7–12	10.3%	12.5%
Philippines	1991	<15	3.9%	–
	1998	13–14	17.9%	–
Singapore	1987	6–19	13.7%	–
	1996	12–15	20.7%	18.6
	1996	6–7	18.5%	28.6
Taiwan	1974	7–15	1.3%	–
	1985	7–15	5.1%	–
	1998	13–14	9.0%	–
Thailand	1987	6–12	4.3%	–
	1998	6–7	9.5%	17.4%
	1998	13–14	14.2%	19.2%

Data summarized from references 2–6, 21–24

in rural Beijing, China using the IUATLD questionnaire on bronchial symptoms from which the ECHRS questionnaire was developed. They found that the prevalence of asthma attacks in the previous 12 months was only 0.67%, much lower than those reported from other ECHRS centres. Further studies are necessary to determine the protective factors against asthma in the rural environment. It is conceivable that a rapid change from a rural to an urban environment is partly responsible for the increasing trend of asthma in many communities in the world.

Asthma morbidity

In addition to increase prevalence of asthma, available data also suggest a worldwide increase in the rate of hospitalization for asthma starting in 1960s (39). These trends could not be explained by changes in diagnostic categories or medical practice and probably reflect an increase in the prevalence of severe asthma (40–41). Most of the data on asthma hospitalization came from Western countries.

Asthma mortality

Asthma mortality rates had remained relatively stable during the first half of the century (42). However, during the last half of the century, there has been a gradual increase in asthma mortality in the 5- to 34- year-old group in many countries (39). During 1960s, there was a marked increase in asthma mortality in at least 7 countries. In New Zealand there were two "epidemics", in the 1960s and the 1980s (39). Available evidence indicates

that the major cause of these "epidemics" was the use of high-dose preparations of beta-2-agonists, isoproternol in the 1960s and fenoterol in the 1980s (39). When these preparations were withdrawn from the market in New Zealand, the epidemics ended. Since the late 1980s, asthma mortality rates have gradually fallen in some, but not all, countries. The reduction in mortality has been attributed to the greater use of inhaled corticosteroids; however, the time-trend evidence is not conclusive (43–45).

There have been only a few studies on the trend of asthma mortality in Asia. A study in Japan (46) has shown an increase in asthma mortality in the 10–24 and 15–44 year-old age groups between 1984 and 1996. However, asthma fatality rate peaked in 1987 in most age groups (10–24, 15–44 and 45–64 years) suggesting that the increase in asthma mortality in the two younger age groups was due to the increase in asthma prevalence in that country (46). In Singapore, an increase in asthma mortality was observed in children aged 4 to 14 years from 0.21/100,000 person years in 1976–80 to 0.72 /100,000 person years in 1991–95 but no increase was noted in other age groups (47). Marked ethnic differences in mortality rates were observed in those aged 5–34 years, lowest in Chinese, and highest in Malay subjects. In Hong Kong, asthma mortality of the 5–44 year old group showed a gradual decline between two periods, 1984–86 and 1992–94; this was associated with an increase in anti-asthmatic medications especially the use of inhaled steroids (48).

Risk Factors in Asthma

Atopy

Atopy is the most important risk factors for asthma in both children and adults. In children, the odds ratio for the association between increased nonspecific bronchial hyperresponsiveness (the characteristic in asthma) and skin test reactivity range between 1.5–9.2 in children and 0.6–2.6 in adults indicating that atopy plays a more important role in children than adults (49). In children, there is a relationship between the size of the wheal diameter to relevant allergens, representing the intensity of atopy, and the likelihood of asthma. However, studies of Chinese population in different parts of Asia have demonstrated striking differences in asthma prevalence despite similar prevalence of sensitization supporting that other risk factors are important in the development of asthma (2).

Family history and genetics

Asthma and other atopic disorders are familial in nature. Parental history of asthma has been found to be an important risk factor for asthma after adjusting for atopy (50). Even in nonatopic children, a positive family history of asthma increases risk of asthma by 2 to 3 times (50). The prevalence of asthma in subjects whose parents were not atopic was 8%, 15.8% when one parent was atopic and 28.6% if both parents were atopic. It is difficult to determine how much can be attributed to genetic predisposition and how much to environment.

Research in the last two decades has shown that these conditions are complex genetic disorders that do not conform to a simple Mendelian patterns of inheritance. In addition to the familial concordance of allergic disorders, there is evidence to suggest that specific end-organ manifestations such as allergic rhinitis (nose), atopic dermatitis (skin) or asthma (airways) are in part familial. Presumably separate genes predispose to specific clinical manifestations of the allergic phenotype.

In 1989, Cookson et al (51) first reported identification of a locus containing an atopy gene on chromosome 11q but other investigators were not able to confirm their results. Since then six loci have been implicated by independent investigators (52,53). On chromosome 6q21, there is an important region that contains the genes for the major histocompatibility (MHC) molecules and the tumour necrosis factor a gene (TNF α). On chromosome 5q, there are many candidate genes for asthma and allergy such as interleukin 4 (IL-4) and β_2-adrenergic receptor genes. Chromosome 11q13 has been linked to a variety of different phenotypes and the β chain of the high affinity IgE receptor. Chromosome 13q and 12q have also been linked to asthma and related phenotypes. Linkages have been replicated in all these regions and for most of them, multiple candidate genes have been suggested as the reason

for the linkage. However, no DNA sequence variations that alter protein expression have been definitely incriminated as "asthma mutations".

Of the multiple candidate genes located in these regions a few specific polymorphisms have been reported to be associated with asthma and allergic phenotypes. Of these, IL-4, IL-4 receptor α, $ß_2$ adrenergic receptor, TNF α, HLA and $α_1$ antitrypsin genes are more closely associated with allergy and asthma phenotypes (52,53). ADAM33 gene, expressed in lung fibroblasts and bronchial smooth muscles, has recently been linked to asthma (LOD, 2.94) and bronchial hyperresponsiveness (LOD, 3.93) by a genome wide scan on 460 Caucasian families (54). Functional analysis has yet to be carried out to determine the significance of the ADAM gene variants. The majority of these studies have been conducted among Caucasian populations; only a few were conducted among other ethnic groups. In each ethnic group, several linkages were identified but the linked genes were not the same for each group.

There have been a few studies carried out in Japan showing the association of atopic asthma with polymorphism of the IgE receptor gene (55,56) and one study demonstrating the association of the IL4Rα variant (Ile50Val) with atopy (55). In Singapore, significantly higher prevalence of asthma was found among Indian and Malay population than the Chinese suggesting possible genetic differences (6). No association between Ile50Val and atopy was found in all three ethnic groups in Singapore (56). Among Hong Kong Chinese, the prevalence of IL-4 promoter C590T polymorphism was very high but the polymorphism was not associated with asthma (57). A study in Hong Kong failed to establish any links between HLA-DQ and HLA-DR genotypes and skin test reactivity or the degree of bronchial reactivity (58). It is likely that more data on genetics and asthma and allergy of the Asian population will become available in the near future.

Indoor aeroallergens

Exposure to indoor allergens is an important risk factor for sensitization and asthma (59).

House dust mite

There are four major species of house dust mites: *Dermatophagoides* spp., *Euroglyphus maynei*, *Bloomia tropicalis*, *Lepidoglyphus destructor* (60). They thrive best in places with high humidity, moderate temperatures and an adequate supply of food that are provided amply by human skin scales. There are two major groups of mite allergens. Group I allergens (Der p I and Der f I) are proteolytic enzymes secreted from the digestive tract of mites and are found in high concentrations in their fecal pellets. Group II (Der p II and Der f II) allergens are found both in the fecal pellets and mite bodies. Panels of monoclonal antibodies have been produced against most of the allergens (61). These monoclonal antibodies have been used extensively for measuring environmental exposure to these allergens using an ELISA assay. The climate of Hong Kong is favourable for the proliferation of house dust mite. Over 80% of children with asthma react on skin testing to the mite allergen (62).

There have been many studies providing evidence that sensitization to house dust mites is an important risk factor for asthma in many parts of the world (63). There is a dose-response relationship between the level of exposure to house dust mite allergen and the risk of sensitization (64). The threshold level of allergen for sensitization in atopic children is 2 μg/g dust while the comparable level for nonatopic children is approximately 50 to 80 μg/g dust (65). The risk for sensitized children having current asthma doubled with every doubling levels of Der p1 between 0.7 and 50 μg/g dust. The odds ratios for developing asthma in those sensitized compared to those not sensitized vary between 2 to 21 (65). In a prospective study, Sporik and colleagues (66) have shown that exposure to high levels of mite allergens during the first year of life is associated with subsequent increased risk for sensitization and for asthma. In asthmatic children, exposure to house dust mite allergen is linked to disease severity (67–69).

The above studies provided good evidence that exposure to house dust mites is causally related to asthma. On the other hand, some recent studies indicated that while dust mite allergen exposure results in sensitisation, the relationship with asthma development is less clear. Peat et al (64) studied

school children in 6 different regions in Australia. In these regions, house dust mite allergen exposure ranged from undetectable to very high levels, depending on climatic conditions. Sensitization to house dust mite was more frequently found among children living in high house dust mite allergen regions than in children living in low house dust mite region. However, children living in low mite allergen regions had a higher prevalence of sensitisation to other allergens and the prevalence of asthma was similar in all 6 regions. Similar observations were made in Tucson and New Mexico in the United States (70,71). In 3 prospective cohort studies in the United Kingdom (72), United States (73) and Norway (74) involving large number of children, no significant association was found between early exposure to house dust mite allergen and the development of wheeze in the first 2 years of life. A study in Germany did not observe any association between early exposure to house dust mite allergen at 6 months of life and the risk of doctor-diagnosed asthma at age 7 years (75).

There is also no evidence to suggest that the increase in prevalence of asthma during the last three decades in many parts of the world is due to an increase in exposure to house dust mite allergen.

Pet allergens

Pets are found in 40–50% of homes in many Western countries (76). Surveys in Western countries have shown that 5 to 15% of the general population and 40 to 70% of patients with asthma have positive immediate skin test reaction to cat and/or dog (77).

Both cat and dog allergens have been identified (63). Cat allergen has been well characterised and studied. The most important cat allergen is Fel d I as most of the IgE antibodies in cat-sensitive subjects are directed against this allergen (63). Fel d I is present in salivary glands, hair follicles, saliva, and lacrimal fluid. There have been few studies of sensitivity to dog allergen and its relationship with asthma until very recently. The aerodynamic characteristics of Can f I, the important dog allergen, are similar to Fel d I (78). Levels of 8 μg Fel d I/gm and 10 μg Can f I/gm dust have been proposed as significant exposures leading to attacks of asthma (79). There is a dose-response relationship between exposure to cat allergen and the prevalence of sensitisation (79).

In Western countries, measurable amounts of Fel d I are found in almost every home, even in homes without cats (80). Studies in Scandinavian schools have shown that while dust mite allergen levels were low in classrooms, high levels of both cat and dog allergens were found on both smooth and carpeted floors, with approximately 11 times more on carpeted floors (81). Levels of cat and dog allergens were much higher on chairs than on floors, suggesting that students and teachers brought in allergens on their clothing.

In developing countries, especially in cities, fewer families have pets because of overcrowding. There have been very few studies measuring pet allergens in Asian countries. In Hong Kong, only 7.5% of families have a pet and cat allergen levels are low in the homes (82). Sensitization to cat occurred in 15 % of children with asthma in Hong Kong (83). Measurements of allergens in public places have not been carried out in Asian countries.

Published literature on the effects of exposure to pets in the home on the risk of asthma has been contradictory. While some studies have shown an increase in risk of asthma and wheezing in children (84), others found exposure to pets in early life to be protective (85–87). A meta-analysis was carried out by Apelberg et al (88) who reviewed 32 articles that fulfilled the criteria of focusing on exposure within the first two years of life or exposure preceding the outcome. The authors came to the conclusion that exposure to pets appears to be associated with an increase risk of asthma and wheezing in older children (> 6 years) but a lower risk in younger (< 6 years) exposed children compared to nonexposed children and that this finding could not be explained by selection bias.

Cockroach allergen

Cockroaches are ubiquitous and are also highly allergenic. Two major groups of cockroach allergens have been identified: Blatella germanica and Periplaneta americana. The allergen, Bla g II, is an aspartic protease, which is a digestive enzyme secreted by cockroach in the faeces (89).

Cockroach populations are highest in crowded urban areas. Almost all studies relating cockroach allergen exposure and asthma have been conducted in industrialized countries. In a study of dust samples collected from homes of 87 children with moderate to severe asthma, 26% of bedroom dust

samples had detectable levels of cockroach allergens (90). Over 80% of the children whose bedroom Bla g I or Bla g II level greater than 1 U/gm demonstrated skin sensitivity to the cockroach allergen. The prevalence of sensitization was directly related to the level of bedroom exposure. In inner city areas in Chicago, exposure to cockroach allergen is also an important cause of hospitalization for acute asthma (91). Rosentreich et al (92) have also shown that immediate hypersensitivity to cockroach allergens is common among children with asthma in a large cohort living in seven cities in the Northeast and Midwest of the United States. The degree of exposure in children with positive skin tests to cockroach allergen is correlated with their risk of hospitalization. Thus, there is considerable evidence to support that cockroach is another important indoor allergen in asthma.

The role of exposure to cockroach allergens and asthma in Asian countries has yet to be defined. In Hong Kong, cockroach is the second most common allergen that patients with asthma reacted to (31).

Moulds or fungi

In subtropical areas in Southeast Asia, humidity is high and is conducive to the growth of not only house dust mites but also moulds. Home dampness has been used as a surrogate for mould level. A study in Taiwan has demonstrated an association of home dampness with asthma (93), similar to those published in industrialized countries (94). The role of indoor moulds in asthma has not been studied extensively because of the lack of standardized allergens.

Food allergens

Food allergens are mainly responsible for atopic dermatitis, gastrointestinal disturbance and urticaria/angioedema. However, children with atopic dermatitis have a higher prevalence of asthma and allergic rhinitis (95–97). Studies on prophylactic measures including breast-feeding, delay introduction of solids, dietary restrictions by mothers of high risk infants either prenatally or after birth up to 12 months of age, have demonstrated a significant reduction in the prevalence of these atopic disorders (atopic dermatitis, urticaria and gastrointestinal disturbance due to food allergy), but no reduction in allergic rhinitis or asthma (95–97).

Infections

While there is overwhelming evidence for viral infections leading to acute exacerbations of asthma, the role of viral infection in the induction of childhood asthma and atopy is not known. Children with bronchiolitis due Respiratory Syncytial Virus (RSV) infection have a higher prevalence of BHR and wheeze but not the rate of atopic sensitization compared with controls (98). A longitudinal follow-up study of a birth cohort in Tucson, Arizona has found an increase in recurrent wheeze in children with RSV infection at the age of 6; however at the age of 13, the difference between groups no longer exist (99). Thus wheezing associated with viral infection may have a better prognosis than atopic asthma.

Several studies have found an inverse relationship between viral infection and the development of atopy and asthma. Children who had measles had about half the rate of atopic sensitization than those who had been vaccinated (100). Italian military recruits who were seropositive for hepatitis A had a significantly lower prevalence of positive skin test reaction to common allergens and atopic disease compared with the seronegative recruits (101). Moreover, among recruits with negative hepatitis A serology, those from a large family were at the lowest risk for developing atopic diseases presumably from frequent childhood viral infections (102).

Other infections were also found to be protective. Shirakawa et al (103) reported that among BCG-vaccinated Japanese school children, those with a positive tuberculin reaction had less atopic disorders than those with a negative tuberculin reaction. Those with a positive tuberculin reaction also had a higher level of IFN-a suggesting possible suppression of Th2 cells. Among Finnish children and young adults with active tuberculosis, the prevalence of subsequent allergic disease was lower compared with a group of matched controls; however, the prevalence of asthma was slightly higher (104). Among Norwegian adults who routinely received BCG vaccination as adolescents, the size of reaction to tuberculin testing was not related to total or specific IgE or positive skin test reaction to common

aeroallergens (105). In Hong Kong where BCG vaccination at birth is the usual practice, no correlation was found between tuberculin reactivity and asthma or asthma symptoms in school children (106).

The number of siblings correlated inversely with the prevalence of self-reported inhalant allergy, hay fever, atopic dermatitis, and immediate skin test reactivity (107). The relationship is stronger with the presence of older siblings than with younger brothers and sisters. It has been postulated that infection in early childhood, transmitted by contact with older siblings, may provide protection against the development of atopic disorders (108,109). Over the past century, declining family size, improved household conditions and higher standards of personal hygiene, have reduced the opportunity for cross-infection in young families. More recently, inverse relations have also been reported between day care attendance in early life and the development of atopic sensitisation, total IgE and asthma in later childhood (110). Strachan was the first one to propose the hygiene hypothesis to be responsible for the increase in prevalence of allergic diseases in recent decades (108). This hypothesis fits well in the Th1/Th2 paradigm for allergic diseases (111).

In most of the developing countries in Asia, the prevalence of asthma and asthma-like symptoms is low compared to Western countries. This difference cannot be explained by genetic differences between ethnic groups. Even among Chinese of the same ethnic background living in different parts of Asia, significant differences were found in the prevalence of asthma, being lowest in rural China and highest in Hong Kong (31). A more recent study comparing the prevalence of asthma and other allergic disease in children in Urumqi, Beijing and Hong Kong has found that the prevalence of these disorders — highest in Hong Kong and lowest in Urumqi— is inversely related to the standard of living (112). These findings are compatible with the "hygiene hypothesis".

Endotoxin

Several cross-sectional studies have shown that children who grew up on a farm have less allergic diseases and asthma (36,37,113–115). Children who lived on farms with livestock had the lowest prevalence of allergen diseases. Because farm animals are a rich source of endotoxin, it has been suggested that exposure to endotoxin protects against the development of atopy and allergic diseases (116). Endotoxin strongly stimulates the production of IL-12 leading to upregulation of IFN-gamma (117). Braun-Fahrhander et al (118) recently reported a cross-sectional study of 812 schoolchildren from Europe showing that endotoxin levels in dust samples from the child's mattress were inversely related to the occurrence of atopic asthma and allergic sensitization.

Exposure to air pollution

There is no doubt that air pollution aggravates pre-existing asthma. In the laboratory, almost all major air pollutants including respirable suspended particles (PM_{10}), ozone, oxides of nitrogen and sulphur dioxide can cause acute broncho-constriction in asthmatics (119).

There have been many studies from different parts of the world showing a direct relationship between levels of air pollutants and hospitalization visits to emergency room and unscheduled visits to doctors for treatment of asthma (120). Significant relationships between levels of air pollutants and indices of severity of asthma such as the peak expiratory flow rate (121). Urban traffic pollution has become a major problem in most cities in Asia including Hong Kong. Several studies have been carried out on the effects of air pollution on asthma in Hong Kong. A direct relationship was found between hospital admission with asthma and the levels of each air pollutant, PM_{10}, ozone and nitrogen dioxide (122–123). A consistent and strong relationship between emergency room visits for asthma and the level of ozone and nitrogen dioxide while the relationship with PM_{10} was not so evident after adjustment for ozone and nitrogen dioxide (124). However, the recent study, Pollution Effects on Asthmatic Children in Europe (PEACE), involving 14 European centres on two panels of at least 75 children between 6 to 12 years of age with chronic respiratory symptoms followed for at least 2 months failed to show significant correlation between changes in PM_{10}, black smoke,

SO_2, NO_2 and change in respiratory health (125). This finding is at variance with the results of other panel studies conducted in the USA and in Europe (126). The only possible reason for the discrepancy in the finding is the relatively short period of observation in the PEACE study.

While there is no doubt that air pollution exacerbates asthma, there is no evidence to suggest that air pollution is responsible for the induction of asthma. However, recent literature suggest that increasing exposure to traffic pollutants may be of relevance to the inception of allergic diseases. In Japan, an increase in prevalence of cedar pollinosis (allergic rhinitis) was found in areas with high traffic exposure and high pollen counts (127). The prevalence of wheeze, chronic cough and phlegm were higher in women living close to major roads in the Dutch and Japanese studies (128–130) but no objective measurement of disease was available. A more recent study in Dresden, East Germany confirmed the association of high levels of air pollution and increased prevalence of cough and phlegm but not hay fever, BHR and atopy (131). Wang et al (132) conducted a large-scale epidemiological study of 165,173 schoolchildren aged 11 to 16 years in Taiwan as part of the ISAAC. They found a significant association between outdoor air pollution and asthma after controlling for potential confounding variables. Total suspended particulates, nitrogen dioxide, carbon monoxide and ozone all displayed an independent association with asthma.

In Hong Kong, a study of school children living in a heavily polluted district by traffic has demonstrated a significantly higher prevalence of sorethroat, cough, wheeze and BHR compared with those living in a less polluted district (133,134). When legislation was implemented to reduce fuel sulphur content, there was a significant reduction in sulphur dioxide levels and sulphate concentration in respirable particles. The reduction in pollutant level was associated with a reduction in respiratory symptoms and BHR in children in the polluted district (135) and cardiorespiratory mortality (136).

In the laboratory, diesel exhaust particles have been shown to act as adjuvants and increase the production of specific IgE antibodies. Furthermore, exposure to diesel particles after nasal allergen challenge has resulted in increased expression of Th2 type cytokines and enhanced eosinophil adhesion to nasal epithelial cells (137). Diesel exhaust is the major contributor to particulate matter in most urban areas. It is more harmful than other types of particles because of its small size (< 2 um), allowing penetration to peripheral airways (138). Diesel particles can also absorb allergens from grass pollen onto their surface and may act as potential carriers to increase the deposition in the lung.

Exposure to environmental tobacco smoke (ETS)

There is consistent evidence that exposure to ETS increases the risk for lower respiratory tract infections in infancy and childhood (139,140). Asthmatic children whose mothers smoked were found to have more severe asthma compared with those whose mothers did not smoke (141,142). Several large cohort studies have shown that ETS exposure was a risk factor for the inception of asthma in children (143–146). In the British birth cohort study (144), follow up of children to the age of 10 years has demonstrated a 14% increase in childhood wheezy bronchitis when mothers smoked more than 4 cigarettes/day; this increased to 49% when mothers smoked more than 14 cigarettes/day. Maternal smoking during pregnancy increased the risk for developing asthma about 2-fold (144). Thus there is convincing evidence of a link between exposure to ETS and the development of childhood asthma. However, the evidence of exposure to ETS and atopic sensitization is conflicting.

Lifestyle factors

One explanation for the increase in the prevalence of asthma in developed countries is the sedentary lifestyle and concomitant increase in obesity among children. There have been a number of recent reports on decreasing physical activity and increasing body mass among American children (147,148). A direct correlation has been shown between obesity and hours spent in passive, visual entertainment (148). The question is whether decreased physical activity, for which obesity is a

surrogate measure, could directly influence asthma (149). Support for this notion is the observation that full expansion of the lungs can decrease lung resistance. It is hypothesized that by reducing the extent to which bronchial muscle is stretched, reductions in deep breathing associated with a sedentary lifestyle may contribute to airway narrowing and asthma (150). Positive associations have been found between body mass index (BMI) and lower ventilatory function (151), wheeze, asthma or BHR (152). However the findings were not consistent, especially for boys.

Breast feeding

Breastfeeding protects infants from both respiratory and gastrointestinal infections and reduces exposure to allergens in cow's milk (153,154). There is now accumulating evidence that breastfeeding may protect against the development of asthma (155,156). A recent meta-analysis showed that children who are breast fed for at least 3 months of age are protected from development of asthma with an odds ratio of 0.80 (95% CI 0.66–0.97) (157).

Dietary factors

Omega-3-fatty acid intake is associated with asthma (158,159). Several epidemiological studies showed that people who eat fish, which has omega-3 fatty acids, regularly have fewer asthmatic symptoms (159,160). However, supplementation of diet with omega-3 fatty acids has been disappointing as a treatment for established asthma (161,162).

Summary

Epidemiological studies of asthma performed in the past 2 decades have provided important information with respect to the occurrence of asthma in different regions of the world. Multi-centred studies using standardized methodology have allowed meaningful comparison across countries and accurate monitoring the trends of asthma prevalence. These studies have also generated several hypotheses relating to the development of asthma and related allergic disorders. Studies from different regions of the world have provided important information on the many possible genetic and environmental factors for asthma. Given the diverse socioeconomic and ethnic background along with the rapid changing economy and modernization, the Asian region provides ample opportunities to explore the roles of various genetic and environmental factors in the pathogenesis of asthma and related atopic disorders.

References

1. Beasley R, Crane J, Lai CK, Pearce N. Prevalence and etiology of asthma. *J Allergy Clin Immunol* 2000; 105:S466–72.
2. Lai CKW, Douglass C, Ho SS, Chan J, Lau J, Wong G, Leung R. Asthma epidemiology in the Far East. *Clin Exp Allergy* 1996; 26:5–12.
3. Nishima S. A study on the prevalence of bronchial asthma in schoolchildren in western districts of Japan æ comparison between the studies in 1982 and 1992 with the same methods and same districts. *Arerugi* 1993; 42:192–204.
4. Hsieh KH, Shen JJ. Prevalence of childhood asthma in Taipei, Taiwan and other Asian Pacific countries. *J Asthma* 1988; 25:73–82.
5. Leung R, Wong GWK, Lau J, Ho A, Chan JKW, Choy D, Douglass C, Lai CKW. Prevalence of asthma and allergy in Hong Kong schoolchildren: an ISAAC study. *Eur Respir J* 1997; 10:354–60.
6. Goh DY, Chew FT, Quek SC, Lee BW. Prevalence and severity of asthma, rhinitis, and eczema in Singapore schoolchildren. *Arch Dis Child* 1996; 74:131–5.
7. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J* 1998; 12:315–35.

8. Janson C, Anto J, Burney P. et al. The European Community Respiratory Health Survey: what are the main results so far? European Community Respiratory Health Survey II. *Eur Respir J* 2001; 18:598–611.
9. ISAAC steering Committee. Phase II Modules of the International Study of Asthma and Allergies in Childhood (ISAAC). 1998.
10. von Mutius E, Illi S, Hirsch T, et al. Frequency of infections and risk for asthma, atopy and airway hyperresponsiveness children. *Eur Respir J* 1999; 14:4–11.
11. Weiland SK, von Mutius E, Hirsch T, et al. Prevalence of respiratory and atopic disorders among children in the East and West of Germany five years after unification. *Eur Respir J* 1999; 14:862–70.
12. Stein RT, Holberg CJ, Morgan WJ, et al. Peak flow variability, methacholine responsiveness and atopy as markers for detecting different wheezing phenotypes in childhood. *Thorax* 1997; 52:946–52.
13. Phankingthongkum S, Daengsuwan T, Visitsunthorn N, et al. How do Thai children and adolescents describe asthma symptoms? *Pediatr Allergy Immunol* 2002; 13:119–24.
14. Enright PL, McClelland RL, Newman AB, et al. Underdiagnosis and undertreatment of asthma in the elderly. Cardiovascular Health Study Research Group. *Chest* 1999; 116:603–13.
15. Janssens JP, Pache JC, Nicod LP. Physiological changes in respiratory function associated with ageing. *Eur Respir J* 1999; 13:197–205.
16. Burney PG, Laitinen LA, Perdrizet S, et al. Validity and repeatability of the IUATLD (1984) Bronchial symptoms Questionnaire: an international comparison. *Eur Respir J* 1989; 2:940–5.
17. Pekkanen J, Pearce N. Defining asthma in epidemiological studies. *Eur Respir J* 1999; 14:951–7.
18. Peat JK, Toelle BG, Marks GB, Mellis CM. Continuing the debate about measuring asthma in population studies. *Thorax* 2001; 56:406–11.
19. Pearce N, Pekkanen J, Beasley R. Role of bronchial responsiveness testing in asthma prevalence surveys. *Thorax* 2000; 55:352–4.
20. Gibson PG, Henry R. Shah S, Toneguzzi R, Francis JL, Norzila MZ, Davies H. Validation of the ISAAC video questionnaire (AVQ 3.0) in adolescents from a mixed ethnic background. *Clin Exp Allergy* 2000; 30:1181–7.
21. Sole D, Vanna AT, Yamada E, Rizzo MC, Naspitz CK. International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire: validation of the asthma component among Brazilian children. *J Invest Allergo Clin Immunol* 1998; 8:376–82.
22. Lai CKW, Chan JKW, Chan A, Wong G, Ho A, Choy D, Lau J, Leung R. Comparison of the ISAAC video questionnaire (AVQ 3.0) with the ISAAC written questionnaire for estimating asthma associated bronchial hyperreactivity. *Clin Exp Allergy* 1997; 27:540–5.
23. European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996; 9:687–95.
24. Pearce N, Sunyer J, Cheng S, et al. Comparison of asthma prevalence in the ISAAC and the ECRHS. ISAAC Steering Committee and the European Community Respiratory Health Survey. International Study of Asthma and Allergies in Childhood. *Eur Respir J* 2000; 16:420–6.
25. von Mutius E. The rising trends in asthma and allergic disease. *Clin Exp Allergy* 1998; 28(suppl 5):45–9.
26. Wieringa MH, Vermeire PA, Brunekreef B, et al. Increased occurrence of asthma and allergy: critical appraisal of studies using allergic sensitization, bronchial hyper-responsiveness and lung function measurements. *Clin Exp Allergy* 2001; 31:1553–63.
27. Peat JK, van den Berg RH, Green WF. et al. Changing prevalence of asthma in Australian children. *BMJ* 1994; 308:1591–6.
28. Goren AI, Hellmann S. Changing prevalence of asthma among schoolchildren in Israel. *Eur Respir J* 1997; 10:2279–84.
29. von Mutius E, Weiland SK, Fritzsch C, et al. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. *Lancet* 1998; 351:862–6.
30. Burr ML. Butland BK. King S. Vaughau-Williams E. Changes in asthma prevalence: two surveys 15 years apart. *Arch Dis Child* 1989; 64:1118–25.
31. Leung R, Ho P. Asthma, allergy. and atopy in three south-east Asians populations. *Thorax* 1994; 49:1205–10.
32. Wong GW, Li ST, Hui DS, et al. Individual allergens as risk factors for asthma and bronchial hyperresponsiveness in Chinese children. *Eur Respir J* 2002; 19:288–93.

33. Wong GW, Hui DS, Chan HH, et al. Prevalence of respiratory and atopic disorders in Chinese schoolchildren. *Clin Exp Allergy* 2001; 31:1225–31.
34. Ng TP, Hui KP, Tan WC. Prevalence of asthma and risk factors among Chinese, Malaysia and Indian adults in Singapore. *Thorax* 1994; 49:347–51.
35. Downs SH, Marks GB, Mitakakis TZ, Leuppi JD, Car NG, Peat JK. Having lived on a farm and protection against allergic diseases in Australia. *Clin Exp Allergy* 2001; 31:570–5.
36. von Ehrenstein OS, von Mutius E, Illi S, Baumann L, Bohm O, von Kries R. Reduced risk of hay fever and asthma among children of farmers. *Clin Exp Allergy* 2000; 30:187–93.
37. Riedler J, Eder W, Oberfeld G, Schreuer M. Austrian children living on a farm have less hay fever asthma and allergic sensitization. *Clin Exp Allergy* 2000; 30:194–200.
38. Chan-Yeung M, ZhangLX, Tu DH, et al. The prevalence of asthma and asthma-like symptoms among adults in rural Beijing, China. *Eur Respir J* 2002; 19:853–8.
39. Beasley R. The burden of asthma with specific reference to the United States. *J Allergy Clin Immunol* 2002; 109:S482–9.
40. Gergen PJ, Weiss KN. Changing patterns of asthma hospitalization among children: 1979 to 1987. *JAMA* 1990; 264:1688–92.
41. Williams MH Jr. Increasing severity of asthma from 1960 to 1987. *N Engl J Med* 1989; 320:1015–6.
42. Pearce N, Beasley R, Crane J, Burgess C. Epidemiology of asthma mortality during the twentieth century. In: Eds. Sheffer AL. *Fatal Asthma.* New York: Marcel Dekker Inc 1998, 13–9.
43. Ernst P, Spitzer WO, Suissa S, Cockcroft D, Habbick B, Horwitz RI, rt al. Risk of fatal asthma in relation to inhaled corticosteroid use. *JAMA* 1992; 268:3462–4.
44. Sly RM. Association of decreases in asthma mortality with increases in sales of inhaled corticosteroids [letter] *J Allergy Clin Immunol* 2000; 105:71–4.
45. Gioldman M, Rachmiel M, Gendler L, Katz Y. Decrease in asthma mortality rate in Israel from 1991–1995: Is it related to increased use of inhaled corticosteroids? J Allergy Clin Immuno 2000; 105:71–4.
46. Tanihara S, Nakamura Y, Oki I, Yanagawa H. Trends in asthma morbidity and mortality in Japan between 1984 and 1996. *J Epidemiol* 2002; 12:217–22.
47. Ng TP, Tan WC. Temporal trends and ethnic variations in asthma mortality in Singapore, 1976–1995. *Thorax* 1999; 54:990–4.
48. Kumana CR, Kou M, Lauder IJ, Ip MS, Lam WK. Increasing use of inhaled steroids associated with declining asthma mortality. *J Asthma* 2001; 38:161–7.
49. Postma DS, Kerstjens HAM, Ten Hacken NHT. Asthma: Epidemiology and risk factors. In: *Comprehensive Respiratory Medicine.* Eds. Albert R, Spiro S, Jett J. London: Mosby, 1999, Chapter 40.1–40.7.
50. Meijer B, Bleecker ER, Postma DS. Genetics. In: *Asthma. Basic Mechanism and Clinical Management.* Eds. Barnes PJ, Rodger IW, Thomson NC. San Deigo: Academic Press 1998, 35–46.
51. Cookson WO C.M., Sharp PA, Faux JA, Hopkins JM. Linkages between immunoglobulin E responses underlying asthma and rhinitis and chromosome 11q. *Lancet* 1992; I:1292–5.
52. Sanford A, Weir T, Pare P. The genetics of asthma. *Am J Respir Crit Care Med* 1996; 153:1749–65.
53. Sandford A, Pare P. The genetics of asthma: the important questions. *Am J Respir Crit Care Med* 2000; 161:S202–6.
54. Van Eerdewegh P, Little RD, Dupuls J, et al. Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. *Nature* 2002; 418:426–30.
55. Noguchi E, Shibasaki M, Arinami T, Takeda K, Yokouchi Y, Kobayashi K, Imoto N, Nakahara S, Matsui A, Hamaguchi H. No association between atopy/asthma and the Ile50val polymorphism of IL-4 receptor. *Am J Respir Crit Care Med* 1999; 160:342–5.
56. Tan EC, et al. IL-4R alpha gene IleVal polymorphism, *Allergy* 1999; 54:1005–7.
57. Chan H, Lai CKW, Wong GWK, Sandford A, Pare PD, Chan-Yeung M. IL-4 receptor and IL-4 promoter polymorphisms among Hong Kong schoolchildren. *Am J Respir Crit Care Med* 2001; 161:A202.
58. Li PKT, Lai CKW, Poon ASY, Ho ASS, Chan CHS, Lai KN. Lack of association between HLA-DQ and –DR genotypes and asthma in southern Chinese patients. *Clin Exp Allergey* 1995; 25:323–31.
59. Wahn U, Lau S, Bergmann R, Kulig M, Forster J, Bergmann K. Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol* 1997; 99:763–9.
60. Platts-Mills TA E, de Weck AL. Dust mite allergens and asthma — a world wide problem. *J Allergy Clin*

Immunol 1989: 83:416–27.
61. Platts-Mills TA E, Thomas WR, Aalberse RC, Vervloet D, Chapman MD. Dust mite allergens and asthma: Report of a second international workshop. *J Allergy Clin Immunol* 1992; 89:1046–60.
62. Leung R. Lam CW K, Ho A, Chan JK W, Choy D, Lai CK W. Allergic sensitization to common environmental allergens in adult asthmatics in Hong Kong. *HKMJ* 1997; 3:211–7.
63. Platts-Mills TA E, Vervlet D, Thomas WR, Aalberse RC, Chapman MD. Indoor allergens and asthma: Report of the third international workshop. *J Allergy Clin Immunol* 1997; 100:S1–S24.
64. Peat JK, Tovey E, Toelle BG, Haby MM, Gray EJ, Mahmic A Woolcock AJ. House dust mite allergens. A major risk factor for childhood asthma in Australia. *Am J Respir Crit Care Med* 1996; 153:141–6.
65. Lau S, Falkenhorst G, Weber A, Werthmann I, Lind P, Buettner-Goetz P, Wahn U. High mite-allergen exposure increases the risk of sensitization in atopic children and young adults. *J Allergy Clin Immunol* 1989; 84:718–25.
66. Sporik R, Holgate S, Platts-Mills T, Coswell J. Exposure to house-dust mite allergen (Der p1) and the development of asthma in childhood. *N Engl J Med* 1992; 323:502–7.
67. Chan-Yeung M, Manfreda J, Dimich-Ward J, Lam J, Ferguson A, Warren P, Simons E, Broder I, Chapman M, Platts-Mills TA E., Becker A. Mite and cat allergen levels in homes and severity of asthma. *Am J Respir Crit Care Med* 1995; 152:1805–11.
68. Kivity S, Solomon A, Soferman R, Schwarz Y, Mumcuoglu K, Topilsky M. Mite asthma in childhood. A study of the relationship between exposure to house dust mite and disease activity. *J Allergy Clin Immunol* 1993; 91:844–9.
69. Peat JK, Tovey E, Gray EJ, Mellis CM, Woolcook AJ. Asthma severity and morbidity in a population sample of Sydney school children: Part II. Importance of house dust mite allergen. *Aust NZJ Med* 1994; 24:270–6.
70. Halonen M, Stern DA, Wright AL, Taussig LM, Martinez FD. Alternaria as a major allergen for asthma in children raised in a desert environment. *Am J Respir Crit Care Med* 1997; 155:1356–61.
71. Sporik R, Ingram JM, Price W, Sussman JH, Honsinger RW, Platts-Mills TAE. Association of asthma with serum IgE and skin tests reactivity to allergen among children living at high altitude: tickling the dragon's breath. *Am J Respir Crit Care Med* 1995; 151:1388–92.
72. Gold DR, Burge HA, Carey V, Milton FK, Platts-Mills TAE, Weiss ST. Predictors of repeated wheeze in the first year of life. *Am J Respir Crit Care Med* 1999; 160:227–36.
73. Burr ML, Miskelly FG, Butland BK, Merrett TG, Vaughan-William E. Environmental factors and symptoms in infants at high risk of allergy. *J Epdemiol Community Health* 1989; 43:125–32.
74. Nafstad P, Oie L, Mehl R, Gaarder PI, Lodrup-Carlsen KC, Botten G, et al. Residential dampness problems ad symptoms and signs of bronchial obstruction in young Norwegian children. *Am J Respir Crit Care Med* 1998; 157:410–4.
75. Lau S, Illi S. Sommerfield C, Niggermann B, Bergmann R, von Mutius E, et al. Early exposure to house dust mite and cat allergens and development of childhood asthma: a cohort study. Multicentre Allergy Study Group. *Lancet* 2000; 356:1392–7.
76. Brunekreef B, Groot B, Hoek G. Pets, allergy and respiratory symptoms in children. *Int J Epidemiol* 1992; 21:338–42.
77. Kjellman B, Pettersson R. The problem of furred pets in childhood atopic disease. Failure of an information program. *Allergy* 1983; 38:65–73.
78. Custovic A, Green R, Fletcher A, Smith A, Picke AC, Chapman M, Woodcock A. Aerodynamic properties of the major dog allergen Can f 1: distribution in homes, concentration, and particle size of allergen in the air. *Am J Respir Crit Care Med* 1997; 155:94–8.
79. Ingram JM, Sporik R, Rose G, Honsinger R,Chapman MD, Platts-Mills TAE. Quantitative assessment of exposure to dog (Can f 1) and cat (Fel d1) allergens: relationship to sensitization and asthma among children living in Los Alamos, New Mexico. *J Allergy Clin Immunol* 1995; 96:449–56.
80. Quirce S, Dimich-Ward H, Chan H, Ferguson A, Becker A, Manfreda J, Simons E, Chan-Yeung M. Major cat allergen (Fel d1) in the homes of patients with asthma and their relationship to sensitization to cat dander. *Ann Allergy Asthma Immunol* 1995; 75:325–30.
81. Enberg RN, Shamie SM, McCullough J, Ownby DR. Ubiquitous presence of cat allergen in cat-free buildings: probable dispersal from human clothing. *Ann Allergy* 1993; 70:471–4.

82. Munir AK M, Einarsson R, Schou C, Dreberg SK G. Allergens in school dust. I. The amount of the major cat (Fel d1) and dog (Can f1) allergens in dust from Swedish schools is high enough to probably cause perennial symptoms in most children with asthma who are sensitized to cat and dog. *J Allergy Clin Immunol* 1993; 91:1067–74.
83. Leung R, Lam WK, Chan A, Lee M, Chan HS, Pang SW. Lai CKW. Indoor environment of residential homes in Hong Kong — relevance to asthma and allergic disease. *Clin Exp Allergy* 1998; 28:585–90.
84. Noertjojo K, Dimich-Ward H, Obata H, Manfreda J, Chan-Yeung M. Exposure and andomizedon to cat dander: asthma and asthma-like symptoms. *J Allergy Clin Immunol* 1999; 103:60–5.
85. Svanes C, Jarvis D, Chinn S, Burney P. Childhood environment and adult atopy: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999; 103:415–20.
86. Roost H-P, Kunil N, Schindler C, Jarvis D, et al. Role of current and childhood exposure to cat and atopic sensitizatioin. *J Allergy Clin Immunol* 1999; 104:941–7.
87. Remes ST, Castro-Rodriguez JA, Hollberg CJ, Martinez FD, Wright AL. Dog exposure in infancy decrease the subsequent risk of frequent wheeze but not of atopy. *J Allergy Clin Immunol* 2001; 108:509–15.
88. Apelberg BJ, Aoki Y, Jaakkola JJK. Systematic review: exposure to pets and risk of asthma and asthma-like symptoms. *J Allergy Clin Immunol* 2001; 107:455–60.
89. Arruda LK, Vailesa LD, Mann BJ, Shannon J, Fox JW, Vedvisk TS, et al. Molecular cloning of a major cockroach (Blattella germanica) allergen, Bla g2. *J Biol Chem* 1995; 270:19563–8.
90. Sarpong SB, Hamilton RG, Eggleston PA, Adkinson NF Jr. Socio-economic status and race as risk factors for cockroach allergen exposure and sensitization in children with asthma. *J Allergy Clin Immunol* 1996; 97:1393–01.
91. Kang BC, Johnson J, Veres-Thorner C. Atopic profile of inner-city asthma with a comparative analysis on the cockroach-sensitive and ragweed-sensitive subgroups. *J Allergy Clin Immunol* 1993; 92:1393–401.
92. Rosenstreich D.L., Eggleston P., Kattan M, Baker D, Slavin RG, Gergen P, Mitchell H, McNiff-Mortimer K, Lynn H, Ownby D, Malveaux F. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner city children with asthma. *N Eng J Med* 1997; 336:1356–63.
93. Yang C, Tien Y, Hsieh H, Kao W, Lin M. Indoor environmental risk factors and childhood asthma: a case-control study in subtropical area. *Paediatr Pulmonol* 1998; 26:120–4.
94. Dales R, Burnett R, Zwanenburg H. Adverse health effects among adults exposed to home dampness and molds. *Am Rev Respir Dis* 1991; 143:505–9.
95. Hide D, Matthews S, Matthews L, Stevens M, Rideout S, Twiselton R, Gant C, Arshad S. Effect of allergen avoidance in infancy on allergic manifestations at age of two years. *J Allergy Clin Immunol* 1994; 93:842–6.
96. Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: Follow up at age seven years in a prospective andomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 1995; 95:1179–90.
97. Marini A, Agosti M, Motta G, Mosca F. Effects of a dietary and environmental prevention programme on the incidence of allergic symptoms in high atopic risk infants: three years follow-up. *Acta Pediatr Suppl* 1996; 414:1–22.
98. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med.* 2000; 161:1501–7.
99. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ, and the group health medical associates. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995; 332:133–8.
100. Shaheen SO, Aabt P, Hall AJ, Barker DJP, HEYES CB, Shiell AW, et al. Measles and atopy in Guinea-Bissau. *Lancet* 1996; 347:1792–6.
101. Matricardi PM, Rosmini F, Ferrigno L, Nisini R, Rapicetta M, Chionne P, Stroffolini T, Pasquini P, D'Amelio R. Cross-sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis A virus. *BMJ* 1997; 314:999–1007.
102. Matricardi PM FF, Franco A, Caprio G, Murru F, Cioffi D, Ferrigno L, Palermo A, Ciccarelli N, Rosmini F. Sibship size, birth order, and atopy in 11371 Italian young men. *J Allergy Clin Immunol* 1998; 101:439–44.
103. Shirakawa T, Enomoto T, Shimazu S, Hopkin JM. The inverse association between tuberculin responses and atopic disorder. *Science* 1997; 275:77–9.
104. von HertzenL, Klaukka T, Mattila H, et al. Mycobacterium tuberculosis infection and the subsequent development of asthma and allergic conditions. *J Allergy Clin Immunol* 1999; 104:1211–4.

105. Omenaas E, Jentoft HF, Vollmer WM, et al. No relationship between tuberculin reactivity and atopy in BCG vaccinated young adults. *Thorax* 2000; 55:454–8.
106. Wong GW, Hui DS. Tam CM. Chan HH. Fok TF, Chan-Yeung M, Lai CK. Asthma. atopy and tuberculin responses in Chinese schoolchildren in Hong Kong. *Thorax* 2001; 56:770–3.
107. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989; 299:1259–60.
108. Strachan DP, Harkins LS, Johnston ID, Anderson HR. Childhood antecedents of allergic sensitization in young British adults. *J Allergy Clin Immunol* 1997: 99:6–12.
109. Shaheen SO. Changing patterns of childhood infection and the rise in allergic disease. *Clin Exp Allergy* 1995; 25:1034–7.
110. Kramer U, Heinrich J, Wjst M, Wichmann HE. Age of entry to day nursery and allergy in later childhood. *Lancet* 1999; 353:450–4.
111. Romagnani S. The Th1/Th2 paradigm and allergic disorders. *Allergy* 1998; 53(46 Suppl):12–5.
112. Zhao TB, Wang A, Chen Y, Xiao M, Duo L, Liu G, Lau YL, Karlberg J. Prevalence of childhood asthma, allergic rhinitis and eczema in Hong Kong, Urumqi and Beijing. *J Paediatr Child Health* 2000; 36:128–33.
113. Braun-Fahrlander CH, Gassner M, Grize L, Neu U, Sennhauser FH, Varonier HS, Vuille JC, Whthrich B and the Scarpol Team. Prevalence of hay fever and allergic sensitization in farmer's children and their peers living the same rural community. *Clin Exp Allergy* 1999; 29:28–34.
114. Ernst P and Cormier Y. Relative scarcity of asthma and atopy among rural adolescents raised on farm. *Am J Respir Crit Care Med* 2000; 161:1563–6.
115. Kilpelinen M, Terho EO, Helenius H and Koskenvuo M. Farm environment in childhood — prevents the development of allergies. *Clin Exp Allergy* 2000; 30:201–8.
116. Martinez FD. Maturation of immune responses at the beginning of asthma. *J Allergy Clin Immunol* 1999; 103:355–61.
117. Holt PG, Sly PD, Bjorksten B. Atopic versus infections diseases in childhood: a question of balance. *Pediatr Allergy Immunol* 1997; 8:53–8.
118. Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grize L, Maisch S, Carr D, Gerlach F, Bufe A, Lauener RP, Schierl R, Renz H, Nowak D, von Mutius E. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002; 347:869–77.
119. Viegi G, Enarson D. Human health effects of air pollution from mobile sources in Europe. *Int J Tuberc Lung* 1998; 2:947–67.
120. World Health Organization. Guidelines for air quality. WHO, Geneva 1999. www.who.int/peh/air/aorguides2.htm
121. Vedal S, Petkau J, White R, Blair J. Acute effects of ambient inhalable particles in asthmatic and nonasthmatic children. *Am J Respir Crit Care Med* 1998; 157:1–10.
122. Wong TW, Lau TS, Yu TS, Neller A, Wong SL, Tam W, Pang SW. Air pollution and hospital admission for respiratory and cardiovascular diseases in Hong Kong. *Occup Environ Med* 1999; 56:679–83.
123. Wong GWK, Ko FWS, Lau TA, Li ST, Hui D, Pang SW, Leung R, Fok TF, Lai CKW. Temporal relationship between air pollution and hospital admissions for asthmatic children in Hong Kong. *Clin Exp Allergy* 2001; 31:565–9.
124. Vedal S, Brumm J, Brauer M, Tsui M, Tong HK, Wong YK, Petkau J, Chan-Yeung M Acute effects of air pollution on asthma emergency room visits in Hong Kong. *Am J Respir Crit Care Med* 2001; 161:A562.
125. Roemer W, Hoek G, Brunekreef B. Pollution effects on asthmatic children in Europe, the PEACE study. *Clin Exp Allergy* 2000; 30:1067–75.
126. Dockery DW, Pope CA III. Acute respiratory effects of particulate air pollution. *Annu Rev Public Health* 1994; 15:107–32.
127. Ishizaki T, Koizumi K., Ikemori R, Ishyama Y, Kushibiki E. Studies of prevalence of Japanese cedar pollinosis among the residents in a densely cultivated area. *Ann Allergy* 1987; 58:265–70.
128. Brunekreef B, Janssen NA, de Hartog J, Harssema H, Knape M, van Vliet P. Air pollution from truck traffic and lung function in children living near motorways. *Epidemiol* 1997; 8:298–303.
129. Nitta H, Sato T. Nakai S, Maeda K, Aoki S, Ono M. Respiratory Health associated with exposure to automobile exhaust. I. Results of cross-sectional studies in 1979, 1982, 1983. *Arch Environ Health* 1993: 48:53–8.
130. Oosterlee A. Drijver M, Lsbert E, Brunekreef B. Chronic respiratory symptoms in children and adults living along streets with high traffic. *Occup Environ Med* 1996; 53:241–7.

131. Hirsch TH, Weiland SK, von Mutius E, Safeca AF, Grafe H, Csaplovics E, et al. Inner city air pollution and respiratory health and atopy in children. *Eur Respir J* 1999; 14:669–77.
132. Wang TN, Ko YC, Chao YY, Huang CC, Lin RS. Association between indoor and outdoor air pollution and adolescent asthma from 1995 to 1996 in Taiwan. *Environ Research* 1999; 81:239–47.
133. Ong SG, Wong CM, Tam TH, Tam AYC, Dainel L, Hedley AJ. Studies on the respiratory health of primary school children in urban communities of Hong Kong. *The Science of Total Environment* 1991; 106:121–35.
134. Tam A, Wong C, Lam T, Ong S, Peters J, Hedley A. Bronchial responsiveness in children exposed to atmospheric pollution in Hong Kong. *Chest* 1994; 106:1056–60.
135. Wong CM, Lam TH, Peters J, Hedley AJ, Ong SG, Tam AY C., Liu J, Spiegelhalter DJ. Comparison between two districts of the effects of an air pollution intervention on bronchial responsiveness in primary school children in Hong Kong. *Int J Epidmiol Community Health* 1998; 52:571–8.
136. Terada N, Maesako K, Hiruma K, Hamano N, Houki G, Konno A. Diesel exhaust particulates enhance eosinophil adhesion to nasal epithelial cells and cause degranulation. *Int Arch Allergy Immunol* 1997; 114:167–74.
137. Hedley AJ, Wong C-M, Thach TQ, Ma S, Lam TH, Anderson HR. Cardiorespiratory and all-cause mortality after restrictions on sulphur content of fuel in Hong Kong: an intervention study. *Lancet* 2002; 360:1646–52.
138. Diaz-Sanchez D, Dotson AR, Takeneka H, Saxon A. Diesel exhaust particles induce local IgE production in vivo and alter the pattern of IgE messenger RNA isoforms. *J Clin Invest* 1994; 94:1417–25.
139. Strachan DP, Cook DG. Passive smoking and lower respiratory illness in infancy and childhood. *Thorax* 1997; 52:905–14.
140. Chen Y, Li W, Yu S. Influence of passive smoking on admissions for respiratory illness in early childhood. *BMJ* 1986; 293:303–6.
141. Cook DG, Strachan DP. Health effects of passive smoking: 3. Parental smoking and prevalence of respiratory symptoms and asthma in school age children. *Thorax* 1997; 52:1081–94.
142. Neuspiel DR, Rush D, Butler NR, Golding J, Bijur PE, Kerzon M. Parental smoking and post-infancy wheezing in children: a prospective cohort study. *Am J Public Health* 1989; 79:168–71.
143. Murray AB, Morrison BJ. The effect of cigarette smoke from the mother on bronchial responsiveness and severity of symptoms in children with asthma. *J Allergy Clin Immunol* 1986; 77:575–81.
144. Ehrlich RI, Du Toit D, Jordaan E, Zwarenstein M, Potter P, Volmink JA, Weinberg E. Risk factors for childhood asthma and wheezing: importance of maternal and household smoking. *Am J Respir Crit Care Med* 1996; 154:681–8.
145. Martinez F, Antognoni G, Marci F, et al. Parental smoking enhances bronchial responsiveness in nine-year old children. *Am Rev Respir Dis* 1988; 138:518–23.
146. Gortmaker S, Walker DK, Jacobs FH, Rich-Ross H. Parental smoking and the risk of childhood asthma. *Am J Pub Health* 1982; 72:574–9.
147. Weitzman M, Gortmaker S, Walker D, Sobol A. Maternal smoking and childhood asthma. *Pediatr* 1990; 85:505–11.
148. Troiano RP, Flegal KM, Kuczmarski RJ, Campbell SM, Johnson CL. Overweight prevalence and trends for children and adolescents. The National Health and Nutrition Examination Survey. 1963–1991. *Arch Ped Adoles Med* 1995; 149:1085–91.
149. Gortmaker SL, Must A, Sobol AM, Peterson K, Colditz GA, Dietz WH. Television watching as a cause of increasing obesity among children in the United states. 1986–1990. *Arch Pediatr adolesc med* 1995; 149:1085–91.
150. Crater SE, Platts-Mills TAE. Searching for the cause of the increase in asthma. *Current Opinion in Pediatrics* 1998; 10:594–9.
151. Platts-Mills TAE, Sporik RB, Chapman MD, Heymann PW. The role of domestic allergens. *Ciba Found Symp* 1997; 206:173–89.
152. Lazarus R, Colditz G, Berkey CS, Speizer FE. Effects of body fat on ventilatory function in children and adolescents. *Pediatr Pulmonol* 1997; 24:187–94.
153. Howie PW, Forsyth JS, Ogston SA, Clark A, V du Florey C. Protective effect of breast-feeding against infection. *BMJ* 1990; 300:11–6.
154. Wold AE, Alderberth I. Does breastfeeding alter the infant's immune responsiveness? *Acta Pediatr* 1998; 87:946–9.

155. McConnochie KM. Roghmann KJ. Breast feeding and maternal smoking as predictors of wheezing in children 6 to 10 years of age. *Pediatr Pulmonol* 1986; 2:260–8.
156. Burr ML, Limb ES, Maguire MJ, et al. Infant feeding, wheezing and allergy: a prospective study. *Arch Dis Child* 1993; 68:724–8.
157. Wright Al, Holberg CJ, Taussig LM, Martinez FD. Relationship of infant feeding to recurrent wheezing at age 6 years. *Arch Pediatr Adolesc Med* 1995; 149:758–63.
158. Peat JK, Li J. Reversing the trend: reducing the prevalence of asthma. *J Allergy Clin Immunol* 1999; 103:1–10.
159. Britton J, Pavord I, Richards K, et al. Dietary sodium intake and the risk of airway hyperreactivity in a random adult population. *Thorax* 1994; 59:875–80.
160. Schwartz J, Speizer FE. The relationship of dietary fish intake to level of pulmonary function in the first National Health and Nutrition Survey (NHANES I). *Eur Respir J* 1994; 7:1821–4.
161. Weiss ST. Diet as a risk factor for asthma. The rising trends in asthma. Ciba Foundation Symposium 206. Chichester Wiley 1997, 244–57.
162. Peat JK, Salome CM, Woolcock AJ. Factors associated with bronchial hyperresponsiveness in Australian adults and children. *Eur Respir J* 1992; 5:921–9.
163. Hodge L, Salome CM, Hughes JM, et al. Effect of dietary intake of omega–3 and omega6 fatty acids on severity of asthma in children. *Eur Respir J* 1997; 11:361–5.

2 Asthma Management

Mary Ip and Moira Chan-Yeung

Diagnosis

The classical symptoms of asthma are episodic cough, wheeze and dyspnoea, which are often brought on by certain precipitating factors such as weather change, upper respiratory tract infections, exposure to irritants and exercise. However, not all symptoms are present in all patients and some may only present with persistent cough (1). In other patients, particularly older patients, symptoms are more insidious rather than episodic and tend to be more persistent.

The diagnosis of asthma is based on the demonstration of airflow obstruction which improves either spontaneously or after bronchodilator in a patient with compatible symptoms. Measurement of lung function test over time is important for monitoring the course of disease. In asthma, the essential lung function parameters to be determined comprise of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) and their ratio measured by spirometry. The variation of these parameters over time or improvement of these parameters with treatment, such as bronchodilators or a course of steroids, confirms the diagnosis. The American Thoracic Society defines "reversibility" as a change of FEV_1 of at least 12% and 200 mls (2). A simpler test is the measurement of peak expiratory flow rate (PEFR) by a simple device, the peak flow meter. However, measurement of PEFR do not always reflect accurately the degree of obstruction, especially in children when air-trapping can be severe without much change in PEFR (3,4). A 15% change in PEFR in response to bronchodilator or a course of steroids or a spontaneous fluctuation of over 20–30% favour the diagnosis of asthma (5). Home measurement of PEFR allows patients, particularly those with severe asthma, to monitor the degree of airflow obstruction at home and adjust medications according to self-management plans (6).

Both spirometry and PEFR are effort dependent, and proper performance of the tests is important. Interpretation of test results requires reference values for the specific population since "normal" lung function values vary in different ethnic groups even after adjustment for sex, age and height (see chapter on Lung Function Testing).

In patients with mild asthma, spirometry may be normal when it is done during symptom-free periods. Some patients may have no wheeze or rhonchi on auscultation but have significant airflow obstruction on objective testing. Furthermore, patients who have had the disease for a long time may not have a reversible element on bronchodilator testing, and may be confused to be suffering from irreversible airflow obstruction due to other conditions such as smoking-related chronic obstructive pulmonary disease (COPD) or even bronchiectasis.

Other tests that may be helpful in the diagnosis

of asthma include measurements of nonnallergic bronchial hyperresponsivenesss (BHR) with bronchial challenge tests or determination of atopic status (7), but these tests have low specificity for a diagnosis of asthma. Although nonallergic BHR is a characteristic feature in asthma, it may be present in other diseases such as allergic rhinitis, COPD, bronchiectasis and cystic fibrosis (8) while atopy may be present in the absence of asthma. Measurement of nonallergic BHR is used to establish the diagnosis of asthma in patients who present atypically, such as only having persistent cough.

Atopy can be determined by performing allergen skin prick tests to a battery of common allergens or by measuring specific IgE antibodies in the serum; the latter is more expensive. It is well known that subjects can be atopic without having asthma, and adult-onset asthma is usually not associated with specific allergic sensitization. Moreover, the presence of specific sensitization does not necessarily mean that it is the cause of the patient's asthma. The causal relationship has to be established with careful history taking of the association of symptoms and allergen exposure.

Chest radiograph does not have not much diagnostic value in asthma, but it is useful for exclusion of other diseases. This is especially important when patients present with chronic cough. Some specific causes of asthma such as allergic bronchopulmonary aspergillosis may have special features on chest radiographs.

Diagnosis of asthma is particularly difficult in children and elderly who have difficulty performing lung function tests. In such circumstances, the diagnosis is often based on clinical judgement of the characteristic symptoms and/or physical findings of wheezing when a patient presents during an acute attack. Other causes similating such features need to be considered such as foreign body inhalation or viral bronchiolitis in children, and COPD, left ventricular failure, or even endobronchial tumour in adults.

Management of Asthma

Once the diagnosis of asthma has been established, it is necessary to assess the severity of asthma and to determine the triggers of attacks for each patient. It is important to determine the severity of asthma according to current international consensus guidelines based on expert opinion for the implementation of stepwise asthma management plans (9). Determination of asthma triggers is important for prevention of acute episodes.

The goals for asthma management include the following: to relieve symptoms; to prevent continuing symptoms, altered lifestyle due to asthma, development of irreversible airflow obstruction and premature death; and to achieve the above goals with minimal side effects of drugs. The management of asthma consists of pharmacologic treatment and environmental control.

Pharmacologic Treatment

Medications in asthma are essentially classified as either relievers or controllers, although some drugs may have both properties.

Relievers

Relievers are drugs that give instant symptomatic relief and hence they all have bronchodilating properties.

Beta$_2$-agonists

Short-acting beta$_2$-agonists These drugs are probably the most long-standing medications available for asthma treatment. The drugs in use nowadays are mostly beta 2-selective (eg. salbutamol, terbutaline) and have less cardiac stimulation, although some countries in Asia still use non-selective beta$_2$-agonists such as isoproterenol in Japan. Both oral and inhaled preparations are available, but the inhaled route is preferred because it is faster in onset of action and it carries much fewer side effects.

Inhaled bronchodilators have a rapid onset of action in several minutes, and the duration of bronchodilating action is about 4–6 hours although this is markedly shorter during severe asthma attacks. They are usually recommended on an "as necessary" basis for symptomatic relief, and the frequency of use becomes a good indicator of disease control. They are also useful when taken before exercise to prevent exercise-induced asthma.

Long-acting beta$_2$-agonists Long acting oral beta$_2$-agonists have been available for a long time, usually as slow release preparations, eg. salbutmol SR, or bambuterol, the pro-drug of terbutaline. More recently, inhaled preparations of long acting beta$_2$-agonists have been widely marketed. These drugs (eg. formoterol, salmeterol) have a longer duration of bronchodilating action of 12–24 hours. This class of drugs is considered very convenient as they provide longer duration of symptom control, but this also leads to concern that its regular use may mask the severity of asthma, and may also cause tolerance due to down regulation of beta-receptors. So far, although there have been some conflicting studies of attenuation of bronchoprotective effect or bronchodilating action in long-term use of these drugs (10,11), there is no clinically observed decrease in efficacy. The use of long-acting beta$_2$-agonists also reduces exercise induced bronchospasm (11).

Since this class of drugs does not have any significant anti-inflammatory effect, they are recommended to be ALWAYS combined with the use of inhaled corticosteroids (ICS) (9, 12,13). In various national and international guidelines, they are positioned as add-on therapy when asthma control is not adequate even after ICS has been given (9). Adding long-acting beta$_2$-agonists to patients with suboptimally controlled asthma while on low or moderate doses of ICS resulted in better control of airway inflammation and clinical symptoms of asthma, equivalent if not better than increasing the dose of ICS (13–17). These findings have led to the development of fixed dose combinations of long acting beta$_2$-agonists and ICS which are usually more convenient leading to greater compliance. However, such fixed combinations do pose limitations in dosing flexibility eg. during acute exacerbation increase use of the combination preparation to give more ICS will inevitably increase the dose of long-acting beta$_2$-agonists which may not be desired.

Due to its long duration and slower onset of action, long-acting beta$_2$-agonists were previously not recommended as acute relievers, but to be used on a regular basis. Recent studies suggest that certain preparations such as formoterol can function effectively and safely as an acute reliever during acute exacerbations of asthma (18).

Both oral and inhaled long-acting beta$_2$-agonists have side effects similar to short-acting beta$_2$-agonists. As expected, the oral form has more side effects and less consistent bronchodilatation.

Anti-cholinergic drugs

These are not recommended routinely in chronic treatment of asthma except in those with co-existent smoking-related COPD, or the few asthmatics who really cannot tolerate the side-effects of beta$_2$-agonists (9).

Theophyllines

Oral slow release preparations of theophylline have been popular in the past, but have fallen out of favour in developed countries due to its relative toxicity and the advent of the inhaled long acting beta$_2$-agonists.

Side effects of theophylline include gastrointestinal upset and palpitation. Toxicity of theophylline may result in headache, confusion or even convulsion. When given in high doses, plasma levels need to be monitored periodically especially when there are potential interactions with other drugs or conditions affecting theophylline metabolism. At low doses, side effects are of concern only in a minority of subjects. There is some evidence that theophyllines may have anti-inflammatory effects at a dose lower than that required for optimal brochodilatation (19,20). Currently, it is recommended to be added when asthma is not well controlled on low/moderate doses of ICS (9). In this capacity, it shares the same position as long-acting beta$_2$-agonists and leukotriene antagonists. It has the advantage of being much less expensive than the other two classes of agents. It is useful especially when given for control of persistent nocturnal symptoms despite regular anti-inflammatory therapy (21), and in this situation, the one dose given at night usually does not require plasma level monitoring.

Controllers

Asthma is now known to be a disease with persistent airway inflammation. Full control of asthma in most subjects, other than those with very mild disease, will require regular use of medications with anti-inflammatory properties.

Corticosteroids

Inhaled corticosteroids (ICS) are now considered the cornerstone in the treatment of persistent asthma. There is strong evidence for its clinical efficacy in reducing asthma symptoms, frequency of exacerbations, risk of fatal asthma as well as improving the quality of life (22–26). They also result in improvement and preservation of lung function (22–24). In parallel with improvement in these clinical parameters, there is also strong evidence for its anti-inflammatory effects based on studies of cellular and cytokine profile of airway secretions or airway biopsies, as well as tests of airway hyperresponsiveness (27,28). Although there is evidence that changes in inflammatory cell profile occur in the asthmatic airway even after one dose of ICS (29), the clinical effects of ICS on symptoms and lung function are observed after one to two weeks while the improvement usually peaks at about two to four weeks, depending on the severity of asthma and the dose and potency of ICS used (24). Since there are inter-individual variations in asthma severity and intra-individual variations in asthma severity over time, the dose-response curves differ and thus dosages should be tailored in individuals and in the same individual over time. Being a "preventive" medication, it has to be used on a regular long-term basis.

Chronic oral steroid use is notorious for its side effects. This has caused much concern over the possibility of side effects, especially systemic side effects, with the prolonged continuous use of ICS, sometimes for life, in asthmatics. Most of the studies of side effects of ICS have been conducted in adults.

Local side effects of ICS include oral thrush, dysphonia and throat irritation with cough. Oral candidiasis can be significantly reduced through the use of spacer devices and mouth-rinsing to decrease deposition of the drug on the tongue and pharynx. Treatment with local anti-fungal agents is effective. Hoarseness of voice is much more difficult to resolve. Dose reduction of ICS and the use of spacers may decrease the problem.

Systemic absorption of ICS may occur through mucosa of the airways and the oral cavity, and the risk of systemic side effects is always worrisome. The side effect profile varies with different generic formulae of ICS, and studies have demonstrated that budesonide and fluticasone propionate have less systemic effects than beclomethasone diproprionate (BDP) and triamcinolone (24,30). Systemic absorption and side-effects may be reduced with the use of large volume spacers (31,32). In general, no significant side effects are observed at doses below the equivalent of 400–500 μg BDP per day in adults or 100–200 μg BDP per day in children (9,24,30,33). At higher doses, there may be biochemical markers of depressed bone turnover and decreased bone mineral density, but there is no established evidence of osteoporosis in adults (24,30,34). In children, short term decrease in bone growth has been reported but the ultimate height attained by asthmatic children taking ICS has not been less compared with those not taking ICS (33,35,36). It is important to bear in mind that uncontrolled or severe asthma itself affects growth adversely. There is little data on the risk of side effects of ICS in infants and very young children. Laboratory evidence of adrenal suppression is seen with high doses of ICS, but its clinical relevance is not established (24,30,32).

In a minority of subjects with very difficult asthma, chronic oral steroids in low dose may still be required to achieve relative stabilization of disease. It is important to optimize all other aspects of asthma management as well as other medications in such individuals so as to keep the oral steroid dependency to a minimum.

Chromones

This group of drugs includes sodium chromoglycate, which has been used in children for many year, and nedocromil sodium. They have been shown to reduce symptoms, BHR, frequency of exacerbation and to improve lung function (37,38). However, they are less efficacious than ICS. Few side-effects have been reported with this class of agents.

Leukotriene antagonist

This is a new class of anti-asthma drugs that include the cysteinyl leukotrine-1 receptor antagonists (eg. Monteleukast, Pranleukast, Zafirleukast), and the 5-lipoxygenase inhibitors (eg. Zileuton). They are all only available in the oral form.

Leukotriene antagonists are considered to be

a group of preventive agents. They have been shown to decrease airway inflammation, improve asthma control and lung function, and they also have variable bronchodilating properties that are seen over a few hours of taking the drug (39–41).

Leukotriene antagonists are now considered as an option in add-on therapy for asthma not optimally controlled by low, moderate or high dose of ICS (9,39,41–44). Some studies have shown that leukotriene antagonists allow tapering of ICS (42) or improve asthma control (43,44) while others did not demonstrate any benefit (45). It may be of particular value in aspirin intolerant asthma (46). Its use as monotherapy in place of low dose ICS in mild asthma has been studied but such a role is not yet established.

These drugs have relatively few side effects. Liver toxicity has been reported with the 5-lipoxygenase inhibitors. Churg-strauss syndrome has been also reported with the use of monteleukast but the general consensus is that the drug probably unmasked the vasculitic syndrome by allowing oral steroid withdrawal.

Anti-allergic agents

H-1 antagonists and other oral antiallergic agents have been used for treatment of asthma. There is no evidence to support their efficacy, except for some benefit in those with rhinitis as well (47). Astemizole and terfenadine have been rarely reported to be associated with arrhythmias (9).

Systemic steroid-sparing agents

Immunomodulating drugs such as methotrexate, cyclosporin and gold have been tried. There is no conclusive evidence of their benefits and they may cause significant adverse side-effects, hence they are only indicated in highly individualized difficult patients and their use must be closely monitored by specialists (9,48–50). Macrolides (oleandromycin) act by decreasing metabolism of glucocorticosteroid (51). and may not be steroid sparing in the true sense.

Immunotherapy

Allergen-specific immunotherapy has been popular in some countries for the treatment of allergic diseases, especially rhinitis. Its benefit in asthma is controversial, and a recent Cochrane review has shown this therapy to be of some efficacy (52). However, the effect is relatively small compared with the currently available anti-inflammatory drugs, especially ICS. Immunotherapy does carry significant potential adverse effects, including fatality from severe asthma exacerbations or anaphylactic reactions. There are still many unanswered issues, such as the subset of patients to benefit most, the possible variation in efficacy of various allergen-specific therapy, long term effectiveness, and the difference in various outcome measures (9). Hence it should only be considered when strict environmental preventive measures and pharmacologic therapy have failed to control asthma (53). Immunotherapy is only to be practiced by specialists experienced in the procedure and in a venue medically equipped for dealing with acute adverse reactions.

Routes and devices for drug administration

Both oral and inhaled preparations are available for bronchodilators and steroids. For chromones, only metered dose inhalers are available, while theophyllines are not available in inhaled form.

Side effect profile is obviously much better in the inhaled preparations of $beta_2$-agonists and steroids. This is particularly relevant for steroids where inhaled preparations are doubtlessly the route of choice in management of chronic asthma.

There are several kinds of inhaled devices, including metered dose aerosol inhalers (MDI), MDI with spacers, dry powder inhalers (DPI) and nebulizers. Spacers have the advantage of improving airway deposition without great need for coordination, but the large volume spacers are clumsy especially for young ambulatory asthmatics.

Metered dose inhalers previously contained chloroflurocarbon (CFC) as the propellent, which is beginning to be phased out due to its environmental unfriendliness. Alternatives are

DPIs or MDIs using propellants such as hydrofluroalkanes (HFA), which have been shown to be effective and safe (54–56). The phasing out process of CFC MDIs is slower in Asia compared to western countries, and the cost of different replacement formulations is likely a major determining factor.

Nebulizers are not advocated for chronic use in most asthmatics, but they are very popular in some places in Asia, likely related to wide publicity from commercial advertisement. Most subjects use it for delivery of bronchodilators for symptomatic relief, which can be dangerous as subjects may delay using appropriate anti-inflammatory drugs or seeking treatment for acute severe asthma. For home use, they should be reserved for some young asthmatics when parents find the use of face mask for applying MDI aerosols difficult, or for older asthmatics who are well educated in recognizing their own disease severity and who live far away from medical help. The nebulizer device may help these asthmatics to buy time in seeking treatment or to get over minor episodes.

Alternative and complementary therapy

Although the benefits of alternative and complementary medicine have not been adequately researched, their use is very popular in many communities for health maintenance and treatment of diseases, and asthma and allergies are among the common indications (57,58). There is no proper documentation of their use in asthma in Asian communities, but personal observations suggest that they are not uncommonly used as adjunct to accepted western medical treatment or even sometimes as the only form of regular treatment in mild asthma. More well described therapeutic methods include acupuncture, herbal medicine, ayurvedic medicine, buteyco, hypnosis and homeopathy (9,57–61). These methods, including acupuncture, have not been subjected to rigorous applied or basic research (58–61) and good evidence for their efficacy is lacking. Considering their popularity and the amount of healthcare expenditure they accounted for, more rigorous research to prove facts and dispel myths are called for.

Treatment of acute asthma

The first line drug for treatment of acute asthma is high doses of short-acting beta$_2$-agonists given by nebulization or multiple doses of aerosol MDI or DPI. Continuous nebulization or repeated doses may be useful in severe attacks (9). The recent outbreak of severe acute respiratory syndrome (SARS) due to coronavirus has prompted a change in hospital practice of nebulization to spacer device in some places in Asia (see Chapter on SARS). The addition of anti-cholinergic drugs in a significant exacerbation has been shown to improve the magnitude and duration of bronchodilation or to reduce hospital admission (62,63).

When there is indication that asthma control deteriorates, self management plans suggest that subjects should increase, usually double, the dose of ICS (9), although there is no good evidence for this dosage nor its efficacy in preventing the full exacerbation. However, in those attending emergency departments for acute asthma, studies have shown that giving high doses of ICS may prevent relapse following discharge (64), or help early recovery and decrease need of hospitalization (65).

It is advocated that systemic steroids be given early in the course of an acute attack, as they can prevent progression of severity of the attack, decrease the need for emergency room visit or hospital admission, and reduce early relapse (9). Depending on severity, oral or intravenous route may be used, and it has been shown that the oral route is as effective as the intravenous route. The exact benefits of adding ICS in those already given systemic steroids have not been clarified, although one would surmise that early introduction or increase of ICS may allow better control after stopping the short course of systemic steroids.

The use of intravenous aminophylline in acute attacks has become less popular since inhaled bronchodilators are often effective and relatively safe even in large doses. Systematic review of literature did not find evidence of additional benefit of intravenous aminophylline compared to standard care with beta$_2$-agonists in adults, and side-effects are increased (66). There has been a study that demonstrated some benefit of aminophylline in children who are not responding to large doses of

inhaled beta$_2$-agonists, inhaled ipratropium and intravenous steroids (67). Toxicity of methylxanthines is anticipated to be higher in ill patients on multiple medications and loading doses should not be given in those who have been taking maintenance oral theophyllines.

In patients who do not respond to initial treatment in the emergency department, intravenous magnesium sulphate may be considered (68).

Oxygen supplement should always be given if available in those who are hypoxaemic. High flow rates of oxygen should be given if indicated.

Most of the asthmatic exacerbations are not related to bacterial infections, and antibiotics should not be "routinely" given (9). Mucolytics have not been shown to be of benefit although patients often request to have treatment for viscous sputum which is indicative of underlying airways inflammation.

Intubation and mechanical ventilation remain the final treatment option for very severe acute asthma refractory to drug treatment. The role of non-invasive ventilation in acute asthma has not been established since the airway pressure in acute severe asthma is usually very high. Non-invasive ventilation is mainly used in subjects who do not have severe asthma and whose respiratory failure is due to underlying COPD or restrictive lung disease.

Environmental Control

The most common factors affecting asthma patients include allergens, respiratory irritants and viral infections. Allergens and irritants are encountered both indoors and outdoors.

Indoor aeroallergens

Indoor aeroallergens are the most important risk factors responsible for asthma (69,70), and the most common are house dust mite, pets (cat and dog) and cockroaches. Numerous studies have demonstrated the relation between the risk of sensitization and the level of exposure to allergen (71,72). Atopic subjects tend to be sensitized to house dust mite allergen at a lower level than nonatopic subjects. Thus it is important to reduce exposure to these allergens as much as possible by avoidance measures.

In general, there are 3 approaches to control of exposure to indoor allergens (73):

1. control of reservoirs of allergen in beds, carpets, furnishings, and clothing which are the main source of exposure;
2. control of source of new allergens; and
3. direct control of aeroallergens.

A combination of effective measures directed at different sites is required.

House dust mites

House dust mites live on human dander and proliferate best in hot and humid climates. The allergens are present mainly in the fecal pellets. They are present in high concentrations among mattresses, duvets, soft furnishing, and clothing. Mite allergens, after dust disturbance, are mainly associated with large particles (> 10 μm diameter) (74); only 10 to 20% of the allergens remain airborne 15 minutes after disturbance. Thus measurement of airborne dust mite allergen has not been very successful and dust mite allergen level has been estimated from settled dust samples. The current method of expressing allergen exposure, μg allergen/gm dust, is practical for epidemiologic studies, but has limited value in relating symptoms to exposure.

Table 1 shows the measures of reducing mite allergen levels from different places in the home (75). For bedding, the most effective method is to use an impermeable mattress cover and to wipe the encasing each week with a damp cloth to remove any allergen. Pillows, blankets, and duvets should be encased or washed very regularly with hot water (temperature > 130°F).

Carpets are major reservoirs of many indoor allergens. Carpets yield more dust on vacuuming and have a higher concentration of allergen in the dust samples than those collected from smooth floors. There is no way of rendering a carpet completely free of allergen. The use of acaricides such as tannic acid and benzyl benzoate has not been proven to be useful on a long-term basis.

Hard surface cleaning with a damp cloth can remove about 90% of allergens. Damp dusting should be done at least once a week. Vacuum cleaning is useful to remove excess dust and to

Table 1. Recommended Avoidance Measures for Mite Allergens[73]

Beds
- Mattress: encasement with vapour impermeable vinyl cover
- Blankets/duvets: encasement or washing every 1 to 2 months in water greater than 130° F to kill mites; remove allergen by washing
- Pillows: encasement

Floor
- No fitted carpets
- Smooth floors cleaned by damp mopping
- Loose rugs: 3 hours direct sunlight kill mites

Soft furnishings
- Replace with furniture that can be cleaned easily

Clothing
- Wash regularly

Acaricides
- Not recommended for long term use

Mechanical devices
- Vacuum cleaners: use good air filter and double thickness bags
- Air filters: minor role

House design
- To ensure a dry indoor climate

reduce reservoirs of allergens. To be effective, vacuum cleaners should have good air filters and have a double layer of bags for collecting dust. Air cleaning alone with devices has not been proven to be effective. Mite allergens settle quickly after disturbance and are not affected by an air filtering device at a distance.

Although it is likely that house dust mite allergen levels are high in many homes in Asian countries, studies on effectiveness of avoidance measures have not been carried out.

Pet allergen

Cat and dog allergens can be detected in almost all houses, even in those without the animals in many communities (76). Cat allergen is found in small particles < 5 μm and a high proportion remains airborne after disturbance (77). The allergen is being carried on people's clothing from homes to public places and schools (77). The only way to reduce exposure to cat allergen is to remove and relocate the cat. When cats are removed from rooms, allergen levels drop by 70% and when they are removed permanently, the levels in reservoirs decline slowly over months and years. This can be accelerated by removing the reservoirs such as contaminated carpets, rugs and soft furnishing. A combined strategy of washing the cat, washing the hard flooring and increasing air filtration has been found to be helpful in reducing exposure (78).

Because of overcrowding in most Asian cities, a smaller proportion of homes has pets (79). Again, there have not been studies carried out to assess the degree of compliance in giving up pets.

Cockroach allergen

Cockroach allergy has been found to be strongly associated with asthma in studies of inner-city population in the United States and in France (80,81). Cockroach allergens are found in most settled dust especially in kitchens. It is difficult to reduce cockroach allergen except by extermination with insecticides and meticulous house keeping and cleaning (82).

There are very few studies on the role indoor aeroallergens on asthma in Asian countries with very few exceptions (see chapter on Asthma

Table 2. Recommended Avoidance Measures for Furred Pet Allergens[74]

Control source
- Eviction of pets from home
- Confine animal outdoors
- Confining animals to certain parts of the home usually does not work
- Allergen is very persistent after eviction of animals; aggressive cleaning and removal of contaminated items required

Washing of pets
- Allergen returns to cats within days
- Wash cat-contaminated clothing regularly is better than washing the cat.

Control of reservoir
- Bed: encasing and wash;
- Furnishing: use those that can be cleaned
- Carpets: remove
- Clothing: wash regularly

Mechanical device
- Air filters more useful because cat allergen remains airborne for longer time

Epidemiology). As the findings of studies done in western countries may not be applicable to Asian countries, researchers are encouraged to collect data in their own locality.

Outdoor aeroallergens

The most important outdoor aeroallergens include pollen and moulds (83). During pollen or mould season, it is advisable for patients with asthma or rhinitis to remain indoors and to close windows and doors.

Outdoor air pollution

Outdoor air pollutants such as respirable particles, oxides of nitrogen, sulphur dioxide and ozone may exacerbate asthma. In many industrialized countries, considerable efforts have been made in reducing industrial air pollution. However, at present, in many major cities in industrialized or developing countries, traffic pollution becomes a major problem. Increase in air pollution has been found to be associated with increase in mortality and morbidity from asthma, other respiratory and cardiovascular diseases (84). Diesel exhaust from traffic pollution is responsible for a high proportion of fine particles, which are most harmful (84). Exposure to diesel particles has been associated with increase in respiratory symptoms and sensitization to allergens. There should be concerted efforts from both governments and citizens to reduce air pollution from both industrial and traffic pollution by using energy sources other than fossil fuels.

Indoor air pollution

Indoor irritants such as environmental tobacco smoke, are health risks (85). Every effort should be made to reduce exposure of asthmatics (particularly children) to environmental tobacco smoke by making at least the home a smoke-free place. Parents and other caregivers, if they cannot give up smoking, should refrain from smoking inside the home or in the presence of the children when outside.

Food allergy

Manifestations of food allergy are mostly on the skin giving rise to atopic dermatitis, urticaria or in the gastrointestinal tract giving rise to abdominal colic, nausea, vomiting or diarrhea. Food allergy

may present as angioedema of the larynx causing difficulty in breathing. Some patients complain that alcohol aggravates asthma. Avoidance of food to which the patient is allergic is essential in the management of asthma.

Aspirin sensitivity

About 15% of patients with nonallergic adult-onset asthma give a history of aspirin sensitivity and sinusitis. Sensitivity to aspirin can lead to severe anaphylaxis and severe asthma. The pathogenesis of aspirin induced asthma is not entirely clear. Recent studies suggest that it is due to continued and relentless formation of arachidonate products (86). Patients who are sensitive to aspirin may also be sensitive to other nonsteroidal anti-inflammatory drugs (NSAID). Thus avoidance of NSAID drugs is recommended.

A program of desensitization has been carried out in aspirin sensitive subjects with significant improvement of nasal symptoms, better control of asthma and reduce requirement of oral steroids (86). Leukotriene antagonists have been found to be useful in patients with aspirin sensitivity (46).

Exercise induced asthma

It is important to keep patients as active as possible. In patients with exercise induced asthma, the best method of prevention is to keep asthma under good control. The use of beta$_2$-agonist before exercise has been recommended to prevent exercise-induced bronchoconstriction.

Prevention

The ideal way to prevent a disease is to prevent its onset (primary prevention). If not possible, the next aim is to induce remission (secondary prevention). Finally in those with persisting chronic disease, the aim is directed at reducing the severity of disease and avoiding severe adverse outcomes (tertiary prevention).

Primary prevention

So far, there have been only 2 published randomized controlled trials of allergen avoidance in the primary prevention of asthma (87,88). In the Isle of Wight study (87), intervention measures of food and dust mite avoidance were applied at birth on high-risk infants (those with history of asthma or allergies among the first-degree relatives). A significant reduction in "asthma" was found during the 12 months of life; however, the difference in the incidence of asthma between the intervention and the control group was no longer significant at 2 years of life (89) In the study conducted in Japan (90) high-risk infants were identified on the basis of early manifestation of atopy and then randomized into two groups with one group receiving house dust mite avoidance measures. Significant reductions in house dust mite sensitization and incidence of wheezing episodes were found in the intervention group at one-year follow-up. Several such trials are still in progress (91–93).

It should be pointed out that it is very difficult to make a diagnosis of asthma in infants at one or two years of age because wheeze can occur with viral infections in infants in this age group and may not be due to asthma. Only long-term follow-up studies of these cohorts can determine the effectiveness of allergen avoidance in the primary prevention of asthma.

Secondary prevention

It has been shown that between 30 to 70% of children with asthma or wheezing illness in childhood would experience remission during adolescence (75). It is not known whether any therapeutic intervention can improve the chance of remission. Long-term clinical trials of allergen avoidance or the use of ICS have not yet been carried out for secondary prevention in asthma.

Tertiary prevention

At present, most of the measures directed towards asthma prevention are tertiary, i.e. preventing acute exacerbation of asthma. The most important

measure for tertiary prevention is to control asthma well with appropriate use of medications, educate patients how to use these medications and the reasons for doing so and how to increase or reduce medications according to the severity of asthma. The triggering factors for asthma attacks and the appropriate measures to reduce exposure should be identified, if at all possible, for each patient. There have been many studies of house dust mite avoidance resulting in improvement in asthma control in both children and adults (75).

Patient Education

In the management of asthma, education of patient is mandatory. The goal of education is control of asthma by increasing patients' knowledge and thereby changing the behaviour and improving self-management skills of the patients. Asthma education is effective only in the presence of effective asthma therapy and should be provided at each patient contact.

Patients should learn how to take medications correctly, understand the differences between "quick-relief" and "long-term preventive" medications, avoid triggers, monitor their own status using symptoms, recognize signs that asthma is worsening and take action, and to seek medical help as appropriate.

Self-management plan

Many asthma treatment guidelines have included self-management action plans which give specific instructions for patients to increase or initiate medications based on changes in symptoms or in PEFR (94–99). Many studies have demonstrated the usefulness of asthma self-management plan in reducing health care utilization (hospitalization, emergency room visits and unscheduled visits to doctors for asthma treatment), improving quality of life, reducing courses of oral steroids and improving lung function (100–103).

A written asthma action plan should be prepared with the patient with the following information:

1. the daily medication to take — list the names and doses of bronchodilators and steroids
2. how to recognize and treat worsening asthma — when to increase medications and by how much.
3. how and when to seek medical attention — list indicators such as PEFR reading below a specified value, shortness of breath at rest; list the name, telephone number of the physician or clinic.

Guidelines for Asthma Management — An Asian Perspective

Many countries have established their own guidelines for management of asthma (95,97–99). In 1992, the National Heart, Lung and Blood Institute and the World Health Organization established the Global Initiatives for Asthma (GINA) (104). An international panel was established to determine a global strategy for asthma management and prevention including guidelines for asthma management, which have been since then periodically updated (9). The workshop report has been translated into many languages and disseminated to many parts of the world including many Asian countries where the GINA guidelines were modified and adapted for use (105). The differences of the individual guidelines lie mainly in the prioritization of use of standard medications.

In China, as early as 1992, many doctors in Shanghai, Guangzhou, Beijing and other cities have adapted and adopted the GINA guidelines (105). The asthma education program for the medical profession and for the public has improved asthma care in China. One of the key strategies for asthma management in the GINA guidelines is the use of inhaled steroids. Although more and more physicians and paediatricians have accepted this therapy in China, the proportion of patients receiving ICS was is far less than that in western countries. Inhaled steroids only constituted 19% of total sales of anti-asthmatic drugs while in Canada it was 51% in the same year. The reasons for not using steroids were as follows:

1. patients prefer oral medications and they believe that inhaled medications are only used in severe situations;
2. inhaled steroids are ineffective because of poor inhalation techniques;

3. inhaled steroids are ineffective because it takes two to three weeks for maximal effects;
4. inability in obtaining inhaled steroids from hospital pharmacies;
5. the high cost of the drug.

The latter is a major impediment since the annual income of many people in China is still very low (annual GDP in 1995 < 765 USD) and cannot afford inhaled steroids. Theophylline in combination with low dose inhaled steroids has been found to be effective and as a result, theophylline has been introduced into the guidelines for the management of asthma in China.

A recent study regarding asthma symptoms, healthcare utilization and management has been conducted in 8 areas in Asia, including China, Hong Kong, Korea, Malaysia, Philippines, Singapore, Taiwan and Vietnam (Asthma insights and reality in Asia-Pacific, AIRIAP) (106). Of the 3207 subjects with physician-diagnosed asthma, daytime symptoms and sleep disturbances in the past four weeks were reported by about half of the subjects. Unscheduled healthcare visits, including emergency room visits and hospitalization, has occurred in at least 44% of subjects in the past 12 months. There were significant differences among the various places with the highest rate in Hong Kong at 82%. Even in those with severe persistent asthma, a third of them regarded their disease as being well or completely controlled. The findings confirmed the impression that overall asthma control in many communities in Asia is suboptimal.

The use of ICS or other preventive medications was lower than that recommended by international guidelines for the degree of asthma severity based on the reported symptoms, and the underuse was particularly apparent in those with severe persistent asthma. The overall rate of ICS use at 3.6% was lower than that reported by Europeans at 23% (107) and similar to that in USA (108). Again the pattern of ICS drug usage varied among countries, with the highest in Taiwan (26.3%) and lowest in Korea (1.2%). Reasons for failure to follow physicians' instructions on medications were similar to those reported previously, including fear of side effects, concern over long term use, lack of immediate effect, lack of effective over time, lack of symptoms and cost.

The study also showed a general lack of patient knowledge about the nature of asthma and the drugs, a low utilization of lung function testing with only one third of the subjects having had a spirometry done in the past year, and a very low knowledge of peak flow monitoring.

A similar study in Japan has reported similar findings (109). It demonstrated that over half of the patients had persistent symptoms and 60–70% had some limitation of activities of daily life, with a large gap between subjective perception of asthma and objective findings in those with severe asthma. There was a very low knowledge of the disease nature of asthma, and the use of ICS was low at 12% in adults and 5% in children. 50% of adults and only 20% of children reported ever having undergone any lung function test.

A recent report from Thailand on asthma management in children also observed underuse of objective assessment measure, frequent use of theophylline and antibiotics and late introduction of systemic corticosteroids in acute asthma (110). Preference for oral $beta_2$-agonists and theophyllines as bronchodilators, and preference for ketotifen as the preventive medication were noted (110).

In summary, asthma management has evolved globally over the past two decades, with emphasis on patient education of the various aspects of asthma, use of inhaled medications, emphasis on the use of preventive medications, and the use of new drugs such as long acting $beta_2$-agonists and leukotriene antagonists as well as combined drug preparations. Such practices have been adapted and adopted by many countries in Asia, even though they may not yet be fully compliant with international recommendations. Improved outcome in morbidity and mortality have been attributable to such management changes (105,111–114). It should be noted, however, that much less attention has been placed on environmental control in Asian countries compared to Western countries to prevent acute exacerbations (115). Outdoor air pollution and indoor air pollution due to environmental tobacco smoke are major problems in many Asian urban cities.

Adherence to international recommendations is more prevalent in teaching hospitals or specialist practice than district hospitals or general practice (116,117). Asthma, being a very common disease, is often treated and followed up by general

practitioners. It is imperative that dissemination and promotion of update information on asthma management should be carried out widely among various sectors of the profession (118). Cost is a major factor that hinders the use of some medications that are considered to be highly recommended by international consensus – eg. the higher cost of inhaled medications compared to their oral counterparts, preventive medications compared to relievers, DPIs and HFA MDIs compared to traditional MDIs. The high cost of new drugs and limited healthcare budget are very important issues in the Asian region (119). It remains the task of the healthcare profession to lobby the government as well as the industry to make the drugs more available to asthmatics as better control of asthma has been shown to reduce both the direct and the indirect cost of asthma care.

References

1. Irwin RS, Madison JM. The persistently troublesome cough. *Am J Respir Crit Care Med* 2002; 165:469–74.
2. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. *Am Rev Respir Dis* 1991; 144:1202–18.
3. Sawyer G, Miles J, Lewis S, Fitzharris P, Pearce N, Beasley R. Classification of asthma severity: should the international guidelines be changed? *Clin Exp Allergy* 1998; 28:1565–70.
4. Eid N, Yandell B, Howell L, Eddy M, Sheikh S. Can peak expiratory flow predict airflow obstruction in children with asthma? *Pediatrics* 2000; 105:354–8.
5. Quanjer PH, Lebowitz MD, Gregg I, Miller MR, Pederson OF. Peak expiratory flow: conclusions and recommendations of a Working Party of the European Respiratory Society. *Eur Respir J* 1997; 24(suppl):2S–8S.
6. National Asthma Education and Prevention Program. Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 1997. www.nhlbi.nih.gov
7. Cockcroft DW, Hargreave FE. Airway hyperresponsiveness. Relevance of random population data to clinical usefulness. *Am Rev Respir Dis* 1990; 142:497–500.
8. O'Byrne P. Bronchial challenges by pharmacologic agents. In: Clark TJH, Godfrey S, Lee TH, Thomson NC, eds. *Asthma,* 4th edition. London: Arnold; 2000. p.92–103.
9. GINA. www.ginasthma.com
10. Cheung D, Timmers MC, Zwinderman AH, Bel EH, Dijkman JH, Sterk PJ. Long-term effects of a long-acting beta 2-adrenoceptor agonist, salmeterol, on airway hyperresponsiveness in patients with mild asthma. *N Engl J Med* 1992; 327:1198–203.
11. Nelson JA, Strauss L, Skowronski M, Ciufo R, Novak R, McFadden ER Jr. Effect of long-term salmeterol treatment on exercise-induced asthma. *N Engl J Med* 1998; 330:141–6.
12. Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF Jr, Sorkness CA, et al. Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomised controlled trial. *JAMA* 2001; 285:2583–93.
13. Lemanske RF Jr, Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV, et al. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. JAMA 2001; 285:2594–603.
14. Kips JC, O'Conner BJ, Inman MD, Svensson K, Pauwels RA, P'Byrne PM. *Am J Respir Crit Care Med* 2000; 161:996–1001.
15. Pauwels RA, Lofdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med* 1997; 337:1405–11.
16. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Allen & Hanburys Limited UK Study Group. *Lancet* 1994; 344:219–24.
17. Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. *Am J Respir Crit Care Med* 1996; 153:1481–8.

18. Tattersfield AE, Lofdahl CG, Postma DS, Eivindson A, Schreurs AG, Rasidakis A, et al. Comparison of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial. *Lancet* 2001; 357:257–61.
19. Kidney J, Dominguez M, Taylor PM, Rose M, Chung KF, Barnes PJ. Immunomodulation by theophylline in asthma. Demonstration by withdrawal of therapy. *Am J Respir Crit Care Med* 1995; 151:1907–14.
20. Sullivan P, Bekir S, Jaffar Z, Page C, Jeffrey P, Costello J. Anti-inflammatory effects of low-dose oral theophylline in atopic asthma. *Lancet* 1994; 343:1006–8.
21. Weinberger M, Hendeles L. Theophylline in asthma. *N Engl J Med* 1996; 334:1380–8.
22. Mash B, Bheekie A, Jones PW. Inhaled vs oral steroids for adults with chronic asthma. *Cochrane Database Syst Rev* 2000; 2.
23. Haahtela T, Jarvinen M, Kava T, Kiviranta K, Koshinen S, Lehtonen K, et al. Comparison of a beta 2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991; 325:388–92.
24. Barnes PJ, Pederson S, Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. *Am J Respir Crit Care Med* 1998; 157:S1–53.
25. The Children Asthma Management Program Research Group. Long term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000; 343:1054–63.
26. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000; 343:332–6.
27. Jeffery PK, Godfrey RW, Adelroth E, Nelson F, Rogers A, Johansson SA. Effects of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma. A quantitative light and electron microscopic study. *Am Rev Respir Dis* 1992; 145:890–9.
28. Djukanovic R, Wilson JW, Britten KM, Wilson SJ, Walls AF, Roche WR, et al. Effect of an inhaled corticosteroid on airway inflammation and symptoms in asthma. *Am Rev Respir Dis* 1992; 145:669–74.
29. Gibson PG, Saltos N, Fakes K. Acute anti-inflammatory effects of inhaled budesonide in asthma: a randomized controlled trial. *Am J Respir Crit Care Med* 2001; 163:32–6.
30. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systemic review and meta-analysis. *Arch Intern Med* 1999; 159:941–55.
31. Selroos O, Halme M. Effect of a volumatic spacer and mouth rinsing on systemic absorption of inhaled corticosteroids from a metered dose inhaler and dry powder inhaler. *Thorax* 1991; 46:891–4.
32. Brown PH, Greening AP, Crompton GK. Large volume spacer devices and the influence of high dose beclomethasone dipropionate on hypothalamo-pituitary-adrenal axis function. *Thorax* 1993; 48:233–8.
33. Ribeiro LB. Budesonide: safety and efficacy aspects of its long-term use in children. *Pedoatr Allergy Immunol* 1993; 4:73–8.
34. Tattersfield AE, Town GI, Johnell O, Picado C, Aubier M, Braillon P, Karlstrom R. Bone mineral density in subjects with mild asthma randomized to treatment with inhaled corticosteroids or non-corticosteroid treatment for two years. *Thorax* 2001; 56:272–8.
35. Silverstein MD, Yunginger JW, Reed CE, Petterson T, Zimmerman D, Li JT, et al. Attained adult height after children asthma: effect of glucocorticoid therapy. *J Allergy Clin Immunol* 1997; 99:466–74.
36. Agertoft L, Pederson S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med* 2000; 343:1064–9.
37. Devalia JL, Rusznak C, Abdelaziz MM, Davies RJ. Nedocromil sodium and airway inflammation in vivo and in vitro. *J Allergy Clin Immunol* 1996; 98:S51–7.
38. Edwards AM. Sodium cromoglycate (Intal) as an anti-inflammatory agent for the treatment of chronic asthma. *Clin Exp Allergy* 1994; 24:612–23.
39. Salvi SS, Krishna MT, Sampson AP, Holgate ST. The anti-inflammatory effects of leukotriene-modifying drugs and their use in asthma. *Chest* 2001; 119:1533–46.
40. Lipworth BJ. Leukotriene-receptor antagonists. *Lancet* 1999; 353:57–62.
41. Drazen JM, Israel E, O'Byrne PM. Treatment of asthma with drugs modifying the leukotriene pathway. *NEJM* 1999; 340:197–206.
42. Lofdahl CG, Reiss TF, Leff JA, Israel E, Noonan MJ, Finn AF, et al. Randomised, placebo controlled trial of effect of a leukotriene receptor antagonist, montelukast, on tapering inhaled corticosteroids in asthmatic patients. *BMJ* 1999; 319:87–90.

43. Virchow JC, Prasse A, Naya I. Summerton L, Harris A. Zafirlukast improves asthma control in patients receiving high-dose inhaled corticosterids. *Am J Respir Crit Care Med* 2000; 162:578–85.
44. Busse W, Nelson H. Wolfe J, Karlberg C, Yancey SW. Rickard KA. Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma. *J Allergy Clin Immunol* 1999; 103:1075–80.
45. Robinson DS, Campbell D, Barnes PJ. Addition of leukotriene antagonists to therapy in chronic persistent asthma: a randomised double-blind placebo-controlled trial. *Lancet* 2001 357:2007–11.
46. Dahlen SE, Malmstrom K, Nizankowska E. Dahlen B, Kuno P, Kowalski M, Lumry WR, Picado C, Stevenson DD, Bousquet J, Pauwels R. Holgate ST, Shahane A. Zhang J. Reiss TF, Szczeklik A. Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist: a randomised, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med* 2002; 165:9–14.
47. Grant JA, Nicodemus CF, Findlay SR, Glovsky MM, Grossman J, Kaiser H, et al. Cetirizine in patients wit h seasonal rhinitis and concomitant asthma: prospective, randomised, placebo-controlled trial. *J Allergy Clin Immunol* 1995; 95:923–32.
48. Davies H, Olson L, Gibson P. Methotrexate as a steroid sparing agent for asthma in adults. *Cochrane Database Syst Rev* 2000; (2):CD00391.
49. Lock SH, Kay AB, Barnes NC. Double-blind placebo-controlled study of cyclosporin A as a corticoseteroid-sparing agent in corticosteroid -dependent asthma. *Am J Respir Crit Care Med* 1996; 153:509–14.
50. Bernstein IL, Bernstein DI, Dubb JW, Faiferman I, Wallin B. A placebo-controlled multicenter study of auranofin in the treatment of patients with corticosteroid-dependent asthma. Auranofin Multicenter Drug Trial. *J Allergy Clin Immunol* 1996; 98:317–24.
51. Siracusa A, Brugnami G, Fiordi T, Areni S, Severini C, Marabini A. Troleandomycin in the treatment of difficult asthma. *J Allergy Clin Immunol* 1993; 92:677–82.
52. Abramson M, Puy R, Weiner J. Immunotherapy in asthma: an updated systematic review. *Allergy* 1999; 54:1022–41.
53. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *J Alergy Clin Immunol* 1998; 102:558–62.
54. Pavia D. Efficacy and safety of inhalation therapy in chronic obstructive pulmonary disease and asthma. *Respirology* 1997; 2(suppl 1):S5-S10.
55. Ramsdale JW, Klinger NM, Ekholm BP, Colice GL. Safety of long term treatment with HFA albuterol. *Chest* 1999; 115:945–51.
56. Gross G, Thompson PJ, Chervinsky P, Burgt JV and the Study Group. Hydrofluoroalkane-134a beclomethasone dipropionate, 400 mg, is an effect as chlorofluorocarbon beclomethasone dipropionate, 800 mg, for the treatment of moderate asthma. *Chest* 1999; 115:343–51.
57. Davis PA, Gold EB, Hackman RM, Stern RM, Gershwin ME. The use of complementary/alternative medicine for the treatment of asthma in the United States. *J Investig Allergol Clin Immunol* 1998; 8(2):73–7.
58. Huntley A, Ernst E. Herbal medicines for asthma: a systemic review. *Thorax* 2000; 55(11):925–9.
59. Linde K, Jobst K, Panton J. Acupuncture for chronic asthma. Cochrane Database Syst Rev 2000; (2):CD000008.
60. Linde K, Jobst KA. Homeopathy for chronic asthma. *Cochrane Database Syst Rev* 2000; (2):CD000353.
61. Hondras MA, Linde K, Jones AP. Manual therapy for asthma. *Cochrane Database Syst Rev* 2000; (2):CD001002.
62. Garrett JE. Combined anticholinergic therapy in the management of acute asthma. *Respirology* 1997; 2:S17–S18.
63. Rodrigo G, Rodrigo C, Burschintin O. A meta-analysis of the effects of ipratropium bromide in adults with acute asthma. *Am J Med* 1999; 107:363–70.
64. Rowe BH, Bota GW, Fabris L, Therrien SA, Milner RA, Jaono J. Inhaled budesonide in addition to oral coricosteroids to prevent asthma relapse following discharge from the emergency department: a randomized controlled trial. *JAMA* 1999; 281:2119–26.
65. Singhi S, Nanerjee S. Nanjundaswamy H. Inhaled budesonide in acute asthma. *J Paediatr Child Health* 1999; 35:483–7.
66. Parameswaran K, Belda J, Rowe BH. Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma. *Cochrane Database Syst Rev* 2000; (4):CD002742.
67. Yung M, South M. Randomised controlled trial of aminophylline for severe acute asthma. *Arch Dis Child* 1998; 79:405–10.
68. Rowe BH, Bretzlaff JA, Bourdon C. Bota GW, Camargo CA Jr. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. *Cochrane Database Syst Rev* 2000; (2):CD001490.

69. Gelber L, Seltzer L, Bouzoukis J, Pollart S, Chapman M, Platts-Mills T. Sensitization and exposure to indoor allergens as risk factors for asthma patients presenting to hospital. *Am Rev Respir Dis* 1993; 147:573–578.
70. Platts-Mills TA E., Vervlet D, Thomas WR, Aalberse RC, Chapman MD. Indoor allergens and asthma: Report of the third international workshop. *J Allergy Clin Immunol* 1997; 100:S1–S24.
71. Lau S, Falkenhorst G, Weber A, Werthmann I, Lind P, Buettner-Goetz P, Wahn U. High mite-allergen exposure increases the risk of sensitization in atopic children and young adults. *J Allergy Clin Immunol* 1989; 84:718–25.
72. Peat JK, Tovey E, Toelle BG, Haby MM, Gray EJ, Mahmic A, Woolcock AJ. House dust mite allergens. A major risk factor for childhood asthma in Australia. *Am J Respir Crit Care Med* 1996; 153:141–6.
73. Tovey E, Marks G. Methods and effectiveness of environmental control. *J Allergy Clin Immunol* 1999; 103:179–91.
74. Platts-Mills TA E, Heymann PW, Longbottom JL, Wilkins S. Airborne allergens associated with asthma: Particle sizes carrying dust mite and rat allergens measured with a cascade impactor. *J Allergy Clin Immunol* 1986; 77:850–7.
75. Eggleston PA, Bush RK. Environmental allergen avoidance: an overview. *J Allergy Clin Immunol* 2001; 107:S403–5.
76. Quirce S, Dimich-Ward H, Chan H, Ferguson A, Becker A, Manfreda J, Simons E, Chan-Yeung M. Major cat allergen (Fel d1) in the homes of patients with asthma and their relationship to sensitization to cat dander. *Ann Allergy Asthma Immunol* 1995; 75:325–30.
77. Munir AK M, Einarsson R, Schou C, Dreberg SK G. Allergens in school dust. I. The amount of the major cat (Fel d1) and dog (Can f1) allergens in dust from Swedish schools is high enough to probably cause perennial symptoms in most children with asthma who are sensitized to cat and dog. *J Allergy Clin Immunol* 1993; 91:1067–74.
78. Wood RA, Johnson EF, Can Natta ML, Chen PH, Eggleston PA. A placebo-controlled trial of a HEPA air cleaner in the treatment of cat allergy. *Am J Respir Crit Care Med* 1998; 158:115–20.
79. Leung R, Lam WK, Chan A, Lee M, Chan HS, Pang SW, Lai CK W. Indoor environment of residential homes in Hong Kong — relevance to asthma and allergic disease. *Clin Exp Allergy* 1998; 28:585–90.
80. Sarpong SB, Hamilton RG, Eggleston PA, Adkinson NF. Socioeconomic status and race as risk factors for cockroach allergen exposure and sensitization in children with asthma. *J Allergy Clin Immunol* 1996; 97:1393–401.
81. Eggleston PA, Wood RA, Rand C, Nixon J, Chen PH, Luk P. Removal of cockroach allergen from inner city homes. *J Allergy Clin Immunol* 1999; 104:842–6.
82. Eggleston PA, Arruda LK. Ecology and elimination of cockcroaches and allergens in the home. *J Allergy Clin Immunol* 2001; 107:S422–9.
83. Hyde H. Atmospheric pollen grains and spores in relation to allergy. Clin Allergy 1972; 3:109–126.
84. World Health Organization. Guidelines for air quality. WHO, Geneva 1999. www.who.int/peh/air/aorguides2.htm.
85. Samet JM, Marbury MC, Spengler JD. Health effects and sources of indoor air pollution, Part I. *Am Rev Respir Dis* 1987; 136:1486–508.
86. Stevenson D. Aspirin-sensitive asthma. In: *Asthma.* Eds. Barnes PJ, Grunestein WM, Leff A, Woolcock AJ. Philadelphia: Lippincott-Raven, 1997, 2025–40.
87. Arshad SH, Matthews S, Gant C, Hide DW. Effect of allergen avoidance on development of allergic disorders in infancy. *Lancet* 1992; 339:1439–97.
88. Chan-Yeung M, Manfreda J, Dimich-Ward H, Ferguson A, Watson W, Becker A. A randomized clinical trial on the effectiveness of a multifaceted intervention measures in the primary prevention of asthma in high risk infants. *Arch Pediatr Adolescent Med* 2000; 154:657–63.
89. Hide D, Matthews S, Matthews L, Stevens M, Rideout S, Twiselton R, Gant C, Arshad S. Effect of allergen avoidance in infancy on allergic manifestations at age of two years. *J Allergy Clin Immunol* 1994; 93:842–6.
90. Nishioka K, Yasueda H, Saito H. Preventive effect of bedding encasement with microfine fibers on mite sensitization. *J Allergy Clin Immunol* 1998; 101:28–32.
91. Hide D, Matthews S, Matthews L, Stevens M, Rideout S, Twiselton R, Gant C, Arshad S. Effect of allergen avoidance in infancy on allergic manifestations at age of two years. *J Allergy Clin Immunol* 1994; 93:842–6.

92. Custovic A, Simpson BM, Simpson A, Woodcock A, Low allergen environment can be achieved and maintained throughout pregnancy and in early life. *J Allergy Clin Immunol* 1998; 101(suppl):S81.
93. Frederick JM, Gill LS, Warner JO, Colwell BM, Warner JA. Allergen avoidance in the homes of asthmatic patients during pregnancy. *J Allergy Clin Immunol* 1998; 101 (suppl):S26.
94. Beasley R, Cushley M. Holgate ST. A self-management plan in the treatment of adult asthma. *Thorax* 1989; 44:200–4.
95. British Thoracic Society Research Unit of the Royal College of Physicians of London. Guidelines for management of asthma in adults: I- chronic persistent asthma. *BMJ* 1990; 301:651–3.
96. Clark NM. Asthma self-management education: research and implications for clinical practice. *Chest* 1989; 95:1110–3.
97. Canadian asthma consensus report: Summary of recommendations. *CMAJ* 1999; 161(11 suppl):S1–S12.
98. National Asthma Education Program EP Report: Guidelines for the diagnosis and management of asthma. Statement on technical standards for peak flow meters. National Institute of Health, National Heart, Lung and Blood Institute. January 1991.
99. Woolcock A, Rubinfeld A, Seale J, et al. Asthma management plan. *Med J Aust* 1989; 151:650–3.
100. Ignacio-Garcia JM, Gonzalez-Santos P. Asthma self-management education program by home monitoring of peak expiratory flow. *Am J Respir Crit Care Med* 1995; 151:353–9.
101. Lahdensuo A HT, Herrala J, Kava T, Kiviranta K, Kuususto P, Peramaki E, Poussa T, Saavelainen S, Svahn T. Randomized comparison of guided self management and traditional treatment of asthma over one year. *BMJ* 1996; 312:748–52.
102. Charlton I, Charlton G BJ, Mullee M. Evaluation of peak flow and symptoms only self-management plans for control of asthma in general practice. *BMJ* 1990; 301:1355–9.
103. Grampian asthma study of integrated care (GRASSIC). Effectiveness of self monitoring of peak flow in patients with asthma. *BMJ* 1994; 308:564–7.
104. World Health Organization. Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention NHLBI/WHO Workshop Report. National Institutes of Health. January 1995.
105. Zhong NS. Adapting GINA guidelines for asthma management in China. International meeting of implementing GINA management strategies for asthma. Global initiative for asthma. 5–6 November 2000, Guangzhou, China.
106. Lai CKW, de Guia TS, Kim YY, Kuo SH, Mukhopadhyay Amartya, Soriano JB, Trung PL, Zhong NS. Zainudin N, Zainudin BMZ. Asthma control in Asia-Pacific: The asthma insights and reality in Asia-Pacific study. (Submitted)
107. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2002; 16:802–7.
108. Adams RJ, Fuhlbrigge A, Guilbert T, Lozano P, Martinez F. Inadequate use of asthma medication in the United States: Results of the Asthma in American national population survey. *J Allergy Clin Immuol* 2002; 110:58–64.
109. Adachi M, Morikawa A, Ishihara K. Asthma insights and reality in Japan (AIRJ). Arerugi 2002; 51:411–20.
110. Vichyanond P, Hatchaleelaha S, Jintavorn V, Kerdsomnuig S. How pediatricians manage asthma in Thailand. *Pediatr Pulmonol* 2001; 32:109–14.
111. Choy DK, Tong M, Ko F, Li ST, Ho A, Chan J, Leung R, Lai CK. Evaluation of the efficacy of a hospital-based asthma education programme in patients of low socio-economic status in Hong Kong. *Clin Exp Allergy* 1999; 29:94–90.
112. Kumana CR, Kou M, Luder IJ, Ip Mary SM, Lam WK. Increasing use of inhales steroids associated with declining asthma mortality. *Journal of Asthma* 2001; 38:161–7.
113. Hui SH. Leung TF. Ha G. Wong E, Li AM, Fok TF. Evaluation of an asthma management program for Chinese children with mild-to-moderate asthma in Hong Kong. *Pediatr Pulmonol* 2002; 33:22–9.
114. Ghosh CS, Ravindran P. Joshi M, Stearns SC. Reductions in hospital use from self management training for chronic asthmatics. *Soc Sci Med* 1998; 46(8):1087–93.
115. Ng TP. Adult asthma prevalence, morbidity and mortality and their relationships with environmental and medical care factors in Singapore. *Asian Pac J Allergy Immunl* 1999; 17(3):127–35.
116. Ip MSM. So SY, Lam CLK, Lam WK. Chan JCK, Tse MHW. Trends in asthma therapy in Hong Kong, 1987–1992. *Journal of Asthma* 1993; 30(6):475–83.

117. Lee PL, Luo JP, Shieh WM, Nien CT, Yang PC, Kuo SH. Hospital-based management of acute asthmatic exacerbation: an assessment of physicians' behavior in Taiwan. *J Asthma* 2001; 38:575–83.
118. Tan NC, Chow MH, Goh P, Goh LG, Lim TK. Primary care doctors' practice in the management of adult asthma patients. *Singapore Med J* 2002; 43:061–6.
119. Watson JP. Lewis RA. Is asthma treatment affordable in developing countries? *Thorax* 1997; 52:589.

3 Bronchiectasis

Kenneth Tsang, Clara Ooi and Mary Ip

Introduction

Bronchiectasis is defined pathologically as permanent dilatation of one or more bronchi. Although nicknamed as an "orphan" disease in the West, it is nevertheless a very common disease among the Chinese and other Orientals. The precise prevalence of bronchiectasis is not known, but it is likely to be under-diagnosed with many of the sufferers being erroneously diagnosed as suffering from COPD, particularly if they have been smokers.

Epidemiology

Following the epidemics of influenza and pertussis, bronchiectasis was a very common disease in the West after World War I. However, its incidence has declined in developed countries over the last few decades. In Hong Kong, bronchiectasis is a common disease. Hospital authority statistics show a hospital admission rate of about 32.9 per 100,000 of the population, and a mortality rate of on 1.95 per 100,000 population in 1997 (1). As most patients with bronchiectasis are managed as outpatients and many cases are under-diagnosed, the prevalence is likely to be under-estimated. Cystic fibrosis (CF), the commonest inherited lethal disease, is the predominant cause of bronchiectasis in Western countries, and afflicts about one in 2000–4500 live births in Caucasians. It is extremely uncommon in Chinese or other oriental populations.

Aetiology

The aetiology of bronchiectasis is diverse, and bronchiectasis is the final common path of a number of very different diseases. A recent study in Hong Kong showed that most patients, like their counterparts in the West, suffer from idiopathic bronchiectasis (2). Intensive investigation of patients with bronchiectasis revealed etiological factors, which have implications for prognosis or specific treatment, such as immunodeficiency, aspiration or ciliary defects, in 15% of patients (3). It is likely that in areas with high prevalence of pulmonary tuberculosis, which is less intensively treated, and where the use of antimicrobial agents is less liberal for severe lower respiratory tract infection, that post infective causes are more prominent. Some of the causes of bronchiectasis are listed in Table 1.

Post-infective

Infections such as tuberculosis, pertussis (whooping cough) and measles cause necrosis and weakening of the bronchial wall, and were

Table 1. Aetiology of Bronchiectasis[2]

Aetiology
Idiopathic
Congenital • Deficiency of bronchial wall elements • Pulmonary sequestration
Bronchial obstruction • Intrinsic (post-TB stenosis, foreign body, benign tumour etc) • Extrinsic (tumour or lymph node compression)
Gastroesophageal reflux
Granulomatous (TB etc)
Traction (pulmonary fibrosis of any cause including fibrosing alveolitis)
Immunodeficiency • Primary (panhypogammaglobulinaemia or selective immunoglobulin deficiency) • Secondary (AIDS or malignancy)
Diffuse panbronchiolitis
Primary ciliary dyskinesia (including Kartagener's syndrome)
Post-infective (pertussis, measles etc) and post-pneumonic (*Klebsiella pneumoniae, Staphylococcus aureus* etc)

common causes of bronchiectasis. However, with the introduction of vaccination and effective anti-tuberculous drugs, bronchiectasis is arising less frequently from these causes. Other infections include pneumonias caused by Klebsiella, Staphylococcus, and certain viruses.

Idiopathic

The majority of bronchiectasis in Hong Kong and the West are idiopathic in aetiology (2). In a series of 100 patients with bronchiectasis, 83% of patients suffer from idiopathic disease in Hong Kong (2). It is possible that an episode of infection has set the stage for development of bronchiectasis, although these patients can seldom recall a well-defined initial infective episode. It is highly probable that many patients develop idiopathic bronchiectasis via poorly understood immunological mechanisms (2,4–7). It is most likely that this large subgroup of patients will be further refined into subgroups of "known causes" when understanding in the pathogenesis advances.

Congenital causes

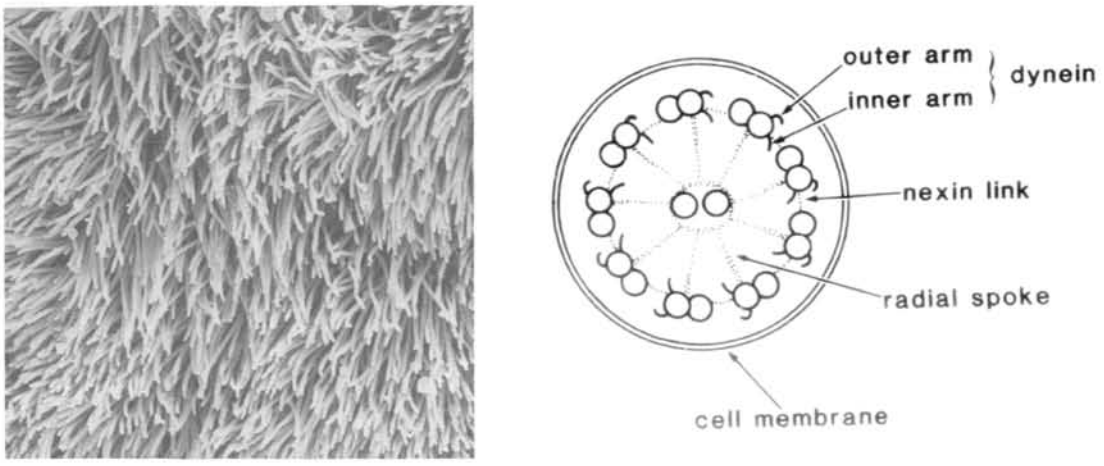
Cystic fibrosis

This genetic condition is the commonest cause of bronchiectasis in the West. Whilst this has been reported among Asians (Indians and Pakistanis), it is very infrequently encountered among the Chinese or other oriental ethnic groups. Bronchiectasis is the usual cause of death in these patients.

Primary ciliary dyskinesia

It has been recognised long ago that some patients with dextrocardia and sinusitis are prone to develop bronchiectasis (Kartagener's syndome). These patients develop chronic upper and lower respiratory tract infections due to ciliary abnormalities.

Cilia are present on the mucosal surface of the respiratory tract, nasal sinuses, Eustachian tubes, lining of the spinal cord and ventricles in the brain, and the oviducts and *vas deferens* (Figure 1). The co-ordinated beating of these microscopic cilia in the respiratory tract serves to



(a) (b)

Figure 1. a) Scanning electron micrograph of the surface of human airway showing cilia orientated in a coordinated fashion (2000x), and b) A schematic sketch of the "9+2" microtubular arrangement of a cilium.

maintain sterility of the airways (8). These cilia could malfunction (immotile or dyskinetic) when the ultrastructure is abnormal. The result is the syndrome of primary ciliary dyskinesia in which a full spectrum of diseases including sinusitis, bronchiectasis, deafness, infertility, and sometimes situs inversus could result (9). Kartagener's syndrome, a triad of dextrocardia, sinusitis and bronchiectasis, is the most commonly recognized subset of primary ciliary dyskinesia (9,10). Whilst up to 25% of patients with dextrocardia might have bronchiectasis (11), some patients without dextrocardia could also suffer from primary ciliary dyskinesia.

Both Kartagener's syndrome and primary ciliary dyskinesia are rare with an estimated incidence of 1/15,000–1/35,000 (12) and 1/12,500 (13) respectively. Kartagener's syndrome is most frequently associated with the absence of dynein arms (site of ATPase activity), which can be readily confirmed at transmission electron microscopy examination of cilia, conveniently sampled from the nose (10,14).

Hypoglobulinaemia

Hypogammaglobulinaemia, IgA deficiency, IgG subclass deficiency.

Others

Bronchial cartilage deficiency etc.

Allergic bronchopulmonary aspergillosis (ABPA)

There is hypersensitivity reaction to Aspergillus in the airways, leading to bronchial asthma and bronchiectasis. The latter occurs predominantly in the proximal airways and upper lobes. A case series of this condition has been reported from India (15), while our experience at the University of Hong Kong suggests that ABPA is exceptionally rare in Hong Kong.

Proximal airway obstruction

Bronchiectasis may develop in the lungs distal to chronic obstruction by foreign body or enlarged lymph nodes due to chronic infections, particularly tuberculosis and slow growing tumours. Foreign body aspiration into the lower respiratory tract in adults is uncommon. The commonest foreign body found in the lower respiratory tract, among the Chinese and some other Orientals, is bone fragments, particularly chicken bone (16). This is probably related to the Chinese and Oriental preference of consuming cooked meat on the bone. Common symptoms of foreign body aspiration include chronic cough, haemoptysis, and fever. Complications include obstructive pneumonitis, atelectasis, bronchiectasis, lung abscess, lung

torsion, and very occasionally endobronchial infection by relatively non virulent organisms such as actinomycosis (17).

Recurrent aspiration

Aspiration into the tracheobronchial tree can sometime be clinically silent and presents as insidious onset of bronchiectasis. Over one third of the population in USA suffers from symptoms of gastro-oesophageal reflux and probably 10% of these subjects might suffer from respiratory symptoms due to the reflux process (18). Gastro-oesophageal reflux has been implicated as the cause of many respiratory diseases particularly asthma, chronic bronchitis, pulmonary fibrosis and bronchiectasis (19–21). Chronic aspiration of stomach contents could cause airway damage via an acidity-mediated erosive process as well as chronic inflammation triggered by aspirated substances (22).

Gastro-oesophageal reflux (GOR) typically presents as heartburn and acid regurgitation and is a commonly encountered condition in the general population. Up to 32% of bronchiectatic patients suffered from upper gastrointestinal symptoms (22). Patients with acid regurgitation or upper abdominal distension have significantly lower FEV_1 and FVC, when compared with their counterparts. The presence of upper abdominal pain and distension is also associated with more extensive bronchiectasis (22). Although the presence of acid regurgitation or heartburn correlates well with acid reflux (23), the absence of symptoms does not exclude the occurrence of GOR. The current gold standard in the investigation of GOR is 24h oesophageal pH monitoring which allows accurate assessment of reflux frequency, severity and duration at both upper and lower oesophagus (24). However, it would be impractical to perform this invasive test on all patients. Studies need to be undertaken to define the clinical and other profiles of patients who have GOR-related bronchiectasis, so that these patients are identified to undergo confirmatory 24h oesophageal pH monitoring.

Traction bronchiectasis

In conditions such as idiopathic pulmonary fibrosis when the airways become dilated under traction from contracting scar tissue in the lung parenchyma. This is often seen in later stages of lung fibrosis such as that encountered in usual interstitial pneumonitis. Most of these patients, however, appear to produce less sputum than their counterparts with idiopathic bronchiectasis.

Diffuse panbronchiolitis

Diffuse panbronchiolitis (DPB), which predominantly affects the Japanese, is a recently recognized idiopathic chronic progressive suppurative and obstructive airway disease, which has distinct pathological and radiological features (9,25). Bronchiectasis is present in advanced disease in diffuse panbrochilitis. Pulmonologists should actively exclude this condition in patients with chronic bronchial sepsis and obstructive lung diseases because it responds well to long term macrolides (see Chapter on Diffuse Panbronchiolitis).

Post transplantation

Bronchiectasis may develop in transplanted lungs in association with bronchiolitis obliterans, which also occurs as a complication of chronic graft versus host disease (GVHD) after bone marrow transplantation (26,27,28). These patients have classical symptoms of bronchiectasis.

Others

A number of conditions have been reported to have a higher association with the occurrence of bronchiectasis, including bronchial asthma (apart from ABPA) (29,30), rheumatoid arthritis, ulcerative colitis, and HIV infection (21).

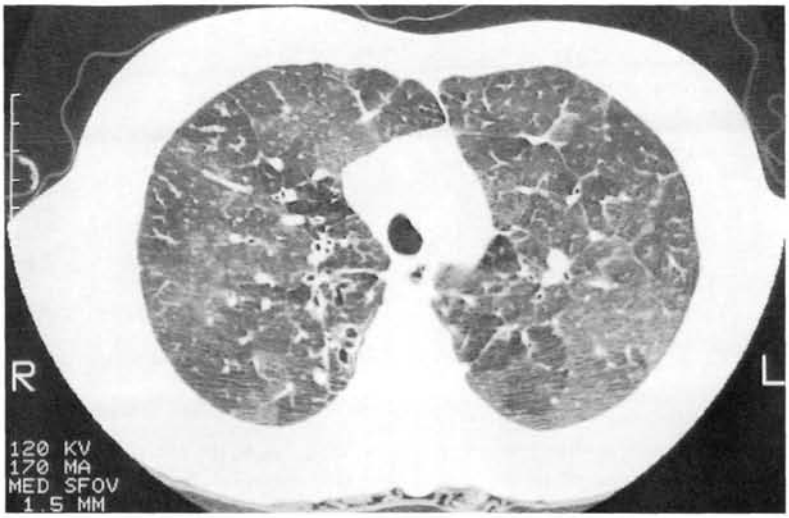


Figure 2. Thoracic high resolution computed tomography of a bone marrow transplant patient who suffers from chronic graft versus host disease, and bronchiolitis obliterans with bronchiectasis. This scan was performed at expiration showing the "mosaic pattern" which indicates air-trapping, along with bronchiectasis.

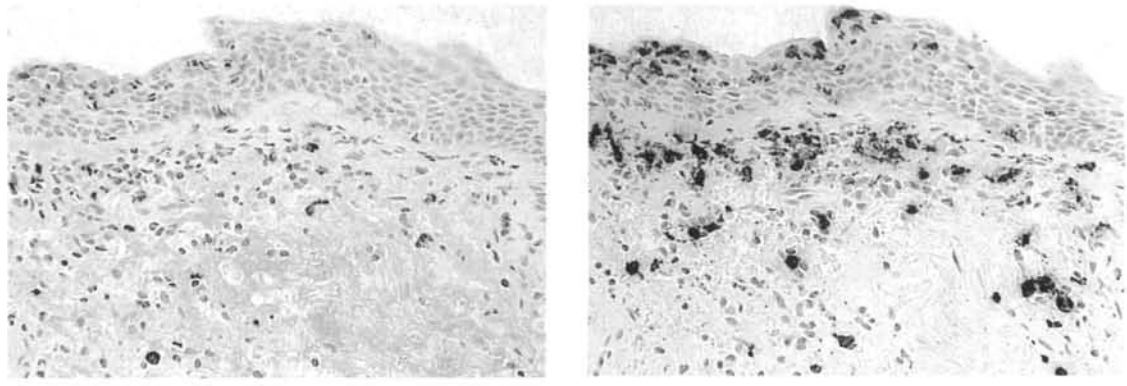
Pathophysiology and Pathogenesis

Bronchiectasis is a chronic infective and inflammatory disease of the tracheobronchial tree and affected patients suffer from recurrent sputum production, hemoptysis, and exacerbations. The pathogenesis of bronchiectasis is poorly understood (7). Although many known causes of bronchiectasis have been identified, between 60–80% of cases are regarded as idiopathic (2,21). Despite the disappearance of the original causative assault to the respiratory tract, such as pertussis, these patients continue to produce significant amounts of sputum, which indicates an underlying active tracheobronchial inflammation.

However, studies in the last two decades have identified infective, inflammatory and enzymatic elements, which are distinct and yet inter-related pathogenic components in the pathogenesis of bronchiectasis. These act together to perpetuate continued airway damage and clinical deterioration in bronchiectasis. While most clinicians recognize the presence of the infective component in the pathogenesis of bronchiectasis, many do not appreciate the need to also address the inflammatory and enzymatic activities. Our recent studies have strongly suggested that the latter two pathogenic components also play very important role in the pathogenesis of bronchiectasis (4–6,31,32,33).

The most frequent isolated respiratory pathogen in early bronchiectasis is *Haemophilus influenzae*. However, more severely affected patients, such as those with copious sputum production and very impaired spirometry, the predominant pathogen is *Pseudomonas aeruginosa*. *P. aeruginosa* is a versatile bacterium, which is virtually impossible to eradicate despite intensive antibiotic therapy. *P. aeruginosa* infection causes considerable morbidity and leads to recurrent exacerbations among patients with bronchiectasis. Both of these pathogens produce exotoxins, which are harmful to the respiratory mucosa and perturb mucociliary clearance (34,35).

Recent studies on the immunopathology of bronchial mucosa in bronchiectasis have revealed an increase in activated CD-8 T-lymphocytes, neutrophils and macrophages in the epithelial, lamina propria and submucosal layers (4,7). This suggests an important role for cell mediated immune response in the progressive airway destruction in bronchiectasis (Figure 3). Intense neutrophil infiltration into the tracheobronchial tree



(a) (b)

Figure 3. Immunohistograph of human bronchus, stained for elastase (brown colour) to identify neutrophils, showing a) relatively low density of neutrophils in the airways of a healthy subject, and b) extensive neutrophil infiltration of the bronchial mucosa of a patient with bronchiectasis. Neutrophils (arrow) are clearly seen to be "gathering" at the subepithelial areas and "migrating through" the epithelial cells (original magnification 250x).

occurs in bronchiectasis, which also aggravates the underlying tracheobronchial damage. Neutrophil-derived toxic products, such as elastase, cause ultrastructural and functional damage and release of pro-inflammatory mediators in the tracheobronchial tree. These elastase and matrix metalloproteinases are likely to further damage the airways, by direct lytic actions on collagen and other connective tissue components, and provoke more inflammatory activities thus perpetuating this vicious circle of events (5,31). There is ample evidence to suggest that this neutrophil influx into the bronchiectatic airways is mediated by pro-inflammatory mediators (4,36). For instance, leukotriene B4 promotes neutrophil migration and degranulation (37); interleukin-1β mediates airway inflammation and fibrosis (38); tumor necrosis factor mediates elastolytic degradation of lung proteoglycans (32) and interacts synergistically with interleukin-1 in prostaglandin induction (39); and interleukin-8 is one of the most potent chemoattractants which also degranulates neutrophils in bronchiectatic airways (40,41).

Neutrophil mediated degradation of bronchial matrix is an important pathogenetic factor in disease progression in bronchiectasis and patients with bronchiectasis ultimately die from progressive lung function impairment and respiratory failure. Neutrophil elastase in the airways would not only degrade lung elastin and collagen, but also proteoglycans which normally maintain the integrity of the lung extracellular matrix (32). Recent work also demonstrates that neutrophil elastase in bronciectatic sputum may complex with heparan sulfate/syndecan 1, proteoglycans present in airway secretions, and this could compromise the inhibitory efficiency of prevailing anti-elastases (42).

H. pylori has been recently identified in the tracheobronchial aspirates in mechanically ventilated patients and the possibility that it might cause ventilator-associated pneumonia has been raised (43). In addition, other bacteria found in the gastric juice have been isolated from the respiratory tract in situations, which favoured bacterial colonization of the stomach and where regurgitation of gastric contents into the respiratory tract can occur (44). A recent study shows a high sero-prevalence of *H. pylori* infection in Chinese patients with bronchiectasis (76%), and this prevalence is significantly higher than that of the normal volunteers (54.3%) and tuberculous patients (52.9%). It is very likely that the abnormally high sero-prevalence is specific to bronchiectasis as there is no association with tuberculosis, another chronic infective and inflammatory lung condition (22). Among the bronchiectatic patients, the sputum producers have significantly higher *H. pylori* sero-prevalence than that of the non-

producers, and there is a correlation between *H. pylori* IgG levels and sputum volume. Further studies are warranted to further evaluate the pathogenic role of *H. pylori* in bronchiectasis.

Clinical Features

Symptoms and signs

Nowadays, the age of onset of non-CF bronchiectasis is usually in adulthood. In the pre-antibiotic era, symptoms of bronchiectasis usually began in the first decade of life after an infective event.

The clinical spectrum varies widely from mild or intermittent to chronic troublesome symptoms of productive cough with copious purulent sputum. Wheezing is commonly reported and may be due to airflow obstruction subsequent on structural destruction of bronchial tree or the co-existence of asthma. Pleuritic pain is not uncommon and may be the first sign of infective flare-up. Many patients also suffer from rhinosinusitis.

There is also a subset of patients with recurrent haemoptysis. Among 176 patients with bronchiectasis, patients with recurrent haemoptysis were reported to be more likely to have a lower 24h sputum volume, higher FEV_1, less cough, and less likely to be a smoker or ex-smoker, than their counterparts (unpublished data).

Those with severe disease develop dyspnoea from loss of lung function and eventually respiratory failure.

The classical physical signs are coarse crackles with or without rhonchi in the chest. Clubbing is not a uniform feature and is present in those with more severe chronic sepsis. Cachexia and signs of respiratory failure are seen in those with long-standing severe disease.

Investigations

The diagnosis of bronchiectasis hinges on the demonstration of a presence of one or more pathologically dilated bronchi, as demonstrated by appropriate imaging, usually in the form of a high resolution CT (HRCT) of the Thorax (45). Clinical diagnosis is difficult as the typical features of sputum production, recurrent exacerbations and occasional haemoptysis could also occur in COPD and tuberculosis. Patients with bronchial carcinoma and COPD could also have some of these symptoms although those from bronchiectasis tend to be more longstanding.

The absence of characteristic features on a plain chest X-ray does not rule out the presence of bronchiectasis as chest X-ray is not a sensitive imaging modality for the diagnosis. Blood tests are unhelpful to make the diagnosis, but could be useful in the evaluation of aetiology of bronchiectasis.

Imaging

Although bronchiectasis may be suspected on clinical grounds from history and physical examination, the diagnosis should be confirmed with imaging.

Chest radiograph

Plain chest X-rays often show findings suggestive of bronchiectasis such as the tram-lines of thickened bronchi but except in cases of cystic diseases, they have no specific diagnostic value and are unreliable.

High resolution computed tomography of the thorax (HRCT)

This is the modality of choice for the morphologic evaluation and diagnosis of bronchiectasis with sensitivity and specificity of 97–98% and 93–99% respectively (46–48). Cardinal features of bronchiectasis on HRCT are: internal bronchial diameter larger than the adjacent pulmonary artery, lack of normal bronchial tapering and presence of peripheral airways within 1 cm of the costal pleura (Figure 4). Other HRCT signs of bronchiectasis include bronchial wall thickening, fluid or mucus filled bronchi, mosaic attenuation (alternating areas of hypo and hyperattenuating lung tissue), centrilobular nodules which may have tree-in bud appearance, and air trapping on expiratory scans. Bronchiectasis associated with post-tuberculosis infection is inevitably due to traction from fibrosis (Figure 5), and the presence of granulomata, which are often calcified, can be found.

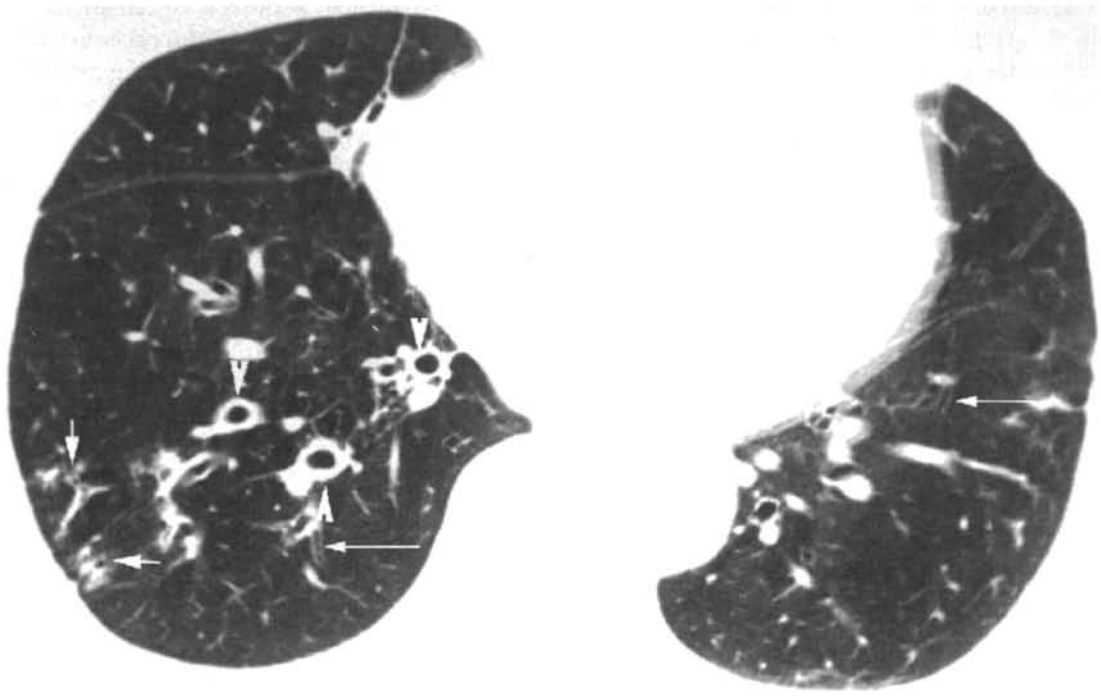


Figure 4. HRCT scan showing bronchiectasis in the right lower lobe. Note internal bronchial wall diameter larger than accompanying artery (arrowheads), lack of bronchial tapering (long arrow) and presence of dilated peripheral airways within 1 cm from the pleura (short arrows).

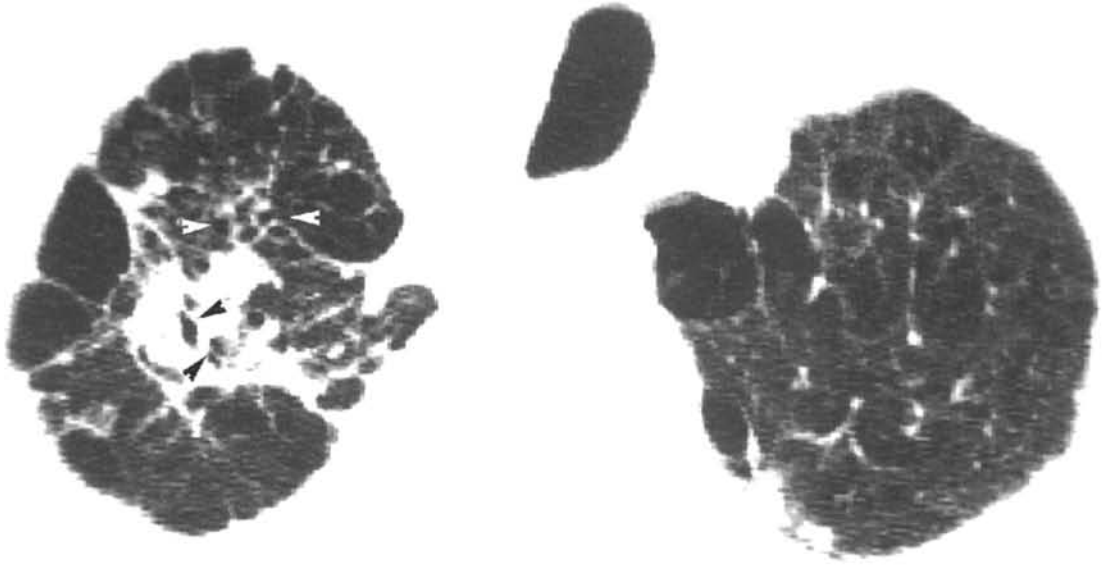


Figure 5. HRCT scan through the upper lobes of a 62-year old man with previous history of tuberculosis showing apical fibrosis with traction bronchiectasis (black and white arrowheads).

HRCT can quantify disease severity according to extent of involvement based on either number of bronchopulmonary segments (49) or percentage of lobar involvement (50–52). Studies have shown that extent of bronchiectasis, bronchial wall thickening and mosaic attenuation are related to lung function indices of obstruction (FEV_1, FEF_{25-75} and FEV_1/FVC) (50,51,53). In one study, bronchial wall thickening was shown to be an independent determinant of airflow obstruction in bronchiectasis (50).

Bronchography

The diagnostic role has virtually been completely replaced by HRCT.

Sputum

Gram's smear and bacterial culture/sensitivity

Smear and culture for AFB *Mycobacterium tuberculosis* infection may complicate bronchiectasis and requires treatment. Atypical mycobacterium not infrequently colonizes damaged airways, and the need for specific treatment requires individual assessment of pathogenicity of the organism concerned.

Smear and culture for fungus Aspergillus is found in cases of ABPA. Candida or occasionally aspergillus may be grown in those who have received a lot of antibiotics, but the pathologic significance of these organisms is not known.

Lung function test

This varies from normal to mixed obstructive-restrictive pattern. Bronchodilator response is often present in the airflow obstruction. There may be co-existing asthma. Prevalence of reversibility of airflow obstruction ranges from 5–40% (29).

Bronchoscopy

This may be needed in those who present with new-onset haemoptysis or when other diseases are suspected. It is probably worth performing bronchoscopy to ensure there is no localized lesion causing obstruction, be it partial or complete, to a single or localised segments of bronchiectasis, especially if the CT scan does not permit complete confidence. Endobronchial lesions such as mucosal swelling, or even sometimes the presence of a small foreign body could significantly contribute to the development of chronic infection and subsequently bronchiectasis, and can sometimes can only be diagnosed at bronchoscopy (17).

Specific tests for underlying causes

Serum globulin

Usually, total serum immunoglobulin level is elevated due to polyclonal increase. It would be decreased in those with hypoglobulinemia as the underlying cause of bronchiectasis and serum levels of Ig G, A, M, D should be checked. Ig G subclass levels are done if indicated.

Sweat test

Since cystic fibrosis lead to bronchiectasis, this test would be done if cystic fibrosis is suspected.

Ciliary study

Ciliated epithelium can be obtained for light microscopy assessment for beat frequency and motility, and transmission electron microscopy assessment, from the inferior nasal turbinate (54). Ciliary assessment should comprise functional and structural evaluation of the cilia as these abnormalities might not occur concomitantly (54). Functional impairment can be classified as immotility, slowing of ciliary beat, and dyskinesia when neighboring cilia beat in different directions i.e. an uncoordinated fashion. Ciliated epithelium can be examined under light microscopy where the percent ciliation can be examined. In addition, most authorities also utilize transmission electron microscopy in the assessment of ciliary ultrastructure.

Aspergillin precipitin and skin prick test

These are useful only when ABPA is suspected.

Blood and sputum eosinophil counts

These are useful particularly in cases when ABPA or asthma (concomitant) are suspected.

Management

There is no cure, nor any effective treatment to reverse the disease process, in bronchiectasis. Unfortunately, alternative treatment has not been shown to be effective in these aspects either. Most patients will go on a slow decline in lung function and worsening of the disease over decades. However, a small group of individuals, who are younger and often very thin individuals, appear to run a more rapidly deterioration course which warrant aggressive treatment.

Conceptually, treatment aims to prevent or reduce the frequency of exacerbations, limit damage to preserve the lung and airways, and maintain good quality of life

General considerations

Good nutrition, regular exercise, no smoking strategy, and fresh air

These are given as general advice to all respiratory patients.

Chest physiotherapy

All patients must be taught to do at least once daily chest physiotherapy, usually in the form of postural drainage. Postural drainage is of utmost importance in bronchiectasis and is not emphasized strongly enough by most medical and nursing personnel. It is particularly important for patients with primary ciliary dyskinesia as these patients have little or no mucocilary clearance, and have to completely rely on coughing and postural drainage for removal of secretions etc from the bronchiectatic airways.

Bronchodilators

It is important to detect and treat concomitant asthma, which is not uncommon in bronchiectasis (29,30). β-agonists such as salbutamol increases ciliary beat frequency in the laboratory and could therefore be theoretically beneficial.

Mucolytics

Mucolytics are often prescribed in Hong Kong and world wide in an effort to facilitate sputum clearance by reducing sputum viscosity. However, there is no proven efficacy except in the use of recombinant DNase for patients with severe cystic fibrosis (55,56). Administration of rhDNase, despite its proven efficacy in CF, could actually increase exacerbation frequency and cause FEV_1 decline in non-CF bronchiectasis (57). In addition, excessive thinning or reduction in viscosity of sputum could make it harder to expectorate. Hence, mucolytics should not be prescribed routinely in bronchiectasis.

Anti-tussive

Similar to mucolytics, many patients with chronic cough receive anti-tussive therapy in the form of cough mixtures. Cough suppression can be harmful as expectoration of sputum is a vital process, particularly in patients with primary ciliary dyskinesia who have bronchiectasis (58). Anti-tussives should not be prescribed routinely in bronchiectasis.

Antibiotics

This remains the mainstay of treatment. However, bronchiectasis is not a mere infective process and therefore prescription of antibiotics does not cure the disease (59,60). While there is little doubt on the benefits of antibiotics in bronchiectasis, there are many uncertainties on their usage. The following regimens may be adopted, depending on severity of disease.

Intermittent administration of intravenous antibiotics for severe infective exacerbations

Exacerbation is defined as the deterioration in respiratory symptoms in bronchiectasis and is not formally defined. It is generally accepted that the deterioration in respiratory symptoms, with or without a fever or other systemic disturbances, constitutes an exacerbation. This generally takes the form of subacute increase in sputum volume and purulence, accompanied by increase in cough, dyspnoea and fatigue. Most authorities accept haemoptysis as an exacerbation. Exacerbations

could be very insidious and sputum volume could deteriorate slowly over months.

Regular elective administration of intravenous antibiotics

Irrespective whether or not there is an exacerbation, this mode of therapy is useful for patients who have very severe and progressive disease who have frequent exacerbations. Indeed, by regularly administering "prophylactic" courses of antibiotic therapy, the "total hospitalization and antibiotic treatment time" becomes less in the long run.

Long term nebulized antibiotics

This is usually administered as long-term maintenance nebulized aminoglycoside (e.g. tobramycin) twice daily (61). This is useful in improving sputum volume and purulence, exacerbation frequency, and general well being for many patients who are affected by severe bronchiectasis. Nebulization of antibiotics, however, is not considered as effective treatment in exacerbations. Treatment with nebulized aminoglycoside therapy improves sputum *P. aeruginosa* density, lung function and hospitalization in CF (62), and reduces sputum *P. aeruginosa* density and myeloperoxidase in non-CF bronchiectasis (63). However, even prolonged treatment with potent antibiotics cannot eradicate *P. aeruginosa* from the bronchiectatic airway or delay the disease progression in bronchiectasis.

Total eradication of the airway bacteria is seldom achieved despite prolonged intensive antibiotic treatment, and the goal of treatment should be to reduce the total microbial load. This reduction in microbial load is beneficial and might also reduce the airway inflammation, which is independently harmful in bronchiectasis (21,31). Over 20% of *H. influenzae* isolates in Hong Kong produce b-lactamase, and are therefore theoretically resistant to amoxycillin. Most oral antibiotics, apart from quinolones, are clinically ineffective for *P. aeruginosa*. Unfortunately, antibiotic resistance is now a widespread problem, and both *H. influenzae* and *Streptococcus pneumoniae* are now also resistant to most of the commonly used antibiotics, albeit at a low to moderate level of resistance (64).

The choice of antibiotics to treat patients with bronchiectasis is not straight forward as many patients have no pathogens isolated in their sputum even during exacerbations. In addition, the presence of respiratory pathogen in sputum does not necessarily imply a pathogenic role as chronic colonization of the airways occurs in bronchiectasis. A study in bronchiectasis in Hong Kong over a decade ago using quantitative cultures of protected catheter brush and bronchoalveolar lavage identified that *H. influenzae* and *P. aeruginosa* and other Gram negative organisms predominated, as opposed to that of mainly *H influenzae, S. pneumoniae* and *S. aureus* reported from the west (65). A more recent study of sputum pathogens from Hong Kong demonstrated an even greater prevalence of *P. aeruginosa* (Table 2), and this is similar to the pattern reported from another Asian country, Thailand (66).

We have recently compared clinical parameters between patients with positive isolation of *P. aeruginosa* in sputum, with those without the organism. Some clinical parameters, including

Table 2. Sputum Pathogen amongst 100 Bronchiectasis Patients in Hong Kong[67]

Respiratory pathogen	*% frequency*
Pseudomonas aeruginosa	33
Haemophilus influenzae	10
Streptococcus pneumoniae	6
Staphylococcus aureus	5
Other Gram-negative bacilli	5
Non-tuberculous Mycobacteria (? pathogenic)	3
Moraxella catarrhalis	2
Yeast (? pathogenic)	1

FEV_1/FVC of < 60% and sputum volume of > 20 ml, are independently associated with a positive sputum isolation of *P. aeruginosa* (67). It, therefore, follows that patients with usually (i.e. pre-morbid) little sputum and good lung function require non-Pseudomonal, while the others require anti-Pseudomonal antibiotics for treatment. The former group includes third generation cephalosporins (intravenous), and b-lactams with lactamase inhibitor such as Augmentin or macrolides (oral). The latter group comprises ceftazidime or aminoglycosides (intravenous), and quinolones such as ciprofloxacin (oral). We have also shown that 10-day course of oral quinolone (e.g. levofloxacin 300 mg b.i.d.) is as effective as intravenous ceftazidime in the empirical treatment of exacerbation in broncheictasis (68). Needless to say, treating exacerbation on an out-patient basis is clearly advantageous in terms of psychological, social as well as economical considerations.

Treatment of haemoptysis in bronchiectasis

Haemoptysis, in the form of frank blood expectoration or production of blood-stained sputum is not an uncommon event for patients with bronchiectasis. Although an alarming symptom, the vast majority of patients with haemoptysis settle on conservative treatment including bed rest, adequate hydration, and antibiotic therapy. Whilst haemoptysis is commonly part of an exacerbation, the presence of blood in the bronchiectatic airway predisposes to further infection in bronchiectasis. The following should be considered:

Bed rest

This often stops haemoptysis or spontaneous resolution has occurred.

Antibiotic treatment

As suggested above.

Tranexamic acid

Although commonly prescribed, there are potentially very serious consequences in the use of "clotting-enhancing" therapy including thrombosis of the cerebral and coronary arteries. In addition, large clots may form in the tracheobronchial tree, which could cause lung collapse, precipitate infection, and other long term sequalae. Most patients with moderate to severe haemoptysis do not require tranexamic acid treatment.

Bronchial artery arteriogram and embolization

This is indicated for massive life-threatening haemoptysis not responding to the above therapy. This entails localization of the bleeding vessel with bronchial arteriography, and then embolizing it with steel-coil or gelfoam material. However, the procedure imposes significant risks and the effect is not permanent. Therefore, it is reserved for management of episodes of life-threatening haemoptysis particularly in patients with generalized bronchiectasis and thus not unsuitable for resection.

Bronchial arteriogram is an invasive procedure requiring transarterial puncture, usually of the common femoral artery. A vascular sheath is placed within the common femoral artery to maintain vascular access, and a catheter inserted and passed in a cephalad direction into the aorta. Selective catheterisation of the right and left bronchial arteries is then performed and non-ionic contrast medium injected to obtain an arteriogram. Arteriographic features suggestive of bronchiectasis include hypertrophied and tortuous bronchial arteries (Figure 6). Evidence of active bleeding is sought, and if found, the catheter is placed as selectively as possible within the bleeding artery avoiding other arterial branches and transcatheter embolization performed with particulate matter or coils. Complications include allergic reactions to contrast media, misplacement of emboli and infection of infarcted lung.

Resection of the bleeding segment

This is only contemplated when the above are ineffective in a patient who is judged to be at high risk of dying from the episode. This will require location of bleeding segment by bronchoscopy, CT scan of the chest, and bronchial arteriography before the operation.

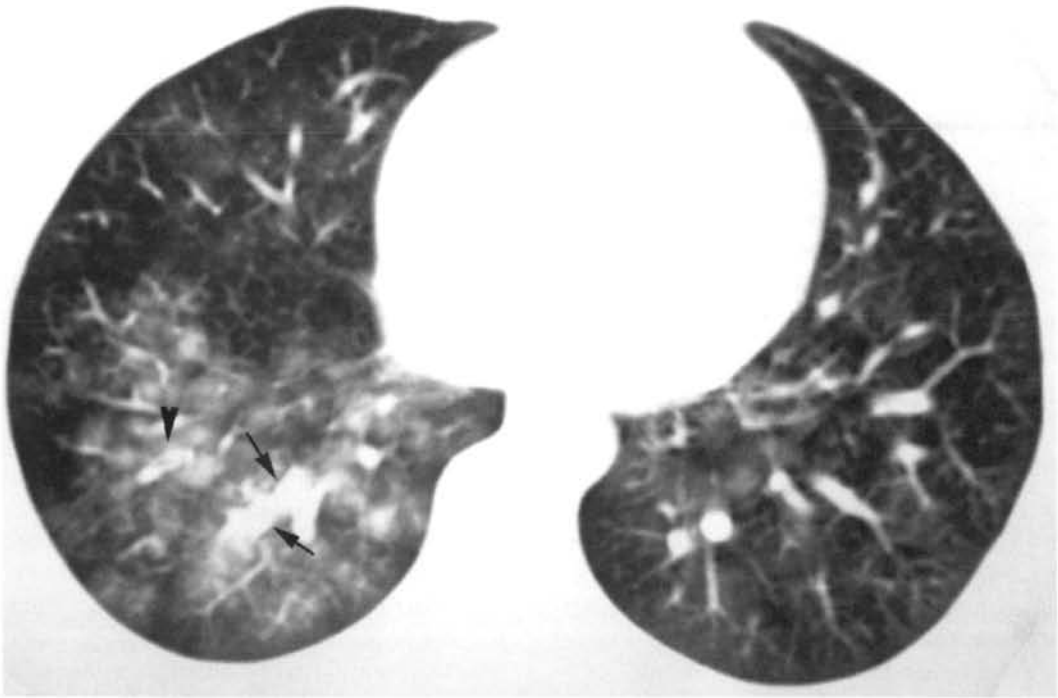


Figure 6. CT scan of a 38-year old woman with repeated haemoptysis showing peribronchial cuffing (arrows), thick-walled bronchus (arrowheads) and patchy ground glass opacification consistent with haemorrhage.

Specific therapy for underlying cause:

- Diffuse panbronchiolitis responds well to long term low dose macrolides (see Chapter on Diffuse Panbrochiolitis), although late stage disease complicated by bronchiectasis will require treatment targeted to bronchiectasis as well
- Globulin replacement is very effective in controlling infections in those with hypogammaglobulinaemia.
- Oral steroid is indicated in cases with ABPA to control the inflammatory response that is the cause of the asthma and bronchiectasis.
- There have been patients whose bronchiectasis symptoms improved tremendously after treatment of coexistent gastroesophageal with reflux proton pump blockers such as omeprazole.
- Progression of bronchiectasis associated with broncholitis obliterans after bone marrow transplant may be reduced by immunosuppression or corticosteroid treatment to control the underlying graft-versus-host disease (26,27) and systemic corticosteroid therapy has been reported to reduce sputum production (26).
- Somatic gene therapy for cystic fibrosis is still in the experimental stage.

Treatment of severe bronchiectasis

Long term oxygen therapy

This should be given to patients with significant hypoxaemia with or without cor pulmonale. However, there is no parallel data on improved survival, which was found in COPD patients who were given long term oxygen therapy.

Long term nocturnal mechanical ventilation

In those patients with severe chronic respiratory failure, nocturnal non-invasive ventilatory support

may be tried although experience is limited and results are probably not as good as in non-infective conditions. There is also always a worry that secretions might be blown more distally into the airways and thus could worsen retention of infected secretions.

Lung transplantation

Patients with bronchiectasis, majority of them due to cystic fibrosis, have undergone heart-lung or double-lung transplantation successfully with two year survival rates of 50–60%. It is hoped that, with public education, more donor lungs will become available in Asia in the future

Anti-inflammatory agents

New therapeutic approaches based on proposed pathogenic mechanisms have been put forward. The rationale of this treatment is to modify the inflammatory response so that tissue damage is minimized. However, there is still no conclusive data on the long-term efficacy of any anti-inflammatory agents, which should not be used routinely.

Inhaled corticosteroid therapy (ICS) appears to be efficacious as an anti-inflammatory agent in bronchiectasis. We have shown that treatment with an 8-week course of high dose (1 mg daily) inhaled fluticasone therapy improves sputum inflammatory indices including leukocyte density and levels of IL-1, IL-8 and LTB4 in steady state bronchiectasis. Treatment does not appear to cause deterioration in infective status, as assessed by sputum bacterial densities (6). Medium and long term effects of ICS therapy in bronchiectasis, however, remain largely unexplored.

We have just completed the first double-blind placebo-controlled randomized study to evaluate the clinical efficacy of medium-term administration of ICS therapy in a cohort of 86 patients with stable bronchiectasis. Treatment with inhaled fluticasone was associated with significantly more patients showing improvement in 24h sputum volume, but not exacerbation frequency, FEV_1, FVC or sputum purulence score, when compared with placebo. It is of note that patients with *P. aeruginosa* infection appear to benefit particularly more as they exhibited significant improvement in 24h sputum volume and exacerbation frequency (unpublished data).

Surgery

The traditional role of surgery in bronchiectasis has declined, although a new role in lung transplantation has emerged. Surgical resection of bronchiectatic lung should be confined to patients who have very localized but troublesome disease (i.e. frequent intractable exacerbations, severe recurrent haemoptysis, or harbouring problematic orgnaisms such as multi-resistant *M. tuberculosis* or *M. avium* complex) or those with massive haemoptysis (if not responsive to conservative treatment) (69,70,71). A bronchiectatic segment, if not causing intractable issues, should not be resected even if it is localized as bronchiectasis could develop in other segments later.

Others

Low-dose long-term erythromycin

Erythromycin (EM) is clinically effective in reducing sputum production on patients with idiopathic or secondary bronchorrhoea (72). EM inhibits respiratory mucus secretion by reducing pulmonary macrophage mucus secretagogue production (72) and reduces *P. aeruginosa* exotoxin(s) production which slow human respiratory ciliary beat *in vitro* (73). We have recently shown, in a double-blind placebo-controlled manner, that 8-week administration of low dose EM (500 mg twice daily) significantly reduces sputum volume and improves lung function in steady state severe idiopathic bronchiectasis (74). However, long term use of these drugs should be individually assessed for each patient.

References

1. HA Statistical Report 1997/98.
2. Tsang KW, Lam SK, Lam WK, Karlberg J, Wong BC, Hu WH, Yew WW, Ip MS. High seroprevalence of *Helicobacter pylori* in active bronchiectasis. *Am J Respir Crit Care Med* 1998; 158(4):1047–51.
3. Pasteur MC, Helliwell SM, Houghton SJ, Webb SC, Foweraker JE, Coulden RA, et al. An investigation into causative factors in patients with bronchiectasis. *Am J Respir Crit Care Med* 2000; 162(4 Pt 1):1277–84.
4. Zheng L, Shum H, Tipoe GL, Leung R, Lam WK, Ooi GC, Tsang KW. Macrophages, neutrophils and tumour necrosis factor-alpha expression in bronchiectatic airways in vivo. *Respir Med* 2001; 95:792–8.
5. Zheng L, Lam WK, Tipoe GL, Shum IH, Yan C, Leung R, Sun J, Ooi GC, Tsang KW. Overexpression of matrix metalloproteinase-8 and -9 in bronchiectatic airways in vivo. *Eur Respir J* 2002; 20(1):170–6.
6. Tsang KWT, Ho PL, Lam WK, Ip MSM, Ho CS, Chan KN, Yuen KY. Fluticasone reduces sputum inflammatory indices in bronchiectasis. *Am J Respir Crit Care Med* 1998: 158:723–7.
7. Lapa e Silva JR, Jones JAH, Noble B, Cole PJ, Poulter LW. The immunological component of the cellular inflammatory infiltrate in bronchiectasis. *Thorax* 1989; 44:668–73.
8. Yarnal JR, Golish JA, Ahmed M, Tomashefski JF. The immotile cilia syndrome. *Postgraduate Medicine* 1982; 71:195–217.
9. Bush A, Cole P, Hariri M, Mackay I., Phillip SG, O'Callaghan C, Wilson R, Warner JO. Primary ciliary dyskinesia: diagnosis and standards of care. *Eur Respir J* 1998; 12:982–8.
10. Tsang KW, Ip M, Ooi CG, Wong MP, Ho CS, Sun Z, Tam CY, Lam WK. Kartagener's syndrome: a re-visit with Chinese perspectives. *Respirology* 1998; 3(2):107–12.
11. Katsuhara K, Kawamoto S, Wakabayashi T, Belsky JL. Situs inversus totalis and Kartagener's syndrome in a Japanese population. *Chest* 1972; 61:56–61.
12. Afzelius BA. The immotile cilia syndrome and other ciliary diseases. *Int Rev Exp Pathol* 1979; 19:1–43.
13. Kroon AA, Heij JM, Kuijper WA, Veerman AJ, van der Baan S. Function and morphology of respiratory cilia in situs inversus. *Clin Otolaryngol* 1991; 16:294–7.
14. Tsang KW, Tipoe GL, Sun J, Ho JCM, Lam B, Zheng L, Ooi GC, Lam WK. Severe bronchiectasis in patients with cystlike structures within the ciliary shafts. *Am J Respir Crit Care Med* 2000; 61:1300–5.
15. Behera D, Guleria R, Jindal SK, Chakrabarti A, Panigrahi D. Allergic bronchopulmonary aspergillosis: a retrospective study of 35 cases. *Indian J Chest Dis Allied Sci* 1994; 36(4):173–9.
16. Chen CH, Lai CL, Tsai TT, Lee YC, Perng BP. Foreign body aspiration into the lower airway in Chinese adults. *Chest* 1997; 112:129–33.
17. Ho JC, Ooi GC, Lam WK, Lam B, Cheung TF, Tsang KW. Endobronchial actinomycosis associated with a foreign body. *Respirology* 2000; 5(3):293–6.
18. Barish CF, Wu WC, Castell DO. Respiratory complications of gastro-oesophageal reflux. *Arch Intern Med* 1985; 45:1882–8.
19. Hu WHC, Hui WM, Lam CLK, Lam SK. Anxiety and depresssion are co-factors determining health care utilisation in patients with dyspepsia: a Hong Kong population-based study. *Gastroenterol* 1997; 112:A153 (abstract).
20. Ayres JG, Miles JF. Oesophageal reflux and asthma. *Eur Respir J* 1996; 9:1073–8.
21. Cole PJ. Bronchiectasis. In: *Respiratory Medicine.* Eds. Brewis RAL, Corrin B, Geddes DM, Gibson GJ. London: Saunders 1995, 1286–1317.
22. Tsang KW, Lam WK, Chan KN, Hu WHC, Ooi GC, Zheng L, Wong BC, Lam SK. *Helicobacter pylori* and upper gastrointestinal symptoms in bronchiectasis. *Eur Respir J* 1999 Dec; 14(6):1345–50.
23. Shi G, Brurley de Varannes S, Scarpignato C, Le Rhun M, Galmiche J. Reflux related symptoms in patients with normal oesophageal exposure to acid. Gut 1995; 37:457–64.
24. DeMeester TR, Wang C, Wesley JA, et al. Techniques, indications, and clinical use of 24 hour oesophageal monitoring. *J Thorac Cardiovasc Surg* 1980; 79:656–70.
25. Tsang KW Diffuse panbronchiolitis: Diagnosis and Treatment. *Clinical Pulmonary Medicine* 2000b; 7:245–52.
26. Morehead RS. Bronchiectasis in bone marrow transplantation. *Thorax* 1997; 52(4):392–3.
27. Philit F, Wiesendanger T, Archimbaud E, Mornex JF, Brune J, Cordier JF. Post-transplant obstructive lung disease ("bronchiolitis obliterans"): a clinical comparative study of bone marrow and lung transplant patients. *Eur Respir J* 1995; 8:551–8.

28. Ooi GC, Peh WCG, Ip M. High resolution computed tomography of bronchiolitis obliterans syndrome after bone marrow transplantation. *Respiration* 1998; 65:187–91.
29. Ip M, So SY, Lam WK, Yam L, Liong E. High prevalence of asthma in patients with bronchiectalsis in Hong Kong. *Eur Respir J* 1992; 5:418–23.
30. Pang J, Chan HS, Sung JY. Prevalence of asthma, atopy and bronchial hyperreactivity in bronchiectasis: a controlled study. *Thorax* 1989; 44:948–51.
31. Tsang KW, Chan KN, Ho PL, Ooi GC, Zheng L, Lam B, Ho JCM, Lam WK. Sputum elastase in steady state bronchiectasis. *Chest* 2000c; 117:420–6.
32. Shum KY, Chan SC, Ip MS. Neutrophil-mediated degradation of lung proteoglycans. Stimulation by tumour necrosis factor α in sputum of patients with bronchiectasis. *Am J Respir Crit Care Med* 2000; 162:1925–31.
33. Shum KY and Ip MS. Degradation of lung matrix proteoglycans in bronchiectasis. In *Proteoglycans in Lung Disease (Lung Biology in Health and Disease* series*)*. Ed. Garg HG. New York: Marcel Dekker, 2002.
34. Tsang KW, Rutman A, Kanthakumar K, Belcher J, Lund A, Roberts DE, Cole PJ, Wilson R. *Haemophilus influenzae* infection of human respiratory mucosa in low concentrations of antibiotics. *Am J Respir Crit Care Med* 1993; 48:201–7.
35. Tsang KW, Rutman A, Dewar A, Tanaka E, Lund V, Cole PJ, Wilson R. *Pseudomonas aeruginosa* infection of human respiratory mucosa in vitro. *Eur Respir J* 1994; 7:1746–53.
36. Zheng L, Tipoe GL, Lam WK, Ho JCM, Shum I, Ooi GC, Leung R, Tsang KWT. Endothelin-1 in stable bronchiectasis. *Eur Respir J* 2000; 16(1):146–9.
37. Ford-Hutchinson AW, Bray MA, Doig MV, Shipley ME, Smith MJH. Leukotriene B, a potent chemokinetic and aggregating substance released from polymorphonuclear leukocytes. *Nature* 1980; 286:264–5.
38. Kelley J. Cytokines of the lung. *Am Rev Respir Dis* 1990; 141:765–88.
39. Elias JA, Gustilo K, Baeder W, Freundlich B. Synergistic stimulation of fibroblast prostaglandin production by recombinant interleukin 1 and tumour necrosis factor. *J Immunol* 1987; 138:3812–6.
40. Eller J, Lapa E Silva JR, Poulter LW, Lode H, Cole PJ. Cells and cytokines in chronic bronchial infection. *Ann NY Academy of Sciences* 1994; 725:331–45.
41. Lundgren JD, Hirata F, Marom Z, Logun C, Steel C, Kaliner M, Shelhamer J. Dexamethasone inhibits respiratory glycoconjugate secretion from feline airways *in vitro* by the induction of lipocortin (lipomodulin) synthesis. *Am Rev Respir Dis* 1988; 137:353–7.
42. Chan SC, Shum KY, Ip MS. Sputum sol in neutrophil elastase in bronchiectasis. Association with soluble syndecan-1 differentially protects it from anti-elastase. *Am J Respir Crit Care Med* 2003; 168:192–8.
43. Mitz HS, Farber SS. Demonstration of *Helicobacter pylori* in tracheal secretions. *J Am Osteopath Assoc* 1993; 93:87–91.
44. Ibanez J, Penafiel A, Raurich JM, Marse P, Paternostro JC, Mata F. Gastrooesophageal reflux and aspiration of gastric contents during nasogastric feeding, the effects of posture. *Intens Care Med* 1988; 14(suppl 2):296abstract.
45. Naidich DP, McCauley DI, Khouri NF, Stitik FP, Siegelman SS. Computed tomography of bronchiectasis. *Journal of Computed Assisted Tomography* 1982; 6:437–44.
46. Grenier P, Maurice F, Musset D, et al. Bronchiectasis: assessment by thin-section CT. *Radiology* 1986; 161:95–9.
47. Young K, Aspestrand F, Kolbenstvedt A. High resolution CT and bronchography in the assessment of bronchiectasis. *Acta Radiol* 1991; 32:439–41.
48. Giron J, Skaff F, Maubon A, et al. The value of thin-section CT scans in the diagnosis and staging of bronchiectasis: comparison with bronchography in a series of fifty-four patients. *Ann Radiol* 1998; 31:25–33.
49. Bhalla M, Turcios N, Aponte V, et al. Cystic fibrosis: scoring system with thin-section CT. *Radiology* 1991; 179:783–8.
50. Ooi GC, Khong PL, Chan-Yeung M, Ho JCM, Chan PKS, Lee JCK, Lam WK, Tsang KWT. HRCT quantification of bronchiectasis with clinical functional correlation. *Radiology* 2002; 225:663–72.
51. Roberts HR, Wells AU, Milne DG, et al. Airflow obstruction in bronchiectasis: correlation between computed tomography features and pulmonary function tests. *Thorax* 2000; 55:198–204.
52. Cartier Y, Kavanagh PV, Johkoh T, et al. Bronchiectasis: accuracy of high-resolution CT in the differentiation of specific diseases. *AJR Am J Roentgenol* 1999; 173:47–52.

53. Smith IE, Jurriaans E, Diederich S, et al. Chronic sputum production: correlations between clinical features and findings on high resolution computed tomographic scanning of the chest. *Thorax* 1996; 51:914–8.
54. Tsang KW, Tipoe GL, Zheng L. Ciliary assessment in bronchiectasis. *Respirology* 2000; 5(2):91–8.
55. Davies J, Trindale MT, Wallis C, Rosenthal M, Crawford O, Bush A. Retrospective review of the effects of rhDNase in children with cystic fibrosis. *Pediatr Pulmonol* 1997; 23:243–8.
56. Cobos N, Danes I, Gartner S, Gonzalez M, Linan S, Arnau JM. DNase use in the daily care of cystic fibrosis: who benefits from it and to what extent? Results of a cohort study of 199 patients in 13 centres. *Eur J Pediatr* 2000; 159:176–81.
57. O'Donnell AE, Barker AF, Ilowite JS, Fick RB. Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. rhDNase Study Group. *Chest* 1998; 113:1329–34.
58. Greenstone M, Rutman A, Dewar A, Mackay I, Cole PJ. Primary ciliary dyskinesia: cytological and clinical features. *Q J Med* 1988; 67:405–30.
59. Ip M, Lam WK, Chan J, Liong E. Systemic effects of airway inflammation in bronchiectasis. *Respiratory Medicine* 1991; 85:521–5.
60. Ip M, Shum D, Lauder IJ, Lam WK, So SY. Effect of antibiotics on sputum inflammatory contents in acute exacerbations of bronchiectasis. *Respiratory Medicine* 1993; 87:449–54.
61. Barker AF, Couch L, Fiel SB, Gotfried MH, Ilowite J, Meyer KC, O'Donnell A, Sahn SA, Smith LJ, Stewart JO, Abuan T, Tully H, Van Dalfsen J, Wells CD, Quan J. Tobramycin solution for inhalation reduces sputum Pseudomonas aeruginosa density in bronchiectasis. *Am J Respir Crit Care Med* 2000 Aug; 162(2 Pt 1):481–5.
62. Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med* 1999; 340(1):23–30.
63. Lin HC, Cheng HF, Wang CH, Liu CY, Yu CT, Kuo HP. Inhaled gentamicin reduces airway neutrophil activity and mucus secretion in bronchiectasis. *Am J Respir Crit Care Med* 1997; 155:2024–9.
64. Ho PL, Yam WC, Cheung TK, Ng WW, Que TL, Tsang DN, Ng TK, Seto WH. Fluoroquinolone resistance among Streptococcus pneumoniae in Hong Kong linked to the Spanish 23F clone. *Emerg Infect Dis* 2001; 7:906–8.
65. Pang JA, Cheng A, Chan HS, Poon D, French G. The bacteriology of bronchiectasis in Hong kOng investigated by protected catheter brush and bronchoalveolar lavage. *Am Rev Respir Dis* 1989; 139:14–7.
66. Palwatwichai A, Chaoprasong C, Vattanathum A, Wongsa A, Jatakanon A. Clinical, laboratory findings and mircrbiologic characterization of bronchiectasis in Thai patients. *Respirology* 2002; 7(1):63–6.
67. Ho PL, Lam WK, Ip MSM, Chan KN, Yuen KY, Tsang KWT. The effects of *Pseudomonas aeruginosa* infection in clinical parameters in steady state bronchiectasis. *Chest* 1998; 114:1623–9.
68. Tsang KW, Chan WM, Ho PL, Chan KN, Lam WK, Ip MS. A comparative study on use of empirical levofloxacin versus ceftazidime in the treatment of exacerbation of bronchiectasis. *Eur Respir J* 1999b; 14(5):1206–9.
69. Chiang TC, Kok VK, Tu HH, Su YM, Yeh CH, Chung MT. Surgical treatment of bronchiectasis. 10 years experience (Taipei). *Zhonghua Yi Xue Zha Zhi* 1999; 62:690–4.
70. Fujimoto T, Hillejan L, Stamatis G. Current strategy for surgical management of bronchiectasis. *Ann Thorac Surg* 2002; 72:1711–15.
71. Ashour M, Al-Kattan K, Rafay MA, Saja DF, Hajjar W, Al-Fraye AR. Current surgical therapy for bronchiectasis. *World J Surg* 1999; 23:1096–104.
72. Marom ZM, Goswami SK. Respiratory mucus hypersecretion (bronchorrhea): a case discussion — possible mechanisms(s) and treatment. *J Allergy Clin Immunol* 1991; 87:1050–5.
73. Tanaka E, Kanthakumar K, Cundell DR, Tsang KW, Taylor GW, Kuze F, Cole PJ, Wilson R. The effect of erythromycin on Pseudomonas aeruginosa and neutrophil mediated epithelial damage. *J Antimicrob Chemother* 1994; 33:765–75.
74. Tsang KW, Ho PL, Ip M, Lam WK, Yuen KY, Amitani R, Tanaka E. The effects of low dose erythromycin in bronchiectasis: a pilot study. *Eur Respir J* 1999; 13:361–4.

4

Chronic Obstructive Pulmonary Disease: Epidemiology

Wan Cheng Tan

Introduction

According to the WHO/World Bank (1,2) COPD is projected to rise worldwide, from the 7th to the 5th position in terms of economic and social burden of the disease in the next 20 years, largely driven by two factors: the rise in tobacco related mortality and morbidity and the aging population. As these factors are most rapidly increasing in the developing world which constitutes a significant part of the Asia Pacific region, this region will therefore face one of its toughest public health challenges, which will exert huge demands on the economic and health care resources, and have an important negative impact on the social and economic progress of the individual countries.

The concept of the total burden of a disease is traditionally described by computing its prevalence and incidence, morbidity and mortality. In recent years, quantification of the economic and social burden caused by the disease has become part of the concept of epidemiology and increasingly relevant in an age of rapidly escalating health care expenditure and changing population demographics.

Under-recognition of the Burden of COPD

The overall burden of COPD is not adequately appreciated worldwide (3). This is due to a number of problems in concept, in communication and in attitude. These difficulties of concept are universal, but are commonly encountered in countries in Asia. They are obstacles in the early diagnosis of the disease and in estimating prevalence, quantifying morbidity and mortality and assessing trends.

Difficulty in detecting early COPD

COPD is often not recognized as symptoms of cough are frequently attributed to the acceptable irritant effects of smoking itself or to other respiratory diseases, or even to aging. These beliefs, which appear to be widely prevalent in Asia, hinder the early diagnosis of the disease (4,5).

Inconsistency in the use of the term COPD

The term COPD has been used in two ways: as a disease entity and as a functional disorder. The more common use of the term COPD had been for describing a functional disorder which affects several diseases, such as bronchiectasis, chronic asthma, panbronchiolitis, bronchiolitis obliterans and post tuberculosis chronic lung disease that are characterized by chronic airflow limitation.

The introduction of the term COPD to describe

the disease entity of chronic bronchitis and emphysema due largely to smoking dates back to 1969 in the UK (6) and 1972 in the USA (7). COPD as a smoking related entity was officially introduced in Japan as recently as 1995 (5).

Even when COPD is considered as a clinical entity due to chronic exposure to inhaled particles and gases largely from tobacco smoke, occupational dusts and biomass combustion indoors, the impact is lost by the frequent and prevalent use of two other synonyms, namely chronic bronchitis (an epidemiological term) and emphysema (a pathologic description). In many countries in Asia, the clinical term COPD is unfamiliar to the public and to even physicians. Rather, "asthma" is used generically to describe all types of chronic airway diseases. Alternatively, COPD is referred to as "cough and dyspnoea" which is also used to refer to asthma and cardiac failure, hence adding to the confusion and poor recognition of the disease (4).

Poor understanding of the risk factors of COPD and the benefits of treatment

Knowledge of COPD is poor among patients and healthcare personnel worldwide (3) including Asia (4,5). This coupled with disinterest and pessimism towards the condition have diverted research away (8) from better understanding of the pathogenesis and pathophysiology of COPD, both of which are essential for a proper appreciation of growing trends in the burden of the disease.

Definition

With the publication of international guidelines, the consensus worldwide is to an affirmation of COPD as a distinct clinical entity (9–13). According to the recent international Guidelines of the Global Initiative for Chronic Obstructive Disease, COPD refers to a disease state due to noxious particles or gases, characterized by chronic airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with abnormal inflammatory response of the lungs (9).

Natural History of COPD

COPD has a variable course in individuals, but is generally a progressive disease, especially if the exposure to noxious particles or gases continues.

Although it is widely stated that 15–20% of smokers develop clinically significant COPD ($FEV_1 < 50\%$ predicted), the proportion of continuously smoking individuals with abnormal lung function is much higher (14–16). The cessation of exposure at any stage of the disease can ameliorate the steep decline in lung function which then returns to a normal decline due to the physiological effects of aging.

There is little information on the natural history of COPD combined with the effects of other coexisting chronic respiratory diseases such as post pulmonary tuberculosis and chronic asthma. In many Asian countries, the occurrence of concomitant pulmonary tuberculosis and COPD is a significant problem, as risk factors for both diseases are prevalent. In patients with both diseases, the lung function abnormality and the disability due to either disease interact and can be quite complex and difficult to differentiate. There is little recent information on the clinical and functional abnormalities for this combined pathophysiology (17). Early studies indicate that the degree of obstructive airway changes in treated patients with pulmonary tuberculosis increases with age, the amount of cigarettes smoked, and the extent of the initial tuberculous disease (18–20). Studies from hospital records in Indonesia suggest that some patients with mild tuberculosis may develop significant airway obstruction (21).

Epidemiology of COPD

Most of the available information on disease burden of chronic lung diseases comes from developed countries (established market economies) (9). Furthermore, comparison of published epidemiological data on prevalence, morbidity and mortality from the developed world is difficult as they vary appreciably due to different methodologies and definitions for COPD.

Prevalence

Methods used in studies of COPD prevalence are based either on self-reported respiratory symptoms, or presence of airflow limitation, or physician diagnosis of COPD. Despite these limitations, all available data show that COPD is a leading cause of morbidity and mortality worldwide and is projected to be the fifth most important cause of morbidity and mortality in the world by 2020 (1).

In the developing world which comprises a large part of the Asia Pacific region, epidemiological data is either patchy or localized or published in the native language (22–27). It is generally felt that the burden of COPD is underestimated in Asian countries due to poor recognition and understanding of the disease (4) or to different terminology and the recent introduction of the term COPD (5).

Global burden of disease study

The most authoritative source for estimates of the burden of respiratory disease for the Asia Pacific region comes from the Global Burden of Disease Study initiated in 1992 by the World Bank in collaboration with the WHO (1,2).

World prevalence of COPD was estimated at 9.34/1000 for males and 7.33/1000 for females of all ages. The estimate was 26.20/1000 for China. The main message is that respiratory diseases represent a major cause of death and disability for all age groups and races in the world.

Study on model estimates of COPD in Asian countries

Although exact figures for prevalence based on actual studies are unavailable, a recent study has generated estimates of prevalence for Asian Pacific countries for comparison and discussion (28). In the absence of epidemiological studies, this interim simplified study was undertaken by the Asia Pacific Round Table Group / Asia Pacific Task Force using a statistical model (29) to project the prevalence of COPD in individual countries of the Asia Pacific region for comparison.

The results of the study suggest that the prevalence of COPD in the region may be significantly greater than previously anticipated. The combined prevalence of 63/1000 for these countries is considerably higher than the overall rate of 39/1000 extrapolated from WHO data (1,2). The estimated rate for China was 65/1000 in this study, 2.5 times greater than that estimated in the WHO study. The COPD prevalence rates projected by the model reflect the high prevalence of risk factors for the disease in Asia (cigarette smoking, exposure to high risk occupations, biomass fuels indoors and air pollution outdoors). The data generated by this study await confirmation by actual studies but can be used to assist policy makers as the first step in determining COPD expenditures and establishing resource allocation priorities.

The BOLD study

The BOLD (Burden of Obstructive Lung Disease) initiative is an ongoing epidemiological study which has been developed as a spin off from the GOLD initiative (9). The primary objective of the BOLD study is to develop a standardized methodology, which can then be used to measure the prevalence and burden of COPD in all countries. Secondary objectives include determination of the prevalence of risk factors for COPD, burden of disability and variations in management of the disease.

Phase 1 of BOLD involved developing both a standardized "cookbook" for estimating COPD prevalence and a model for estimating the burden of COPD. Phase 2, comprising of pilot studies to revise and validate the "cookbook", is being undertaken in one developing country, China, and one developed country, the USA. Once the manual has been validated and published it will enable individual countries to initiate epidemiological trials using a standardized methodology to generate prevalence data for inter-country and inter-region comparisons.

Mortality

Mortality from COPD is considerable. The WHO estimated that there were 2.74 million deaths from

COPD worldwide in 2000 and the trend is increasing. In 1990, COPD was 6th leading cause of death but by 2020, it is projected to rank 3rd. In the USA, it is the only common disease (including stroke and coronary heart disease) in which death rate is increasing instead of falling (9).

Statistics from Asian countries are shown in Figures 1–2 and Tables 1–3. However, it is generally felt that there is an underestimation and misclassification due to a number of factors: the late introduction of the term COPD as a separate disease entity in deaths statistics; the listing of deaths under alternative terms such as chronic bronchitis and emphysema; and the changes in ICD classification (5). Despite these difficulties in terminology, mortality rates from national statistics are the only epidemiological data that are more readily available for comparison. A survey of these figures showed that they are similar or even higher than in those in the west.

In Japan, mortality from COPD in 1999 was 10.4/100,000, making it the 7th leading cause of death (5). In China, deaths from chronic respiratory disease rank first as the cause of all deaths. In 1994 the mortality rate for the whole population was 161.57/100,000 in the rural areas and 94.4/100,000 in cities, with a rising trend (30). In Hong Kong, COPD ranked as the 5th most common cause of death, accounting for 31.1/100,000 of the whole population in 1997 (31). In Singapore, between 1991–1998, COPD deaths occurred in 163/100,000 population aged over 55 years, with four times higher rates in men (28.2 per 10,000) than in women (6.9 per 10,000), and more deaths in the minority ethnic groups (32,33) (Table 2). In Thailand, the mortality is reported to be 500 to 4400/100,000 for men aged 51 and older, and 600 to 3400/100,000 in women (26). In Korea, according to national statistics the overall death rates for COPD have risen from 0.4/100,000 in 1983 to 6.7/100,000 in 2000 (4). However, misclassification into asthma is likely to have accounted for this apparently low rate, as traditional doctors who make up 20% of the medical profession often classify COPD as asthma (4).

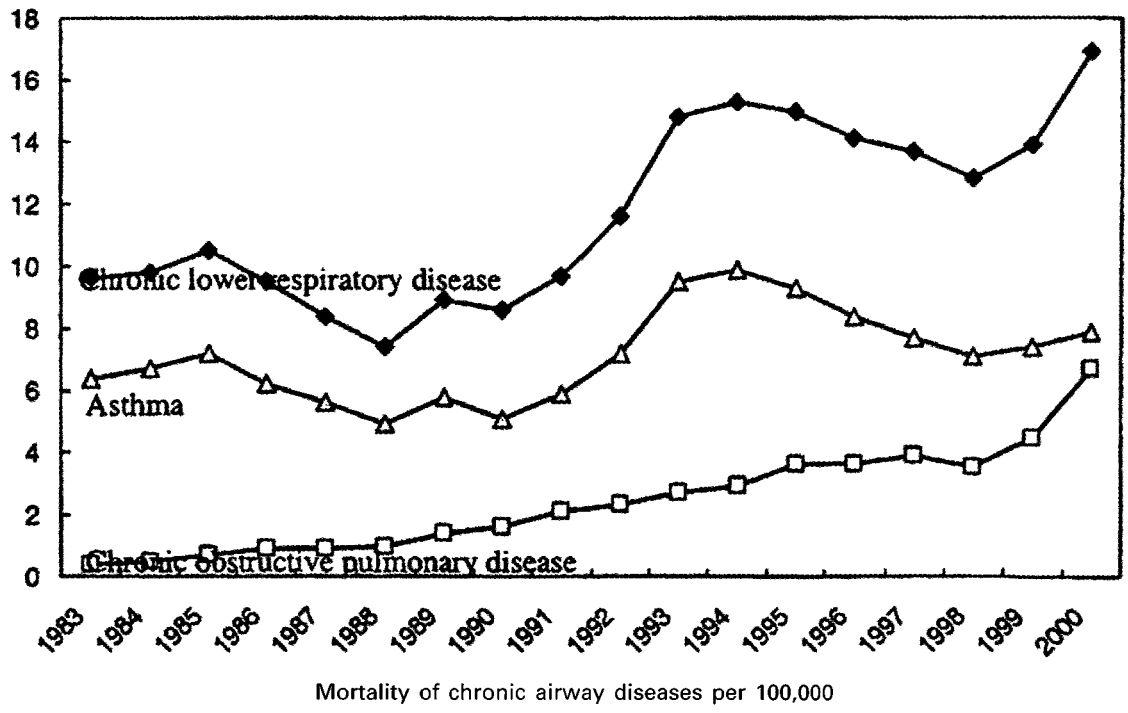


Figure 1. Age standardized mortality rates for chronic obstructive pulmonary disease versus asthma, 1983–2000 in Korea[4]

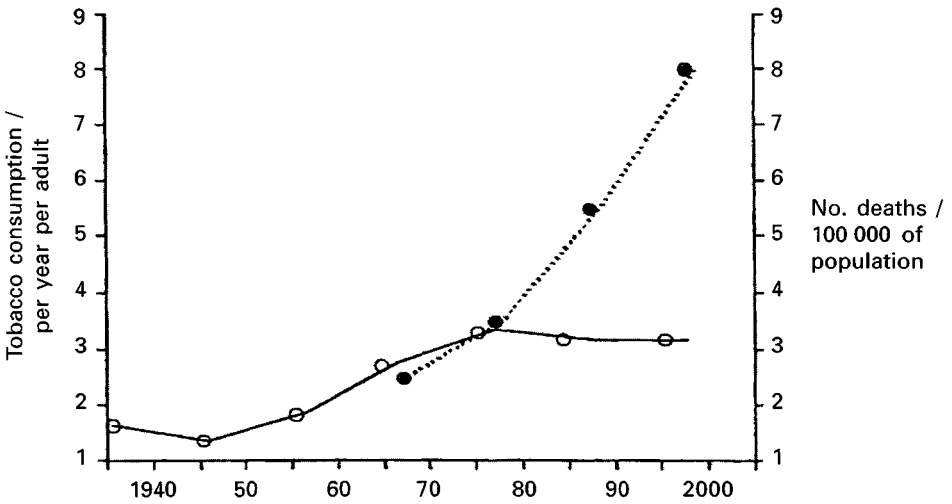


Figure 2. Tobacco consumption (per year per adult) (O) and the rate of death due to chronic obstructive pulmonary disease (COPD) (•) in Japan[34]

Table 1. Mortality Rate of Chronic Respiratory Diseases in China (1984–1994)[30]

Year	*Rank in cause of death*	*Rural area Mortality rate/100 000*	*% Total death*	*Rank in cause of death*	*Cities Mortality rate/100 000*	*% Total death*
1987	1st	143.06	20.83	4th	91.82	15.08
1994	1st	161.57	25.27	3rd	94.40	16.00

Table 2. COPD Hospitalization and Mortality in Population Aged 55 Years and Above, by Gender and Rthnicity, Singapore 1991–98[32]

Characteristics	*Hospitalization*		*Mortality*	
	Rates per 10,000*	*Rate ratio (95% CI)*	*Rates* per 10,000*	*Rate ratio (95% CI)*
Overall	52.4		16.3	
Gender				
Females	18.2	1.00	6.9	1.00
Males	94.1	5.15 (1.07–1.68)	28.2	4.05 (3.40–4.84)
Age groups				
55–64	17.5	1.00	3.5	1.00
65–74	68.0	3.90 (3.44–4.41)	15.4	4.40 (3.35–5.78)
75+	129.5	7.41 (6.56–8.38)	55.9	16.00 (12.4–20.5)
Ethnicity				
Chinese	53.9	1.25 (1.04–1.50)	16.4	1.48 (1.03–2.14)
Malays	45.1	1.07 (0.86–1.34)	19.3	1.76 (1.15–2.68)
Indians	43.9	1.00	10.7	1.00

*Adjusted for gender and age.

Table 3 Disabilities and Mortality in Different Age Groups in Thailand[26]

Age (yrs)	*Khon Kaen Hospital 1994–1998*				*MR (%)*	
	OPD (per person) per year		*IPD (per person) per year*			
	Male	*Female*	*Male*	*Female*	*Male*	*Female*
40–50	16	14	06	04	1	0
51–60	23	15	13	04	05	14
61–70	26	18	12	08	08	06
70+ up	3	27	13	11	44	34

Abbreviations OPD = outpatient department IPD = in patient department MR = mortality rate

Morbidity

This is usually studied by analyzing health care use such as hospitalization and clinic visits The problem is that data on health service use are not helpful for assessing burden of disease in an area where utilization is strongly influenced by the supply of medical services However, data that are routinely available, even though not validated, may provide useful information Hospitalization records from most Asian countries have shown a steady increase in COPD patients over the years, with higher demands on the use of intensive care services, thus increasing the health care burden (Figures 3 and 4) (4,5,26,31–34)

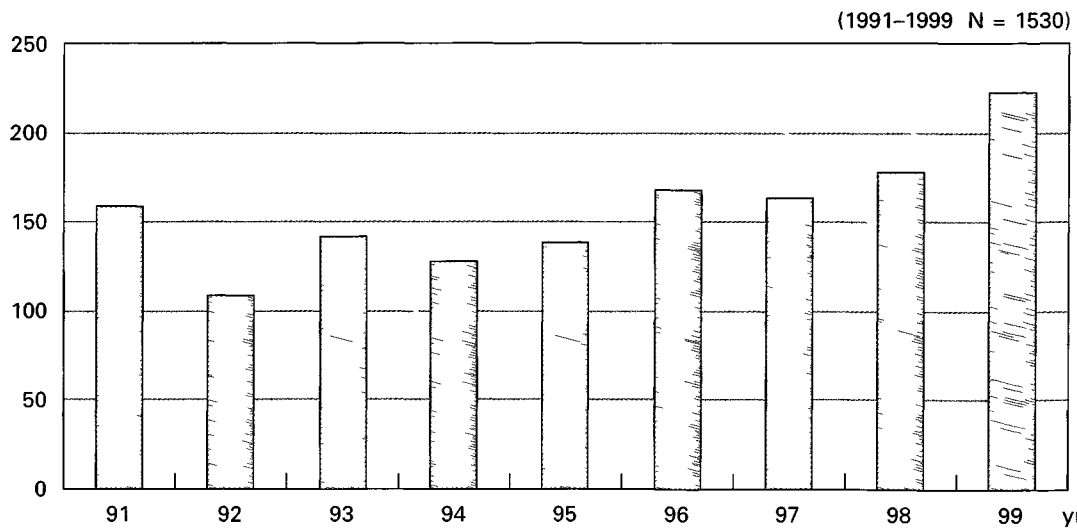


Figure 3 Number of admissions with chronic obstructive pulmonary disease in Seoul National University Hospital[4]

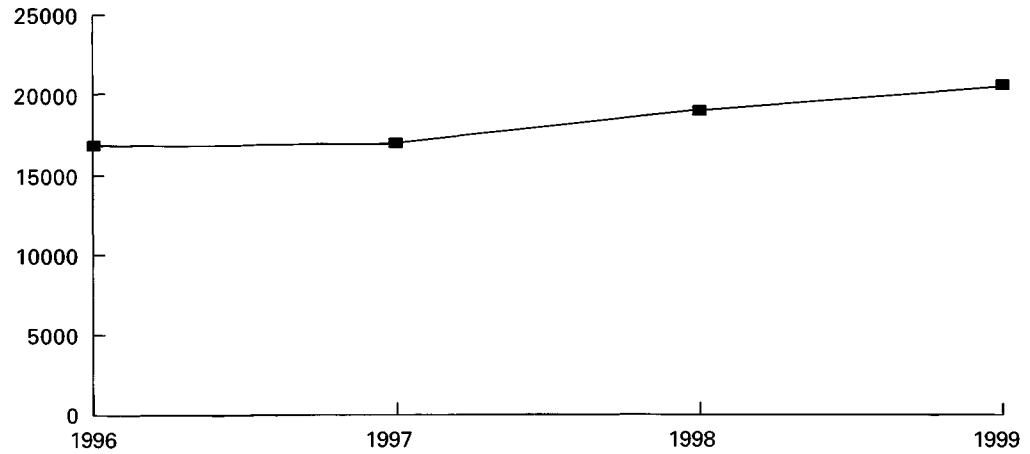


Figure 4. No. of Admissions of COPD via A&E Department (ICD 490, 491, 492, 496) to HA Hospitals (Hong Kong)[31]

Economic and Social Burden of COPD

Data on the direct (cost of health care utilization) and indirect (cost of the consequences of the disability) of COPD are only available from developed countries in the west. They show that total cost for COPD is greater than other common respiratory diseases such as asthma, influenza, pneumonia and tuberculosis (9). The World Bank/ WHO study designed a new measure for quantifying the economic and social burden of a particular disease which can be compared with other diseases, called the disability adjusted life years (DALY). This is a composite of the number of years lost through premature death and the number of years lived with disability adjusted for the severity of the disability. By this measure it is estimated that respiratory diseases account for 20% of the global burden for all diseases today.

The World bank/WHO also projected that the situation will worsen over the next 20 years. COPD, which is currently the 7th leading cause of death and disability world wide, will rise to the 5th position by the year 2020 (1,2).

These dramatic trends in respiratory diseases are attributable to two factors: the rise in tobacco related mortality and morbidity and the aging population. As these factors are most rapidly increasing in the developing world which constitutes a significant part of the Asia Pacific region, this region will therefore face one of its toughest public health challenges, which will exert huge demands on the economic and health care resources, and have an important negative impact on the social and economic progress of individual countries.

Aetiology / Risk Factors

There are four definite known risk factors for development of COPD. These are tobacco smoking, alpha$_1$ antitrypsin (α_1 AT) deficiency, occupational exposure to dusts and fumes and indoor air pollution caused by combustion of biomass / traditional fuels. In developing countries such as rural India and China (35–37), COPD occurs not uncommonly in non-smokers and this is attributed to environmental exposure to smoke from domestic fuels in poorly ventilated living areas. Other potential contributory risk factors include outdoor air pollution, allergy and bronchial hyperresponsiveness, and recurrent childhood respiratory infections. There is some evidence to suggest that these risk factors could be additive for development of COPD.

Smoking

Cigarette smoking is the major factor responsible for the development of COPD. The decline in lung function of susceptible smokers is twice that of non-smokers. This causal relationship is well established for 40 years in both cross-sectional (14) and longitudinal studies (15,16). The cumulative amount of tobacco smoke is related to its adverse effects in a dose-dependent manner. It is expressed as pack years (20 cigarette/pack; no of packs per day x number of years smoked). This index correlates with decline in lung function.

Different types of tobacco smoking are practised in Asian countries. Tobacco can also be sucked, chewed, sniffed, rubbed on the gums, smoked in water pipes, cigars, "rolled-your-own" cigarettes and bidis. The relative risk of these practices to the regular cigarettes smoking has not been reported.

The pattern of cigarette smoking is changing globally (38): it is slowly decreasing in the developed world at a rate of 1% annually and rising in developing countries at a rate of 2%. For example in China, the rates of smoking are extremely high both in the urban and rural areas, the respective rates being 60% and 64% in men and 15% and 9% in women (39). In a comparative study using an algorithm model to estimate the prevalence of COPD in 12 Asian countries, the rates of cigarette smoking extracted from national statistics showed that the overall smoking prevalence rates vary considerably between these countries (15% in Hong Kong to 36% in Japan and Vietnam), Table 4. The striking pattern is the wide discrepancy between men and women. The rates for women range from 2–4% for most of the Southeast Asian countries to 14% for women in Japan. In men the lowest rate was 27% in Singapore and Hong Kong, the highest is 73% in Vietnam, with intermediate high rates 63% in China and South Korea, and 52% in Indonesia. In Asia, Japan has the highest rate for women. Although smoking is still mainly a male habit, details from these national statistics indicate that there is an increase in the trend of smoking in women, especially those in their early twenties. These augur badly for the future, as many countries in Asia are developing in status and can ill afford the health, social and economic burden of smoking-related diseases in general and rising number of COPD patients in particular.

Table 4. Most recent Smoking Prevalence (%) by Country/region and Gender[28]

	Males	*Females*	*Overall*
Australia	28	21	24
China	63	4	34
Hong Kong	27	3	14
Indonesia	51	2	25
Japan	57	14	36
South Korea	63	3	33
Malaysia	49	4	25
Philippines	53	11	31
Singapore	27	3	15
Taiwan	55	3	30
Thailand	39	2	20
Vietnam	73	4	36

Occupational exposure to dust and fumes

Occupational exposure to dusts and chemicals (vapours, irritants and fumes) can also cause COPD, an association, which is not often fully appreciated as diseases caused by these risk factors are often considered separately under the category of occupational lung diseases or pneumoconioses (40,41). The obstructive functional abnormality resulting from single dust exposure alone is well documented (42). The multiplicative effect of a combination of exposure to dust, gas and fumes has also been shown (43).

Indoor air pollution

The association of indoor air pollution from domestic fuel combustion in poorly ventilated houses and the development of COPD in non-smoking women has been widely reported in India, Nepal, Arabia, Mexico and China (35–37,44–45) and is considered as an important non-smoking risk factor, especially in the developing countries (37).

Outdoor air pollution

The harmful effects of high levels of outdoor air pollution in causing worsening in patients with chronic cardiopulmonary diseases are well documented (46,47). The role of cumulative effects of outdoor air pollution in the development of COPD is unclear (48). This question is especially pertinent in many Asian countries, which experience consistent high levels of urban air pollution and recurrent high peak levels of pollution, or haze due to forest fires (49).

Alpha$_1$ antitrypsin deficiency

α_1 AT deficiency is the only known genetic factor, which is definitely linked to the development of emphysematous lung changes of COPD even in non-smokers. α_1 AT is a major circulating inhibitor of serine proteases. Compared with non-affected individuals, people who carry the α_1 AT deficiency gene have a 40-fold increased risk of developing COPD. It most often occurs in the people of Northern European origin, but is considered not to be a significant problem in Asians. In Japan, α_1 AT deficiency is rare and is due to the variant Siiyama (50).

In China, studies reported no definite relationship between α_1 AT deficiency and COPD in Chinese patients as defined by serum α_1 AT level (51). Furthermore, studies involving genotyping of α_1 variants AT alleic gene and electrophoretic phenotyping found no cases of PiZ or PiS in Chinese. Small number of variants such as ME Tokyo and ME irare have been reported but the pathogenetic relevance is unclear (52,53).

Airway hyperresponsiveness

Airway hyperresponsiveness, a hallmark of asthma has also been linked to increased risk of development of COPD, a concept termed the Dutch hypothesis (54) which is popular among clinicians in several Asian countries. Smokers with airway hyperresponsiveness show greater decline of lung function than normal smokers (55). The exact relation is unknown and is confounded by the fact airway hyperresponsiveness could also result from exposure to tobacco smoke and environmental insults.

Infection

Severe childhood infection has been associated with reduced lung function in adult life (56). HIV infection has been shown to accelerate the onset of smoking-related emphysema (57). Both these factors are prevalent in developing countries and may add to the burden of smoking related COPD.

Conclusions

Despite patchy and incomplete epidemiological data, there is existing persuasive evidence to support the fact that the burden of COPD is considerable in Asian countries. Although the recognition of COPD as a disease entity is a recent event in several Asian countries, acceptance is gathering momentum. The morbidity and mortality of COPD is rising worldwide. It is a largely male dominated disease driven by the high rates of tobacco smoking. Non-smoking risk factors, especially air pollution due to indoor fuel smoke are important in large areas of rural Asia and deserve further evaluation and surveillance. If the worse projected scenario is to be averted, there is urgency for multi-dimensional actions in reducing the burden of disease, by decreasing the main risk factors of cigarette smoking and air pollution and improving the management of the disease in all stages of severity.

References

1. Murray CJL, Lopez AD. Evidence-based health policy — lessons from the Global Burden of Disease Study. *Science* 1996; 274:740–3.
2. Murray CJL, Lopez AD. *The Global Burden of Disease: A Comprehensive Assessment of Mortality and*

Disability from Diseases, Injury and Risk Factors in 1990 and Projected to 2020. Cambridge, MA: Harvard University Press 1996.
3. Vermeire P. The burden of chronic obstructive pulmonary disease. *Resp Med* 2002, 96; (suppl C):S3–S10.
4. Shim YS. Epidemiological survey of chronic obstructive pulmonary disease and alpha-1 antitrypsin deficiency in Korea. *Respirology* 2001; 6:S9–S11.
5. Izumi T. Chronic obstructive pulmonary disease in Japan. *Current Opinion in Pulmonary Medicine* 2002; 8:102–5.
6. Authors as well as editors (Crofton J, Douglas A.) Chronic bronchitis and emphysema. In: *Respiratory Diseases.* Oxford: Blackwell 1969, 330–6.
7. United States Public Health Services: The Health Consequences of Smoking. A report of the surgeon general. Washington, DC, US Government printing Office, 1972, DHES Publication HSM, 72–7516.
8. Gross CP, Anderson GF, Powe NR. The relation between funding by the National Institutes of Health and the burden of disease. *N Engl J Med* 1999; 340:1881–7.
9. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO report. NIH, NHLBI publication Number 2701, April 2001.
10. Siafakas NM, Vermeire P, Pride NB, et al. ERS Consensus Statement. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1995; 8:1398–420.
11. American Thoracic Society Statement. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; 152:S77–S120.
12. Guidelines for the management of chronic obstructive pulmonary disease. The Thoracic Society of Australia and New Zealand. *Modern Medicine of Australia* July 1995; 38:132–46.
13. The COPD guidelines Group of the standards of care Committee of the BTS. BTS guidelines for the management of chronic obstructive pulmonary disease. *Thorax* 1997; 52:S1–S28.
14. US department of Health, Education and Welfare. *Smoking and Health: A Report of the Advisory Committee to the Surgeon General of the Public Health Service.* Washington DC: US Department of Health, Education and Welfare, Public Health Service Publication no 113, 1964.
15. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *BMJ* 1977; 1:1645–8.
16. Bates DV. The fate of chronic bronchitis: a report of the ten-year follow-up in the Canadian Department Veterans Affairs Coordinated study of chronic bronchitis. *Am Rev Respir Dis* 1973; 108:1043–65.
17. Hnizdo E, Singh T, Churchyard G. Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment. *Thorax* 2000; 55:32–8.
18. Snider GL, Doctor L, Demas TA, Shaw AR. Obstructive airway disease in patients with treated pulmonary tuberculosis. *Am Rev Resp Dis* 1971; 103:625–40.
19. Birath G, Caro J, Malmberg R & Simonsson BG. Airway obstruction in pulmonary tuberculosis. *Scand J Resp Dis* 1966; 47:27–36.
20. Bromberg PA & Robin ED. Abnormalities of lung function in tuberculosis. *Adv Tuberc Res* 1963; 12:1–5.
21. Nur Aida. Frequency of bronchial hyperreactivity in ex-TB patients. Thesis 1996, Department of Pulmonary Disease Persahabatan Hospital, Jarkarta, Indonesia.
22. Chen XS. Analysis of basic data of the study on prevention and treatment of COPD. *Chin J Tuber Respir Dis* 1998; 21:749–52.
23. Lai CKW, Ho SC, Lau J, et al. Respiratory symptoms in elderly Chinese living in Hong Kong. *Eur Respir J* 1995; 8:2055–61.
24. Woo J, Pang J. Spirometry in healthy elderly Chinese. *Thorax* 1988; 43:617–20.
25. Pandey MR. Prevalence of chronic bronchitis in a rural community of the hill region of Nepal. *Thorax* 1984; 39:331–6.
26. Saenghirunvattana S, Kongngeon V, Aeimrerksiri B, et al. Chronic obstructive pulmonary diseases in Thailand: incidence, prevalence, present status and future trends. *J Med Assoc Thai* 2001; 84:1407–11.
27. Wijaja A. Penelitian Epidemiologi Pengaruh Lingkungan Pada penjakit paru Obstructif Menahun di 37 Puskesmas, Mewakili semua kabupaten di java Timur. Kumpulan Naskah Illmiah Konas VI Perhimpunan Dokter Paru Indonesia (PDPI) Surakarta, 1993. [in Indonesian]
28. Regional COPD Working Group. (COPD) prevalence in 12 Asian-Pacific countries and regions: projections

based on the COPD prevalence estimation model. *Respirology* 2003; 8(2):192–8.
29. Schau BS, Lopez-Vidriero M, Peabody J, et al. Chronic Obstructive Pulmonary Disease: A Prevalence Estimation Model. *Am J Resp Crit Care Med 2000*; 163(5):A799.
30. Zhu YJ. Epidemiological survey of chronic obstructive pulmonary disease and alpha-1–1deficiency in China. *Respirology* 2001; 6:S13–15.
31. Ip MS. Chronic obstructive pulmonary disease in Hong Kong. *Respirology* 2001; 6:S3–S7.
32. Ng TP, Niti M, Tan WC. Trends and Ethnic variations in COPD hospitalization rates in Singapore, 1991–1998. *Am J Respir Crit Care Med* 2001; 163 (5):A694.
33. Tan WC. The epidemiology and clinical management of chronic obstructive pulmonary disease in Singapore. *Respirology* 2001; 6:S17–S20.
34. Tatsumi K. Epidemiological survey of chronic obstructive pulmonary disease in Japan. *Respirology* 2001; 6:S27–S33.
35. Smith KR. National burden of disease in India from indoor air pollution. *Proc Natl Acade Sci USA* 2000; 97:13286–93.
36. Zhang J, Smith KR. Hydrocarbon emissions and risks from cook stoves in developing countries. *J Expo Anal Environ Epidemiol* 1996; 6:147–61.
37. Chen BH, Hong CJ, Pandey MR, Smith KR. Indoor air pollution in developing countries. *World Health Stat Q* 1990; 43:27–38.
38. World Health Organization. World Health Statistics Annual 1995; Geneva, WHO 1995.
39. Wong XZ. Comments on "smoking cessation in China and primary health care". *Br Med J* (Chinese Edition) 2000; 3:101.
40. Lam TH, Ong SG, Baratawidjaja KG. A study of byssinosis in Hong Kong and Jakarta: research methods and objectives. *Am J Ind Med* 1987; 12:767–71.
41. Ng TP, Tsin TW, O'Kelly FJ, Chan SL. A survey of the respiratory health of silica-exposed gemstone workers in Hong Kong. *Am Rev Respir Dis* 1987; 135:1249–54.
42. Oxman AD, Muir DC, Shannon HS, et al. Occupational dust exposure and chronic obstructive lung disease. A systematic review of the evidence. *Am Rev Respir Dis* 1993; 148:38–48.
43. Bakke PS, Baste V, Hanoa R, Gulsvik A. Prevalence of obstructive lung disease in a general population: relation to title and exposure to some airborne agents. *Thorax* 1991; 46:863–70.
44. Perez-Padilla R, Regaldo J, Vedal S, et al. Exposure to bio-mass smoke and chronic airway disease in Mexican women. A case controlled study. *Am J Respir Crit Care Med* 1996; 154:701–6.
45. Koning HW, Smith KR, and Last JM. Biomass fuel combustion and health. *Bull World Health Organization,* 1985; 63:11–26.
46. Rokaw SN, Detels R, Coulson AH, Sayre JW, Tashkin DP, Allwright SS, Massey FJ. The UCLA population studies of chronic obstructive respiratory disease. *Chest* 1980; 78:252–62.
47. Arden Pope C, Bates DV, Raizenne ME. Health effects of particulate air pollution: time for reassessment? *Environ Health Perspect* 1995; 103:472–80.
48. Kunzli N, Kaiser R, Medina S, Studnicka M, Chanel O, Filiger P, Herry M, Forak F, Puybonnieux-Texier V, Quenel P, Schneider J, Seethaler R, Vergnaud J-C, Sommer H. Public health impact of outdoor and traffic-related air pollution: a European assessment. *Lancet* 2000; 356:795–801.
49. Tan WC, Qiu DW, Liam BL, et al. The human bone marrow response to acute air pollution caused by forest fires. *Am J Respir Crit Care Med* 2000; 161:1213–7.
50. Seyama K. State of alpha1-antitrypsin deficiency in Japan. *Respirology* 2001; 6:S35–S38.
51. Chen XY, Cheng XS, Li JZ, et al. Changes of serum elastase, alpha$_1$ antitrypsin, procollagen III, and malonadelhyde in smokers with and without chronic obstructive pulmonary diseases. *Chin J Intern Med* 1999; 38:178–80.
52. Yin QL, Liang ZQ. The frequency distribution of alleic gene of α_1AT in Chinese. *Chin Sci (Part B)* 1980; 10:897–903.
53. Huo JM, Shi YZ, Liu XH, et al. The phenotype and content of α_1AT in patients with COPD. *J Harbin Med Univ* 1990; 24:246–8.
54. Orie NGM, Sluiter HJ, De VriesK, et al. The host factors in bronchitis. In: Bronchitis, and International Symposium. Eds. Orie NGM, Sluiter HJ. Assen, Netherlands: Royal Vangorcum 1961, 43–51.
55. Tashkin DP, Altose MD, Connett JE, et al. Methacholine reactivity predicts changes in lung function over time

in smokers with early chronic obstructive pulmonary disease. The Lung Health Study Research Group. *Am J Respir Crit Care Med* 1996; 153:1802–11.

56. Tager Ib, Segal MR, Speizer FE, Weiss ST. The natural history of forced expiratory volumes. Effect of cigarette smoking and respiratory symptoms. *Am Rev Respir Dis* 1988; 138:837–49.
57. Diaz PT, King MA, Pacht ER, et al. Increased susceptibility to pulmonary emphysema among HIV-seropositive smokers. *Ann Intern Med* 2000; 132:369–72.

5

Chronic Obstructive Pulmonary Disease: Pharmacological Treatment

Wan Cheng Tan

Introduction

Renewed interest in the approach to managing chronic obstructive lung disease (COPD) is a recent phenomenon. A nihilistic attitude towards COPD has long existed among clinicians due to:

1. limited success at primary and secondary prevention (both primary and secondary prevention are aimed at the disease by removing risk factors) of the main causative risk factors;
2. the belief that COPD is a largely irreversible, progressive and self-inflicted disease; and
3. the dearth of effective treatment options.

As a consequence, the overall management of chronic obstructive lung disease has failed to receive adequate attention from the health care community in contrast to the enthusiasm directed at better asthma care including the publication of national and international asthma consensus statements, guidelines and strategies for its treatment.

In the past 5 years, guidelines for management of COPD were published in Europe, the United States, United Kingdom and Australia (1–4) followed by publication of similar guidelines in a few countries in Asia (5–7). The publication and dissemination of the Global Initiative for chronic obstructive pulmonary disease, GOLD guidelines (8), have encouraged several countries to define or update their national consensus on COPD treatment.

The GOLD guidelines adopt the overall approach characterized by a stepwise increase in treatment depending on the severity of the disease. Although largely based on practical considerations, the main advantage of this approach is the proper pre-treatment evaluation of the patient based on clinical and functional parameters in an attempt to detect individuals who are at risk for the disease and should be specifically targeted for preventive intervention. By this approach, the treatment can be systematic, comprehensive, intensive, preventive, and at the same time rationalizes the use of medication in COPD patients who have long been suboptimally treated as if they were suffering from asthma.

To date, smoking cessation is the only modality that can slow the progression of the disease (9). Non-pharmacological treatment is important and essential for a truly comprehensive management plan for COPD patients. It includes pulmonary rehabilitation for all stages of the stable disease; and oxygen therapy, ventilatory support and surgical treatment for the alleviation of end-stage COPD.

Although drug therapy has limited benefits in COPD, in clinical practice it is by far the most readily available form of treatment for COPD patients. In most countries in Asia, it is often the only form of treatment as the availability and

accessibility of non-pharmacological treatment may be limited by the type of health care coverage, the national health care resources and the competition for funds and manpower for all chronic diseases.

This chapter deals with the medications used in the management of stable COPD and its acute exacerbations.

Overview of the Medications

Despite the irreversibility of airway obstruction, as defined by spirometric measurement of forced expiratory volume FEV_1, clinicians and patients recognize that medications can prevent and control symptoms and improve effort tolerance.

The GOLD guidelines recommend the follow general principles for pharmacological treatment (8):

1. A stepwise increase in treatment depending on the severity of the disease.
2. Regular long-term maintenance treatment once frequent symptoms are controlled.
3. Individualization of treatment with monitoring and adjustment for disease worsening.

In many Asian countries, regular follow-up monitoring is often restricted to patients who have severe COPD, (usually $FEV_1 < 50\%$ predicted) with frequent hospitalizations and clinic visits for exacerbations and complications of COPD, while patients with mild to moderate disease may be seen intermittently during infective exacerbations only.

Bronchodilators

The growing realization in recent years that airflow limitation in COPD can be significantly relieved with the use of bronchodilators has changed the clinical approach to treating this disease. This improvement in airflow limitation, if maintained by patient compliance, can result in a sustained improved level of stable lung function. To achieve this goal, inhaled bronchodilators are the most efficient and hence the recommended therapy in most recent algorithms of pharmacological treatment for COPD (1–7).

Bronchodilators are the mainstay of treatment of COPD because of several beneficial effects and are used in two ways: either on an as-needed basis for relieve of persistent or worsening symptoms or on a long-term regular basis to prevent or reduce symptoms. The demonstrated effects are:

1. all categories of bronchodilators have been shown to increase exercise capacity in COPD without necessarily producing an improvement in FEV_1 (10–12) by improving in lung mechanics through reduction in hyperinflation (13),
2. regular treatment with short-acting bronchodilators is cheaper but less convenient than long-acting bronchodilator.

On the other hand, long-acting $beta_2$-agonist and ipratropium bromide have been shown to improve health status/quality of life significantly (13,14).

The choice between $beta_2$-agonist, anticholinergic, theophylline or combination therapy depends on the availability and individual responses in terms of symptom relief and adverse side effects (8). Combination bronchodilators are a method for improving bronchodilation without increasing the dose-dependent adverse side effects of a single drug. A logical approach is the use of bronchodilator according to an algorithm based on increasing disease severity (Table 1 and Figure 1).

Oral bronchodilators

In principle, most of the national guidelines support the recommendation for wider use of inhaled therapy. Inhaled bronchodilators is recommended based on solid evidence that it has a more rapid onset, is more effective and produces fewer side effects because of the smaller dose relative to the oral preparations (8). The GOLD guideline recommends inhaled bronchodilator as the preferred mode of delivery for symptomatic management in stable COPD but does not exclude the use of oral bronchodilators.

In real-life, knowledge does not necessarily lead to clinical implementation as other factors may predominate. The acceptance of any form of therapy by both patients and doctors is a key determinant in the actual usage of the drug. Oral bronchodilators are still widely used for COPD in

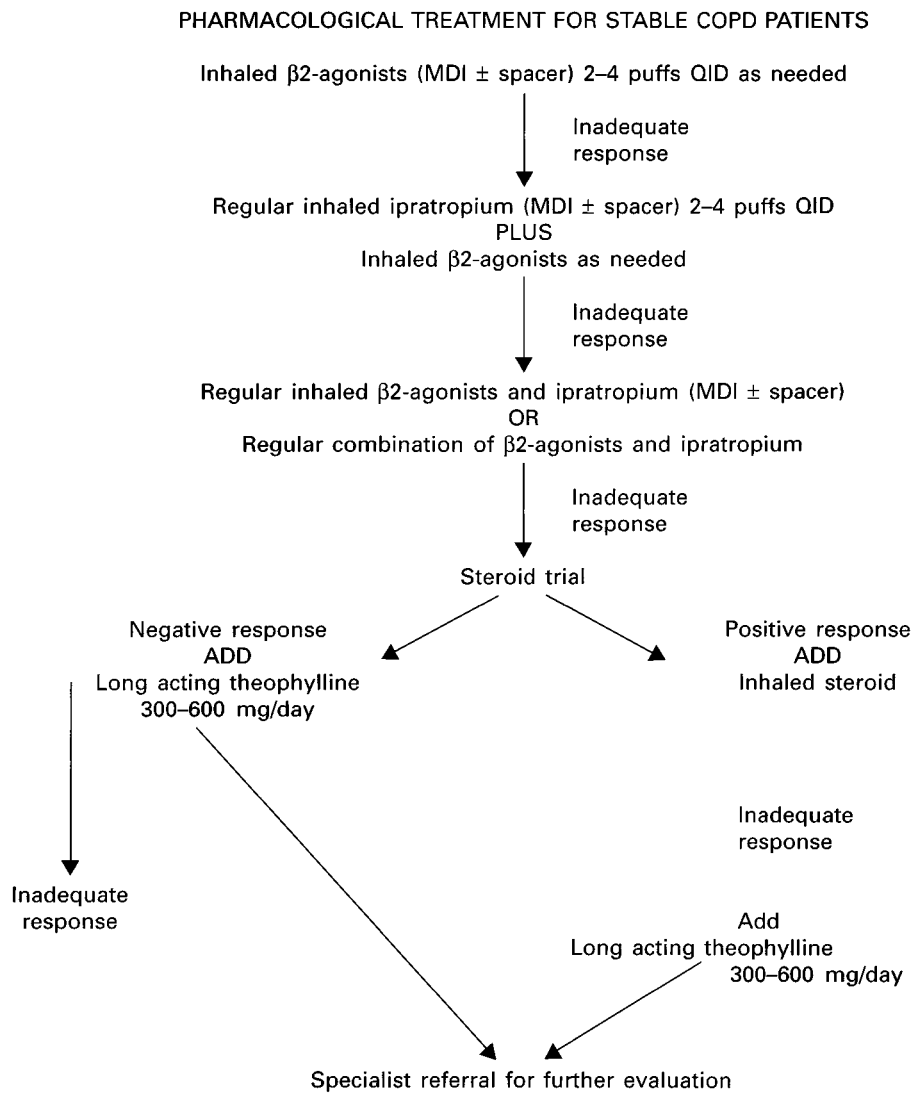
Table 1. Therapy at Each Stage of COPD[8]

Stage	*Characteristics*	*Recommended treatment*
All		• Avoidance of risk factor(s) • Influenza vaccination
0: At Risk	• Chronic symptoms (cough, sputum) • Exposure to risk factor(s) • Normal spirometry	
I: Mild COPD	• FEV_1 / FVC < 70% • $FEV_1 \geq 80\%$ predicted • With or without symptoms	• Short-acting bronchodilator when needed
II: Moderate COPD	**IIA:** • FEV_1 / FVC < 70% • $50\% \leq FEV_1 < 80\%$ predicted • With or without symptoms	• Regular treatment with one or more bronchodilators • Rehabilitation • Inhaled glucocorticosteroids if significant symptoms and lung function response
	IIB: • FEV_1 / FVC < 70% • $30\% \leq FEV_1 < 50\%$ predicted • With or without symptoms	• Regular treatment with one or more bronchodilators • Rehabilitation • Inhaled glucocorticosteroids if significant symptoms and lung function response or if repeated exacerbations
III: Severe COPD	• FEV_1 / FVC < 70% • FEV_1 < 30% predicted or presence of respiratory failure or right heart failure	• Regular treatment with one or more bronchodilators • Inhaled glucorticosteroids if significant symptoms and lung function response or if repeated exacerbations • Treatment of complications • Rehabilitation • Long-term oxygen therapy if respiratory failure • Consider surgical treatments

many Asian countries because they are culturally acceptable, less expensive and do not require the patient to be educated on the inhaler technique. Often the trade-off is between the compliant use of a simple regimen, for example, an inexpensive and familiar drug (e.g. theophylline) that has, albeit a weak bronchodilator effect, against the irregular or improper use of a pharmacologically more potent and more expensive inhaled medication, which requires some skill to administer. As COPD patients are often elderly, they may have reduced dexterity and coordination and hence find it harder to use a simple metered dose inhaler (MDI) than a younger and healthy person. Thus oral medications are often preferred by COPD patients and their doctors and commonly used in maintenance treatment, despite a lower efficacy and greater side effects. There is a need to prescribe simple MDIs with specific and clear training in inhaler usage for the elderly.

Beta$_2$-agonist

Inhaled beta-2-adrenergic agonists are effective bronchodilators with a relatively rapid onset of action. They reduce airway smooth muscle tone and improve expiratory flow, hence reducing dyspnoea. They also improve emptying of the lungs, reduce dynamic hyperinflation at rest and during exercise and hence improving exercise performance (12,15,16). The improvement in FEV_1



Outcome is measured in terms of improvement in FEV_1, FEV_1 / FVC, peak expiratory flow rate, increased six-minute walking distance, decreased dyspnoea or symptom score, and improved quality of life measures.

Figure 1. Hong Kong guideline[5]

does not reliably predict symptomatic improvement from long-term bronchodilator use.

Anticholinergics

Inhaled ipratropium bromide, the only inhaled anticholinergic agent in Asian countries, has been shown to be an effective bronchodilator with a longer action than short acting $beta_2$-agonists. It is more effective in COPD and is associated with a low incidence of side effects because of poor local absorption of the drug. It is often combined with or added to $beta_2$-agonist for treatment of COPD (13). The use of the combination of these two classes of inhaled bronchodilators provides superior bronchodilation than treatment with either of the individual components without added side effects or loss of the positive effects of ipratropium bromide namely that of reduced

exacerbation frequency and lack of tachyphylaxis (15–17).

The management of COPD is likely to receive a boost with the introduction of the new anticholinergic drug, tiotropium, widely anticipated but currently not available yet in Asian countries. This drug shows significant advantages in terms of its prolonged action (> 24 hours) and relative receptor selectivity (blocks M1 & M3, not M2) (18). Once-daily tiotropium has been shown to have superior efficacy to ipratropium bromide four times daily on measures of spirometry, dyspnoea, health status and exacerbations, and also greater improvement in lung function than salmeterol twice daily (10). Furthermore, it is associated with a low incidence of adverse effects of which transient dry mouth is the most frequent.

Combination therapy

Combinations of different types of bronchodilators are aimed at increasing the degree of bronchodilation for equivalent or lesser side effects (13,15–17,20–21).

Examples of such combinations are:

1. metered dose inhalers containing salbutamol and ipratropium bromide; or salmeterol and ipartropium bromide;
2. nebulized solution of salbutamol and ipratropium bromide for acute exacerbation;
3. oral theophylline and inhaled salbutamol (20); and
4. long-acting beta$_2$-agonist and theophylline (21).

Inhaler devices

Inhaled bronchodilator treatment is delivered as a dry aerosol from the pressurized metered dose inhaler (pMDI) or the dry powder inhaler (DPI) or as a wet aerosol by nebulization. There is no evidence of any preference by patients for any type of inhaler other than cost consideration. Patients who had experienced the effect of nebulized bronchodilator in a previous severe exacerbation may pressurize their doctor to prescribe nebulized solution for long-term treatment. Wet nebulizers are not recommended for regular treatment because they are expensive, require appropriate maintenance, and may increase adverse effects due to the high dose delivered (8). However, in Asian practice this mode of treatment may be preferred by patients with severe COPD who had previously received large dose nebulized bronchodilator for severe exacerbations.

Theophylline

In most Asian countries, theophylline is widely used as a bronchodilator for the treatment of COPD. The consensus among physicians is that it is a comparable or less potent bronchodilator than inhaled beta$_2$-agonist or anticholinergic. The additional potential benefits from the other therapeutic effects of theophylline, such as cardiac output increase, systemic and pulmonary vasodilation, increased salt and water excretion, central nervous system stimulation, improved respiratory muscle function, and anti-inflammatory effects (7) have drawn more attention than is justified from outcome of clinical trials.

There is no report in the English literature (22,23) of systematic clinical evaluation of the use of theophylline in Asian patients with COPD (24), although there are a few pharmacokinetic studies in patients with asthma (25–28) which suggest that lower dosages may suffice in Asian patients who may have a decreased metabolism for the drug compared with that reported in the West. However, unpredictable variations in metabolism may occur in Asian patients due to the frequent concomitant use of herbs in holistic preventive therapy or as food (29). Theophylline level is reduced by smoking, alcohol, and the anti-tuberculous drug rifampicin and raised in the elderly, heart failure, liver dysfunction and the concomitant use of cimetidine, macrolide antibiotic (erythromycin) and fluoquinolone (ciprofloxacin). Therapeutic monitoring for target blood levels of theophylline between 5 and 15 μg/ml is recommended (7).

Sustained-release theophylline is often used in combination with inhaled therapy for moderate to severe COPD in Asian countries (7).

Glucocorticosteroid therapy

Unlike in asthma, the role of corticosteroids in COPD is limited by specific indications. There is a no evidence that systemic glucocorticosteroids are beneficial in the long term treatment of patients with COPD while the chronic toxicity of systemic

steroids are well known. Hence, oral corticosteroid is not recommended for COPD (7).

On the other hand, the combined results from four large randomized controlled trials have shown that moderate to high dose of inhaled corticosteroid can benefit symptomatic patients with a documented lung function response to inhaled corticosteroid or those with $FEV_1 < 50\%$ predicted and repeated exacerbations, by reducing symptoms, improving lung function and exercise capacity, and reducing the number of severe exacerbations (30–33). However, the long-term safety of high-dose inhaled corticosteroid in COPD patients is not known. The safety data of inhaled corticosteroids have been derived from the large databases of younger asthmatic patients. It is unclear whether these would equally apply to the elderly, physically deconditioned patients with severe COPD, who have weight loss and muscle wasting. Additionally in many Asian countries, there is the intuitive concern over the reactivation of quiescent pulmonary tuberculosis with the use of long-term, high-dose inhaled corticosteroid for moderate to severe COPD (34).

Other pharmacological treatment

Mucolytic [mucokinetic / mucoregulator] agents

Examples of this group of medications are ambroxol, carbocystein, iodinated glycerol. The regular, long term use of this group of agents remains controversial. A Cochrane meta-analysis (35) cautiously concluded that there may be a reduction in episodes of cough and sputum in mild to moderate COPD patients observed for 2–6 months, and that patients with viscous sputum may benefit from mucolytics. However, the evidence is derived largely from clinical experience and consensus (7).

Despite a lack of firm evidence, mucolytics is a common medication for cough in COPD in Asian countries. The reasons for the popularity are unclear, but may be related to the fact that they are oral medications, the concept of treatment is attractive, simple to understand and culturally acceptable, and the drugs are free from any serious side effects.

Antioxidants

Based on limited data, antioxidants, such as N-acetyl cysteine, have been shown to reduce the frequency of exacerbations and may have a possible role in the treatment of patients with recurrent exacerbations (8). These impressions await the result from ongoing trials.

Just as with mucolytics, this group of drugs has certain holistic appeal to patients. Some guidelines advocate its use for cough together with traditional herbal mucolytic agents (7).

Antitussive

The regular use of antitussive is contraindicated in stable COPD (8). Despite a lack of evidence of any benefit, it is often prescribed. The reason is unclear but may be due to a misconception of the disease process and a lack of consistently effective drugs in COPD.

Vaccines

The role of influenza vaccination in reducing complications and death from influenza in elderly COPD is well established. The recommendation is to use vaccine containing killed or inactivated viruses, administered once or twice each year, before the peak of the anticipated outbreak. WHO has two vaccination formulations per year containing the appropriate virus strains, and made available in February and September. There is no regional study on the effectiveness of influenza vaccine in the tropics. In temperate countries with a single peak, vaccination is given two months before winter. In tropical countries (e.g. tropical Asia: Singapore, Thailand) bimodal peaks may occur, while in other countries, such as Vietnam, there is no seasonality. It is unclear how often and what vaccination formulations should be recommended for tropical Asia. Malaysia has instituted a mandatory influenza vaccination for annual Haj pilgrims departing for Mecca. Overall, vaccination is not widely practiced because of the above uncertainties and because they are not reimbursable (34).

Antibiotics

There is no role for long-term prophylactic antibiotic in stable COPD as shown by many studies (8) and similar recommendations are adopted by most Asian countries (5–7). The main

use of antibiotic is in the treatment of acute infective exacerbations of COPD. There are regional preferences but overall a broad-spectrum antibiotic is given, which is active against *S. pneumoniae, H. influenza* and *M. catarrhalis* (7).

Nicotine replacement therapy

Smoking cessation is the only method, which has been shown to slow the progression decline in lung function in COPD patients. However, many patients with COPD have tried and failed smoking cessation on their own and will require the support of a structured program. The mainstay of any smoking cessation program is effective and sustained practical counseling, behavioural therapy and social support, supplemented by pharmacotherapy if necessary. Nicotine replacement products in any form (gum, inhaler, nasal spray, transdermal patch, sublingual tablet, or lozenges) when used in the setting of a smoking cessation program can produce a quite rate of 35% at 1 year and sustained rate of 22% at 5 years. Another type of drug, the antidepressant bupropion, has also been shown to increase long-term quit rates. These medications are expensive, may not be readily available in all Asian countries and are prescribed selectively only if counselling and support fail.

Management of Chronic Stable COPD

As COPD is a progressive disease, the clinical presentation ranges from being asymptomatic to cough and exertional dyspnoea and later to incapacitating end stage respiratory failure. Most international guidelines, including Asian ones, recommend a systemic algorithmic approach in the management of COPD (Table 1 and Figure 1).

Management of Acute Exacerbations of COPD

The standard treatment for an acute exacerbation consists of administration of inhaled bronchodilators, antibiotic for infection, systemic corticosteroids, and treatment of complications of cardiorespiratory failure. However, there is some reservation expressed by Asian doctors in the use of a short course of systemic corticosteroid for acute exacerbation in Asian patients despite good evidence that they shorten recovery time and help restore lung function more quickly (36–38). The reasons for this concern lie in the difficulty of differentiating an exacerbation of COPD from reactivated pulmonary tuberculosis in countries with a high prevalence of tuberculosis and those patients who have severe COPD with recurrent exacerbations may be exposed to frequent doses of systemic corticosteroids which may reactivate quiescent tuberculosis (34). There is a need for more information of the safety of systemic corticosteroids for acute exacerbations in patients with severe COPD and frequent exacerbations in developing countries with a high prevalence of tuberculosis (39).

References

1. Siafakas NM, Vermeire P, Pride NB, et al. ERS Consensus Statement. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1995; 8:1398–20.
2. American Thoracic Society statement. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; 152:S77–S120.
3. Guidelines for the management of chronic obstructive pulmonary disease. The Thoracic Society of Australia and New Zealand. *Mod Med Aust* 1995; 38:132–46.
4. The COPD guidelines Group of the standards of care Committee of the BTS. BTS guidelines for the management of chronic obstructive pulmonary disease. *Thorax* 1997; 52:S1–S28.
5. Mok T, Tsang K, editors. *Current Management of COPD.* Hong Kong Lung Foundation Ltd. 1999.
6. Guidelines on Organizing Comprehensive Care for Chronic obstructive pulmonary diseases. WW Yew and KS Chan for TN & *Chest* Subcommittee. central Coordinating Committee, Hospital Authority, Jan 2001.
7. Chinese Guidelines of COPD and asthma. Chinese Society of Respiratory Diseases, Chinese Medical Association, Beijing 1998.

8. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI /WHO report. NIH, NHLBI publication Number 2701, April 2001.
9. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV_1. The Lung Health Study. *JAMA* 1994; 272:1497–505.
10. Mahler Da, Matthaway A, Synder PE, et al. Sustained release theophylline reduces dyspnoea in non-reversible obstructive airway disease. *BMJ* 1988; 297:1506–10.
11. Sandralee A, Blosser MD, Steven L, et al. Is an anticholinergic agent superior to a b2 agonist in improving dyspnoea DNA exercise limitation in COPD? *Chest* 1995; 108:730–5.
12. Jenkins Sc, Heaton RW, Fulton TJ, Moxham J. Comparison of domiciliary nebulized salbutamol and salbutamol from a metered-dose inhaler in stable chronic airflow limitation. *Chest* 1987; 91:804–7.
13. Hughes JA, Tobin MJ, Bellamy D, et al. Effects of ipratropium bromide and fenoterol aerosols in pulmonary emphysema. *Thorax* 1982; 36:607–70.
14. Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. *Am J Respir Crit Care Med* 1997; 155:1283–9.
15. Ikeda A, Nishimura K, Koyama H, Izumi T. Bronchodilating effects of combined therapy with clinical dosages of ipratropium bromide and salbutamol for stable COPD: comparison with ipratropium bromide alone. *Chest* 1995; 107:401–5.
16. Guyatt GH, Townsend M, Pugsley SO, et al. Bronchodilators in chronic airflow limitation. Effects on airway function, exercise capacity and quality of life. *Am Rev Respir Dis* 1987; 135:1069–74.
17. Friedman M, Serby CW, Menjoge SS, Wilson JD, Hilleman DE, Witek TJ, Jr. Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD. *Chest* 1999; 115:635–41.
18. Rennard SI. New therapeutic drugs in the management of chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 2002; 8:106–11.
19. Rees PJ. Tiotropium in the management of chronic obstructive pulmonary disease. *Eur Respir J* 2002; 19:205–6.
20. Taylor DR, Buick B, Kinney C, Lowry RC, McDevitt DG. The efficacy of orally administered theophylline, inhaled salbutamol, and a combination of the two as chronic therapy in the management of chronic bronchitis with reversible airflow limitation. *Am Rev Respir Dis* 1985; 131:747–51.
21. Cazzola M, Donner CF, Matera MG. Long acting beta(2) agonists and theophylline in stable chronic obstructive pulmonary disease. *Thorax* 1999; 54:730–6.
22. Murciano D, Auclair MH, Parlente R, Aubier M. A randomized, controlled trial of theophylline in patients with severe chronic obstructive pulmonary disease. *N Engl J Med* 1989; 320:1521–5.
23. McKay SE, Howie CA. Thonson AH, Whitting B, Addis GJ. Value of theophylline treatment in patients handicapped by chronic obstructive pulmonary disease. *Thorax* 1993; 48:227–32.
24. Teramoto S. Effect of sustained release of theophylline on pulmonary physiologic function in elderly patients with chronic obstructive pulmonary disease [Japanese]. *Nippon Ronen Igakkai Zasshi* 2002 1; 39:414–8.
25. Jeong CS, Hwang SC, Jones DW, Ryu HS, Sohn K, Sands CD. Theophylline disposition in Korean patients with congestive heart failure. *Ann Pharmacother* 1994; 28:396–401.
26. Rojanasthien N, Kovjiriyapan K, Manorot M, Pothirat C. Comparative steady-state bioavailability of sustained-release theophylline preparations: Theo-Dur, Uni-Dur and Xanthium. *Asian Pac J Allergy Immunol* 2001; 19:69–78.
27. Chan KW, Lee HS, Ti TY, Tan TH, Feng PH. A comparative study of the use of choline theophyllinate and a sustained-release theophylline in adults with chronic asthma. *Ann Acad Med Singapore* 1985; 14:470–4.
28. Pang JA, Zhang YG, Swaminathan R. The pharmacokinetics and efficacy of slow-release theophylline with asymmetric dosing in asthmatic Chinese. *Chest* 1988; 93:785–9.
29. Fugh-Berman A. Herb-drug interactions. *Lancet* 2000; 355:134–8.
30. Pauwels RA, Lofdahl CG, Laitinen LA, Schouten JP, Postma DS, pride NB, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on chronic obstructive pulmonary disease. *N Eng J Med* 1999; 340:1948–53.

31. Vestbo J, Sorensen T. Lange P, et al. Long term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomized controlled trial. *Lancet* 1999; 353:1819–23.
32. Burge PS, calverley PM, Jones PW, et al. Randomised. double-blind, placebo- controlled study of fluticasone proprionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; 320:1297–303.
33. The Lung Health Study Research Group. Effect of inhaled triamsinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000: 343:1902–9.
34. Regional GOLD consensus Statement — prepared by the Asia-Pacific COPD roundtable group — Advanced draft. Asia Pacific Society of Respirology.
35. Poole PJ, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2000; 2 available from: www.update-software.com or www.updatusa.com.
36. Thompson WH, Nielson CP, Carvalho P, et al. Controlled trial of oral prednisolone in outpatients with acute COPD exacerbation. *Am J Respir Crit Care Med* 1996; 154:407–12.
37. Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease: a prospective randomized controlled trial. *Lancet* 1999; 354:456–60.
38. Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, Light RW, et al. Effect of systemic glucocorticosteroid on exacerbations of chronic obstructive pulmonary disease. Dept of Veterans Affairs Cooperative Study Group. *N Engl J Med* 1999; 340:1941–7.
39. Asian Pacific COPD Roundtable Group Sixth Meeting, 1–2 June 2002, Hong Kong, Summarized Minutes of discussion.

6 Non-invasive Mechanical Ventilation in COPD

Rong Chang Chen and Nan Shan Zhong

Introduction

About 10–15% of patients with chronic obstructive lung disease (COPD) develop respiratory failure, and Cheng et al have shown that 23.1% of 2020 patients with COPD have cor pulmonale (1). COPD is often associated with acute exacerbations of symptoms. In moderate to severe COPD, an exacerbation is associated with not only increased cough, sputum production and breathlessness, but often acute respiratory failure. The mortality of COPD patients admitted to hospital for an acute exacerbation is approximately 10%, and the long-term outcome is poor. Hospitalization for acute exacerbations leads to a significant healthcare burden. Ventilatory support, one of the active medical intervention measures, is of great importance in the management of COPD patients with acute exacerbation.

Rationale for Mechanical Ventilation in COPD

COPD is characterized by the presence of chronic airflow obstruction often associated with emphysema. This airflow obstruction is caused in part by airway inflammation and in part by the loss of alveolar septal tethering of small airways that accompanies the destructive changes of alveoli. During the chronic process, recurrent acute exacerbations lead to a progressive increase in dyspnoea and even development of respiratory failure due to the deterioration of airflow obstruction.

In patients with COPD, inspiratory muscles fatigue may contribute to the development of respiratory failure. In moderate to severe COPD, inspiratory muscles often function poorly for a number of reasons. First, increased airway resistance increases the workload of respiratory muscle. Second, diaphragm flattening and over-inflation of the chest cavity often occur as emphysema is worsening. Because of elevated functional residual capacity, dynamic hyperinflation has been frequently observed in COPD patients not only during exercise but also during breathing at rest (2). Both emphysema and dynamic hyperinflation put the inspiratory muscles to mechanical disadvantage leading to increase in workload and decrease in force. Our study demonstrated that both increased lung volume and threshold loading caused by dynamic hyperinflation contributed to the development of dyspnoea (3). Other factors contributing to the weakness of the diaphragms include malnutrition, muscle atrophy, hypoxaemia and hypercapnia. It has been shown that patients with moderate COPD failed to generate higher transdiaphragmatic pressure in response to increased ventilatory demand (4). They developed abdominal paradoxical breathing during incremental maximal

exercise suggesting diaphragmatic fatigue (4). The imbalance between mechanical load and inspiratory muscle capacity predisposes to inspiratory muscle fatigue and pump failure. As lung function deteriorates, hypoxaemia and hypercapnia develop, further reducing the force of inspiratory muscles. The presence of hypercapnia often indicates task failure of the inspiratory pump. Based on the above findings, assisted mechanical ventilation may eliminate inspiratory muscle fatigue and lung volume reduction surgery may improve the inspiratory muscle function in selected patients.

The goals of mechanical ventilation in COPD are as following:

1. to reverse hypoxaemia that has not been corrected with supplemental oxygen delivered either by nasal cannula or face mask;
2. to reverse severe respiratory acidosis and
3. to relieve respiratory distress and respiratory muscle fatigue.

Methods of noninvasive mechanical ventilation

Noninvasive mechanical ventilation (NIMV) consists of intermittent negative pressure ventilation (NPV) and noninvasive positive pressure ventilation via face or nasal mask (NIPPV). Both NPV and NIPPV have been used for the management of COPD patients. In general, although NPV is effective in reducing electrical excitation and mechanical activities of inspiratory muscles as well as improving dyspnoea and arterial blood gases in COPD patients (6), NPV is less effective than NIPPV. The main disadvantage of NPV is that it limits patients' activities. Other complications, such as sleep disturbance and oesophageal sphincter dysfunction, have been reported with NPV. We have observed that a few patients may develop obstructive apnoea with very short inspiratory time. NIPPV is by far the most commonly used method in the management of COPD. It is more effective because it is easily triggered by and better synchronized with the patient's breathing effort.

Comparison of NIPPV With Invasive Mechanical Ventilation (IMV)

Almost all ventilators and modes of ventilation used for IMV could be used for NIPPV. Table 1 summarizes the difference between IMV and NIPPV in clinical practice. It is important to improve the efficacy by reducing dead space, improving seal condition and facilitating secretion clearance.

The role of NIPPV in COPD

Endotracheal intubation and IMV have been proven to be effective life-support measures in the management of respiratory failure in COPD. However, criteria for intubation are not well defined as yet and the artificial airway may lead to discomfort and complications such as respiratory infection and tracheal injury. Intubation itself increases the mortality of COPD, probably due to nosocomial pneumonia (7,8). In clinical practice, it is difficult for physicians to determine the ideal time for intubation and initiate IMV. NIPPV is an alternative modality to provide ventilatory support.

Table 1. Comparison of NIPPV with Invasive Mechanical Ventilation.

	Non-invasive	*Invasive*
Interface	Mask/Mouth Piece	Intubation/Tracheotomy
Dead Space	Increased	Decreased
Seal Security	Poor	Good
Triggering	Poor	Better
Secretion Clearance	Cough	Suction

Table 2. Indications and Contra-indications for NIPPV.

Indications	*Contra-indications*
1. Respiratory distress with moderate-severe dyspnoea, use of accessory muscles of respiration, abdominal paradoxical breathing. 2. PH < 7.35 with $PaCO_2$ > 45mmHg. 3. Breathing frequency > 25 breaths/min.	1. Respiratory arrest. 2. Cardiorespiratory instability (eg, hypotension with impared perfusion, serious dysrhythmia, myocardial infarction with pulmonary oedema. 3. Uncooperative patients. 4. Recent facial, oesophageal and gastric surgery. 5. Craniofacial trauma or burn. 6. High risk of aspiration (inability to manage secretion). 7. Inability to protect airway. 8. Fixed anatomic abnormalities of the nasopharynx (eg, severe pharyngomalacia) Relative contra-indications: 1. Extreme anxiety. 2. Massive obesity. 3. Copious secretion. 4. Acute respiratory distress syndrome (ARDS) as the aetiology of acute respiratory failure

In addition, patients with severe COPD often have repeated acute exacerbations with development of respiratory failure at times. In this circumstance, it will be difficult to intubate the patient during each episode. As NIPPV could be initiated and weaned more easily, it is used commonly in the management of early stage of respiratory failure or in the weaning process in COPD. The indications and contra-indications for NIPPV are shown in Table 2. Although proper selection of patients may improve the efficacy of NIPPV, the response to NIPPV is more valuable in predicting the success of such treatment. Thus, a trial of NIPPV for 1–2 hours and monitoring the response through arterial blood gases and clinical assessment, will help to select proper candidates for this therapy.

Clinical Applications of NIPPV

Acute exacerbations of COPD

COPD with respiratory failure is the most common disease requiring mechanical ventilation. More than 80% COPD patients develop respiratory failure during acute exacerbations. The frequency of use of mechanical ventilation in COPD patients during an acute exacerbation varies widely, between 3% to 74%, in different studies due to variation in severity of the studied populations (8). In most of the studies, mortality was higher in the intubated group. Although the substantial increase in mortality in intubated patients was related to the severity of the underlying disease, infection related to intubation also contributed to the higher mortality (8). NIPPV is an effective modality of treatment with less morbidity than intubation for selected COPD patients with respiratory failure. Meduri et al (9) were the first to report that NIPPV improves arterial blood gases (ABG) in COPD patients. Since then, there have been many publications on the application of NIPPV in acute exacerbation of COPD. NIPPV not only relieves dyspnoea and improves ABG, but also reduces mortality and intubation rate (6–8). Chen et al (10) conducted a trial on 21 COPD patients with hypercapnic respiratory failure; 11 patients received NIPPV while 10 received conventional therapy as controls. They showed that in those received NIPPV, $PaCO_2$ dropped from 11.3 ± 1.1 kPa to 9.0 ± 1.8 kPa after two hours ventilation. The overall reduction of $PaCO_2$ in NIPPV group was significantly greater than the control group in the 1st and 7th day after treatment. None of the patients in the NIPPV groups required

intubation compared with 5 patients in control group.

In open clinical trials, the success rate of NIPPV was between 51% and 91%. In randomized controlled trials, NIPPV reduced intubation rate by 67%–86% (11–12) as well as the length of ICU stay and mortality (11–13). A meta-analysis reviewed seven randomized, controlled studies of NIPPV in patients with acute respiratory failure but not requiring immediate intubation (14). Most patients in these studies had acute exacerbations of COPD and were randomized to either the early use of NIPPV or the standard care group. Patients in the NIPPV group had a lower rate of intubation (odds ratio 0.20; 95 percent Confidence Interval, % CI, 0.11 to 0.36) and a lower risk of death (odds ratio 0.29; 95 % CI 0.15 to 0.59). In conclusion, NIPPV relieves dyspnoea, improves arterial blood gases, diminishes the need for intubation and reduces mortality and length of hospitalization in selected patients with acute exacerbation of COPD.

Weaning from invasive mechanical ventilation

Patients with end stage of COPD often require invasive mechanical ventilation during acute exacerbation. Although mechanical ventilation has been proven to be an effective life-saving measure, weaning failure often occurs in some patients due to weakness of respiratory muscles. Prolonged mechanical ventilation increases intubation-associated complications, such as ventilator-associated pneumonia. Nava and co-workers (8) conducted a prospective controlled study on the use of NIPPV in facilitating early weaning from IMV. A T-piece weaning trial was attempted 48 hours after intubation of COPD patients with acute hypercapnic respiratory failure. 50 patients who failed in the T-piece weaning trial were randomly assigned into two groups: returning to IMV or extubation followed by NIPPV. The success rate of weaning on 60th day was 88% in the NIPPV group as compared with 68% in the IMV group and the mortality rate was 8% vs 28% ($p < 0.05$) respectively. They concluded that NIPPV during weaning reduced weaning time, shortened duration of ICU admission, decreased the incidence of nosocomial pneumonia, and improved 60-day survival rates.

Wang et al (13) investigated the feasibility of using NIPPV to assist early extubation in COPD patients. Eleven intubated COPD patients with severe hypercapnic respiratory failure due to respiratory infection were enrolled in the study. When infection was under control clinically, patients were extubated followed by NIPPV even though the "standard criteria" of weaning (tidal volume, 8–10ml/Kg; maximum inspiratory pressure (MIP), 18cm H_2O; vital capacity/tidal volume (VC/Vt), 1.6, Frequency/tidal volume (F/Vt) < 105) were not met in most of the patients. Ten patients were successfully extubated. They compared the results with another group of patients with similar clinical condition but NIPPV was not used. Early extubation followed by NIPPV reduced the duration of IMV (7.1 ± 2.9 vs 23.0 ± 14.0 days), the total duration of ventilatory support (13 ± 7 vs 23 ± 14 days) and the incidence of ventilator-associated pneumonia (0/11 vs 6/11). Li et al (15) reported that of the 23 ventilated patients (17 with weaning difficulty and 5 with accidental extubation) 16 (73%) were successfully managed with NIPPV. Our clinical experience suggested that patient selection was critical for early successful extubation. Among patients with well controlled respiratory infection, little airway secretion and no malnutrition, the success rate of NIPPV assisted weaning was around 70% even when their condition did not meet the "standard criteria" of weaning. Patients should be carefully monitored during the weaning process. If there is any deterioration, they should be re-intubated immediately. In conclusion, NIPPV could be used to assist weaning from IMV.

Stable severe COPD

The efficacy of NIPPV in the management of stable severe COPD remains controversial (16,17). As inspiratory muscle fatigue might contribute to the development of respiratory failure, regular intermittent NIPPV has been postulated to rest the chronically fatigued respiratory muscles, and thus improved dyspnoea. Other indications for the use of NIPPV in stable COPD are nocturnal hypoventilation in patients with severe COPD (8)

and sleep apnoea complicating COPD. Nocturnal hypoventilation and sleep fragmentation may create detrimental consequences to respiratory muscles, heart, threshold value of respiratory centre for CO_2 and general health condition.

In 1984, Braun and Marino (18) first published their clinical trial using negative ventilator (Wrap type) in the management of 16 COPD patients. The use of negative pressure ventilation 5 hours per day for 5 months improved patients' respiratory muscles function, FVC and daytime $PaCO_2$. Thereafter, there have been many reports describing the effects of noninvasive positive or negative pressure ventilation in stable COPD patients with conflicting results. The differences in studied populations and methodology used made it difficult to compare the results. Zhang and Zhong (19) reported that daily use of NIPPV, delivered with bi-level positive airway pressure (BiPAP) 2 to 3 hours daily for 3 weeks, to rest the respiratory muscles improved dyspnoea in 67% of COPD patients. Compared with the control group, those who received BiPAP ventilation showed improvement in dyspnoea, which were related to improvement of respiratory muscles strength and not to improvement in lung function (Table 3). Meecham-Jone and colleagues (20) evaluated the efficacy of long-term nasal positive pressure ventilation (NIPPV) together with oxygen therapy in COPD. They found significant improvement in daytime arterial PaO_2 and $PaCO_2$, total sleep time, sleep efficiency, and overnight $PaCO_2$ following 3 months of oxygen plus NIPPV and also when compared with those receiving oxygen therapy alone. The quality of life of the patients also improved significantly. Improvement in daytime $PaCO_2$ was correlated with improvement in overnight $PaCO_2$. Clini and co-workers (21) also reported that NIPPV plus oxygen therapy reduced ICU admissions and improved exercise capacity in severe COPD with hypercapnia, but did not improve long term survival. Zhang and Zhong (22) conducted sleep polysomnography in 25 severe hospitalized COPD patients. These patients had normal daytime arterial blood gases (Sat O_2, $93.8 \pm 3.88\%$; PaO_2 10.08 ± 2.3 kPa and $PaCO_2$ 6.43 ± 3.81 kPa) but all showed oxygen desaturation (Sat $O_2 < 90\%$ and Δ Sat $O_2 > 4\%$) during sleep with 10 (40%) meeting the criterion of obstructive sleep apnoea (over-lap syndrome). Oxygen therapy alone partly improved desaturation but worsened respiratory disturbance. NIPPV together with oxygen therapy not only rectified sleep apnoea, but also ameliorated oxygen desaturation as well as daytime symptoms. On the other hand, there were reports on the lack of effect of NIPPV in stable COPD. Casanova et al (23) compared the efficacy of NIPPV together with long term oxygen therapy (LTOT) with LTOT alone in 52 stable severe COPD in a one year randomized study. The main outcomes measured included rate of acute COPD exacerbations, hospital admissions, intubations, mortality, dyspnoea, gas exchange, pulmonary function and cardiac function. It was shown that there was no difference between the NIPPV and the control

Table 3. Improvement of Dyspnoea after Respiratory Muscle Rest Therapy with NIPPV

	NIPPV (n = 15)	*Control (n = 15)*	*P*
FVC%	67.5 ± 19.1	62.3 ± 14.8	NS
FEV_1%	37.7 ± 17.0	39.9 ± 17.9	NS
TDI	4.7 ± 2.9	0.3 ± 0.6	< 0.01
12 Min walk distance	838 ± 225	820 ± 146	NS
PImax(cmH_2O)	100 ± 17	82 ± 16	< 0.01
Pdimax(cmH_2O)	127 ± 35	97 ± 24	< 0.005
Tlim(min)	2.0 ± 1.7	1.6 ± 0.6	NS

Note TDI transition dyspnoea index
PImax maximal inspiratory pressure
Pdimax maximal transdiaphragmatic pressure
Tlim Diaphragm tolerance time

group except that the Borg dyspnoea rating dropped from 6 to 5 ($p < 0.039$) in NIPPV group. In our experience, mask leakage and sometimes together with upper airway obstruction during sleep are almost inevitable, and these will complicate the evaluation of the efficacy of NIPPV in stable COPD. In summary, the overall efficacy of NIPPV in stable COPD is controversial. COPD patients with hypercapnia, nocturnal hypoventilation or oxygen desaturation might be a sub-group who will benefit from the use of NIPPV.

Technical Problems Contributing to Clinical Efficacy

In general, most of the published studies found that NIPPV improved PaO_2, respiratory muscle strength and symptom scores. However, it remains controversial if NIPPV could lower $PaCO_2$ and be well accepted by the patients. Some technical considerations are raised in terms of CO_2 elimination and compliance during NIPPV in the following discussion.

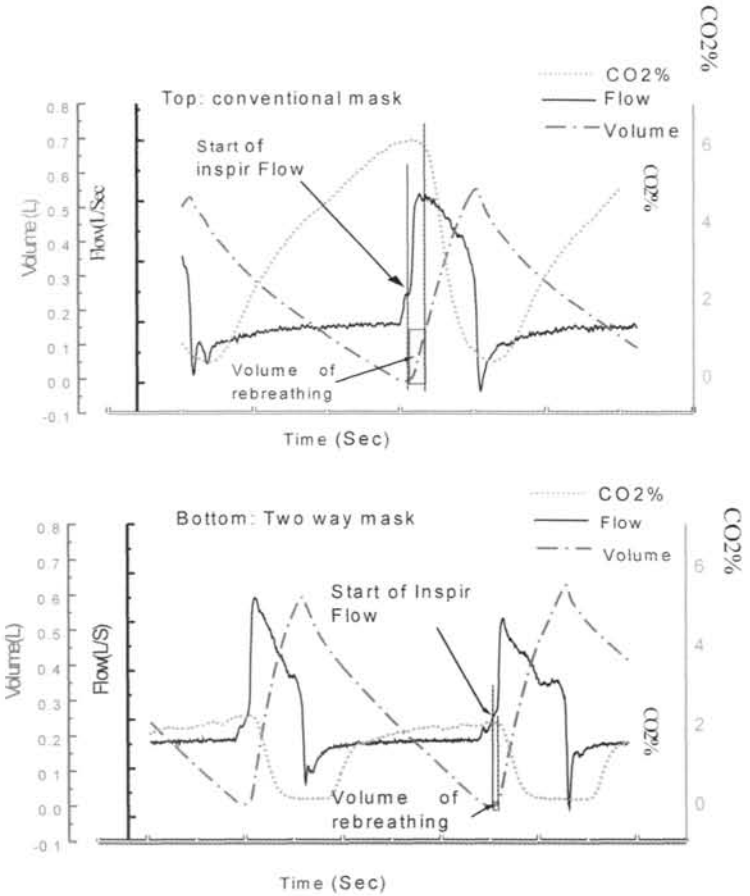
CO_2 elimination in NIPPV

During spontaneous breathing, the extent of alveolar ventilation is the main determinant of $PaCO_2$ level. Many factors, such as tidal volume, minute ventilation, inspiratory effort (pressure) and the impedance of respiratory system, are related to the extent of CO_2 elimination. During mask ventilation, the enlarged dead space in the mask may lead to CO_2 rebreathing, interfering with CO_2 elimination. In some ventilators (such as BiPAP ventilator) with a single tube, there is rebreathing inside the tube (24). This problem becomes more prominent in hypercapnic COPD patients. It is reported that the use of non-rebreathing valve or volume cycle ventilator can prevent CO_2 rebreathing inside the tubing and improve CO_2 elimination in intubated COPD patients (24,25). However, CO_2 retention cannot be solved even with the volume cycle ventilator or non-rebreathing valve when a face mask is used. Recently, we have been monitoring CO_2 concentration, inspiratory and expiratory flow and tidal volume in the conventional facial mask adapted to the BiPAP ventilator. We found that during routine BiPAP ventilation, over 80ml of expired air was re-breathed (Figure 1). The CO_2 concentration in the expired air in patients with hypercapnia was $7.19 \pm 1.72\%$ (26). We have modified the facial mask with a two-way connection instead of one-way and this allows a constant flow of air generated from the BiPAP ventilator to wash out CO_2 inside the mask (Figure 2). This two-way connection reduced the re-breathing volume from 80 ml to almost zero (26). A randomized cross-over study was conducted to evaluate the efficacy of this two-way mask vs the conventional one-way mask by comparing the CO_2 elimination in 8 hypercapnic COPD patients (27). After one hour ventilation with the same setting, the improvement in $PaCO_2$ ($\Delta PaCO_2$, 11.85 ± 8.1 mmHg) and pH (ΔpH: 0.07 ± 0.04) were significantly better in the two-way mask group than in the one-way mask group ($\Delta PaCO_2$, 5.78 ± 10.58mmHg; ΔpH, 0.04 ± 0.04) ($P < 0.05$). This study indicated that the high dead space of the conventional one-way mask in NIPPV hinders the elimination of CO_2 in hypercapnic patients. The use of the two-way facial mask or one with smaller dead space (reducing from 120 ml to 80 ml) is useful clinically in CO_2 elimination.

Compliance

Unlike IMV, patients' compliance is of great importance in the successful management with NIPPV. Patients' compliance is determined by many factors.

1. Mask. The size and shape of the mask are the most important determinants of patients' subjective comfort. The preference for nasal, facial or other types of mask varies among individuals. In clinical practice, nasal mask should be the first choice. If the patient is unable to close his mouth or feels uncomfortable with the nasal mask, facial mask may be used. It is important to fit the patient with a mask that would provide a secure seal. In our clinical practice, we found that leakage between the mask and the face is the most important factor responsible for poor synchronization between patient and ventilator, leading to discomfort.



A: With conventional mask, CO_2 concentration in the mask is > 6% at the beginning of inspiration. There is obvious delay of CO_2 elimination while starting inspiration.
B: With modified two way mask, CO_2 concentration in the mask is < 2% at the beginning of inspiration. There is little delay of CO_2 elimination while starting inspiration.

Figure 1. CO_2, flow and volume monitoring in conventional and modified two way masks in COPD patients with hypercapnia

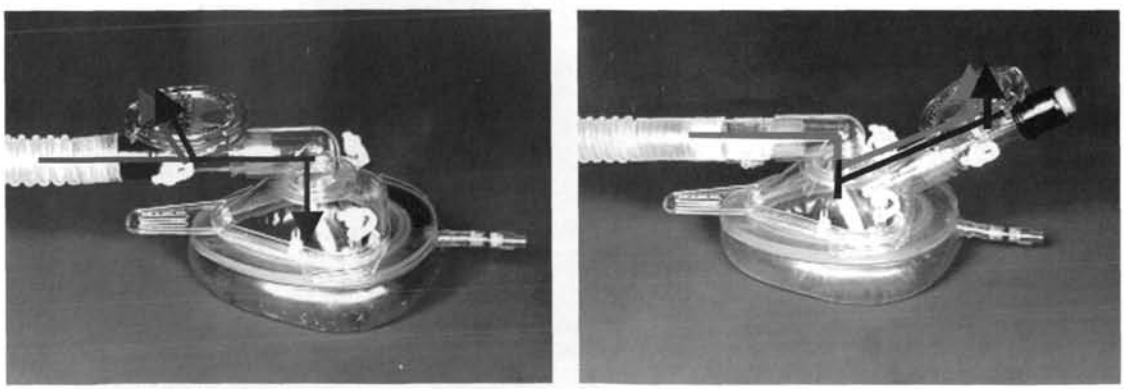


Figure 2. Pictures of two-way (left) one-way (right) mask

2. Procedure of application. The implementation technique will affect the compliance of the patients. If the mask has already been connected to the tubing with the ventilator turned on, most patients will complain of discomfort when this connected mask is fitted up the face. This is because of leakage and poor synchronization before the mask has been applied. Acclimatization is important in ensuring tolerance and efficacy. Most COPD patients need more than 12 cmH_2O (average of 14 cmH_2O) of inspiratory pressure to provide adequate ventilatory support. However, starting with 8 cm H_2O or more of inspiratory pressure will lead to discomfort and intolerance in most of the patients. NIPPV should be initiated with low levels of inspiratory pressure and gradually increased to the target level. In our recent study (26), the average inspiratory airway pressure level (IPAP) was 14.6 ± 2.4 cm H_2O and expiratory positive airway pressure (EPAP) level 3 cm H_2O. The proper adjustment of pressure is based on patient's comfort, clinical assessment and monitored tidal volume (≥ 7 ml/kg).

3. Synchronization between patient and ventilator. Proper triggering and synchronization are important in NIPPV. It is reported that better synchronization mode, such as pressure support, improves patient's compliance (6). However, in patients with rapid breathing (RR > 35 breaths/min), it is difficult to achieve good synchronization because the response of most ventilators is not fast enough. In this circumstance, to start with manual ventilatory bag or manual initiation of inspiration (some ventilator provides this function button) for 5 to 15 minutes may provide with better synchronization (25). It is easier to achieve proper synchronization between the patient and the ventilator when the patient's breathing frequency decreases to < 30 breaths/min.

4. Proper Care. Proper care and close monitoring of the patient are essential for the success of NIPPV implementation. Reported efficacy of NIPPV is usually very good if a research team conducts the study. In ICU setting where patients are monitored closely, most of the reported efficacy is also good. However, the application of NIPPV in hospital wards or at home was less effective (28). Regular checks for leakage, synchronization, upper airway obstruction (during sleep) and airway secretion clearance are essential to ensure patient's comfort and efficacy of NIPPV. Close observation by respiratory therapists or nurses during NIPPV is necessary.

5. Education of the patient. Proper education improves co-operation and dispels mask phobia. Patients should understand the potential benefit of NIPPV and be taught how to disconnect the ventilator tubing and mask in case of discomfort in order to relieve anxiety. Training of patient's breathing manoeuvre (slowly and regularly) and effective cough (deep inspiration before vigorous cough) may help improve the clearance of sputum and the efficacy of NIPPV.

6. Ventilator. There is no data to support which type of ventilator or which mode of ventilation create the best outcome in NIPPV, although there are reports on better comfort and compliance with the pressure support mode. Proper settings of the ventilator are more important than the choice of ventilator in improving patient's compliance and the efficacy of NIPPV.

Side Effects and Limitations of NIPPV

Reported side effects of NIPPV are summarized in Table 4 (6,25). Most of the side effects are mild and preventable. Air leak, mask discomfort and nose bridge lesion can be avoided or minimized by trying on different masks of different models and sizes to ensure the best fit. Dry throat can be prevented by using humidifier or drinking water regularly. Intolerance to ventilator is relatively common. Acclimatization and better synchronization mode of ventilation (such as pressure support etc.) improve tolerance. Some patients have difficulty in keeping their mouths closed while using a nasal mask. If the mouth leak is large enough to interfere with ventilatory support, facial mask should be used. Gastric distension is relatively common in drowsy patients with face mask ventilation. A nasogastric tube should be inserted before initiating and during face mask ventilation in this group of patients. Fortunately, gastric distention rarely occurs in patients who are awake. Upper airway obstruction during sleep occurs almost only in drowsy patients or patients complicated with sleep apnoea. This can be easily prevented with lying on the side or

Table 4. Commonly Reported Side Effects during NIPPV[6,24]

Side Effects	*Percentage (%)*	*Side Effects*	*Percentage (%)*
Aspiration (Face Mask)	5.6	Dry Nose	3.4
Gastric Distention	8	Eye Irritation	16
Mask Discomfort	18	Air Leak	18
Nose Lesion	5.6	Caustrophobia	3.4
Bad Tolerance to Ventilator	17	Upper Airway Obstruction (during sleep)	45
Dry Throat	63	Mouth Leak (Nasal Mask)	17

increase of EPAP level. Aspiration is a serious complication and face mask ventilation should be avoided in patients at risk of aspiration. Careful observation is important in preventing side effects.

Summary

NIPPV has been applied in a wide variety of clinical settings. Prospective, randomized, controlled clinical trials have shown that it is effective in the management of acute exacerbations of COPD, especially in early stage of respiratory failure and in facilitating weaning from IMV. However, the role of NIPPV in patients with stable COPD and its effect on long-term survival of these patients are controversial. It should be emphasized that many factors such as the dead space effect of masks, implementation procedure, proper care and monitoring and synchronization between patient and ventilator contribute to the success of its use. Further investigations are needed in many aspects of NIPPV, such as patient selection, outcome prediction, selection of a suitable ventilator and mode of ventilation in different settings.

References

1. Cheng XS, Li JZ, Zhong ZX, et al. Analysis of basic data on prevention and treatment of COPD and chronic cor pulmonale. *Chi J Tube Respir Dis* 1998; 21:749–52.
2. Haluszka J, Chartrand DA, Grassino AE, et al. Intrinsic PEEP and arterial PCO_2 in stable patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1990; 141:1194–7.
3. Chen RC and Yan S. Perceived inspiratory difficulty during inspiratory threshold and hyperinflationary loading. *Am J Respir Crit Care Med* 1999; 159:720–7.
4. Chen RC, Zhang YG, Luo DF and Zhong NS. Diaphragmatic fatigue and its role in the development of rspiratory insufficiency and cor-pulmonale in COPD. *Chin J Tuberc Respir Dis* 1989; 12:158–60.
5. Bach JR. Update and perspectives on nonivasive respiratory muscle aids (Part 1:The inspiratory aids). *Chest* 1994; 105:1230–40.
6. Ambrosino N, Noninvasive mechanical ventilation in acute respiratory failure. *Eur Respir J* 1996; 9:795–807.
7. A Consensus Conference Report, Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation. *Chest* 1999; 116:521–34.
8. Nava S, Ambrosino N, Clini E, et al. Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial. *Ann Intern Med* 1998; 128(9):721–8
9. Meduri GU, Conoscenti CC. Menashe P, Nair S. Noninvasive face mask ventilation in patients with acute respiratory failure. *Chest* 1989; 95(4):865–70.
10. Chen RC, Zeng YX, Li YM, et al. Pressure support ventilation via facial mask in the management of COPD with chronic respiratory failure during acute exacerbation. *Chi J Tuber Respir Dis* 1992; 15:285–60.

11. Kramer N, Meyer TJ, et al. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med* 1995; 151:1799–806.
12. Brochard L, Mancebo J, Wysogki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995; 333:817–22.
13. Wang C, Shang MY, Huang KW, et al. Sequential non-invasive following short-term invasive mechanical ventilation in COPD induced hypercapnic respiratory failure. *Chin J Tuberc Respir Dis* 2000; 23:212–6.
14. Keenan SP, Kernerman PD, Cook DJ, et al. Effect of noninvasive positive pressure ventilation on mortality in patients admitted with acute respiratory failure: a meta-analysis. *Crit Care Med* 1997; 25:1685–92.
15. Li YM, et al. Noninvasive positive pressure ventilation in the weaning from invasive mechanical ventilation. *Chin Crit Card Med* 2003 (in press).
16. Rossi A. Noninvasive ventilation has not been shown to be ineffective in stable COPD. *Am J Respir Crit Care Med* 2000; 161:688–9.
17. Hill NS. Noninvasive ventilation has been shown to be ineffective in stable COPD. *Am J Respir Crit Care Med* 2000; 161:689–91.
18. Braun NM, Marino WE. Effect of daily intermittent rest of respiratory muscles in patients with severe chronic airflow limitation (CAL). *Chest* 1984; 85:595–605.
19. Zhang YC, Zhong NS. COPD and noninvasive ventilation. *RT International* 1995; Fall:99–104.
20. Meecham-Jones-DJ, Paul-EA, Jones-PW, Wedzicha-JA. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. *Am J Respir Crit Care Med* 1995; 152:538–44.
21. Clini E, Sturani C, Porta R, et al. Outcome of COPD patients performing nocturnal non-invasive mechanical ventilation. *Respir Med* 1998; 92:1215–22.
22. Zhang NF and Zhong NS. Diagnosis and treatment of COPD concurrent sleep apnea. *Chin J Pract Intern Med* 1998; 18:211–3.
23. Casanova C, Celli BR, Tost L, et al. Long-term Controlled Trial of Nocturnal Nasal Positive Pressure Ventilation in Patients With Severe COPD. *Chest* 2000; 118:1582–90.
24. Ferguson GT and Gilmartin M. CO_2 rebreathing during BiPAP ventilatory assistance. *Am J Respir Crit Care Med* 1995; 151:1126–35.
25. Chen RC, Zeng YX, Li Y, et al. Mask pressure support ventilation in respiratory failure due to acute exacerbation of COPD. *Chin J Tuberc Respir Dis* 1992; 15:285–7.
26. Chen RC, Zhang XY, He GQ, et al. Modification of facial mask on the dead space effect in non-invasive mask ventilation. *Chin J Tuberc Respir Dis* 2000; 23(12):734–6.
27. Chen RC, Zhang XY, Zheng ZG, et al. Two-Way Face Mask Could Improve CO_2 Elimination During Non-Invasive Ventilatory Support In COPD? *Eur Respir J* 2000; 16(suppl):14s.
28. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet* 2000; 355:1931–5.

7 Pulmonary Rehabilitation

Teresita de Guia and Percival Punzal

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most important chronic lung diseases seen by physicians in the Asian region. There have been estimates of the burden of chronic obstructive pulmonary disease in the Asia-Pacific region in 12 countries for those aged > 30 year; and the overall prevalence in these countries was estimated to be 6.3% (1). The experiences of healthcare professionals taking care of these patients show the profound medical, social and economic impact of the disease.

In the recent years, despite significant improvement of pharmacologic therapy, the most that can be achieved is temporary relief of symptoms in the majority of patients suffering from moderate to severe disease. This is perhaps the most significant reason for the increasing interest in establishing pulmonary rehabilitation programmes that started in the late 1980s in this region. Historically, application of rehabilitation in patients with chronic lung diseases had been applied primarily to COPD. This led to the first definition of pulmonary rehabilitation by the American College of Chest Physicians in 1974. The definition is as follows:

> Pulmonary rehabilitation is an art of medical practice wherein an individually tailored multidisciplinary programme is formulated through accurate diagnosis, therapy, emotional support and education, stabilizes or reverses both the physio and psycho-pathology of pulmonary diseases and attempts to return the patient to the highest possible functional capacity allowed by his pulmonary handicap and over all life situation (2).

This definition concentrates on the essentials of a successful pulmonary rehabilitation programme which are:

1. the patient,
2. multidisciplinary approach and
3. directed to physiopathology and psychopathology.

The American Thoracic Society has adopted the following definition: "pulmonary rehabilitation as a multidisciplinary programme of care for patients with chronic respiratory impairment that is individually failured and designed to optimize physical and social performance and autonomy (3)".

These programmes are established means of enhancing medical treatment to alleviate symptoms of these patients (4–9). Treatment targets are set both by the patient and the members of the rehabilitation team. The major objectives of the programme are (10–12):

1. Control the symptoms and possible complications

2. Restore the patients to their highest level of independent function
3. Improve performance of activities of daily living
4. Improve exercise tolerance
5. Reduce the number of exacerbations and hospital confinements
6. Improve the overall "quality of life"

Programme Structure

The structure of pulmonary rehabilitation programmes varies from country to country, and in the same country, from centre to centre. Programmes are done either on an in-patient or out-patient basis for a period of 4 to 12 weeks. It is the availability of resources, in most cases, that dictates the type of programme adopted by the medical institution. The pulmonary rehabilitation programme of Kowloon Hospital (Hong Kong) is one with the longest duration (12 weeks) among out-patient programmes (12). Members of the rehabilitation team, likewise, may vary. More commonly it consists of a team of physicians, respiratory and physical therapists, psychologists and nurses. In the pulmonary rehabilitation section of the Philippine Heart Centre, the approach is multidisciplinary involving pulmonary physicians, pulmonary fellows in training and other health care professionals (psychiatrist, respiratory therapists, nutritionist, physical therapists, social workers and hospital chaplain) as members of the team (13,14). Similar approaches have been utilized by programmes in other countries. Generally, the programmes are divided into four phases:

Phase 1 – pre-rehabilitation evaluation, educational sessions and planning of the exercise programme.
Phase 2 – supervised exercise/educational sessions and group support meetings.
Phase 3 – intensive exercise sessions, education reinforcement and group support meetings, post-rehabilitation evaluation.
Phase 4 – follow-up and continuing exercise.

At the completion of the programme, patients are again assessed using identical protocols to gauge the improvement achieved from the programme.

The majority of patients referred to the programme are predominantly elderly males who suffer from moderate to severe obstructive lung disease. Table 1 shows a review of patient populations in some Asian rehabilitation centres.

Patient Selection

Patients are referred to the programme by their primary attending physicians. The majority of those included in the programme are afflicted with COPD (emphysema and chronic bronchitis), asthma, bronchiectasis and tuberculosis. Recently, patients disabled by lung malignancy and interstitial lung disease are also referred to the programme. These are usually patients with disability arising from severe respiratory symptoms, frequent exacerbations, restricted activities and impaired quality of life.

Pre-rehabilitation assessments are done in most of the pulmonary rehabilitation centres in

Table 1. Baseline Data from Different Asian Rehabilitation Centres

	Blanco[14]	*Chan*[12]	*NaNa*[13]	*Choe*[18]
Age (yrs)	65	67	67	57
Male/Female	23/4	143/32	13/2	12/2
FEV_1	0.84 (L)	0.64 (L)	1.21 (L)	40.6 (%)
Baseline 6 min walk (meters)	285	233	379	392
Baseline maximal workload	3.7 (Mets)	31.4 (Watts)	–	57.7 (Watts)

the region (15–17). These evaluations identify the patients' degree of loss of physical & lung function and impaired "quality of life". Likewise, it can identify baseline exercise tolerance, pathophysiologic changes during exercise (such as hypoxaemia and cardiac dysfunction). Most centres utilize entry questionnaires which include psychosocial assessment, questions on symptoms as it affects specific activities e.g. "quality of life" questionnaire (17), and the activities of daily living (ADL) profile (14). Baseline tests included spirometric measurements (pre and post bronchodilator), oximetry or arterial blood gas analysis. Exercise testing before the programme is necessary to ensure the safety and efficacy of the rehabilitation programme.

Exercise tests prior to rehabilitation

1. The six-minute walk test evaluates the exercise capacity of the patient by allowing the patient to walk on a pre-measured track for a period of six minutes with continuous oximetry studies. The distance is then recorded in meters or feet.
2. The incremental symptom limited exercise test on a treadmill or a cycle ergometer is done in centres where the necessary equipment is available. Oxygen saturation is monitored continuously by pulse oximetry. Electrocardiogram is monitored before, during and after the test. Blood pressure is taken at periodic intervals. The workload is increased each minute until the patient reaches a symptom-limited maximum. The test is terminated when one or more of the following are present: oxygen saturation of less than 85%, ST-T wave depression or serious arrhythmia noted on the ECG, or excessively high blood pressure (16). At the end of testing, the patient scores his symptoms of breathlessness and fatigue using the modified Borg's scale (17).

While many investigators use the six-minute walk test as a measurement of the patient's baseline exercise tolerance, others like Blanco and co-workers (14) also used the treadmill for the incremental exercise test. Choe (18) used the bicycle ergometer to determine the VO_{2max} and anaerobic threshold of their patient population. Measurement of VO_{2max} is usually not a part of the programme in most centres.

Educational Programme

The goal of education in pulmonary rehabilitation is to change the health beliefs of patients and their family members so that the treatment will be more readily accepted. Education is an attempt to change patients' perceptions of the disease and how the condition may be most effectively treated (19). Education is generally considered as a necessary part of pulmonary rehabilitation. Most programmes have an educational component for the patient and the family. Invariably, topics included are as follows: anatomy and lung pathophysiology, proper use of medications and oxygen, energy saving techniques, postural drainage and chest physiotherapy, nutritional counselling, early recognition of symptoms and appropriate emergency care. Correct breathing and coughing techniques are taught in most programmes (12–14). Modified methods like air-shift technique, manual chest wall stretching and glossopharyngeal breathing, as done by Chou and co workers (20), are used to achieve a more effective breathing pattern and a faster relief of shortness of breath. In some programmes, sexual counselling is done in group discussions. When necessary, questions are dealt with privately with the patient and his or her partner.

Smoking cessation session/s form an integral part of the programme. Despite the debilitating effects of chronic lung diseases, some patients continue to smoke. Although a number of centres will accept these patients in their programme, some programmes, such as the one offered by Kowloon Hospital in Hong Kong, categorically state that patients should have stopped smoking prior to enrollment (12). In our programme, we accept smokers to give the rehabilitation team the opportunity to initiate smoking cessation. The physician plays a very important role in efforts to stop them from smoking through clinical counselling individually or by group.

Group support meetings are conducted to allow these patients to acquire skills on how to

deal with lifestyle changes imposed by chronic lung diseases. Fear, anxiety and depression inevitably are present in the complex problems of these patients. Great importance is placed on adequate family support. Family members are encouraged to join these sessions.

Exercise Training Programme

Most of the patients referred to the programme have poor exercise tolerance. This becomes more obvious when they do their daily activities. Exercise programmes for both upper and lower extremities are recommended because they improve exercise capacity and lessen shortness of breath (21,22). Stretching is recommended prior to the actual performance of prescribed exercises.

Upper extremity exercise training

Upper body exercise ranges from arm exercises (with or without hand weights) done in repetitions to cycle ergometer performed for 15 minutes (Figure 1). The cycle ergometer is performed initially without any resistive load. As the patient gradually improves, load is added during follow-up exercise sessions. Breathing exercise with coordinated upper body movements (Qi-gong) has been gaining popularity among Filipino patients. Qi-kong is a form of traditional exercise that has its origins in China.

Lower extremity exercise training

Lower limb exercise is a very important component of any pulmonary rehabilitation programme in the region. This form of exercise training programme involves supervised walk on treadmill or cycle ergometer and home walking which the patient performs at duration and levels that he can sustain for several minutes (Figure 2). Training levels are subsequently increased as the patient improves his walking skill and breathing. The goal is to keep the patient moving for 30 minutes continuously. Modifications or combination of exercises are done

Figure 1. Upper body exercise ranges from arm exercises (with or without hand weights), done in repetitions to cycle ergometer performed for 15 minutes.

Figure 2. Supervised walk on treadmill

in some rehabilitation programmes. For example, Nana et al (13) trained patients by combining breathing exercises with stretching manoeuvers of the shoulders, chest, legs, followed by walking. Wang and colleagues (23), on the other hand, used the bicycle ergometer, and each session lasted from 30 to 40 minutes. Training intensity was increased gradually to 40%, 60% and 80% of maximum work rate. Garcia (24) used the treadmill for exercise and advocates a high intensity exercise programme with targets as much as 80% of baseline maximum work rate.

The mechanisms of improvement involve physiologic training effects that include increased skeletal muscle oxidative enzymes (25) and reduction of exercise-induced lactic acidosis (26). Psychological mechanisms such as increased motivation, decrease in dyspnoea and a sense of well being contribute to the improvement. Other forms of exercises like dancing and Tai-chi have been included in some programmes (Figures 1 and 2).

Occupational therapy

In Hong Kong, occupational therapy is part of some programmes (12). This intervention is meant to increase independence in self-care, work and help patients adjust to their physical disabilities. There are 3 levels of intervention: a) functional skills development; b) self care and home management skills training and c) environmental adaptation.

Supplemental Oxygen during exercise

Some patients are hypoxemic at rest while others desaturate during exercise. Patients with severe hypoxemia ($PaO_2 \leq 7.33$ kPa or 55 mmHg) are given continuous oxygen supplement. The oxygen prescription during exercise is determined by the physician during the exercise testing performed prior to rehabilitation. The goal is to maintain an oxygen saturation of greater than 90% at all times. Nasal cannula is the most common mode of oxygen delivery system. Machida et al demonstrated that dyspnoea diminished and the maximum workload tolerated on the treadmill improved in a group of hypoxemic COPD patients after receiving oxygen at 2 litres/min (27).

Research Studies and Current Recommendations in Pulmonary Rehabilitation

Recommendations and evidence grades for the components of pulmonary rehabilitation for patients with COPD have been reported by the joint ACCP/AACVPR pulmonary rehabilitation guideline panel (28) (Table 2).

Grade A — scientific evidence provided by well-designed, well conducted controlled trials (randomized and non-randomized) with statistically significant results that consistently support the guideline recommendation; B — scientific evidence provided by observational studies or by controlled trials with less consistent results to support the guideline recommendation; C — expert opinion.

The recommendations and evidence grades were taken from studies done in American and

Table 2. Summary of the Joint ACCP/ACCVPR Pulmonary Rehabilitation Guidelines

Recommendations	*Grade*
Lower extremity training improves exercise tolerance and is recommend as part of the rehabilitation program	A
Strength and endurance training improves arm function; arm exercise should be included in the rehabilitation program	B
Evidence does not support the routine use of ventilatory muscle training in the rehabilitation program; it may be considered in patients with decreased respiratory muscle strength and breathlessness	B
Evidence does not support the benefits of short-term psychosocial interventions as single modalities; long-term interventions may be beneficial; expert opinion supports inclusion of educational and psychosocial intervention components in the rehabilitation program	C
Pulmonary rehabilitation reduces shortness of breath	A
Pulmonary rehabilitation improves health-related "quality of life"	B
Pulmonary rehabilitation reduces the number of hospital confinements and days of hospitalization	B
Pulmonary rehabilitation may improve survival	C

European centres where pulmonary rehabilitation programmes are considered to be a standard practice in the management of patients suffering from COPD. It will be difficult to come up with a similar review of literature in the Asian setting at this time because there is a lack of well conducted controlled trials (randomized or non randomized). The results of the Asian experience in pulmonary rehabilitation, however, paralleled those reported in the Western literature. Chan and colleagues (12) showed that there was no significant change in the spirometric studies done before and after rehabilitation. Mukty showed that after training a group of patients with chronic lung diseases, purse-lip breathing was able to improve oxygen saturation better than relaxation alone (29). Shortness of breath was significantly decreased both at rest and during exercise (12–14, 30). Several investigators showed an improvement of exercise tolerance after a 4 to 12 week exercise training programme. Table 3 shows the summary of the results from different Asian rehabilitation centres.

Guzman and coworkers (31) showed that these short-term gains in a pulmonary rehabilitation could be sustained several months after graduating from the programme. In a series of patients who were followed up for an average period of 14 months, subjects were able to maintain a high level of exercise tolerance with fewer episodes of exacerbations. Repeat pulmonary function tests showed a slight improvement in FEV_1. The differences between baseline and follow-up spirometric measurements were not statistically significant.

Hospital confinement is inevitable in many patients with chronic lung diseases. Investigators have reported significant reductions in the number of hospitalizations and resulting cost savings after pulmonary rehabilitation compared with the year before rehabilitation. Lertzman and Cherniack (32) reported an average decrease of 20 hospital days per year while Chan and coworkers (12) reported a 37% reduction in hospital days for those who finished their programme. Chou and colleagues (20) similarly reported decreased hospitalization up to 40%. Guzman et al demonstrated a significant reduction from a mean of 6.6 hospital days to 1 hospital day per patient per year (31).

The concept of Quality of Life is based on the WHO definition of health as a "state of

Table 3. Pre and Post-Rehabilitation Exercise Test Results

	Blanco[14] *Pre/Post Rehab*	*Chan*[12] *Pre/Post Rehab*	*Nana*[13] *Pre/Post Rehab*	*Choe*[18] *Pre/Post Rehab*	*Wang*[23] *Pre/Post Rehab*
6 min walk test (metres)	284/378	233/285	379/464	392/459	–
Maximal workload	3.7/4.7 (Mets)	31.4/38.5 (Watts)	–	57.7/64.8 (Watts)	73/91 (Watts)

complete physical, mental and social well-being and not merely the absence of disease". Instruments of QOL determination include SIP (Sickness Impact Profile), QWB (Quality of Well-being Scale). Measures that are specific for respiratory patients are the Chronic Respiratory Questionnaire (CRQ) and the St. George's Respiratory Questionnaire (SGRQ). Chan and co workers (12) used the CRQ and showed moderate improvement in shortness of breath. The same study showed mild improvement in fatigue and emotions in their patients.

Can pulmonary rehabilitation improve the survival of these patients? Results of survival analysis by Ries and colleagues (33) indicated that there was a trend of improvement in survival between groups that received rehabilitation (67%) and those that received education only (56%) (33). Guzman and coworkers (31) reported a higher survival rate among patients who finished the programme than those who did not during the 14 months follow period (Figure 3) but the difference was not statistically significant as in the study by Ries et al (33).

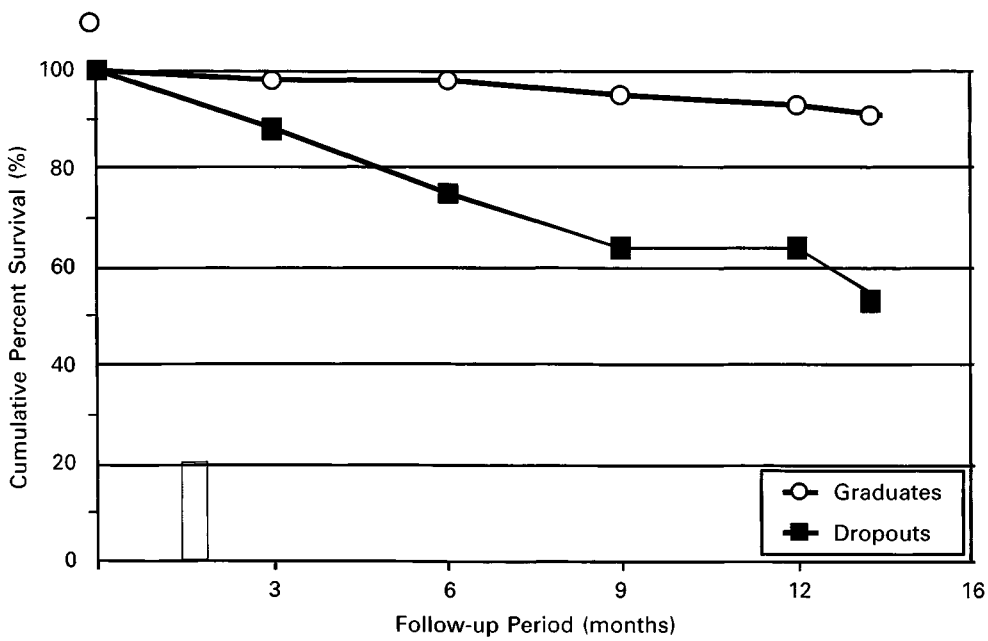


Figure 3. The survival curve of COPD patients using Kaplan-Meier Survival Analysis by A. Guzman et al.[31]

Home Care of Patients with Chronic Lung Diseases

Comprehensive respiratory care usually takes place in a hospital setting. This is not surprising since therapeutic modalities such as oxygen, mechanical ventilation, nebulization and intravenous therapy are standard procedures that require the expertise of physicians and health care workers in acute health care setting. More recently, home care or domiciliary respiratory care has greatly expanded in developed countries (34). Home care permits medical services to be given in the patient's own home. Among possible individuals who can benefit from this programme are:

1. patients discharged home with respiratory equipment such as oxygen, tracheostomy tubes and ventilators;
2. end-stage patients who wish to remain at home;
3. patients who develop acute exacerbations but could be managed at home and
4. patients who require follow-up after a formal pulmonary rehabilitation programme (35).

The home-care team includes the patient, the family, the physician, the pulmonary rehabilitation staff, the hospital discharge planner, the home health agency and the home medical equipment supplier. In Japan, patients with chronic lung diseases comprised the largest group of patients that can benefit from using home care equipment (36). There were 3 types of oxygen delivery systems available for continuous home oxygen treatment: high pressure cylinders, oxygen concentrators and liquid oxygen. The number of patients prescribed with Home Oxygen Therapy (HOT) from 1986 to 1991 was 23,046. About 44.2% receiving this treatment suffered from chronic obstructive pulmonary disease. The majority of patients were between 60 to 70 years old with more males than females. Initially, more than 80% of patients were using the membrane type oxygenator and large oxygen cylinders for oxygen sources. In 1991, the molecular sieve type oxygen concentrator became more popular. In Korea, compressed gas cylinder was the main source of home oxygen therapy (37). Oxygen concentrators were not readily available outside Seoul Metropolitan area. Home ventilator was almost nonexistent due to high cost. Only thirteen patients were noted to be chronic users of mechanical ventilators at home (37). Majority of these patients were afflicted with COPD. In the Philippines, although home respiratory care and mechanical ventilation are being used by patients with chronic lung diseases, the number is very limited. As part of their programme, Chan and coworkers (12) from Hong Kong used home respiratory care as a follow up programme for those patients who graduated from their centre. Home exercises involving breathing, upper and lower body movements were periodically supervised by the rehabilitation staff. This practice, however, has not gained widespread utilization in the Asian region. Home mechanical ventilation has also been used in selected patients with chronic respiratory failure (38).

The Future of Pulmonary Rehabilitation in Asia

Pulmonary rehabilitation in the Asia Pacific region is in its infancy compared to similar programmes in more developed countries. In countries where such programmes exist, the number of patients getting benefits from them and the number of health care practitioners trained in this field is small compared to their counterparts in Western countries. There is, however, a growing interest among physicians and respiratory care practitioners to work towards the establishment of their own programmes. Pulmonary rehabilitation is no longer limited to chronic obstructive lung disease and asthma. Patients who are candidates for lung volume reduction surgery (LVRS) and those with lung problems secondary to thoracic rib cage abnormalities, neuromuscular diseases, and diaphragmatic paralysis can benefit from the programme. The techniques and approaches may vary for different countries, but the goals of the programmes are always the same — to return these patients to the highest possible functional capacity allowed by his and her pulmonary handicap and over-all life situation.

References

1. COPD prevalence in 12 Asia-Pacific countries and regions: Projections based on the COPD prevalence estimation model. Regional COPD Working Group. *Respirology* 2003, 8:192–8.
2. The official statement of American Thoracic Society. *AMJ Resp Crit Care*, 1949, 159:1666–82.
3. Ries AL. Pulmonary rehabilitation. In: *Pulmonary Diseases and Disorders* 2nd ed. Ed. Fishman. New York: McGraw-Hill 1988, 1325–31.
4. Hodgkin JE, Zorn EG. Connors GL. Pulmonary Rehabilitation — Guidelines to Success. Boston: Butterworth Publishers, 1984.
5. Hodgkin JE. Pulmonary rehabilitation: structure, components and benefits. *J Cardiopulmonary Rehabil* 1988; 11:423–34.
6. Ries AL. Position paper of the American Association of Cardiovascular and Pulmonary Rehabilitation: Scientific basis of pulmonary rehabilitation. *J Cardiopulmonary Rehabil* 1990; 10:418–41.
7. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; 15:S77–121.
8. European Respiratory Society. Optimal Assessment and management of COPD. *Eur Respir J* 1995; 8:1398–420.
9. Chen W. Pulmonary rehabilitation program in Kowloon Hospital. Clinical meeting, September 1993 (unpublished).
10. Beytas LR, Connors GL. Organization and management of a pulmonary rehabilitation program. In: *Pulmonary Rehabilitation — Guidelines to Success*. Ed. Hodgkin JE. Philadelphia: JB Lippincott Co 1993, 32–49.
11. Hodgkin JE. Organization of a pulmonary rehabilitation program. In: *Clin Chest Med.* Ed. Make BJ. Philadelphia: WB Saunders Co 1986, 7:541–49.
12. Chan KS. Pulmonary rehabilitation. In: *Current Management of COPD.* Ed. Mok & Tsang. Hong Kong Lung Foundation Ltd 1999, 33–42.
13. Nana A, Tangchitpitaks A, Lek-uthai S, Bovornkitti S. A cost-free rehabilitation program for COPD patients. *Internal Med* 1992; 8:14–6.
14. Blanco EC, Koh A, Punzal PA, de Guia TS. Pulmonary rehabilitation — a multi-disciplinary program for Filipino patients. *Phil J Chest Dis* 1993; 1:1–5.
15. Guyatt GH, Thompson PJ, Berman LB. How should we measure functions in patients with chronic heart and lung disease? *J Chronic Dis* 1985; 38:517–24.
16. Punzal PA, Ries AL, Kaplan RM, Prewitt LM. Maximum intensity exercise training in patients with chronic obstructive pulmonary disease. *Chest* 1991; 100:618–23.
17. Borg GV. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982; 14:377–81.
18. Choe KH, Park YJ, Cho WK, Kin DS, Lin CM. The effect of pulmonary rehabilitation in chronic lung disease. *TB and Respi Dis* 1996; 43:736–45.
19. Gilmartin ME. Patient and family education. *Clin Chest Med* 1986; 7:619–27.
20. Chou CL. Pulmonary rehabilitation in Taipei Veterans General Hospital. May 2000 (Personal communications).
21. Lacasse Y, Wong E. Guyatt GH. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. *Lancet* 1996; 348:1115–9.
22. Ries AL, Ellis B, Hawkins RW. Upper extremity exercise training in chronic obstructive pulmonary disease. *Chest* 1988; 93:688–92.
23. Wang TG, Chen SY, Hsiao SH, Lin KH, Kuo SH, Lien IN. Evaluation of a novel exercise training program in patients with chronic obstructive pulmonary disease. *VJ Rehab Med Assoc ROC* 1999; 27:71–7.
24. Garcia R. Maximum intensity symptom limited exercise training in Filipino patients with chronic obstructive pulmonary disease. *Phil J Chest Dis* 1993; 1:72–81.
25. Maltais F, Leblanc P, Simard C. Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Dis* 1996; 154:442–7.
26. Casaburi R, Patessios A, Ioli F. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis* 1991; 143:9–18.
27. Machida K. Kawabe Y, Toshihiko H, Honda Y. Portable liquid oxygen supply system and exercise tolerance in patients with chronic respiratory failure. *Japan J Appl Physio* 1992; 2:243–50.
28. ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel. Pulmonary Rehabilitation joint ACCP/AACVPR evidence based guidelines. *Chest* 1997; 112:1363–96.

29. Mukty A. Comparison between pursed lip breathing and relaxation techniques in pulmonary rehabilitation, as monitored by oxygen saturation, in emphysema patients. (unpublished).
30. Sanchez F, Viado M. Blanco EC. Punzal PA. Reduction of dyspnea in patients with chronic obstructive pulmonary disease. *Phil J Chest Dis* 1994; 2:35–9.
31. Guzman A, Punzal P. de Guia T. Long term follow-up of COPD patients in a comprehensive pulmonary rehabilitation program. *Phil Heart Center J* 1997; 4:37–40.
32. Lertzman MM, Cherniack RM. Rehabilitation of patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1976; 114:1145–65.
33. Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation in physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann Int Med* 1995; 12:823–32.
34. Make BJ, Gilmartin M. Rehabilitation and home care for ventilator assisted individuals. *Clin Chest Med* 1986; 7:679–91.
35. Dunne PJ, McInturff SL, Darr C. The role of home care. In: *Pulmonary Rehabilitation — Guidelines to Success.* Ed. Hodgkin. JE. Philadelphia: Lippincott 1993, 332–58.
36. Aiba M, Takahashi H, Suzuki T, Ishihara T. Current status of home oxygen therapy in Japan. In: *Progress in Domiciliary and Respiratory Care.* Eds. Kira & Petty. Netherlands, Elsevier Science BV 1994, 41–7.
37. Shim YS. Current status of home oxygen therapy in Korea. In: Eds. Kira and Petty. *Progress in Domiciliary and Respiratory Care.* Netherlands: Elsevier Science BV 1994, 41–7.
38. Chu CM, Yu WC, Tam CM, Lam CW, Hui DS, Lai CK; Hong Kong Home Ventilation Registry; Hong Kong Thoracic Society. Home mechanical ventilation in Hong Kong. *Eur Respir J* 2004; 23:136–41.

8 Lung Volume Reduction Surgery

Wataru Hida , Yoshimochi Kurokawa and Hajime Kurosawa

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most prevalent diseases in industrialized nations and COPD from advanced pulmonary emphysema is a major cause of morbidity and mortality. Up to this time, the final option for selected patients with disabling respiratory failure due to COPD has been lung transplantation. However, recently, lung volume reduction surgery (LVRS) has become a new therapeutic option for patients who are either too old for lung transplantation or as a bridging procedure with the intention of deferring transplantation for younger persons. The concept of this surgical procedure was first conceived by Brantigan and Mueller (1) almost 40 years ago. They reported significant clinical improvement in 75% of patients who had this procedure and this improvement persisted in some patients for more than 5 years. Because of the high early mortality rate of 16%, and few objective data to substantiate the claims of subjective improvement, their procedure never gained widespread acceptance until revisited by Wakabayashi et al in 1991 (2), who utilized laser treatment of diffuse small bulla by a unilateral or bilateral thoracoscopic technique and demonstrated a modest improvement in pulmonary function. Thereafter, in 1995 Cooper et al returned to Brantigan's original notion of surgical resection of severely diseased but nonbullous areas of lung and modified the technique by employing median sternotomy incisions that permitted bilateral resections using a staple (3). The results showed variable clinical relief of dyspnoea and improvement in lung function. In Japan, the first few patients with severe emphysema were treated by CO_2 laser therapy in 1991 (4). Thereafter, many surgical centres worldwide started LVRS programs. At present, there have been more than 550 reported cases of LVRS for emphysema. The purpose of this chapter is to review LVRS for pulmonary emphysema, including our own experience.

LVRS — the Asian Perspective

The use of LVRS has been increasing all over the world. Table 1 shows the reported cases of LVRS in several Asian and other countries based on published papers (5–11), a symposium on pulmonary emphysema in Fukuoka 2000, and personal information (see footnote in Table 1). In North America, where the idea of LVRS was first conceived, over 10,000 LVRS have already been performed in about 50 thoracic surgical centres; and in Europe, about 1,000 cases have been performed in 42 institutions. VRS is also employed in Asia. Many Japanese university hospitals have intensively performed this surgical procedure after

Table 1. Reported Cases with LVRS in Asia and Other Countries (up to the end of 1999)

	Cases with LVRS	*Institutions performing LVRS*	*Operative technique used*	*Increase in FEV1 (3–12 months after operation)*	*Early mortality*
North America	> 10,000	About 50	VATS, median sternotomy	13–96%	0–6%
Europe	1,120	42	VATS, median sternotomy	25–75%	4.8%
Canada	24	2	median sternotomy	54%	8%
Australia	75	2	VATS, median sternotomy	50–55%	5.3%
Japan	601	69	VATS, median sternotomy	20–70%	3.7%
Tohoku University	94		VATS	66%	1.4%
Fukuoka University	83		VATS, median sternotomy	60%	3.7%
Okayama University	76		VATS, median sternotomy	43%	0%
Yamaguchi University	52		VATS, median sternotomy	35%	1.9%
Nara Medical College	45		VATS	33%	2.2%
Tokai University	42		VATS	47%	0%
Other institutions in Japan	235		VATS, median sternotomy		7.6%
China	About 300	About 20	VATS, median sternotomy		
Shanghai First Pulmonary Disease Hospital	32		Thoracotomy, median sternotomy	44%	0%
Chinese Univ. of Hong Kong	17		VATS, median sternotomy	63%	0%
Beijing Chao Yang Hospital	15		VATS	147%	6.6%
Taiwan	93	1	VATS	26%	0%
Singapore	8	1	median sternotomy	50%	*12.0%*
Korea					
Yonsei University College of Medicine	1		VATS		

This table was based on the published papers (5–11), a symposium on pulmonary emphysema in Fukuoka 2000 (reports from Genign J of Shanghai First Pulmonary Disease Hospital in China and Lee Y of Yonsei University College of Medicine in Korea), a questionnaire study in Japan by Shirakusa T and Iwasaki A (Fukuoka Univ.), and personal information from Tan WC (National Univ. of Singapore), Yim APC (Chinese Univ. of Hong Kong), Liu Y (Beijing Chao Yang Hospital in China), Date H (Okayama Univ.), Esato K (Yamaguchi Univ.), Nezu K (Nara Medical Coll), Iwasaki M (Tokai Univ.), Chihara K (Shizuoka City Hosp.), Habuta M (Shinshu Univ.), Morikawa T (Hokkaido Univ.).

Wakabayashi's report (2), and 69 institutions have performed LVRS on 582 patients using VATS or median sternotomy by the end of 1999. In China, over 300 patients with severe emphysema have been operated on while in Taiwan, one institution has experience of LVRS in over 90 patients with bullous emphysema (11). LVRS is also performed in Singapore and Korea.

The improvement in FEV_1 after the operation ranged widely from 20 to 147% in Asia, similar to those reported in North America, Europe and Australia. This improvement depended on the surgical procedure and whether it was bilateral or unilateral. The bilateral approach has been found to be more effective than the unilateral with improvement of over 50% and 20–30% in FEV_1 respectively.

Early mortality defined as the operative 30-day in-hospital mortality ranged from 0 to 12 % in Asia. This also corresponded to the mortality reported in the literatures outside Asia. The variability in mortality may be due to differences in patient selection, surgical procedures, pre-or post-operative management or overall experience after LVRS. The complications according to the results of a questionnaire study in a Japanese group were as follows: prolonged airleak (19.8%), reoperation (7.4%), mechanical ventilation (4.3%), pneumonia (3.9%), interstitial pneumonia (3.3%), cardiac failure (1.6%), postoprerative dissociation of sternal bone (1.6%), and gastrointestinal bleeding (1.0%).

Assessment and Selection of Patients

A standard preoperative assessment for patients with emphysema has not been established. However, both physiological examination and imaging studies have been recommended by the Respiratory Failure Research Committee of Japanese Ministry of Health and Welfare (Table 2) (12), which is basically similar to the recommendation of the ATS (13). The following physiological measurements are recommended:

1. spirometry and lung volume determination performed by both gas dilution methods and body plethysmography;
2. lung mechanics such as lung pressure volume curve and airway resistance;
3. arterial blood gas and diffusing capacity; and
4. exercise testing.

Lung volume measurement is important for determining the degree of hyperinflation and the non-functional air volume (the volume that does not contribute to gas exchange).

Body plethysmography measures the thoracic lung volume including the non-ventilated lung region while the gas dilution method measures the gas volume distributed to the well-ventilated lung area. The difference between the lung volumes measured by the two methods is the non-functional lung volume. Exercise performance is determined by symptom-limited maximal exercise test on a treadmill or bicycle ergometer and the dyspnoea sensation during exercise is estimated by the Borg scale.

The following imaging studies are also recommended. High-resolution computed tomography (CT) of the chest is necessary to determine the location of emphysema represented by areas of low attenuation. Ventilatory and perfusion scanning of the lung is recommended to determine the nonfunctional area. In certain candidates for LVRS in whom the chest CT reveals a homogeneous distribution of emphysematous destruction in all lobes, perfusion scintigraphy can help to select areas with relative hypoventilation or hypoperfusion for resection (15). Finally, echocardiogram or right heart catheterization is also useful to assess the right heart function.

The following criteria for surgery have been advocated based on our own experience and previous publications:

1. severe airflow obstruction with FEV_1 below 1 litre or below 40% of the predicted value;
2. hyperinflated lungs by chest roentgenogram and body plethysmography (very high residual volume (RV));
3. nonfunctional regional areas in the lungs estimated by CT and ventilatory and perfusion scanning;
4. severe dyspnoea (at least over grade III of Fletcher criteria in our department (16)) even after maximal drug treatment;
5. absence of high risk complications such as acute myocardial infarction, severe angina pectoris, acute infection, and who show a stable clinical course; and

Table 2. Indications for Lung Volume Reduction Surgery

Indications

1) Confirmed diagnosis of pulmonary emphysema; clear evidence of hyperinflation, either from imaging studies (roentgenography or computed tomography of the lungs) or from pulmonary-function studies
2) Marked dyspnoea (Fletcher grade IV or greater) despite maximal medical therapy
3) Marked obstruction of airways
   FEV_1 less than 40% of the predicted value after administration of a bronchodilator. Body-plethysmographic residual volume no less than 250% of the predicted value.
4) Clinical status stable for at least 1 month.
5) Uneven distribution of emphysematous areas. Some areas must be resectable.
6) Absolute abstinence from tobacco consumption.
7) Age less than 75 years.

Contraindications

1) Patients who do not meet the criteria stated above
2) Patients with copious secretions from the airways or whose airways are severely diseased
3) Patients with abnormalities of the diaphragm or the chest wall
4) Patients in whom the risks associated with surgery are high because of at least one comorbid condition (examples: myocardial infarction; severe angina; severe infection within the previous 3 months)
5) Patients with liver dysfunction or clotting abnormalities
6) Steroid-dependent patients
7) Ventilator-dependent patients
8) Patients with a mean pulmonary-artery pressure greater than 4.7 kPa
9) Patients with a $PaCO_2$ greater than 8.0 kPa

Measurements Required

1) Electrocardiography
2) Echocardiography
3) Complete pulmonary-function studies: spirometry, flow-volume loop, lung volumes (by both body-plethysmographic and gas-dilution methods, if possible), diffusing capacity of the lung, single-breath nitrogen test, pressure-volume curve of the lung, airway resistance, and arterial blood analysis
4) Computed tomography of the lungs
5) Lung scintigraphy (ventilation and perfusion)

Optional

1) Exercise testing

   Six-minute walk or ten-minute walk (variables to be measured: distance walked, arterial oxygen saturation (SpO_2)).
   Treadmill, cycle ergometer (variables to be measured: minute ventilation, tidal volume, respiratory rate, anaerobic threshold, oxygen consumption, carbon dioxide production, maximal oxygen consumption, heart rate, SpO_2, dyspnoea, etc.
2) Right-heart catheterization
   Post-operative evaluation

The tests and measurements described above may be done as deemed appropriate, 3 months, 6 months, and 1 year after surgery and every year thereafter.

6. highly motivated patients who are compliant with smoke cessation and pulmonary rehabilitation.

Advanced age (> 80 years), severe cachexia and severe pulmonary hypertension (mean pulmonary artery (PA) pressure > 35 mmHg) have been considered contraindications for LVRS. Severe hypercapnia and/or ventilator dependence are common exclusion criteria. However, we believe the issue remains open since we found improvement in pulmonary function and dyspnoea sensation after LVRS even in hypercapnic patients with severe emphysema (17). Recently Criner et al (18) reported ventilator-dependent COPD patients who had successful weaning after LVRS. Figure 1 summarizes the process for determining the suitability of LVRS. The important points are whether the patients have already received maximal medical treatments and whether they have hyperinflated emphysema with a clear target area for resection.

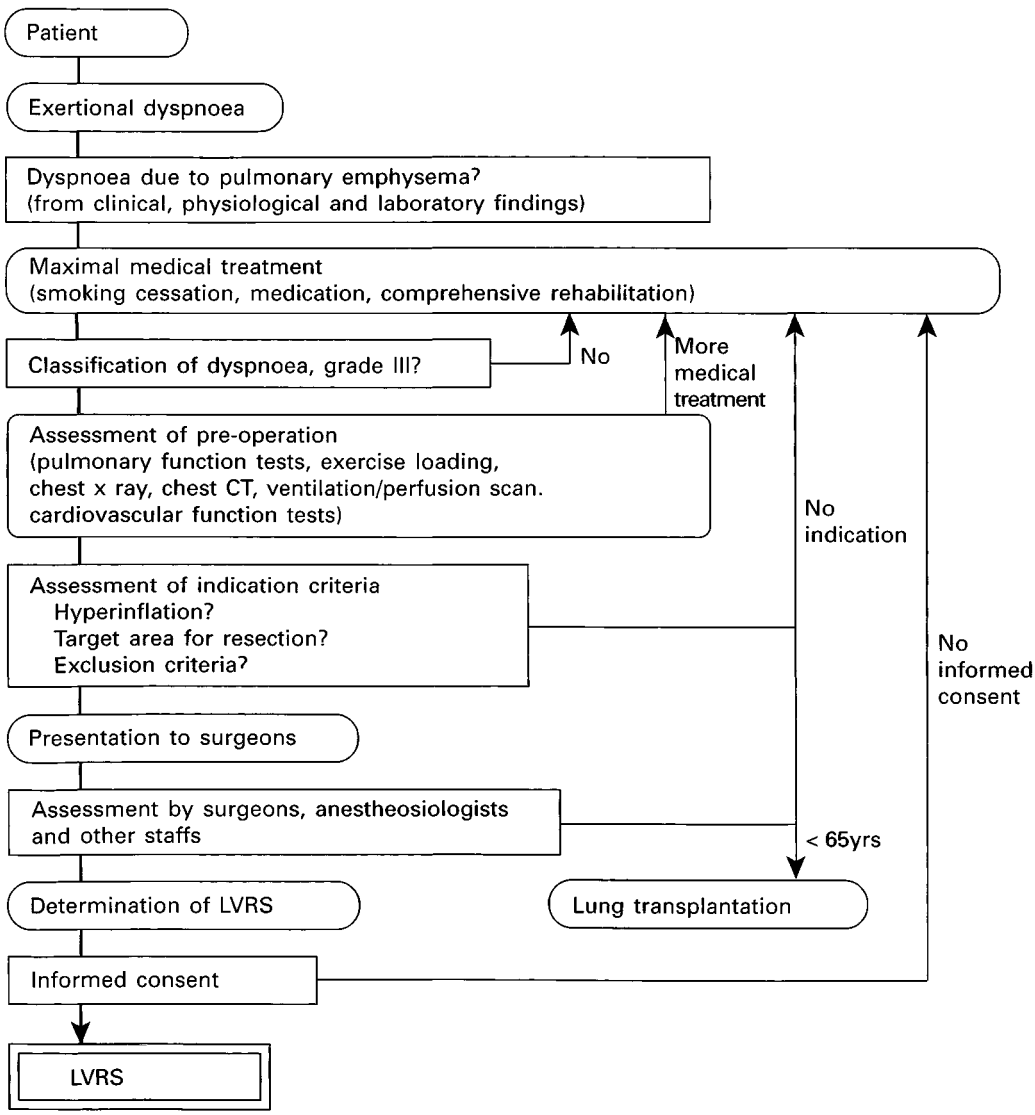


Figure 1. A summary of the process for the determination of the indication for lung volume reduction surgery (LVRS).

Post-operative evaluation is important for follow-up assessment and management. Pulmonary function tests described previously (Table 2) should be done at 3 months, 6 months, and 1 year after surgery, and every year thereafter.

Pulmonary Rehabilitation

Although there are some controversies about pulmonary rehabilitation for the management of patients with COPD, most surgical centres which perform LVRS adopt pre- and post-operative comprehensive pulmonary rehabilitation. Even if pulmonary rehabilitation is not routinely performed preoperatively, rehabilitation after the operation is commonly performed. If patients are referred from remote areas where there is no available preoperative rehabilitation program, a home-based exercise training program before LVRS is useful to maximize exercise tolerance and quality of life (19). The centres in Asia described in Table 1 also adopted pre- and post-operative pulmonary rehabilitation extensively.

The rehabilitation program includes education on proper breathing techniques, anxiety control, muscle stretching and strengthening exercises, and climbing stairs and using a treadmill. As most patients with severe emphysema have a low body mass index which affects respiratory muscle function and poor prognostic factor in COPD, treatment with preoperative nutritional supplement is an integral part of a pulmonary rehabilitation program. Criner et al (20) conducted a prospective, randomized, controlled trial after 8 weeks of pulmonary rehabilitation to examine the effects of 3 months of additional pulmonary rehabilitation or LVRS on the pulmonary functions and quality of life (QOL). Based on their data, bilateral LVRS improved the static lung function, gas exchange, QOL, and breathing pattern during maximal exercise compared with pulmonary rehabilitation alone. Although the effects of pulmonary rehabilitation are not dramatic, pulmonary rehabilitation before and after LVRS is important in contributing to reduction in mortality after surgery, decrease in hospitalization days and improvement of the prognosis.

Surgical Procedures

There are mainly two surgical approaches for lung volume reduction by staples: video-assisted thoracoscopic surgery (VATS) (2,21,22) and sternotomy (3). An approach by posterolateral thoracotomy is rarely used. The thoracoscopic approach offers better visualization for posterior and inferior lung regions than that afforded by median sternotomy, and is less invasive. Several other interventions such as laser therapy, endoloop ligation and fold plication have also been developed. The latter three procedures are commonly performed by VATS.

Stapled LVRS via VATS

Thoracoscopic procedures are performed using a thoracoscope under general and thoracic epidural anesthesia. Surgery is performed with a double-lumen endotracheal tube. The patient is placed in the full lateral decubitus position and a trocar is inserted at the intercostal space. The thoracoscope through the trocar affords maximal visualization of the chest. Additional incisions are generally made under thoracoscopic visualization to enable the insertion of instruments for lung manipulation and stapling. Target areas are identified, lifted with a sponge, and excised using an endoscopic stapling device. Bovine pericardium is usually used to buttress the staple line. The resection removes approximately 20–30% of the volume of each lung. Resected specimens range from 80 to 120 g in weight. Postoperative pain management includes intercostal nerve blocks over the ribs encompassing the trocar sites and oral analgesics. Two or three 28 French chest tubes are inserted and connected to a water-sealed chest drainage system. Suction is not used as long as the patient is in a clinically stable condition. Chest tubes remain in place until all air leaks have subsided.

In bilateral resection, the patient is turned 180° degree after surgery on one side and the opposite side is prepared for contralateral lung volume reduction during the same anesthesia.

Stapled LVRS via sternotomy

A standard median sternotomy is made and the side that shows the worse preoperative lung function, according to quantitative perfusion and ventilation scans, is done first. The pleura is opened and one-lung ventilation is initiated. Under these conditions, the relatively more healthy portions of the lung undergo absorption atelectasis after a few minutes, whereas the most emphysematous portions often remain fully inflated because of poor or absent pulmonary blood flow. Excision is directed to those portions of the lung that remain distended, which in most patients involves predominantly the upper lobes. In some patients there may be a mixture of bullous and nonbullous areas, whereas the majority of patients have diffuse changes with no apparent bulla. Successive applications of the linear stapling device are used to excise a significant portion of the upper lobe. In some patients, the emphysematous process is uniformly severe and portions of all lobes are excised. After excision of one or two areas, the lung is reinflated to assess the adequacy of the volume reduction. If appropriate, the lung is again deflated and additional resection is done. To avoid small air leaks through the staple holes, bovine pericardial strips to buttress the staple line are used. After the final excision, the lung is reinflated and inspected under water for air leaks. Every attempt is made to eliminate air leaks.

On completion of the first side, the lung is fully reinflated. The opposite lung is then deflated and the procedure is done in an identical manner. Two chest tubes are placed on either side and the pleura are closed bilaterally before closure of the sternotomy. Early extubation and avoidance of chest tube suction is important to reduce air leak complications.

Laser therapy

The laser is applied to the lung surface via either an open or thoracoscopic approach and bulla are seen to contract or shrink. No functional lung tissue is removed or damaged by the laser. The original idea was reported by Wakabayashi et al who performed unilateral procedures utilizing the contact tip of an Nd:YAG laser (2). The entire pleural surface of the lung, including the fissures, is treated with the laser until maximal shrinkage is obtained. A CO_2 laser and argon beam coagulator have also been used.

Endoloop ligation of bulla

This procedure is carried out under general anesthesia thoracoscopically and without the endoscopic stapler for the management of bullous emphysema (23,24). The superficial bulla is collapsed by stabbing it with the tip of the electrocautery. The shrunken bulla is twisted to its base until the normal lung parenchyma is reached at which point the endoloop is applied and the preformed loop is tightened using a knot advancer. After ligation of all bullae, the lung is manually inflated, and if no bullae protude and the consistency of the underlying lung parenchyma appears normal, the ligation is considered adequate. Finally, talcum powder is routinely insufflated to enhance the postoperative pleurodesis (23,24). Whether this technique is applicable to diffuse emphysema has not been proven.

Fold plication

This procedure is performed thoracoscopically during unilateral pulmonary ventilation with the patient in the lateral position (25,26). A scalpel-less automatic suture device is used for fold plication, which is performed by first exerting traction on the apex of the target lung. The two staplers are positioned on the right and left so that there is no gap between the tips of the instruments and the staplers are then fired. The peripheral side is folded so that the staple line becomes the apex of the fold. After folding again, a stapler is fired at the more central target zone.

Which surgical procedure is better?

VATS is the more frequently performed technique world wide and in Asia. Based on a study by questionnaires by Shirakusa and Iwasaki in Japan unilateral LVRS using VATS was performed in 44.2%, bilateral LVRS using VATS 23.7% and

median sternotomy in about half of the LVRS procedures (29.4%). Cases in which only the thoracotomy approach was used were a minority (2.7%). In our centre, all surgical procedures were VATS.

Kotloff et al (27) compared the effects of bilateral LVRS by VATS with those by median sternotomy. The VATS and median sternotomy approaches lead to similar improvement in pulmonary function and exercise tolerance although VATS was associated with a significantly lower incidence of respiratory failure and a tendency toward decreased in-hospital mortality.

The hospital costs of LVRS are related directly to the duration of the stay in the intensive care unit, the length of the hospital stay, operative procedures and respiratory therapy. Hospital costs per case ranged from about $12,000 to $120,000 in North America (28). The hospital costs for the VATS procedure are less than those for sternotomy (about $27,000 and $37,300, respectively) (29). In Japan, total hospital costs for LVRS are approximately US$11,000, about one third of those in North America.

Which is more effective, the stapling or laser procedure?

McKenna et al (21) designed a randomized, prospective trial to compare the efficacy of staple lung reduction and laser procedure performed unilaterally by thoracoscopy. Delayed pneumothorax after discharge occurred more often with the laser procedure than with the staple procedure. The mean postoperative improvement in FEV_1 was significantly greater for patients undergoing the staple than those undergoing the laser procedure. Thus, a lower morbidity and a greater overall improvement in the clinical status were demonstrated with staple lung reduction than with the laser procedure. At present there are very few hospitals which employ the laser procedure, the efficacy of which is questionable.

Recently, Akahane et al (30) reported a very interesting study on the effects of laser ablation on elastase-induced emphysematous lung in animals. They irradiated the rats' lung eight weeks after elastase treatment using a contact Nd:YAG laser. They found that at 4 weeks after laser irradiation the lung volume-associated increase in elastic recoil diminished, and there were marked fibrous scars beneath the pleura, and that the volume reduction only 10% of TLC. These findings may explain why laser pneumoplasty is less useful than the stapler method in LVRS.

McKenna et al (31) studied the benefits of unilateral or bilateral staple LVRS using VATS. They found that bilateral staple LVRS produced greater overall improvement than the unilateral procedure, and the improvement appeared to be comparable to that of median sternotomy.

There have been no studies which reported comparisons between the stapled method with VATS or sternotomy and endoloop ligation or fold plication. However, the latter two procedures seem to be simple, cost-effective and minimally invasive.

Outcome

Effects on ventilatory functions

As shown in Table 1, most institutions all over the world reported significant improvement in spirometry. The improvement of ventilatory function in 42 patients with LVRS performed from 1993 to 1997 in our centre are shown in Table 3 (32). The FEV_1 increased significantly at 3 months after LVRS, and the increase in the mean FEV_1 was from 0.79 litres before LVRS to 1.14 litres after LVRS. This improvement is comparable with the results from other countries (Table 1) or those by Young et al (5) who systematically reviewed the results of FEV_1 in 925 patients. The interquartile range of FEV_1 in these patients was 0.64~0.73 litres before LVRS and rose to 0.91~1.07 litres 3~6 months after LVRS with a pre/post difference of 0.23~0.36 litre. More interestingly, we found that the reduction in lung volume had a significant correlation with the improvement in FEV_1 after surgery (Figure 2). McKenna et al (31) also found a significant correlation between the mass of lung tissue resected and the postoperative change in FEV_1.

Elastic recoil of the lung and lung compliance could also be altered after surgery. We observed that the maximal elastic recoil at TLC (Pesmax) increased, and the static lung compliance (Cst, slope of the pressure-volume curve at FRC)

Table 3. Pulmonary Function before and 3 Months after LVRS (n = 42)

	Before LVRS	*After LVRS*	*p value*
SVC (L)	2.44 ± 0.76	2.63 ± 0.59	NS
FEV1 (L)	0.79 ± 0.35	1.14 ± 0.46	< 0.0001
PaO_2 (kPa)	9.3 ± 1.41	10.0 ± 0.19	< 0.001
$PaCO_2$ (kPa)	6.1 ± 1.5	5.5 ± 0.68	< 0.01
pH	7.40 ± 0.03	7.40 ± 0.03	NS
AaDO2 (kPa)	3.21 ± 1.27	3.23 ± 1.08	NS
TLC (L)	7.89 ± 1.18	6.93 ± 1.11	< 0.0001
FRC (L)	6.05 ± 1.15	5.05 ± 1.04	< 0.0001
RV (L)	5.28 ± 1.17	4.22 ± 1.03	< 0.0001
TLCHe (L)	6.20 ± 1.22	6.01 ± 1.08	NS
FRCHe (L)	4.58 ± 1.08	4.33 ± 0.76	NS
DLco (ml/min/kPa)	1.24 ± 0.52	1.24 ± 0.47	NS
Cst (L/cmH_2O)	0.46 ± 0.25	0.33 ± 0.19	< 0.01
Pes max (cmH_2O)	11.2 ± 4.9	14.9 ± 6.31	< 0.01
Raw ($cmH_2O/L/sec$)	4.9 ± 1.9	4.4 ± 1.9	NS

Means±SD. n = 42 SVC, slow vital capacity; FEV_1, forced expiratory volume in one second; TLC, FRC and RV, total lung capacity, functional residual capacity and residual volume measured by body plethysmography, respectively; TLCHe and FRCHe, total lung capacity and functional residual capacity measured by He gas dilution method, respectively; PaO_2 and $PaCO_2$, arterial oxygen and bicarbonate tension, respectively; $AaDO_2$, alveolar-to- arterial oxygen tension, Cst, static compliance evaluated between FRC and FRC + 0.5 L in the P-V curve, Pes max, maximal esophageal pressure; Raw, airway resistance (32).

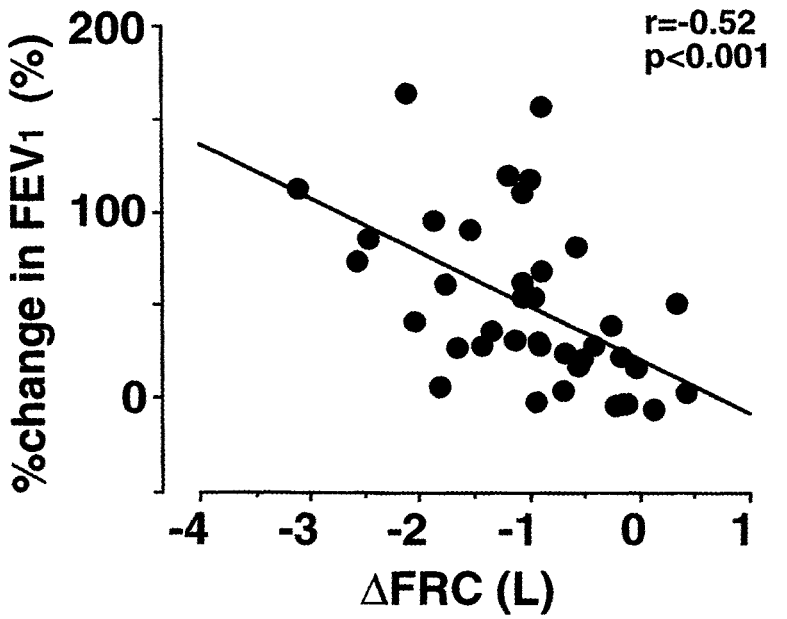


Figure 2. The relationship between volume change (ΔFRC) and increase of FEV_1 before and after LVRS. ΔFRC had a negative relation to % change in FEV_1. Here, ΔFRC = FRC (3 months after LVRS) — FRC (before LVRS). The % change in FEV_1 = 100 x (FEV_1 (3 months after LVRS) — FEV_1 (before LVRS))/FEV_1 (before LVRS). A greater reduction of FRC shows a greater improvement of airway obstruction.

decreased after LVRS (Table 3). However, other investigators showed an increase in the elastic recoil at TLC after surgery, but did not show a significant change in Cst at FRC (33,34,35). Increased elastic recoil would increase the traction tissue force surrounding the airway wall and would decrease the collapsibility of the airway, resulting in increased expiratory flow. Furthermore, volume reduction would induce an expansion of the remaining lung, which may have been oppressed by the nonfunctional lung. The improvement in maximal expiratory airflow can be attributed to the increased lung elastic recoil, which can induce a decrease in airway resistance (34,35).

Effects on arterial blood gas

The effects of LVRS on arterial blood gas are not consistent. Most studies reported an improvement of PaO_2, but no significant change in $PaCO_2$ after surgery, which may imply that LVRS improves oxygenation without improving alveolar ventilation, suggesting that ventilation-perfusion ($\dot{V}_A/\dot{Q}$) heterogeneity is reduced. Some investigators showed not only an improvement of PaO_2 but also a decrease in $PaCO_2$, suggesting there is an increase in alveolar ventilation in addition to the improvement of $\dot{V}_A/\dot{Q}$ heterogeneity. In our study, increases in PaO_2 (from 9.3 to 10.0 kPa) and decreases in $PaCO_2$ (from 6.1 to 5.5 kPa) were found. However, alveolar-to-arterial oxygen tension ($AaDO_2$) did not change significantly (Table 3) implying that alveolar ventilation was primarily increased after LVRS. Albert et al (36) reported that LVRS arterial blood gases improved in some patients and worsened in others and that the effects of LVRS on PaO_2 resulted from alterations in $\dot{V}_A/\dot{Q}$ heterogeneity.

Effects on diffusing capacity

The effects of LVRS on diffusing capacity are also variable, with some showing an increase (37) while others showed no change (33,38). The mechanisms are not clear. We did not find a significant change in the diffusing capacity in our patients (Table 3).

Effects on lung volume

The mean values of the total lung capacity (TLC), functional residual capacity (FRC) and residual volume (RV) measured by plethysmography decreased significantly from 7.89, 6.05, 5.28 litre to 6.93 (12% reduction), 5.05 (17% reduction), 4.22 (20% reduction) litre, respectively, after surgery (Table 3). The bilateral approach tended to produce a greater magnitude of short-term functional improvement compared to the unilateral procedure (39). However, based on the studies that directly compared unilateral to bilateral procedures, the magnitude of improvement following unilateral volume reduction exceeded half of that following bilateral LVRS (31,40).

On the other hand, the lung volumes (TLC and FRC) measured by the helium dilution method did not change significantly after LVRS (Table 3). As the lung volume measured by the helium dilution method reflects the functional lung volume, the lack of a change in this lung volume before and after surgery suggests that functional lung areas have not been resected by the surgical procedure.

The changes in "nonfunctional gas volume" before and after LVRS correlated significantly with changes in FRC by body plethysmography (ΔFRCbox) (41). If the stapled lung tissue had been functionally normal, the ΔFRCbox would not correlate with the nonfunctional gas volume. Therefore, the significant correlation between nonfunctional gas volume and ΔFRCbox probably mean the site resected by the stapled procedure is nearly equal to the non-functional lung site.

Effects on respiratory muscle function

The inspiratory muscle strength measured by mouth pressure during maximal inspiratory efforts has been shown to increase significantly after LVRS (42). Moreover, based on the more direct measurements of transdiaphragmatic pressure (Pdi), maximal Pdi increased after LVRS (43,44,45).

The possible mechanisms of improvement of respiratory muscle function are summarized in Figure 3. Patients with advanced emphysema have a flattened diaphragm, which is not capable of

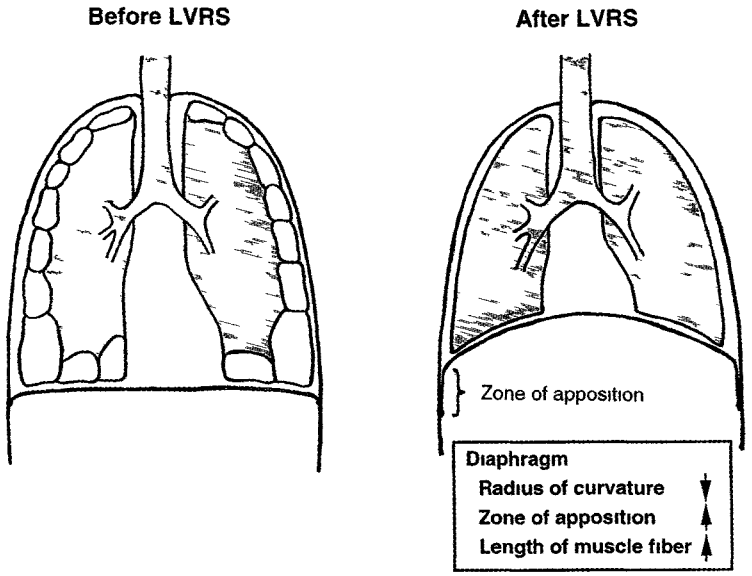


Figure 3 Scheme of possible change of diaphragm after LVRS Decrease in radius of curvature increase in zone of apposition and increase in length of muscle fiber would be possible after LVRS These changes may induce an increase in diaphragmatic strength

effective contraction to ventilate the lung Flattened diaphragms of these patients have larger radius if we assume that the diaphragm is a part of a sphere and the force generated by the diaphragm at a given tension would be small After surgery, the radius of the diaphragm curvature decreases and the force generated by the diaphragm increases Other changes in diaphragm also occur after surgery such as a greater zone of apposition, dome formation, and increase in the length of the diaphragm (43,45) These alterations of diaphragm shape increase the strength of diaphragm

The efficiency of the respiratory muscles could also be improved after surgery We measured oxygen consumption of respiratory muscles using a closed circuit device equipped with a 9 L Collins spirometer that allows a continuous increase in an external dead space (46) Using this method we found the efficiency of the respiratory muscles as reflected by a high oxygen consumption in COPD patients was below normal but improved after surgery when oxygen consumption of respiratory muscle decreases (47) The reduction in oxygen consumption of respiratory muscles could be due to overall improvement in the mechanical properties of the lung, changes in the pattern of recruitment of abdominal muscles to a greater contribution of the diaphragm (48) and improvement in nutrition (49,50)

Effect on exercise performance

LVRS improves exercise performance as shown by increases in maximal oxygen uptake and maximal minute ventilation during incremental maximal treadmill exercise test and increases in 6 minutes walking distance after LVRS (33,51,52,53) The mechanism of improvement of exercise performance is not clear but may be due to the reduction in dynamic hyperinflation during exercise associated with a marked improvement in the diaphragm function after LVRS (42) Furthermore, LVRS improves dyspnoea sensation during exercise probably due to the reduction of dynamic hyperinflation (38,42), and would contribute to a reduction in breathlessness in the activities of daily life (51) Pulmonary hemodynamics did not change after LVRS during exercise (54)

Effects on hemodynamics

COPD, especially during exercise, can cause an increase in the pulmonary artery pressure by hypoxic pulmonary vasoconstriction or a decrease in the vascular bed associated with the remodelling of pulmonary vessels (55,56). As LVRS improves pulmonary function and hypoxemia, hypoxic vasoconstriction reduces, pulmonary resistance and right ventricular function improve. On the other hand, LVRS may result in the deformation of vessels, removal of a significant amount of the pulmonary vascular bed, and an increase in the pulmonary artery pressure due to increased venous return. Weg et al (57) showed that there was pulmonary hypertension after LVRS although patients had symptomatic improvement and improved FEV_1. They speculated that the mechanism was due to an increase in the pulmonary vascular resistance from a decrease in the cross-sectional area after LVRS because they did not observe an increase in cardiac output and hypoxemia after LVRS. Other investigators also did not find an improvement of pulmonary hemodynamics at rest or during exercise (58,59). However, a recent study by Haniuda et al showed that the effects of LVRS on the cardiopulmonary circulation were important, especially during exercise, and that the beneficial effects of LVRS might be dependent on the improved ventilatory function and preserved cardiac function that can tolerate the reduced pulmonary vascular bed by LVRS (60). These variable effects of LVRS may be related to differences in the state of pulmonary hypertension in such patients before surgery, removal of the portion of lung tissue containing diseased vessels, and changes in lung mechanics. Further studies will be necessary to clarify the changes in pulmonary hemodynamics (56).

Effects on chemosensitivity

Some investigators observed an improvement of hypercapnia in severe emphysema after surgery (33,37,61,62) and postulated the following reasons: reduced airflow limitation, hyperinflation and air trapping, increased elastic recoil, and improved respiratory muscle function, which enables the lung and chest wall to act more effectively as a pump, thereby increasing the alveolar ventilation (62). These changes could also alter the respiratory drive and the ventilatory response to hypercapnia.

Celli et al (63) found that the mouth pressure 0.1 second after the onset of an occluded inspiration ($P_{0.1}$), an index of neuromuscular inspiratory drive, in the resting state was higher for emphysema patients compared with the control subjects. There was also a significant decrease in $P_{0.1}$ response to CO_2 after LVRS.

The ventilatory ($\dot{V}_E$) and $P_{0.1}$ response to CO_2 in our patients before and 3 months after LVRS (64) are summarized as follows. The pre-operative reduced VE response to CO_2 was shifted upwards and its slope, expressed as $\Delta\dot{V}_E/\Delta P_{ET}CO_2$, also increased after LVRS. The $P_{0.1}$ response to CO_2 ($\Delta P_{0.1}/\Delta P_{ET}CO_2$) after LVRS was not uniform and could be classified into three groups: patients with a decrease, no change, and an increase in the $P_{0.1}$ response to CO_2. In the first group, the increased central drive before LVRS was attenuated to the control level after LVRS. In the third group, the depressed central drive before LVRS was augmented and returned to the normal level after LVRS.

The causes of this alteration in the $P_{0.1}$ response to CO_2 after LVRS is not clear. The chemosensitivity to CO_2 in COPD may be affected by the blood gas level and/or mechanical efficiency of the respiratory system (65). The decrease in the $P_{0.1}$ response to CO_2 after LVRS (the first group) could not be explained by effects of volume reduction, as a decrease in FRC after LVRS would increase $P_{0.1}$ response due to an increase in the resting length of the inspiratory muscle. One possibility is that chemosensitivity to CO_2 is greater in the more hypoxemic environment before LVRS than when PaO_2 is improved after LVRS. In contrast, the increase in the $P_{0.1}$ response to CO_2 after LVRS (the third group) could be explained by effects of volume reduction. The differences in $P_{0.1}$ response may also be explained by a difference in load compensation to airway obstruction in COPD patients. There may be one type of patients who breathe with stronger load compensation against airway obstruction, such patients have a lower $\dot{V}_E$ response but higher $P_{0.1}$ response to CO_2 before LVRS. In this group, improvement of airway obstruction by LVRS increases the $\dot{V}_E$ response to CO_2 but reduce the $P_{0.1}$ response to

CO_2. The other type of patients, however, breathe with less load compensation against airway obstruction; such patients have both lower $\dot{V}_E$ and $P_{0.1}$ responses to CO_2, and, both responses would increase after LVRS. The former is compatible with the $P_{0.1}$ response of the first group and the latter with that of the third group in our study.

Effects on dyspnoea and QOL

Severe COPD patients suffer from profound exertional dyspnoea. Dyspnoea is an important determinant of the quality of life in patients with emphysema, and involves central processing of a number of different afferent pathways, such as mechanoreceptors of respiratory muscles and the lung, and peripheral chemoreceptors. The mechanisms of dyspnoea in emphysema may be explained by:

1. the increase in the inspiratory muscle tension which must overcome the increase in airflow resistance caused by airway narrowing, mucous secretions, and loss of elastic recoil; and
2. hyperinflation which has become less effective in generating tension because of the shortened inspiratory muscles and the increase in the radius of the curvature of the diaphragm.

The mechanical impairment of inspiratory muscles increase the respiratory motor output, resulting in an increase in dyspnoea (66,67). Furthermore, hypoxemia or hypercapnia also stimulates the peripheral chemoreceptors or central chemoreceptors, respectively, leading to an increase in the respiratory motor output, resulting in an increase in dyspnoea.

LVRS may improve dyspnoea in patients with emphysema by improvement in airway obstruction, hypoxemia, hypercapnia, respiratory muscle function and/or hyperinflation. All these factors reduce the motor command from the respiratory controller.

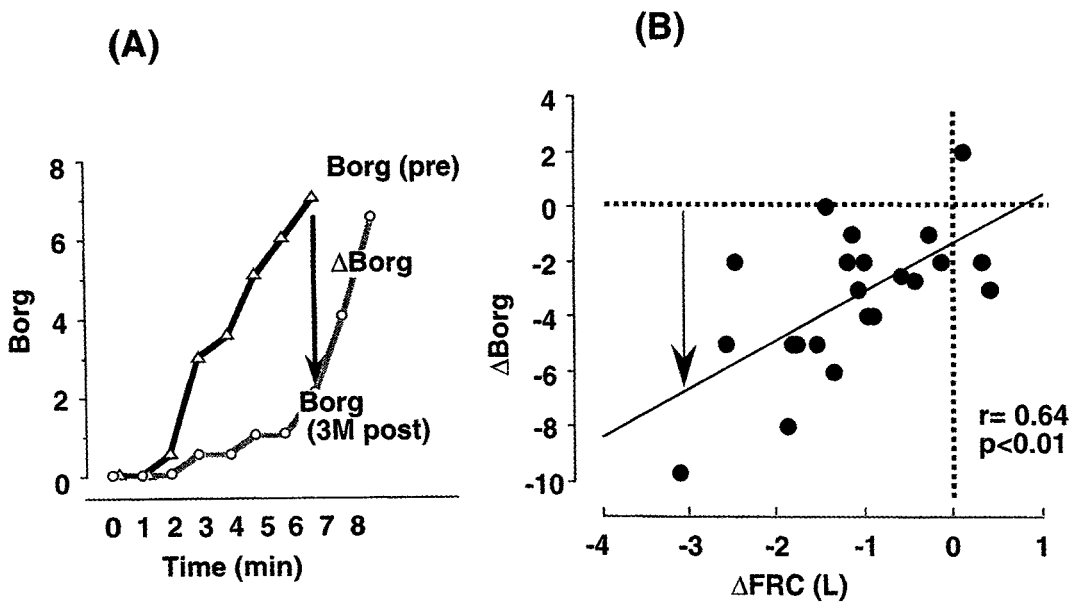


Figure 4. (a) The representative curve of dyspnoea sensation during exercise. Triangles show the curve before LVRS, and open circles after LVRS. Change of Borg scale (ΔBorg) shows the difference in the Borg scale at the maximal exercise level before LVRS. (b) The relationship between volume change (ΔFRC) and improvement of dyspnoea sensation during exercise before and after LVRS. ΔFRC showed a significant correlation to ΔBorg. A greater reduction of volume was followed by a greater improvement of the dyspnoea sensation during exercise.

We found a significant correlation between reduction of FRC and improvement in dyspnoea sensation after surgery. A greater volume reduction was followed by a greater improvement in dyspnoea sensation (Figure 4). Thus, a major factor of reducing dyspnoea sensation may be an improvement of dynamic hyperinflation (42).

There have been a few reports measuring the QOL using the Chronic Respiratory Disease Questionnaire, the Nottingham Health Profile and SF36 (5) and found improvement in QOL after LVRS. The improvement of QOL is associated with a reduction in dependency on supplemental oxygen by 36–71% after LVRS (21,68,69).

Prediction of outcomes

As described above, pulmonary function parameters are very important for evaluating candidates suitable for LVRS. Ingenito et al reported that inspiratory lung resistance measured by an oesophageal balloon catheter system correlated with improvement of FEV_1 after LVRS (70). They concluded that preoperative lung resistance during inspiration is a useful measure for selecting patients with emphysema for lung volume reduction surgery. They suggested that patients with preoperated lung resistance less than 10 cm of water per litre per sec had a favorable response to LVRS and their FEV_1 increased at least 0.2 litre above baseline values after surgery. Patients with a higher inspiratory pulmonary resistance have an increased intrinsic airway resistance due to chronic airway inflammation, and should be excluded.

The pre-operative residual capacity may be useful to predict improvement of dyspnoea and exercise capacity. Figure 5 shows a significant negative relationship between the preoperative residual volume, and the change of dyspnoea sensation before and after surgery. When the predicted RV is more than 200% of the predicted the improvement in dyspnoea was considerable.

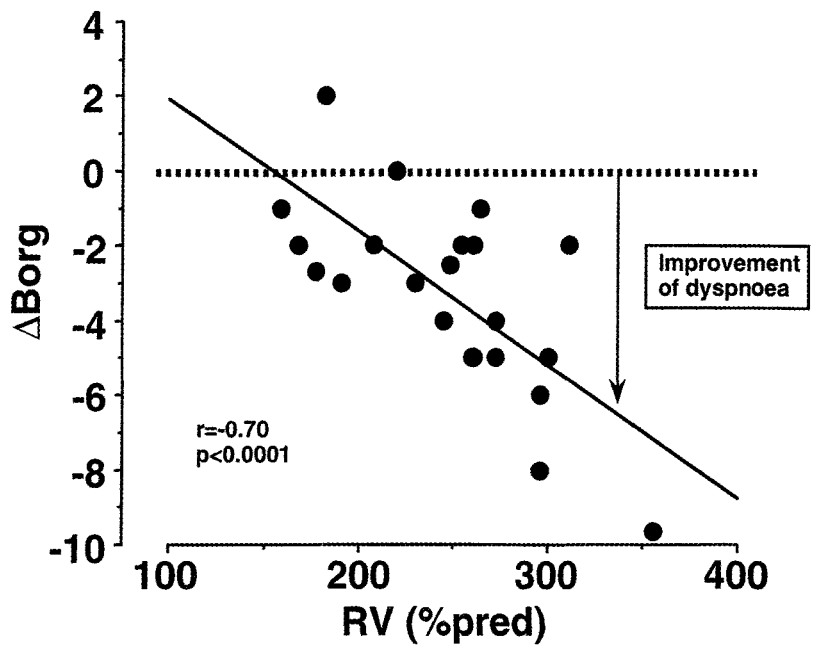


Figure 5. The relationship between change of dyspnoea sensation (ΔBorg) during exercise before and after LVRS and preoperative residual volume. A greater residual volume at pre-operation showed a greater improvement of dyspnoea during exercise, particularly, over 200% of RV of predicted value.

Recently, Date et al (71) reported that the distribution of emphysema in the lungs and the degree of pleural adhesion were predictors of improvement in FEV_1 after bilateral LVRS. They described that improvement in FEV_1 was greater in patients with upper lobe type emphysema than in those with lower lobe or mixed type emphysema, and that severe pleural adhesions limited the improvement of FEV_1 after LVRS. Thus, preoperative morphological evaluation by CT scan, and ventilation and perfusion scanning are important.

Follow-up study of pulmonary function after LVRS

Follow-up studies after LVRS are limited. Generally, the decrease in FEV_1 with age has been considered to be 20–30 ml per year in healthy non-smokers and ex-smokers, 60–80 ml per year in continuing smokers, and 40–80 ml per year in patients with COPD. On the other hand, 1 year or longer follow-up studies after LVRS, has shown that the increase in FEV_1 generally peaks at about 3–6 months, and after 6 months, the FEV_1 declines gradually. The decline in FEV_1 is variable depending on the report and the postoperative FEV_1 slope seems to be greater than that of healthy subjects or COPD patients (72). Cordova et al reported a FEV_1 loss of 140 ml per year (51) while Gelb et al reported that the decline of FEV_1 was approximately 210 ml per year from 6 months to 24 months after LVRS (73). Patients who showed a greater improvement in FEV_1 3–6 months after LVRS also showed a more rapid decline (74). In our study, the maximally increased FEV_1 3 months after surgery gradually declined at the rate of 60 ml per year, similar to those without volume reduction surgery. However, FEV_1 3 years after surgery was still greater than the baseline FEV_1 before surgery. Post-LVRS reductions in TLC, FRC and RV were also maintained throughout the three years of follow-up.

Very recently, the first report of a randomized, controlled trial of LVRS on a small number of patients with severe emphysema was published (75). The effectiveness of LVRS was compared with that of intensive medical treatment including a smoking-cessation program at follow-up periods ranging from 6 to 12 months. Significant benefits in terms of FEV_1, shuttle-walking distance, and quality of life was found in the surgical group compared with the medical treatment group. However, long-term follow-up is needed to confirm the usefulness of this surgical procedure.

Prognosis after LVRS

There has been a controversy about the survival after LVRS. Gelb et al (76) reported that the actual survival at 1, 2, 3, and 4 years after LVRS was 96%, 81%, 69%, and 54%, respectively. This survival is greater than patients with similar representing impairment without surgery reported previously (77), where the survival rate of 3 years was 69%. We also studied for five years the survival prognosis of 72 patients who had LVRS with the thoracoscopic procedure, and compared it with 73 patients with disease of similar severity but had conservative therapies. In the LVRS group, 14 patients died: 8 due to respiratory failure, 3 operation-associated death, 2 cerebrovascular diseases and one lung cancer. In the non-surgical group, 17 patients died: 10 due to respiratory failure, 4 lung cancer, one each due to myocardial infarction, sudden death and suicide. The survival at 1, 3 and 5 years after LVRS was 93.1%, 82.4% and 72.3%, respectively. On the other hand, in the non-surgical group, the survival at 1, 3 and 5 years was 92.8%, 64.2% and 52.3%, respectively (78). The difference between the two survivals after 3 years was significant. This 3-year survival rate after LVRS was also greater than the survival rate (63%) reported by the respiratory failure research committee of Japanese Ministry of Health and Welfare (61), and those reported by Burrows et al (77) in medically treated patients.

To assess the benefits of LVRS, the National Emphysema Treatment Trial (NETT), a well designed multicentre, randomized controlled randomized trials was started in October 1997 in the USA comparing medical therapy alone and medical therapy plus LVRS for treatment of patients with severe emphysema (79,80). The first paper by the NETT research group reported that LVRS in severe emphysema patients with FEV_1 less than 20% of their predicted value and with either a radiologically homogeneous emphysema

or DL_{CO} that was no more than 20% of their predicted value. resulted in a higher risk of death during the first 30 days than did medical treatment (80). The overall mortality rate for three years was also higher in patients with LVRS than patients with medical treatment.

The difference between the results of the NETT study and those of others may be due to difference of the severity or distribution of emphysema. The result of the NETT study suggest that patients who have extremely low pulmonary function and homogeneous emphysema should not be considered for LVRS.

Summary

In selected COPD patients, LVRS may improve pulmonary function, blood gas exchange, respiratory muscle strength, dyspnoea sensation, quality of life and survival. However, there is considerable variability in the baseline assessment, types of operations performed, procedures involved in preoperative, intraoperative and postoperative care, and type and completeness of follow-up evaluations in the various reports. Moreover, publications on LVRS deal with relatively small numbers of selected patients without long-term follow-up or comprehensive assessment of risks, benefits, and costs. The role of LVRS in the management of COPD has yet to be defined.

Acknowledgements

The authors thank Mr. Bent Bell for reading the manuscript, the Respiration Function Group for the pulmonary function testing and Laser Treatment Group and collaborators for the surgical procedure. This effort was supported in part by Grant-in-Aid for Scientific Research (No. 10557056, 10470146 and 10877096) from the Ministry of Education, Science, Sports and Culture of Japan.

References

1. Brantigan O, Mueller E. Surgical treatment of pulmonary emphysema. *Am Surg* 1957; 23:789–804.
2. Wakabayashi A. Thoracoscopic laser pneumoplasty in the treatment of diffuse bullous emphysema. *Ann Thorc Surg* 1995; 60:936–42.
3. Cooper JD, Trulock EP, Triantafillou AN, Patterson GA, Pohl MS, Deloney PA, Sundaresan RS, and Roper CL. Bilateral pneumonectomy (volume reduction) for chronic obstructive pulmonary disease. *J Thorac Cardiovasc Surg* 1995; 109:106–19.
4. Mouri M, Hayashi K, Komatsu H, Shiraishi Y, Sagara Y, Mitoma Y, Hukushima K, Machida K, Kawabe Y, Satoh K, Ohtsuka Y, Hebisawa A, Katayama T. Possibility of CO_2 laser abration for pulmonary emphysema using thoracoscopy (Japanese). 1992 Study reports by Respiratory Failure Research Committee, Japanese Ministry of Health and Welfare. Yamafuji Pub. Sapporo 1993, 212–5.
5. Young J, Fry-Smith A, Hyde C. Lung volume reduction surgery (LVRS) for chronic obstructive pulmonary disease (COPD) with underlying severe emphysema. *Thorax* 1999; 54:779–89.
6. Shimizu Y, Date H, Yamamoto M, Nagahiro K, Endoh M. Lung volume reduction surgery (LVRS) for pulmonary emphysema. State of the world. *Nihon Kyobu Rinshou* 1999; 58:183–7.
7. Hamacher J, Russi EW, Weder W. Lung volume reduction surgery. A survey on the European experience. *Chest* 2000; 117:1560–7.
8. Miller JD, Malthaner RA, Goldsmith CH, Cox G, Higgins D, Stubbing D, Kitching A, Newman TE, McDonald E. Lung volume reduction for emphysema and the Canadian Lung Volume Reduction Surgery (CLVR) Project. *Can Respir J* 1999; 6:26–32.
9. Snell GI, Solin P, Chin W, Rabinov M, Williams TJ, Esmore DS, Smith JA. Lung volume reduction surgery for emphysema. *MJA* 1997; 167:529–32.
10. Porter SH, Ruffin RE, Pfitzner J, Peacock M, Southcott AM, Homan S. Videoscopic lung volume reduction surgery in an Australian public teaching hospital. *Aust NZJ Med* 2000; 30:202–8.
11. Liu HP, Chang CH, Lin PJ, Cheng KS, Wu YC, Liu YH. Emphysema surgery — loop ligation approach. *Eur J Cardiothorac Surg* 1999; 16 (suppl 1):S40–43.

12. Hida W. III Standards and guidelines for therapy. 4. Lung volume reduction surgery. In *Guidelines for the Diagnosis and Management of Chronic Respiratory Failure.* edited by Respiratory Failure Research Committee, Japanese Ministry of Health and Welfare. Tokyo, Medical Review Co., Ltd. 1999, 80–4.
13. Fein AM, Branman SS, Casaburi R, Irvin CG, Make BJ, Rodarte JR, Solway J. Lung volume reduction surgery. *Am J Respir Crit Care Med* 1996; 154:1151–2.
14. Haraguchi M. Shimura S, Hida W, Shirato K. Pulmonary function and regional distribution of emphysema as determined by high-resolution computed tomography. *Respiration* 1998; 65:125–9.
15. Thurnheer R, Engel H, Weder W, Stammberger UZ, Laube I, Russi EW, Bloch KE. Role of lung perfusion scintigraphy in relation to chest computed tomography and pulmonary function in the evaluation of candidates for lung volume reduction surgery. *Am J Respir Crit Care Med* 1999; 159:301–10.
16. Fletcher CM. The clinical diagnosis of pulmonary emphysema — an experimental study. *Proc R Soc Med* 1952; 45:577–84.
17. Mitsui K, Kurokawa Y, Kaiwa Y, Ando K, Kurosawa H, Hida W, Satomi S. Thoracoscopic lung volume reduction surgery for pulmonary emphysema patients with severe hypercapnia. *Jp J Thorac Cardiovasc Surg* 2001; 49:481–8.
18. Criner GJ, O'Brien G, Furukawa S, Cordova F, Swartz M, Fallahnejad M, D'Alonzo G. Lung volume reduction surgery in ventilator-dependent COPD patients. *Chest* 1996; 110:877–84.
19. Debigare R, Maltais F, Whittom F, Deslauriers J, LeBlanc P. Feasiblity and efficacy of home exercise training before lung volume reduction. *J Cardiopulm Rehabil* 1999; 19:235–41.
20. Criner GJ, Cordova FC, Furukawa S, Kuzma AM, Travaline JM, Leyenson V, O'Brien GM. Prospective randomized trial comparing bilateral lung volume reduction surgery to pulmonary rehabilitation in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1999; 160:2018–27.
21. McKenna RJ, Brenner M, Gelb AF, Mullin M, Singh N, Peters H, Panzera J, Calmese J, and Schein MJ. A randomized, prospective trial of stapled lung reduction versus laser bullectomy for diffuse emphysema. *J Thorac Cardiovasc Surg* 1996; 111:317–22.
22. Bingisser R, Zollinger A, Hauser M, Bloch KE, Russi EW, Weder W. Bilateral volume reduction surgery for diffuse pulmonary emphysema by video-assisted thoracoscopy. *J Thorac Cardiovasc Surg* 1996; 112:875–82.
23. Liu HP, Chang CH, Lin PJ, Hsieh HC, Chang JP, Hsieh MJ. Video-assisted thoracic surgery — the Chang Gung experience. *J Thoracic Cardiovasc Surg* 1994; 108:834–40.
24. Liu HP, Chang CH, Lin PJ, Chu JJ, Hsieh MJ. An alternative technique in the management of bullous emphysema. Thoracoscopic endoloop ligation of bullae. *Chest* 1997; 111:489–93.
25. Swanson SJ, Mentzer SJ, DeCamp MM Jr, Bueno R, Richards WG, Ingenito EP, Reilly JJ, Sugarbaker DJ. No-cut thoracoscopic lung plication: a new technique for lung volume reduction surgery. *J Am Coll Surg* 1997; 185:25–32.
26. Iwasaki M, Nishiumi N, Kaga K. Kanazawa M, Kuwahira I, Inoue H. Application of the fold plication method for unilateral lung volume reduction in pulmonary emphysema. *Ann Thorac Surg* 1999; 67:815–7.
27. Kotloff RM, Tino G, Bavaria JE, Palevsky HI, Hansen-Flaschen J, Wahl PM, Kaiser LR. Bilateral lung volume reduction surgery for advanced emphysema. A comparison of median sternotomy and thoracoscopic approaches. *Chest* 1996:110:1399–406.
28. Elpern EH, Behner KG, Klontz B, Warren WH, Szidon P, Kesten S. Lung volume reduction surgery. An analysis of hospital costs. *Chest* 1998; 113:896–9.
29. Ko CY, Waters PF. Lung volume reduction surgery:a cost and outcomes comparison of sternotomy versus thoracoscopy. *Am Surg* 1998; 64:1010–3.
30. Akahane T, Kurokawa Y, Chiba R, Yaegashi H, Takahashi T, Satomi S. Effects of Nd:YAG laser irradiation on morphometry and lung function in elastase-induced emphysema in rats. *Lasers Surg Med* 1998; 23:204–12.
31. McKenna RJ, Brenner M, Fischel RJ, and Gelb AF. Should lung volume reduction for emphysema be unilateral or bilateral? *J Thorac Cardiovasc Surg* 1996; 112:1331–9.
32. Kurosawa H, Hida W, Kurokawa Y, Shirato K. Why LVRS improves pulmonary function. (Japanease) *Kokyu to Junkan* 1997; 45:855–60.
33. Sciurba FC, Rogers RM, Keenan RJ, Slivka WA, Gorcsan J III, Ferson PF, Holbert JM, Brown ML, Landreneau RJ. Improvement in pulmonary function and elastic recoil after lung-reduction surgery for diffuse emphysema. *N Engl J Med* 1996; 334:1095–9.

34. Gelb AF, Zamel N, McKenna RJ, Jr, Brenner M. Mechanism of short-term improvement in lung function after emphysema resection. *Am J Respir Crit Care Med* 1996; 154:945–51.
35. Gelb AF. McKenna RJ,Jr, Brenner M, Fischel R, Baydur A, Zamel N. Contribution of lung and chest wall mechanics following emphysema resection. *Chest* 1996; 110:11–7.
36. Albert RK, Benditt JO, Hildebrandt J, Wood DE, Hlastala MP. Lung volume reduction surgery has variable effects on blood gases in patients with emphysema. *Am J Respir Crit Care Med* 1998; 158:71–6.
37. Keenan RJ, Landreneau RJ, Sciurba FC, Ferson PF, Holbert JM, Brown ML, Fetterman LS, Bowers CM. Unilateral thoracoscopic surgical approach for diffuse emphysema. *J Thorac Cardiovasc Surg* 1996; 111:308–16.
38. O'Donnell DE, Webb KA, Bertley JC, Chau LKL, Conlan AA. Mechanisms of relief of exertional breathlessness following unilateral bullectomy and lung volume reduction surgery in emphysema. *Chest* 1996; 110:18–27.
39. Teschler H, Thompson AB, Stamatis G. Short- and long-term functional results after lung volume reduction surgery for severe emphysema. *Eur Respir J* 1999; 13:1170–6.
40. Kotloff RM, Tino G, Palevsky HI, Hansen-Flaschen J, Wahl PM, Kaiser LR, Bavaria JE. Comparison of short-term functional outcomes following unilateral and bilateral lung volume reduction surgery. *Chest* 1998; 113:890–5.
41. Kaiwa Y, Kurokawa Y, Ando K, Nakagawa A, Mitsui K, Miki H, Kurosawa H, Hida W, Satomi S. Correlation of unilateral thoracoscopic lung volume reduction with improvement in lung function and exercise performance in patients with severe pulmonary emphysema. *Sur Today* 1999; 29:718–23.
42. Martinez FJ, Montes de Oca M, Whyte RI, Stetz J, Gay SE, Celli BR. Lung-volume reduction improves dyspnea, dynamic hyperinflation, and respiratory muscle function. *Am J Respir Crit Care Med* 1997; 155:1984–90.
43. Lando Y, Boiselle PM, Shade D, Furukawa S, Kuzma AM, Travaline JM, Criner GJ. Effect of lung volume reduction surgery on diaphragm length in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159:796–805.
44. Criner G, Cordova FC, Leyenson V, Roy B, Travaline J, Sudarshan S, O'Brien G, Kuzma AM, Furukawa S. Effect of lung volume reduction surgery on diaphragm strength. *Am J Respir Crit Care Med* 1998; 157:1578–85.
45. Bellemare F, Cordeau M-P, Couture J, Lafontaine E, Leblanc P, Passerini L. Effects of emphysema and lung volume reduction surgery on transdiaphragmatic pressure and diaphragmatic length. *Chest* 2002; 121:1898–910.
46. Takishima T, Shindoh C, Kikuchi Y, and Hida W. Aging effect on oxygen consumption of respiratory muscles in humans. *J Appl Physiol* 1990; 69:14–20.
47. Shindoh C, Hida W, Kikuchi Y, Taguchi O, Miki H, Takishima T, Shirato K. Oxygen consumption of respiratory muscles of patients with COPD. *Chest* 1994; 105:790–7.
48. Benditt JO, Wood DE, McCool FD, Lewis S, Albert RK. Changes in breathing and ventilatory muscle recruitment patterns induced by lung volume reduction surgery. *Am J Respir Crit Care Med* 1997; 155:279–84.
49. Christensen PJ, Paine R III, Curtis JL, Kazerooni EA, Iannettoni MD, Martinez FJ. Weight gain after lung volume reduction surgery is not correlated with improvement in pulmonary mechanics. *Chest* 1999; 116:1601–7.
50. Donahoe M, Rogers RM, Wilson DO, Pennock BE. Oxygen consumption of the respiratory muscles in normal and in malnourished patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989; 140:385–91.
51. Cordova FC, O'Brien G, Furukawa S, Criner GJ. Stability of improvements in exercise performance and quality of life following bilateral lung volume reduction surgery in severe COPD. *Chest* 1997; 112:907–15.
52. Ferguson GT, Fernandez E, Zamora MR. Improved exercise performance following lung volume reduction surgery for emphysema. *Am J Respir Crit Care Med* 1998; 57:1195–203.
53. Stammberger U, Bloch KE, Thurnheer R, Bingisser R, Weder W, Russi EW. Exercise performance and gas exchange after bilateral vide-assisted thoracoscopic lung volume reduction for severe emphysema. *Eur Respir J* 1998; 12:785–92.
54. Oswald-Mammosser M, Kessler R, Massard G, Wihlm J-M, Weitzenblum E, Lonsdorfer J. Effect of lung volume reduction surgery on gas exchange and pulmonary hemodynamics at rest and during exercise. *Am J Respir Crit Care Med* 1998; 158:1020–5.

55. Hida W, Taguchi O, Kikuchi Y, Ohe M, Shirato K, and Takishima T. P wave height during incremental exercise in patients with chronic airway obstruction. *Chest* 1992; 102:23–30.
56. Hida W, Tun Y, Kikuchi Y, Okabe S, Shirato K. Pulmonary hypertension in patients with chronic obstructive pulmonary disease: Recent advances in pathophysiology and management. *Respirology* 2002; 7:3–13.
57. Weg IL, Rossoff L, McKeon K, Graver LM, Schrf SM. Development of pulmonary hypertension after lung volume reduction surgery. *Am J Respir Crit Care Med* 1999; 159:552–6.
58. Kubo K, Koizumi T, Fujimoto K, Matsuzawa Y, Yamanda T, Haniuda M, Takahashi S. Effects of lung volume reduction surgery on exercise pulmonary hemodynamics in severe emphysema. *Chest* 1998; 114:1575–82.
59. Oswald-Mammosser M, Kessler R, Massard G, Wihim J-M, Weitzenblum E, Lonsdorfer J. Effects of lung volume reduction surgery on gas exchange and pulmonary hemodynamics at rest and during exercise. *Am J Respir Crit Care Med* 1998; 158:1020–5.
60. Haniuda M, Kubo K, fujimoto K, Aoki T, Yamada T, Amano J. Different effects of lung volume reduction surgery and lobectomy on pulmonary circulation. *Ann Surg* 2000; 231:119–25.
61. Aida A, Miyamoto K, Nishimura M, Aiba M, Kira S, Kawakami Y. The Respiratory Failure Research Group in Japan: Prognostic value of hypercapnia in patients with chronic respiratory failure during liong-term oxygen therapy. *Am J Respir Crit Care Med* 1998; 158:188–93.
62. Shade D, Jr., Cordova F, Lando Y, Travaline JM, Furukawa S, Kuzma AM, Criner GJ. Relationship between resting hypercapnia and physiologic parameters before and after lung volume reduction surgery in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159:1405–11.
63. Celli BR, Montes de Oca M, Mendez R, Stetz J. Lung reduction surgery in severe COPD decreases central drive and ventilatory response to CO2. *Chest* 1997; 112:902–6.
64. Kurosawa H, Kikuchi Y, Okabe S, Oikawa M, Wu D, Tun Y, Tabata M, Shirato K, Hida W. Hypercapnic ventilatory response in patients with COPD who were treated with lung volume reduction surgery. *Am J Respir Crit Care Med* 1998; 157:A282.
65. Hida W. Role of ventilatory drive in asthma and chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 1999; 5:339–43.
66. Chonan T, Altose MD, Cherniack NS. Efects of expiratory resistive loading on the sensation of dyspnea. *J Appl Physiol* 1990; 69:91–5.
67. Chonan T, Hida W, Kikuchi Y, Shindoh C, and Takishima T. Role of CO_2 responsiveness and breathing efficiency in determining exercise capacity of patients with chronic airway obstruction. *Am Rev Respir Dis* 1988; 138:1488–93.
68. Cooper JD, Patterson GA, Sundaresan RS, Trulock EP, Yusen RD, Pohl MS, Lefrak SS. Results of 150 consecutive bilateral lung volume reduction procedures in patients with severe emphysema. *J Thorac Cardiovasc Surg* 1996; 112:1319–30.
69. Brenner M, Yusen R, McKenna R Jr, Sciurba F, Gelb AF, Fischel R, Swain J, Chen JC, Kafie F, Lefrak SS. Lung volume reduction surgery for emphysema. *Chest* 1996; 110:205–18.
70. Ingenito EP, Evans RB, Loring SH, Kaczka DW, Rodenhouse JD, Body SC, Sugarbaker DJ, Mentzer SJ, DeCamp MM, Reilly. Relation between preoperative inspiratory lung resistance and the outcome of lung-volume-reduction surgery for emphysema. *N Engl J Med* 1998; 338:1181–5.
71. Date H, Goto K, Souda R, Endou S, Aoe M, Yamashita M, Andou A, Shimizu N. Predictors of improvement in FEV_1 (forced expiratory volume in 1s) after lung volume reduction surgery. *Surg Today* 2000; 30:328–32.
72. Fessler HE, Wise RA. Lung volume reduction surgery. *Am J Respir Crit Care Med* 1999; 159:1031–5.
73. Gelb AF, Brenner M, McKenna RJ Jr, Fischel R, Zamel N, Schein MJ. Serial lung function and elastic recoil 2 years after lung volume reduction surgery for emphysema. *Chest* 1998; 113:1497–506.
74. Brenner M, McKenna RJ Jr, Gelb AF, Fischel RJ, Wilson AF. Rate of FEV1 change following lung volume reduction surgery. *Chest* 1998; 113:652–9.
75. Geddes D, Davies M, Koyama H. Hansell D, Pastoring U, Pepper J, Agent P, Cullinan P, MacNeill SJ, Goldstraw P. Effect of lung-volume-reduction surgery in patients with severe emphysema. *N Engl J Med* 2000; 343:239–45.
76. Gelb AF, McKenna RJ Jr, Brenner M, Schein MJ, Zamel N, Fischel R. Lung function 4 years after lung volume reduction surgery for emphysema. *Chest* 1999; 116:1608–15.
77. Burrows B, Earle RH. Course and prognosis of chronic obstructive lung disease: a prospective study of 200 patients. *N Engl J Med* 1969; 280:397–404.

78. Kitamuro H, Kurosawa H, Hida W, Kikuchi Y, Okabe S, Tabata M, Tun Y, Adachi T, Kurokawa Y, Shirato K. Survival rate after lung volume reduction surgery. *Am J Respir Crit Care Med* 1999; 159:A924.
79. National Emphysema Treatment Trial Research Group: rationale and design of the national emphysema treatment trial (NETT): A prospective randomized trial of lung volume reduction surgery. *J Thorac Cardiovasc Surg* 1999; 118:518–28.
80. National Emphysema Treatment Trial Research Group: Patients at high risk of death after lung-volume-reduction surgery. *N Eng J Med* 2001; 345:1075–83.

9 Diffuse Panbronchiolitis

Young Whan Kim and Yukihiko Sugiyama

Introduction

Diffuse panbronchiolitis (DPB) is a chronic inflammatory respiratory disease of unknown aetiology. DPB is characterized by chronic inflammation localized primarily in the region of the respiratory bronchiole just distal to the terminal bronchiole, known as the transitional zone between the airway and the pulmonary parenchyma (1). DPB is a clinicopathologic entity distinct from bronchial asthma, chronic bronchitis, pulmonary emphysema, bronchiectasis, and alveolitis. It is manifested clinically by chronic cough, sputum and dyspnoea; physiologically by chronic airflow limitation; radiologically by hyperinflation and diffuse small nodules; and histologically by typical bronchiolar lesions (2). Additionally, DPB is thought to be a sinobronchial syndrome because most of DPB patients have paranasal sinusitis (1).

DPB was first reported in Japan in 1969 (2) and has been known worldwide since the report of a nationwide survey in 1983 (1). Although several cases of DPB have been reported from western countries, DPB occurs primarily among East Asian people, especially Japanese and Koreans (3).

Although the aetiology of DPB is unknown, recent genetic studies on DPB patients revealed the HLA association of this disease (4–6) and a possible candidate for a susceptibility gene locus (7).

The prognosis of DPB was grave before the advent of long-term low-dose erythromycin therapy (8,9). The introduction of long-term low-dose macrolide therapy has improved considerably the survival of these patients.

Epidemiology and Aetiology

Epidemiology

The nationwide survey of DPB in Japan conducted from 1980 to 1982 collected more than 1,000 cases of probable DPB and 82 histologically confirmed cases from 1978 to 1980 (1). The clinical diagnostic criteria for DPB in this survey were as follows:

1. Symptoms: chronic cough, sputum, and dyspnoea
2. Physical signs: rales and rhonchi
3. Chest X-ray film: diffusely disseminated fine nodular shadows, mainly in the lower lung fields with hyperinflation of the lungs
4. Lung function studies (at least three conditions among the four abnormalities listed)
   (a) $FEV_1/FVC < 70\%$
   (b) $VC < 80\%$ of the predicted value
   (c) $RV > 150\%$ of the predicted value
   (d) $PaO_2 < 80$ mmHg

According to the survey, cases with DPB were distributed throughout all districts of Japan. The

patients ranged from the second to the eighth decade of life in both sexes, but the majority present after middle age. The male to female ratio was approximately 1.4 to 1 and there was no preponderance of smokers. More than 75% of the patients had a previous history of, or were suffering from, chronic paranasal sinusitis. Chronic paranasal sinusitis is one of the characteristics of DPB, and the incidence of chronic paranasal sinusitis in the patients' family was 20%. Chronic bronchitis (30.4%), bronchiectasis (26.2%), and bronchial asthma (24.2%) were most frequently suspected or diagnosed before the diagnosis of DPB (10). The five-year survival rates of patients from the onset of dyspnoea with or without pulmonary infection due to *P. aeruginosa* were 70 and 80 percent, and the ten-year survival, 30 and 71 percent, respectively. The second nationwide survey conducted in 26 major hospitals all over Japan in 1988 showed that the average survival time of the patients who died of DPB from the onset of exertional dyspnoea was 14.1 +/– 9.7 years (11).

In Korea, five cases of DPB were reported in 1992 (3) followed by other case reports (12,13). The nationwide survey of DPB in Korea was conducted from 1997 to 1999 using the clinical criteria of Homma that was used in the nationwide survey in Japan (1) and pathologic criteria of Kitaichi (14). A total of 132 patients were found, including 47 biopsy-proven cases, at 14 major university hospitals in Korea. The patients were distributed in all districts of Korea. The male to female ratio was 1.1:1, and age ranged from the third to the ninth decade (mean, 48.9 years old). The disease incidence peaked during the fifth and sixth decades, and its duration before diagnosis ranged from less than one month to 20 years (mean, 5 years). Prior to diagnosis, many patients had been treated for bronchiectasis, miliary tuberculosis, chronic bronchitis, bronchial asthma or hypersensitivity pneumonitis. Only 15% of patients were smokers, and very few had been occupationally exposed to particles or gases. About one half of the patients had a history of chronic paranasal sinusitis or suffering from it at the time of examination. Cold hemagglutinin was positive in 53% of cases, somewhat lower than in Japan. The titre was quite low in Korean patients (19/24 were under 1:128) as compared with the results from Japan.

Even though there are several reports of DPB among Chinese (15–17), the number of patients in China reported in the literature is not remarkable when compared with the numbers in Japan and Korea. The clinical profile of Chinese DPB patients is different from Japanese patients (17). The typical features of increased risk in HLA-B54 subjects, cold hemagglutinaemia, increased rheumatoid factor and IgA seen in Japanese patients were not present in Chinese DPB patients.

Recently, there have been case reports of DPB in Thailand (18). Outside Asia, only sporadic cases were reported among Caucasians in Europe and America (19–23).

Aetiology

The cause of DPB is unknown. Although the clinical features and course of DPB are somewhat similar to those of cystic fibrosis, the sweat electrolyte concentration is normal, and there is no exocrine function abnormality in DPB patients (24). In addition, there has been no case report of cystic fibrosis among Japanese or Koreans, and the F508 mutation of the cystic fibrosis gene has not been found in DPB (25). Abnormalities associated with other sinobronchial syndromes, including immotile cilia syndrome, IgA deficiency, and IgG subclass deficiency, are absent in patients with DPB (24) suggesting that DPB is a different disease entity.

There is some evidence that genetic factors are involved in the development of DPB. Familial cases of DPB have been reported in Japan (26–28), and in monozygotic twins in Korea (29). Moreover, it is usual for some siblings of the patients with DPB to have only chronic sinopulmonary infection and chronic paranasal sinusitis (30).

Genetic studies of Japanese and Korean DPB patients have suggested that HLA genes contribute to genetic predisposition in DPB (4–6). The human leukocyte antigen (HLA) system is essential for the appropriate immune response mediated by T-cell receptors and associations between HLA types and diseases, particularly those with a presumed immune aetiology, have been extensively studied (31). In 1990, Sugiyama and coworkers serologically typed HLA-A, -B, and -C antigens

of 38 patients with DPB and demonstrated that there was a significant increase in the frequency of B54 compared to controls (63.2 vs 11% respectively; relative risk, 13.30; $p < 0.001$) (4). This result was noteworthy because HLA-B54 is a serotype found predominantly in East Asians (32). HLA-B54 antigen has been found in about 11% Japanese, 12.5% Korean and 10% Chinese and not in any other ethnic groups (4–6). These data suggest that DPB may be rare or nonexistent in races without the B54 or B54-related haplotype. In a recent study, Keicho and coworkers found positive associations between A11, B54, and Cw1 and DPB (5). Of these, the B54 antigen showed the strongest association, odds ratio (OR) = 3.4, $p = 0.0004$. They also showed that 37% of the DPB patients possessed the HLA-B*5401 allele, conserved predominantly in East Asians, compared with 15% of healthy volunteers ($X^2 = 12.4$, $p = 0.0004$). They concluded that the distinctive molecular structure of HLA-B alleles or a closely linked gene in the HLA region contributes to a genetic predisposition in diffuse panbronchiolitis

In Korea, HLA-B54 is not associated with DPB (6). The frequency of HLA-A11 was significantly increased in Korean DPB patients compared with controls (53.3% vs 17.5%, $p < 0.001$, OR = 5.4). In addition, increased frequencies of HLA-B55 (16.7% vs 3.5%, $p < 0.001$, OR = 5.5), B62 (36.7% vs 16%, $p < 0.01$, OR = 3.0), and Cw4 (23.3% vs 8.5%, $p < 0.05$, OR = 3.3) were also observed in patients compared with controls. Significant increases in the frequencies of A11-associated haplotypes were also observed in patients compared with the controls: A11-Cw1 (16.0% vs 1.9%, $p < 0.001$, OR = 12.1), Cw1-B55 (7.9% vs 1.0%, $p < 0.001$, OR = 9.8), and A11-B62 (12.9% vs 2.2%, $p < 0.001$, OR = 7.9). Although the frequency of the HLA-B54 antigen itself was not increased, the frequencies of A11-B54 and A11-Cw1-B54 haplotypes were increased in patients.

In summary, there are striking ethnic differences in the association of HLA class I antigens with DPB between Koreans and Japanese. The frequency of HLA-B54, which had been reported to have a strong positive association with DPB in Japanese (4,5), was not significantly different between the Korean patient and control groups (13.3% versus 12.5%). On the other hand, the frequency of A11 was significantly increased in Korean patients while HLA-B55 appeared to have an equivalent degree of positive association with the disease in both Japanese and Korean patients. Other HLA antigens showing weak or variable associations were A11 and Cw1 in Japanese and B62 and Cw4 in Korean patients.

Two different hypotheses can be postulated for the mechanisms involved in the association of HLA class I antigens with the susceptibility to DPB (6). The first is that an aetiologic agent utilizes the HLA antigen itself as an immunologic target for the pathogenesis of the disease, and ethnic differences in HLA association arise from a different distribution of HLA antigens involved in the pathogenesis of the disease. This is unlikely due to the fact that the HLA-A11 and B54 antigens, showing the strongest positive association with the disease in Korean and Japanese patients, respectively, have quite similar distribution in both ethnic groups (32). The second hypothesis is that the association of HLA antigens with the disease represents linkage disequilibria to the same disease gene(s) even if different HLA antigens are identified as risk factors in different ethnic groups. The latter view is supported by the differences and similarities in the HLA association with DPB between Korean and Japanese patients. Other strong evidence supporting this view could be obtained from the results of haplotype analysis. Some of the A11-associated haplotypes showed much stronger positive association with the disease compared with the A11 antigen itself. The HLA-B54 and Cw1 antigens have shown a positive association with the disease only in Japanese and not in Korean patients. However, it is interesting that A11-associated haplotypes involving these antigens (A11-B54, A11-Cw1) showed a significant positive association in Korean patients. The findings of these studies indicate that the disease gene(s) involved in DPB is likely to be located between HLA-A and HLA-B loci and showing different linkage disequilibria with HLA-A and HLA-B genes among Koreans and Japanese. Therefore, it is also conceivable that a founder mutation in a "DPB-related" gene close to the HLA-A and HLA-B locus has occurred on a chromosome bearing the ancestral allele and that the disease allele thus generated has expanded with evolution of the ancestral alleles in East Asia,

including Japan and Korea This ancestral mutation hypothesis could explain why DPB is observed predominantly in East Asia

Further genetic study by Keicho and coworkers (7) recently localized the major disease-susceptibility locus for DPB within 200 kb in the class I region 300 kb telomeric of the HLA-B locus on the chromosome 6p21 3

Because the association between particular alleles of the HLA-A and B genes and the disease is not 100%, unidentified genetic and environmental factors may play roles in the pathogenesis of DPB It is also possible that the pathogenesis of DPB is heterogenous as multiple disease processes may give rise to the same clinical entity A study has shown a specific allele at the IL-8 locus in chromosome 4q to be associated with DPB suggesting that genes other than those of the HLA system may also contribute to genetic predisposition (33) IL-8 is thought to play a role in the pathogenesis of DPB by attracting neutrophils into the lungs (34)

A number of nongenetic aetiologies have been investigated In Japan, a number of reported cases of DPB have been associated with human T lymphotropic virus type I (HTLV-1) Moreover, there is a likelihood that HTLV-1 is associated with some cases of DPB in Japan However, this association requires further verification (35) Other infectious agents have not been reported to be associated with DPB (36) There is a report that DPB recurred in a lung allograft after lung transplantation suggesting that DPB might be a systemic disease (37)

Pathogenesis

There is evidence to suggest that the pathogenesis of DPB is related to some immunologic defect Abnormalities of immunologic parameters including cold hemagglutinin, rheumatoid factor, IgA and CD4/CD8 ratio are usually seen in DPB patients (10) Some investigators have suggested that the elevated cold hemagglutinin titre may be caused by B cell activation (polyclonal stimulation) due to cell wall lipopolysaccharide associated with chronic Gram-negative pulmonary infection, primarily *Hemophilus influenzae* or *Pseudomonas aeruginosa* which are frequently isolated in the sputum of DPB patients (38)

Neutrophil-mediated inflammation is one of the characteristic pathologic features of DPB (34,39) In the bronchoalveolar lavage fluid of DPB patients, a significant neutrophilia and high levels of interleukin-8 (34) and leukotriene B4 (40), which has potent chemotactic activity for neutrophils, are seen These findings improve following erythromycin treatment, suggesting that the accumulation of neutrophils in airway lumen may have an important role in the pathogenesis of DPB (34,40) Lymphocyte-mediated inflammation is another pathologic feature of DPB The histopathology of DPB is characterized by a thickening of the walls of the respiratory bronchioles, with infiltration of lymphocytes, plasma cells, and histiocytes (1) Additionally, bronchus-associated lymphoid tissue (BALT) hyperplasia is usually observed in DPB (41) The absolute number of BALF lymphocytes is significantly increased in DPB patients (42) Activated T cells accumulate in the lungs of DPB patients, the percentage of BALF CD8+HLA-DR+ cells is high while CD4/CD8 ratio is decreased (42) There is also a report that CD3+, CD8+, and CD4+ cells bearing the HLA-DR antigen are increased in the peripheral blood (43) These lymphocyte abnormalities also improve following macrolide treatment (42,43)

Erythromycin and other macrolides are well known to be very effective in the treatment of DPB (8,9) Even though the exact mechanisms of erythromycin on DPB have not been fully clarified yet (44), erythromycin is thought to have an anti-inflammatory action on neutorophils (45,46) and lymphocytes (47) These findings suggest that DPB patients have some immunological hyperreactivity, and that macrolide antibiotics may be effective in these patients by suppressing such activity (42)

Several diseases with immunological defects were reported to be associated with DPB such as Good syndrome (48), bare lymphocyte syndrome (49), Non-Hodgkin's lymphoma (50), adult T-cell leukemia (51), malignant thymoma, Sjogren's syndrome (52), rheumatoid arthritis (53), ulcerative colitis (54), and IgA nephropathy (55)

Clinical Findings

Clinical manifestations

Almost all affected patients have a history of chronic paranasal sinusitis, usually with onset before adolescence (56). They often undergo sinus surgery without any benefit. Chronic cough and copious sputum are the main symptoms that appear at the onset of disease, or after several years of sinus disease. These symptoms usually occur in the second to fifth decade (mean age, 39.5 years) (57), but may also occur from the first to the seventh decade. Two-thirds of the patients are non-smokers, and there is no sex predominance. Auscultation of the chest reveals coarse crackles throughout, but more strongly in the middle and lower lung fields. Wheezes, rhonchi and/or squawk can also be heard. In the early and mid-phase of the disease, *Hemophilus influenzae* or, less frequently, *Streptococcus pneumoniae* is found in the patient's sputum. In advanced phases, patients develop lung destruction and/or bronchiectasis with cough productive of large amounts of purulent sputum and progressive dyspnoea. Chronic respiratory failure and cor pulmonale ensue punctuated by frequent exacerbations from recurrent infection and inflammation. At that stage, *Pseudomonas aeruginosa* is invariably found, which is speculated to be an opportunistic infection of the damaged airways rather than a cause of the disorder. Colonization with *P. aeruginosa* appears to be associated with a worse prognosis since these organisms produce various products that can damage airways. The prognosis of this disease had been very poor before the advent of macrolide therapy.

Blood and serologic studies

Leukocytosis is common and anaemia is rare. The level of C-reactive protein and erythrocyte sedimentation rate are elevated. Increased titers of serum IgG and IgA are found (58). Rheumatoid factor is often positive, but the rheumatoid arthritis hemagglutination test, which is more specific for rheumatoid arthritis, is negative. The most characteristic feature is a persistent elevation of the cold agglutinin titre to 4- to 16-fold (x512 to x2048; normal, less than x128) (58,59). It has been reported that cold agglutinin in DPB is polyclonal, containing IgG and, in some cases, IgA as well as IgM, and has anti-I specificity (60). These findings are similar to those found in infections, such as those caused by *Mycoplasma* species. In DPB, however, tests for antibody against *Mycoplasma pneumoniae are negative.*

The percentage of activated (HLA-DR positive) CD4+ and CD8+ lymphocytes in the peripheral blood is increased, and both percentages return to normal levels after erythromycin therapy (43). No consistent decrease or defect of serum immunoglobulins (IgG, IgA, IgM, IgD and IgE) is found, although the levels of IgG and IgA reactively increase due to chronic pulmonary infection. Analysis of bronchoalveolar lavage (BAL) fluid from patients with DPB demonstrates evidence of persistent inflammation. A significant increase of neutrophils in BAL fluid is found and the number of neutrophils decreases after erythromycin therapy (39,44). Additionally, the number of CD8+ T lymphocytes increases and the concentrations of elastase, leukotriene B4 and interleukin-8 also increase in BAL fluid (40,42).

Lung imaging studies

Chest radiology

The chest radiograph changes are characteristic and helpful in diagnosis. Typical radiographic findings are diffusely disseminated small nodular shadows up to 2 mm in diameter with indistinct margins, most prominent over both lung bases, and lung hyperinflation caused by air trapping. Slight bronchiectasis usually develops in the middle lobe and lingula, which appears as tramlines on the radiograph. With the progression of disease, some patients show cystic changes and/or diffuse bronchiectasis (Figure 1).

Nakata et al (61) have identified five chest radiographic patterns: hyperinflation of both lungs only (Type I); hyperinflation with bilateral nodular shadows whose combined area does not exceed the area of one lung (Type II); hyperinflation with bilateral nodular shadows throughout the lungs (Type III); the Type III pattern plus tram lines (Type IV); and the Type IV pattern plus cystic shadows and/or pneumonia (Type V) (Figure 2).

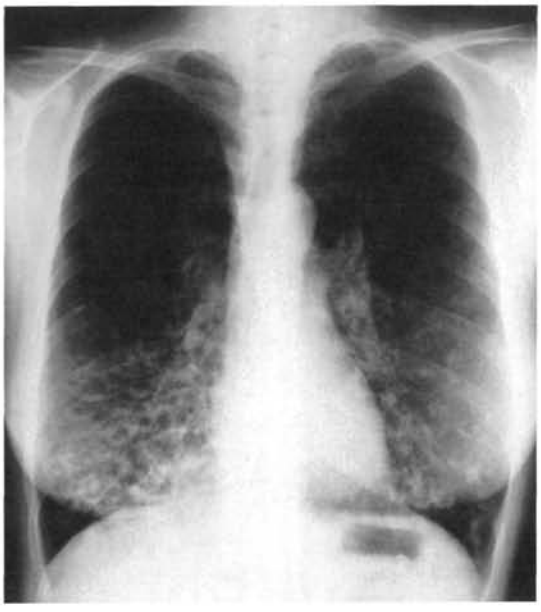


Figure 1. A progressive case (type V): Cystic changes and bronchiectasis are seen

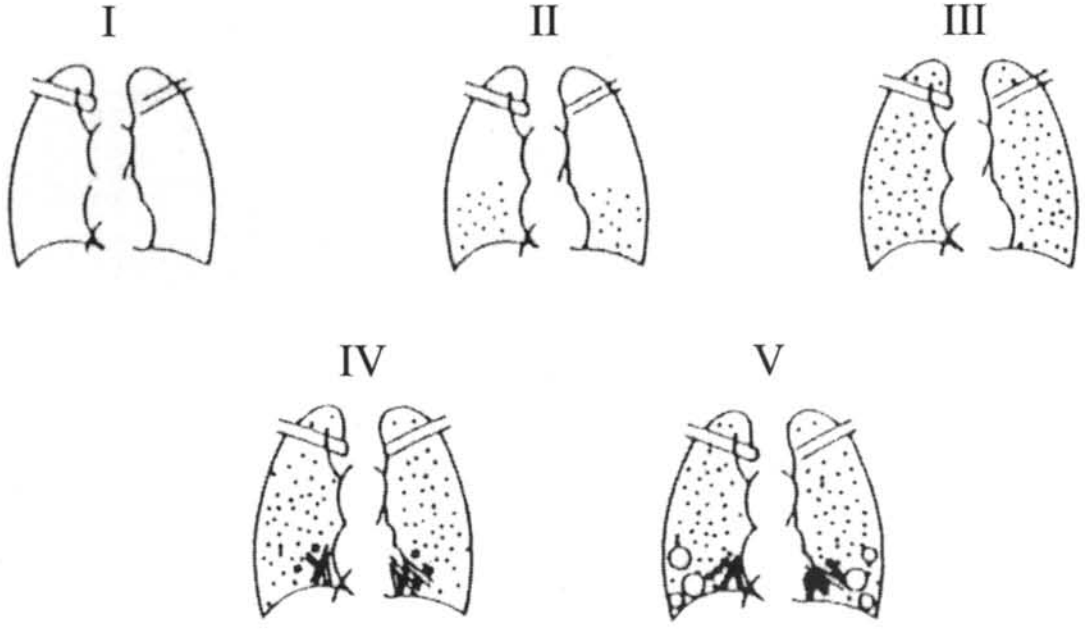


Figure 2. Radiographic classification of diffuse panbronchiolitis[61]
I. Overinflation only, no nodules
II. Bilateral nodular shadows without exceeding one lung field
III. Bilateral nodular shadows scattered throughout whole lungs
IV. III + tramlines
V. IV + cystic shadows or pneumonia

Computed tomography

Computed tomography (CT), especially high-resolution computed tomography (HRCT) is useful in the diagnosis of DPB and in evaluation of its progression (Figure 3). The CT findings of DPB are diffuse, small nodular shadows located in the centrilobular regions, dilatation of small bronchi and bronchioles, and bronchial and bronchiolar wall thickening. The small nodular and liner opacities represent dilated bronchioles filled with intrabronchial fibrosis or secretion (62). The small rounded opacities are separated and distributed around the ends of bronchovascular branchings and in centrilobular regions.

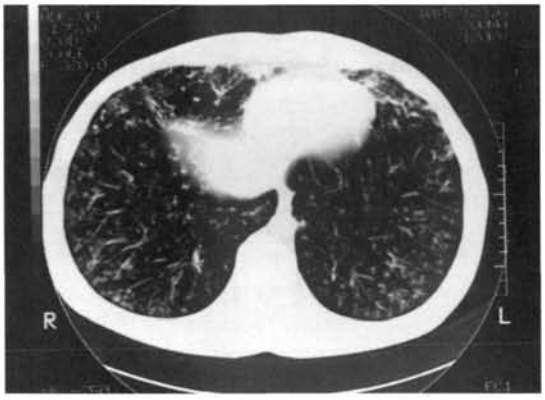


Figure 3. CT scans of diffuse panbronchiolitis. Diffusely disseminated nodular shadows in centrilobular regions are demonstrated.

Akira et al (63) classified the radiographic or HRCT findings into four types as follows: Type I, small nodules located around the ends of bronchovascular branchings; Type II, small nodules located in a centrilobular area and connected to small linear opacities branching 1 mm apart; Type III, nodules accompanied by ring-shaped or small ductal opacities connected to proximal bronchovascular bundles; and Type IV, large cystic opacities accompanied by dilated proximal bronchi. This classification, based on CT findings, reflects the clinical stages and pathologic changes in the course of the disease.

Pulmonary function testing

Pulmonary function testing typically discloses marked obstructive impairment. In some patients, especially those with progressive disease, a mixed obstructive-restrictive pattern may be seen. The residual volume (RV) and the ratio of RV to total lung capacity (RV/TLC) are usually increased. Hypoxaemia is an early and common blood gas abnormality and is associated with hypercapnia in the late stage. The patients finally succumb to chronic respiratory failure and pulmonary hypertension with right ventricular failure.

Pathological findings

Macroscopically, the cut surface of the lungs is hyperinflated with many yellowish nodular lesions, 2 to 3 mm or larger in diameter, scattered throughout the lungs. Bronchiolectasis and bronchiectasis of various degrees are found. Miscroscopically, the typical features include thickening of the walls of the respiratory bronchioles with infiltration of lymphocytes, plasma cells, and histiocytes. These chronic inflammatory lesions are mostly centrilobular but extension towards the peribronchiolar tissues is also common. In the advanced stage, narrowing and constriction of respiratory bronchioli due to infiltration by these cells, proliferation of lymphoid follicles, accumulation of foamy cells within the wall and bronchioli are found. Pathological changes other than hyperinflation are not seen in the alveoli of the distal lobules. Sato et al. reported that DPB presents bronchus-associated lymphoid tissue hyperplasia more frequently than other respiratory diseases (41).

Diffuse panbronchiolitis and rheumatoid arthritis

Some cases of DPB are accompanied by rheumatoid arthritis. To date, we have encountered 5 such cases including 1 autopsied case (64) and one case diagnosed by thoracoscopic lung biopsy. We reported two such cases with the same HLA haplotype, A24-B54-Cwl-DR4 (65). As described in a previous part of this chapter, an increase of

B54 is found in the HLA analysis in DPB patients. This antigen, B54, is known to form part of the characteristic Japanese haplotype A24/A11-B54-Cwl-DR4 (66). Consequently, the frequency of DR4 also increased in the DPB patients in our study (60.0%) compared with the controls (37.9%) (4), and the frequency of HLA-DR4 was suggested to be increased due to linkage disequilibrium with HLA-B54. However, the association of rheumatoid arthritis with HLA-DR4 is well established in various ethnic groups including Japanese (67–69). Because the frequency of HLA-B54 is significantly increased among patients with DPB and since B54 is correlated with DR4 as the extended haplotype, both DPB and rheumatoid arthritis have the same HLA haplotype correlation including B54 and DR4. Therefore, it is likely that more Japanese patients with DPB accompanied by rheumatoid arthritis will be encountered in the future (65).

Bronchiolar lesions and obliterative bronchiolitis in rheumatoid arthritis closely resembling DPB both clinically and pathologically have also been reported (70). Further studies will be needed to clarify these similarities.

Prognosis and Treatment

Diffuse panbronchiolitis was previously a chronic and progressive illness with a poor prognosis. Untreated, the 5-year survival rate from the patient's first visit was 42%, and the 10-year survival rate was 25.4% (71). In one study, the 10-year survival rate for those infected with *P. aeruginosa* was only 12%. The prognosis for DPB patients improved significantly following Kudoh's introduction of long-term, low-dose erythromycin of 600mg daily. Kudoh et al demonstrated a marked improvement in subjective (cough, copious sputum, and dyspnoea) and objective (chest radiographic findings and hypoxaemia) measures of the patient's condition following prolonged therapy (average, 20 months) (28).

A recent double-blind placebo-controlled trial of erythromycin therapy in DPB confirmed its efficacy in this disease (72). The 5-year rate survival had improved to 71.0% from 1980 to 1984 and 93.4% after 1985 (9).

Low-dose erythromycin therapy, 400 or 600 mg daily, is a primary therapy for DPB and should be started as soon as possible after diagnosis. Although clinical effects could be found at 2 or 3 months, at least 6 months is needed to judge its efficacy. After subjective and objective effectiveness has been achieved ($PaO_2 \geq 70$ mmHg, and sputum < 10ml/day), the therapy could be stopped at the end of 2 years. Re-administration of erythromycin is recommended in the event of recurrence. In progressive cases with diffuse bronchiectasis and chronic respiratory failure, in which erythromycin therapy has some beneficial effects, continuous therapy for at least 2 years is needed. In patients with side effects to erythromycin, 14-membered ring new macrolides, clarithromycin or roxithromycin can also be used with similar efficacy.

Mechanisms of erythromycin therapy

Because serum and sputum erythromycin levels were below the minimum inhibitory concentrations for common superinfecting organisms such as *H. influenzae and P. aeruginosa,* improvement could not be attributed to the drug's antibacterial action (73). The mechanisms of long-term erythromycin therapy against DPB have been intensively studied.

Erythromycin interferes with neutrophil chemotaxis and decreases the number of neutrophils in BAL fluid following challenge with Gram-negative bacteria (44). The marked neutrophilia present in BAL fluid in patients with DPB was reduced after erythromycin therapy (39). Erythromycin does not directly affect neutrophil function (74) but suppresses neutrophil chemotactic activity such as IL-8 and/or leukotriene B4 (44) thus can indirectly reduce neutrophils in the airway lumen.

Erythromycin also suppresses hypersecretion of the airways in patients with DPB. Erythromycin inhibits respiratory glycoconjugate secretion from human airways in vitro (75). Tamaoki et al. reported that erythromycin inhibits chloride secretion across canine tracheal epithelial cells and noted that this action possibly reflected its clinical efficacy in the treatment of airway hypersecretion (76). Suga et al. administered erythromycin to a patient with broncholoalveolar carcinoma with bronchorrhoea and obtained a marked reduction in the volume of sputum (77).

Erythromycin has suppressive effects on lymphocytes. Our group reported that the percentage of activated T cells with expression of HLA-DR decreased in the peripheral blood of DPB patients after erythromycin therapy (43). In vitro, erythromycin (47) and roxithromycin (78) suppressed the proliferative response of human lymphocytes stimulated with mitogens and antigens. Keicho et al reported that erythromycin promoted differentiation in human monocyte-macrophage lineage, altering their functions (79).

Additionally, erythromycin reduced the mortality rate of mice with *P. aeruginosa* bacteraemia (80), and inhibited the production of elastase by these bacteria without affecting its proliferation in vitro (81). Takizawa et al reported that erythromycin suppressed IL-6 mRNA expression by human bronchial epithelial cells (82). Controversially, data on the effects of the long-term administration of erythromycin on cytokine production showed upregulated expression of cytokine mRNA in rat alveolar macrophages (83). Recently Abe et al. reported that clarithromycin (14-membered ring macrolide) repressed IL-8 gene transcription mainly via the activator protein (AP)-1 binding site in human bronchial epithelial cells (84). Thus macrolides might have a suppressive effect on cytokine expression in human cells and this newly identified possible mode of action may have relevance to its clinical effectiveness in airway inflammatory diseases.

Acknowledgements

The authors thank Dr. Jae-Joon Yim and Mrs. Miyuki Ohtsuka for their arrangement of this manuscript.

References

1. Homma H, Yamanaka A, Tanimoto S, Tamura M, Chijimatsu Y, Kira S, Izumi T. Diffuse panbronchiolitis: A disease of the transitional zone of the lung. *Chest* 1983; 83:63–9.
2. Yamanaka A, Saeki S, Tamura S, Saito K. The problems of chronic obstructive pulmonary disease: Especially concerning about diffuse panbronchiolitis (Japanese). *Intern Med* 1969; 23:442–51.
3. Kim YW, Han SK, Shim YS, Kim KY, Han YC, Seo JW, Im JG. The first report of diffuse panbronchiolitis in Korea: five case reports. *Intern Med* 1992; 31:695–701.
4. Sugiyama Y, Kudoh S, Maeda H, Suzaki H, Takaku F. Analysis of HLA antigens in patients with diffuse panbronchiolitis. *Am Rev Respir Dis* 1990; 141:1459–62.
5. Keicho N, Tokunaga K, Nakata K, Taguchi Y, Azuma A, Bannai M, Emi M, Ohishi N, Yazaki Y, Kudoh S. Contribution of HLA genes to genetic predisposition in diffuse panbronchiolitis. *Am J Respir Crit Care Med* 1998; 158:846–50.
6. Park MH, Kim YW, Yoon HI, Yoo VG, Han SK, Shim YS, Kim WD. Association of HLA class I antigens with diffuse panbronchiolitis in Korean patients. *Am J Respir Crit Care Med* 1999; 159:526–9.
7. Keicho N, Ohashi J, Tamiya G, Nakata K, Taguchi Y, Azuma A, Ohishi N, Emi M, Park MH, Inoko H, Tokunaga K, Kudoh S. Fine localization of a major disease-susceptibility locus for diffuse panbronchiolitis. *Am J Hum Genet* 2000; 66:501–7.
8. Kudoh S, Uetake T, Hagiwara K, Hirayama M, Hus LH, Kimura H, Sugiyama Y. Clinical effect of low dose long term erythromycin chemotherapy of diffuse panbronchiolitis. *Jpn J Thorac Dis* 1987; 25:632–42.
9. Kudoh S, Azuma A, Yamamoto M, Izumi T, Ando M. Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. *Am J Respir Crit Care Med* 1998; 157:1829–32.
10. Homma H. Diffuse panbronchiolitis. *Jap J Med* 1986; 329–34.
11. Izumi T. A nation-wide survey of diffuse panbronchiolitis in Japan and the high incidence of diffuse panbronchiolitis seen in Japanese respiratory clinics. In: Sarcoidosis and Other Granulomatous Disorders. Eds. Grassi C, Rizzato G, Pozzi E. New York: Elsevier Science Publishers, 1988, 753–7.
12. Kim YW, Park KY, Yoo CG, Han SK, Shim YS, Kim KY, Han YC. Clinical effect of low-dose long-term erythromycin on diffuse panbronchiolitis (Korean). *Tuberc Respir Dis* 1994; 41:127–4.
13. Kim CH., Kho WJ, Jang SH, Yoo CG, Kim YW, Heo DS, Han SK, Shim YS. Long-term follow-up of patients with diffuse panbronchiolitis after erythromycin therapy (Korean). *Korean J Int Med* 1997; 53:414–9.

14. Kitaichi M. Comparative pathology of inflammatory airways disease: a report made after the 1987 Milan congress. *Sarcoidosis* 1992; 9:625–8.
15. Chu YC, Yeh SZ, Chen CL, Chen CY, Chang CY, Chiang CD. Diffuse panbronchiolitis: report of a case. *J Formosan Med Assoc* 1992; 91:912–5.
16. Hu H, Liu YN. The first case of diffuse panbronchiolitis reported in China. *Therap Res* 1996; 17:339–44.
17. Tsang KWT, Ooi CGC, Ip MSM, Lam WK, Ngan H, Chan YET, Hawkins B, Ho C, Amitani R, Tanaka E, Itoh H. Clinical profiles of Chinese patients with diffuse panbronchiolitis. *Thorax* 1998; 53:274–80.
18. Chantarotorn S, Palwatwichai A, Vattanathum A, Tantamacharik D. Diffuse panbronchiolitis, the first case reports in Thailand. *J Med Assoc Thai* 1999; 82:833–8.
19. Poletti V, Patelli M, Poletti G, Bertanti T, Spiga L. Diffuse panbronchiolitis observed in an Italian. *Chest* 1990; 98:515–6.
20. Randhawa P, Hoagland MH, Yousem SA. Diffuse panbronchiolitis in North America. *Am J Surg Pathol* 1991; 15:43–7.
21. Homer RJ, Khoo L, Smith GJ. Diffuse panbronchiolitis in a Hispanic man with travel history to Japan. *Chest* 1995; 107:1176–8.
22. Fitzgerald JE, King TE Jr., Lynch DA, Tuder RM, Schwarz MI. Diffuse panbronchiolitis in the United States. *Am J Respir Crit Care Med* 1996; 154:497–503.
23. Martinez JA, Guimaraes SM, Ferreira RG, Pereira CA. Diffuse panbronchiolitis in Latin America. *Am J Med Sci* 2000; 319:183–5.
24. Sugiyama Y. Diffuse panbronchiolitis. *Clin Chest Med* 1993; 14:765–72.
25. Akai S, Okayama H, Shimura S, Janny Y, Sasaki H, Jakishima T. Delta F508 mutation of cystic fibrosis gene is not found in chronic bronchitis with severe obstruction in Japan. *Am Rev Respir Dis* 1992; 146:781–3.
26. Suzuki M, Usui K, Tamura N, Araki T, Chijimatsu Y, Washizaki M, Inatomi K, Homma H. Familial cases of diffuse panbronchiolitis. *Jpn J Thorac Dis* 1981; 19:645–51.
27. Danbara T, Matsuoki R, Nukiwa T, Natori H, Arai T, Kira S. Familial occurrence of diffuse panbronchiolitis accompanied by elevation of cold agglutinin titer in a father and his two daughters. *Jpn J Thorac Dis* 1982; 20:597–603.
28. Makiguchi K, Sakaino H, Yoshimura N, Ichioka N, Takayama S, Tsutsui H, Chida M, Miyasato I, Taniai S, Marumo F. Diffuse panbronchiolitis in two brothers with different clinical courses. *Jpn J Thorac Dis* 1991; 29:1190–4.
29. Han KM, Choi PS, Lee SO, Chun JC, Kim DM, Kim HS, Moon SC Kim KI, Park SK. Two cases of diffuse panbronchiolitis in monozygotic twins (Korean). *Korean J Int Med* 1996; 51:668–74.
30. Sugiyama Y, Kitamura S. Chronic sinusitis among family members of patients with diffuse panbronchiolitis. *Jpn J Thorac Dis* 1995; 33:140–3.
31. Tomlinson IPM, Bodmer WF. The HLA system and the analysis of multifactorial genetic disease. *Trends Genet* 1995; 11:493–8.
32. Imanishi T, Akaza T, Kimura A, Tokunaga K, Gojobori T. Allele and haplotype frequencies for HLA and complement loci in various ethnic groups. 1991, Vol. 1. In: *HLA*. Eds. K. Tsuji, M. Aizawa, and T. Sasazuki. New York: Oxford University Press, 1992, 1065–220.
33. Emi M, Keicho N, Tokunaga K, Katsumata H, Souma S, Nakata K, Taguchi K, Ohishi N, Azuma A, Kudoh S. Association of diffuse panbronchiolitis with microsatellite polymorphism of the human interleukin 8 (IL-8) gene. *J Hum Genet* 1999; 44:169–72.
34. Koga T. Neutrophilia and high level of interleukin 8 in the bronchoalveolar lavage fluid of diffuse panbronchiolitis. *Kurume Med J* 1993; 40:139–46.
35. Matsuse T, Fukuchi Y, Hsu CY, Nagase T, Higashimoto N, Teramoto S, Matsui H, Sudo E, Kida K, Morinari H, Fukayama M, Ouchi Y, Orimo H. Detection of human T lymphotropic virus type I proviral DNA in patients with diffuse panbronchiolitis. *Respirology* 1996; 1:139–44.
36. Miyashita N, Niki Y, Nakajima M, Kawane H, Matsushima T. Chlamydia pneumoniae infection in patients with diffuse panbronchiolitis and COPD. *Chest* 1998; 114:969–71.
37. Baz MA, Kussin PS, Van Trigt P, Davis RD, Roggli VL, Tapson VF. Recurrence of diffuse panbronchiolitis after lung transplantation. *Am J Respir Crit Care Med* 1995; 151:895–8.
38. Iwata M, Sato A, Colby T. Diffuse panbronchiolitis. In: *Diseases of the Bronchioles*. Ed. Epler GR. New York: Raven Press, 1994, 153–79.

39. Ichikawa Y, Koga H, Tanaka M, Nakamura M, Tokunaga N, Kaji M. Neutrophilia in bronchoalveolar lavage fluid of diffuse panbronchiolitis. *Chest* 1990: 98:917–23.
40. Oda H, Kadota J-I, Kohno S, Hara K. Leukotriene B4 in bronchoalveolar lavage fluid of patients with diffuse panbronchiolitis. *Chest* 1995; 108:116–22.
41. Sato A. Chida K. Iwata M, hayakawa H. Study of bronchus-associated lymphoid tissue in patients with diffuse panbronchiolitis. *Am Rev Respir Dis* 1992; 146:473–8.
42. Mukae H. Kadota J, Kohno S, Kusano S, Morikawa T, Matsukura S, Hara K. Increase in activated CD8+ cells in bronchoalveolar lavage fluid in patients with diffuse panbronchiolitis. *Am J Respir Crit Care Med* 1995; 152:613–8.
43. Sugiyama Y. Sugama Y. Takeuchi K, Kudo S. Kitamura S. Analysis of peripheral lymphocyte subsets and changes due to erythromycin therapy in patients with diffuse panbronchiolitis. *Jpn J Thorac Dis* 1990; 28:1574–80.
44. Kadota J. Sakito O, Kohno S, Sawa H, Mukae H, Oda K, Kawakami K, Fukushima K, Hiratani K, Hara K. A mechanism of erythromycin treatment in patients with diffuse panbronchiolitis. *Am Rev Respir Dis* 1993; 147:153–9.
45. Ichikawa Y, Ninomiya H, Koga H, Tamaka M, Kinoshita M, Tokunaga N, Yano T, Oizumi K. Erythromycin reduces neutrophils and neutrophil-derived elastolytic-like activity in the lower respiratory tract of bronchiolitis patients. *Am Rev Respir Dis* 1992; 146:196–203.
46. Oda H, Kadota J, Kohno S, Hara K. Erythromycin inhibits neutrophil chemotaxis in bronchoalveoli of diffuse panbronchiolitis. *Chest* 1994; 106:1116–23.
47. Keicho N, Kudoh S, Yotsumoto H, Akagawa KS. Antilymphocytic activity of erythromycin distinct from that of FK506 or cyclosporin *A. J Antibiot (Tokyo)* 1993; 46:1406–13.
48. Chijimatsu Y, Nakazato Y, Homma H, Mizuguchi K. A case of Good syndrome complicated by diffuse panbronchiolitis. *Jpn J Thorac Dis* 1982; 20:803–8.
49. Sugiyama Y, Kudoh S, Kitamura S. A case of the bare lymphocyte syndrome with clinical manifestations of diffuse panbronchiolitis. *Jpn J Thorac Dis* 1989; 27:980–3.
50. Mimura T, Yoshimura K, Nakamori Y, Nakata K, Tanimoto H. Non-Hodgkin lymphoma associated with diffuse panbronchiolitis. *Jpn J Thorac Dis* 1987; 25:1211–8.
51. Ono K, Shimamoto Y, Matsuzaki M, Sano M, Yamaguchi T, Kato O, Yamada H, Yamaguchi M. Diffuse panbronchiolitis as a pulmonary complication in patients with adult T-cell leukemia. *Am J Hematol* 1989; 30:86–90.
52. Okano A, Sato A, Suda I, Yasuda K, Iwata M, Chida K. A case of diffuse panbronchiolitis complicated by malignant thymoma and Sjoegren's syndrome. *Jpn J Thorac Dis* 1991; 29:263–8.
53. Yamanishi Y, Maeda H, Hiyama K, Ishioka S, Yamakido M. Rheumatoid arthritis associated with diffuse panbronchiolitis. *Intern Med* 1998; 37:338–41.
54. Desai S, Gephardt G, Stoller J. Diffuse panbronchiolitis preceding ulcerative colitis. *Chest* 1989; 45:1342–4.
55. Kurihara I, Nakayama K, Sato H, Saito T. Diffuse panbronchiolitis and IgA Nephropathy: Relation to bronchus-associated lymphoid tissue. *Nephron* 1999; 81:450–1.
56. Suzaki H, Kudoh S, Sugiyama Y, Maeda H, Nomura Y. Sinobronchial syndrome in Japanese people. *Am J Rhinol* 1990; 4:133–9.
57. Izumi T. *Annual Report on the Study of Interstitial Lung Diseases.* Ministry of health and Welfare in Japan, 1983, p3.
58. Hirata T, Nishikawa S, Izumi T. An immunological study on diffuse panbronchiolitis. *Jpn J Chest Dis* 1979; 38:90–5.
59. Sugiyama Y, Izumi T, Kitamura S, Takaku F, Suzaki H. Levels of cold hemagglutinin in patients with diffuse panbronchiolitis and various respiratory diseases. *Kokyu* 1984; 3:694–9.
60. Takizawa H, Tadokoro K, Miyoshi Y, Horiuchi T, Ohta K, Shoji S, Miyamoto T. Serological characterization of cold agglutinin in patients with diffuse panbronchiolitis. *Jpn J Thorac Dis* 1986; 24:257–63.
61. Nakata K, Tanimoto H. Diffuse panbronchiolitis. *Jpn J Clin Radiol* 1981; 26:1133–42.
62. Nishmura K, Kitaiohi M, Taumi T, Itoh H. Diffuse panbronchiolitis: correlation on high-resolution CT and pathologic findings. *Radiology* 1992; 104:779–85.
63. Akira M, Kitatani F, Yong-Sik L, Kito N, Yamamoto S, Higaohihara T, Morimoto S, Ikozoe J, Kozuka T. Diffuse panbronchiolitis:Evaluation with high-resolution CT. *Radiology* 1988; 168:433–8.

64. Sugiyama Y. Saitoh K. Kano S. Kitamura S. An autopsy case of diffuse panbronchiolitis accompanying rheumatoid arthritis. *Resp Med* 1996; 90:175–7.
65. Sugiyama Y, Ohno S, Kano S, Maeda H, Kitamura S. Diffuse panbrochiolitis and rheumatoid arthritis: A possible correlation with HLA-B54. *Intern Med* 1994; 33:612–4.
66. Tokunaga K, Omoto S, Akaza T. Akiyama N. Amemiya H, Naito S, Sasazaki T, Satoh H, Juji T. Haplotype study on C4 polymorphism in Japanese. Association with MHC alleles, complotypes, amd HLA-complement haplotypes. *Immunogenetics* 1985; 22:359–65.
67. Maeda H, Juji T, Mitsui H, Sonozaki H, Okitsu K. HLA DR4 and rheumatoid arthritis in Japanese people. *Ann Rheum Dis* 1981; 40:299–302.
68. Stastny P. Association of the B-cell alloantigen DRw4 with rheumatoid arthritis. *N Engl J Med* 1978; 298:869–71.
69. Karr RW, Rodey GE, Lee T, Schwarts BD. Association of HLA-DRw4 with rheumatoid arthritis in black and white patients. *Arthritis Rheum* 1980; 23:1241–5.
70. Hayakawa H, Sato A, Imokawa S, Toyoshima M, Chida K, Iwata M. Bronchiolar disease in rheumatoid arthritis. *Am J Respir Crit Care Med* 1996; 154:1531–6.
71. Nakada K, Inatomi K. Prognosis and treatment. *Annual Report on the Study of Diffuse Interstitial Lung Disease.* Ministry of Health and Welfare in Japan 1981, 21.
72. Yamamoto M. Therapeutic effect of erythromycin on diffuse panbronchiolitis. Double-blind, placebo-controlled study. *Annual Report on the Study of Diffuse Interstitial Lung Disease.* Ministry of Health and Welfare in Japan 1991, 18–20.
73. Nagai H, Shishido H, Yoneda R, Yamaguchi E, Tamura A, Kurashima A. Long-term low-dose administration of erythromycin to patients with diffuse panbronchiolitis. *Respiration* 1991; 58:145–9.
74. Hojo M, Fujita I, Hamasaki Y, Miyazaki M, Miyazaki S. Erythromycin dose not directly affect neutrophil functions. *Chest* 1994; 105:520–3.
75. Goswami SK, Kivity S, Marom Z. Erythromycin inhibits respiratory glycoconjugative secretion from human airways in vitro. *Am Rev Respir Dis* 1990; 141:72–8.
76. Tamaoki J, Isono K, Sakai N, Kanemura T, Konno K. Erythromycin inhibits Cl secretion across canine tracheal epithelial cells. *Eur Respir J* 1992; 5:234–8.
77. Suga T, Sugiyama Y, Fujii T, Kitamura S. Broncholoalveolar carcinoma with bronchorrhoea treated with erythromycin. *Eur Respir J* 1994; 7:2249–51.
78. Konno S, Adachi M, Asano K, Okamoto K, Takahashi T. Inhibition of human T-lymphocyte activation by macrolide antibiotic, roxithromycin. *Life Sci* 1992; 51:PL231–6.
79. Keicho N, Kudo S, Yotsumoto H, Akagawa KS. Erythromycin promotes monocyte to macrophage differentiation. *J Antibiotics* 1994; 47:80–9.
80. Hirakata Y, Kaku M, Tomono K, Tateda K, Furuya N, Matsumoto R, Araki R, Yamaguchi K. Efficacy of erythromycin Lactobionate for treating Pseudomonas aeruginosa bacteremia in mice. *Antimicrob Agents Chemother* 1992; 36:1198–203.
81. Sakata K, Yajima H, Tanaka K, Sakamoto Y, Yamamoto K, Yoshida A, Dohi Y. Erythromycin inhibits the production of elastase by Pseudomonas aeruginosa without affecting its proliferation in vitro. *Am Rev Respir Dis* 1993; 148:1061–5.
82. Takizawa H, Desaki M, Ohtoshi T, Kikutani T, Okazaki H, Sato N, Akiyama N, Shoji S, Hiramatsu K, Ito K. Erythromycin suppresses interleukin 6 expression by human bronchial epithelial cells: A potential mechanism of its anti-inflammatory action. *Biochem Biophys Res Commun* 1995; 210:781–6.
83. Sugiyama Y, Yanagisawa K, Tominaga S-I, Kitamura S. Effects of long-term administration of erythromycin on cytokine production in rat alveolar macrophages. *Eur Respir J* 1999; 14:1113–6.
84. Abe S, Nakamura H, Inoue S, Takeda H, Saito H, Kato S, Mukaida N, Matsushima K, Tomoike H. Interleukin-8 gene repression by clarithromycin is mediated by the activator protein-blinding site in human bronchial epithelial cells. *Am J Repir Cell Mol Biol* 2000; 22:51–60.

10 Obstructive Sleep Apnoea

Mary Ip and C G Guilleminault

Introduction

Obstructive sleep apnoea (OSA) syndrome describes the condition in which a subject suffers from recurrent complete or partial cessation of breathing due to functional occlusion of the upper airways during sleep. There are major concerns regarding the impact of associated morbidity and mortality, mainly with regards to neurobehavioural and cardiovascular consequences.

The term "obstructive sleep apnoea" cannot be found in classic medical texts in the early 1970s, while it takes up a chapter in almost every current general medical or respiratory text. Charles Dickens, in his novel *The Pickwick Papers* in the 1830s, described a character, the fat boy Joe, who was always dozing off, and the term "Pickwickian" was coined for a sleepy patient with gross obesity and cor pulmonale with no other obvious cause (1). One of the early clinical observations of OSA could be dated back to the masterful description by Dr. Broadbent of St Mary's Hospital in London in 1877: "When a person is lying on his back in heavy sleep and snoring loudly, it very commonly happens ... . inspiration fails to overcome the resistance in the pharynx of which stertor or snoring is the audible sign, and then there will be perfect silence through two, three or even four respiratory periods in which there is ineffectual chest movements; finally air enters with a loud snort ... ." (2). With the advent of sleep recordings, it was realized that majority of patients with Pickwickian syndrome actually suffered from sleep disordered breathing (3). On the other hand, OSA is now known to afflict in protean manifestations many more people than those with full blown Pickwickian syndrome. Hence OSA is not a new disease, but with the rapid expansion in knowledge on this condition, it has certainly taken up a new face with a high profile.

Epidemiology

Prevalence

The common occurrence of sleep disordered breathing in Caucasian populations has been recognized since the 1980s, although awareness among Asian populations has only been more widely spread in the past decade. Much of the awareness was brought about by published data from population studies which demonstrated a high prevalence of symptomatic and asymptomatic OSA in adults. Different methodologies and criteria for diagnosis of OSA have been used in various studies, and interpretation and comparison of prevalence data must take into account these methodological differences.

Adults

Prevalence studies have been mostly conducted in adults, especially in middle-aged men. In western populations, the prevalence of symptomatic OSA range from about 1–5% in middle-aged men and 1–2% in middle aged women (4–11). The prevalence of asymptomatic OSA is considerably higher, affecting as many as over 25% of men (4,5,6,9) and 9–28% of women in various studies, depending on the respiratory event cutoff as well as the target age range (5,8,9,10).

It has been previously perceived that OSA would not be as common in Asian populations, probably due to the fact that obesity, the major risk factor for OSA, is less prevalent than in western communities. A community-based study in middle-aged Chinese in Hong Kong has been recently reported (12,13). Using questionnaires followed by full polysomnograms in voluntary samples, 4.1% of men aged 30–60 years old were found to suffer from symptomatic OSA, defined as apnoea-hypopnoea index (AHI) $\geq$ 5 and excessive daytime sleepiness (12). Similarly, the study in middle-aged Chinese women showed a prevalence of 2.1%, although the prevalence ranged from 0.5% in the fourth decade to 6.1% in the sixth decade of life (13). The prevalence of asymptomatic sleep disordered breathing at AHI $\geq$ 5 is relatively lower than in Caucasian studies, at 8.8% and 3.7% in men and women respectively, although this could have been underestimated due to the voluntary basis for polysomnogram studies, thus favouring inclusion of only those with symptoms. Compared to male counterparts, women had less severe degree of sleep disordered breathing. The overall male to female ratio with symptomatic OSA was 2:1, but increased from 1.3:1 in the group with mild OSA (AHI 5–15) to 9:1 in the group with severe OSA (AHI > 30), despite comparable body mass indices (BMI) in men and women with OSA.

Another study conducted on a university student population at a mean age of 19.4 years in Hong Kong, using questionnaires and random sampling with home sleep monitoring, reported that snoring was prevalent while sleep disordered breathing, defined by AHI of > 5, occurred in a minimum of 0.1% of the cohort (14).

In Singapore, a household survey has been conducted among its 20–74 years old multi-ethic community comprising of Chinese, Malays and Indians (15). Symptoms of snoring and sleep disturbances, hypertension and self-reported weight and height, and objective measurement of neck circumference were recorded. The study reported that the prevalence of snoring showed pronounced ethnic differences among Chinese (6.2%), Malay (8.1%) and Indian (10.9%). The minimum whole population prevalence of sleep breathing-related disorder, defined by a diagnostic triad of frequent habitual snoring, apnoeic symptoms during sleep and/or wide neck circumference/hypertension, was 0.43%. Marked ethnic differences similar to that of snoring prevalence were observed, and the differences were only partly explained by known factors of sex, age and body habitus.

A few epidemiologic studies have been conducted in Japan. A multi-centre collaborative study on sleep problems (COSP) has reported that, of 2851 males (mean age 41 years) and 3864 females (mean age 41 years) recruited from new outpatients during 1994 and 1995, habitual snoring was seen in 16% and 6.5% while cessation of breathing was observed in 1.8 and 0.3% of males and females respectively (16). Habitual snoring was significantly correlated with body mass index, cigarette smoking and alcohol consumption. Furthermore, more habitual snorers reported excessive daytime sleepiness than non-habitual snorers at 17.8% vs 6.6% in men, and 21.5% vs 9.7% in women.

Another prevalence study in Japan utilizing questionnaires returned by over 3240 presumably healthy subjects in four hospitals in different cities reported prevalence rates of about 14% and 8.5% for habitual snoring and excessive daytime sleepiness respectively (17). Observed apnoea episodes were reported in a range of 1.3–4.2% from the four sample groups. Subsequently, sleep studies were conducted in subjects selected by suggestive symptoms, and the projected prevalence of OSA in the entire study population was 1.4–1.94%.

A study comprising of questionnaires and sleep studies has been recently completed in Bombay, India (18). The study population consisted of healthy Indian males between 35 to 65 years of age attending a teaching hospital for a routine health check. Seven hundred questionnaires were

distributed and 658 responded; of these 171 were snorers and 487 non-snorers. The mean BMI was 24. All snorers (n = 171) and 25% of non-snorers (n = 122) were offered home sleep studies; 151 snorers and 103 non-snorers agreed. In all, 250 sleep studies (150 snorers and 100 non-snorers) were analyzed. The prevalence of sleep disordered breathing defined as AHI ≥ 5 was 19.5% and that of OSA syndrome (AHI ≥ 5 + excessive daytime sleepiness) was 7.5%. For the first time, the prevalence of sleep disordered breathing in an Indian cohort was documented with sleep studies, and demonstrated a prevalence of OSA syndrome higher than that reported in other Asian ethnic groups so far. The data also corroborated with the higher prevalence of snoring in Indians among the multi-ethnic study population in Singapore (15).

Table 1 outlines some population-based studies in adults, highlighting the methodologies and prevalences of different ethnic populations.

Table 1. OSA Prevalence Studies in Adults

Reference & Country	*Country*	*Sex/Age Ethnicity*	*Methodology*	*Prevalence & definitions for OSA*
(5) Young T et al, 1993, USA	Caucasians	Men & women 30–60 years	Q: 3,515, PSG: 625	Men: 4%*, women: 2%* Men: 25%†, women: 19%†
(6) Olson, 1995, Australia	Caucasians	Men & women 35–69 years	Q & PSG n = 441	Men: 5.7%§, Women: 1.2%§
(7) Ohayon et al, 1997, UK	Caucasians	Men & women 20–100 years	Telephone interview: 2,078 men, 2,894 women	Men 35–64 year: 3.5%# Women 35–64 year: 1.5%#
(15) Ng et al, 1998, Singapore	Chinese, Malays	Men & women 20–74 years	Frequent loud snoring, apnoeic symptoms during sleep, hypertension/wide neck circumference	Whole population: 0.43% Men: 0.61%, women: 0.22%
(9) Bixler et al, 2001, USA	Caucasians 20–100 years	Men & women	Q: 4,364 men, 12,219 women PSG: 741 men, 1,000 women	Men: 3.9%** Women: 1.2%** premenopause 0.6% post-menopause without HRT: 2.7% post-menopause with HRT: 0.5%
(10) Duran et al, 2001, Spain	Spanish 30–70 years	Men & women	Q, BP & portable respiratory record: 2,148 Q, BP + PSG: 555	Men: 19%‡, women: 15%‡
(12) Ip et al, 2001, Hong Kong	Chinese	Men 30–60 years	Q: 784 men PSG: 153 men	Men: 4.1%*, 8.8%†, 6.3%‡, 5.3%§
(13) Ip et al, 2004 Hong Kong	Chinese	Women 30–60 years	Q: 854 women PSG: 105 women	Women: 2.1%*, 3.7%†, 1.4%‡, 0.8%§
(18) Udwadia et al, 2004, India	Indian	Men 35–65 years	Q: 658 PSG: 250	Men: 7.5%*, 19.5%†

Q = Questionnaire respondents
PSG = polysomnogram
BP = blood pressure
* = AHI ≥ 5 plus symptom of EDS
** = AHI ≥ 10 plus daytime symptoms
† = AHI ≥ 5
‡ = AHI ≥ 10
§ = AHI ≥ 15
# = Minimal criteria of International Classification of Sleep Disorders 1996

Adolescents and children

Obstructive sleep apnoea is even more under-recognized in children than in adults and prevalence of sleep disordered breathing in children has not been well studied. The attention of paediatricians was drawn by the first careful documentation of sleep breathing parameters and clinical features in children in 1979 (19). Most epidemiologic studies were based on symptomatology reported by parents, and only a few had objective data. The lack of standardization of the definition of OSA in children on either polysomnogram criteria or clinical features makes accurate determination of the prevalence of sleep disordered breathing very difficult (11,20,21). Prevalence rates may differ significantly among age groups of narrow range in childhood, and apparently peak at 3–5 years old. To date, prevalence estimates range from 0.4% to 10% (11), and the wide variation is probably in part due to the lack of uniform language in the diagnosis of sleep apnoea in paediatric age groups.

A study among 1142 Thai school children aged 6–13 years demonstrated that 8.5% were habitual snorers, and snoring was associated with rhinitis and tonsillar hypertrophy (22). Of the snorers, eight reported symptoms suggestive of sleep apnoea and were investigated with polysomnography which showed AHI of 0.6–4.7 per hour. Seven of the eight children fulfilled the criteria for OSA syndrome, giving a prevalence of 0.69%, all being mild, in this cohort.

Some studies focused on prevalence of sleep disordered breathing among obese children (23,24). In Singapore, questionnaire screening in over 3000 6–18 year-olds who were seen for obesity at the school health service followed by polysomnographic studies in over 140 of them selected by symptoms, showed a minimum prevalence of OSA of 0.7% (24). Further discriminant analysis suggested a prevalence as high as 5.7% in this obese cohort, comparable to that of 7% reported in a group of morbidly obese Caucasian children and adolescents (23).

Risk factors

Risk factors in adults

Body habitus. The majority of subjects diagnosed with sleep apnoea in sleep clinics are obese although this may be partially biased by the high index of suspicion for OSA in those who are overweight and hence referral for sleep studies. In epidemiologic studies of different countries and races, BMI is consistently correlated with apnoea-hypopnoea index (11). Neck circumference, reflecting adiposity and soft tissue mass in the neck region surrounding the upper airway, has been shown to be an even better predictor of OSA in some studies (25,26). Others have suggested that upper body fat distribution was a more important determinant than generalized obesity (27,28). However, it must be noted that in every population, there are OSA subjects who are not overweight, therefore one must not be guided by obesity alone in the suspicion for OSA. In the elderly, obesity is a less important risk factor (11,29).

In the study of middle aged Chinese in Hong Kong , significant determinants of sleep disordered breathing in either sex, defined by AHI of ≥ 5, were BMI and age. On comparison with Caucasian data (5), there was a trend towards a smaller impact of BMI on AHI (12,13).

Despite being well established as a risk factor, the exact mechanisms by which obesity predispose to collapse of the upper airways during sleep has not been clearly defined. Increased mass loading at the neck from adipose tissue deposition at certain strategic sites have been suggested as an important factor (30). Increased work of breathing from general or abdominal obesity may be another mechanism leading to increased negative intraluminal pressure generation at the upper airway and hence greater propensity to collapse (31).

Craniofacial morphology. Craniofacial abnormalities have long been reported to contribute to OSA. Abnormal features that have been consistently described are small posteriorly placed mandible, narrow posterior airway space, enlarged tongue and soft palate, and inferiorly placed hyoid bone (32,33). Some of these features have also been found to determine the severity of sleep disordered breathing. Such bony or soft-tissue features are believed to lead to a smaller or more collapsible upper airway predisposing to apnoea or hypopnoea during sleep.

In an analysis of craniofacial factors in

Caucasian OSA subjects according to body habitus, bony factors were more important in lean subjects, both bony and soft tissue factors contributed in moderately obese subjects, while soft tissue abnormalities appeared to be the dominant factor in obese subjects (34). Similarly, a study in Japanese subjects suggested that upper airway soft tissue enlargement and bony abnormalities were of greater pathogenetic role in obese and non-obese OSA subjects respectively (35). However, the criteria for obesity in this study was set at BMI of 27 and above, which is now considered to be too high for Asians (36). It is possible that if the appropriate BMI criteria is applied, further subcategories of bony or soft tissue abnormalities may be seen according to different levels of obesity.

Computed tomographic (CT) cephalometric analysis in 25 Chinese subjects with OSA and 25 BMI-matched controls showed that OSA subjects had lower hyoid position, longer nasal cavities, more mandibular retronagthism, bigger tongue and smaller upper airway (37). Further CT cephalometric study in 92 Chinese subjects with AHI ranging from normal to severe OSA confirmed most of these craniofacial features, and also identified that OSA subjects had smaller ratio of velopharynx to hypopharynx (38).

Several studies comparing OSA in Caucasians and Asians have shown that Asian subjects have greater severity of illness as indicated by higher respiratory disturbance indices, compared to Caucasian patients matched for age, sex and BMI (39,40,41). However, there has been recent modification of the BMI criteria for overweight and obesity among Asians, with a lowering of the BMI to ≥ 23 for overweight and ≥ 25 for obesity, compared to corresponding values of ≥ 27 and ≥ 30 for Caucasians (36). Hence, comparison of body habitus between Asians and Caucasians using absolute values of BMI may be misleading and Asians may have more severe OSA by virtue of actually having greater degree of obesity on ethnic peer comparison. Nonetheless, within the same ethnic group, it has still been demonstrated that increments in BMI may not contribute as much to increments in AHI among Asians (12). Our study of 92 subjects with computerized tomography also demonstrated that after adjustment for BMI and sex, relative mandibular retronagthia and longer soft palate were associated with severe OSA, but not with mild/moderate OSA, offering further support to the hypothesis that craniofacial factors may contribute to a more severe degree of sleep disordered breathing in Chinese subjects (38).

In a study comparing 43 Caucasian and 30 Chinese men with OSA and Class II, Division I malocclusions, matched for age, skeletal pattern, BMI and AHI, significant craniofacial discrepancies were seen between the two ethnic groups (42). Chinese had more severe mandibular retronagthism and other cephalometric and upper airway morphologic differences. How these differences affected sleep disordered breathing have not been explored, but the findings suggested that therapy targeting at craniofacial factors should note the existence of ethnic differences in these parameters.

Sex. It has always been observed in clinical practice that there is a male predominance of OSA in adults. In clinic-based series, the numbers of male far exceed that of female patients. In Hong Kong, earlier case series have reported male:female ratios of about 5:1 (43,44). Similarly, a series of 59 patients seen in Ramathidbodi Hospital, Thailand during 1994–1997 reported a ratio of 7.4 :1 (45). However, epidemiologic studies have consistently demonstrated that the OSA prevalence ratio of men to women is approximately 2:1, much lower than that of clinical series. This discrepancy between community surveys and clinic populations may be attributed to a number of factors. Women tend to under-report their symptoms (46). Men may be more concerned about symptoms of fatigue and daytime sleepiness that affect their work, while not all women are engaged in full time work and may not be as concerned about such symptoms. Many of our male patients present because their wives are concerned about their spouses' health. Patterns of healthcare utilization may also differ between men and women. In Asian societies where the social status of men are higher than women, a higher presentation rate to the healthcare system due to symptoms of OSA would not be unexpected. Finally, doctors may also be more alerted to the possibility of OSA in men and disregard typical symptoms in women (47). With increasing awareness of occurrence of OSA in women, it is anticipated that the index of suspicion by both

doctors and the lay community will increase and more women will present themselves and receive proper diagnosis and treatment.

The pathogenetic mechanisms underlying the disparity between sexes are not clearly elucidated, and have focused on the role of sex hormones. The relationship of testosterone and OSA is very controversial (48). Menopause, with the decline in oestrogen and an increase in androgenic influence, has been consistently reported to be associated with a significant increase in prevalence of OSA. Post-menopausal women also have a higher AHI than pre-menopausal women even after adjusting for BMI and neck circumference (49). However, menopause is closely connected to age, and it is difficult to separate definitively the influence of age and hormonal changes. Post-menopausal women on hormonal replacement have been reported to have OSA prevalence similar to that of pre-menopausal group, in contrast to post-menopausal women of similar age but not on hormonal replacement who had a much higher prevalence of OSA (9). These findings suggest an important contribution toward OSA from the menopausal status itself, independent of age.

Other factors that may lead to a male dominance in OSA include inherent morphological and functional differences in the upper airway (50) as well as differences in exposure to exogenous potential risk factors such as alcohol and smoking.

Age Most adult prevalence studies have shown a progressive increase in prevalence of OSA with age in mid life, but this trend does not apply uniformly to other age sectors. Several studies have found that OSA is highly prevalent in people older than 65 years, but among the elderly, there is no further rise in prevalence (10,51,52). It is not known if this implies a natural decline in incidence or survival bias due to a higher mortality in those with OSA.

Others. Ventilatory control, especially through effects on upper airway muscle function, has been postulated to be important in the pathogenesis of apnoea/hypopnoea and the subsequent resumption of breathing (53).

Lifestyle habits such as alcohol drinking and smoking have been reported to be risk factors for OSA (11). Depending on the prevalence of these habits in the community, their contribution to the prevalence and severity of OSA may differ.

Rhinitis as a risk factor for OSA has been controversial (11), and warrant thorough research since rhinitis is very common and is amenable to treatment.

Risk factors in children

The factors predisposing to OSA in children are not identical to that of adults. Most of the data come from clinic-based series with their inherent bias. It is generally accepted that abnormalities in the upper airway play a more important role than obesity in the development of OSA in children. The usual cause of pharyngeal narrowing in children is adenotonsillar enlargement (21). Upper and lower respiratory problems were also found to be associated with OSA in a study of children 2–12 years old (54).

Although obesity is not the dominant risk factor in children, symptoms of snoring and apnoeas during sleep and polysomnogram documented sleep disordered breathing in obese children have been reported to be much higher than age-matched general cohorts. In adolescence, the pattern of risk factors is similar to that of adults and the role of obesity assumes greater importance (55).

The role of craniofacial factors, excluding that of gross abnormalities, in the pathogenesis of OSA in children is not well delineated. It is possible that children with OSA, even on correction with tonsillectomy, may be predisposed to development of OSA in later life (56).

Much less commonly, the occurrence of OSA in children is due to other anatomical abnormalities, either as part of a serious developmental disorder or just an isolated skeletal variation. Some of these congenital conditions are Down's syndrome (causing large tongue or tonsils), Pierre Robin syndrome (causing micronagthia), and mucopolysaccharidoses (causing soft tissue deposition with upper airway narrowing).

Genetic influence

Familial tendency for OSA has been reported in Caucasians and African-Americans (57,58). Familial aggregation may reflect genetic inheritance of certain pathogenetic traits such as body habitus, craniofacial morphology or

ventilatory control. Part of it may be attributed to similar environmental exposure promoting certain modifiable risk factors.

Pathophysiology

As the name of the condition implies, there are events of cessation of breathing (apnoeas) due to obstruction of the upper airway during sleep. In reality, the respiratory events embrace full blown apnoeas as well as events when breathing are only decreased (hypopnoeas). These events occur as a result of complete or partial functional occlusion of the upper airways at the level of the pharynx when the subject falls asleep, and they lead to similar physiologic responses (59). Hence respiratory event counts now include both apnoeas and hypopnoeas. The dimunition of pharyngeal muscle tone during sleep and negative inspiratory pressure in the pharyngeal lumen set the scene for possible functional collapse at that site (31,53). In subjects with predisposing risk factors as discussed previously, apnoeas and hypopnoeas may then occur.

With the complete or partial cessation of breathing, hypoxaemia and hypercarbia ensue, as well as a cascade of other pathophysiological events. Increased sympathetic discharge is well documented with increase in catecholamine production and muscle sympathetic nerve activation (60,61). There is relative bradycardia during the apnoea with tachycardia at the resumption of breathing (62). Systemic arterial blood pressure cyclically increase after each obstructed breathing event (59,61), while pulmonary blood pressure also increase transiently and recurrently (63).

There is growing interest in the cellular and biochemical changes accompanying OSA. Many of these changes have a potential role in promoting cardiovascular and metabolic morbidity. There is a suggestion of participation of natriuretic peptides and renin-angiotensin-aldosterone system in the regulation of pressure and volume of the circulatory system (64). Some established atherogenic mechanisms have been described in OSA, including increased platelet activation (65) and clotting activity (66), decreased nitric oxide production (67), impaired endothelial function (68), increased lipid peroxidation (69), increased insulin resistance (70), increased oxidative stress (71.72) and vascular adhesion of leukocytes (72). The ultimate clinical relevance of these changes associated with OSA towards development of atherosclerosis is the key question to be answered by much more research. A randomized controlled study of the effect of CPAP on endothelial function in otherwise healthy OSA demonstrated that endothelial dysfunction in OSA can be restored by CPAP treatment (73). The connotation of this finding is significant as endothelial dysfunction is widely accepted to be a marker of atherosclerosis and a predictor of cardiovascular diseases.

Clinical Features

Although there is a myriad of clinical features in OSA, the cardinal symptoms often quoted are habitual loud snoring and excessive daytime sleepiness (Table 2).

Table 2. Common Clinical Features of OSA in Adults

Symptoms:
• Heavy loud snoring
• Excessive daytime sleepiness
• Excessive fatigue or lack of energy
• Decreased concentration or memory
• Witnessed apnoeas
• Sleep choking
• Dry or sore throat on wakening
• Urinary frequency during sleep
• Wake up feeling unrefreshed
• Morning headache
Physical signs:
• Overweight or obese
• Thick neck
• Receding chin
• Swollen uvula
• Hypertension

There have been a number of case series in the English literature reporting on the clinical features of OSA in various Asian populations (43,44,45,74), and more in non-English local journals. These subjects usually had florid OSA

features since they were identified at the time when OSA was just beginning to gain awareness in the various Asian communities.

Daytime sleepiness is a cardinal symptom of OSA (75,76) but it is both non-sensitive and non-specific. Daytime sleepiness is usually assessed subjectively with structured scales that assess the possibility of falling asleep in various circumstances, such as the Epworth Sleepiness Scale (77) or Stanford Sleepiness Scale (75). The degree of daytime sleepiness does not necessarily correlate with objective measurements of sleep apnoea severity. Some subjects may experience fatigue or loss of energy or difficulty in concentration rather than really falling asleep. People may also be reluctant to admit that they fall asleep during work, as they are concerned about being labelled as lazy or inefficient. The symptom is not specific because there are many causes of sleepiness, in particular poor sleep habits with sleep deprivation.

In some patients with daytime sleepiness, the classical pattern of apnoeas or hypopnoeas is not seen but they have sleep disordered breathing in the form of recurrent episodes of increased resistance to airflow at the upper airway with increasing respiratory effort and subsequent cerebral arousals. The condition has been coined the "upper airways resistance syndrome" (UARS) (78,79).

On physical examination, features that may be present in the adults include varying degrees of obesity, thick neck, retronagthia, micronagthia, tonsillar hypertrophy, oedematous looking uvula (75,76). The western literature has suggested that features of right heart failure are seen only when there is significant co-morbidity that predisposes to cor pulmonale, such as COPD or obesity-hypoventilation (63). However, experience among some clinicians in Asia suggests that there are still occasional cases of severe untreated OSA who present late with type II respiratory failure and cor pulmonale attributed to OSA per se.

Subjects with OSA not uncommonly have other diseases associated with obesity, such as hypertension, diabetes mellitus, dyslipidemia and coronary artery disease. Although acromegaly and hypothyroidism are known to be associated with OSA (75,80), sleep apnoea is rarely the presenting feature of the endocrine disorder. Routine blood testing for hypothyroidism or acromegaly among OSA patients is not recommended but a high clinical index of suspicion would be helpful. Indeed we have diagnosed an occasional case of acromegaly among those referred for sleep studies.

Despite the higher prevalence of OSA in the elderly, the prevalence of obesity, sleepiness or hypertension do not show a parallel increase (8,29, 51,52). Possible reasons behind this discrepancy include different clinical manifestations, survivor bias, and a higher AHI threshold for pathogenic sequelae of OSA in the elderly.

Children also have a different pattern of clinical features. They are usually not obese, and may even have failure to thrive. Instead of presenting with daytime sleepiness as in adults, they have poor learning, behavioural problems, attention deficits, hyperactivity. Cor pulmonale may be present in severe untreated subjects. Parents often observe snoring, hyperextension of neck, laboured breathing with dilated nares and intercostal retraction during sleep (21,81).

Long Term Morbidity

Neurocognitive and neurobehavioural morbidity

A wide range of neurocognitive deficits have been reported in OSA, mainly in those with severe disease in terms of apnoea-hypopnoea index, oxygen saturation, and sleepiness. These deficits include impairment of vigilance, concentration, short-term memory and visuomotor skills (82–84). Psychological impairment such as depression has also been reported (83). However, most of the studies did not have appropriate control groups and the effect of confounding factors such as age, education level, socioeconomic status cannot be excluded. Treatment of OSA with nasal continuous positive airway pressure (nCPAP) has demonstrated improvement in these neurobehavioural impairment (85).

Untreated OSA is associated with an increased risk of traffic accidents and the risk is reduced with treatment of OSA (86,87). There is very little data regarding the relationship between OSA and accidents related to other occupations or activities of daily living.

In a disease such as OSA where the onset is indistinct and symptoms are relatively non-specific, evaluation of health related quality of life (HRQOL) is particularly useful. HRQOL has been demonstrated to be impaired in patients with OSA compared with the normal population, and AHI was an independent determinant of HRQOL (88,89). In an analysis of 300 subjects presenting to our sleep clinic, using SF-36, a generic HRQOL instrument, we found that subjects with severe OSA and sleepiness had poorer quality of life compared to those with neither OSA nor sleepiness. Independent determinants of poor quality of life in this cohort were excessive daytime sleepiness and to a lesser extent, comorbid cardiovascular disease, age and BMI. In contrast to the previous two population-based studies, the presence of OSA as defined by AHI ≥ 5 was not a significant factor in our study. This was probably due to the fact that our subjects were referred for certain symptoms and were not representative of the general population.

Disease-specific HRQOL instruments have the advantage of being able to detect subtle differences related to the characteristics of the disease. The Calgary Sleep Apnoea Quality of Life Index (SAQLI) is an OSA-specific instrument (90) that has the additional advantage of accounting for negative effect of intervention-induced side-effects, enabling it to be more sensitive in the assessment of treatment response in OSA. Since the reliability of quality of life measurement tools are highly contingent upon language and culture, it is important to have appropriate validation of such instruments. We have recently validated a Chinese version of the SAQLI which may have a wider application in the Chinese population (91).

Treatment with nCPAP has also been shown to improve quality of life in subjects with OSA (92).

OSA and cardiovascular disease

The strong association of OSA and various cardiovascular diseases is well documented. A number of studies have reported an increased risk of cardiovascular morbidity and mortality with OSA or snoring, controlled for confounding factors (93–98). OSA may have a pathogenic role in cardiovascular diseases, it may pose an acute adverse physiologic mileau in pre-existent cardiovascular diseases, or it may merely share common aetiologic factors such as obesity with cardiovascular diseases. The exact relationship remains to be defined, but there is growing evidence that all three components may exist. Obviously, the cardiovascular morbidity and mortality attributable to OSA, either by causality or aggravation, is of great prognostic and therapeutic implications in OSA, and hence a focus of ongoing research.

OSA and systemic hypertension

A strong association of OSA and hypertension has long been observed. Hypertension occurs in 30–50% of OSA subjects in clinical series, while one third of subjects with essential hypertension have OSA (93). The prevalence varies in relation to the referral pattern of the sleep clinic and also the awareness of the association. In a study conducted in 1995 in a tertiary referral Hypertension Clinic, we demonstrated that at least 18% of patients followed up for "essential hypertension" were suffering from previously unrecognized OSA of moderate or even severe degree (99).

Due to the strong possibility of comorbidity, the independent causal role of OSA in hypertension has taken a long time to be established, but the evidence is accumulating. Several cross sectional epidemiologic or case controlled studies have shown that increase in AHI or oxygen desaturation was significantly related to increase in blood pressure, even after controlling or matching for known confounding factors (100,101). A prospective follow-up study of 700 subjects over a period of 4 years in Wisconsin showed that the odds ratios for development of hypertension were 1.4, 2.0 and 2.9 for subjects with AHI 0–4.9, 5–14.9 and ≥ 15 respectively, compared to those with an AHI of zero events per hour (98). CPAP therapy has also been shown to produce a small decrease of about 1.5 mm Hg in 24 hours diastolic blood pressure, which was significant between the hours of 2 am and 10 am, and the decrease was greater in those with significant nocturnal hypoxaemia (102).

OSA and the heart

OSA exerts acute physiological changes that

predisopose to myocardial ischaemia during sleep. Nocturnal ECG changes of ischaemia during post-apnoeic periods have been demonstrated in patients with coronary artery disease and co-existing OSA compared with those without OSA (103). Whether nocturnal ischaemia can be induced by OSA in those without existing coronary artery disease is much more controversial, and is probably less likely (93). Cross-sectional analysis of the Sleep Heart Health Study cohort identified a modest independent association between OSA and coronary artery disease (95). OSA subjects may have worse prognosis in terms of mortality after hospitalization for coronary artery disease (96).

In a Singapore study of 432 inpatients of multiethnicity, OSA was independently associated with ischaemic heart disease (104). Malays had the highest prevalence of OSA but the lowest prevalence of ischaemic heart disease. After adjustment for OSA, there was a reduction in the risk of ischaemic heart disease, suggesting that OSA was a confounder in the relationship between race and ischaemic heart disease.

The literature regarding left ventricular function and OSA is controversial. There are several common confounders in the relationship, including the presence of hypertension, obesity, or diabetes mellitus. Both systolic and diastolic dysfunction which are independent of hypertension have been described in OSA (93,105). On the other hand, a study involving over 500 subjects did not find an independent association of OSA with increased left ventricular mass or left ventricular diastolic dysfunction (106). Heart failure itself may contribute to the occurrence of OSA through mechanisms of unstable respiratory drive. In an analysis of 450 consecutive patients with congestive heart failure, Cheyne Stokes respiration with central apnoea was seen in 33% and OSA in 38%, defined at AHI > 10 (107). The presence of OSA was related to only BMI in men and to only age in women.

Short term nCPAP treatment improved left ventricular ejection fraction in patients with end-stage heart failure who also had OSA (108,109).

OSA and arrhythmia

Cyclical bradycardia and tachycardia are commonly seen in OSA. Other pathologically significant rhythm disturbances have been described in OSA, but studies have shown conflicting evidence regarding whether these are due to OSA or confounders. Among the arrhythmias, extreme bradycardia with ventricular asystole, attributed to enhanced vagal tone is more convincingly associated with OSA (110).

OSA and stroke

A high prevalence of OSA has been reported in patients with stroke (111). However, since the objective documentation of sleep apnoea in the majority of subjects was done only after the stroke, it is difficult to ascertain if OSA was present before stroke and posed an independent predisposing risk for stroke, or it was merely a sequel of the neurological event. Furthermore, spontaneous improvement in the sleep apnoea on follow up may be seen (112,113). Treatment of OSA post-stroke resulted in improvement in well being and blood pressure (114) although compliance to CPAP was low in a group of Chinese patients (113).

OSA and pulmonary hypertension

The Pickwickian syndrome classically describes grossly obese sleep apnoea subjects with cor pulmonale. Recent Caucasian series have suggested that although mild degree of pulmonary hypertension is not uncommon in OSA, significant right heart failure only occurs in the presence of comorbidities such as obesity or chronic obstructive pulmonary disease with daytime hypoxaemia (62,115). However, there have been reports in literature (62) and anecdotal experience of untreated OSA patients who developed right heart failure without obvious lung disease or morbid obesity. Children with untreated OSA may have features of cor pulmonale (21).

OSA and the metabolic syndrome

Many subjects with OSA have features of the metabolic syndrome, comprising of insulin resistance, dyslipidemia, central obesity, hypertension and which is highly associated with cardiovascular disease (28,116,117). While the clustering of OSA and these risk factors may be explained by the common link of obesity, it is also postulated that OSA may provide a stress stimulus which triggers or aggravates the metabolic variables, thus conferring independent predisposition to atherosclerosis and cardiovascular diseases.

The relationship between insulin resistance and OSA has been repeatedly studied. Results are so far controversial, with a favourable trend towards an independent association between insulin resistance and OSA in cross-sectional studies (69,94,118). An open study recently reported that treatment of OSA reduced insulin resistance (119).

Diagnosis

The standard diagnostic method for sleep apnoea is polysomnography, which comprise of recordings of sleep stages (with electroencephalogram and electro-oculogram), respiratory events (airflow at mouth and nose with pressure transducers and/or thermistors , respiratory movements with throracic and abdominal strain gauge belts), oxygen saturation with pulse oximeter, and other useful signals, such as snoring with tracheophone, body position with position sensor, leg movements with electromyogram. The advent of computerized systems has made such recordings more easily accessible. However, the test remains very expensive especially in terms of manpower required for accurate connections and overnight monitoring for acquisition of data.

Although full polysomnography is recommended as the "gold standard" diagnostic method for sleep apnoea in some countries (90), in many patients, simpler recordings such as limited sleep studies without recording of sleep stages may suffice to make a diagnosis of sleep apnoea (120). Although such recordings may be falsely negative if the subject did not sleep, they often provide sufficient information for diagnosis, especially in the more florid cases. They cannot detect other sleep disorders causing daytime sleepiness, such as upper airway resistance syndrome, narcolepsy, and periodic leg movement.

An overnight oximetry with the pattern of recurrent dips in oxygen saturation against a normal or near normal baseline saturation in someone with compatible clinical features is highly suggestive of a diagnosis of OSA (Figure 1). When both sleep oximetry and symptoms improve with a trial of nCPAP, the diagnosis is considered well clinched. However, oximetry patterns can only be confidently interpreted when subjects do not have other coexistent respiratory problems which in themselves lead to oxygen desaturation during sleep, making the superimposed pattern of recurrent dips from sleep apnoea no longer distinctive. Sleep oximetry cannot distinguish between central or obstructive events, but central events are not immediately responsive to nCPAP. Oximeters vary in their sensitivity, thus some patients with lesser degree of destauration may be missed. Similar to limited sleep studies, oximetry cannot be used to diagnose other sleep related disorders. Obviously, the use of such a simple diagnostic method that is not very sensitive nor specific is highly contentious in well developed countries, but in the context of communities with extremely limited healthcare resources, it may well contribute to identifying some patients where polysomnographies are not available either because referral to sleep laboratories is beyond affordability or the waiting time is unrealistically long.

In occasional patients, more invasive or sophisticated diagnostic devices may be required for documentation of specific signals. The measurement of oesophageal pressures is needed for establishing a diagnosis of upper airway resistance syndrome. The number of patients requiring such investigations are small and the establishment of such facilities should be limited to quarternary referral sleep disorders units.

Treatment

General measures

Weight control is always advocated in OSA subjects who are overweight or obese. Weight reduction may result not only in improvement of OSA (11), but also in reduction of the risk of developing or the severity of coexistent obesity-related diseases such as hypertension, diabetes mellitus.

Alcohol, through its effect on both sleep staging and muscle tonicity, can precipitate or aggravate snoring and sleep apnoea. In general, subjects should be advised to avoid drinking alcohol before sleep, although in practice, one has no hard evidence to advise against drinking in moderation as long as the person is willing to use nCPAP faithfully.

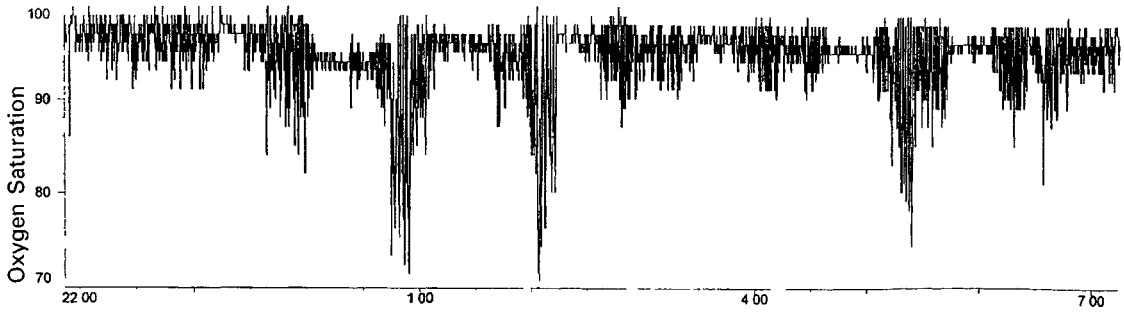


Figure 1a. Oximetry tracing from 11 pm to 6 am in a patient with OSA, showing recurrent dips in oxygen saturation

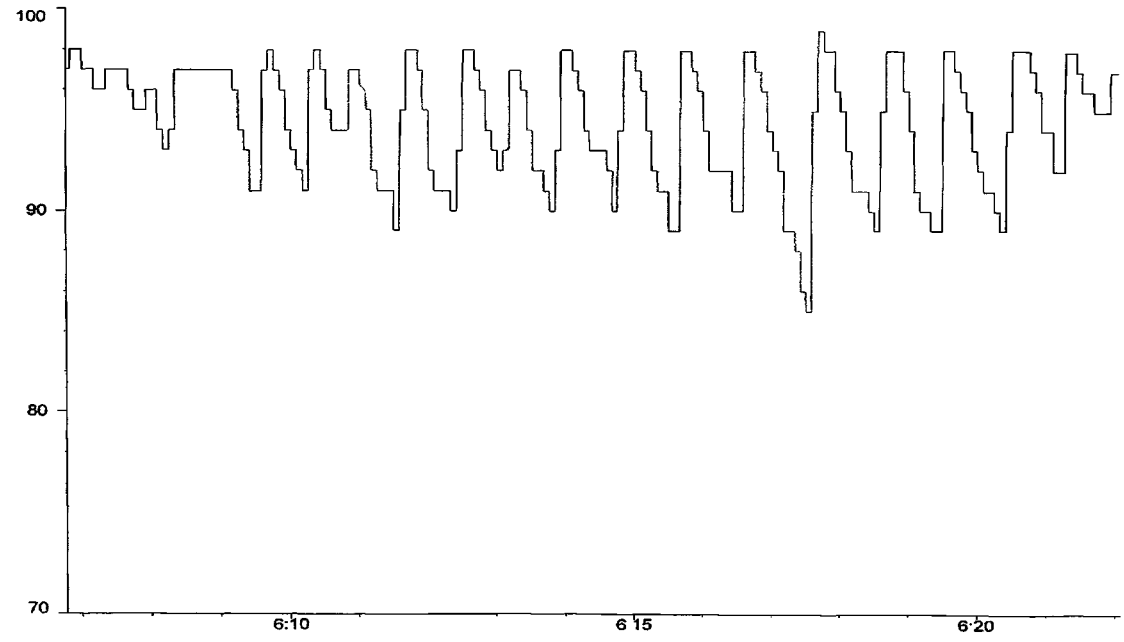


Figure 1 b. Oximetry tracing over 15 minutes at 6 am showing recurrent dips in oxygen saturation lasting over 10 seconds and less than 1 minute

Nasal continuous positive airway pressure (nCPAP)

Currently, nCPAP is the accepted first-line interventional treatment for symptomatic OSA. The treatment is based on the theory of mechanical splinting of the upper airway to prevent its collapse, using a positive pressure delivered through the nose with tight-fitting devices over the nose or nose and mouth (122). The use of nCPAP correct many of the acute pathophysiologic events in OSA and also other intermediary biochemical changes. It can improve symptoms, quality of life and daytime function including risks of traffic accidents in OSA (84,86,123).

To assess the pressure requirements to abolish obstructed breathing events, titration of the pressure has been done with full polysomnography documentation. The advent of automated titration CPAP systems allowed adequate assessment of pressure requirements in the vast majority of patients with OSA (124), and has been successfully

used in a number of sleep laboratories worldwide.

These "intelligent" CPAP devices, which adjust the delivered pressure according to the degree of obstruction as reflected by changes in upper airway airflow or pressures, can be used for treatment, instead of the classical fixed pressure mode. Since these machines vary their pressures from night-to-night and throughout the night, no prior CPAP titration is necessary. Such devices are theoretically more comfortable as the pressures will not be maintained at high levels unnecessarily. Some models have been compared to constant pressure devices in clinical trials and have been reported to be of similar efficacy and the mean pressure requirement was slightly lower. Whether this translates into better compliance has not been definitively proven although there is preliminary evidence for such (125). Frequent changes in pressures may not be realistically advantageous in those patients who have very severe degrees of OSA throughout the night. These models are more expensive than the usual constant pressure models.

Bi-level machines, which are more expensive than constant pressure models, are considered the model of choice for patients with obesity-hypoventilation syndrome, because they can deal with both obstructed events and hypoventilation events. They show little advantage in those with pure OSA except in occasional patients who cannot tolerate expiring against positive pressure.

Nasal CPAP is consistently effective when properly used, but it is a relatively cumbersome device giving rise to a number of side-effects. Patient acceptance and long term compliance pose substantial problems. Side effects of nCPAP include discomfort due to wearing of tight-fitting mask, nasal irritation, throat dryness, air leakage with eye irritation, and noise of machine (126). Patient-mask interface is an important factor in the patient's tolerance of this treatment and efforts must be put into choosing the most appropriate mask for the individual. Nasal symptoms such as runny nose are quite common, and may require treatment with nasal steroids. The addition of warm humidifier is often helpful.

Patients may not be compliant in using the device every night or during sleep throughout the night. It is not uncommon for patients to report that they use it irregularly: some may take off the mask after a few hours of sleep while others may find the mask removed unknowingly when they wake up in the morning. Studies conducted in UK and USA, where CPAP devices are provided by the healthcare system either free or through insurance reimbursement, showed that about two thirds of subjects were still using the device at a median follow up period of about two years (126,127). In those who were still using it, the median duration of use per night was about 5.7 hours (127). In Hong Kong, where nCPAP is not provided by the healthcare system, initial reluctance to buy or rent the CPAP device after titration is not uncommon, especially in those who claim few subjective symptoms (personal observation). Determinants of CPAP compliance include severity of subjective sleepiness and/or AHI (126,127). Reinforced patient support as a measure to facilitate compliance is advocated (128) although this has not been effective in a group of Chinese patients in Hong Kong (129).

Surgery

Many different kinds of surgical procedures have been conducted for treatment of OSA in attempts to modify pharyngeal anatomy or by-pass the pharynx (130). Tracheostomy is no doubt the first and most effective, although it is rarely needed nowadays except in patients with complicated congenital syndromes when other modalities of treatment for life-threatening OSA is considered not feasible.

Uvulopalatopharyngoplasty is based on the rationale that removal of soft tissue in the uvulopalatopharyneal area widens the upper airway lumen and thus improve OSA (131). Some studies showed a 50% short-term response rate but the overall literature about this method suffers from the lack of proper controlled studies or adequate objective documentation of sleep disordered breathing parameters. The procedure carries a definite morbidity and mortality. Hence, it is getting out of favour in general.

Many other modes of surgery have been described and the more well known ones are maxillo-mandibular advancement/osteotomy, hyoid myotomy and suspension and tongue base reduction (130,132). Various surgical modalities

may be performed singly or in combination, in one phase or multiple phases. Short term results of some of the more extensive surgical procedures have been reported to be good, but such procedures require surgical expertise and intensive post-operative support, and results may depend significantly on the experience and expertise of the individual centre.

More systematically conducted trials with good documentation of patient characteristics, surgical procedures and objective outcome data are required before one can recommend surgery as a first-line treatment in OSA.

Oral appliances

Oral appliances are devices placed intra-orally during sleep to prevent the occurrence of OSA. They include tongue retaining devices and mandibular advancing devices. The latter are the predominant type of devices being used currently, and there are many different designs (133,134). Comparison of oral appliances is hampered by different devices being used and different criteria for defining response.

Depending on the criteria for response, oral appliances have been reported to improve OSA in about 37–75% of subjects (133–136). The efficacy of mandibular advancing devices in mild/moderate OSA have been demonstrated in placebo-controlled randomized studies (135,136), and also in comparison studies with nCPAP (137). Compared to nCPAP, oral appliances resulted in a lesser complete control of sleep disordered breathing and symptoms, but have a higher short-term compliance rate as well as acceptance rate (133–137). However, longer term compliance in mild and moderate OSA has been shown to decrease by about 50% (138).

Based on the premise that craniofacial anatomic factors are of greater pathogenetic contribution in Asians than in Caucasians with OSA, it has been postulated that mandibular devices targeting at alteration of anatomy would find a bigger role in the management of OSA among Asian subjects. In an open study of 24 Chinese subjects with mild to moderate OSA, oral appliances have shown similar response rate as compared to those in Caucasians. We have recently completed a randomized controlled study of mild /moderate OSA with three treatment arms consisting of conservative measures alone, conservative measures with nCPAP and conservative measures with oral appliance (data submitted for publication). The oral appliance group had a significant reduction of AHI from a mean of 24 to 10, as well as improvement in symptoms and health related quality of life. Comparison of the three treatment modalities showed that nCPAP group had the best response in terms of objective parameters of sleep disordered breathing and quality of life, while the group with only conservative management showed no change. However, despite the better objective results of CPAP, only half of the patients in CPAP group agreed to continue with the device after the study compared to over 90% of subjects in the oral appliance group, suggesting that the true effectiveness of the two may be highly comparable.

We are also conducting an ongoing study of a non-adjustable mandibular advancing device in subjects with severe OSA who have persistently refused the use of nCPAP. Of the seven subjects evaluated so far, all showed some decrease in AHI, with an improvement from baseline mean AHI of 54 to 21. The acceptance and compliance to oral appliance were high at 100% and over 90% respectively in this group. Even if complete control of sleep disordered breathing cannot be achieved with the device, oral appliance may be better than no treatment at all in subjects with severe OSA in terms of symptom relief and long term morbidity.

Oral appliances are assumed to work by increasing pharyngeal volume and/or decreasing pharyngeal collapsibility (133,134). Placebo-controlled studies demonstrated that placebo devices which did not advance the mandible did not cause any change in OSA status, suggesting that mandibular advancement is an important mechanism (135,136). However, the correlation between the degree of mandibular advancement and the degree of improvement has been controversial in the literature (133,134). The degree of vertical opening achieved by the device may also be one of the determinants of the outcome. We have investigated the upper airway of oral appliance users with volumetric computed tomographic scans. There was an overall increase in upper airway volume, with a selective decrease

in hypopharynx cross-sectional area in good responders. These changes may improve OSA by widening the upper airway aperture as well as dampening inward suction pressure downstream of the more collapsible velopharynx (data submitted for publication).

In summary, oral appliances do not consistently correct physiological parameters such as AHI to "normal" values in all individuals, and occasional patients may even deteriorate. However, treatment acceptance and compliance are apparently better than nCPAP in certain groups of patients, such as those with mild/moderate sleep apnoea and those who strongly dislike nCPAP for whatever reason. Predictors of good response have not been clearly delineated, but most series suggest that a lower baseline AHI, BMI or neck circumference and some cephalometric variables are associated with a better outcome (133,134,139). Short term side effects include increased salivation, temperomandibular joint discomfort, tooth discomfort, and dryness of oral mucosa, but these usually do not result in discontinuation of use and they disappear or decrease after several weeks. Long term side-effects are still being closely monitored, and changes in dental occlusion have been reported, the clinical significance of which is not known (140,141). Oral appliances are currently recommended to be an alternative option to nCPAP in those with mild or moderate OSA and those who are unwilling to use nCPAP (142). Since the response is not uniform, it is important to document objective response by follow up sleep studies rather than relying only on subjective symptoms. Long term follow up for side-effects and compliance is also essential.

Radiofrequency

Radiofrequency tissue ablation has been used as treatment for snoring and OSA. Ablation of the tongue base and/or soft palate has been reported to be beneficial in a few small series of patients with OSA (143,144), with about 50% of the subjects showing an average of 50% reduction in AHI. It was recently reported that there was an increase in hypopnoea two years after treatment although apnoea index and symptoms remained improved (145). Occasional serious side-effects such as severe tongue ulceration may occur. At this point, the role of radiofrequency ablation of tongue base in treatment of OSA is as yet undetermined, and should not be applied non-discriminately. Radiofrequency ablation to hypertrophied nasal turbinates has been reported to have beneficial effects on the acceptance of nCPAP and could lower the pressure requirements (146). Being technically simpler with minimal side-effects, it may be worth applying in appropriate patients.

Medication

So far, no effective medication been identified. Modafinil, a wakefulness-promoting drug, has been tried as treatment for residual sleepiness in CPAP-treated OSA (147). It does not improve OSA events, and should not be regarded as treatment for OSA itself.

Who to treat and how to treat?

The practicing clinician constantly encounters the problems of deciding which patient requires active intervention and the best treatment option for the individual patient.

Treatment of any disease is essentially aimed at relief of symptoms and prevention/alleviation of long term morbidity and mortality. It is uniformly accepted that treatment for OSA is indicated if a patient is symptomatic, such as having significant daytime sleepiness that affects daily activities. However, assessment of symptoms is usually subjective, and patients may have adjusted to the chronic symptoms and do not find them disturbing. In the absence of symptoms, the concern for adverse vascular sequel forms the basis of treatment. Although there is progressive wealth of data showing adverse physiological and biochemical events attributed to OSA, the evidence for an independent causal or aggravating role of OSA in cardiovascular and cerebrovascular diseases has not been firmly established. The best evidence so far is in the contribution of OSA towards the development of hypertension. Even less is known regarding the effect of treatment of OSA on clinical cardiovascular outcomes due to

the paucity of well-designed studies. The chance of performing prospective long-term randomized controlled trials is hampered by the ethical concerns of withholding treatment for prolonged periods in the face of prolific evidence of short-term physiological or biochemical abnormalities that can be corrected by treatment.

In the USA, consensus statements for indications of treatment, based on available evidence as well as expert opinion, have been published (76,142,148). The criteria for nCPAP treatment include: AHI ≥ 5 and symptoms; AHI ≥ 5 and pre-existent cardiovascular disease including hypertension and AHI ≥ 30 regardless of symptoms. In practice, in patients who are relatively asymptomatic, the evidence of benefit of active treatment has not been established (149), and the acceptance and long term compliance of currently available treatment such as nCPAP is relatively low (126,127).

Apart from the incomplete evidence base for treatment in some scenarios, the problem is compounded by patient acceptance and compliance with certain modes of treatment, which is not purely guided by treatment response. This is well illustrated in our previously described study of treatment in mild/moderate OSA. Although the nCPAP group had the best response in terms of symptoms, sleep disordered breathing parameters and even quality of life, the highest numbers of subjects in the nCPAP group refused to continue in their assigned treatment mode. Reasons given were financial constraints, dislike of the idea of using nCPAP, and side-effects. This highlights the multiple reasons that may affect patients' preference of a certain treatment mode, which may bear little correlation with the objective response to treatment.

In clinical practice, the current state of knowledge regarding the risks of untreated OSA, and the pros and cons of various modes of treatment should be made known to the patient. In most cases who are considered to meet the criteria for active interventional treatment, nCPAP would be recommended. For those who reject or fail non-invasive treatment, full disclosure of the risks and benefits, and the lack of good pre-treatment predictors of eventual outcome of other modalities such as oral appliances and surgery, are required.

Issues Pertinent to Asia

Recognition and diagnosis of OSA

Accurate diagnosis of sleep apnoea syndromes require sleep laboratory facilities for overnight sleep studies. Such facilities are expensive, due to the cost of the equipments as well as the technical manpower required. Despite such problems, sleep laboratories have been established in the past decade in Asia, including Hong Kong, Singapore, the mainland of China, Japan, Thailand, India, Taiwan and Korea. Most of these laboratories tend to be small, with two to four beds. The emergence of computerized diagnostic systems has facilitated the establishment of sleep laboratories since they are more user-friendly than previous polysomnogram set up. Computerized scoring, although not as accurate as manual scoring, does provide the diagnosis in many cases without the need of laborious manual scoring which is not affordable in many places.

Predisposing risk factors

Despite obesity being less of a problem in most Asian populations compared with Caucasian populations, it is still the major risk factor for having OSA as shown in the epidmiologic studies or case series from Asia. In some big cities in China, the prevalence of overweight is rapidly increasing (150). In Beijing, it has been reported that the average BMI of both children and adults in the community have increased compared with a decade ago (151). Hence, lifestyle modification for the prevention of obesity is an important measure that should be advocated for prevention and management of obesity-related diseases, of which OSA is only one.

Treatment options

Nasal CPAP is widely used in Asia, although these devices are usually imported from countries outside Asia. Some countries such as China have produced their own brands. The utility of nCPAP is partly influenced by the economic development and healthcare financing system in that locality. In most

Asian countries, patients have to pay for the devices themselves with no reimbursement from either national or personal health insurance, and this may pose a limiting factor to its use. The use of nCPAP in more remote rural areas may also be hampered by the availability of electricity supply.

It is important to provide adequate information regarding the potential risks and benefits of various modes of treatment, especially invasive ones, to the patient before treatment. There is a risk globally, certainly not the lesser in Asia, that certain modes of treatment, some of which are not without morbidity or even mortality, are applied liberally, outstripping the evidence-based efficacy. Objective documentation of response with sleep studies is essential in some of the less consistently efficacious modes of treatment.

Sleep medicine as a professional discipline

In most healthcare systems in Asia, sleep medicine is not a distinct entity. Disciplines that manage sleep apnoea patients are respiratory specialists, otolaryngologists, and psychiatrists, probably in descending order of frequency. Similarly, most sleep laboratories are run by these disciplines in the same order of frequency, while a minority offer integrated multidisciplinary programmes for patients with various sleep disorders.

The need for professional training in sleep medicine has increased substantially over the past decade. Previously, most physicians engaged in sleep medicine in Asia have been trained for varying periods in sleep centres with established expertise outside Asia, often through a combination of short intensive courses and clinical exposure. Subsequently, they accumulated experience through clinical practice. With the nidus of experienced personnel, more in-house basic training can now be provided. In places such as Hong Kong and Singapore, where there are structured systems for specialty accreditation, training in sleep related breathing disorders is a mandatory component for accreditation in specialties such as respiratory medicine.

The need for professional training for allied health staff, especially technical support staff in sleep laboratories, is now gaining recognition. However, there is no distinct career path for sleep technicians in most healthcare systems in Asia, and there is no established standards for qualifications. A growing number of staff who work in this area are seeking more formal training and accreditation offered by international bodies, such as the qualification of Registered Polysomnographic Technician.

In summary, sleep related breathing disorders is rapidly gaining recognition in both the professional and lay community in Asia. There is huge potential for epidemiologic, clinical and basic research and healthcare development in this field in Asia.

Acknowledgement

The authors thank Dr. K Chin for assistance in obtaining the published data on epidemiology in Japan.

References

1. Burwell CS, Robin ED, Whaley RD, Bickelmann AG. Extreme obesity associated with alveolar hypoventilation — a Pickwickian syndrome. *Am J Med* 1956; 21:811–8.
2. Broadbent WH. Cheyne-Stokes respiration in cerebral haemorrhage. *Lancet* 1877; 1:307–9.
3. Gastaut H, Tassinari CA, Duron B. Polygraphic study of diurnal and nocturnal (hypnic and respiratory) episodal manifestations of Pickwick syndrome. *Rev Neurol (Paris)* 1965; 112:568–79.
4. Gislason T, Almqvist M, Eriksson G, Taube A, Boman G. Prevalence of sleep apnea syndrome among Swedish men: an epidemiological study. *J Clin Epidemiol* 1988; 41:571–6.
5. Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993; 328:1230–5.
6. Olson LG, King MT, Hensley MJ, Saunders NA. A community study of snoring and sleep-disordered breathing: Prevalence. *Am J Respir Crit Care Med* 1995; 152:711–6.

7. Ohayon M, Guillemenault C, Priest RG, et al. Snoring and breathing pauses during sleep: telephone interview survey of a United Kingdom population sample. *BMJ* 1997; 314:860–3.
8. Bixler E, Vgontzas A, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men. *Am J Respir Crit Care Med* 1998; 157:144–8.
9. Bixler E, Vgontzas A, Lin H. Ten Have T, Rein J, Vela-Bueno A, Kales A. Prevalence of sleep-disordered breathing in women. *Am J Respir Crit Care Med* 2001; 163:608–13.
10. Duran J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *Am J Respir Crit Care Med* 2001; 163:685–9.
11. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea. A population health perspective. *Am J Resp Crit Care Med* 2002; 165:1217–39.
12. Ip MSM, Lam B, Lauder IJ, et al. A community study of sleep-disordered breathing in middle-aged Chinese men in Hong Kong. *Chest* 2001; 119:62–9.
13. Ip MSM, Lam B, Tang LCH, Lauder IJ, Ip TY, Lam WK. A community study of sleep-disordered breathing in middle-aged Chinese women in Hong Kong: prevalence and gender differences. *Chest* 2004, 1:127–34.
14. Hui DSC, Chan JKW, Ho ASS, et al. Prevalence of snoring and sleep-disordered breathing in a student population. *Chest* 1999; 116:1530–6.
15. Ng TP, Seow A and Tan WC. Prevalence of snoring and sleep breathing-related disorders in Chinese, Malay and Indian adults in Singapore. *Eur Respir J* 1998; 12:198–202.
16. Kayukawa Y, Shirakawa S, Hayakawa T, Imai M, Iwata N, Ozaki N, Ohta T. Habitual snoring in an outpatient population in Japan. *Psych and Clin Neurosciences* 2000; 54:385–92.
17. Ohta Y, Kawakami Y, Takishima T, Kuriyama T, Suetsugu S, Kuno K, Hishikawa Y, Togawa K, Katayama S, Okada T. Sleep disordered breathing in Japan — an overview. *Nihon Kyobu Shikkan Gakkai Zasshi* 1993; 31(Suppl):12–8.
18. Udwadia ZF, Doshi AV, Lonkar SG, Singh CI. Prevalence of sleep-disordered breathing and sleep apnea in middle-aged urban Indian men. *Am J Respir Crit Care Med* 2004; 169:168–73.
19. Guilleminault C, Eldridge FL, Simmons FB, Dement WC. Sleep apnea in eight children. *Pediatrics* 1976; 58:23–30.
20. Tang JP, Rosen CL, Larkin EK, DiFiore JM, Arnold JL, Surovec SA, Youngblut JM. Redline S. Identification of sleep-disordered breathing in children: variation with event definition. *Sleep* 2002: 25:72–9.
21. Marcus CL. Sleep-disordered breathing in children. *Am J Respir Crit Care Med* 2001; 164:16–30.
22. Anuntaseree W, Rookkapan K, Kuasirikul S, Thongsuksai P. Snoring and obstructive sleep apnea in Thai school-age children : prevalence and predisposing factors. *Pediatr Pulmonol* 2001; 32:222–7.
23. Mallory GB, Fiser DH, Jackson R. Sleep-associated breathing disorders in morbidly obese children and adolescents. *J Pediatr* 1989; 115:892–7.
24. Chay OM, Goh A, Abisheganaden J, et al. Obstructive sleep apnea syndrome in obese Singapore children. *Pediatric Pulmonology* 2000; 29:284–90.
25. Stradling JR, Crosby JH. Predictors and prevalence of obstructive sleep apnoea and snoring in 1001 middle aged men. *Thorax* 1991; 46:85–90.
26. Hoffstein V, Mateika S. Differences in abdominal and neck circumferences in patients with and without obstructive sleep apnoea. *Eur Respir J* 1992; 5:377–81.
27. Grunstein R, Wilcox I, Yang TS, Gould Y, Hedner J. Snoring and sleep apnoea in men: association with central obesity and hypertension. *Int J Obes Relat Metab Disord* 1993; 17:533–40.
28. Newman AB, Nieto FJ, Guidry J, Lind BK, Redline S, Shahar E, Oickering TG, Quan SF. Relation of sleep-disordered breathing to cardiovascular disease risk factors. *Am J Epidemiol* 2001; 154:50–9.
29. Young T, Sleep-disordered breathing in older adults: is it a condition distinct from that in middle-aged adults? *Sleep* 1996; 19:529–30.
30. Mortimore IL, Marshall I, Wraith PK, Sellar RJ. Douglas NJ. Neck and total body fat deposition in nonobese and obese patients with sleep apnea compared with that in control subjects. *Am J Respir Crit Care Med* 1998; 157:280–3.
31. Hudgel DW. Mechanisms of obstructive sleep apnea. *Chest* 1992; 101:541–9.
32. Lyberg T, Krogstad O, Djupesland G. Cephalometric analysis in patients with obstructive sleep apnea syndrome: I. Skeletal morphology. *J Laryngol Otol* 1989; 103:287–92.
33. Lyberg T, Krogstad O, Sjupesland G. Cephometric analysis in patients with obstructive sleep apnea: II. Soft

tissue morphology. *J Laryngol Otol* 1989; 103:293–7.
34. Ferguson KA, Takashi O, Lowe AA, et al. The relationship between obesity and craniofacial structure in obstructive sleep apnea. *Chest* 1995; 108:375–81.
35. Sakalibara H, Tong M. Matsushita K. Hirata M, Konishi Y, Suetsugu S. Cephalometric abnormalities in non-obese and obese patients with obstructive sleep apnoea. *Eur Respir J* 1999; 13:403–10.
36. International Diabetes Institute, World Health Organization. *The Asia-Pacific Perspective: Redefining Obesity and Its Treatment.* Melbourne, Australia: Health Communication Australia Pty Ltd, 2000; 15–21.
37. Peh WC, Ip MSM. Chu FS, Chung KF. Computed tomographic cephalometric analysis of Chinese patients with obstructive sleep spnoea. *Australas Radiol* 2000; 44:417–23.
38. Lam B. Ooi CGC, Peh WCG, Lauder I, Tsang KWT, Lam WK, Ip MSM. Computed tomographic evaluation of the role of craniofacial and upper airway morphology in obstructive sleep apnoea in Chinese. *Respir Med* 2004; 98:301–7.
39. Ong KC, Clerk AA. Comparison of the severity of sleep-disordered breathing in Asian and Caucasian patients seen at a sleep disorders center. *Respir Med* 1998; 92:843–8.
40. Li KK, Powell NB, Kushida C, Riley RW, Adornato B, Guilleminault C. A comparison of Asian and white patients with obstructive sleep apnea syndrome. *Laryngoscope* 1999; 109:1937–40.
41. Li KK, Kushida C, Powell NB, Riley RW, Guilleminault C. Obstructive sleep apnea syndrome: a comparison between far-east Asian and white men. *Laryngoscope* 2000; 110:1689–93.
42. Liu Y, Lowe AA, Zeng X, Fu M, Fleetham JA. Cephalometric comparisons between Chinese and Caucasian patients with obstructive sleep apnea. *Am J Orthod Dentofacial Orthop* 2000; 117:479–85.
43. Ip MSM, Tsang KWT, Lam WK, Lam B. Obstructive sleep apnea syndrome: an experience in Chinese adults in Hong Kong. *Chin Med J (Engl)* 1998; 111:257–60.
44. Chan JKW, Ho A, Leung RCC, Lai CKW. Sleep apnoea/hypopnoea syndrome. *HKMJ* 1996; 2:34–9.
45. Preutthipan A, Suwanjutha S, Chantarojanasiri T. Obstructive sleep apnea syndrome in Thai children diagnosed by polysomnography. *Southeast Asian J Trop Med Public Health* 1997; 28:62–8.
46. Redline S, Kump K, Tishler PV, Browner I, Ferrette V. Gender differences in sleep disordered breathing in a community-based sample. *Am J Respir Crit Care Med* 1994; 149:722–6.
47. Young T, Hutton R, Finn L, Badr S, Palta M. The gender bias in sleep apnea diagnosis — Are women missed because they have different symptoms? *Arch Intern Med* 1996; 156:2445–51.
48. Matsumoto AM, Sandblom RE, Schoene RB, Lee KA, Giblin EC, Pierson DJ, Bremner WJ. Testosterone replacement in hypogonadal men: effects on obstructive sleep apnoea, respiratory drives, and sleep. *Clin Endocrinol* 1985; 22:713–21.
49. Dancey DR, Hanly PJ, Soong C, Lee B, Hoffstein V. Impact of menopause on the prevalence and severity of sleep apnea. *Chest* 2001; 120:151–5.
50. Mohsenin V. Gender differences in the expression of sleep-disordered breathing — role of upper airway dimensions. *Chest* 2001; 120:1442–7.
51. Young T, Shahar E, Nieto FJ, et al. Predictors of sleep-disordered breathing in community-dwelling adults. *Arch Intern Med* 2002; 162:893–900.
52. Ancoli-Israel S, Kripke D, Klauber M, Mason W, Fell R, Kaplan O. Sleep-disordered breathing in community dwelling elderly. *Sleep* 1991; 14:486–95.
53. Malhotra A and White DP. Pathogenesis of obstructive sleep apnea syndrome. In: Breathing disorders in sleep. Eds. McNicholas WT and Phillipson EA. WB Saunders. 2002, 57–63.
54. Redline S, Tishler PV, Schluchter M, Aylor J, Clark K, Graham G. Risk factors for sleep-disordered breathing in children. *Am J Respir Crit Care Med* 1999; 159:1527–32.
55. Sanchez-Armengol A, Fuentes-Pradera M, Capote-gil F, Garcia-Diaz E, Cano-Gomez S, Carmona-Bernal C, Castillo-Gomez J. Sleep related breathing disorders in adolescents aged 12 to 16 years. *Chest* 2001; 119:1393–400.
56. Guilleminault C, Partinen M, Praud JP, Quera-Salva A, Powell N, Riley R. Morphometric facial changes and obstructive sleep apnea in adolescents. *J Paediatr* 1989; 114:997–9.
57. Mathur R, Douglas NJ. Family studies in patients with the sleep apnea-hypopnea syndrome. *Ann Intern Med* 1995; 122:174–8.
58. Redline S, Tishler PV, Tosteson TD, et al. The familial aggregation of obstructive sleep apnea. *Am J Respir Crit Care Med* 1995; 151:682–7.

59. Gould GA, Whyte KF, Rhind GB, Airlie MA, Catterall JR, Shapiro CM, et al. The sleep hypopnea syndrome. *Am Rev Respir Dis* 1988; 137:895–8.
60. Somers VK, Dyken ME, Clary MP. Abbound FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 1995: 96:1897–904.
61. Dimsdale JE, Coy T, Ancoli-Israel S, Clausen J. The effect of sleep apnea on plasma and urinary catecholamines. Sleep 1995; 18:377–81.
62. Weiss JW, Remsburg S, Garpestad E, Ringler J, Sparrow D, Parker JA. Hemodynamic consequences of obstructive sleep apnea. *Sleep* 1996; 19:388–97.
63. Marrone O, Bonsignore MR. Pulmonary haemodynamics in obstructive sleep apnoea. Sleep Medicine Reviews 2002; 6:175–93.
64. Baruzzi A, Riva R, Cirignotta F, et al. Atrial natriuretic peptide and catecholamines in obstructive sleep apnea syndrome. *Sleep* 1991; 14:83–6.
65. Sanner BM, Konermann M. Tepel M, Groetz J, Mummenhoff C, Zidek W. Platelet function in patients with sleep apnoea syndrome. *Eur Resp J* 2000; 16:648–52.
66. Chin K, Ohi M, Kita H, Noguchi T, Otsuka N, Tsuboi T, Mishima M, Kuno K. Effects of NCPAP therapy on fibrinogen levels in obstructive sleep apnea syndrome. *Am J Resp Crit Care Med* 1996; 153:1972–6.
67. Ip MSM, Lam B, Chan LY, et al. Circulating nitric oxide is suppressed in obstructive sleep apnea and is reversed by nCPAP. *Am J Respir Crit Care Med* 2000; 162:2166–71.
68. Duchna HW, Guilleminaut C, Stoohs RA, et al. Vascular reactivity in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* 2000; 161:187–91.
69. Barcelo A, Miralles C, Barbe F, Vila M, Pons S, Agusti AGN. Abnormal lipid peroxidation in patients with sleep apnea. *Eur Respir J* 2000; 16:644–7.
70. Ip MSM, Lam B, Ng MMT, Lam WK, Tsang KWT, Lam KSL. Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med* 2002; 165:670–6.
71. Schultz R, Mahmoudi S, Hattar K, Sibelius U, Olschewski H, Mayer K, Seeger W, Grimminger F. Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea. Impact of continuous positive airway pressure therapy. *Am J Respir Crit Care Med* 2000; 162:566–70.
72. Dyugovskaya L, Lavie P, Lavie L. Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients. *Am J Respir Crit Care Med* 2002; 165:934–9.
73. Ip MSM, Tse HF, Lam B, Tsang KWT, Lam WK. Endothelial function in obstructive sleep apnea and response to treatment. *Am J Respir Crit Care Med* 2004; 169:348–53.
74. Charoenpan P, Thanakitcharu S, Muntarbhorn K, Kunachak S, Boongird P, Likittanasombat K, Suwansathit W. Sleep apnea syndrome in Ramathidbodi Hospital: clinical and polysomnographic baseline data. Respirology 1999; 4:371–4.
75. Guilleminault C, van den Hoed J, Mitler MM. Clinical overview of the sleep apnea syndromes. In: *Sleep Apnea Syndromes.* Eds. Guilleminault C, Dement WC. New York: Liss 1978, 1–12.
76. American Sleep Disorders Association (ASDA). Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurment techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999; 22:667–89.
77. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991; 14:540–5.
78. Guilleminault C, Stoohs R, Clerk A, Cetel M, Maistros P. A cause of excessive daytime sleepiness. The upper airway resistance syndrome. *Chest* 1993; 104:781–7.
79. Guilleminault C, Kim Y,D, Palombini L, Li K, Powell N. Upper airway resistance syndrome and its treatment. *Sleep* 2000; 23(suppl 4):S197–200.
80. Ip MSM, Tan KCB, Ho CM, Lam KSL. Effect of Sandostatin LAR@ on sleep apnoea in acromegaly — correlation with computerized tomographic cephalometry and hormonal activity. *Clinical Endocrinology* 2001; 55:477–83
81. Guilleminault C, Pelayo R, Leger D, Clerk A, Bocian RCZ. Recognition of sleep-disordered breathing in children. *Pediatrics* 1996; 98:871–82.
82. Kim HC, Young TB, Matthews CG, Weber SM, Woodard AR, Palta M. Sleep-disordered breathing and neuropsychological deficits: a population-based study. *Am J Respir Crit Care Med* 1997; 156:1813–9.

83. Engleman H, Joffe D. Neuropsychological function in obstructive sleep apnoea. *Sleep Medicine Reviews* 1999; 3:59–78.
84. George CF, Boudreau AC, Smiley A. Simulated driving performance in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 1996: 154:175–81.
85. Douglas NJ. Systemic review of the efficacy of nasal CPAP. *Thorax* 1998; 53:414–5.
86. Teran-Santos J, Jimenez-Gomez A, Cordero-Guevara J and the cooperative group Burgos-Santander. The association between sleep apnea and the risk of traffic accidents. *N Eng J Med* 1999; 340:847–51.
87. Findley L, Smith C, Hooper J, Dineen M, Suratt PM. Treatment with nasal CPAP decreases automobile accidents in patients with sleep apnea. *Am J Respir Crit Care Med* 2000; 161:857–9.
88. Baldwin CM, Griffitch KA, Nieto FJ, O'Connor GT, Walsleben JA, Redline S. The association of sleep-disordered breathing and sleep symptoms with quality of life in the Sleep Heart Study. *Sleep* 2001; 24:96–105.
89. Finn L,Young T, Palta M, Fryback DG. Sleep-disordered breathing and self-reported general health status in the Wisconsin Sleep Cohort Study. *Sleep* 1998; 21(7):701–6.
90. Flemons WW, Reimer M. Development of a disease-specific health-related quality of life questionnaire for sleep apnea. *Am J Respir Crit Care Med* 1998; 158:494–503.
91. Mok WYW, Lam CLK, Lam B, Cheung MT, Yam L, Ip MSM. A Chinese version of the sleep apnea quality of life index was evaluated for reliability, validity and responsiveness. *J Clin Epidemiol* 2004; 57:470–8.
92. Douglas NJ, Engleman HM. Effects of CPAP on vigilance and related functions in patients with the sleep apnoea/hypopnea syndrome. *Sleep* 2000; 23(suppl 4):S147–9.
93. Leung RST, Bradley TD. Sleep apnea and cardiovascular disease. *Am J Respir Crit Care Med* 2001; 164:2147–65.
94. Lam B, Ip MSM. Obstructive sleep apnea and cardiovascular diseases. *Clin Pul Med* 2002; 9:171–6.
95. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease — Cross sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2001; 163:19–25.
96. Peker Y, Hedner J, Kraiczi H, et al. Respiratory disturbance index: an independent predictor of mortality in coronary artery disease. *Am J Respir Crit Care Med* 2000; 162:81–6.
97. Peker U, Hedner J, Norum J, Kraiczi H, Carlson J. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea — A 7-year follow up. *Am J Respir Crit Care Med* 2002; 166:159–65.
98. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl Med* 2000; 342:1378–84.
99. Ip M, Chung KF, Chan KN, et al. High prevalence of previously unrecognized obstructive sleep apnea in Chinese subjects with essential hypertension. *Lung* 1999; 7:391–400.
100. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnea syndrome as a risk factor for hypertension : population study. *Brit Med J* 2000; 320:479–82.
101. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. *JAMA* 2000; 283:1829–36.
102. Faccenda JF, Mackay TW, Boon NA, Douglas NJ. Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. *Am J Respir Crit Care Med* 2001; 163:344–8.
103. Peled N, Abinader EG, Pillar G, et al. Nocturnal ischemic events in patients with obstructive sleep apnea syndrome and ischemic heart disease. *J Am Coll Cardiol* 1999; 34:1744–9.
104. Tan KK, Khoo KL, Low JA, et al. Ethnicity, obstructive sleep apnoea and ischaemic heart disease. *Ann Acad Med Singapore* 1999; 28:214–6.
105. Fung JW, Li TS, Choy DK, Yip GW, Ko FW, Sanderson JE, Hui DS. Severe obstructive sleep apnea is associated with left ventricular diastolic dysfunction. *Chest* 2002; 121(2):422–9.
106. Niroumand M, Kuperstein R, Sasson Z, Hanly PJ. Impact of obstructive sleep apnea on left ventricular mass and diastolic function. *Am J Respir Crit Care Med* 2001; 163:1632–6.
107. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *Am J Respir Crit Care Med* 1999; 160:1101–6.
108. Malone S, Liu PP, Holloway R, Rutherford R, Xie A, Bradley TD. Obstructive sleep apnoea in patients with dilated cardiomyopathy: effects of continuous positive airway pressure. *Lancet* 1991; 338:1480–4.

109. Kaneko Y, Floras JS, Usui K, et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. *N Engl J Med* 2003; 348:1233–41.
110. Harbison J, O'Reilly P, McNicholas WT. Cardiac rhythm disturbances in the obstructive sleep apnea syndrome: effects of nasal continuous positive airway pressure therapy. *Chest* 2000; 118:591–5.
111. Bassetti C, Aldrich MS. Sleep apnea in acute cerebrovascular diseases: final report on 128 patients. *Sleep* 1999; 22:217–23.
112. Parra O, Arboix A, Bechich S, et al. Time course of sleep-related breathing disorders in first-ever stroke or transient ischemic attack. *Am J Respir Crit Care Med* 2000; 161:375–80.
113. Hui DSC, Choy DKL, Wong LKS, Ko FWS, Li TST, Woo J, Kay R. Prevalence of sleep-disordered breathing and continuous positive airway pressure compliance — results in Chinese patients with first-ever ischemic stroke. *Chest* 2002; 122:852–60.
114. Wessendorf TE, Wang YM, Thilmann AF, Sorgenfrei U, Konietzko N, Teschler H. Treatment of obstructive sleep apnoea with nasal continuous positive airway pressure in stroke. *Eur Respir J* 2001; 18:623–9.
115. Bradley TD, Rutherford R, Grossman RF, et al. Role of daytime hypoxemia in the pathogenesis of right heart failure in the obstructive sleep apnea syndrome. *Am Rev Respir Dis* 1985; 131:835–9.
116. Wilcox I, McNamara SG, Collins FL, Grunstein RR, Sullivan CE. "Syndrome Z": the interaction of sleep apnoea, vascular risk factors and heart disease. *Thorax* 1998; 53:S25–8.
117. Ip MSM, Lam KSL, Ho C, Tsang KWT, Law WK. Serum leptin and vascular risk factors in obstructive sleep apnea. *Chest* 2000; 118:580–6.
118. Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *Am J Respir Crit Care Med* 2002; 165:677–82.
119. Harsch IA, Schahin SP, Radespiel-Troger M, eta al. Continuous positive airways pressure treatment rapidly improves insulin sensitivity in patients with obstructive sleep apnea syndrome. *Am J Resp Crit Care Med* 2004; 169:156–62.
120. Douglas NJ. Home diagnosis of the obstructive sleep apnoea/hypopnoea syndrome. *Sleep Med Rev* 2003; 7:3–7.
121. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA* 2000; 284:3015–21.
122. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet* 1981; 1:862–5.
123. White J, Cates C, Wright J. Continuous positive airways pressure for obstructive sleep apnea. Cochrane Data Base System Rev 2002; (2) CD001106.
124. Teschler H, Berthon-Jones M, Thompson AB, Henkel A, Henry J, Konietzko N. Automated continuous positive airway pressure titration for obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* 1996; 154:734–40.
125. Meurice JC, Marc I, Series F. Efficacy of auto-CPAP in the treatment of obstructive sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 1996; 153:794–8.
126. McArdle N, Devereux G, Heidarnejad H, Engleman HM, Mackay TW, Douglas NJ. Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 1999; 159:1108–4.
127. Krieger J, Kurtz D, Petiau C, Sforza E, Trautmann D. Long-term compliance with CPAP therapy in obstructive sleep apnea patients and in snorers. *Sleep* 1996; 19:S136–43.
128. Chervin RD, Theut S, Bassetti C, Aldrich MS. Compliance with nasal CPAP can be improved by simple interventions. *Sleep* 1997; 20:284–9.
129. Hui DS, Chan KJ, Choy DK, Ko KW, Li TS, Leung RC, Lai CK. Effects of augmented continuous positive airway pressure education and support on compliance and outcome in a Chinese population. *Chest* 2000; 117:1410–6.
130. Sher AE. Upper airway surgery for obstructive sleep apnea. *Sleep Med Reviews* 2002; 6:195–212.
131. Fujita S, Conway W, Zorick F, et al. Surgical correction of anatomical abnormalities in obstructive sleep apnea syndrome: Uvulopalatopharyngoplasty. *Otolaryngol Head Neck Surg* 1981; 89:923–34.
132. Conradt R, Hochban W, Heitmann J, Brandenburg U, Cassel W, Penzel T, Peter JH. Sleep fragmentation and daytime vigilance in patients with OSA treated by surgical maxillomandibular advancement compared to CPAP. *J Sleep Res* 1998; 7:217–23.
133. Menn SJ, Loube DI, Morgan TD, Mitler MM, Berger JS, Erman MK. The mandibular repositioning device:

Role in the treatment of obstructive sleep apnea. *Sleep* 1996; 19:794–800.
134. Lindman R, Bondemark L. A review of oral devices in the treatment of habitual snoring and obstructive sleep apnoea. *Swed Dent* J 2001; 25:39–51.
135. Mehta A, Qian J, Petocz P, Darendelier MA, Cistulli PA. A randomized, controlled study of a mandibular advancement splint for obstructive sleep apnea. *Am J Respir Crit Care Med* 2001; 163:1457–61.
136. Gotsopoulos H, Chen C, Qian J, Cistulli PA. Oral appliance therapy improves symptoms in obstructive sleep apnea. *Am J Respir Crit Care Med* 2002; 166:743–8.
137. Ferguson KA, Ono T, Lowe AA, Keenan SP, Fleetham JA. A randomized crossover study of an oral appliance vs nasal-continuous positive airway pressure in the treatment of mild-moderate obstructive sleep apnea. *Chest* 1996; 109:1269–175.
138. Clark GT, Sohn JW, Hong CN. Treating obstructive sleep apnea and snoring: assessment of an anterior mandibular positioning device. *J Am Dent Assoc* 2000; 131:765–71.
139. Liu Y, Lowe AA, Fleetham JA, Park YC. Cephalometric and physiologic predictors of the efficacy of an adjustable oral appliance for treating obstructive sleep apnea. *Am J Orthod Dentofacial Orthop* 2001; 120:639–47.
140. Rose EC, Staats R, Virchow, Jr C, Jonas IE. Occlusal and skeletal effects of an oral appliance in the treatment of obstructive sleep apnea. *Chest* 2002; 122:871–7.
141. Fritsch KM, Iseli A, Russi EW, Bloch KE. Side effects of mandibular advancement devices for sleep apnea treatment. *Am J Respir Crit Care Med* 2001; 164:813–8.
142. American Sleep Disorders Association (ASDA). Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances. An American Sleep Disorders Association Report. *Sleep* 1995; 18:511–3.
143. Powell NB, Riley RW, Troell RJ, Li K, Blumen MB, Guilleminault C. Radiofrequency volumetric tissue reduction of the palate in subjects with sleep-disordered breathing. *Chest* 1998; 113:1163–74.
144. Powell NB, Riley RW, Guilleminault C. Radiofrequency tongue base reduction in sleep-disordered: A pilot study. *Otolaryngol Head Neck Surg* 1999; 120:656–64.
145. Li KK, Powell NB, Riley RW, Guilleminault C. Temperature-controlled radiofrequency tongue base reduction for sleep-disordered breathing: Long-term outcomes. *Otolaryngol Head Neck Surg* 2002; 127:230–4.
146. Powell NB, Zonato AI, Weaver EM, Li K, Troell R, Riley RW, Guilleminault C. Radiofrequency treatment of turbinate hypertrophy in subjects using continuous positive airway pressure: a randomized, double-blind, placebo-controlled clinical pilot trial. *Laryngoscope* 2001, 111:1783–90.
147. Pack AI, Black JE, Schwartz JR, Matheson JK. Modafinil as adjunct therapy for daytime sleepiness in obstructive sleep apnea. *Am J Respir Crit Care Med* 2001; 164:1675–81.
148. Loube D, Gay PC, Strohl KP, et al. Indications for positive airway pressure treatment for adult obstructive sleep apnea patients. A consensus statement. *Chest* 1999; 115:863–6.
149. Barbe F, Mayoralas LR, Duran J, et al. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness: a randomized, controlled trial. *Ann Intern Med* 2001; 134:1015–23.
150. Wu Y, Zhou B, Tao S, Wu X, Yang J, Li Y, Zhao L, Xie G. Prevalence of overweight and obesity in Chinese middle-aged populations: Current status and trend of developmemt. *Zhonghua Liu Xing Bing Xue Za Zhi* 2002; 23:11–5.
151. Ke You G, De Wei F. The magnitude and trends of under- and over-nutrition in Asian countries. *Biomed Environ Sci* 2001; 14:53–60.

Part II Infections

11 Community Acquired Pneumonia

Amita V Doshi and Zarir F Udwadia

Definition

Pneumonia is defined as an inflammation and consolidation of the lung due to an infectious agent. Pneumonia that develops outside the hospital is considered community acquired. Pneumonia developing 72 hours after admission to hospital is nosocomial, or hospital acquired. Pneumonitis is occasionally used as a synonym for pneumonia, particularly when inflammation of the lung has resulted from a non-infectious cause, such as a chemical or radiation injury.

Aetiology and Epidemiology

Pneumonia is a pulmonary infection caused by a variety of pathogens. Thus pneumonia is not a single disease but a group of specific infections, each with a different epidemiology, pathogenesis, clinical presentation and clinical course. The common organisms causing community acquired pneumonia are given in Table 1.

Pneumonia is a common disease, and attack rates are highest at the extremes of age. Pneumonia is the sixth leading cause of death in the United States and the UK (1). Records from the early part of the twentieth century show a steady decline in reported mortality from pneumonia that antedated the arrival of antibiotics. At around 1950, and coinciding with the beginning of the antibiotic era, mortality rate from pneumonia levelled off and remained fairly constant. This mortality rate is heavily weighted against the elderly, being 35 and 21 per 100,000 respectively for men and women aged 55–64 years compared with 775 and 572 per 100,000 for those aged 75–84 years (2).

Table 1. Common Organisms Causing Community Acquired Pneumonia

Microbial pathogens
Streptococcus pneumoniae
Mycoplasma pneumoniae
Haemophilus influenzae
Chlamydia pneumoniae
Legionella pneumophilia
Oral anaerobes
Moraxella catarrhalis
Staphylococcus aureus
Nocardia spp.
Viruses
Influenza virus
Cytomegalovirus
Respiratory syncytial virus
Measles virus
Varicella-zoster virus
Fungi
Histoplasma capsulatum
Coccidioides immitis
Blastomyces spp.
Mycobacterium tuberculosis
Chlamydia psittaci

This predilection of pneumonia for the elderly is not new and led William Osler in 1898 to describe the condition as "the friend of the aged".

The true incidence of pneumonia acquired in the community is unknown and undoubtedly many pneumonic episodes are treated by primary care physicians as 'lower respiratory tract infection' or 'bronchitis' without recourse to chest radiographs. Overall estimates of the annual incidence of community acquired pneumonia (CAP) vary from 2 and 12 cases per 1000, being highest in infants and in the elderly (3). Estimates from the USA run to 4 million cases annually with an attack rate of 12 per 1000 adults (4). The annual incidence of community acquired pneumonia in those aged over 65 years has been estimated to be between 25 and 44 cases per 1000, while the incidence in subjects of similar age living in institutions such as residential and nursing homes was two to eight times higher.

Pneumonia in children is a considerable problem especially in poorer countries. About 15 million children worldwide die each year as a consequence of acute respiratory infections, one third of them from pneumonia and 96% of these deaths occur in developing countries (5). Although there may be large differences in the incidence of childhood pneumonia between communities in rich and poor countries (6), the huge differences in mortality rates alluded to are more likely to be explained by the lack of effective antimicrobial therapy and other supportive measures (7).

The global burden of disease study showed that lower respiratory tract infections would be the fourth commonest cause of death globally in the year 2010 (8). In developing Asian countries the importance of pneumonia cannot be underestimated. In India, pneumonia and respiratory infections are by far the commonest cause of morbidity in children accounting for about 30% of all child mortality (9). Datta and his co-workers in New Delhi obtained data suggesting that 38% of urban child deaths in India were caused by pneumonia (10). This works out to a staggering 1.4 million child deaths / year caused by pneumonia in India alone.

Most series on the aetiology of CAP from the west have listed *Streptococcus pneumoniae* as the most commonly isolated pathogen. In recent studies, *S. pneumoniae* accounted for 55% of all pneumonia in Kauppinen's series of 125 cases from Finland (11), 29% of the 268 hospitalized patients from the Netherlands (12), and 43% of patients hospitalised in Lieberman's series from Israel (13). Other bacteria implicated commonly in most western series include *Haemophilius influenzae* and *Mycoplasma pneumoniae*. It is difficult to compare the data on aetiology from different studies because each study used different culture methods and serological tests. However Fine et al performed a meta-analysis on 127 published pneumonia studies from across the globe and confirmed that in a total of 33,148 patients, *S. pneumoniae* ranked first, being isolated in 4432 patients. *H. influenzae* and *Mycoplasma* ranked second and third in 833 and 507 patients respectively (14).

In many large series however, no pathogen can be identified despite comprehensive bacteriological and serological testing. Thus in Bohte's series, the aetiology of the pneumonia remained undiagnosed in 40% of the 268 hospitalized patients with CAP (12). In the meta-analysis by Fine, et al. no etiological agent could be identified in the overwhelming majority of patients (14). It is believed that most of these patients without a specific identifiable pathogen probably were infected by *S. pneumoniae*. It is also possible that there are additional agents that have not yet been identified or recognised.

Great interest has also focussed in the last decade on the prevalence of atypical pneumonia. This term was originally coined by Reinmann in 1938 to denote infection caused by a specific group of pathogens; *Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Legionella* (15). The relative prevalence of these atypical pathogens has been discussed in two large recent series. Mundy et al found a prevalence rate of only 8% out of 385 CAP patients hospitalised over a year in Johns Hopkins hospital (16). At the other end of the prevalence spectrum, Lieberman's study of 346 hospitalized patients showed that one or more of these 3 atypical pathogens could be identified in no less than 63% of patients (13).

Review of Asian studies on epidemiology of CAP

There is much less data on aetiology of pneumonia

from developing countries in general and Asia in particular. The high cost of routinely performing microbiological and serological tests in all patients with CAP is probably the main reason for this lack of data. Besides, as discussed earlier, the ability to determine the microbiological diagnosis of CAP remains poor even in the developed world. Furthermore, the cost effectiveness of making such an exact microbiological diagnosis has long been debated. At our hospital, a tertiary referral centre, a comprehensive pneumonia screen would cost Rs 6000 (i.e. around US$120). Spending this sum of money when the income per capita stands at Rs 11,300 would be an unjustifiable luxury outside of formal epidemiological studies. Empirical antibiotics started promptly, as per existing guidelines would be the preferred approach. However the Asian region is very diverse and existing British and American guidelines cannot and should not be blindly transposed to this region without some idea of local prevalences. A detailed review of the available epidemiology of microbial aetiology from the Asian region is therefore outlined here.

From Japan where pneumonia is the fourth leading cause of death, an elegant study by Ishida and colleagues from Okayama (17) investigated the aetiology of CAP in 318 adults hospitalized with pneumonia. This study was a prospective 3 year analysis and the authors went to great lengths (cultures, atypical serology, viral serology and bronchoscopic and trans-thoracic aspirate analysis where necessary) to establish a specific microbiological diagnosis for each of 326 episodes of CAP in their population. Causative pathogens were identified in 199 episodes (61%) with *Streptococcus pneumoniae* being the commonest pathogen (23%), followed by *H. influenzae* (7.4%), *Mycoplasma pneumoniae* (4.9%) and *Klebsiella pneumoniae* (4.3%). The most conspicuous difference from the West was the very low incidence of pneumonia due to *Legionella* species which accounted for only 2 episodes. Differences in the air-conditioning systems in Japanese homes were postulated to be responsible for this. A Japanese Working Party for Legionellosis headed by the Japanese Ministry of Health reviewed all confirmed *Legionella* cases in the country and found only 28 patients in an 11 year period (19).

Other smaller prospective studies from other parts of Japan (20) and Hong Kong (21) showed no major differences in the etiological agents causing pneumonia in these parts of Asia and the Western world. However, there are other Asian studies which do show important regional variations and these need to be highlighted here. A study by Tan et al from Singapore showed a microbiological spectrum quite different from that seen in the West (22). In this series of 57 cases admitted to an ICU for severe CAP over a 4 year period, the commonest pathogen encountered was *Burkholderia (Pseudomonas) pseudomallei* which accounted for 10 cases. *S. pneumoniae* was infrequently encountered being found in only 2 patients. The overall mortality in this series was 67% which is much higher than in most Western series. This was attributed to the high incidence of unrecognised *B. pseudomallei* infection in the region under study with its high accompanying mortality. In Thailand where melioidosis is endemic, a study by Boonsawat et al (23) showed *B. pseudomallei* was by far the commonest etiological agent for CAP in this region accounting for 62 of 113 cases (55%). The overall mortality in this series was also higher than reported from the West mainly due to bacteraemia and death in the *B. pseudomallei* group.

Tuberculosis presenting as an acute pneumonia should never be forgotten in the Asian continent. Osler used to teach that tuberculosis should be the sole differential diagnosis in any pneumonia that failed to resolve appropriately and this axiom holds true even today in much of Asia which bears the burden of most of the world's tuberculosis. In Tan's series (22), 16% of patients had tuberculosis. Another prospective study of 96 consecutive adults hospitalised with CAP in a University hospital in Singapore (24) found *Mycobacterium tuberculosis* to be the commonest pathogen, accounting for 21% of all cases of CAP, exceeding those caused by *S. pneumoniae* (12%) and *H. influenzae* (5.2%). A prospective study of CAP from Hong Kong (25) enrolled 90 adults hospitalised at the Prince of Wales Hospital and found that tuberculosis presented as CAP in 12% of patients. The authors noted that it could not be differentiated from other causes of pneumonia on clinical or radiological grounds. In this study pneumococcal infection was diagnosed in only 12% of patients. A Japanese study (26) of 188

cases of CAP found that *Mycobacterium tuberculosis* was the cause of 11% of all cases. These studies emphasise the role of pulmonary tuberculosis as an important cause of pneumonia in the Asian context.

A study from China (27) again pointed out interesting differences in aetiology of pneumonia with a much higher incidence of *Klebsiella, Pseudomonas* and *Staphylococcal* pneumonia than would normally be seen in the West. A study from Taiwan (28) similarly showed the commonest pathogen to be *K. pneumoniae* and not *S. pneumoniae*.

Turning to atypical pneumonia, there is a fair amount of data on the prevalence of *Legionella, Mycoplasma* and *Chlamydia* pneumonia from the Asian region. Whilst *Legionella* pneumonia is believed to be uncommon in Japan as discussed earlier, Vijayasingam found this pathogen to be endemic in Singapore accounting for 14% of samples tested serologically (28). A study by Chaudhry (30) showed that *Legionella* was an important pathogen in India accounting for 15% of all patients hospitalized with CAP. In contrast *Legionella* was a rare cause of pneumonia in Taiwan with a presumptive disease in 5% and confirmed disease in none of the 180 patients with atypical pneumonia (31). *Mycoplasma pneumoniae* is also being reported with increasing frequency from the Asian region with a study from Vellore in South India revealing it to account for a fifth of adults with CAP (32). Another study from New Delhi in Northern India showed that 35% of patients had atypical pneumonia caused by *Mycoplasma pneumoniae* (33). When appropriate serological tests are used even *Chlamydia pneumoniae* is well represented in Asian series. A study from the National Defense centre in Taipei, Taiwan showed *Chlamydia* accounted for 11% of all cases of CAP (34). In Japan, 7.9% of 214 patients with CAP satisfied the criteria for diagnosis of acute infection due to *Chlamydia,* the third leading cause for CAP following *S. pneumoniae* (21.5%) and *H. influenzae* (8.4%) (35). Such findings underpin the importance of including antibiotics with proven activity against atypical organisms in the initial empirical antibiotic therapy for CAP in these parts of Asia.

Hospital-based surveillance of community-acquired infections can provide important data for health-policy decisions. A prospective multicentre hospital surveillance survey of *S. pneumoniae* disease from 6 major centres in India yielded important data (36). The commonest pneumococcal serotype was Type 1, which accounted for 25% of Indian invasive serotypes. Similar studies from neighbouring Pakistan (37), and Bangladesh (38), have revealed different serotypes in these countries and regional variations must be taken into account when vaccine formulations are recommended. Penicillin resistance was not encountered in the isolates in this Indian series but close surveillance is needed as neighbouring Pakistan reported that 9% of their invasive isolates were penicillin resistant. By contrast penicillin resistance is clearly an important problem in other parts of Asia such as Japan. A study from Nagasaki noted that 50% of 49 cases of pneumococcal pneumonia were caused by penicillin resistant pneumococci (39) while intermediate and high grade resistance to penicillin were found in 22% and 6 % of isolates in Kyoto (40). The importance of such studies cannot be overemphasized. Vigilance and surveillance will go a long way in countering the spread of antibiotic resistance.

We would like to share the results of our study (41,42) where 100 patients with CAP admitted to two hospitals in Bombay (1 private and 1 public hospital) over a period of one and a half years were prospectively studied. Despite a thorough search for the etiologic agent, no organism could be identified in 44% of the patients. *Strep pneumoniae* was the commonest organism accounting for CAP in 22% of patients followed by *Chlamydia* in 14% and *Haemophilus* in 9%. Atypical organisms accounted for 19% of all cases. TB was an important cause of CAP accounting for 7% of the patients. These results are interesting as they demonstrate regional variations in etiologic agents causing CAP in India. A higher incidence of *Chlamydia* (14%) was seen in Bombay as compared to Delhi and Vellore but the incidence of *Mycoplasma* in Bombay was only 3% (as against 35% in Delhi (33) and 20% in Vellore, South India (32)) and that of *Legionella* was 2% (as against 15% in Delhi (30)).

Thus, to conclude this section, a review of studies on the aetiology and epidemiology of CAP from Asia reveals similarities and differences from Western series. Such studies are vital to our understanding of local patterns in different parts

of the vast Asian continent. Antibiotic guidelines can then be rationalized for different regions.

Clinical Manifestations

Community acquired pneumonia has traditionally been thought to present as either of two syndromes: the typical presentation and the atypical presentation. Although recent data suggest that these two syndromes may be less distinct than was once thought, the characteristics of the clinical presentation may nevertheless have some diagnostic value.

The **"typical" pneumonia syndrome** is characterized by the sudden onset of fever, chills, cough and pleuritic chest pain. The cough is usually productive, may be rusty in colour and sometimes frankly bloody. In case of an anaerobic infection it may have a foul odour. Fever is usually present, but some patients may be hypothermic (a poor prognostic sign) and some (20%) are afebrile at the time of presentation. On physical examination, crackles are heard over the affected area of the lung, and physical findings of consolidation (dullness to percussion, increased tactile, and vocal fremitus, whispering pectoriloqui and bronchial breath sounds) are present in about 20% of patients. A pleural friction rub is heard in about 10% of cases. The typical pneumonia syndrome is usually caused by the most common bacterial pathogen in CAP, *S. pneumoniae*, but can also be due to other bacterial pathogens, such as *H. influenzae, Staphylococcus aureus* and mixed aerobic and anaerobic components of the oral flora. Elderly patients usually present with fewer symptoms than younger patients. An interesting study on pneumonia in elderly in Bangkok, Thailand (43) showed that pneumonia in the elderly might present with no fever, no cough, no signs of parenchymal infiltration but significant mental changes.

The **"atypical" pneumonia syndrome** is characterized by a more gradual onset, a dry cough, a prominence of extrapulmonary symptoms (such as headache, myalgias, fatigue, sore throat, nausea, vomiting and diarrhoea) and abnormalities on chest radiographs despite minimal signs of pulmonary involvement (other than crackles) on physical examination. Atypical pneumonia is classically produced by *Mycoplasma, Legionella* and *Chlamydia* and the less frequently encountered pathogens *Coxiella burnetii, Francisella tularensis, H. capsulatum* and *Coccidioides immitis*. *Mycoplasma* pneumonia may be complicated by erythema multiforme, haemolytic anemia, bullous myringitis, encephalitis and transverse myelitis. *Legionella* pneumonia is frequently associated with deterioration in mental status, renal and hepatic abnormalities and marked hyponatraemia. Pneumonia due to *Histoplasma capsulatum* and *C. immitis* is often accompanied by erythema nodosum. In *Chlamydia* pneumonia, sore throat, hoarseness and wheezing are relatively common. A clinical study of *Mycoplasma* pneumonia by Hwang and colleagues in China (44) showed that all patients with *Mycoplasma* pneumonia complained of fever and cough; 63% had dry cough and 37% had sputum production. Upper respiratory tract complaints such as rhinorrhoea, sore throat or ear ache were seen in 57%. 55% of patients had gastrointestinal symptoms of anorexia, nausea, vomiting and diarrhoea. Other complaints included myalgia/arthralgia (29%), headache (30%), general malaise (32%), dyspnoea (17%) and chest pain (20%).

Certain **viruses** produce pneumonia that is usually characterized by an atypical presentation i.e. chills, fever, dry cough and predominance of extrapulmonary symptoms. Primary viral pneumonia can be caused by influenza virus (usually as part of a community outbreak in winter), respiratory syncytial virus (in children and immunocompromised individuals), measles, varicella zoster (accompanied by the characteristic rash), and cytomegalovirus (in patients compromised by HIV infection or immunosupressive drugs). The latest addition is the Coronavirus which caused the recent outbreak of severe acute respiratory syndrome (SAR) (see Chapter 18). Furthermore, influenza, measles and varicella can predispose to secondary bacterial pneumonia as a result of destruction of the mucociliary barrier of the airways.

Tuberculosis typically presents with fever, night sweats, cough and shortness of breath and sometimes pleuritic chest pain and blood streaked sputum. Several weeks usually elapse before the patient seeks medical attention because of the gradual worsening of these symptoms, by which

time he or she will have lost considerable weight. Sometimes a more acute tuberculous pneumonia may occur as discussed under "aetiology". As Chan and co-authors stressed in their study of aetiology of CAP in Hong Kong (25), pulmonary tuberculosis could be difficult to differentiate from other causes of acute pneumonia on clinical or radiological grounds.

Table 2 gives a partial list of clues to the cause of pneumonia that may be obtained from the history and physical examination.

Table 2. Clues to the Aetiology of Pneumonia from the History and Physical Examination

Feature	*Organism*
Environmental	
Exposure to contaminated air-conditioning cooling towers, recent travel associated with a stay in hotel, exposure to a grocery store mist machine, visit or recent stay in hospital with contaminated potable water	*Legionella pneumophilia*
Outbreak of pneumonia in shelters for homeless men, jails, military training camps	*S. pneumoniae* *M. Tuberculosis* *Chlamydia pneumoniae*
Exposure to contaminated bat caves, excavation in endemic areas	*Histoplasma capsulatum*
Animal contact	
Exposure to infected parturient cats, cattle, sheep or goats	*Coxiella burnetii*
Exposure to turkeys, chickens, ducks or birds	*Chlamydia psittaci*
Travel history	
Travel to Thailand or other countries in Southeast Asia	*Burkholderia(Pseudomonas) pseudomallei (melioidosis)*
Pneumonia in immigrants from Asia or India	*M. tuberculosis*
Occupational history	
Pneumonia in health-care workers in a large city with patients infected with HIV	*M. tuberculosis*
Host factors	
Diabetic ketoacidosis	*S. pneumoniae* *Staphylococcus aureus*
Alcoholism	*S. pneumoniae* *Klebsiella pneumoniae* *S. aureus*
COPD	*S. pneumoniae* *H. influenzae* *Morexella catarrhalis*
Physical findings	
Periodontal disease with foul-smelling sputum	Anaerobes
Absent gag reflex, altered level of consciousness, or a recent seizure	Oral aerobic and anaerobic bacteria due to aspiration
Erythema multiforme	*Mycoplasma*
Erythema nodosum	*M. tuberculosis* *Chlamydia pneumoniae*

Investigations

Chest radiography

An abnormal chest radiograph is a *sine qua non* for pneumonia, providing an immediate visual impression of the extent of involvement. It can confirm the presence and location of pulmonary infiltrate; assess the extent of the pulmonary infection; detect pleural involvement, pulmonary cavitation or hilar adenopathy; and gauge the response to antimicrobial therapy. However, chest radiographs may be normal when the patient is unable to mount an inflammatory response (e.g. in agranulocytosis) or is in the early stage of an infiltrative process (e.g. in hematogenous *S. aureus* pneumonia or in *Pneumocystis* pneumonia associated with AIDS).

It is emphasized that almost every causative agent can produce a wide variety of different radiographic appearances, so that it is unwise to assume that a confluent lobar pneumonia is bound to be caused by *S. pneumoniae* despite the high probability. Similarly, cavitation need not be due to *S. aureus* but may occur in necrotizing Gram negative pneumonias, such as those caused by *Klebsiella pneumoniae*, or pneumonia arising from the aspiration of anaerobic bacteria or even from infection with *S. pneumoniae* when serotype 3 is involved. A study from Shizuoka Hospital, Japan (45) attempted to correlate radiological findings with etiological agents. Whilst pleural fluid accumulation and cavitation occurred in tuberculosis mimicking an acute pneumonia, lobar, segmental and lobular shadows did not correlate with any particular pathogen. Thus whilst certain radiographic patterns are more commonly associated with some microbial agents than with others, it is difficult to predict the aetiology of pneumonia from the radiological appearance.

Radiographic response to treatment usually lags behind clinical improvement and pneumococcal pneumonia (especially bacteraemic forms) may take 6 weeks to clear on the chest film (46). *S. aureus* and *Legionella* are amongst the slower resolving pneumonia. Age is the single most important predictor of the speed of resolution. In elderly patients, pneumonia resolves at much slower rate than in younger patient. Persistent, recurrent, worsening shadowing may indicate either inappropriate treatment or bronchial obstruction by a foreign body, or more commonly, tumour, particularly in patients over the age of 60 years. At times, computed tomography may be especially useful in distinguishing different processes, e.g. pleural effusion versus underlying pulmonary consolidation, pulmonary abscess versus empyema with an air-fluid level.

Laboratory identification of infecting organisms

Laboratory investigation of a case of pneumonia should not delay treatment with antibiotics, the choice of which is based on the knowledge of the likely pathogens and an estimation of the severity of the infection. The lengths to which the clinician is prepared to investigate the microbiological cause of a case of pneumonia is likely to be determined by the severity of the illness at presentation, its response to initial treatment and the laboratory facilities available.

Sputum microscopy and culture

In poorer, developing Asian countries, sputum examination is cheap, easy to perform and often the mainstay of microbial diagnosis of CAP. Simple Gram's staining of sputum which can be performed even at bedside will give an immediate and accurate indication of the pathogen involved if large numbers of any one pathogen are seen. According to Macfarlane, such positive Gram's stains have been shown to have a high specificity in the case of pneumococcal and staphylococcal pneumonia though the sensitivity is low (47).

A few practical points about sputum testing need to be laboured here as they are particularly relevant in developing countries. First and foremost, one must ensure that the sample sent to the laboratory is truly expectorated sputum and not saliva. The presence of more than 25 squamous cells per high-power field indicates a sputum sample of poor quality and precious resources may be saved by requesting a repeat sample instead of proceeding with sputum culture (48). The second problem is that lower respiratory secretions are often contaminated by upper respiratory

commensals during expectoration and isolation of a potential pathogen may not reflect what is actually occurring in the lungs. A laboratory trick to counter this is to wash or dilute the sputum so that only bacteria present in large numbers will grow on culture. The third problem is that even a single dose of antibiotic can interfere with the culture of common pathogens such as *S. pneumoniae* and *H. influenzae*. This is almost certainly the reason why so many hospital based series of CAP from Asia and the West have no pathogen isolated in the majority of patients despite a careful search. The majority of patients hospitalized for pneumonia have already received one or more courses of antibiotics prior to hospitalization resulting in the poor sputum yield. Finally, in as many as a quarter of all patients with pneumonia, sputum is not produced. All these problems conspire to make sputum culture a relatively insensitive method for diagnosis of bacterial pneumonia. Less than 50% of patients with bacteraemic pneumococcal pneumonia will have pneumococci isolated from their sputum.

A study from a public hospital (49) in a poor part of India showed that attention to details with bedside innoculation and dilution of the sputum specimen resulted in a higher yield (34%) of *S. pneumoniae*. If the sputum sample reached the laboratory late or did not undergo dilution, the yield of *S. pneumoniae* and Gram-positive cocci was significantly reduced with higher numbers of Gram-negative rods indicating their overgrowth.

Since tuberculosis not uncommonly mimics pneumonia in Asian countries, it is worth doing Acid Fast Bacilli staining on sputum samples. It is the policy of our microbiology laboratory to perform Ziehl-Nielsen staining on all sputum samples sent to the laboratory for routine bacterial culture. This has often helped clinicians to make an early diagnosis of tuberculosis even when this has not been initially suspected.

Certain bacteria that can cause CAP are notoriously difficult to culture. *Legionella* is one such example and whilst occasional isolation on charcoal yeast extract medium may be possible, in the Asian context, such a procedure would be expensive and time consuming and perhaps best performed in only 1 or 2 central reference laboratories in each country.

Sputum immunodetection

The diagnostic rate of pneumococcal pneumonia can be markedly increased by testing for pneumococcal polysaccharide capsular antigen in countercurrent immunoelectrophoresis or latex agglutination. This antigen can also be detected in blood and urine and an advantage of this test is that it is not affected by prior use of antibiotics. The sputum antigen is positive in about 80% of pneumococcal pneumonias whilst urine and serum are positive in 36–45% and 9–23% of cases respectively. The antigen remains detectable for 7–14 days after bacteraemic pneumococcal pneumonia. A study from Shanghai compared pneumococcal antigen detection by the coagglutination technique with sputum Gram stain and sputum culture (50). The positive yield was 46% by the latex coaggutination test, 27% by Gram staining and 17% by culture.

Other pathogens that may be detected by sputum immunodetection include *Legionella pneumophilia, Chlamydia pneumoniae* and *Pneumocystis carinii*.

Blood culture

In the initial evaluation of a patient with pneumonia, at least two blood samples for culture should be obtained from different venepuncture sites. A positive culture may be obtained in 10–30% of cases, the higher percentage applying to pneumococcal pneumonia. This provides a specific diagnosis of the pathogen, and is also of prognostic importance because bacteraemia is an indicator of more severe infection.

Pleural fluid

If a pleural effusion is present in a patient suspected of pneumonia, it should always be examined to exclude an empyema. Gram's and acid fast stains may be useful. The culture of pathogenic organisms is always significant and valuable. The fluid is always an exudate and some biochemical findings (low pH, high lactate dehydrogenase, low glucose) have been used to predict which parapneumonic effusions may develop into empyemas (51).

Standard acute and convalescent serological testing

The usual serological tests involve the measurement of complement-fixing antibody levels in the blood, although more sensitive Enzyme-linked immunosorbent assay (ELISA) and immunofluoroscent tests are beginning to replace them. Serological tests may be used for infections caused by *Mycoplasma pneumoniae, Chlamydia spp., Coxiella burnetii* and *Legionella* spp. By its nature, the complement-fixing test (CFT) is seldom of immediate value and when positive usually provides diagnostic information retrospectively, as two paired sera are required in order to demonstrate a fourfold rise in convalscent-phase antibody titre. It is usual to wait about 14 days between the two samples, although in some infections, such as *Mycoplasma*, a rise may be detected earlier; whilst in others, notably *Legionella*, the rise may take several weeks. The problem with paired sampling is that the results are likely to come too late to be of clinical relevance.

Invasive methods for obtaining respiratory secretions

Other methods for obtaining respiratory secretions are more invasive and may be associated with morbidity. Their use is therefore confined to patients who are severely ill and in whom it is considered important to identify the organism rather than relying on an initial empirical antimicrobial approach or in whom such approach has already been tried and failed.

Transtracheal aspiration

Transtracheal aspiration may be carried out in patients who are unable to produce sputum or in whom the response to the chosen antibiotic is poor. Although the sensitivity of the procedure is high (approaching 90%), the specificity is low. It is assumed that the tracheobronchial tree below the larynx is sterile, but false-positive results occur in patients with chronic lung disease due to tracheobronchial colonization. The technique has also been applied when anaerobic lung infection is suspected. A group from Japan performed this technique on 387 patients over an 8 year period from 1990–1998 and isolated anaerobes in 20% of patients with CAP (52). Popular several decades ago, transtracheal aspiration is rarely carried out today.

Percutaneus transthoracic needle puncture

This procedure employs a small gauge needle that is advanced into the area of pulmonary consolidation with computed tomographic guidance. It requires that the patients cooperate, have good hemostasis and be able to tolerate a possible associated pulmonary haemorrhage or pneumothorax. Patients on mechanical ventilation cannot undergo lung puncture because of the high incidence of complicating pneumothorax. The diagnostic yield from this procedure ranges from 33 to 85%.

Fibreoptic bronchoscopy

Fibreoptic bronchoscopy is usually safe, well tolerated and has become the standard invasive procedure used to obtain lower respiratory tract secretion from seriously ill or immunocompromised patients with complex or progressive pneumonia and in patients with ventilator associated pneumonia. It picks up oropharyngeal contaminants unless special precautions are taken using a protected specimen brush (PSB). The PSB can be combined with or used separately from bronchoalveolar lavage (BAL) to obtain quantitative cultures, usually on ventilated patients in an intensive care setting (53). The diagnostic threshold for pneumonia, rather than airway colonization, has been reported as 10^3cfu/ml in respiratory secretions obtained by PSB. On the other hand, BAL subtends a wide area of tissue and lung secretions are diluted between 10 and 100 fold, so that when interpreting results, a threshold of 10^4 cfu/ml may be taken. By combining PSB and BAL and by counting intracellular organisms, Chastre and colleagues (54) claimed a sensitivity of 100% (compared with 86% for either technique alone) and a specificity of 96%. Bronchoscopy can therefore provide clues in the difficult case when other methods have failed, even when the picture has been clouded by almost inevitable prior use of antimicrobials. Infection with less usual organisms, such as

Legionalle spp, *M. tuberculosis, P. carinii*, other fungi or anaerobes may also be detected in such cases as well as the occasional unsuspected predisposing cause like the mechanical narrowing of a bronchus. On the other hand, negative results have to be treated with caution in patients already treated with antimicrobial therapy, since this may be due to antibiotic suppression of the organisms or the infiltrate was of non-infective cause, as may be so in over 40% of cases (55).

In a study in China by Zhong and colleagues (56), secretions from the lower respiratory tract were taken for bacterial culture using Japanese made single-sheath catheter brush (SSC) via fibreoptic bronchoscope in 53 cases with CAP. The results showed that bacteria were isolated in 42 out of 53 patients, the organism being pathogenic in 39 out of 53 (73.5%). Among the bacteria isolated from the 42 cases, Gram-negative bacilli accounted for the highest rate of 36% and pneumococcus the next of 31%. Only 3 cases yielded contamination, and SSC was therefore suggested to be convenient and practical.

Lung biopsies

Transbronchial, thoracoscopic or open lung biopsies tend to be reserved for diffuse pulmonary infiltrates of undetermined cause and in the context of suspected infection, and are occasionally carried out in sick immunocompromised hosts in whom the presence of an unusual opportunistic pathogen is likely and less invasive diagnostic approaches such as BAL have failed to identify the cause (57).

Newer microbiological techniques

The tantalizing promise of new methods for the rapid detection and identification of specific organisms using molecular genetic technique seems close to being fulfilled but for most laboratories and clinicians, it has yet to be delivered, largely because of financial constraints. DNA probes have been developed for characterizing target organisms and minute amounts of target DNA can be amplified by the polymerase chain reaction (PCR) to improve the chance of their detection by the DNA probe so that the sensitivity of the test is increased. A PCR assay has recently been tested on the serum of patients with bacteraemic pneumococcal pneumonia and was found to have a sensitivity of 100% and specificiy of 94% (58). Similar probes have been, or are being developed for a wide range of organisms including *Legionella pneumophila, Mycoplasma pneumoniae, Neisseria meningitidis, Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides immitis, Mycobacterium tuberculosis, Mycobacterium intracellulare* and *Mycobacterium kansasi* (59). Thus the identification of mycobacterial infection may take hours rather than weeks, although the organism still requires culture in order to allow antimicrobial sensitivities to be confirmed. These tests are generally outside the reach of all but a few referral laboratories in developing Asian countries.

In a study done by Honda and colleagues in Japan (60), serologic data was compared with data obtained by capillary PCR to establish the efficacy of capillary PCR for the determination of *Mycoplasma* infection in samples obtained from throat swabs, BAL fluid and sputum of patients with *Mycoplasma* pneumonia. It was found that capillary PCR had a sensitivity of 80.6%.

Arterial oxygen saturation and blood gas analysis

Oxygen saturation as a screen followed by arterial blood gas analysis when desaturation is evident should be carried out in order that hypoxaemia may be corrected. This also helps to gauge the severity of the infection. The need for an inspired oxygen of 35% or more to maintain the oxygen saturation above 90% implies severe pneumonia; so does a PaO_2 of 60 mmHg or less or a $PaCO_2$ of 50 mm Hg or more. These findings signal that assisted ventilation may become necessary.

Other laboratory findings

The white cell count is frequently raised in bacterial pneumonia, with neutrophilia. Elderly patients are not always able to mount such a response. Sometimes when sepsis is overwhelming there may be leucopaenia. A lymphocytosis may occur in viral infections or in those due to

"atypical" organisms. The white cell count may be normal in viral pneumonia.

Numerous nonspecific biochemical abnormalities have been noted, such as a raised blood urea, bilirubin. transaminases and alkaline phosphatase. Hyponatremia due to inappropriate antidiuretic hormone secretion may occur in *Legionella* infection. The presence of cold agglutinins in patient's citrated blood is seen in over 50% of cases of *Mycoplasma pneumoniae*.

Urinalysis may detect small amounts of protein and both red and white blood cells may be seen on microscopy. As mentioned above, pneumococcal antigen may be detected in urine more frequently than in blood but less frequently than in sputum. *Legionella* antigen may also be detected in urine by ELISA, indicating *L. pneumophilia* type 1 infection (thought to account for about 80% of human legionellosis), and this test is well worth doing for a rapid answer in severely unwell patients with pneumonia.

Management

Whilst Western countries have clear guidelines (61,62,63) on the appropriate initial antibiotics for a patient with CAP, no similar guidelines are available for Asia. Indeed, because of the vastness and disparity of different parts of this continent, no guidelines could hope to be all-encompassing. Hence, as stressed in the section on "aetiology", the local epidemiology must be first established by carefully and prospectively performed regional studies. Thus, based on the firm knowledge of local epidemiology of microbial organisms and antibiotic sensitivity, patient population profile and economic issues, local guidelines can be individualized for different Asian countries. Blindly transposing Western guidelines to Asian countries would clearly be inappropriate. Worse still, however, would be empirical treatment given without knowledge or consideration of local epidemiological conditions. Furthermore, a mechanism for regular review at a regional level should ideally be in place to take account of changing patterns of disease such as the reduced susceptibility of common organisms to standard antibiotics and emergence of new or previously unknown pathogens. Such a review by Lim from Singapore (64) noted that there had been a 60-fold increase in the incidence of penicillin resistance in *S. pneumoniae* between 1987 and 1997. The review also noted a small increase in the number of cases of Legionnaire's disease and the marked increase in the incidence of mellioidosis. Similar reviews from Thailand (23) show that mellioidosis has become the commonest cause of CAP in this region.

When a patient with pneumonia first presents to a general practitioner or a hospital, the cause of pneumonia is generally not known. Whilst sputum and blood culture should be collected at the outset, treatment must start empirically on what is perforce empirical grounds. The first decision the doctor has to make is: "Can this patient with CAP be successfully managed as an outpatient or should he be hospitalized?" The second and even more important question is "What should my empirical choice of antibiotic be?"

Outpatient versus hospital treatment of pneumonia

The majority of patients presenting with CAP can be treated with oral antibiotics and managed successfully as outpatients. The physician making this decision must be confident that this patient is not so ill that the parenteral route is mandatory. In addition such a patient must be relatively non-toxic, have limited disease, should not be significantly immunocompromised and likely infected by an organism generally sensitive to an oral regimen. Table 3 lists 10 criteria that are very useful in deciding whether or not to hospitalize a patient with CAP. In our opinion any patient meeting any one of these criteria is more safely managed in hospital as such a patient is at an increased risk of death from pneumonia.

OPD-treatment. For patients treated in the community in poorer countries, cost is often an important deciding factor. Cheap but reasonably effective antibiotic choices in these poorer parts of Asia would include oral amoxycilllin or ampicillin, co-trimoxazole or a tetracycline derivative. A recent trial from one of the poorest area of the developing world showed that co-trimoxazole was cheap, and yet as effective as

Table 3. Criteria for Hospitalization/ Markers of Severity

1)	Elderly patient (> 65 years of age).
2)	Prior hospitalization for community acquired pneumonia in < 1 year.
3)	Significant comorbidity (e.g. kidney, heart, liver or lung disease; diabetes mellitus; alcohol abuse; neoplasm; immunosuppression)
4)	White blood cell count < 4 X 10^9/L or > 30 X 10^9/L.
5)	S. aureus, gram-negative bacilli or anaerobes as the suspected cause of pneumonia.
6)	Suppurative complications (e.g. empyema, arthritis, meningitis, endocarditis.
7)	Failure of outpatient management.
8)	Inability to take oral medication.
9)	Tachypnea (> 30/min); tachycardia (> 140/ min); temperature > 38.3°C (101°F); hypotension (< 90 mmHg systolic) (< 12 kPa systolic); hypoxaemia (arterial Po_2 < 60 mm Hg) (< 8 kPa systolic); blood urea ≥ 7 mmol/L; acute alteration of mental status.
10)	Chest radiograph with multilobar or spreading shadows.

more expensive antibiotics in 134 Gambian children with pneumonia (65). It is important that general practitioner and rural health care providers are not seduced by the latest (and generally most costly) antibiotics. Responsible prescribing by this group of front line physicians will go a long way in preventing the emergence of antibiotic resistance. The impact that a rational antibiotic policy can make in reducing pneumonia mortality, even in the poorest part of rural India, can be seen from an inspiring study by Bang et al (66). This was a community based intervention trial to reduce childhood mortality from pneumonia in 6176 children in 58 villages in Gadchiroli, India. These interventions included mass education about childhood pneumonia and case management of pneumonia by trained paramedics and village health workers who were taught to recognize childhood pneumonia and treat it with co-trimoxazole. After a year of intervention, pneumonia specific childhood mortality was significantly reduced in the intervention area as compared to a control area of 44 villages (8.1 vs 17.5 deaths per 1000 children under 5 years). The difference in infant mortality (89 vs 121 per 1000) and total under-5 mortality (28.5 vs 40.7 per 1000) were highly significant. The cost of co-trimoxazole was US$0.025 per child per year. This worked out to a mere $2.64 per child saved.

Another antibiotic which is a reasonable first choice and relatively inexpensive is erythromycin. In many Asian regions where atypical pathogens are frequently encountered, this would be an appropriate initial choice. A study from Taiwan showed it to be as effective as the more expensive (but better tolerated) clarithromycin (67). However, high resistance rates of typical bacterial pathogens to macrolides are found in many places in Asia (www.alexander-network.com/), and using erythromycin alone as empirical treatment is not recommended in these areas, such as Hong Kong (68).

If cost is not a factor, then oral antibiotics with a wider range including a β-lactamase stable antibiotic such as a co-amoxyclav or a second or third generation oral cephalosporin such as cefuroxime axetil could be used. Other effective oral choices would be a newer macrolide such as azithromycin or clarithromycin or a newer quinolone such as levofloxacin. The efficacy of these newer drugs in the Asian context have been borne out in studies from this region. A study from Jakarta in 34 patients with CAP showed a 95–100% clinical response rate to either azithromycin given 500 mg daily for 3 days or clarithromycin 500 mg bid for 10 days (69). No adverse reactions were noted in either of the treatment groups. Another study from Singapore by Oh showed oral cefuroxime or amoxycilin-clavulanate were both very effective and well-tolerated choices in 48 patients with moderately severe CAP (70). The emerging role of the quinolones was established from a study from Bangkok on 28 patients with moderately severe CAP who were treated with oral ofloxacin with excellent results (71). The newer quinolones (eg levofloxacin) though much more expensive have an even broader spectrum of action that includes atypical pathogens and even

penicillin-resistant pneumococcus and would be a good oral choice in areas where penicillin resistant pneumococcus is a problem. One of the concerns is the potential masking of tuberculosis mimicking other bacterial pneumonias (72).

Hospitalized patients. These patients are likely to be more ill at the outset or have associated co-morbid conditions and should ideally receive intravenous antibiotics from the start. The initial choice of antibiotics is based on local epidemiology plus an assessment of how severe the pneumonia is. A number of clinical, laboratory and radiological pointers to severe pneumonia have been noted but there is no simple way to identify all those at risk. Studies of the British Thoracic Society have pointed out that the presence of 2 or more of the following 3; respiratory rate ≥ 30/minute, diastolic BP ≤ 80 mmHg and blood urea ≥ 7 mmol/litre, confer a 9 to 20 fold increase in the risk of death (61). This is a sensitive though not very specific rule but one that can be easily applied at the bedside. A Japanese study on 121 patients with CAP indicated that the following 9 findings were associated with severity of disease (73): age of at least 65 years, an underlying disease of the respiratory or central nervous system, dyspnoea, a pulse rate ≥ 90/min, a respiratory rate ≥ 25/min, an albumin concentration ≤ 3.5 g/dl, a blood urea nitrogen level of at least 20 mg/dl, a $PaO_2 \leq 60$ mm Hg or a saturation ≤ 90% and a high score on the extent of roentgenographic evidence of pulmonary infiltrates.

In the ill, hospitalized patients all probable pathogens must be covered and an intravenous β-lactamase stable penicillin (e.g. co-amoxyclav) or a cephalosporin (e.g. cefuroxime or cefotaxime or ceftriaxone) together with a macrolide provide good initial cover for the majority of typical and atypical pathogens likely to be encountered.

The American Thoracic Guidelines recommend that in all severely ill, hospitalized CAP, antibiotic cover for Staphylococcus with flucloxacillin, supported by rifampicin, and also for Gram-negative enteric bacilli including *Pseudomonas aeruginosa* should be given (62). We do not regard this approach necessary in the initial management of younger previously healthy patients.

Duration of treatment

The antimicrobial treatment for uncomplicated pneumonias due to *S. pneumoniae,* anaerobes, *H. influenzae* and *M. catarrhalis* should be continued for 7–10 days. The duration of treatment for *Mycoplasma* and *Legionella* infection is 2 to 3 weeks. However the presence of *S. aureus* or Gram-negative enteric bacilli or the development of suppurative complications requires a more prolonged course of therapy (e.g. 2 weeks for nonbacteraeamic staphylococcal pneumonia, 4 weeks for bacteraemic staphylococcal pneumonia and 4 to 6 weeks in case of an empyema).

Assessment of response to initial antimicrobial therapy

Once antimicrobial treatment is initiated, it is important to monitor the patient for clinical response. Normally no change in antimicrobial treatment should be considered within the first 72 hours unless initial diagnostic studies identify a pathogen not covered by original empirical therapy (e.g. *M. tuberculosis*), a resistant pathogen is isolated from blood or another sterile site (i.e. pleural fluid), or there is clinical deterioration. Even when antimicrobial treatment is appropriate, clinical improvement may be delayed by other host factors: coexisting illness, advanced age, structural abnormalities of the respiratory tract, particularly COPD, and unrecognized immunosuppression, e.g. AIDS. Bacteraemic patients and patients with Gram-negative or staphylococcal pneumonias are generally slower to respond. The virulence of the infectious agent may also delay response.

In appropriately treated patients, clinical response is often rapid, especially among patients without prior coexisting disease. In this population, fever usually disappears within 2–4 days, and the leucocytosis resolves by the fourth or fifth day of therapy. Physical findings remain abnormal in up to 40% of patients at day 7. The chest radiograph may not normalise at 4 weeks even in young (< 50 years old), previously healthy individuals and may not reach baseline for up to 6 months in the elderly, patients with COPD, or alcoholic patients. Chest radiographic abnormalities may worsen

initially, but significant early (< 48 hours) deterioration of chest radiograph, defined as a 50% or greater increase in the size of the infiltrate, progression to significant involvement of multiple lobes, or development of a large pleural effusion should raise concern that therapy is inadequate.

Supportive treatment in pneumonia

Respiratory support

Patients who are in obvious respiratory distress with tachypnoea are at increased risk of dying and need close monitoring, particularly if they are beginning to show evidence of exhaustion with drowsiness or confusion. Sometimes improvement in oxygenation can be achieved by postural drainage so that the "good lung" is dependent. Occasional patients may tolerate high flow oxygen via a nasal continuous positive airway pressure system or nasal ventilation if they are sufficiently cooperative, not too tachypnoeic and not too troubled by cough and sputum production. In other patients, intubation and mechanical ventilation may be necessary.

Supportive measures

Pneumonia complicated by septic shock requires energetic management of hypotension. Pleuritic pain can be relieved by simple nonsedative analgesics. Physiotherapy is of no benefit in acutely ill patients who find cooperation difficult and who may easily become exhausted, but it may assist expectoration of sputum in less ill patients and in those who are recovering. Bronchoscopy may help to find the aetiologic agent and to clear secretions or to rule out an endobronchial obstruction in case of a non-resolving pneumonia.

Table 4 gives a list of factors that could be responsible for poor response of pneumonia to treatment.

Table 4. Factors Involved in Poor Response to Empirical Antimicrobial Therapy

Incorrect microbiologic diagnosis
Inappropriate antimicrobial agent or dosing regimen
Drug-resistant organism
Drug hypersensitivity or drug fever
Tuberculosis can mimic pyogenic pneumomia, also consider unusual organisms such as Actinomyces or Nocardia spp.
Infectious complication: empyema, metastatic spread, superinfection
Presence of endobronchial obstruction
Reconsider the pneumonia diagnosis: Could it be pulmonary embolism, malignancy, vasculitis, drug reaction, eosinophilic pneumonia or cryptogenic organising pneumonia

Prognosis

The outcome of community acquired pneumonia depends on early diagnosis and effective antimicrobial therapy along with the age of the patient, the severity of disease along with the underlying co-morbid conditions. Pneumonia in the elderly is particularly dangerous due to frequent absence of classical symptoms and also higher incidence of adverse effects to antibiotics.

In a study by Chen and colleagues in Taiwan (74), the following variables were associated with a poor prognosis: septic shock, use of ventilatory support, treatment in intensive care unit, development of adult respiratory distress syndrome, Klebsiella pneumonia in patients with alcohol habit, male gender, presence of ultimately fatal underlying disease, an initial AaDO2 > 200 mmHg and an arterial pH < 7.25. Dey and colleagues in Delhi (75) reported that old age, history of smoking, presence of chronic obstructive airways disease, late presentation to hospital, systolic and diastolic hypotension, high blood urea, low serum albumin and development of septic shock were associated with a poorer prognosis. 35% of elderly patients and 14% of young patients with CAP in this study succumbed to fulminant sepsis or respiratory failure. Patients who were alcoholic, over 60 years of age, or had congestive cardiac failure were more vulnerable to severe pneumococcal infection with significant mortality, despite appropriate empirical antimicrobials (76).

Clinical analysis of 890 patients with CAP (77) requiring hospitalization in Japan showed that the prognosis was poor despite adequate antimicrobial treatment in the elderly patients with an efficacy rate of 74.3% and a mortality rate of 9.5% as opposed to 88% and 1.7% respectively in the non-elderly. The most important factors affecting the prognosis were the general condition of the elderly patients and delay in an adequate diagnosis and treatment due to atypical clinical findings.

In an analysis of 231 patients with CAP in Japan (78), liver cirrhosis, diastolic hypotension (< 60 mm Hg) (< 8 kPa) and hypoxaemia (< 50 mmHg) (< 6.67 kPa) were found to be important prognostic factors during the acute stage of pneumonia, and that alcoholism, malignancy, hypoalbuminemia and renal complications were significantly correlated with hospital death and 1-year mortality. 6.5% of deaths occurred in one month, 13.9% at hospital discharge and 19.9% 1-year later.

Prevention

The prevention of pneumonia aims at strengthening the host's responses once the pathogen is encountered. This includes the use of chemoprophylaxis or immunization for patients at risk. Chemoprophyalxis can be administered to patients who have encountered or are likely to encounter the pathogen before they become symptomatic. (e.g. amantadine during a community outbreak of influenza A, isoniazid for tuberculosis, or trimethoprim-sulfamethoxazole for pneumocystis). Vaccines are available for immunization against *S. pneumoniae, H. influenzae* type b, influenza viruses A and B, and measles virus. Of these, pneumococcal and influenza vaccines are found to be most effective and are indicated in patients over 65 years of age and in patients with cardiovascular diseases, pulmonary diseases, diabetes mellitus, alcoholism, liver cirrhosis and immunosuppression (HIV infection, chronic renal failure, organ transplant recipients, sickle cell disease, post-splenectomy state, haematologic and lymphatic malignancies). The currently available 23-valent pneumococcal vaccine covers 88% of the serotypes causing systemic disease as well as 8% of related serotypes. The increasing prevalence of multiantibiotic resistance among pneumococci makes the pneumococcal immunization of high-risk individuals of utmost importance. The effect of pneumococcal vaccine lasts for 7–10 years after which it may be repeated. The influenza vaccine should be given yearly in high-risk individuals. In Asia, issues of cost and the lack of data from large scale studies on populations within the region have hampered the widespread adoption of vaccination.

References

1. Barltett JG, Mundy LM. Community-acquired pneumonia. *N Engl J Med* 1995; 333:1618–24.
2. Office for National Statistics. *1997 Mortality Statistics, Cause.* London: The Stationery Office, 1998.
3. Macfarlane J. Community-acquired pneumonia. *Br J Dis Chest* 1987; 81:116–27.
4. Macfarlane J. An overview of community-acquired pneumonia with lessons learned from the British Thoracic Society Study. *Semin Respir Infect* 1994; 9:153–65.
5. Gwatkin DR. How many die? A set of demographic estimates of the annual numbers of infant and child deaths in the world. *Am J Publ Health* 1980; 70:1286–9.
6. Foy HM, Cooney MK, Maletzky AJ, Graystone JT. Incidence and etiology of pneumonia, croup and bronchiolitis in pre-school children belonging to a pre-paid medical group over a four-year period. *Am Epidemiol* 1973; 97:80–92.
7. Chretien J, Holland W, Macklem P, et al. Acute respiratory infection in children. A global public health problem. *N Eng J Med* 1984; 310:982–4.
8. Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global burden of disease study. *Lancet* 1997; 349:1498–504.
9. Steinhaff MC, John TJ. Acute respiratory infections of children in India. *Pediatric Research* 1983; 17:1032–5.

10. Datta Banik. Some observations on feeding programmes, nutrition and growth of pre-school children in an urban community. *Indian Journal of Paediatrics* 1977; 139–49.
11. Kauppiner MT, Herva E, Kujala P. The etiology of community acquired pneumonia among hospitalised patients during a Chlamydia pneumonia epidemic in Finland. *J Infect Dis* 1995; 172:1330–5.
12. Bohte R, Hermani J, van den Broek PJ. Early recognition of Streptococcus pneumoniae in patients with community-acquired pneumonia. *Eur J Clin Microbiol Dis* 1996; 15:201–5.
13. Lieberman D, Schlaeffer F, Boldui I, et al. Multiple pathogens in adult patients admitted with community-acquired pneumonia: a one year prospective study of 346 consecutive patients. *Thorax* 1996; 51:179–84.
14. Fine MJ, Smith MA, Carson CA, et al. Prognosis and outcome of community-acquired pneumonia: a meta analysis. *JAMA* 1996; 275:134–41.
15. Reimann LM. An acute infection of the respiratory tract with atypical pneumonia. *JAMA* 1938; 116:2377–82.
16. Mundy LM, Auwaerter PG, Oldach D, et al. Community acquired pneumonia: impact on immune status. *Am J Respir Crit Care Med* 1995; 152:1309–15.
17. Ishida T, Hashimoto T, Arita M, et al. Etiology of community-acquired pneumonia in hospitalised patients: a 3 year prospective study in Japan. *Chest* 1998; 114:1588–93.
18. Bryan CS. Pneumonia in Japan. *Chest* 1998; 114:1509–11.
19. Arakawa M, Nakahama C, Taguchi Y, et al. Culture-positive Legionella pneumonia in Japan, 1980–1990. Working Party for Legionellosis, Japanese Ministry of Health and Welfare. *Kansenshogaku Zasshi* 1992; 66:1513–23.
20. Motomura K, Takasugi M, Furumoto A, et al. Clinical features and etiology of community-acquired pneumonia at a general hospital between 1994 and 1997. *Nihon Kokyuki Gakkai Zasshi* 2000; 38:267–72.
21. Cohen MA, Pang JC. A retrospective study of community-acquired pneumonia in Hong Kong with special reference to choice of antibiotics. *Singapore Med J* 1989; 30:141–4.
22. Tan YK, Khoo KL, Chin SP. Aetiology and outcome of severe community acquired pneumonia in Singapore. *Eur Respir J* 1998; 12:113–5.
23. Boonsawat W, Boonam P, Tangdajahiran T, et al. Community-acquired pneumonia in adults at Srinagarind Hospital. *J Med Assoc Thai* 1990; 73:345–52.
24. Hui KP, Chin NK, Chow K, et al. Prospective study of the etiology of adult community acquired bacterial pneumonia needing hospitalisation in Singapore. *Chest* 1993; 103:1637–8.
25. Chan CHS, Cohen M, Pang J. A prospective study of community acquired pneumonia in Hong Kong. *Chest* 1992; 101:442–6.
26. Koyama H, Honda K, Okuda K, et al. Predictive factors of etiologic agents of community-acquired pneumonia presenting at a district general hospital. *Nihon Kyobu Shikkan Gakkai Zasshi* 1991; 29:1111–8.
27. Luo B, Huang Y, Qui W, et al. A prospective study on etiologic bacteria in 200 patients with pneumonia. *Hunan I Ko Ta Hsueh Pao* 1998; 23:453–7.
28. Chen CW, Jong GM, Shiau JJ. Adult bacteremic pneumonia: bacteriology and prognostic factors. *J Formos Med Assoc* 1992; 91:754–9.
29. Vijayasingam SM, Narendran K, Meers PD. Community-acquired Legionellosis in Singapore. *Ann Acad Med Singapore* 1991; 20:817–20.
30. Chaudhry R, Dhawan B, Dey AB. The incidence of Legionella pneumophilia: a prospective study in a tertiary care hospital in India. *Trop Doct* 2000; 30:197–200.
31. Hsu CM, Huang LM, Kao YF, et al. Prevalnce of Legionella pneumophilia infection in children and its role in pediatric community-acquired atypical pneumonia. *Erh Ko I Hsueh Hui Tsa Chih* 1996; 37:188–92.
32. Nadar S, Hoque S, Brahmadattan KN, et al. A hospital based study of community acquired Mycoplasma and Legionella lower respiratory tract infections in Southern India. *The Indian Practitioner* 1997; 50; 6:481–6.
33. Chaudhry R, Nazima N, Dhawan B. Prevalance of Mycoplasma pneumoniae and Chlamydia pneumoniae in children with community acquired pneumonia. *Indian J Pediatrics* 1998; 65:717–21.
34. Wu JS, Lin JC, Chang FY. Chlamydia pneumonia infection in community acquired pneumonia in Taiwan. *J Microbiol Immunol Infect* 2000; 33:34–8.
35. Ishida T, Hashimoto T, Arita, et al. Multicentre screening of Chlamydia pneumonia by ELISA method. *Kansenshogaku Zasshi* 1999; 73:70–5.

36. Invasive Bacterial Infection Surveillance (IBIS) Group. Prospective multicentre hospital surveillance of Streptococcus pneumoniae disease in India. *Lancet* 1999; 353:1216–20.
37. Mastro TD, Ghafoor A, Nomani NK, et al. Antimicrobial resistance of pneumonia in children with acute lower respiratory infection in Pakistan. *Lancet* 1991; 337:156–9.
38. Sahas k, Rikitomi N, Biswas D, et al. Serotypes of Streptococcus pneumoniae causing invasive childhood infection in Bangladesh, 1992–1995. *L Clin Microbiol* 1997; 35:785–7.
39. Watanale H, Sata S, Kawakami K, et al. A comparative clinical study of pneumonia by penicillin resistant and sensitive Streptococcus pneumoniae in a community hospital. *Respirology* 2000; 5:59–64.
40. Komori T, Takabayashi T, Kuse T, et al. Antibiotic resistance of clinical isolates of Strep. pneumoniae. *Karsenshogaku Zasshi* 2000; 94:43–50.
41. Udwadia ZF, Doshi AV, Joshi JM, et al. Etiology of community acquired pneumonia in India. *Eur Respir J* 2003; 22:5445.
42. Udwadia ZF, CAP in India: what bugs? what tests? what drugs? *Int J Tuberc Lung Dis* 2003; 7(11):S132-S133.
43. Limthongkul S, Charoenlap P, Wongthim S, et al. Bacterial pneumonia in the elderly. *J Med Assoc Thai* 1994; 77:169–75.
44. Hwang JJ, Chen KL, Tsai MS, et al. Clinical study of Mycoplasma pneumoniae pneumonia. *Kao Hsiung I Hsueh Tsa Chih* 1993; 9:204–11.
45. Handa K, Kayama H, Okuda T, et al. Can radiologic features of community acquired pneumonia presume etiologic agents? *Rinsho Hoshasen* 1990; 35:225–33.
46. Jay SJ, Johanson WG, Pierce AK. The radiographic resolution of streptococcus pneumoniae pneumonia. *N Engl J Med* 1975; 293:798–801.
47. Macfarlane JT. Community acquired pneumonia. In: *Recent Advances in Respiratory Medicine*, No. 5. Ed. Mitchell D. London: Churchill Livingstone 1991, 109.
48. Pellegrino MB, Privitera A, Primavera A, et al. Microbiological considerations of the etiological agents of lower respiratory tract infections. *J Chemotherapy* 1992; 4: 211–9.
49. Verenkar MP, Pinto MJ, Savir R, et al. Bacterial pneumoniae; evaluation of various sputum culture methods. *J Postgrad Med* 1993; 39:60–2.
50. Zhang XP, Deng KE Ye YQ, et al. Rapid detection of pneumococcal antigens in sputa in patients with community acquired pneumonia by coagglutination. *Med Microbiol Immunol (Berlin)* 1988; 177:333–8.
51. Light RW. The management of parapneumonic effusions and empyema. *Curr Opin Pulmon Med* 1998; 4:227–9.
52. Konishi M, Mori K, Yoshimoto E, et al. Clinical evaluation of anaerobic infctions in patients with bronchopulmonary infections diagnosed by transtracheal aspiration. *Kansenshogaku Zasshi* 1999; 73:675–80.
53. Baker AM, Dowton DL, Haponik EF. Decision making in nosocomial pneumonia. An analytical approach to the interpretation of quantitative bronchoscopic cultures. *Chest* 1995; 107:85–95.
54. Chastre J, Trouillet JL, Fagon JV. Diagnosis of pulmonary infection in mechanically ventilated patients. *Semin Respir Infect* 1996; 11:65–76.
55. Meduri GU, Mauldin GL, Wunderink RG, et al. Causes of fever and pulmonary densities in patients with clinical manifestations of ventilator-associated pneumonia. *Chest* 1994; 106:221–35.
56. Zhong CY, Li R, Li DL. Etiological diagnoses in 53 cases of pneumonia. *Chung Hua Nei Ko Tsa Chih* 1991; 30:487–8, 521.
57. Macfarlane JT. Lung biopsy. *Br Med J* 1985; 290:97–98.
58. Salo P, Ortqvist A, Leinonen M. Diagnosis of bacteraemic pneumococcal pneumonia by amplification of pneumolysin gene fragment in serum. *J Infect Dis* 1995; 171:479–82.
59. Schluger NW, Rom WN. The polymerase chain reaction in the diagnosis and evaluation of pulmonary infections. *Am J Respir Crit Care Med* 1995; 152:11–6.
60. Honda J, Yano T, Kusaba M, et al. Clinical use of capillary PCR to diagnose Mycoplasma pneumonia. *J Clin Microbiol* 2000; 38:1382–4.
61. British Thoracic Society. Guidelines for the management of community-acquired pneumonia in adults admitted to hospital. *Br J Hosp Med* 1993; 49:346–50.
62. American Thoracic Society. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity and initial antimicrobial therapy. *Am Rev Respir Dis* 1993; 148:1418–26.

63. Mandell LA, Niederman MS. The Canadian community-acquired pneumonia consensus group. Antimicrobial treatment of community-acquired pneumonia in adults. Can *J Infect Dis* 1993; 4:25.
64. Lim TK. Emerging pathogens for pneumonia in Singapore. *Annals of the Academy of Medicine, Singapore* 1997; 26:651–8.
65. Campbell H, Byass P, Forgie IM, et al. Trial of co-trimoxazole versus procaine penicillin with ampicillin in treatment of community acquired pneumonia in young Gambian children. *Lancet* 1988; 2(8621):1182–4.
66. Bang AT, Bng RA, Tale O, et al. Reduction in pneumonia mortality by means of community based intervention trial in Gadchiroli, India. *Lancet* 1990; 336(8709):201–206.
67. Jang TN, Liu CY, Wang FD, et al. A randomised comparative study on the safety and efficacy of clarithromycin and erythromycin in treating community acquired pneumonia. *Chung Huo I Hsueh Tsa Chih (Taipei)* 1995; 55:302–6.
68. Ho PL, Yung RWH, Tsang DNC, Que TL, Ho M, Seto WH, Ng TK, Yam WC, Ng WWS. Increasing resistance of *Streptococcus pneumoniae* to fluoroquinolones: results of a Hong Kong mult-center study in 2000. *J Antimicrob Chemother* 2001: 48: 659–65.
69. Soepandi P, Mangunnegeno H, Yunus F, et al. The pattern of microorganisms and the efficacy of new macrolides in acute lower respiratory tract infections. *Respirology* 1998; 3:113–7.
70. Oh HM, Ng AW, Lea SK. Cefuroxime compared to amoxicillin-clavulanic acid in the treatment of community acquired pneumonia. *Singapore Med J* 1996; 37:255–7.
71. Youngchaiyud P, Permpikul C, Thamlikitkul V, et al. Treatment of community acquired pneumonia with ofloxacin. *J Med Assoc Thai* 1991; 74:61–5.
72. Dooley KE, Golub J, Goes FS, Merz WG, Sterling TR. Empiric treatment of community-acquired pneumonia with fluoroquinolones , and delays in the treatment of tuberculosis. *Clin Infect Dis* 2002; 34:1607–2.
73. Tanabe J, Taniguchi M, Higo A, et al. Clinical and laboratory findings associated with severity of community-acquired pneumonia. *Nihon Kyobu Shikkan Gakkai Zasshi* 1997; 35:854–62.
74. Chen CW, Jang GM, Shiacu JJ, et al. Adults bacteraemic pneumonia: bacteriology and prognostic factors. *J Formos Med Assoc* 1992; 8:754–9.
75. Dey AB, Nagarkar KM, Kumar V. Clinical presentation and predictors of outcome in adult patients with community acquired pneumonia. *Natl Med J India* 1997;10:169–72.
76. Leelarasamee A, Dhiraputra C, Hunnangkul S. Severe pneumococcal infection at a Thai hospital. *Int J Infect Dis* 1999; 3:147–52.
77. Kobashi Y, Fujita K, Karino T, et al. Clinical analysis of community-acquired pneumonia requiring hospitalisation in a community hospital- comparison of elderly and non-elderly patients. *Kansenshogaku Zasshi* 2000; 74:43–50.
78. Watart M, Ohe M, Kuminoto E, et al. Mortality and prognostic factors in patients with community acquired pneumonia: an analysis of 231 cases. *Nihon Kokyuki Gakkai Zasshi* 2000; 38:509–17.

12 AIDS and the Lungs

Charn Kiatboonsri and Chaicharn Pothirat

Introduction

It is now well into the third decade of acquired immunodeficiency syndrome (AIDS) after the 1981 outbreaks of *Pneumocystis carinii* pneumonia (PCP) and Kaposi's sarcoma (KS) among previously healthy homosexual males in the United States. In 1983, the causative agent was discovered, which was subsequently called the human immunodeficiency virus (HIV). The World Health Organization estimated that 34.3 million people were infected by HIV by the year 2000, with 95% living in developing countries. About 90% of HIV-seropositive patients were between 15 and 45 years old, with a male to female ratio of 5 to 1. The estimate for Southeast Asia numbered more than 5.8 million people(1,2), with China accounting for over 500,000 people(3). In the late 1980s the organism was noted among intravenous drug users in Thailand, Myanmar and India. The seroprevalence in this group of patients dramatically increased from 1.2% in 1988 to 45% in 1991. The latest statistics showed that over 80% of all reported cases of HIV infection in Asia were in Thailand and in India, and the mode of disease transmission was primarily unprotected sexual intercourse with female prostitutes (4,5). The virus was seen in as many as 30–65% of female prostitutes in various cities in these countries. From 1984 to September 2002, there were 278,034 cases of AIDS and symptomatic HIV patients in Thailand, and 63,672 had died (6).

The lung is the most frequently involved organ, and over 90% of the complications are caused by various infectious aetiologies. Table 1 shows a list of common respiratory disorders (7). Nowadays, with the use of highly active antiretroviral therapy (HAART), death and opportunistic infections have decreased by 60–90% while more non-infectious complications have surfaced (8,9). In Thailand as well as several other developing countries, there are governmental and private efforts to widen the practice of HAART by selling these medications at lower prices than previously charged. Even with this trend, there are very few studies in Asia addressing these non-infectious complications.

Infectious Aetiologies

HIV-associated respiratory tract infections are the most important causes of morbidity and mortality among AIDS patients in the world. Various agents have been identified, some with geographical predilection, e.g., *Histoplasma capsulatum* is often seen in the United States while *Penicillium marneffei* is found in Northern Thailand. The levels of CD4 cell count are also important (Table 2) (2). When the levels are above 500 cells/μL, the organisms involved tend to be the same as those without HIV infection; but these patients are afflicted with greater frequency and higher

Table 1. Common Respiratory Disorders among Patients with HIV Infection[7,52]

1. Virus
   - Cytomegalovirus (CMV)
   - Adenovirus
   - *Herpes simplex*
   - Measles
   - *Herpes zoster*
2. Bacteria
   - *Streptococcus pneumoniae*
   - *Hemophilus influenzae*
   - *Chlamydia pneumoniae*
   - *Staphylococcus aureus*
   - *Pseudomonas aeruginosa*
   - *Moraxella catarrhalis*
   - *Rhodococcus equi*
   - *Nocardia* species
3. Mycobacteria
   - *Mycobacterium tuberculosis* (TB)
   - *Mycobacterium avium* complex (MAC)
   - Other non-tuberculous mycobacteria (NTM)
4. Fungi
   - *Pneumocystis carinii*
   - *Cryptococcus neoformans*
   - *Penicillium marneffei*
   - *Histoplasma capsulatum*
   - *Aspergillus* species
5. Parasites
   - *Toxoplasma gondii*
   - *Strongyloides stercoralis*
6. Malignancies
   - Kaposi's sarcoma
   - Non-Hodgkin's lymphoma
   - Bronchogenic carcinoma
7. Other Disorders
   - Sinusitis
   - Bronchitis/bronchiectasis
   - Lymphocytic interstitial pneumonitis
   - Nonspecific interstitial pneumonitis
   - Bronchiolitis obliterans organizing pneumonia
   - Primary pulmonary hypertension

Table 2. CD4 Levels and Respiratory Diseases[2]

CD4 levels	*Diseases*
All	Common illness (bronchitis, sinusitis, pharyngitis)
300–400	Bacterial pneumonia; pulmonary TB
200–300	Recurrent bacterial pneumonia; NTM
100–200	PCP; disseminated TB; KS
< 100	Disseminated MAC; CMV; fungi

organism loads than HIV-negative counterparts. Bacterial pneumonias predominate between 200 and 400 cells/μL. The risk of pneumocystis carinii pneumonia (PCP) increases 40% yearly as well. Once the levels drop below 200 cells/μL, acute lower respiratory tract infections occur more and opportunistic agents need to be considered as much as typical bacteria. With levels below 100 cells/μL, pneumonia caused by cytomegalovirus (CMV) or *Mycobacterium avium* complex (MAC) develop frequently. In addition, patients with pneumonia may be afflicted with more than one organism, and have higher severity of illness and mortality rates than those without HIV infection. Tuberculosis (TB) can be seen at all levels with different clinical presentations. In developing countries, TB and other fungal diseases may feature rather prominently (10,11).

Prior to 1997, a study using bronchoalveolar lavage (BAL) technique among 103 HIV-seropositive inpatients with suspected pulmonary infections in Chiangmai, Thailand was able to identify infectious organisms in 95% of the cases (Table 3) (12). Mixed infections were found in 24.5%, mostly (87.5%) with 2 organisms. Unpublished surveillance at the same center in later years revealed different results. A retrospective review of pneumonia cases between 1999 and 2000 without BAL found bacteria, *P. carinii*, *M. tuberculosis* and fungi to be the culprits in that order of prevalence. In 2001, a prospective inpatient study using BAL in severe pneumonia

Table 3. Infectious Aetiologies among HIV-seropositive Inpatients in Chiangmai, Thailand[12]

Agents	*1995*		*1999*	*2001*
	Isolates (%)	*Cases (%)*	*Cases (%)*	*Cases (%)*
P. carinii	28.9	35.7	21.6	25.0
Bacteria	19.8	24.5	49.1	28.2
Fungi	31.4	38.8	6.0	8.9
C. neoformans	18.2	22.4		
P. marneffei	13.2	16.3		
M. tuberculosis	9.9	12.2	13.8	27.4
Nocardia species	5.0	6.1		
Cytomegalovirus	4.1	5.1	0.9	
Herpes virus	0.8	1.0		

without clinical response after 3 to 5 days of empirical therapy revealed the leading cause to be *M. tuberculosis*, followed by *P. carinii*, bacteria and fungi. Of note is that 95% of the patients did not receive HAART and 20% were on PCP prophylaxis.

Cumulative statistics from the Department of Public Health in Thailand show that, from September 1984 to 2002, leading opportunistic infections among patients with AIDS included pulmonary or extrapulmonary tuberculosis (25%), PCP (18.2%), cryptococcosis (14.9%), candidiasis of the oesophagus, trachea, bronchi or lung (4.6%) and recurrent bacterial pneumonias (3.2%) (6). An autopsy study of 143 adults with AIDS in Mumbai, India from 1988 to 2000 found pulmonary pathology in 126 cases (88%) (13). The most prevalent cause was, again, tuberculosis (59%), followed by bacterial pneumonia (18%), CMV pneumonitis (7%), cryptococcosis (6%), PCP (5%), aspergillosis (3%), and toxoplasmosis (1%).

Bacteria

HIV-infected patients with lower respiratory tract infections present similarly to those without HIV. Symptoms include high-grade fever, chills, productive cough, dyspnoea and pleuritic chest pain. Signs include tachyponea, tachycardia, cyanosis, diaphoresis, consolidation, rhonchi and crackles. Leukocytosis is typically present, and bacteraemia occurs more often than in HIV-seronegative patients. In fact, HIV should be suspected when patients have oral candidiasis, recurrent pneumonia and bacteraemia. Common radiographic patterns include lobar consolidation and patchy infiltration. Haematogenous dissemination characteristically leads to multiple nodules from 1–3 cm in diameter, predominantly in the lower lobes, which rapidly cavitate. This pattern is most often seen with *Staphylococcus aureus*. Occasionally multiple cavities of 1–2 cm are seen as in necrotizing pneumonia. Lung abscesses with air-fluid levels are commonly caused by *S. aureus, Pseudomonas aeruginosa, Rhodococcus equi* and *Nocardia* species. Pneumonia can progress rapidly, leading to septic shock, dissemination, acute respiratory distress syndrome and multi-organ failure. Common causes for opportunistic infections due to bacteria include *R. equi* and *Nocardia* species. There is no evidence of higher prevalence of atypical bacteria or anaerobes.

In a prospective study of 1,225 admissions of 599 patients with HIV, bacteria accounted for 9% of the pneumonias(14). Of these, 72% were community-acquired pneumonia (CAP) and 28% were hospital-acquired pneumonia (HAP). The most common causative bacteria for CAP were *Streptococcus pneumoniae* (25%), *P. aeruginosa* (25%), *Hemophilus influenzae* (12.5%), *S. aureus*

(10%) and *Klebsiella pneumoniae* (3.7%). Other bacteria included *Streptococcus viridans, Eschericia coli, Serratia marcescens, H. parainfluenzae, Enterobacter aerogenes, Acinetobacter baumanii, Burkhoderia bronchiseptica, Legionella pneumophila* and group C streptococci. For HAP, *P. aeruginosa* topped the list at 38.7%, followed by *S. aureus* (25.8%), *E. coli* (6.4%) and *S. pneumoniae* (6.4%). Other bacteria found included *H. influenzae, S. viridans, Enterococcus* species, *S. liquefaciens* and *Proteus mirabilis.*

In Chiangmai, Thailand, 24 out of 98 hospitalized HIV-positive patients had pyogenic bacterial pneumonia (12). *S. aureus* was the most common pathogen (33%), followed by *S. pneumoniae* (21%), *H. influenzae* (21%), *P. aeruginosa* (11%), *Xanthomonas maltocida* (4%) and *R. equi* (4%). *Nocardia* species accounted for 6 patients with CAP.

In general, *S. pneumoniae* is the leading cause of bacterial respiratory disease with bacteraemia among HIV-infected patients. Bacteraemia occurs 10 times more often than in HIV-negative controls, and may be present in as many as 75% (2). This is also the most common cause of non-bacteraemic bacterial pneumonia in HIV-positive patients, resulting in mortality almost 5 times of other patients. The involved serotypes are the same as those afflicting HIV-negative patients. *H. influenzae,* particularly type b and non-typable strains, is a rather common cause of pneumonia. *P. aeruginosa* is a common cause for recurrent bacterial pneumonia in severe AIDS (15). *Legionella* can be more commonly seen concurrently with *P. carinii* or mycobacteria (2).

R. equi, a normal soil organism, causes lung abscesses in immunocompromised patients (2,16). The first AIDS-related case appeared in the literature in 1986. In Thailand, no cases of *R. equi* were documented until 1993 with the report of lung diseases in 3 AIDS patients in Maharaj Hospital, and the tally went up to 33 in just 3 years later. The Central Chest Hospital near Bangkok, Thailand, found that the cumulative statistic until January 1999 was 17 patients, with 14 having HIV seropositivity. In another series of 4 HIV-positive patients from northern Thailand, 3 had CD4 count of 10 cells/μL (17). This is a facultative intracellular Gram-positive aerobe which may appear coccoid, or has a long, curved, clubbed shape. It is variably acid fast, and thought to be intermediate between fast-growing non-tuberculous mycobacteria (NTM) and *Nocardia.* Risk factors for infection include exposure to farm dust or horses or other infected patients. *R. equi* can survive and replicate inside alveolar macrophages, so clearance requires adequate T cell function, especially that of CD8 cells. Pathologically there is inflammatory infiltrate of neutrophils and macrophages which have abundant, foamy or granular cytoplasm with numerous Gram-positive bacilli. Caseating granulomas can be present. Many cases have intracytoplasmic Michaelis-Guttmann bodies suggestive of malakoplakia. Clinically the onset is insidious and patients have fever, malaise, dyspnoea, productive cough and pleuritic chest pain. Some have extra-thoracic involvement, most often in the eyes, subcutaneous tissue, central nervous system, vertebrae and lymph nodes. Usually chest radiographs show a round opacity or consolidation in the upper lobe which may undergo cavitation with an air-fluid level in 2–4 weeks. Pleural effusion is seen in 20% of patients. The organism can be isolated from the blood, respiratory secretions and lymph nodes, easily cultured on nonselective media and mistaken for diphtheroids. Severely ill patients should be treated with a combination of 2 antimicrobials including vancomycin, ciprofloxacin, clindamycin and aminoglycosides for 3–6 weeks (18,19). Alternative regimens include erythromycin plus rifampin or vancomycin plus imipenem for up to 6 months (16,17). This should be followed by a maintenance phase of erythromycin plus rifampin to prevent relapse. Occasionally surgical excision of the infected tissues may be needed. Prognosis is very poor in spite of therapy.

N. asteroides frequently causes disseminated infection with duration of symptoms from 1 to 6 months before diagnosis. A review of HIV-seropositive patients at the Central Chest Hospital in Thailand from January 1994 to December 1995 found 34 cases of pulmonary nocardiosis (20). Almost all were male with a mean age of 30.7 years, ranging from 22 to 50 years. Cough was present in 90%, and other symptoms included dyspnoea (47%), fever (41%), hemoptysis and chest pain (18%). Another review of pulmonary nocardiosis in HIV-infected patients from northeast

Thailand found 25 cases from January 1996 to March 1998 (21). The mean age was 30.5 years with a range of 23 to 57 years. Male comprised 84% of the cases. All presented with fever, cough and dyspnoea, and 60% had symptoms for greater than 3 weeks before admission. None had received co-trimoxazole prophylaxis for PCP. Approximately half of the patients had leukocytosis with neutrophil predominance. Coexisting opportunistic infections were seen in 64% with tuberculosis being the most common. Case reports from Singapore on 4 HIV-positive patients with nocardiosis found 2 cases with only pulmonary disease, another with disseminated disease involving the lung, brain and soft tissues and the other with cervical lymph node abscess (22). Cavitation is typical, and lobar or multilobar air-space consolidation, commonly of the upper lobes, is seen in more than half of the patients (2,20,21,22). Reticulonodular infiltration as well as effusion and mass-like lesions have also been described (20). A positive culture from respiratory specimens is definitive, but may take up to 4 weeks to grow. Antibiotics should include at least 6–12 months of co-trimoxazole, imipenem and a third-generation cephalosporin, followed by low-dose maintenance to prevent relapse (23). Mortality rates are roughly 30% (20,21). Poor prognostic factors include delayed diagnosis, presence of other opportunistic infections and the absence of co-trimoxazole therapy (21).

Mycobacteria

HIV-seropositive patients are at risk of developing primary and reactivation tuberculosis (24). Tuberculosis is the only HIV-related infection transmissible to normal hosts. Since 1993, TB has been included as an AIDS-defining illness. About 5–15% per year of HIV-infected persons with positive tuberculin-test develop tuberculosis (2,25). This translates into a life-time risk of 30%, which is higher than the 5–10% life-time risk among HIV-seronegative people. A high and increasing prevalence of HIV seropositivity among patients with tuberculosis is seen worldwide. HIV-related tuberculosis reached 1 million cases and caused 30% of the expected 2.5 million AIDS related deaths in 1999 (26). In 1993, 52–68% of HIV-infected patients in Thailand and India developed tuberculosis (27,28). From 1989 to 1994, TB prevalence among HIV-infected patients in Chiangmai, Thailand escalated from 5% to 40% (11). In a study in Ho Chi Minh City, Vietnam, the prevalence of HIV seropositivity among TB patients increased from 0.5% to 4% from 1995 to 2000 (29). The association between HIV and tuberculosis is due to a decrease in the number and dysfunction of T helper-1 lymphocytes, defects in macrophage function, and possibly a reduction in the activation of CD8 and B lymphocytes. This would lead to reactivation of the disease; however, primary infection can occur in developed countries. The annual risks of tuberculous infection in areas of high HIV-seropositivity are higher than those in less prevalent areas. Tuberculosis also leads to local production of tumor necrosis factor-α (TNF-α), interleukin-1 and interleukin-6, which induce HIV replication in latently infected cells (2,24).

Radiographic patterns of pulmonary TB depend on the level of the immunity. Patients in non-endemic areas with CD4 of more than 200 cells/μL present as post-primary TB, similar to HIV-seronegative people (24,30). Only 30% of those with lower immunity present as such, and the rest tend to be different from those who are HIV-negative. Hilar or mediastinal lymphadenopathy has been reported in 20–60%, cavitary lesions in 0–40%, other atypical findings (middle or lower lobe predominance and miliary or diffuse reticulation) in 4–60%, pleural effusion in 10–40%, and normal radiographs in 3–15% (2,24,31). This is influenced by the localities and levels of immunosuppression. The most commonly described abnormality on computed tomography (CT) is enlarged hilar and mediastinal lymph nodes with low attenuation.

When immunity is relatively preserved, the clinical manifestations of TB among HIV-positive patients are similar to seronegative counterparts. With declining immunity, other patterns occur. For example, extrapulmonary disease is seen in 70% of those with CD4 of less than 100 cells/mL, compared to 28% among those with levels of more than 300 (2). Overall, only 40–55% of HIV-positive patients with tuberculosis react to tuberculin skin testing. An induration of 5 mm has thus been recommended as a positive reading. Positive sputum smears and cultures are seen at

about the same rates in both seropositive and seronegative patients with pulmonary TB. HIV has also been associated with multidrug-resistant TB (MDR-TB).

Because of poverty in Thailand, most HIV-seropositive patients with TB tend to seek medical care with atypical features seen with dropping CD4 levels. A clinical pattern of acute tuberculous pneumonia consists of high fever, dyspnoea, cough or pleuritic chest pain. Chest radiographs are consistent with lobar pneumonia frequently seen in the middle or lower lobes. This pattern may also be seen in patients at early stages of HIV infection, or seronegative or diabetic patients (32). The other pattern is that of interstitial pneumonia which is very much similar to that seen with PCP or bacterial pneumonias. Acid-fast stains are usually non-productive. Of note is that patients do not appear as ill or as restless as those with typical bacterial pneumonias. A retrospective chart review of 60 HIV-positive patients with TB in Hong Kong also found that 93% presented with CD4 of less than 200 cells/μL (33). Extrapulmonary and disseminated disease was seen in 63%; however, symptoms were similar to seronegative patients. Radiographic patterns were as seen in other studies, i.e., 38% of the patients had primary patterns including pleural effusion, intra-thoracic lymphadenopathy and consolidation in the middle and lower lobes. As many as 8.4% had normal radiographs. Acid-fast bacilli were identified in 55% of those with pulmonary disease. Mycobacteraemia was detected by BACTEC system in 33% of those with disseminated disease.

At least 3 sputum specimens need to be examined for the presence of mycobacteria. If patients cannot expectorate, specimens may be obtained by sputum induction or BAL. A period of therapeutic trial may be considered. Cultures should be performed to rule out NTM or to assess sensitivities which may be important for surveillance of MDR-TB and for cases of drug allergies. Pleural fluid culture may be positive in 90% despite the 15% yield of smear. Pleural biopsy may find acid-fast bacilli in 70% and granulomas in 88% (34). As in HIV-seronegative patients, adenosine deaminase assay can aid in the diagnosis of TB pleuritis (35).

For TB patients not on protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs), the treatment regimen can be the same as that in HIV-seronegative patients. The first choice should be a standard short-course regimen consisting of 2 months of isoniazid (INH or H) plus rifampin (RMP or R) plus pyrazinamide (PZA or Z) plus ethambutol (EMB or E), followed by 4 more months of HR (2HRZE/4HR). The United States Center for Disease Control (CDC) recommends that the HR phase may be extended to 7 months or until after cultures have become negative for 4 months (24). If possible, this should be integrated with directly-observed therapy (DOT) to reduce the occurrence of rifampin-monoresistant and MDR-TB, which are especially problematic among this group of patients. The Central Chest Hospital near Bangkok, Thailand, found that *M. tuberculosis* resistant to rifampin and multi-drug resistant strains in HIV-positive patients had been increasing over the years (Table 4) (36). However, the percentage of patients with strains resistant to at least 1, 2 or 3 drugs did not change. Seropositive patients tend to have more side effects such as skin lesions or hepatitis than seronegative patients, and these overlap with the reactions from antiretroviral drugs (ARV; Table 5) (8,24). In addition, there are drug-drug interactions between rifamycins and antiretroviral drugs (Table 6) (8). Since rifabutin (RFB) is a less potent inducer of cytochrome P-450 CYP3A while being as effective as rifampin, it can be a replacement in patients taking PIs and NNRTIs, except delavirdine, with dosage adjustment in both RFB and ARV as in Table 7 (8). Although rifapentine permits once-weekly administration in HIV-seronegative patients, its use is not recommended because of rapid emergence of rifamycin-monoresistance. If HAART has not been started, it should be postponed until at least after 1 to 2 months of anti-TB therapy. If the initial regimen contains RMP, a switch to RFB should be done 2 weeks before the addition of HAART. In patients who need both treatment simultaneously, regimens without RMP may be substituted, such as 2HZES/$7H_3Z_3S_3$ (S = streptomycin) or 2HSE/16HE or 2HZE/16HE or 18HZE (37). These regimens may be inferior to those containing a rifamycin for the entire course. If HAART is started after initial clinical improvement early in the course of anti-TB therapy, up to 36% of patients can develop paradoxical worsening of disease, compared with

Table 4. Prevalence of Drug Resistance in HIV-seropositive TB patients of Central Chest Hosptal, Thailand[36]

M. tuberculosis	*1989–1993*	*1996*	*Significance*
Sputum specimens	406	376	
Resistance to:			
INH	13.8%	15.7%	NS
RMP	8.9%	14.3%	$P < 0.01$
STM	15.8%	9.3%	$P < 0.01$
EMB	1.5%	1.3%	NS
Multi-drug	2.7%	8.8%	$P < 0.01$
Percentage of patients with strains resistant to at least -			
1 drug	46.8%	42.8%	NS
2 drugs	8.1%	6.9%	NS
3 drugs	3.2%	3.7%	NS

Table 5. Side Effects from Anti-TB Drugs and ARV[8,24]

Side Effects	*Anti-TB drugs*	*Antiretroviral drugs*
Rash	PZA, RMP, RFB, INH	Nevirapine, delavirdine, efavirenz, abacavir
Nausea, vomiting	PZA, RMP, RFB, INH	Zidovudine, ritonavir, amprenavir, indinavir
Hepatitis	PZA, RMP, RFB, INH	Nevirapine, protease inhibitors, immune restitution among patients with chronic viral hepatitis
Leukopenia, anaemia	RFB, RMP	Zidovudine

Table 6. Effects of Rifamycins and ARV on the Area-under-the-Curve of Each Drug[8]

ARV	*RMP*		*RFB*	
	RMP on ARV	*ARV on RMP*	*RFB on ARV*	*ARV on RFB*
PIs				
Saquinavir	↓80%	Unknown	↓46%	↑45%
Ritonavir	↓35%	None	None	↑400%
Indinavir	↓90%	Unknown	↓24%	↑270%
Nelfinavir	↓82%	Unknown	↓0–23%	↑200%
Amprenavir	↓81%	Unknown	↓14%	↑400%
Lopinavir/ritonavir	↓75%	Unknown	None	↑300%
NNRTIs				
Nevirapine	↓37%	Unknown	↓16%	None
Delavirdine	↓96%	None	↓80%	↑342%
Efavirenz	↓13%	None	None	↓38%

Table 7. Dosage Adjustment for RFB and ARV[8]

ARV regimen with	*RFB*	*ARV dose*
PIs		
Nelfinavir (+ 2 NRTIs)	150 mg qd, or 300 mg int	1250 mg q 12 hours
Indinavir (+ 2 NRTIs)	150 mg qd, or 300 mg int	1000 mg q 8 hours
Amprenavir (+ 2 NRTIs)	150 mg qd, or 300 mg int	No change
Saquinavir (+ 2 NRTIs)	300 mg qd or int	1600 mg q 8 hours
Ritonavir (any combinations)	150 mg biw	No change
NNRTIs		
Efavirenz (+ 2 NRTIs)	450–600 mg qd or biw	No change
Efavirenz (+ PI except ritonavir)	300 mg qd or int	↑indinavir
Nevirapine	300 mg qd or int	No change
NRTIs		
Dual or triple	300 mg qd or int	No change

Notes int = intermittent, either twice- or thrice- weekly,
biw = twice a week,
NRTI = nucleoside reverse-transcriptase inhibitor

7% of those not taking HAART (24). This is caused by restoration of immunity towards mycobacterial antigens in patients with advanced HIV infection just starting ARV (see Immune Restitution section). The risk of death in HIV-positive patients with TB is twice that in those without TB, independent of the CD4 count. Data on first year survival after the diagnosis of TB from Chiang Rai, Thailand, found that HIV-positive patients fared worse than HIV-negative patients at 35.07% vs. 86.64%, with an odds ratio of 6.80 (95% confidence interval 5.69–10.11) (38). The most important predictor of mortality is still related to the degree of immune suppression such as negative tuberculin tests, prior opportunistic infections and low CD4 cell count.

Of all NTM, *M. avium-intracellulare* complex (MAC) is found in 96–98% of HIV-infected patients in developed countries (39). MAC and *M. kansasii* infections were reported in 624 AIDS patients (0.3% of all AIDS-related conditions) over a span of 18 years in Thailand, while other NTM totaled 1880 (0.8%) over this same period (6). Without prophylaxis in those patients at risk, the incidence of MAC is 20% at 1 year and 40% at 2 years following the diagnosis of AIDS (2). The most common symptoms are persistent fever, fatigue and weight loss, with other complaints of cough, dyspnoea, diarrhoea, abdominal pain, night sweats, and anorexia (2,40). Findings include cachexia, hepatosplenomegaly, lymphadenopathy, anaemia and occasional cutaneous lesions containing acid-fast bacilli. CD4 counts are less than 50–75 cells/μL. Radiographic and CT findings are similar to those of tuberculosis. Acid-fast staining of the sputum is positive in only 16% compared with 86% for *M. tuberculosis* (41). Even if this organism is seen in BAL fluid, it may be just a colonizer. Aggregates of macrophages stuffed with organisms are seen in histological sections without granulomatous inflammation or necrosis. Mycobacteraemia is present in over 85% (42). The lungs are usually involved after hematogenous dissemination. In a study of HIV-infected patients with unexplained prolonged fever and/or weight loss in Thailand, MAC was recovered from the blood in 5 and from bone marrow in 3 out of 37 patients (40). Diagnosis requires that the organism is seen in more than 1 sputum sample or 1 sputum sample plus 1 BAL sample, with the exclusion of

other pathogens. Survival is only 4 months without therapy, and 11 months with ethambutol plus either clarithromycin or azithromycin. A third drug, either RMP, RFB, ciprofloxacin or amikacin, may be added to this regimen (43).

A 2-year retrospective chart and culture review at the Central Chest Hospital in Thailand found pulmonary infections due to *M. kansasii* in 9 patients (44). All were males and 5 were HIV-positive. One patient refused anti-HIV testing but had clinical features and oral hairy leukoplakia. Common symptoms included coughing, dyspnoea, weight loss and fever. Chest pain and haemoptysis were also seen. Chest radiographs mostly revealed bilateral patchy and nodular infiltrations with multiple cavities. Other reports showed more unilateral disease. There were no pleural effusions, hilar or mediastinal lymphadenopathy, or miliary pattern. Resistance to INH was seen in 44%, RMP in 33%, and multidrug resistance was observed in 22%. All strains were sensitive to EMB, streptomycin (S) and ofloxacin. Sputum conversion was achieved in all patients, but 2 HIV-seropositive patients died from other opportunistic infections.

Fungi

The prevalence of fungal pneumonia and the aetiologic agents vary depending on locality. *P. carinii* is the most frequent cause of fungal pneumonia, and *Cryptococcus neoformans* ranks second worldwide. In a report from Bombay, India, *P.* carinii was recovered by BAL cytology and transbronchial biopsy (TBB) in 3 out of 5 HIV-positive patients presenting with interstitial pneumonitis (45). This pattern was also observed in a study of HIV-infected inpatients between 1992 and 1993 in Chiangmai, Thailand (12). *P. marneffei* was the next most frequently implicated fungal pathogen in northern Thailand. *Aspergillus* species were rarely seen. In fact, in roughly one thousand cases who underwent BAL over a period of 10 years, we found this to be the cause in fewer than 5 cases.

P. carinii pneumonia is the first opportunistic infection in 15% of HIV-infected patients on prophylaxis, and 45% of those not taking prophylaxis (2). It is a harbinger of death in the United States, but this is somewhat less important in other areas of the world where the prevalence of TB is higher. The strongest risk factor for PCP is the degree of immunosuppression as indicated by the CD4 count. Approximately 95% of patients with PCP have CD4 count of fewer than 200 cells/μL. This infection is reduced by the use of antibiotic prophylaxis among those with counts less than 200 cells/mL. PCP can also occur during the profound lymphopenia seen in primary HIV infection. An insidious onset of fever and dry cough over 2–4 weeks before seeking medical care is typical (2,3). Fever may be of low or high grade. Progressive dyspnoea on exertion ensues. About 5% of patients do not have symptoms, while the presence of productive cough with shaking chills and pleuritic chest pain should suggest another diagnosis (2). Tachypnea is common, so is tachycardia and cyanosis. Auscultation is usually normal, but rhonci and crackles may be heard in the periphery. Occasionally there is hepatosplenomegaly and pneumothorax. Pleural effusion, though not often detected, is exudative with organisms seen in the fluid (2,46). Anaemia, lymphopenia and hypoalbuminaemia are common. A high level of serum lactate dehydrogenase (LDH) is a very sensitive indicator among those symptomatic patients (2,47).

TNF-α seems to play a key role in the defence against the organism albeit by an unknown mechanism. It should be noted that alveolar lymphocytes of patients infected with *P. carinii* have higher quantity of HIV compared to those uninfected, and this may be the effects of TNF-α (2). On gross examination, the disease typically involves several lobes on both lungs, but patients on prophylaxis can have a lobar pattern either diffusely or as nodules. Microscopically, one typically finds alveolo-interstitial inflammation, type II pneumocyte proliferation and vacuolated eosinophilic "exudates" within alveolar spaces which are cysts and trophozoites mixed with host materials. Patients on prophylaxis may present atypically with diffuse alveolar damage, granulomas, bronchiolitis obliterans organizing pneumonia, vascular infiltration, parenchymal calcification, necrosis and cyst formation.

Normal chest radiographs may be seen in 10%, but the most common pattern is that of bilateral, symmetrical, ground-glass, finely granular or reticular opacities, often with perihilar,

lower-zone predominance (2,3). Occasionally atypical manifestation may be seen including localized interstitial or alveolar infiltration, and cyst or bullae formation. Pneumatoceles occur in 5–35% of patients, more commonly in the upper lobes. These, in addition to smoking history and aerosolized pentamidine, are risk factors for pneumothorax which are seen in 5–10%. High-resolution CT (HRCT) mainly reflects the radiographic findings. Whereas ground-glass attenuation progressing to consolidation is observed initially, subacute or resolving disease usually presents as irregular linear opacities and interlobular septal thickening. A normal HRCT finding practically rules out PCP (48).

PCP causes restrictive defects in pulmonary function testing, associated with a low diffusing capacity (DL_{CO}), respiratory alkalosis, hypoxaemia and arterial desaturation with exercise (2,49,50). PCP is unlikely if DL_{CO} is normal (47). Desaturation is defined as a value lower than 90% or more than 3% decrease after exercise (51). After recovery from pneumonia, lung volumes return to normal but diffusing capacity, though improved, never normalizes. These tests all have high sensitivities, but low specificities (2).

The best strategy to diagnose PCP remains undetermined. Smear of expectorated sputum has a low yield of only 9% in Thailand (52). Mucus digestion followed by centrifugation of the sediment can increase the yield. Sputum induction has an overall sensitivity of about 67% (2). Patients must not be too dyspnoeic, nauseated or uncooperative, and must be able to produce sputum after hypertonic saline nebulization. BAL is the procedure of choice for the diagnosis due to its high sensitivity, greater than 95%, in the absence of prolonged empiric therapy. The yield is greatest when performed in the areas of high radiographic involvement. TBB does not add much to the yield, except in patients on prophylactic pentamidine (53), but significantly increases the risk of bleeding and pneumothoraces. In a study using BAL in Chiangmai, Thailand, the prevalence of PCP among HIV-positive patients hospitalized for pneumonia was 35.7%, and this was part of mixed infections in 28.6% (12).

The drug of choice for PCP is co-trimoxazole (trimethoprim/sulfamethoxazole) which is effective in 70–80%. The efficacy and side effects are comparable to pentamidine, but the cost is much less (54). The recommended dosage is trimethoprim 20 mg/kg/d and sulfamethoxazole 100 mg/kg/d, divided into tid or qid for 2–3 weeks. Intravenous injection should be used in severe cases then a switch to tablets is made once the condition improves. If side effects develop, the dosage may be reduced 25% with the same efficacy (55). Side effects include fever, rash, headaches, nausea, emesis, leucopenia, and thrombocytopenia. If severe reactions occur, the antibiotic needs to be changed to intravenous pentamidine at 4 mg/kg/d. Observe signs of hypotension and follow leukocyte counts, serum electrolytes, calcium, glucose and renal function. If renal insufficiency develops, reduce the dosing frequency to every other day or the dose to 2–3 mg/kg/d (55,56). Clindamycin (450–600 mg tid – qid) plus primaquine (15 mg bid), either oral or intravenous form, can be another alternative, especially for resistant *Pneumocystis* with an efficacy of 80% (57). For less severe cases, trimethoprim (20 mg/kg/d) plus dapsone (100 mg/kg/d) can replace co-trimoxazole in those unable to tolerate co-trimoxazole (58,59). Corticosteroids should be started within 3 days for moderate to severe cases, which results in halving the mortality rates and faster resolution of symptoms and hypoxaemia (60). Partial pressures of oxygen in these cases are less than 70 mm Hg or oxygen saturations less than 92%. The steroid can be prednisolone at 1–2 mg/kg/d in 2–3 divided doses, or high-dose hydrocortisone, methylprednisolone or dexamethasone initially with a tapering course over 2–3 weeks.

Mortality rate was as high as 25% during the first episode at the beginning of the epidemic. This has decreased to less than 15% due to ARV and prophylactic drugs against *P. carinii* (2). Long-term survival remains poor however, with more than half alive 1 year after the diagnosis, 40% after 2, and 6% after 4 years. Factors found to influence in-hospital death in patients admitted to the intensive care unit include functional status, time since AIDS diagnosis, HIV disease stage, high LDH, hypoalbuminaemia, a simplified acute physiology score, the need for and duration of mechanical ventilation, and neutrophilia in BAL (61). Persistence of organisms and delayed clearance after adequate therapy are risk factors

for early relapse and impaired survival (2). The disease seems to have entered the "third era" of PCP and respiratory failure. Although the incidence rate for respiratory failure is decreasing, the mortality rate from such an episode is increasing. Patients who develop respiratory failure despite appropriate antibiotics and systemic corticosteroids have a very poor prognosis.

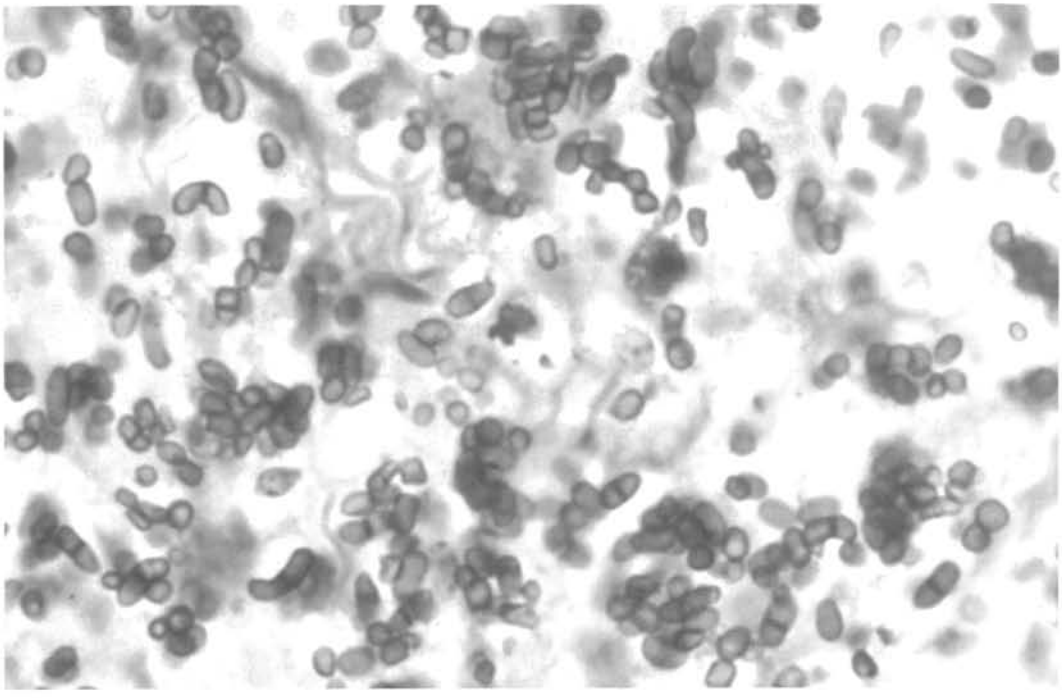
C. neoformans is the cause of the most common systemic fungal infection in patients with HIV, usually when the CD4 count is less than 100 cells/μL. The organism is seen worldwide especially in soil contaminated with birds' feces. After entry by inhalation, unencapsulated fungi are ingested by neutrophils, but those with capsules induce granuloma formation and require cell-mediated immunity to destory. Due to the immune defects in patients with AIDS, the fungi spread to other sites such as the meninges and skin (62).

Most cases of pneumonia are clinically silent, and up to 30% may be coinfected with *P. carinii* or other organisms. Pulmonary symptoms and signs are nonspecific. Onset may be acute or insidious, with fever, headache, cough, dyspnoea and pleuritic chest pain. Haemoptysis is uncommon. The course can be so severe that patients develop acute respiratory distress syndrome. The most common radiographic findings are a diffuse reticulonodular infiltration similar to those seen in PCP (50–60%) or discrete nodules (30%), the latter seen among those with less severe immunocompromise. Less common manifestations include ground-glass opacities, consolidation, cavitary or mass lesions, miliary nodules, lymphadenopathy, pleural effusions or even a normal pattern (2,63,64). Sputum smear and culture are positive in less than 25%, and bronchoscopy is usually needed (65). In one study, sputum, if available, provided a diagnosis in 62.5%, while BAL gave a yield of 31.2% (12). The fungus appears as an encapsulated yeast by Gram's, Kinyoun or Wright stains. Cryptococcal antigen may be detected in BAL or serum (66,67).

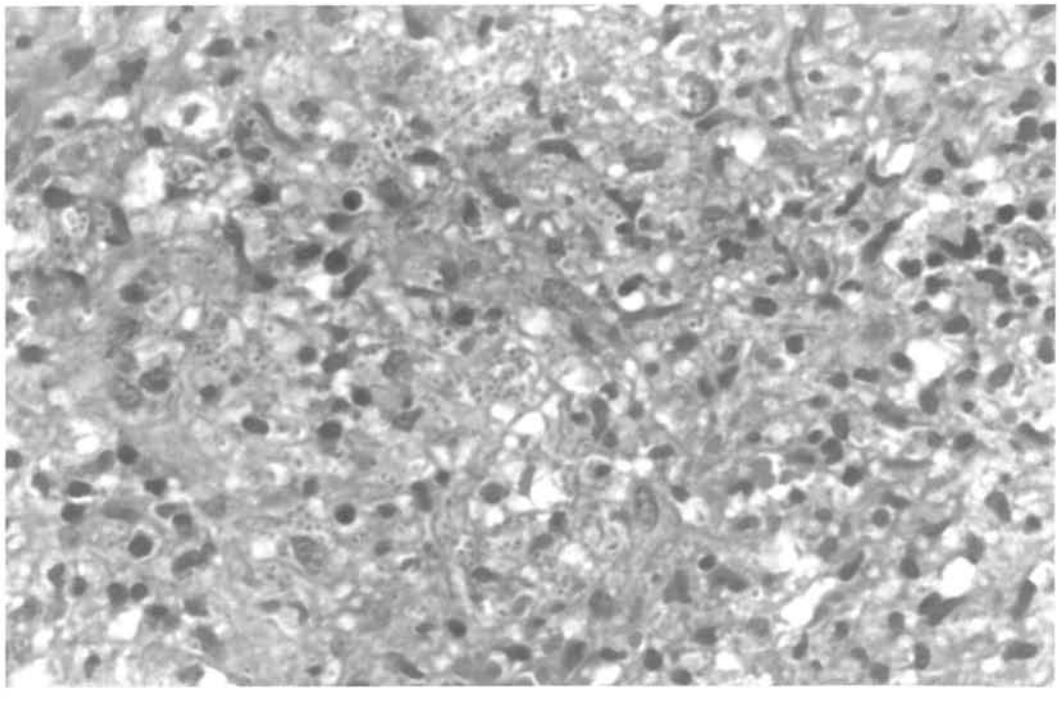
Treatment is with 2 weeks of amphotericin B at 0.5 mg/kg/d, followed by 8–10 weeks of oral fluconazole at 400 mg/d (68). For patients who have pneumonia with minimal or no meningeal involvement, a 6–10 week course of oral fluconazole may be used. Itraconazole is not an effective alternative since it does not have good penetration into the central nervous system (69), but it may be used after the patient has already received 2 weeks of amphotericin B (70). Liposomal amphotericin B, due to its high costs, is reserved for cases with high risks of side effects such as renal toxicity (71). Less than 50% of AIDS cases with cryptococcal infection survive more than 1 year (2). Prognosis is even worse in cases with meningitis and respiratory failure.

In parts of Southeast Asia including northern Thailand, *P. marneffei* spreads widely among patients with AIDS (10,72,73). This fungus is also endemic in the southern part of China. Recently 4 cases were reported from Manipur, India, with presumptive diagnosis in at least 20 additional patients (74). Over a span of 18 years, there have been 5477 reported cases among AIDS patients in Thailand (2.4% of all AIDS-related conditions) (6). The route of entry is believed to be via inhalation and via skin cuts in contact with contaminated soil. If the immunity is relatively preserved, the fungus will be destroyed or confined in a granuloma. Necrosis, neutrophilic infiltration, and yeast-like cells are seen both intracellularly and extracellularly. The yeast cells resemble *H. capsulatum* var. *capsulatum* in size, shape and invasion into the reticuloendothelial system but they divide by fission instead of budding (Figure 1). On Gram's stain, they appear as very large gram-negative rods. Granulomas may show up on chest radiograph similar to tuberculous or cryptococcal scars. Once the CD4 drops below 100 cells/μL, the fungus spreads haematogenously to the skin, bone marrow, liver, lymph nodes, and the central nervous system. Occasionally the disease can be caused by reactivation (75,76).

Patients present nonspecifically with cough, dyspnoea, weight loss, high fever which may be acute or chronic, and quite often with symptoms and signs of other organ involvement. The characteristic skin lesions appear as well circumscribed dark red papules with central umbilication or necrosis, and crusting at the edges, which resemble giant molluscum contagiosum (77). Anaemia is also common. Roughly half may have coinfection with other organisms. Most chest radiographs show diffuse interstitial infiltration which may be reticulonodular, reticular or miliary. Other patterns are also seen, such as consolidation with or without cavities, hilar or mediastinal



(a) PAP smear from bronchoalveolar lavage fluid. Notice sausage-shaped yeast cells with central septation



(b) H&E staining from transbronchial biopsy showing mononuclear cell infiltration

Figure 1. Results from bronchoscopy in a patient with *Penicillium marneffei* infection

lymphadenopathy and pleural effusion (Figure 2) (10). Mass lesion was reported in one case (77). If the patient could provide a sputum sample, the diagnostic efficacy was 83.3%; otherwise, the yield was 38.5% with BAL (12).

Treatment for *P.* marneffei includes amphotericin B (0.5 mg/kg/d) or oral itraconazole (400 mg/d) for 8–12 weeks. Fluconazole is ineffective (78). Within 2 weeks of therapy, the skin lesions resolve, but radiographic changes may take several months to a few years to resolve (73).

H. capsulatum is a soil fungus found in areas of birds' or bats' droppings. Histoplasmosis occurs in 2% of AIDS patients in the United States (2), and has been reported from Africa and the Far East (79). There have been 517 reported cases or 0.2% of all AIDS-defining conditions in Thailand. The fungus enters via spore inhalation, which can result in progressive primary infection or latent infection with subsequent reactivation. Dissemination occurs in 75% of patients infected with *H. capsulatum*, usually with CD4 of less than 100 cells/μL. The symptoms and signs of disseminated disease are nonspecific, with fever, cough, weight loss, diarrhoea, anaemia, lymphadenopathy and hepatosplenomegaly being the most common (2,80,81). Leukopenia and thrombocytopenia are seen. Radiographic findings are nonspecific, ranging from diffuse nodular opacities to consolidation. Small pleural effusions and hilar or paratracheal lymphadenopathy have been described. Radiographic and HRCT pictures of miliary histoplasmosis are similar to miliary TB. Diagnosis is confirmed by detecting *Histoplasma* polysaccharide antigen in serum or urine or by finding the organism in the sputum, BAL, blood, bone marrow, lymph nodes or skin lesions. Cure rates with itraconazole are as high as 85% (82). In the first 3 days, patients should take 200 mg po tid, followed by 200–400 mg qd for 4–6 weeks. Severe cases should start with amphotericin B.

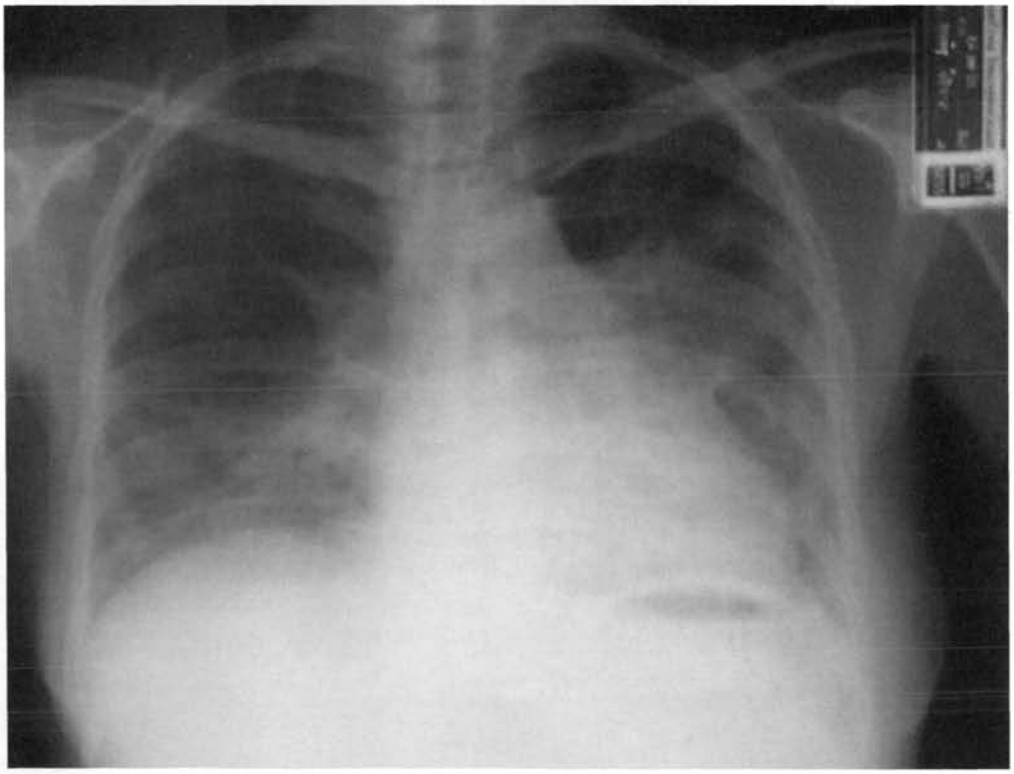


Figure 2. Chest radiograph of a patient with Penicilliosis. There is diffuse alveolar infiltration resembling *Pneumocystis Carinii* pneumonia.

Pulmonary aspergillosis occurs in 0.1–1% of AIDS patients (2,83). Most cases have neutropenia, a history of broad-spectrum antibiotic or corticosteroid use, CD4 of less than 50 cells/μL or on anti-neoplastic medications (83,84,85). Almost 80% of affected patients have parenchymal invasion. Symptoms are insidious and progressive, and consist of fever, cough, chest pain and dyspnoea. Chest radiographs show cavitary lesions especially of the upper lobes, localized alveolar infiltrates and diffuse infiltrations which may be nodular, reticulonodular or reticular. Aspergillomas have been seen in upper lobar cavities. About half the patients have bilateral air-space or interstitial opacities. Tracheobronchial aspergillosis is seen in 20% of patients. Patients present with dyspnoea and cough with wheezing. Chest radiographs may be normal or may show atelectases or patchy haziness. Diagnosis requires a positive culture from a normally sterile site or demonstration of tissue invasion. Although recovery of the fungus from sputum or BAL may be just colonization, such findings in a compatible presentation without other identifiable causes should provide a basis of therapy (86). The drug of choice is amphotericin B. Surgery is reserved for those patients with localized disease or massive haemoptysis. HAART should be given afterwards to reduce recurrence. Despite amphotericin B, mortality rates may be as high as 90% (85). More than half of those with invasive aspergillosis die as a result of massive haemoptysis, progressive respiratory failure or systemic dissemination (2).

Viruses

HIV itself has been implicated as the cause of pulmonary disease in some patients, in the absence of apparent opportunistic infection or neoplasm (2). Patients usually have reduced DL_{CO} and lymphocytic alveolitis. It is possible that lymphocytic interstitial pneumonitis (LIP) and nonspecific interstitial pneumonitis (NSIP) are reaction to the viral infection.

The role of CMV is unclear. In a study of 114 HIV-infected patients with pneumonia, pathological CMV pneumonitis was seen in only 2. However, in another review of 54 autopsies of AIDS patients, 39 (72%) had CMV infection, 31 (57%) of whom had pneumonitis, and CMV was the only identifiable organism in 2 cases (2). In yet another autopsy study, 64% had CMV infection but only half died from respiratory failure and they had other coinfections (87). Homosexual patients tend to develop more CMV pneumonitis than other risk groups (88). CMV infection in organs other than the eyes, liver, spleen and lymph nodes had been reported in 511 cases (0.2% of AIDS-related conditions) over 18 years in Thailand. In a study from Chiangmai, Thailand, the organism was recovered in 5.1% of HIV patients admitted for pneumonia and the patients all had other infections as well (12). Patients usually present with fever, dyspnoea and dry cough, indistinguishable from PCP, or other pneumonias from bacteria or fungi. Some patients may also present with CMV retinitis. The most common radiographic finding is that of bilateral ground-glass opacities or areas of consolidation. Lung biopsy is not usually performed. BAL recovers mixed neutrophilic and mononuclear infiltration with typical Cowdry A intranuclear and cytoplasmic inclusions (89). Although specific, typical histopathological and cytologic studies from bronchoscopy are not sensitive enough. BAL culture has a yield of 50% but this is not specific enough because asymptomatic patients also have similar yields (89,90). Treatment should be given to those patients with symptoms and evidence of only CMV infection. One of our coauthors gave ganciclovir at 5 mg/kg IV q 12 hours for 2 weeks, and 7 out of 10 patients improved both clinically and radiographically. Foscarnet is an alternative albeit with less evidence than ganciclovir.

Parasites

Approximately 40% of patients with pneumonia due to *Toxoplasma gondii* have AIDS (91,92). Pathogenesis is by reactivation, and most cases present with CNS symptoms (2,91). Cerebral toxoplasmosis had been reported in 6042 cases (2.6% of AIDS-related conditions) in Thailand (6). Only about 0.5% of these also have pneumonia with fever, cough, dyspnoea, and a reticulonodular or ground-glass appearance of chest radiographs. This clinical presentation is very much like that of PCP, TB or fungal pneumonias. Lobar

consolidation as well as pleural effusion may be seen. CD4 is typically less than 100 cells/μL. Diagnosis is made by BAL or TBB showing trophozoites on Giemsa stain. Immunoglobulin-M does not usually rise in patients with AIDS and immunoglobulin-G (IgG) only reflects a history of infection which may not be responsible for the current pneumonia (7,93). The absence of IgG makes this diagnosis unlikely. The treatment is a 2–3 week course of pyrimethamine plus sulfadiazine. Pyrimethamine is given at 200 mg for the first dose, followed by 50–75 mg qd. The dosage for sulfadiazine is 4–6 g qd. Leucovorin at 10–20 mg qd is added to prevent anaemia (94). Clindamycin at 1200 mg qd is a substitute for sulfadiazine (95). Cure rates are about 50–77% (91), but relapse is high (96).

Strongyloides stercoralis is found worldwide especially in the tropics and in warm climates. The larva tunnels through the skin of the feet. Most patients are asymptomatic or have minimal gastrointestinal symptoms. Larval dissemination to various sites such as the lungs occurs in patients with immunodeficiency. Despite this fact, this is uncommon among AIDS patients in endemic areas (97). This diagnosis should be suspected in a severely febrile patient with gastrointestinal and pulmonary symptoms including dyspnoea and cough (2,98). Wheezing is heard. Coexisting parasitaemia and bacterial meningitis are common. Chest radiograph shows diffuse fine nodular, reticulonodular or miliary pattern and air-space consolidation. Larvae can be recovered in the sputum and BAL fluid, and eosinophilia is characteristically absent in severe cases. Treatment is with thiabendazole at 25 mg/kg bid for 5–14 days. Alternatively albendazole or ivermectin may be used (99,100).

Non-Infectious Aetiologies

About 25% of AIDS patients have malignant neoplasm, 3 of which are included in the case definition of AIDS: Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL) and cervical carcinoma (2). KS and NHL make up over 90% of these AIDS-defining malignancies. HIV-seropositive patients may present with other non-neoplastic abnormalities. Prominent in this group is non specific interstitial pnemonitis (NSIP) in adults or lymphocytic interstitial pneumonia (LIP) in children. Secondary alveolar proteinosis may develop with TB or PCP (101). Idiopathic bronchiolitis obliterans with organizing pneumonia (BOOP) is rare, but the organizing feature may be seen secondary to infection (102).

Kaposi's sarcoma (KS)

KS occurs in 15–20% of HIV-infected male homosexuals, and in 1–3% of seropositive heterosexuals (2). An autopsy study of HIV-seropositive patients in Mumbai found 1 case of KS, representing 1% of the series (13). It is the cause of pulmonary disease in one-quarter to one-third of patients with extrapulmonary KS, and about half of deaths with cutaneous KS also have pulmonary involvement at autopsy (103). Other involved sites include oral and intestinal mucosa. Patients may be asymptomatic or complain of dyspnoea, non-productive cough, occasionally with blood-streaked sputum, fever and chest pain (104). Auscultation is often unremarkable (105). Currently human herpesvirus 8 (KS-associated herpesvirus or KSHV) has been linked to the pathogenesis of the tumor. The positive and negative predictive values of KS for those with or without antibodies to KSHV were 82% and 75%, respectively. The median time from HIV seroconversion to development of KS was 33 months (106). Grossly, the small, indurated, reddish or purplish lesions are mostly in the pleural or bronchovascular interstitium. These may result in nodules or consolidation. Lymph nodes may be enlarged. Radiographs show bilateral, ill-defined, nodular or linear infiltrations, often with a perihilar predominance, which makes it difficult to differentiate from infection. Other findings include Kerley B lines, pleural effusion (30–70%), hilar or mediastinal lymphadenopathy (5–15%), and 5–15% can have normal radiographs (103). The effusion, which can be unilateral or bilateral, is clear or serosanguinous. Characteristically HRCT reveals irregularly shaped, spiculated or poorly defined nodules, predominantly with perihilar and peribronchoarterial distribution, bronchial wall thickening, septal thickening, areas of ground-glass or air-space consolidation, and pleural effusion.

Bronchoscopic finding of violaceous or bright-red, irregularly-shaped, flat or slightly raised plaques, most often at the carina of segmental and large subsegmental bronchi is diagnostic (105,107). This disease is rare in Thailand (6). Overall there were 326 reported cases or 0.1% of AIDS-defining diseases in Thailand. KS can regress on HAART and intensive chemotherapy. Radiation therapy may have a role for symptomatic airway obstruction by such lesions. Pulmonary involvement has median survival of between 2 and 10 months. Indices for poor prognosis include pleural effusion, severe breathlessness, absence of cutaneous lesions, CD4 less than 100 cells/μL, previous opportunistic infection, leukopoenia or anaemia, and the absence of radiographic response to treatment.

Non-Hodgkin's lymphoma (NHL)

NHL occurs in 2–10% of HIV-infected patients, with increasing prevalence upon worsening immune status (2,9). The lung is the most common site of extra-nodal disease (30%). Generally the disease is high-grade, widely disseminated and extra-nodal at presentation. Small, non-cleaved cell (Burkitt-like) type accounts for one-third, and the remaining cases are mostly of diffuse large cell (immunoblastic) type. Almost all cases are from B-cell lineage. Typically patients have cough, dyspnoea and pleuritic chest pain. CD4 count is less than 100 cells/μL. Multiple nodular or diffuse interstitial infiltrations and pleural effusions are the most common radiographic findings. The nodules are well-circumscribed and may cavitate or have air bronchogram. Lymphadeopathy may be present in about 30% (108). The procedures that give high yields are open-lung biopsy (75%), thoracentesis (75%) and TBB (58%) (109). One of our co-authors found a case proven by TBB in a patient with dry cough, and enlarging cavitary lesion on chest radiograph. Immunoblastic and Burkitt's lymphoma accounted for 529 cases or 0.2% of all AIDS-related diseases in Thailand (6). Median survival from the time of diagnosis is 4–6 months. Chemotherapy may help some patients into remission.

Non-AIDS defining malignancies

Although these neoplasms are not indicative of AIDS, they do occur more among AIDS patients (2,110,111,112,113). Hodgkin's disease is not usually prevalent in the lung.

Lung cancer, predominantly of adenocarcinoma type, occurs at a young age and behaves aggressively in quite a large number of HIV seropositive patients. The reason for this may be related to genomic instability in the tumor. Autopsy series in Mumbai found 1 case of squamous cell carcinoma or 1% of the patients in the study (13). Patients are typically smokers with minimal or no AIDS symptoms. Pulmonary complaints include cough, haemoptysis, pleuritic chest pain and dyspnoea. Chest radiograph may reveal a single or multiple masses, haziness or pleural effusion. Prognosis is poor with survival in a matter of a few months (110,111).

There are no reports of increased incidence of other tracheal and bronchial tumors in HIV-infected patients. In one of our co-author's research, a case of tracheal fibrous histiocytoma presenting with asthma-like cough was found.

Nonspecific interstitial pneumonitis (NSIP)

NSIP is possibly the most common lung abnormality in seropositive adults (2). In a study of 5 HIV-seropositive patients with interstitial pneumonitis in Bombay, India, PCP was present in 3, and the remaining 2 presumably had NSIP because of good response to prednisolone (45). Pathology shows lymphocytic infiltrations of the peribronchiolar, perivascular and interlobular septal interstitium. Minimal or no involvement of the alveolar interstitium is seen. Most patients present with fever, cough, and mild dyspnoea or without symptoms. Though radiographically resembling PCP, immunosuppression is less advanced and LDH is closer to normal. Resolution or stabilization occurs regardless of therapy. Administration of corticosteroids may be considered in severe cases (114,115).

Lymphocytic interstitial pneumonitis (LIP)

LIP, though rare in adults, is relatively common in children and ranks second only to PCP (2,116). The lung parenchyma, especially alveoli, is infiltrated with mature lymphocytes and plasma cells. The lymphocytes are primarily T-cells and polyclonal. Patients present with insidious onset of dyspnoea, cough and fever. CD8 lymphocytosis, diffuse hypergammaglobulinaemia and Sjögren-like disorders are common (114). Chest radiographs show reticular or reticulonodular infiltrations, multiple 2–5 mm nodules and ground-glass appearance. Diagnosis is made by TBB. Corticosteroid can ameliorate dyspnoea, improve oxygenation, and may make the disease quiescent (114,116). A study of BAL in HIV-seropositive patients with pulmonary infection found one case (1%) of adult HIV-seropositive patient with LIP in Thailand (12).

Acute eosinophilic pneumonia

There was one case report of acute eosinophilic pneumonia confirmed by pathology (117) and 3 other patients diagnosed by eosinophilia in BAL fluid (118,119). Patients have acute febrile illness, hypoxaemia, and bilateral pulmonary infiltrations. High numbers of eosinophils (> 25% in cell differential counts) are seen in BAL fluid or in lung biopsy specimens without allergy, infection or other known causes (120). The pneumonia responds very well to high-dose glucocorticoids. It is likely that the disease is more prevalent than thought because patients tend to be treated with steroids for a mistaken diagnosis of PCP (121).

Pulmonary hypertension

In a review of 131 cases, Mehta et al. found that pulmonary hypertension occurred approximately 33 months after HIV serodiagnosis (122). HIV was diagnosed after pulmonary hypertension in 6%, and HIV was the sole risk factor in 82%. Patients presented with progressive dyspnoea (85%), cor pulmonale (30%), non-productive cough (19%) and moderate to severe pulmonary hypertension. Chest radiographs revealed prominent pulmonary arteries and cardiomegaly which agreed with electro-cardiogram. Echocardiography showed right ventricular dilatation. On average, patients expired about 6 months after this diagnosis. Autopsy showed plexogenic arteriopathy. In another report of 76 patients, the level of systolic pulmonary arterial pressure did not correlate with the number of CD4; however, patients with AIDS had higher average pressure (123). The incidence of pulmonary hypertension seems to decrease with HAART.

Alveolar haemorrhage

A prospective study found that alveolar haemorrhage occurred rather frequently (103). Symptoms were usually very mild. Approximately 1% had haemoptysis and 10% had haemosiderin-laden macrophages in BAL fluid. The disease was associated with the following conditions: KS, thrombocytopenia (less than 60,000/cu mm), pleural effusion and CMV pneumonitis.

Asthma

There have been no reports on the comparison between the incidences of asthma among patients with and without HIV. The prevalence of asthma among HIV-infected outpatients was 15% in one study (124). These patients tended to have CD4 count above 200 cells/μL. In another study involving patients with CD4 count below 200 cells/μL, the mean IgE level was higher in those with HIV than those without; however, the prevalence of allergy did not increase (125). There have been conflicting reports on bronchial hyperresponsiveness among HIV-infected patients (126,127). More than half of the patients with PCP have bronchial hyperresponsiveness as well as good response to bronchodilators (128). Some even present with classic asthma in agreement with our experience.

Bronchiectasis

The disease can be seen relatively frequently in both adults and children, although there have been

more reported cases in the paediatric population (129,130,131). Patients tend to be recovering from pneumonia, have recurrent or chronic infections, sinusitis or are active smokers. Symptoms include easy fatigue, cough, haemoptysis and those of infected bronchiectasis. Some cases may become very severe within 1 year (132). Diagnosis is by chest radiograph or even better by HRCT (131).

Emphysema

A study using HRCT of the chest found that smokers with HIV had more emphysema than those without HIV (133). The prevalence was as high as 40% among those with more than 12 pack-year smoking history. BAL did not reveal any organisms but found higher numbers of cytotoxic lymphocytes.

Immune Restitution Syndrome

Immune restitution syndrome is an acute symptomatic or paradoxical deterioration of a pre-existing condition brought on by functional recovery of the immune system. This classically occurs in HIV-seropositive patients with PCP, CMV or TB (134,135). Manifestations include fever, worsening infiltrates, serositis, cutaneous lesions, peripheral and mediastinal lymphadenopathy, with a marked reduction in HIV burden and tuberculin reactivity (136). These reactions are generally self-limited, lasting 10 to 40 days with a median of 15 days. Occasionally patients develop respiratory failure (137).

A review of English medical literature found 46 HIV-positive cases with this syndrome related to infections (138). All occurred after initiation of HAART. Infecting organisms were either slow growers or opportunistic pathogens of relatively low virulence. The organisms involved included *M. tuberculosis* (35.4%), CMV (29.1%), MAC (18.7%), *Cryptococcus* species (8.4%), and *M. xenopi* (2.1%). The median interval before the occurrence of this syndrome for mycobacteria and fungi was 11 days while that for viruses was 42 days. Fever occurred in about 75% of mycobacterial and cryptococcal infections.

There was a report from Canada documenting acute respiratory failure in a Vietnamese patient who started ARV 2 months after therapy for tuberculosis (139). Necrotizing granulomas with acid-fast bacilli were seen on lung biopsy but cultures were negative. Polymerase chain reaction confirmed this to be *M. tuberculosis*. The patient improved rapidly following corticosteroid therapy. This reaction was also reported to occur 3 weeks after starting HAART in a Japanese study, and patients improved after treatment with corticosteroid (140).

There are other incidents of immune restitution unrelated to infections. Subacute hypersensitivity pneumonitis has been reported in a patient having contact with birds after receiving HAART (141). Immune restitution may be responsible for sarcoid-like lung disorder after initiation of HAART (142,143,144). One of our co-authors has seen a patient on nevirapine who was suspected of sarcoidosis with interstitial infiltration and large hilar adenopathy, which resolved after stopping and recurred with re-challenge of the medication.

The diagnosis of this entity should be made only after exclusion of other possibilities such as inadequate antimicrobial therapy, emergence of drug-resistant strains or superinfection or other non-infectious complications. A short course of glucocorticoid may be needed in severe cases.

Diagnostic Approach

History may provide some clues to the diagnosis. Sudden onset raises the possibility of bacterial pneumonia, while chronic disease is probably due to *P. carinii*, fungi and tuberculosis. Homo- or bisexuality increases the likelihood for CMV and KS. Staphylococcal sepsis should be suspected in intravenous drug users. Meanwhile prophylaxis against PCP makes it less likely to develop the disease. Usual symptoms include fever, cough and dyspnoea. Haemoptysis is seen with TB and KS. Pleuritic chest pain occurs with bacterial pneumonia, pleural effusion and pneumothorax.

Signs are not very useful in general. Serious vital signs should prompt urgent bronchoscopy rather than a waiting period of empirical therapy. Occasionally one cannot find any abnormalities. Sometimes signs of consolidation are present, which

suggest bacterial pneumonia, or extrapulmonary signs are seen, e.g., meningeal signs.

Chest radiographs are occasionally normal early in the course of PCP, TB and MAC. Other patterns that are seen are listed in Table 8 (7).

Bacterial aetiologies are suspected when white blood cell counts are higher than 15,000/cu.mm with more than 80% neutrophils or 10% bands. Leukopenia or agranulocytosis implies severe bacterial infection or bone-marrow involvement by TB or fungi or drug reactions, e.g., sulfa drugs or ARV. A normal white blood cell count is suggestive of TB, fungi, parasites or certain viruses. LDH, arterial blood gas, exercise testing and DL_{CO} aid in the diagnosis of PCP. Pleural effusions need to be analyzed by staining and culturing.

Table 8. Abnormal Chest Radiographic Patterns in Common Opportunistic Infections[7]

A. Interstitial-alveolar infiltrates
   PCP
   Cryptococcosis/penicilliosis
   CMV
   Bacteria
B. Reticulonodular-micronodular infiltrates
   TB
   Cryptococcosis/penicilliosis
   PCP
C. Focal infiltrates
   Bacteria — *Nocardia*
   TB
   Cryptococcosis/penicilliosis
D. Adenopathy
   TB
   Fungal infections
E. Effusion
   Bacteria — *Nocardia*
   TB
   Fungal infections

Respiratory specimens include sputum, BAL, TBB and open lung biopsy (OLB). Patients who cannot expectorate may be able to give a sputum specimen after ultrasonic induction with 3% NaCl. BAL could be employed in patients without sputum production, with non-diagnostic sputum, who fail empirical therapy, or who have severe pneumonia. The procedure is very safe and effective in over 95%. On the contrary, TBB does not increase the yield of BAL, but does add risks of bleeding and pneumothorax. Its role is primarily limited to those cases with non-diagnostic BAL or those suspected of non-infectious aetiologies. OLB is likewise done in patients with non-diagnostic BAL and TBB. Specimens may be examined by fresh smear or by staining techniques such as Gram's stain, Kinyoun's stain, Wright's stain, modified acid-fast stain and Gomori's methanamine silver (GMS) stain. Cultures should be obtained for bacteria, mycobacteria and fungi.

A study of 70 patients in Chiangmai, Thailand found that 20% of patients could provide sputum spontaneously, and 13% could be induced (52). Sputum induction gave a diagnosis in 69.2%, mostly by staining (Tables 9 and 10). PCP could be diagnosed by sputum analysis in only 9.1%, which was much less than other infections (36.2%). Mixed infections which were found in 25% could not be diagnosed by sputum examination (12).

Table 9. Diagnostic Efficacy by Sputum[52]

Yield	*Method*		
	Spontaneous (20%)	*Induced (13%)*	*Both (33%)*
Diagnostic	19 (95%)	9 (69.2%)	33 (84.8%)
Staining	10 (52.6%)	5 (55.6%)	15 (53.6%)
Culture	2 (10.5%)	4 (44.4%)	6 (21.4%)
Staining + culture	7 (36.8%)	0	7 (25.0%)
Staining ± culture	17 (89.5%)	0	22 (78.6%)
Non-diagnostic	1 (5.0%)	4 (30.8%)	5 (15.2%)

Table 10. Diagnostic Efficacy and Yield of Sputum Examination by Organism[52]

Pathogen	*N*	*Efficacy (%)*		*Yield*	*(%)*
P. carinii	22	2/4	(50)	2/22	(9.1)
Non-*P. carinii*	69	25/38	(65.8)	25/69	(36.2)
Bacteria	23	8/13	(61.5)	8/23	(34.8)
Nocardia	5	2/4	(50)	2/5	(40)
Mycobacteria	12	5/7	(71.4)	5/12	(41.7)
Fungi	29	10/14	(71.4)	10/29	(34.5)
P. marneffei	13	5/6	(83.3)	5/13	(38.5)
C. neoformans	16	5/8	(62.5)	5/16	(31.2)
Mixed organisms	19	0/9	(0)	0/19	(0)

More than half of the patients in Thailand do not have a definitive diagnosis of pneumonia by sputum analysis or BAL. A study was performed on a decision process based primarily on history, physical examination and chest radiographs to arrive at a presumptive diagnosis (145). The rules used in the decision process were as follows:

1. **Pneumonia** was defined as fever with pulmonary infiltrations.
2. **Pneumocystosis** had diffuse alveolo-interstitial infiltrates without evidence of left ventricular failure or fluid overload.
3. **Bacteriosis** was fever with acute onset and at least one of the following:
   a. Localized alveolar infiltration
   b. Typical patterns of septic emboli
   c. Diagnostic or compatible associated pleural effusions
4. **Mycobacteriosis** had one of the following:
   a. Typical post-primary tuberculous or miliary infiltration
   b. Hilar or mediastinal lymphadenopathy
   c. Insidious onset of fever with localized infiltrations on chest radiographs
   d. Diagnostic or compatible associated pleural effusions
5. **Mycosis** included any type of pulmonary infiltration with extra-pulmonary sites of fungal infection, excluding those due to *Candida*, or with diagnostic associated pleural effusions.

These rules were compared with the results from BAL, and were found to be useful for the diagnosis of pneumocystosis and bacteriosis provided that patients had good follow-up (Table 11) (145). Mixed infections were outside the scope of these rules.

Table 11. Utility of Presumptive Diagnosis[145]

Presumptive diagnosis (95% CI)	*Sensitivity (95% CI)*	*Specificity %*	*Accuracy +*	*Predictive Value −*	
Pneumocystosis (N = 35)	83 (70–90)	75 (67–83)	78	63	90
Bacteriosis (N = 24)	46 (36–56)	94 (89–99)	82	69	85
Mycobacteriosis (N = 12)	83 (76–90)	85 (76–92)	84	42	98
Mycosis (N = 30)	24	100	72	100	70

Empirical Therapy

Pulmonary complications of HIV vary depending on the level of immune deficiency, local infectious epidemiology, illness severity and duration and methods of study. Immunodeficiency can be assessed by the presence of oral candidiasis and/or the level of CD4 in the peripheral blood. If patients are minimally immune deficient, the majority can respond to pathogen-specific therapy as well as HIV-seronegative patients. Exceptions occur among the poor in the city and patients in developing countries (146). Bacteraemia due to *S. pneumoniae* carries a mortality rate of over 50%, which is higher than the rate in HIV-negative patients including the elderly (147). When it is difficult to rule out PCP, high-dose co-trimoxazole should be given, which can cover other common bacteria as well as *Nocardia* (23). With the advent of HAART, pulmonary complications of HIV should be considered as 4 separate groups:

1. Patients without prophylaxis or HAART
2. Patients on prophylaxis without HAART
3. Patients on HAART without prophylaxis
4. Patients on both HAART and prophylaxis

Patients without prophylaxis or HAART

Patients with CD4 above 200 cells/μL have clinical features similar to those without HIV infection except more frequent and more severe bacterial bronchitis and pneumonia (52). Opportunistic infections occur rarely, and TB presents similarly to those without HIV (30,31). Common bacteria causing pneumonia in Thailand include *S. pneumoniae, H. influenzae, S. aureus* and *P. aeruginosa*, which are similar to those reported in developed countries (12,148). Initial empirical therapy needs to cover these core organisms.

Patients with CD4 below 200 cells/μL are at risk for common infections as well as opportunistic infections and other non-infectious complications. The list of pathogens broadens even further with diminishing CD4 level. It is probably more prudent to be aggressive at obtaining a tentative diagnosis, and treat accordingly.

Non-infectious causes can be masked by concurrent infection, so they may need to be treated at the same time. Since HIV-associated malignancies all have poor prognosis despite therapy, patients and loved ones should be counselled so that an appropriate decision regarding care can be made.

Patients on prophylaxis without HAART

In 1999, the United States Public Health Services and the Infectious Disease Society of America issue guidelines on prophylaxis (149). Despite the guidelines, the protective efficacy for PCP is about 50–70%. A study in Thailand found that compliance rate with INH prophylaxis for HIV-positive tuberculin converters was 56.2%, and 1.1% developed TB at 1 to 3 months after starting INH (150). One of our co-authors distributed questionnaires on disease prophylaxis to 83 primary physicians and 31 pulmonologists and found that there were more patients on prophylaxis which was mostly secondary against PCP (151). Primary prophylaxis against TB or *S. pneumoniae* was almost nonexistent. Secondary prophylaxis against *P. marneffei* did not last long due to the high cost of the medicine.

Patients on HAART without prophylaxis

HAART has lowered the incidence of opportunistic infections and KS, but some non-infectious complications have increased (99,152,153). This group of patients may be divided into:

1. **HAART failure.** Approximately 10–30% of patients have drug resistance and 50% have partial response in lowering the viral loads which remain detectable in the blood (154). Infections still occur more frequently among these patients but not as much as those without HAART. Even though viral loads continue to rise, the magnitude is less than would have been without HAART (155,156).
2. **Inappropriate withdrawal of prophylaxis.** Patients should continue to receive prophylaxis for 3–6 months during immune restoration phase because they still remain susceptible. There is also the immune restitution syndrome previously described.
3. **Antiretroviral complications.** Nucleoside analogs can cause lactic acidosis, while

abacavir can cause hypersensitivity pneumonitis which may lead to ARDS.

Patients on both HAART and prophylaxis

Patients with complete response to HAART and on prophylaxis rarely develop opportunistic infections after 3 months. Prophylaxis against fungi and CMV may be discontinued. Infections are mainly those of non-HIV patients, but NHL and lung cancer increase. One of our coauthors found no deaths among 15 patients who responded to HAART during a mean follow-up of 38 months, ranging from 6 to 80 months. This is in contrast to 7 deaths out of 8 patients who either did not take or did not respond to HAART during a follow-up of 30 months, ranging from 10 to 54 months.

Preventive Measures

Minimizing exposure to possible sources is the first rule for HIV-infected patients at risk for developing infections (Table 12) (96,157). The next measure is to provide active vaccinations as appropriate. Vaccination against *S. pneumoniae* should be given to those newly infected patients with a CD4 level of over 200 cells/μL who never received the 23-polyvalent vaccine within 5 years. Patients whose CD4 level is less than 200 cells/μL should be vaccinated, and once again if the level is above 200 cells/μL. Revaccination should be done every 3–5 years thereafter (149,157). Influenza vaccine should be administered annually. It is generally prudent to avoid live viral vaccines.

Drugs for primary and secondary chemoprophylaxis against common opportunistic infections are outlined in Tables 13 and 14 (96,100,149,154,157,159,161), respectively. Primary prophylaxis against PCP should be given to patients with CD4 less than 200 cells/μL, pregnant women, and to those with oropharyngeal candidiasis, and considered for those with AIDS, unexplained weight loss, chronic fever and prior pneumonia of any type. The alternative regimen of thrice-weekly co-trimoxazole is not as effective as that of a daily regimen. Prophylaxis against PCP can be stopped when CD4 rises above 200 cells/μL for 3–6 months (158). In addition, co-trimoxazole, as well as azithromycin and clarithromycin, reduce the frequency of bacterial respiratory tract infections. Although co-trimoxazole taken for PCP prophylaxis can reduce the incidence of bacterial pneumonia, the reliance on this to prevent pneumonia is not encouraged due to the potential introduction of resistant bacteria. Of note, while primary prophylaxis against *T. gondii* follows the PCP guidelines, secondary prophylaxis should be given lifelong.

While primary prophylaxis against fungal infections is controversial, the use of fluconazole against cryptococcosis at 200 mg/d in patients with CD4 of less than 100 cells/μL has been shown to be effective (159). Secondary prophylaxis with 200–400 mg/d of fluconazole is also recommended

Table 12. Avoidance Measures for Certain Lung Pathogens[96,157]

Pathogen	*Sources*
P. carinii	Patients with active PCP
T. gondii	Undercooked red meat; cats that scavenge outdoor food; trash; gardening
M. tuberculosis	Prisons; homeless shelters; certain health care settings
Cytomegalovirus	If seronegative, avoid transfusion with seropositive blood products; unprotected sexual intercourse; child care
C. neoformans	Avian faeces; ground-sweeping; walking bare-footed
P. marneffei	Avian faeces; ground-sweeping; walking bare-footed
H. capsulatum	Caves; avian faeces.

Table 13. Primary Prophylaxis[96,100,157,159]

Pathogen	*Prophylaxis*
P. carinii	Co-trimoxazole, 1 SS or DS tablet qd – tiw Alternatives: co-trimoxazole 1 DS tiw; dapsone 100 mg qd + pyrimethamine 50 mg qw + leucovorin 25 mg qw; dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg qw; atovaquone 1500 mg qd; aerosolized pentamidine 300 mg qm
T. gondii	Co-trimoxazole, 1 DS tablet qd Alternatives: co-trimoxazole 1 SS qd; dapsone 50 mg qd + pyrimethamine 50 mg qw + leucovorin 25 mg qw; atovaquone 1500 mg qd
M. tuberculosis	
INH-sensitive	INH 300 mg + B6 50 mg qd x 9 ms; INH 900 mg + B6 100 mg biw x 9 ms; RMP 600 mg + PZA 20 mg/kg qd x 2 ms. Alternatives: RFB 300 mg + PZA 20 mg/kg qd x 2 ms; RMP 600 mg qd x 4 ms
INH-resistant	RMP 600 mg + PZA 20 mg/kg qd x 2 ms. Alternatives: RFB 300 mg + PZA 20 mg/kg qd x 2 ms; RMP 600 mg qd x 4–6 ms; RFB 300 mg x 4–6 ms
MDR	Consultation with experts
M. avium complex	Azithromycin 1200 mg qw; clarithromycin 500 mg bid Alternatives: RFB 300 mg qd; azithromycin 1200 mg qw + RFB 300 mg qd
C. neoformans	Fluconazole 200 mg qd
S. stercoralis	Thiabendazole 25 mg/kg; ivermectin 200 mg/kg

Notes: SS = single-strength; DS = double-strength; tiw = thrice-weekly; qw = once weekly; qm = once monthly.

Table 14. Secondary Prophylaxis[96,149,154,157,161]

Pathogen	*Prophylaxis*
P. carinii	Same as primary prophylaxis
T. gondii	Sulfadiazine 500–1500 mg qid + pyrimethamine 25–75 mg + leucovorin 10–15 mg qd Alternatives: clindamycin 300 mg qid or 450 mg tid + pyrimethamine 25–75 mg + leucovorin 10–25 mg qd
M. avium complex	Clarithromycin 500 mg bid + EMB 15 mg/kg ± RFB 300 mg qd Alternatives: azithromycin 500 mg + EMB 15 mg/ kg ± RFB 300 mg qd
Cytomegalovirus	Ganciclovir 5–6 mg/kg iv x 5–7 days or 1000 mg po tid; foscarnet 90–120 mg/kg qd Alternative: cidofovir 5 mg/kg qow
C. neoformans	Fluconazole 200–400 mg qd Alternatives: amphotericin B 0.6–1 mg/kg qw – tiw; itraconazole 200 mg qd
H. capsulatum	Itraconazole 100–200 mg qd – bid Alternative: amphotericin B 1 mg/kg qw
P. marneffei	Itraconazole 200 mg qd

Notes: qow = every other week.

(160). For penicilliosis, there have been no reports on primary prophylaxis, and the use of itraconazole for this purpose is not encouraged due to the high cost and the fear of creating resistance to *Candida*. Secondary prophylaxis with itraconazole (200 mg po qd) is however recommended (161). In addition to the roles described, fluconazole is effective for mucosal candidiasis, and itraconazole can prevent histoplasmosis and cryptococcosis but not candidiasis.

Primary prophylaxis against TB is more appropriately called treatment of latent infection, which includes those with close contact with other patients with active TB, and those with positive tuberculin test (at least 5 mm induration with 5-TU PPD). If the exposure has been with MDR-TB, a combination of at least 2 sensitive drugs for 12 months may be used. INH prophylaxis does not prevent TB in anergic HIV-positive patients (24). There were reports of successful secondary prophylaxis in Africa (162).

Primary prophylaxis for MAC should be started when CD4 drops below 50 cells/μL and can be stopped when it is higher than 100 cells/μL for 3–6 months; but secondary prophylaxis should be given lifelong. Azithromycin, given for MAC prophylaxis, may have additional activity against PCP. Primary prophylaxis is not recommended for herpesviruses, however, episodic treatment is given with a high rate of success. Eosinophilic patients in endemic areas may take a single dose of thiabendazole or ivermectin at 200 mg/kg for prophylaxis against *S. stercoralis* (100).

Lastly, HIV-seropositive patients who smoke should be strongly encouraged to quit, which will decrease the risks for respiratory tract infections, emphysema, bronchial hyperresponsiveness and lung cancer.

References

1. Joint United Nations Programme on HIV/AIDS. *Report on the Global HIV/AIDS Epidemic.* Geneva, Switzerland; UNAIDS; June 2000.
2. Fraser RS, Müller NL, Colman N, Paré PD. "The Pulmonary Manifestation of Human Immunodeficiency Virus Infection." In: *Fraser and Paré's Diagnosis of Diseases of the Chest,* 4th ed. Eds. Philadelphia: W.B. Saunders Company 1999, 1641–97.
3. Xu KF, Lu W, Li L, et al. Pulmonary complications in patients with AIDS: A report from a Beijing hospital. *Respirology* 2000; 5:419–21.
4. Brown T, Sittirai W, Vanichseni S, et al. The recent epidemiology of HIV and AIDS in Thailand. *AIDS* 1994; 8(Suppl 2):S131–41.
5. Division of Epidemiology, Ministry of Public Health, Thailand. Reports on Disease Surveillance. 1997.
6. Division of Epidemiology, Ministry of Public Health, Thailand. http://epid.moph.go.th/epi32_aids.html. October 17, 2002.
7. Pothirat C. Pulmonary infection in HIV infected patients. How to approach. *Thai Tuberc J Chest Dis* 1996; 17(2):137–44.
8. Burman WJ, Jones BE. Treatment of HIV-related tuberculosis in the era of effective antiretroviral therapy. *Am J Respir Crit Care Med* 2001; 164:7–12.
9. Wolff AJ, O'Donnell AE. Pulmonary manifestations of HIV infection in the era of highly active antiretroviral therapy. *Chest* 2001; 120:1888–93.
10. Supparatpinyo K, Khamwan C, Baosoung V, et al. Disseminated *Penicillium marneffei* infection in Southeast Asia. *Lancet* 1994; 344:110–3.
11. Payanandana V, Kladphuang B, Talkitkul N, et al. Information in preparation for an external review by the national tuberculosis programme, Thailand. Tuberculosis Division, Department of Communicable Disease Control, Ministry of Public Health, 1995.
12. Pothirat C, Lertprasertsuke N, Tharavichitkul P. Bronchoalveolar lavage of pulmonary infections in HIV seropositive patients. *Thai Tuberc J Chest Dis* 1995; 16:213–20.
13. Lanjewar DN, Duggal R. Pulmonary pathology in patients with AIDS: An autopsy study from Mumbai. *HIV Med* 2001; 2(4):266–71.
14. Marrie TJ. Community-Acquired Pneumonia. *Clin Infect Dis* 1994; 15:501–15.

15. Baron AD, Hollander H. *Pseudomonas aeruginosa* Bronchopulmonary infection in late human immunodeficiency virus disease. *Am Rev Respir Dis* 1993: 148:992.
16. Termsetthacharoen S. Sudsamart C, Boonmeeyen S. *Rhodococcus equi*: An emerging opportunistic pathogen in an AIDS patient. *Thai J Tuberc Chest Dis* 2000; 21:27–39.
17. Watanabe H, Kobayashi S, Watanabe K, et al. Pulmonary infection caused by *Rhodococcus equi* in HIV-infected patients: Report of Four Patients from Northern Thailand. *J Infect Chemother* 2000; 6:229–32.
18. Drancourt M, Bonnet E, Gallais H, et al. *Rhodococcus equi* infection in patients with AIDS. *J Infect* 1992; 24:123–31.
19. Cury JD, Harrington PT, Hosein IK. Successful medical therapy of *Rhodococcus equi* pneumonia in patients with HIV infection. *Chest* 1992; 102:1619–21.
20. Chuchottaworn C, Termsetjaroen S, Poonmee N. Pulmonary nocardiosis in Thai HIV seropositive patients. *Thai AIDS J* 1996; 8:153–4.
21. Karnkawinpong O. Pulmonary nocardiosis in HIV seropositive patients, Supprasitthiprasong Hospital 1997–1998. *Thai J Tuberc Chest Dis* 1998; 19:241–9.
22. Lee CC, Loo LW, Lam MS. Case reports of nocardiosis in patients with human immunodeficiency virus (HIV) infection. *Ann Acad Med Singapore* 2000; 29:119–26.
23. Uttamchandani RB, Daikos GI, Reyes RR, et al. Nocardiosis in 30 Patients with advanced HIV infection: Clinical features and outcome. *Clin Infect Dis* 1994; 18:348–53.
24. Havlir DV, Barnes PF. Tuberculosis in patients with human immunodeficiency virus infection. *N Engl J Med* 1999; 340:367–73.
25. Antonucci G, Girardi E, Raviglione HC, et al. Risk factors for tuberculosis in HIV-infected persons. A prospective study. *JAMA* 1995; 274:143–8.
26. Zumla A, Malon P, Henderson J, Grange JM. Impact of HIV infection on tuberculosis. *Postgrad* Med *J* 2000; 76:259–68.
27. Tansuphaswasdikul S. Thai experiences on the diagnostic approaches and management of pulmonary complications in HIV infection. (Abstract). Proceedings of the 17th Eastern Regional Conference on Tuberculosis and Respiratory Diseases of the IUATLD, Eastern Region, Bangkok, Thailand, 1–4 November 1993.
28. Kaur A, Babu PG, Jacob M, et al. Clinical and laboratory profile of AIDS in India. *J Acquired Immunodeficiency Syndrome* 1992; 5:883–9.
29. Quy HT, Nhien DT, Lan NT, et al. Steep increase in HIV prevalence among tuberculosis patients in Ho Chi Minh City. *AIDS* 2002; 16(6):931–2.
30. Greenberg SD, Fraser D, Suster B, et al. Active pulmonary tuberculosis in patients with AIDS: Spectrum of radiographic findings (including a normal appearance). *Radiology* 1994; 193:115–9.
31. Jones BA, Young SMM, Antoniskis D, et al. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. *Am Rev Respir Dis* 1993; 148:1292–7.
32. Pothirat C, Jiemsripong K, Kiratikanong P. Acute tuberculous pneumonia. *J Infect Dis Antimicrob Agents* 1988; 4:166–74.
33. Lee MP, Chan JWM, Ng KKP, et al. Clinical manifestations of tuberculosis in HIV-infected patients. *Respirology* 2000; 5:423–6.
34. Frye MD, Pozsik CJ, Sahn SA. Tuberculous pleuritis and HIV disease. *Chest* 1995; 108:102S.
35. Riantawan P, Chaowalit P, Wongsangiem M, et al. Diagnostic value of pleural fluid adenosine deaminase in tuberculous pleuritis with reference to HIV coinfection and a Bayesian analysis. *Chest* 1999; 116:97–103.
36. Amatayakul N. Kamnuankun M, Chuchottaworn C. Prevalence of antituberculous drug resistance in human immunodeficiency virus seropositive tuberculosis patients of Central Chest Hospital. *Thai J Tuberc Chest Dis* 1998; 19:73–80.
37. British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: Recommendations of the Joint Tuberculosis Committee of the British Thoracic Society. *Thorax* 1998; 43:536–48.
38. Chaimanee B, Panich V, Kantipong P. et al. Survival during the first year after diagnosis of HIV-positive and HIV-negative tuberculosis patients in Chiang Rai. *Thai J Tuberc Chest Dis* 1994; 15:237–43.
39. Pozniak A. Atypical mycobacteria in AIDS. In: *AIDS and Respiratory Medicine.* Eds. Zumla A, Johnson M, Miller R. London: Chapman & Hall Medical 1997, 199–233.
40. Sathapatayavongs B. Disseminated MAC infection in HIV/AIDS. *Thai AIDS J* 1996; 8:145.

41. Modilevsky T, Sattler FR, Barnes PF. Mycobacterial disease in patients with human immunodeficiency virus infection. *Arch Intern Med* 1989; 149:2201–5.
42. Hawkins CC, Gold JW, Whimbey E, et al. *Mycobacterium avium* complex infections in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1986; 105:184–8.
43. Horsburgh CR Jr, Havlik JA, Ellis DA, et al. Survival of patients with acquired immunodeficiency syndrome and disseminated *Mycobacterium avium* complex infection with and without antimycobacterial chemotherapy. *Am Rev Respir Dis* 1991; 144:557–9[A].
44. Dujneungkunakorn T, Chuchottaworn C, Riantawan P, et al. Pulmonary *Mycobacterium kansasii* infection: Clinical characteristics, radiological findings, susceptibility, and outcome. *Thai J Tuberc Chest Dis* 1998; 19:159–66.
45. Bijur S, Menon L, Lyer E, et al. *Pneumocystis carinii* pneumonia in human immunodeficiency virus infected patients in Bombay: Diagnosed by bronchoalveolar lavage cytology and transbronchial lung biopsy. *Indian J Chest Dis Allied Sci* 1996; 38:227–33.
46. Afessa B. Pleural effusion and pneumothorax in hospitalized patients with HIV infection. *Chest* 2000; 117:1031–7.
47. Zaman MK, White DA. Serum lactate dehydrogenase levels and *Pneumocystis carinii* pneumonia: Diagnostic and prognostic significance. *Am Rev Respir Dis* 1998; 137:796–800.
48. Moskovic E, Miller R, Rearson M. High-resolution computed tomography of *Pneumocystis carinii* pneumonia in AIDS. *Clin Radiol* 1990; 42:239–43.
49. Smith DE, Forbes A, David S, et al. Diagnosis of *Pneumocystis carinii* pneumonia in HIV antibody positive patients by simple outpatient assessments. *Thorax* 1992; 47:1005–9.
50. Stover DE, Meduri GU. Pulmonary function tests. *Clin Chest Med* 1988; 9:473–9.
51. Smith DE, Forbes A, Davies S, et al. Diagnosis of *Pneumocystis carinii* pneumonia in HIV antibody positive patients by simple outpatient assessments. *Thorax* 1992; 47:1005–9.
52. Pothirat C, Lertprasertsuke N, Tharavichitkul P. Sputum analysis of pulmonary infections in HIV seropositive patients (Abstract). Proceedings of the 13th Asia Pacific Congress of Diseases of the Chest. Hong Kong, 5–8 December 1994, p 321.
53. Jules-Elysee K, Stover DE, Zaman MB, et al. Aerosolized pentamidine: Effect on diagnosis and presentation of *Pneumocystis carinii* pneumonia. *Ann Intern Med* 1990; 112:750–7.
54. Klein NC, Duncanson FP, Lenox TH, et al. Trimethoprim-sulfamethoxazole versus pentamidine for *Pneumocystis carinii* pneumonia in AIDS patients: Results of a large prospective randomized treatment trial. *AIDS* 1992; 6:301–5.
55. Sattler FR, Cowan R, Nielsen D, Ruskin J. Trimethoprim-sulfamethoxazole compared with pentamidine for treatment of *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. *Ann Intern Med* 1988; 109:280–7.
56. Miller RF. Prevention and treatment of *Pneumocystis carinii* pneumonia in patients infected with HIV. *Drug Ther Bull* 1994; 32:12–5.
57. Noskin GA, Murphy RL, Black JR, Phair JP. Salvage therapy with clindamycin/primaquine for *Pneumocystis carinii* Pneumonia. *Clin Infect Dis* 1992; 14:183–8.
58. Hardy WD, Feinberg J, Finkelstein DM, et al. Results from recent therapeutic trials for opportunistic infections from the United States. *AIDS* 1994; 8:S4–15.
59. Medina I, Mills J, Leoung G, et al. Oral therapy for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome: A controlled trial of trimethoprim-sulfamethoxazole versus trimethoprim-dapsone. *N Engl J Med* 1990; 323:776–82.
60. National Institutes of Health-University of California Expert Panel for Corticosteroids as Adjunctive Therapy for *Pneumocystis* Pneumonia. Consensus Statement on the use of corticosteroids as adjunctive therapy for *Pneumocystis* pneumonia in the acquired immunodeficiency syndrome. *N Engl J Med* 1990; 323:1500–4.
61. Speich R, Opravil M, Weber R, et al. Prospective evaluation of a prognostic score for *Pneumocystis carinii* pneumonia in HIV-infected patients. *Chest* 1992; 102:1045–8.
62. Chuck SL, Sande MA. Infections with *Cryptococcus neoformans* in the acquired immunodeficiency syndrome. *N Engl J Med* 1989; 321:794–9.
63. Clark RA, Sande MA. Infections with *Cryptococcus neoformans* infection in 68 patients infected with human immunodeficiency virus. *Rev Infect Dis* 1990; 12:768–77.

64. Chechani V, Kamholz SL. Pulmonary manifestations of disseminated cryptococcosis in patients with AIDS. *Chest* 1990; 98:1060–5.
65. American Thoracic Society. Fungal infections in HIV infected persons. *Am J Respir Crit Care Med* 1995; 152:816–22.
66. Baughman RP, Rhodes JC, Dohn MN, et al. Detection of cryptococcal antigen in bronchoalveolar lavage fluid: A prospective study of diagnostic utility. *Am Rev Respir Dis* 1992; 145:1226–9.
67. Eng RH, Bishburg E, Smith SM, et al. Cryptococcal infections in patients with acquired immunodeficiency syndrome. *Am J Med* 1986; 81:19–23.
68. Nelson MR, Fisher M. Cartledge J, et al. The role of azoles in the treatment and prophylaxis of cryptococcal disease in HIV infection. *AIDS* 1994; 8:651–4.
69. De Gan J, Portegies P, Tiessens G, et al. Itraconazole compared with amphotericin B plus flucytosine in AIDS patients with cryptococcal meningitis. *AIDS* 1992; 6:185–90.
70. Vanderhorst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with acquired immunodeficiency syndrome. *N Engl J Med* 1997; 337:15–21.
71. Coker RJ, Viviani M, Gazzard BG, et al. Treatment of cryptococcosis with liposomal amphotericin B (AmBisome) in 23 Patients with AIDS. *AIDS* 1993; 7:829–35.
72. Duong TA. Infection due to *Penicillium marneffei*, an emerging pathogen: Review of 155 reported cases. *Clin Infect Dis* 1996; 23:125–30.
73. Cheng NC, Wong WW, Fung CP, et al. Unusual pulmonary manifestations of disseminated *Penicillium marneffei* infection in three AIDS patients. *Med Mycol* 1998; 36:429–32.
74. Singh PN, Ranjana K, Singh YI, et al. Indigenous disseminated *Penicillium marneffei* infection in the State of Manipur, India: Report of four autochthonous cases. *J Clin Microbiol* 1999; 37:2699–702.
75. Peto TEA, Bull R, Millard PR, et al. Systemic mycosis due to *Penicillium marneffei* in a patient with antibody to human immunodeficiency virus. *J Infect* 1988; 16:285–90.
76. Jones PD, See J. *Penicillium marneffei* infection in patients infected with human immunodeficiency virus: late presentation in an area of nonendemicity. *Clin Infect Dis* 1992; 15:744.
77. McShane H, Tang CM, Conlon CP. Disseminated *Penicillium marneffei* infection presenting as a right upper lobe mass in an HIV positive patient. *Thorax* 1998; 53:905–6.
78. Supparatpinyo K, Nelson KE, Merz WG, et al. Response to antifungal therapy by human immunodeficiency virus infected patients with disseminated *Penicillium marneffei* infections and *in vitro* susceptibilities of isolates from clinical specimens. *Antimicrob Agents Chemother* 1993; 37:2407–11.
79. Hay RJ. Fungal Infections. In *AIDS and Respiratory Medicine.* Eds. Zumla A, Johnson M, Miller R. London: Chapman & Hall Medical 1997, 263–76.
80. Wheat LJ, Slama TG, Zeckel M. Histoplasmosis in the acquired immunodeficiency syndrome. *Am J Med* 1985; 78:203–10.
81. Wheat LJ, Connolly-Stringfield PA, Baker RL, et al. Disseminated histoplasmosis in the acquired immunodeficiency syndrome: Clinical findings, diagnosis and treatment, and review of the literature. *Medicine* 1990; 69:361–74.
82. Wheat J. Halner R, Korzun AH, et al. Itraconazole treatment of disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome. *Am J Med* 1995; 98:336–42.
83. Miller WT Jr, Sais GJ, Frank I, et al. Pulmonary aspergillosis in patients with AIDS. Clinical and radiographic correlations. *Chest* 1994; 105:37–44.
84. Denning DW, Follansbee SE, Scolaro M, et al. Pulmonary aspergillosis in the acquired immunodeficiency syndrome. *N Engl J Med* 1991; 324:654–62.
85. Minamoto GY, Burham TF, Vander Els NJ. Invasive aspergillosis in patients with AIDS. *Clin Infect Dis* 1992; 14:66–74.
86. Lortholary O, Meyoha MC, Dupont B, et al. Invasive aspergillosis in patients with acquired immunodeficiency syndrome: Report of 33 cases. *Am J Med* 1993; 95:177–87.
87. Wallace JM, Hannah J. Cytomegalovirus pneumonitis in patients with AIDS. *Chest* 1987; 92:198–203.
88. Gullant JE, Moore RD, Richman DD, et al. Incidence and natural history of cytomegalovirus disease in patients with advanced human immunodeficiency virus cisease treated with zidovudine. The Zidovudine Epidemiology Study Group. *J Infect Dis* 1992; 166:1223–7.

89. Hayner CE, Baughman RP, Linnemann CC, et al. The relationship between cytomegalovirus retrieved by bronchoalveolar lavage and mortality in patients with HIV. *Chest* 1995; 107:735–40.
90. Mann M, Shelhamer J, Masur H, et al. Lack of clinical utility of bronchoalveolar lavage cultures for cytomegalovirus in HIV infection. *Am J Respir Crit Care Med* 1997; 155:1723–8.
91. Pomeroy C, Filice GA. Pulmonary toxoplasmosis. A review. *Clin Infect Dis* 1992; 14:863–70.
92. Mariuz P, Bosley EM. Luft BJ. Toxoplasmosis in individuals with AIDS. *Infect Dis Clin* 1994; 8:365–81.
93. Evans GT, Schwartzman JD. Pulmonary toxoplasmosis. *Semin Respir Infect* 1991; 6:51–7.
94. McCabe RE, Oster S. Current recommendation and future prospects in the treatment of toxoplasmosis. *Drug* 1989; 38:973–87.
95. Dannemann B, McCutchan JA, Israelski D, et al. Treatment of toxoplasmosis encephalitis in patients with AIDS, a randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. *Ann Intern Med* 1992; 116:33–43.
96. Lane HC, Laughon BE, Falloon J, et al. Recent advances in the management of AIDS-related opportunistic infections. *Ann Intern Med* 1994; 120:945–55.
97. Gompels MM, Todd J, Peters BS, et al. Disseminated strongyloidiasis in AIDS: Uncommon but important. *AIDS* 1991; 5:329–32.
98. Woodring JH, Halfhill H, Reed JC. Pulmonary strongyloidiasis: Clinical and imaging features. *Am J Roentgenol* 1994; 162:537–42.
99. Pitisuttithum P, Supanaranond W, Chindanond D. A randomized comparative study of albendazole and thiabendazole in chronic strongyloidiasis. *Southeast Asian J Trop Med Public Health* 1995; 26:735–8.
100. Torres JR, Isturitz R, Murillo J, et al. Efficacy of ivermectin in the treatment of strongyloides complicating AIDS. *Clin Infect Dis* 1993; 17:900–2.
101. Tran Van Nhieu J, Vojtek AM, Bernaudin JF, et al. Pulmonary alveolar proteinosis associated with *Pneumocystis carinii*: Ultrastructural identification in bronchoalveolar lavage in AIDS and immunocompromised non-AIDS patients. *Chest* 1990; 98:801–5.
102. Joseph J, Harley RA, Frye MD. Bronchiolitis obliterans with organizing pneumonia in AIDS. *N Engl J Med* 1995; 332:273–4.
103. Aboulafia DM. The epidemiologic, pathologic, and clinical features of AIDS-associated pulmonary Kaposi's sarcoma. *Chest* 2000; 117:1128–45.
104. Fouret PJ, Touboul JL, Maynaud CM, et al. Pulmonary Kaposi's sarcoma in patients with acquired immunodeficiency syndrome: A clinicopathological study. *Thorax* 1987; 42:262–8.
105. Huang L, Schnapp LM, Gruden JF, et al. Presentation of AIDS-related pulmonary Kaposi's sarcoma diagnosed by bronchoscopy. *Am J Respir Crit Care Med* 1996; 153:1385–90.
106. Jeyapalan M, Steffenson S. Diagnosis of pulmonary Kaposi's sarcoma in AIDS patients. AIDS patient care. *STDs* 1997; 11:9–12.
107. Judson MA, Sahn SA. Endobronchial lesions in HIV-infected individuals. *Chest* 1994; 105:1314–23.
108. Bazot M, Cadranel J, Benayoun S, et al. Primary pulmonary AIDS-related lymphoma: Radiographic and CT findings. *Chest* 1999; 116:1282–6.
109. Ray P, Antoine M, Mary-Krause M, Lebrette MG, et al. AIDS-related primary pulmonary lymphoma. *Am J Respir Crit Care Med* 1998; 158:1221–9.
110. Albu E, Reed M, Pathak R, et al. Malignancy in HIV/AIDS: A single hospital experience. *J Surg Oncol* 2000; 75:11–8.
111. Ricaurte JC, Hoerman MF, Nord JA, Tietjen PA. Lung cancer in HIV-infected patients: A one-year experience. *Int J STD AIDS* 2001; 12:100–2.
112. Katariya K, Thurer RJ. Thoracic malignancies associated with AIDS. *Semin Thorac Cardiovasc Surg* 2000; 35:124–39.
113. Gallagher B, Wang Z, Schymura MJ, Khan A, Fordyce EJ. Cancer incidence in New York State acquired immunodeficiency syndrome patients. *Am J Epidemiol* 2001; 154:544–56.
114. Schneider RF. Lymphocytic interstitial pneumonitis and nonspecific interstitial pneumonitis. *Clin Chest Med* 1996; 17:763–6.
115. Suffredini AF, Ognibene FP, Lack EE, et al. Nonspecific interstitial pneumonitis: A common cause of pulmonary disease in the acquired immunodeficiency syndrome. *Ann Intern Med* 1987; 107:7–13.

116. Marolda J, Pace B, Bonforte RJ, et al. Pulmonary manifestations of HIV infection in children. *Pediatr Pulmonol* 1991; 10:231–5.
117. Glazer CS, Cohen LB, Schwarz MI. Acute eosinophilic pneumonia in AIDS. *Chest* 2001; 120:1732–5.
118. Mayo J, Collazos J, Martinez E, et al. Acute eosinophilic pneumonia in a patient infected with the human immunodeficiency virus. *Tuber Lung Dis* 1995; 76:77–9.
119. Libre J, Tor J, Mila F. Acute eosinophilic pneumonia. *N Engl J Med* 1990; 322:634–6.
120. Pope-Harman A, Davis W, Allen E, et al. Acute eosinophilic pneumonia: A summary of 15 cases and review of the literature. *Medicine* 1996; 75:334–42.
121. Skiest DJ, Keiser P. Clinical significance of eosinophilia in HIV-infected individuals. *Am J Med* 1997; 102:449–53.
122. Mehta NJ, Khan IA, Metha RN, Sepkowitz DA. HIV-related pulmonary hypertension. Analytic review of 131 cases. *Chest* 2000; 118:1133–41.
123. Pellicelli AM, Barbaro G, Palmieri F, et al. Primary pulmonary hypertension in HIV patients: A systemic review. *Angiology* 2001; 52:31–41.
124. Lin RY, Lazarus TS. Asthma and related atopic disorders in outpatients attending an urban HIV clinic. *Ann Allergy Asthma Immunol* 1995; 74:510–5.
125. Wright DN, Nelson RP Jr, Ledford DK, et al. Serum IgE and human immunodeficiency virus (HIV) infection. *J Allergy Clin Immunol* 1990; 85:445–52.
126. Poirier CD, Inhaber N, Lalonde RG, Ernst P. Prevalence of bronchial hyperresponsiveness among HIV-infected men. *Am J Respir Crit Care Med* 2001; 164:542–5.
127. Wallace JM, Stone GS, Browdy BL, et al. Nonspecific airway hyperresponsiveness in HIV disease. Pulmonary Complications of HIV Infection Study Group. *Chest* 1997; 111:121–7.
128. Schnipper S, Small CB, Lehach J, et al. Pneumocystis carinii pneumonia presenting as asthma: Increased bronchial hyperresponsiveness in pneumocystis carinii pneumonia. *Ann Allergy* 1993; 70:141–6.
129. Sheikh S, Madiraju K, Steiner P, Rao M. Bronchiectasis in pediatric AIDS. *Chest* 1997; 112:1202–7.
130. Verghese A, al-Samman M, Nabhan D, Naylor AD, Rivera M. Bacterial bronchitis and bronchiectasis in human immunodeficiency virus infection. *Arch Intern Med* 1994; 154:2086–91.
131. King MA, Neal DE, St John R, Tsai J, Diaz PT. Bronchial dilatation in patients with HIV infection: CT assessment and correlation with pulmonary function tests and findings at bronchoalveolar lavage. *Am J Roent* 1997; 168:1535–40.
132. Bard M, Coudere L, Saimot A, et al. Accelerated obstructive pulmonary disease in HIV-infected patients with bronchiectasis. *Eur Respir J* 1998; 11:771–5.
133. Diaz PT, King ER, Wewers MD, et al. HIV infection increases susceptibility to smoking-induced emphysema. *Chest* 2000; 117:369–72.
134. Michelet C, Arvieux C, Francois C, et al. Opportunistic infections occurring during highly active antiretroviral treatment. *AIDS* 1998; 12:1815–22.
135. Rodriguez-Rosado R, Soriano V, Dona C, Gonzalez-Lahoz J. Opportunistic infections shortly after beginning highly active antiretroviral therapy. *Antir Ther* 1998; 3:229–31.
136. Narita M, Ashkin D, Hollender E, et al. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med* 1998; 158:157–61.
137. Wislez M, Bergot E, Antoine M, et al. Acute respiratory failure following HAART introduction in patients treated for pneumocystis carinii pneumonia. *Am J Respir Crit Care Med* 2001; 164:847–51.
138. Cheng VCC, Yuen K, Chan W, et al. Immunorestitution disease involving the innate and adaptive response. *Clin Infect Dis* 2000; 30:882–92.
139. Kunimoto DY, Chui L, Nobert E, et al. Immune mediated "HAART" attack during treatment for tuberculosis. *Int J Tuberc Lung Dis* 1999; 3:944–7.
140. Oka S. Unexpected reactions following highly active anti-retroviral therapy in patients with HIV-1 infection and tuberculosis. *Respirology* 2000; 5: 427.
141. Morris AM. Subacute Hypersensitivity pneumonitis in an HIV-infected patient receiving antiretroviral therapy. *Thorax* 2000; 55:625–7.
142. Naccache JM. Sarcoid-like pulmonary disorder in human immunodeficiency virus-infected patients receiving antiretroviral therapy. *Am J Respir Crit Care Med* 1999; 159:2009–13.

143. Wohlrab JL, Read CA, O'Donnell AE. Granulomatous interstitial lung disease in patients with human immunodeficiency virus on highly active antiretroviral therapy. *Chest* 2000; 118:288S.
144. Lenner R, Bregman Z, Teirstein AS, DePalo L. Recurrent pulmonary sarcoidosis in HIV-infected patients receiving highly active antiretroviral therapy. *Chest* 2001; 119:978–81.
145. Pothirat C, Lertprasertsuke N, Tharavichitkul P. Presumptive diagnostic criteria of pulmonary infection in HIV seropositive patients (Abstract). Proceedings of the European Respiratory Annual Congress. Barcelona, Spain, 16–20 September 1995.
146. Gilks CF. The clinical challenge of the HIV epidemic in the developing world. *Lancet* 1993; 342:1037–9.
147. Pesola GR, Charles A. Pneumococcal bacteremia with pneumonia: Mortality in acquired immunodeficiency syndrome. *Chest* 1992; 101:150–5.
148. Afessa B, Green B. Bacterial pneumonia in hospitalized patients with HIV infection. *Chest* 2000; 117:1017–22.
149. USPHS/IDSA Prevention of Opportunistic Infections Working Group 1999. USPHS/IDSA Guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *Ann Intern Med* 1999; 131:873–908.
150. Cheepsattayakorn A. Isoniazid prophylactic therapy in HIV-infected individuals. *Thai J Tuberc Chest Dis* 1998; 19:149–57.
151. Pothirat C. HIV and lung infection in Southeast Asia. Joint Scientific Meeting of Hong Kong Thoracic Society and American College of Chest Physicians (Hong Kong & Machau Chapter). Hong Kong Convention and Exhibition Center, Hong Kong, 10–11 March 2001.
152. Kaplan JE, Hanson D, Dworkin MS, et al. Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2000; 30:S5–14.
153. Rabkin CS, Testa MA, Huang J, et al. Kaposi's sarcoma and non-Hodgkin's lymphoma incidence trends in AIDS Clinical Trial Group Study Participants. *J Acquir Immune Defic Syndr* 1999; 21:S31–3.
154. Bozzette SA, Berry SH, Duan N, Frankel MR. The care of HIV-infected adults in the United States. HIV Cost and Services Utilization Study Consortium. *N Engl J Med* 1998; 339:1897–904.
155. Ledergerber B, Egger M, Opravil M, et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients. A Prospective Cohort Study. Swiss HIV Cohort Study. *Lancet* 1999; 353:863–8.
156. Deeks SG, Barbour JD, Martin JN, et al. Sustained CD4+ T cell response after virologic failure of protease inhibitor-based regimens in patients with human immunodeficiency virus infection. *J Infect Dis* 2000; 181:946–53.
157. Kovacs JA, Masur H. Prophylaxis against opportunistic infections in patients with human immunodeficiency virus infection. *N Engl J Med* 2000; 342:1416–29.
158. Soriano V, Dona C, Rodriguez-Rosado R, et al. Discontinuation of secondary prophylaxis for opportunistic infections in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS* 2000; 14:383–6.
159. Powderly WG, Finkelstein DM, Feinberg J, et al. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1995; 332:700–5.
160. Bozzette SA, Larsen RA, Chi J, et al. A placebo-controlled trial of maintenance therapy with fluconazole after treatment of cryptococcal meningitis in the acquired immunodeficiency syndrome. *N Engl J Med* 1991; 324:580–4.
161. Supparatpinyo K, Perriens J, Nelson KE, Sirisanthana T. A controlled trial of itraconazole to prevent relapse of *Penicillium marneffei* infection in patients infected with the human immunodeficiency virus. *N Engl J Med* 1998; 339:1729–43.
162. Fitzgerald D, Desvarieux M, Severe P, et al. Effect of post-treatment isoniazid on prevention of recurrent tuberculosis in HIV-1 infected individuals: A randomized trial. *Lancet* 2000; 356:1470–4.

13 Influenza

Joseph S M Peiris and Kwok Yung Yuen

Introduction

Kilbourne has aptly called influenza "an invariant disease caused by a variant virus". The first convincing description of an influenza pandemic was in 1580 although there are descriptions of possible pandemics that date back to the twelfth century. As with pandemics in our own era, that of 1580 started in Asia, it spread throughout Europe within a 6 month period and subsequently spread to America (1).

The Virus

Influenza virus is an enveloped virus with a segmented RNA genome. There are three types of influenza viruses, types A, B and C, which are epidemiologically and antigenically distinct. All three types cause human infection but only influenza A and B cause significant human disease. The viral envelope contains two surface glycoproteins, the haemagglutinin (H) and neuraminidase (N) (Figure 1). Subtypes of influenza A virus are recognised based on antigenic differences in the H and N antigens. These are numbered in the order of their recognition. The first H and N antigens to be recognised following the initial isolation of the virus in the 1930s are designated H1 and N1 antigens and the virus is designated the H1N1 subtype. Subsequently two other H subtypes (H2, H3) and one other N subtype (N2) have appeared in the human population. Human influenza viruses are designated according to their type, the place of first isolation, the laboratory isolate number, the year of isolation and virus subtype. Thus, A/Sydney/05/97 (H3N2) denotes an influenza virus of type A, first isolated in Sydney, the fifth influenza strain isolated in that laboratory in 1997 and carrying H and N antigens belonging to the subtypes H3 and N2 respectively.

Epidemics of influenza A and B occur every few years, when the antigens of the virus surface change sufficiently to partially evade pre-existing host immunity. This is termed "antigenic drift" and occurs due to immune selection of variants derived from mutations of the virus RNA (Figure 2). Less often, an influenza A virus containing a radically different H or N antigen ("antigenic shift") appears in humans and the lack of pre-existing immunity in the human population may then result in a pandemic. This occurred three times during the last century, the so-called "Spanish-flu" pandemic caused by the H1N1 virus in 1918, the "Asian-flu" pandemic associated with the H2N2 subtype virus in 1957 and the "Hong Kong-flu" pandemic due to the H3N2 virus in 1968. The new pandemic virus usually displaces its predecessor (Figure 3), but in 1977, the H1N1 subtype reappeared and has co-circulated with the H3N2 subtype up to now (2).

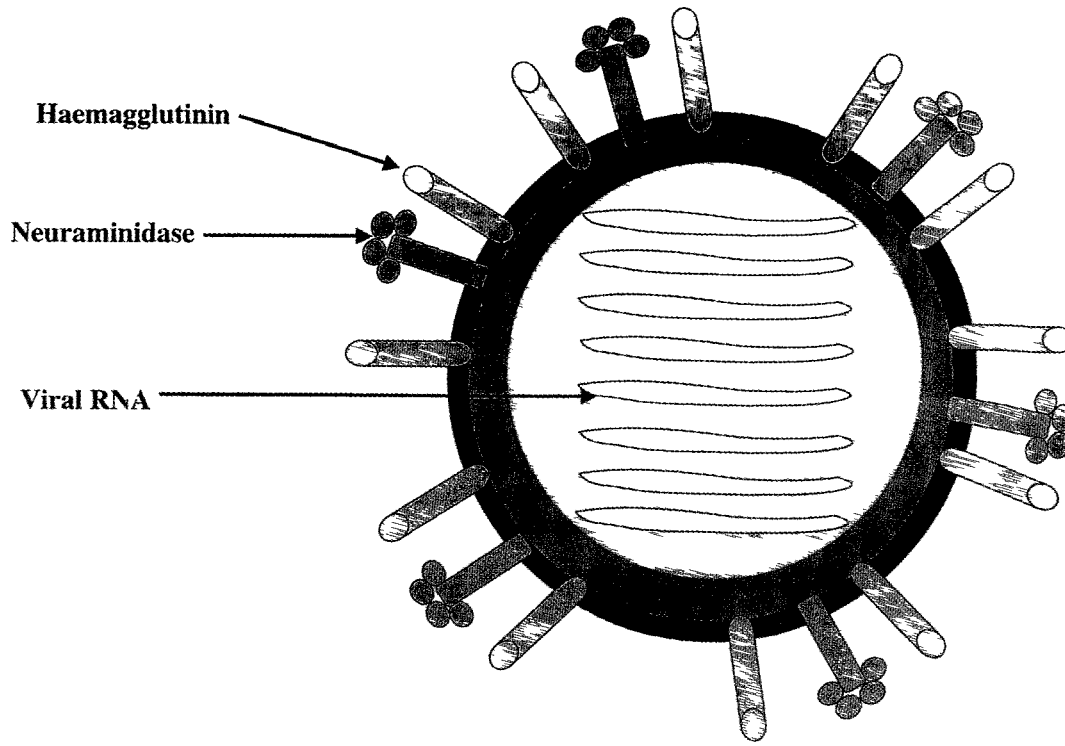


Figure 1 Schematic diagram of the influenza virus

	92–3	93–4	94–5	95–6	96–7	97–8	98–9
A (H3N2)							
A/Beijing/353/89	*						
A/Beijing/32/92		*					
A/Shangdong/9/93			*				
A/Johannesburg/33/94				*			
A/Wuhan/359/95					*	*	
A/Sydney/5/97							*
A (H1N1)							
A/Singapore/6/86	*	*	*	*	*		
A/Bayern/7/95						*	
A/Beijing/262/95							*

Figure 2 Antigenic drift of influenza A viruses

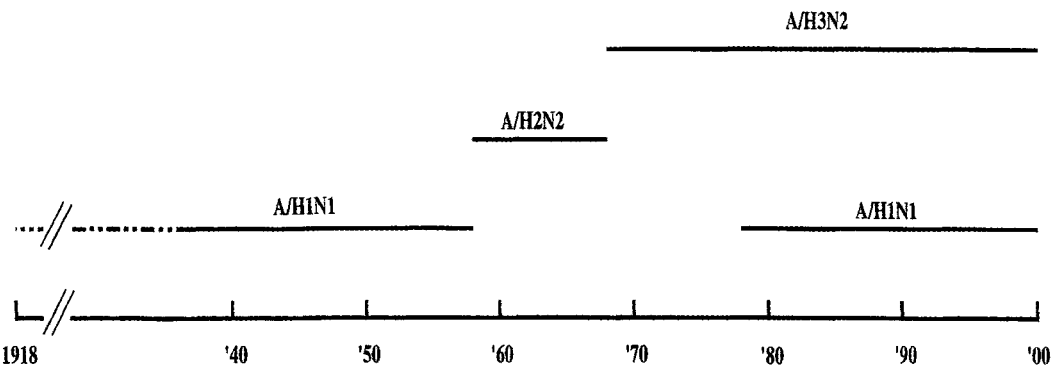


Figure 3. Influenza A pandemics of the twentieth Century

The source of new H or N subtype antigens associated with pandemic viruses is the avian reservoir and it is now recognised that pandemic influenza A is a zoonosis (3). So far, 15 distinct H subtypes and 9 N subtypes have been identified in the aquatic bird populations of the world. In 1957, the previously circulating H1N1 human virus acquired a novel haemagglutinin (H2), neuraminidase (N2) and one other internal gene from an avian virus. This occurred through reassortment (i.e. mixing) of the genomes of human H1N1 and an avian H3N2 virus within a single cell, the progeny virus having 3 gene segments from the avian virus and 5 gene segments from the previous H2N2 human influenza virus. Similarly, in 1968 a novel avian H3 antigen gene and one other internal gene were acquired by the previous human H2N2 virus, leading to the emergence of the pandemic H3N2 "Hong Kong flu" virus (2). Two of the pandemics this century originated in the southern China region and it has been suggested that the so-called "Spanish flu" also had its origins in this same region (4). This has led to the hypothesis that this region is an epicenter for the genesis of influenza pandemics, possibly because of the close interactions between large numbers of aquatic avian species, pigs and humans.

Without a genetic reassortment event between human and avian viruses, it is rare for an avian virus to directly cross the species barrier and infect humans. However, this did occur in Hong Kong in 1997 with dramatic consequences — the so-called "bird flu" incident where 18 patients were infected with an H5N1 subtype virus leading to 6 deaths (5).

In influenza B, antigenic drift occurs by similar mechanisms as described for influenza A and leads to regular epidemics. However, there is no established zoonotic reservoir and no genetic reassortment leading to the introduction of new H or N subtypes. Thus pandemics of influenza B do not occur.

Epidemiology

In countries with a temperate climate, influenza is a markedly seasonal winter disease, occurring within a 6–8 week period. In tropical regions (e.g. Singapore), infection occurs all year around, while in sub-tropical climates (e.g. Hong Kong), infection peaks between February and April, sometimes followed by a second peak in the summer (May-August) (Figures 4 and 5) (6,7). The seasonality of influenza B is less predictable.

The focused outbreak in temperate regions allows the clinical burden of influenza to be readily recognised. During epidemic years, there is an increase in outpatient consultations, hospital admissions and excess morbidity and mortality in high-risk groups, all of which occur over a short period of time. Influenza associated hospitalisation, complications and mortality are increased in patients with underlying chronic cardiovascular or pulmonary disorders, chronic metabolic disorders (including diabetes), renal dysfunction, hemoglobinopathies, immunosuppression and those over 65 years of age. Women in the second and third trimester of pregnancy are also at increased risk of influenza complications (Table 1)

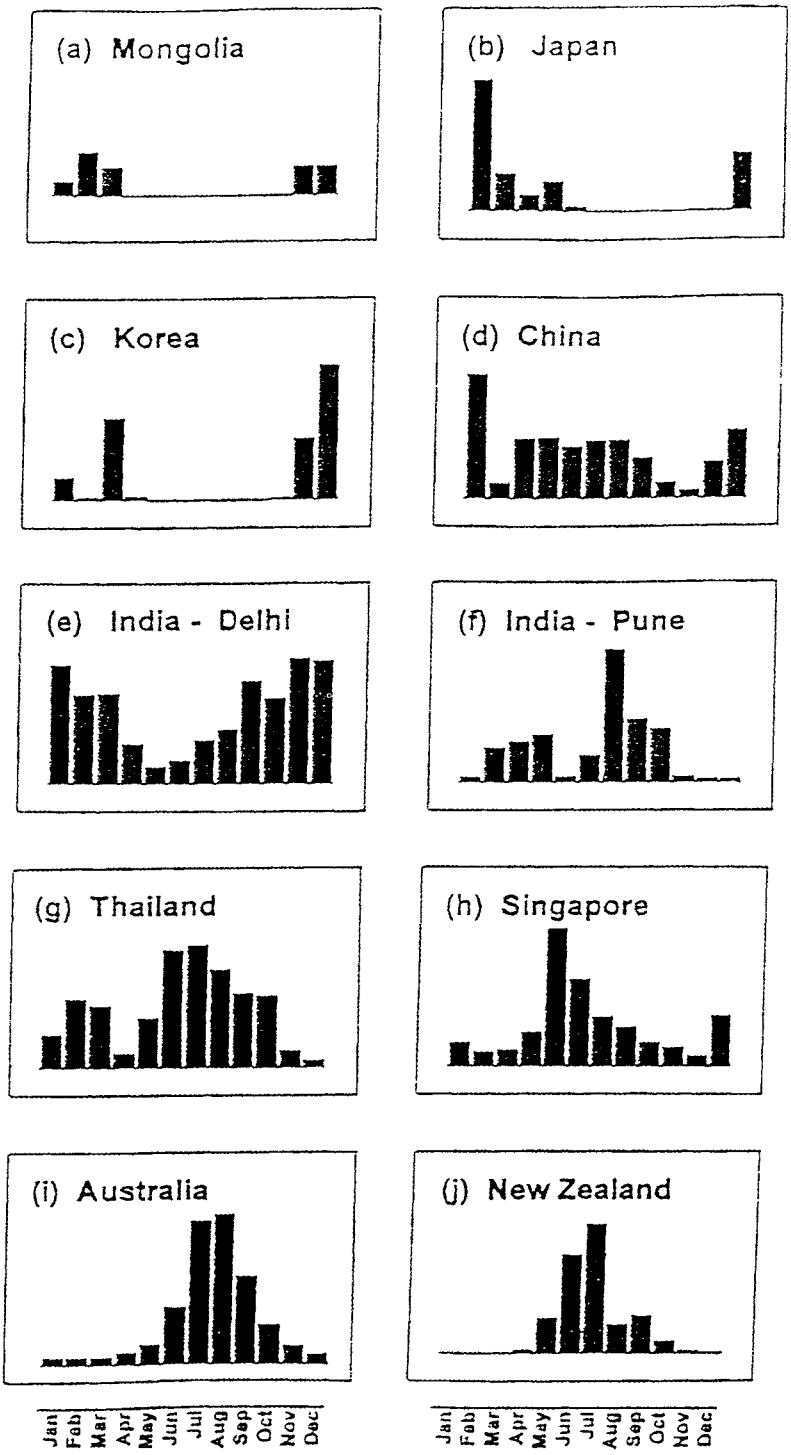


Figure 4. The seasonality of influenza in Asia. Incidence of influenza isolates by month reported in: (a) Mongolia, (b) Japan, (c) Korea, (d) China, (e) India (New Delhi), (f) India (Pune), (g) Thailand, (h) Singapore, (I) Australia and (j) New Zealand (from AW Hampson 1999, reproduced with kind permission of Elsevier Science Ltd)

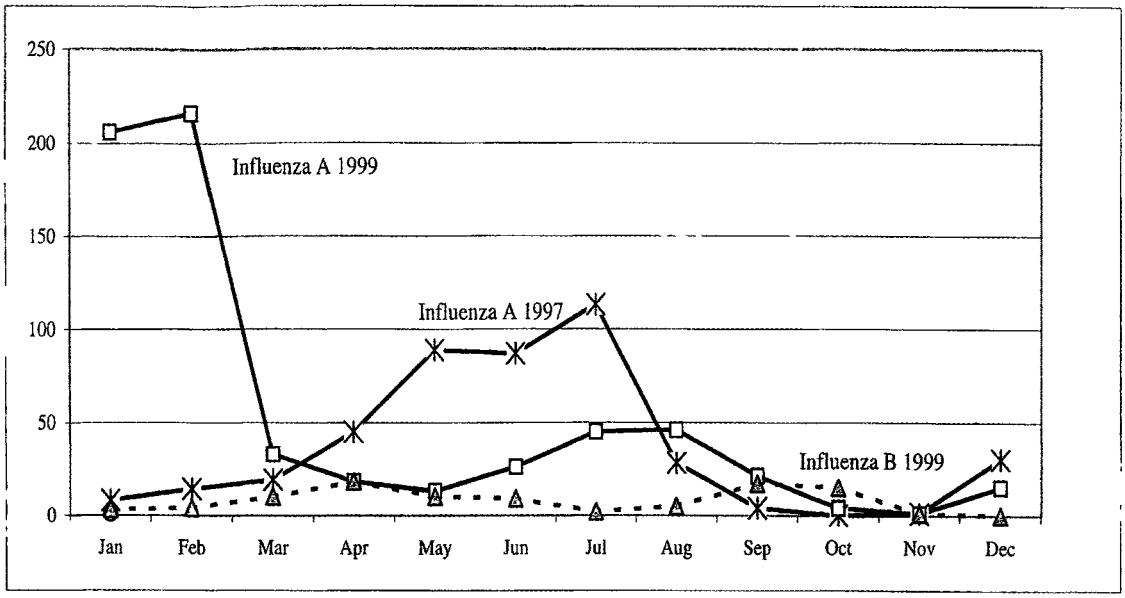


Figure 5. The seasonality of influenza A and B in Hong Kong (based on laboratory diagnoses at the Department of Microbiology, Queen Mary Hospital, Hong Kong: KH Chan & JSM Peiris — unpublished data)

Table 1. Estimates of the Clinical Impact of Influenza in Non-Pandemic Years in the USA

Age (years)	*High-risk group?**	*Hospitalization rates (per 100,000 population)*
> 65	No	200 — > 1000
45–64	Yes	80–400
45–64	No	20–40
15–44	Yes	40–60
15–44	No	20–30
5–14	Yes	200
5–14	No	20
0–4	Yes	500
0–4	No	100

*Including persons with chronic disorders of the respiratory, cardiovascular and renal systems, and patients with chronic metabolic diseases, hemoglobinopathies or immunosuppression (31)

(31). In the USA, excess mortality from pneumonia and influenza increases from 0.3 per 100,000 population in those aged < 65 years to 18 per 100,000 in those over 65 years of age. Similarly, the incidence of influenza related deaths and excess hospitalisation is 1.3 and 30 per 100,000 respectively in those < 65 years and increases to 73 and 160 per 100,000 respectively, in those > 65 years (8).

In the tropics and subtropics with a more diffuse influenza seasonality, the clinical impact of the disease is less apparent and less well documented. Strategies such as "excess mortality" that is used to document the clinical impact of

influenza in temperate regions are not applicable in the absence of a clear disease seasonality. During pandemics, data suggest that the total influenza related deaths in the Philippines and Taiwan were at least as severe as that documented for the USA (8). In a non-pandemic year (1994) in the Philippines, influenza and pneumonia morbidity was estimated to be 472 and 636 per 100,000 population. Pneumonia is the fourth leading cause of death in the age group over 65 years in Hong Kong and the rate per 100,000 ranges from 300 to 610 (9). In a study of influenza-associated hospitalization in children, it was found that hospitalization rates in Hong Kong were much greater that those reported in the USA (10). An analysis of influenza-associated excess mortality in the elderly in Hong Kong revealed rates similar to those reported in the USA (11). Thus, influenza morbidity and mortality in the tropics and sub-tropics are no less significant than that reported in the temperate regions.

Pathogenesis

The virus attaches to the sialic acid residues of cell surface glycoproteins. Viral replication occurs in the columnar epithelial cells leading to desquamation of the epithelium down to the basal cell layer. The pathology may involve the entire respiratory tract. Infection results in decreased ciliary clearance, impaired phagocyte function and increased adherence of bacteria to viral infected cells, all of which promote the occurrence of secondary bacterial infection. Viraemia and virus dissemination is uncommon in humans, though it has been occasionally detected in the brain, heart and the foetus (after infection during pregnancy). One reason for restriction of influenza to the respiratory tract is thought to be the need for cleavage of the virus haemagglutinin precursor by cellular proteases, which are restricted to the respiratory and gastrointestinal tracts. In some avian species, mutations at this haemagglutinin cleavage site, which allows a wider range of proteases to act on the precursor protein, results in a highly pathogenic virus which disseminates widely. However, a similar phenomenon has not been documented as yet in humans.

Local and systemic antibody responses and cytotoxic T cells contribute to host protection. Infection by an influenza virus results in long-lived immunity to homologous reinfection. However, the continual antigenic change in the virus allows it to keep continually ahead of the host immune response and to be the "oldest emerging virus, still continuing to emerge" (12).

Clinical Features

The incubation period of influenza A and B is between 1 to 4 days, and a person may be infectious from the day before the onset of illness to around 5 days after. The clinical presentation can vary from asymptomatic infection, a mild coryzal illness or the typical influenza syndrome to the complications of influenza. Influenza cannot always be distinguished from other respiratory viral infections on clinical grounds. However the typical influenza syndrome occurs in around half of those infected and is relatively characteristic in adults. It is characterised by an abrupt onset of fever, associated with chills, headache, sore throat, myalgia and sometimes prostration. Initially, the cough is non-productive. Coryza often appears later in the illness. Less common symptoms include vomiting, diarrhoea, hoarseness, substernal tenderness and photophobia (Figure 6). The pharynx is inflamed but usually does not have an exudate. Small tender cervical lymphadenopathy is often present. Crackles or wheezing is heard in around 10% of the patients. The acute illness usually resolves in 4 to 5 days, but cough, weakness, and fatigue may persist for weeks thereafter (13).

During an influenza outbreak, the clinical diagnosis of influenza in adults is reasonably accurate. In a recent study of previously well adults, the positive predictive value of a clinical diagnosis of influenza based on the presence of fever alone was 77% and cough together with fever was 79%. But these same symptoms have poor predictive value for influenza at times when surveillance cultures show that influenza activity in the community is low (14). The World Health Organisation definition of influenza-like illness (ILI) is that of fever (> 38°C) associated with a cough or sore throat and the application of this case definition had good predictive value during

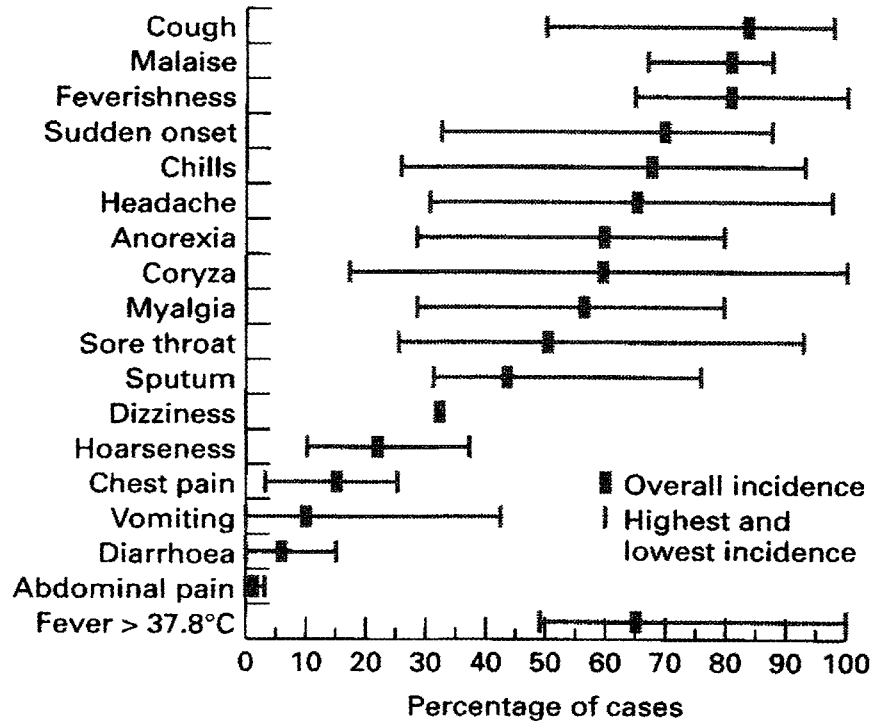


Figure 6. The clinical features of influenza. Overall incidence (and range) of symptoms recorded in adults with virologically confirmed uncomplicated influenza A. Data compiled from 10 studies between 1937–1992 (from Nicholson KG 1998, reproduced with kind permission of Blackwell Science, Ltd, Oxford).

influenza outbreaks in Hong Kong (15). Thus, the key to reliable clinical diagnosis of influenza is knowledge of "real time" virological surveillance of influenza activity in the community.

In contrast, in the elderly (16) and in children, the clinical features of influenza are less reliable in differentiating the virus from other respiratory pathogens. In children, fever tends to be higher, and otitis media or gastro-intestinal manifestations such as abdominal pain, diarrhoea and vomiting are seen more often. However, other viruses can also cause a similar clinical presentation. Febrile convulsions and complex seizures in particular are more common with influenza A in contrast to other respiratory viral infections (17). Infants with influenza may present as croup or bronchiolitis.

The clinical features of influenza A and B are indistinguishable although influenza B generally tends to affect younger patients. Although serological evidence suggests that influenza C is a common infection in the human population, it is rarely associated with clinical disease. When it is, the clinical syndrome is that of coryza rather than the "influenza syndrome." Rarely, influenza C has been associated with pneumonia and bronchitis.

Complications of Influenza

Age, prior immunity to the infecting virus, residential status (i.e. institutional care), presence of underlying diseases, pregnancy, smoking and immunosuppression all influence the severity of influenza A and B viruses. The influenza A subtype H3N2 appears to be more severe than that caused by H1N1or influenza B viruses. During pandemics the severity of the illness and of its complications are usually greater.

While excess mortality has been clearly documented in association with influenza in the elderly, much of this increased risk is attributable to the fact that the elderly are more likely to have other predisposing underlying diseases. The death rate in those over 65 years of age without

underlying risk factors was increased 20 fold in the presence of one "high risk" medical condition and 30 fold in those with two such conditions. Elderly in residential homes are clearly a group at particularly high risk of acquiring influenza during outbreaks and suffering its complications. In diabetics, influenza increases the risk of pneumonia, loss of control of diabetes and of diabetic ketoacidosis in insulin-dependent diabetics. Pregnant women acquiring influenza during the third trimester are at increased risk of hospitalization and cardio-respiratory complications. There is no convincing evidence of developmental abnormalities in the foetus (13).

Common (i.e. occurs in >10% of symptomatic patients) complications of influenza include exacerbations of asthma and chronic obstructive airways disease, acute bronchitis, pneumonia and otitis media (in children). Other complications include myocarditis, encephalopathy, encephalitis and in-patients with influenza B infection, myositis. Virus associated haemophagocytic syndrome in childhood is a rare complication of viral infections including influenza.

Respiratory complications of influenza

The most common complications of influenza involve the respiratory tract and include acute bronchitis, exacerbations of asthma and chronic obstructive airways disease and pneumonia in adults and also include otitis media and croup in children (13,18). Even in previously healthy individuals, influenza leads to airway hyper-reactivity, peripheral airway dysfunction and abnormal gas exchange, which can persist for weeks. Influenza (as well as other respiratory viral infections) can precipitate wheezing in asthmatic children and adults. And an increase in asthma related mortality is noted during influenza epidemics (13).

Pneumonia following influenza may be a primary viral pneumonia or secondary to bacterial superinfection. The former occurs earlier in the illness without involvement of secondary bacterial pathogens and carries a poor prognosis. In contrast, secondary bacterial pneumonia is more common, may occur early or later in the illness and usually has a better prognosis if recognised and treated (19). During the pandemic of 1918, pneumonia was more often seen in the healthy young adult and was a major cause of mortality. In contrast, during inter-pandemic years, pneumonia complicating influenza occurs most often in those with underlying diseases and at the extremes of age (13).

Primary viral pneumonia manifests 1 to 5 days after the onset of influenza and is not common. In new pandemics, around 20% of patients hospitalized with pneumonia may have a primary viral disease (19). On examination, there are crackles and wheezes but evidence of consolidation is usually absent. Radiologically, there is bilateral involvement but it is not possible to reliably differentiate primary viral pneumonia from secondary bacterial pneumonia, except when lung abscesses are detected in the latter. The total leukocyte count is usually elevated. At post mortem, there is no evidence of consolidation, but bloody fluid can be expressed from the cut surface of the lung. The trachea, bronchi and bronchioles are involved with loss of the ciliated epithelium, the presence of a serosanguinous discharge and irregular haemorrhagic areas. The alveoli have inflammatory cell infiltration, fibrin and oedema and intra-alveolar haemorrhages are seen especially in the lower lobes. Hyaline membranes line the alveolar ducts and alveoli. Virus can be isolated from the lungs for 4 to 21 days after the onset of the disease. In some patients, long-term complications such as pulmonary fibrosis and obliterative bronchiolitis have been reported but the true incidence of such complications is unclear.

Secondary bacterial pneumonia following influenza is associated with *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae* and other bacteria. The illness may be continuous with the initial influenzal illness or may be bimodal in nature. Radiologically, there is evidence of lobar or lobular shadowing. Staphylococcal involvement is more likely in those with underlying diseases and carries a worse prognosis and accounts for the majority of cases undergoing post-mortem examination. Mortality due to secondary bacterial pneumonia associated with staphylococcal infection affects all ages while that associated with other pathogens primarily affects those over 55 years of age. Bacterial

superinfection may occur concurrently and both the bacterial pathogen and influenza virus can be isolated from the lung in some patients.

Cardiovascular complications

Excess deaths due to ischemic heart disease have been noted in association with influenza outbreaks, and immunisation was documented to reduce congestive cardiac failure by over 25% in the elderly. Influenza has also been associated with myocarditis and pericarditis.

Neurological complications

Influenza A is an important cause of febrile convulsions in childhood, especially complex febrile seizures (17). Influenza is also associated with postinfectious encephalomyelitis or Guillain Barre syndrome with normal or abnormal CSF findings. In Japan, a true influenza A encephalitis associated with viral nucleic acid detection in the CSF has been reported (20). Reye's syndrome consists of encephalopathy and fatty liver degeneration in children associated with viral infections of the upper respiratory tract and influenza in particular. The risk of this complication is increased by salicylate use. The use of salicylates in children should be discouraged, and children on long-term salicylate use for other indications should have effective influenza prophylaxis.

An association between the 1918 influenza pandemic and encephalitis lethargica and post-encephalitis Parkinson's disease has been made by a number of authors although an aetiological link remains unproven to date.

Infection in the Immunocompromised

The immunocompromised are clearly at increased risk of influenza associated pneumonia and death. The morbidity and mortality is associated with a primary viral pneumonia rather than secondary bacterial infection and is particularly increased in patients acquiring infection soon after transplant (especially during the pre-engraftment phase in bone marrow transplant recipients) or adjunctive immunosuppression associated with anti-rejection therapy (21). Adults appear to be at greater risk of complications than children. Data on patients with HIV or AIDS is limited, but it appears that it is less severe than in transplant recipients.

Influenza virus shedding is prolonged in the immunocompromised, and poses a threat for nosocomial infection. Conversely, many immunocompromised patients acquire influenza nosocomially from other patients or caregivers (21).

Influenza Associated With Avian Subtypes

Human disease associated with unusual avian influenza A virus subtypes has been recognised recently, in particular, during the H5N1 avian-flu incident in Hong Kong during 1997. Older children and adults acquiring infection with the avian influenza H5N1 had an unusually severe disease course in the absence of predisposing underlying diseases (5). Lymphopenia, gastro-intestinal manifestations, raised liver enzymes and renal failure were unusually prominent. Lower respiratory tract involvement occurred in the absence of secondary bacterial infection. The overall mortality was 33%, and it was higher (50%) in older children and adults. Haemophagocytosis was a key observation at post-mortem (22). The virus was poorly adapted for human to human transmission (23). The outbreak was contained by the slaughter of poultry in the live bird-markets in Hong Kong. Subsequently, infection with another avian subtype, H9N2 virus, was also documented, although this infection was mild and self-limited (24). In 2003–4, widespread outbreaks of H5N1 disease in poultry across Asia (25) were associated with additional transmission to humans (26,27). The clinical presentation was similar to that observed in the outbreak in Hong Kong in 1997 although the overall mortality rates were even higher. Some of these recent H5N1 isolates in humans and poultry have acquired resistance to amantadine and rimantadine (25).

Laboratory Diagnosis

A well-collected specimen is the first (and often the most important) determinant in successful laboratory diagnosis. Nasopharyngeal aspirates (secretions aspirated from the back of the nose into a mucus trap) or washes are superior to nasopharyngeal or throat swabs for the detection of respiratory viruses and also offer the advantage of rapid diagnosis for a number of viruses using immunofluorescence antigen detection methods. Swabs need to be placed in viral transport medium immediately upon collection and kept cool (around 4°C) until they are ready for processing in the laboratory. More invasive specimens such as endotracheal aspirates, bronchoalveolar lavage or lung biopsy, when available, provide even better information. If it is not possible to collect aspirates, nasopharyngeal swabs are an alternative and provide higher sensitivity than conventional nose or throat swabs. When nose and throat swabs are collected, they should be placed in the same vial of transport medium. The collection of swabs from both sites yields better results that a single swab.

The laboratory methods used for detecting a virus in clinical specimens are viral culture, antigen detection and, more recently, nucleic acid detection. Virus culture usually takes a few days to yield a result and provides a retrospective diagnosis. However, an ideal bedside test is yet to be developed. Most of these rapid tests yield higher sensitivity with nasopharyngeal aspirates rather than nose/throat swabs and in children rather than adults, the reason being that viral titres are relatively higher in nasopharyngeal aspirate and in children.

Nucleic acid detection methods such as RT-PCR are being evaluated and are promising. They are more expensive in general, and take longer to complete than antigen detection methods.

Serological diagnosis is possible, provided acute and convalescent serum samples are taken to document a significant increase in antibody titres. Complement fixation tests are routinely used because they are cross-reactive with all variants of a given influenza type. Haemagglutination inhibition tests are more sensitive but require that separate antigens to be used for the H3N2 and H1N1 virus subtypes.

Laboratory diagnosis is important in managing patients hospitalised with suspected influenza or its complications. Rapid diagnosis is now feasible (see above), with antigen detection methods (immunofluorescence, EIA) (28) that provide rapid results within a few hours. These have direct impact on patient management, and can be cost saving by reducing antibiotic use and hospital stay (29). Rapid laboratory diagnosis able to discriminate between influenza A and B is useful for decisions on antiviral use since some of the less expensive antivirals have activity only against influenza A. In the general practice setting, however, routine laboratory tests are not usually possible and no truly "bedside" test is yet available. Provided "real time" virological surveillance indicates influenza activity in the community, clinical features have good predictive value for influenza in a general practice setting (see above) and are adequate for guiding decisions on antiviral use.

Antiviral Therapy

Antiviral drugs of proven clinical efficacy for treatment of influenza A include the viral M2 protein inhibitors, amantadine and rimantadine and the more recently available neuraminidase inhibitors zanamivir and oseltamivir (Table 2). Rimantadine is not licensed for use in a number of countries. Newer neuraminidase inhibitors are currently on clinical trials (30). Only the neuraminidase inhibitors are active against influenza B. Amantadine and rimantadine have comparable efficacy in treatment and chemoprophylaxis, but rimantadine leads to less neurological side effects. If treatment is commenced early, there is a 1 to 2 days reduction in the clinical symptoms. The main route of elimination of amantadine and rimantadine is the kidney and liver respectively. Resistance to amantadine and rimantadine arises readily with approximately 30% of patients shedding resistant virus from 3 to 4 days of therapy (31). The resistant mutants are not reduced in virulence or transmissibility. Amatadine and rimantadine are effective for chemoprophylaxis of family contacts and in institutional outbreaks provided the index case has not been treated with the same drug. When the index case has been treated with the same drug, failure of prophylaxis sometimes occurs, the reason being the emergence and transmission of

Table 2. Recommended Daily Dosages of Antivirals for Influenza

Antiviral agent	*14–64 years*	*Over 65 years*
Amantadine: Treatment or prophylaxis	100 mg twice daily orally for 3–5 days.	100 mg once daily orally for 3–5 days. Reduced dose if side effects.
Rimantadine: Treatment or prophylaxis	100 mg twice daily orally for 3–5 days.	100 or 200 mg daily orally for 3–5 days.
Zanamivir: Treatment	10 mg twice daily by inhalation for 5 days.	10 mg twice daily by inhalation for 5 days.
Oseltamivir: Treatment	75 mg twice daily orally for 5 days.	75 mg twice daily orally for 5 days.

Notes
1 In patients with renal failure, dosage reduction of amantadine and rimantadine may be required No dosage reduction is required for zanamivir Insufficient data is available on oseltamivir
2 Amantadine and rimantadine resistant mutants appear within 3 to 5 days Stop treatment as soon as symptoms subside, and do not use for longer than 5 days

resistant strains from the index case receiving treatment. In such a situation, it may be logical to consider treatment of the ill patients with a neuramindase inhibitor while using amantadine or rimantadine for prophylaxis.

In comparison to previous influenza drugs (amantadine and rimantadine), neuramindase inhibitors appear to have less adverse effects than amantadine, and emergence of resistance is less of a problem. Even when resistance emerges, such mutants are less transmissible and are reduced in virulence. When treatment is commenced within 36 to 48 hours, there is a 1 to 2 days clinical benefit. In children, there is also data to suggest the reduction of otitis media (32,33).

There are as yet few controlled clinical trials directly comparing the neuraminidase inhibitors and the M2 inhibitors amantadine or rimantadine. In the one study done to date, zanamivir was superior and had less side effects compared to rimantadine in the control of influenza outbreaks in long care facilities.

In treating the immunocompromised, it may be advisable to consider using a combination of M2 inhibitors and the neuraminidase inhibitor, thereby reducing the risk of emergence of resistant viruses.

In patients with renal dysfunction, dose adjustment of amantadine, rimantadine and oseltamivir may be required but no dose adjustment is required for the inhaled drug zanamivir.

Prevention

Immunisation is the method of choice for the prevention of influenza. Antiviral chemoprophylaxis is an option to be considered for short-term prophylaxis in those who have not been immunised or when there are contra-indications to administration of the vaccine. However, antiviral chemoprophylaxis is less practicable in tropical countries where influenza circulates throughout many months of the year.

Vaccines

The vaccine includes antigens from the two current subtypes of human influenza A (H3N2 and H1N1) and influenza B viruses. To keep abreast of the continual change in the surface antigens of the virus (see above), vaccine composition must be modified on an annual basis, and annual immunisation is required. Current influenza vaccines are made from egg grown viruses that have been inactivated and formulated as either whole virus preparations, split virus vaccines or subunit vaccines. Split virus and subunit vaccines

are associated with fewer side effects in children (< 12 years of age) and are therefore the preferable choice (34). Previously unvaccinated children require two doses of the vaccine at least one month apart, but a single dose appears adequate for adults. The vaccines are safe, the most common side effect being soreness at the injection site lasting a few days. The effectiveness of the vaccine depends on the age and immunocompetence of the vaccinee and the antigenic relatedness between the vaccine and outbreak virus. In healthy persons < 65 years of age, and in years where there is a good antigenic match between the vaccine antigen and the circulating virus, the vaccine prevents illness in approximately 70% to 90% of persons. Although the immunogenicity and efficacy of the vaccines in the elderly are lower than in young adults, it is still effective in reducing influenza-related complications, hospitalizations and mortality and has been demonstrated to be cost saving.

The duration of protection is limited and therefore vaccine administration should be timed to precede the expected peak of influenza activity. This is straightforward in temperate climates with a definite seasonality of influenza but more difficult in tropical countries with influenza activity all year round.

Influenza vaccine is recommended to those groups at highest risk of morbidity (Table 3). These recommendations vary from country to country. They usually include patients in chronic care facilities (especially the elderly), those with chronic cardio-pulmonary, lung or renal diseases, diabetes mellitus, haemoglobinopaties and the immunocompromised. In addition, some countries extend the recommendation to all elderly persons over 65 years of age, pregnant women who will be in the second or third trimester during the influenza season, children receiving long term aspirin therapy (potentially at risk of Reye's syndrome if they acquire influenza), health care workers (particularly those in contact with the high risk patient groups above) and household members of persons in high risk groups. There is presently no consensus on the use of influenza vaccine in HIV infected patients.

An intranasally administered cold adapted live attenuated vaccine has undergone clinical trials with promising results and may offer advantages of easier administration, greater efficacy (especially in years where there is a poor match between the vaccine strain and the circulating virus) and has greater patient acceptability.

Table 3. Influenza Immunization Recommendations

Immunization is recommended for persons with:
• Chronic cardiopulmonary, lung, or kidney disease
• Diabetes mellitus
• Elderly (> 65 years of age)
• Immunosuppression
• Severe anaemia
• Pregnant women who will be in the 2nd or 3rd trimester during the peak influenza season
• Children and teenagers receiving long-term aspirin therapy
• Residents and staff of chronic care facilities
• Persons in frequent contact with anyone in a high risk category (eg family members, nurses, volunteers)

References

1. Potter CW. Chronicle of influenza pandemics. In: *Textbook of Influenza.* Eds. KG Nicholson, RG Webster, AJ Hay. Oxford: Blackwell Scientific 1998, 219–64.
2. Webster RG, Bean WJ, Gorman OT, Chambers TM, Kawaoka Y. Evolution and ecology of influenza A viruses. *Microbiological Reviews* 1992; 56:152–79.
3. Shortridge KF. Pandemic influenza: a zoonosis. *Semin Resp Inf* 1992; 7:11–25.
4. Shortridge KF. The 1918 "Spanish' flu: pearls from swine? *Nature Medicine* 1999; 5:384–5.
5. Yuen KY, Chan PKS, Peiris M, et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. *Lancet* 1998; 351:467–71.
6. Hampson AW Epidemiological data on influenza in Asian countries. *Vaccine* 1999; 17: S19–23.

7. Chew FT, Doraisingham S, Ling AE, Kumarasinghe G, Lee BW. Seasonal trends of viral respiratory tract infections in the tropics. *Epidemiol Infect* 1998; 121:121–8.
8. Simonsen L. The global impact of influenza on morbidity and mortality. *Vaccine* 1999; 17:S3–10.
9. Philips DR. Experiences and implications of demographic ageing in the Asia-Pacific region. *HK Journal of Gerentology* 1995; 9:20–9.
10. Chiu SS, Lau YL, Chan KH, Wong WHS, Peiris JSM. A population-based study defining influenza related hospitalization in children in Hong Kong. *New Eng J Med* (in press).
11. Wong CM & Peiris JSM (unpublished data).
12. Webby RJ & Webster RG. Emergence of influenza A viruses. Phil Trans. R Soc. Lond. 2001; 356:1817–28.
13. Nicholson KG. Human influenza. In: *Textbook of Influenza.* Eds. KG Nicholson, RG Webster, AJ Hay. Oxford: Blackwell Scientific 1998, 219–64.
14. Monto AS, Gravenstein S, Elliot M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. *Arch Intern Med* 2000; 160:3243–7.
15. Kong WM. A review of the Hong Kong influenza surveillance system. Public Health & Epidemiology Bulletin. Department of Health, Hong Kong, China 2000; 9:37–42.
16. Nicholson KG, Kent J, Hammersley V. Acute viral infections of upper respiratory tract in elderly people living in the community: comparative, prospective, population based study of disease burden. *BMJ* 1999; 315:1060–4.
17. Chiu SS, Tse CYC, Lau YL, Peiris M. Influenza A infection is an important cause of febrile seizures. Pediatrics 2001: www.pediatrics.org/cgi/content/full/108/4/e63.
18. Goh SK, Johan A, Cheong TH, Wang YT. A prospective study of interactions with atypical pneumonia organisms in acute exacerbations of chronic bronchitis. *Ann Acad Med Singapore* 1999; 28:476–80.
19. Hers JF Ph. Masurel N, Mulder J. Bacteriology and histopathology of the respiratory tract and lungs in fatal Asian influenza. *Lancet* 1958; 2:1141–3.
20. Mori SI, Nagashima M, Sasaki Y, et al. A novel amino acid substitution at the receptor binding site on the haemagglutinin of H3N2 influenza viruses isolated from 6 cases with acute encephalopathy during the 1997–1998 season in Tokyo. *Arch Virol* 1999; 144:147–55.
21. Whimbey E, Elting LS, Couch RB, Lo W, Williams L, Champling RE, Bodey GP. Influenza A virus infections among hospitalised adult bone marrow transplant recipients. *Bone Marrow Transplant* 1994; 13:437–40.
22. To KF, Chan PKS, Chan KF, et al. Pathology of fatal human infection associated with avian influenza A H5N1 virus. *J Med Virol* 2001; 63:242–6.
23. Buxton Bridges C, Katz JM, Seto WH, et al. Risk of influenza A (H5N1) infection among health care workers exposed to patients with influenza A (H5N1), Hong Kong. *J Infect Dis* 2000; 181:344–8.
24. Peiris M, Yuen KY, Leung CW, et al. Human infection with influenza H9N2. *Lancet* 1999; 354:916–7.
25. Li KS, Guan Y, Wang J, Smith GJ, et al. Genesis of a highly pathogenic and potentially pandemic H5N1 influenza virus in eastern Asia. *Nature* 2004; 430:209–13.
26. Peiris JS, Yu WC, Leung CW, et al. Re-emergence of fatal human influenza A subtype H5N1 disease. *Lancet* 2004; 363:617–9.
27. Tran TH, Nguyen TL, Nguyen TD, et al. World Health Organization International Avian Influenza Investigative Team. Avian influenza A (H5N1) in 10 patients in Vietnam. *N Engl J Med* 2004; 350:1179–88.
28. Chan KH, Maldeis N, Pope W, et al. Evaluation of the Directigen FluA+B test for rapid diagnosis of influenza virus type A and B infections. *J Clin Microbiol* 40:1675–80.
29. Woo PCY, Chiu SS, Seto WH, Peiris M. Cost effectiveness of rapid diagnosis of viral respiratory tract infections in paediatric patients. *J Clin Microbiol* 1997; 35:1579–81.
30. Gubareva LV, Kaiser L, Hayden FG. Influenza virus neuramindase inhibitors. *Lancet* 2000; 355:827–35.
31. Hayden FG, Belshe RB, Clover RD, Hay AJ, Oakes MG, Soo W. Emergence and apparent transmission of rimantadine resistant influenza virus in families. *N Eng J Med* 1989; 321:1696–702.
32. Monto AS, Webster A, Keene O. Randomized placebo controlled studies of inhaled zanamivir in the treatment of influenza A and B: pooled efficacy analysis. *J Antimic Chemo* 1999; 44:Topic B:23–9.
33. Nicholson KG, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. *Lancet* 2000; 355:1845–50.
34. Centers for Disease Control. Prevention and control of influenza. *MMWR* 2000; 49: (RR03):1–38.

14 Tropical Infections and the Lungs

Chaicharn Pothirat and Suchai Charoenratanakul

Introduction

Tropical area refers to the geographic region locating between the Tropic of Cancer and the Tropic of Capricorn. The countries included in this area located in Asia, Africa, Central and South America, Northern Australia and Pacific islands, are mostly developing or underdeveloped. High temperatures and high humidity characterize the climate in the tropics. Temperature is the major governing factor for the distribution of many tropical diseases because many reservoirs such as arthropods, snails and vertebrates have life cycles that are limited by heat and cold. Most of them cannot survive in cold and dry weather in temperate zones so their distributions are confined to tropics. The limited distribution of reservoirs, many of which also serve as vectors, determines the spread of the agents and then the diseases. Rainfall, flooding and other sources of water are essential for the increasing numbers of some vectors and reservoirs and thus increasing transmission of the agents and diseases. Geographic barriers such as rivers, mountain ranges and oceans can also limit the spread of some tropical infectious diseases requiring vectors or intermediate hosts for their transmission to human. In addition, human behaviour can influence the distribution of all tropical infectious diseases, especially those caused by organisms which are transmitted from person to person. Such agents may persist wherever people travel and may not be affected by environmental factors whereas agents requiring a vector and/or intermediate host for human transmission may have a restricted distribution due to environmental factors (climate, rainfall, and geographic barriers) as well as human behaviour. The common human behaviour in the tropics favouring disease transmissions are eating poorly cooked or raw intermediate (or paratenic) host tissue; bared foot walking on soil ground, muddy area, or in natural water-source; eating by using fingers to pick up the food into the mouth; and sleeping without nets. Public health measures are very important in the control of various tropical infections. These measures include improved sanitation, raised standard of living, vaccination, vector or reservoir control by source reduction and pesticides, improvement of housing, drug prophylaxis, effective treatment and health education to avoid risky behaviour for acquiring the diseases. Infected travellers and immigrants from tropical countries are responsible for the spreading of person-to-person transmitted diseases to non-tropical countries. Importing of reservoir hosts or vectors that can be viable in non-tropical areas may also promote emergence of tropical infectious diseases in non-tropical countries.

Pulmonary involvement of tropical infections that are still mainly confined to tropical areas is the focus of this chapter. These diseases may mainly affect the lungs or their pulmonary

manifestations is important for making diagnosis, selecting treatment and predicting outcome of the systemic disease. Nowadays, pulmonary tuberculosis is a global epidemic disease and thus not included.

Dengue Haemorrhagic Fever

Epidemiology and aetiology

Dengue haemorrhagic fever (DHF) is a mosquito-borne viral infection that has a widespread distribution in the tropics (1). Humans are infected with dengue viruses by the bite of an infective Ades aegypti mosquito. DHF epidemics are mostly reported from Asia (Southeast Asia, Philippines, India, Pakistan, and Sri-Lanka), Central and South America, East and West Africa and Pacific Islands. It is one of the leading causes of hospitalization and death among children in many Southeast Asian countries (2).

Pathophysiology

The primary pathophysiologic abnormality seen is an acute increase in vascular permeability without vascular pathological change that leads to leakage of plasma into extravascular compartment, resulting in hemoconcentration, hypotension or shock.

Clinical features

The spectrum of illness ranges from asymptomatic or mildly symptomatic to fatal haemorrhagic disease. The clinical manifestations are divided into three phases.

The first phase is the febrile phase, characterized by an abrupt onset of high sustained fever with constitutional symptoms (ie. anorexia, vomiting, myalgia, headache, lethargy). This period usually lasts for a few days to one week. Pain in right hypochondrium or abdominal pain, maculopapular rash and petichiae can also be observed.

The second phase is the toxic phase, characterized by an abrupt fall in temperature with clinical deterioration. The patient become restless, develop cold limbs, tachycardia followed by haemorrhagic manifestation or shock (Dengue Shock Syndrome, DSS). DSS exclusively occurs in the secondary heterotypic infection. Haemorrhagic manifestation is associated with thrombocytopenia appearing 24 hours before or after the patient becomes afebrile. The most common haemorrhagic manifestation is scattered petechiae on the extremities but also on the trunk and other parts of the body. In severe cases, gastrointestinal haemorrhage, manifested by haematemesis or melena or both, often occur. The shock is characterized by the warning signs of tachycardia, narrowed pulse pressure, orthostatic hypotension, hemoconcentration, restlessness or somnolence and peripheral cyanosis. It is commonly caused by plasma leakage and infrequently by blood loss. This toxic phase usually lasts for 24–48 hours. Pulmonary manifestations may appear during febrile or toxic phase. A sorethroat and a nonproductive cough can be found in 9–23% of cases (3). In severe cases, tachypnea out of degree of fever will result in respiratory alkalosis, associated with other warning signs of shock. Abnormal chest radiographs are usually reported as pleural effusion (25–30%) or pneumonia (7–12%). Pleural effusions are more commonly found in severe or fatal cases (4). The mechanism of pleural fluid is partly due to increase permeability of capillaries permitting fluid leakage into serous space. The composition of pleural fluid is a filtrate from blood, lacking inflammatory cells. One of the major components is protein especially albumin, the level of which is commonly more than 60% of that in blood. Immunoglobulins as well as C3 complement are found in the pleural fluid without any evidence of inflammatory process (5). Pulmonary haemorrhage in dengue haemorrhagic fever is surprisingly rare in reported cases. In severe cases, bleeding is often associated with disseminated intravascular coagulation (DIC) in which shock, massive pulmonary haemorrhage and ARDS can occur.

The final phase is the recovery phase, characterized by dramatic improvement of well being with disappearance of haemorrhagic or shock manifestations. The platelet count increases and returns to normal in the next few days.

Clinical investigations

The confirmed serologic diagnosis is a positive IgM antibody titre to dengue virus antigen in preserved serum sample. The IgM antibody persists for a few months after acute infection. The diagnosis by using IgG antibody test requires paired acute and convalescent phase serum samples to demonstrate a fourfold or greater rise in specific antibody because the IgG persists for life.

Treatment

Most of the patients without shock or serious bleeding can be successfully managed at home. Family members should be instructed to keep a careful watch for warning signs of deterioration, bleeding or shock with a daily doctor visit, platelet and haematocrit check at the clinic or hospital. Aspirin and NSAIDS are prohibited for use as antipyretics or symptomatic drugs. Patients should be hospitalized immediately if any signs of shock supervene. Intravenous fluid therapy with physiologic saline-glucose solution is the mainstay of treatment and should be promptly loaded in the first few hours till signs of shock disappear and optimal urine output is obtained. The intravenous fluid rate is then reduced by keeping balance with the output and degree of hemoconcentration. Other volume expanders such as plasma, dextran solution are indicated only in those who show inadequate response with standard fluid therapy. Blood transfusions are contraindicated in the absence of significant internal bleeding because of potentially increasing the risk of pulmonary oedema due to pulmonary vascular leakage at this stage. The same risk applies to over energetic intravenous fluid therapy during the toxic phase. Prolonged intravenous therapy in recovery phase is also associated with this risk due to the shift of plasma fluid back to vascular component mechanism.

Prognosis

The prognosis is good in patients without shock, with spontaneous recovery in one week. For those who develop shock, fatality can occur especially in those who are late in seeking medical treatment.

Prevention

Prevention and control, nowadays, depend on prevention from mosquito bite during daytime and controlling the mosquito vector in and around the area where transmission occurs by eliminating larval source of the mosquito (6). The dengue vaccine is being developed but not yet available.

Scrub Typhus

Epidemiology and aetiology

Scrub typhus is a zoonotic disease of widespread distribution in various parts of Southeast Asia, India, Japan, Taiwan and Australia (7–13). The reported cases of scrub typhus in Thailand have increased three fold between 1988–1997 (14). The etiologic agent is *Rickettsia tsutsugamushi* and its reservoirs are wild rodents especially rats. The vectors are larval trombiculid mites (chiggers) which usually inhabit grassy or low jungle areas. The disease can occur in all seasons throughout the year, especially in rainy seasons, because more chiggers attach to rodents during this period (15).

Pathophysiology

Human is an accidental host, infected by the bite of an infected chigger. The organisms spread through the dermis and subsequently to the regional lymph nodes, bloodstream and then to the host cells. The histopathologic lesions are disseminated perivasculitis and focal interstitial infiltration. The most clinically important lesions are interstitial pneumonia and meningoencephalitis.

Clinical features

The vast majority of patients do not report the feeling of any "bite". The primary lesion, forming a few to several days after the bite at the site of inoculation, starts from a papule and evolves into a typical painless ulcer with black necrotic centre and reddish rim, the so called "eschar" (Figure 1) which is an important clue to diagnosis but unfortunately can be found in only half of the

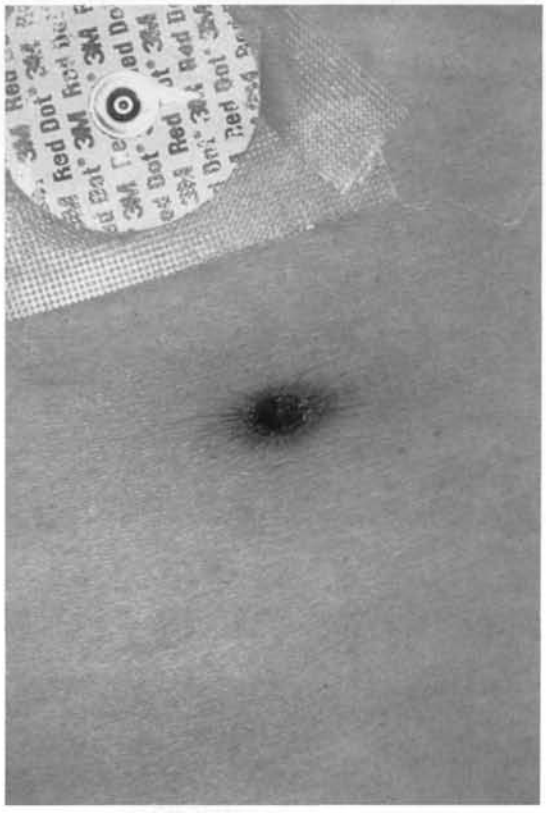


Figure 1. The eschar, which starts from a papule and evolves into a typical painless ulcer with black necrotic center and reddish rim

cases (7–9). The eschar is mostly single but sometimes multiple. The distributions of eschar lesions are commonly found on moist intertriginous surfaces (axilla, perineum, and groin), trunks or proximal limbs. Classically, the illness begins insidiously in two thirds of the patients with a prodrome of headache, malaise and anorexia and a few with slightly tender regional lymph nodes. A few days later the high spiking fever with chills becomes sustained, and severe headache and myalgia are invariable. The eyes are commonly injected (30–80%) and sometimes subconjunctival or retinal haemorrhages occur (7–9). Generalized lymphadenopathy is the most common physical finding. Maculopapular rash, commonly involving the trunk, has been reported in 30–70% of American servicemen during the first week of illness and last for a few days to two weeks but may be difficult to find in Asians (7–9,13). The absence of eschar and the presence of high fever, normal white blood cell count and lymphocytosis often lead to mistaken diagnosis of Dengue haemorrhagic fever, typhoid fever or even bacterial sepsis in cases with moderate leukocytosis (17). Serious complications of pulmonary, cardiovascular, renal, central nervous and coagulation systems can occur (8,9,13,17,18). Pulmonary involvement is common and always present in mild to severe cases. Most cases have transient slight or moderate elevation of respiratory rate (24–30 per minute) which do not always correspond to the degree of fever (8). A nonproductive hacking cough, is found in less than half and sometimes becomes a severe troublesome symptom (8,9,13). Rhonchi or basal crepitations are commonly found. The usual radiographic pattern is an interstitial infiltrate predominantly in the lower lung zones (8,15). Lobar and bronchopneumonia are less common and pleural effusion is rare. These clinical and radiographic findings are identical with other atypical pneumonia (such as those caused by Mycoplasma, Chlamydia and Legionella) and an erythromycin or a newer macrolide may be selected for treatment instead of tetracycline or doxycycline (11). In severe cases, typical clinical features and radiographic pictures of ARDS not uncommonly occur (8,9,11,13,15–17). The patient becomes rapidly and progressively tachypneic, cyanotic and exhausted. Lung signs, commonly crepitations, are scanty but radiographic appearance is surprisingly extensive. Renal failure, shock or DIC are seen in fatal cases (17). Delay in diagnosis, both in the early course of illness and in the ARDS stage, is usually due to inexperience of doctor and lack of typical eschar lesion. Fatality is usually the result of delayed diagnosis and appropriate treatment (13,17).

Clinical investigations

The Weil-Felix test using the Proteus OX-K antigen is used widely in endemic areas, but it has an unacceptably low sensitivity (50–70%) (7–9). The rapid dot-blot enzyme immunoassay and enzyme-linked immunosorbent assay (ELISA) has recently been developed with much improved accuracy in serodiagnosis of this disease (19,20).

Treatment

The drug of choice is tetracycline 2 g/day, doxycycline (especially in renal failure patient) 200 mg/day or chloramphenical (in cases in whom typhoid fever cannot be excluded) 2 g/day, for 7 days. Most patients become afebrile and most symptoms disappear within 48 hours after treatment has been started. Azithromycin may be useful in pregnant women (21). In cases responding poorly to doxycycline as evidenced in some areas in the northern part of Thailand, rifampicin may be useful but exclusion of active tuberculosis is necessary before treatment is started (22,23).

Prognosis

Early antibiotic treatment shortens the disease course, reduces mortality and accelerates convalescence. Patients usually become afebrile within 24–48 hours after receiving proper antibiotic treatment. On the other hand, delayed diagnosis and treatment increase mortality and morbidity. Late presentation, presence of respiratory failure, meningoencephalitis, renal failure, DIC and shock are associated with high risk of death.

Prevention

Chemoprophylaxis with doxycycline 200 mg weekly in high-risk persons is shown to be effective (24). Preventive measures of contact with chiggers such as avoiding sitting or lying on the jungle ground, and tugging the trousers into the boots can reduce the risk of infection.

Melioidosis

Epidemiology and aetiology

Melioidosis is an infectious disease caused by the bacterium *Burkolderia pseudomallei* (previously named *Pseudomonas pseudomallei*) which is widely distributed in water and soil in the tropics. Endemic areas are found in Southeast Asia, Northern Australia, South China, the Indian subcontinent, Central and South America and parts of Africa. There have been a large number of reported cases from Southeast Asia especially Thailand. Recently, there have been increasing reported cases in non-endemic areas: the United States, Canada and Western Europe. These cases occur in refugees from endemic areas and native residents who have traveled to endemic areas in the past.

Pathophysiology

The infection is acquired by direct inoculation of contaminated soil and water into abraded skin or open wounds; inhalation of contaminated dust or aspiration of contaminated water. The infection may be latent for months or years before it becomes symptomatic or it may be apparent very early (3–14 days) after exposure especially in those who live in endemic areas.

Clinical features

Clinical manifestations vary from asymptomatic to rapid progressive septic shock. Pulmonary involvement may present as a primary site of infection or as a part of the multiorgan dissemination in septicaemic patients. In the acute form, majority of cases develop symptoms suddenly within a few days to two weeks after exposure. The presentations are usually indistinguishable from other severe bacterial community-acquired pneumonia or other gram-negative septicaemia (25,26). Acute pneumonia usually presents with sudden onset of high spiking fever, prostration, dyspnoea, pleuritic chest pain and productive cough or haemoptysis. The chest radiograph reveals lobar consolidation which may be single or multiple with no lobe predilection. Pleural effusion, empyema or lung abscess formation is not uncommonly found. More commonly, the pulmonary involvement is secondary to haematogenous spread. Only a half has evidence of a primary site of infection, usually located in the lung or skin and soft tissue. The presentation is often dominated by systemic features of sepsis with evidence of bacterial dissemination in various organs: lung, liver (liver abscess), spleen (splenic abscess), skin and soft

tissue (pustules, subcutaneous abscesses), central nervous system (meningitis, encephalitis), bones and joints (osteomyelitis, septic arthritis) and the urinary tract. The chest radiograph is abnormal in 60–80% of cases (27). Common radiological patterns are diffuse, miliary or nodular infiltrates, or multiple foci of patchy infiltrates. These features often evolve into frank infiltrates with cavitation. Rapid progressive septic shock, multiorgan failure and ARDS are always terminal features in fatal cases.

In the subacute form, most cases develop symptoms long after exposure to a primary infection or a reactivation of latent disease. This form is characterized by an illness manifested by fever, night sweat, weight loss, cough or haemoptysis lasting from weeks to months. Abscess in various organs such as liver, spleen, soft tissue and skin may be encountered. The lungs are predominantly affected as smoldering pneumonia, frequently with cavitation in the upper lobes (Figure 2). Pleural effusion and empyema can also be found. The clinical manifestations of chronic febrile illness with such a radiographic feature are often confused with tuberculosis and lung abscess. Relative sparing of the apices, absence of hilar adenopathy and calcifications may help to distinguish from tuberculosis (27).

In the chronic form, patients can have infections lasting months to years with minimal symptoms and remain afebrile. This form is often seen in nonendemic area patients who have travelled to endemic areas in the distant past. The common manifestations are prolonged low-grade fever, cough, haemoptysis, weight loss and pleuritic chest pain. The chest radiographs almost always reveal upper lobe involvement, occasionally concomitant with lower lobe involvement (28). Dry cavitation is found in almost all cases, with nodular infiltrates in the minority. Pleural effusion is uncommon and hilar adenopathy is rare. In general, the radiographic appearance is very similar to that of active pulmonary tuberculosis but the tendency to resolve with minimal residual scars, apical sparing, absence of calcification and hilar lymphadenopathy can be helpful in differentiating the two diseases.

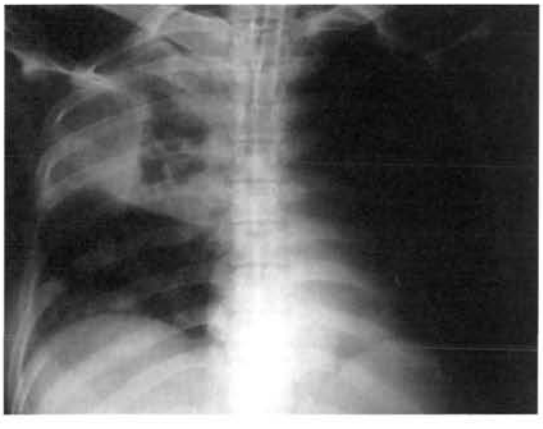


Figure 2. Cavitation in the upper lobes in subacute mellioidosis

Clinical investigations

The diagnosis should be considered in any patient who lives or has ever been in endemic areas, and who present with severe pneumonia, lung abscess, septicaemia or chronic lung infections involving upper lobes. Gram-stained smear of sputum or pus from sites of infection may reveal bipolar or irregular staining gram-negative rods. Though this finding is nonspecific, it is helpful towards a presumptive diagnosis and the physician can start empirical therapy. Definite diagnosis can be achieved by isolation of the organisms from sputum, blood, pus from pustules or abscesses. The clues to *B. pseudomallei* in a cultured specimen include the following: a distinctive sweet smelling odor in a fresh culture; wrinkled (daisy head) appearance of older colonies; an oxidative-positive gram-negative bacillus with bipolar or irregular staining; and resistance to aminoglycosides and penicillin but sensitivity to chloramphenicol, co-trimoxazole and tetracycline (29,30). The development of selective culture media to reduce contaminated growth of other bacteria and the use of automated culture systems to detect the organism more rapidly have improved the identification of *B. pseudomallei*. The lack of recognition of the organism in sputum containing mixed flora by an inexperienced technician is a common error. It is strongly suggested that the clinician should notify the microbiologist of his clinical suspicion so that the specimen can be properly examined and the organism identified.

In acute form, blood culture and culture of sputum or pus from other sites of infection are usually positive. In subacute form, sputum culture is also commonly positive. In cases with no sputum or in the chronic form, serologic tests become very useful (30). The commonly used serologic tests are indirect haemagglutination and complement fixation tests both of which have highly sensitive diagnostic indices for pulmonary melioidosis. The titres remain increased for several months to more than two years after the onset of disease. There is no correlation between the initial titre and prognosis. In patients with disease relapse, the titre tends to increase at the time of relapse or shortly after. Because of a high frequency of seropositivity among people who live in endemic areas, the diagnostic titre should be higher than usual to avoid false positive results but this will lead to the decrease in the sensitivity of the test. However, a high titre (> 1:640) is highly suggestive of active melioidosis and fourfold rise in IHA titre is consistent with active infection. Several ELISA systems for detection of specific IgG and IgM antibodies in the blood by using various purified antigenic components of the bacteria as antigens and for detection of bacterial antigens in urine are being developed (31,32).

Treatment

The specific treatment of choice for acute severe melioidosis is an initial combination of ceftazidime at the highest recommended dose (6–8 g/ day) with one other antibiotic such as co-trimoxazole (trimethoprim 10 mg/kg/day and sulfamethoxazole 50 mg/kg/day), doxycycline (4 mg/kg/day), chloramphenicol (100 mg/kg/day) for 2–4 weeks according to clinical response (33,34). Following parenteral treatment, prolonged oral antibiotics for at least 20 weeks are needed to prevent relapse (35). The oral antibiotics recommended to prevent relapse are the combination of chloramphenicol 40 mg/kg/day (for 2 months), doxycycline (4 mg/kg/day) and co-trimoxazole (trimethoprim 10 mg/kg/day and sulfamethoxazole 50 mg/kg/day) or monotherapy with a high dose of amoxicillin and clavulanate (60 mg/kg/day of amoxicillin and clavulanic acid 15 mg/kg/day). In clinical practice, many physicians in Thailand prescribe a duration of oral antibiotics of 6–12 months depending on the result of clinical response and culture, and monotherapy with either co-trimoxazole or doxycycline or combination of the two is common (36). The response to treatment is usually slower than other gram-negative bacterial infections, especially in those having multiple small abscesses in various organs. The large extrapulmonary abscess should be surgically drained whenever possible under antibiotic coverage. In life threatening situations with a clinical suspicion of melioidosis, high dose empiric intravenous antibiotic administration (e.g., ceftazidime, imipenam) is warranted since delay in treatment is associated with a very high mortality (34). For patients with less severe diseases such as subacute or chronic forms, the treatment can be initiated with combination oral antibiotics for the same duration as mentioned above.

Prognosis

Even with optimum treatment, the mortality from acute severe melioidosis is still high (30–40%). Those who survive may have significant morbidity and relapse. The chronic form has a low mortality rate but the patients may suffer from long term morbidity.

Prevention

No effective preventive measures are available for those whose occupations involve soil and water such as fishing and farming.

Leptospirosis

Epidemiology and aetiology

Leptospirosis is a zoonotic disease of worldwide distribution and it is common in the tropics and in developing countries. Leptospirosis is caused by the group of spirochetes of the genus Leptospira comprising 28 serological groups of all pathogenic strains. Human infection most commonly results from indirect or direct exposure to infected rat urine through urine-contaminated water or soil,

and dogs, cats, livestock and wild mammals are also sources (37).

Leptospirosis is an important health problem in tropical countries where rainfall is heavy and the soil is either neutral or alkaline. Epidemics often follow heavy rainfall or flooding. The major recent outbreaks of leptospirosis occurred in Brazil (in 1988) and in Nicaragua (in 1995) when there were 1061 cases with 50 deaths and 2000 cases with at least 40 deaths were recorded (38,39). In Thailand, the most recent major outbreaks occurred in Northeastern region during 1997 with 2334 cases and 113 deaths; 1998 with 2229 cases and 102 deaths; and 1999 with 5964 cases and 279 deaths (40,41). Most victims are farmers whose potential risk factors are walking through water; plowing, fertilizing and pulling out sprouts in wet areas for more than 6 hours a day (42). The peak prevalence of the disease is during September-November each year. The most recent epidemiological situation in various countries can be divided into 2 groups, the group in which the incidence of the disease has been increasing (Thailand, Philippines, Australia, China and Andaman islands) and the group in which the incidence of the disease has been decreasing (Japan, New Zealand, Netherlands, Taiwan and Korea) (43). In the first group, the risk factors are high occupational exposure (farmers, sewer workers) and epidemics associated with flooding. In the latter group, reported cases are slaughterhouse employees, meat inspectors, and people rafting or swimming in natural fresh contaminated water sources.

Pathophysiology

Once the leptospira penetrate mucous membranes or skin, they disseminate to all parts of the body. These spirochetes penetrate, invade and proliferate in various tissues especially liver, kidneys, heart and lungs. Lung pathology may reveal congestion, mild interstitial inflammatory response, intraalveolar haemorrhage or diffuse alveolar damage. The ultrastructural findings of the pulmonary vascular endothelium are uniform and constant. Capillary lesions are characterized by swollen endothelial cells with an increase in pinocytotic vesicles and giant dense bodies in their cytoplasm, aggregation of platelets to the stimulated endothelium and preserved intravascular junctions (44).

Clinical features

The clinical features vary from mild to severe febrile illness characterized by fever, myalgia, headache, conjunctivitis, jaundice, leukocytosis, aseptic meningitis, hepatitis, nephritis, and haemorrhagic episodes. Pulmonary involvement is common but usually mild and often overlooked. The most common symptom is a nonproductive cough occurring in 25–70% of cases, and which is prominent at the beginning of the leptospiraemic phase. Haemoptysis has been reported in 3–25% and chest pain may occur in 10% (38). Haemoptysis also presents early, varying from scanty amount disappearing within a few days to massive life threatening episodes (45). Pulmonary haemorrhage without haemoptysis is not unusual and frequently occurs with thrombocytopaenia in the absence of DIC (46). In severe pulmonary involvement, fulminant respiratory failure and ARDS may be the primary clinical features of the illness and they are associated with high risk of death (46,48).

The prevalence of chest radiographic abnormalities varies between 20–70% in most reports (47,49,50). No correlation has been found between the degree of jaundice and pulmonary involvement. The chest radiographic abnormalities are not specific and may mimic other common diseases such as bacterial pneumonia, tuberculosis and pulmonary emboli. These abnormalities can be extensive in the absence of physical signs and may be discovered unexpectedly, although those most severely affected usually have respiratory symptoms. The commonest abnormality is nonsegmental pulmonary opacities commonly found in lower lobes and the peripheral lung fields due to a haemorrhagic pneumonitis rather than representing bacterial pneumonia. The predominantly unilateral distribution of these abnormalities makes fluid overload a less likely cause. The size of opacities varies from snowflake-like, small, patchy lesions to confluent massive areas of consolidation which differ in appearance from classical pneumococcal pneumonia by the

absence of sharply delineated segmental or lobar consolidation. Linear opacities extending laterally and upwards from the cardiac borders are also commonly observed (49). They are 3–4 mm thick and 7–9 cm long. The upper and lower borders are irregular with short linear extensions into the surrounding lung. These findings represent areas of subsegmental collapses that may appear uni-or bilaterally. Pleural effusion is uncommon (0–9%) and lymphadenopathy is not found (47,49,50). In the cases that deteriorate and develop respiratory failure, confluence of diffuse bilateral infiltrates is the usual radiographic appearance (Figure 3) (49). The resolution of infiltrates on the chest x-ray film occurs faster than in other forms of bacterial pneumonia with no residual scarring.

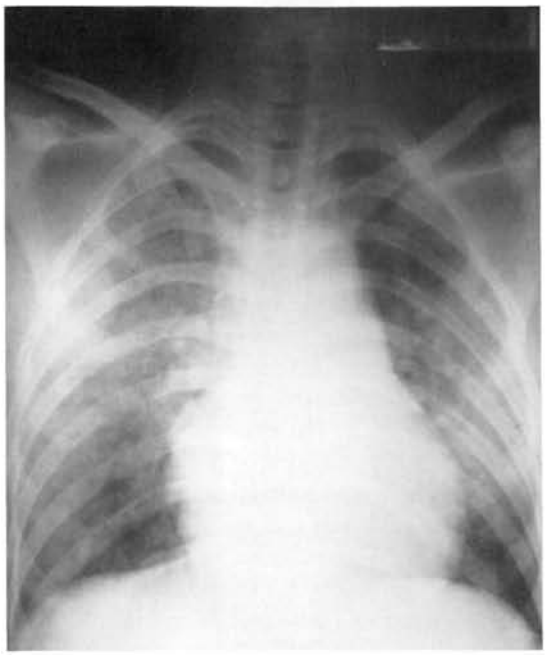


Figure 3. Confluence of diffuse bilateral infiltrates in leptospirosis

Clinical investigations

Diagnosis is usually confirmed by serological test (51). The standard serological test is the microscopic agglutination test (MAT) for detecting specific antileptospiral antibodies. A fourfold rise in titre between the acute phase serum and the convalescent phase serum is a positive diagnostic test. Other immunologic tests that are commonly used for screening include ELISA, macroscopic agglutination test and immunofluorescent antibody test (IFA).

Treatment

The effectiveness of antimicrobial therapy in treating leptospirosis has been difficult to assess because of high variability of the clinical course, although in severe cases, antibiotic therapy is effective even when treatment is delayed. Most authors agree that results are good if treatment has begun early up to the fourth day of evolution. Antibiotics commonly used are penicillin G and doxycycline. Either oral doxycycline 100 mg twice daily or penicillin G 2.4 to 3.6 million units daily for 7 days is effective in shortening the clinical course.

Prognosis

The prognosis depends on the disease severity and associated complications. In general, advanced age, the presence of jaundice, acute renal failure and acute respiratory failure are associated with high morbidity and mortality.

Prevention

Prevention is difficult because it is almost impossible to eliminate the large animal reservoir of infection but wearing waterproof rubber boots should be recommended for high-risk persons. Immunization for the high occupational risk population is being used in Japan, Italy, Spain and Israel. The major problem with human vaccination is that immunity is serovar-specific and it is very difficult to select all the potentially important serovars in the vaccines (52). The prophylactic drug, doxycycline 200 mg orally administered weekly, for people at risk in endemic areas has been shown to be effective in Panama (53). The problem is that most of the infected people are asymptomatic or mildly symptomatic so it may not be cost-effective if the drug is to be administered to all.

Salmonellosis

Epidemiology and aetiology

Salmonellosis, one of the endemic enteric diseases in developing countries, is a disease related to poor sanitation, lack of education and poverty. The disease is caused by Salmonella species such as *S. typhi, S. typhimurium, S. cholerasuis, S. paratyphi, S. enteritidis.*

Pathophysiology

Eating or drinking contaminated food or water transmits the disease. The organism penetrates the lymphoid tissue of gastrointestinal tract. Haematologic dissemination then carries the organism to the reticuloendothelial system (liver, spleen, and bone marrow) and other parts of the body.

Clinical features

Pulmonary manifestations of salmonellosis can be classified into 4 groups:

1. acute bronchitis
2. acute pneumonia
3. empyema thoracis
4. lung abscess.

The most common is acute bronchitis manifested by mild cough with sticky sputum in 28–86% but it is not a prominent symptom. Pulmonary manifestations of the other 3 groups occur in only 1% of all cases of salmonellosis (54). Pneumonia, the second most common pulmonary manifestation, was present in 11% in one large reported series (55). The chest radiographic appearance is either lobar or bronchopneumonia. These pneumonic patients usually are of advanced age with severe underlying diseases (such as malignancy, diabetes mellitus). Those with severe pulmonary symptoms carry a high mortality rate (56). *S. cholerasuis* and *S. typhi* are the causative organisms in nearly a half of the cases but they are rarely found in the sputum. Empyema thoracis is uncommonly reported. In recent literature review, there were 18 cases of empyema thoracis reported during 1919–1986 and *S. typhimurium* was the causative agent in 40% of cases (57). Lung abscess is rare and mostly caused by *S. typhi.* In Thailand, an endemic area for salmonella infection, there have been reported cases of rare pulmonary manifestations including interstitial pneumonia, necrotizing pneumonia, large rapid ballooning pneumatocele-like cavity (58–60). In the AIDS epidemic era, non-typhoidal salmonella infection may complicate the course of AIDS and *S. typhimurium* is the most common organism isolated from the blood (61). The course of illness is different from that of the immune-competent patient. There is a higher incidence of bacteraemia in the former group. The incidence of bacteraemia in the normal host with gastroenteritis is 1–4% but 75–100% in immune-deficient host. The disease tends to respond poorly to antibiotics and relapse on discontinuation of therapy is common. There is increasing evidence that persistent S. typhimurium bacteraemia is an early infection in AIDS. However, *Salmonella typhi* infection in HIV-positive patient is rarely reported.

Clinical investigations

For the diagnosis of salmonellosis, blood culture is the preferred method during the first two weeks of illness. Bone marrow cultures are positive in more than 90% of the patients. Urine and stool cultures are less frequently positive. The Widal test for agglutinating antibodies against the somatic (O) and flagella (H) antigen is widely used for serodiagnosis. The test is usually positive after 2–3 weeks of infection. An O agglutination titre of > 1:80 or a fourfold increase supports the diagnosis of typhoid fever but it is non-specific and of low sensitivity. A new indirect ELISA to detect antibodies to *S. typhi* outer membrane protein which is apparently highly specific and sensitive for *S. typhi* diagnosis is being developed (62).

Treatment

Chloramphenicol is still the drug of choice for treating typhoid fever and its complications. Third generation cephalosporins, ciprofloxacin and ofloxacin are also effective and can be used in

chloramphenicol resistant cases or in leukopaenic patients.

Prognosis

The pneumonic patients have a high mortality rate because they are usually of advanced age or have severe comorbidities such as AIDS, malignancy and diabetes mellitus. Recurrences are common especially in AIDS patients.

Prevention

Improved sanitation and hygienic measures in handling food and drinking water can reduce the risk of salmonella infection.

Penicilliosis Marneffei

Epidemiology and aetiology

Penicillium marneffei is one of a few Penicillium species that cause human disease, both in normal and immunosuppressed persons (63). Human infection is increasingly reported since 1988; all are cases from Southeast Asia especially Thailand (64). *P. marneffei* is found mainly in the soil in Southeast Asia (Thailand, Vietnam), South China and Hong Kong.

Pathophysiology

Human infection is thought to occur through aerosol inhalation or direct skin contact with contaminated soil. Recently reported cases mostly occur in acquired immunodeficiency subjects.

Clinical features

Clinical manifestations are characterized by acute or prolonged febrile illness with nonspecific constitutional symptoms. Physical examination reveals anaemia, lymphadenopathy, hepatosplenomegaly and diffuse papular skin eruptions with central necrosis or umbilication resembling molluscum contagiosum (Figure 4). Pulmonary manifestations commonly present as cough or dyspnoea. In AIDS patients, pneumonia may be the prominent manifestation of the disease, and frequently indistinguishable from other causes of infections such as cryptococcosis, pneumocystosis, tuberculosis, CMV infection or bacterial pneumonia (65). In a prospective bronchoalveolar lavage study in hospitalized HIV infected pneumonic patients at Chiang Mai University Hospital, *P. marneffei* was found in approximately 40% of cases of pulmonary fungal infections and 16% of all cases of hospitalized pneumonia. In a half of these patients, *P. marneffei* was found as mixed infection with other pathogens (66). Chest radiographic findings are nonspecific but frequently bilateral, including reticulonodular or miliary infiltrations, reticular infiltrations, consolidation with or without cavities, pleural effusion and hilar or mediastinal adenopathy.

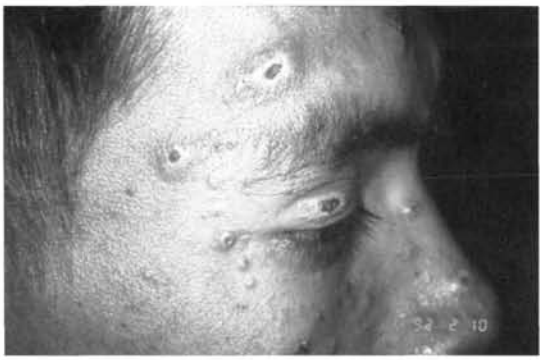


Figure 4. Anaemia, lymphadenopathy, hepatosplenomegaly and diffuse papular skin eruptions with central necrosis or umbilication resembling molluscum contagiosum

Clinical investigations

The diagnosis can be made from Gram-stain or Wright-stain smear of sputum or BAL fluid (67). The characteristic morphology of the organism on stained smear is a sausage-shaped gram negative rod with central septation (Figure 5) but sometimes yeast like morphology predominates and may be easily overlooked. Sputum or BAL culture is highly sensitive for diagnosis. Blood culture is

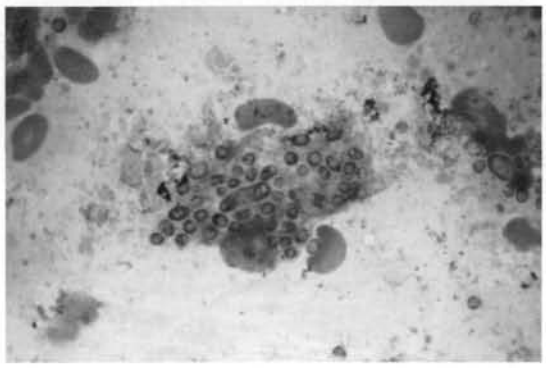


Figure 5. The characteristic morphology of *Penicillium marneffei* on stained smear is a sausage-shaped gram negative rod with central septation.

usually positive in cases with disseminated infection.

Treatment

The treatment drug of choice is amphotericin B (0.5 mg/kg/day intravenous infusion) or itraconazole (400 mg/day orally) for 8–12 weeks (68). In AIDS patients, relapse is common after treatment is stopped, so itraconazole (200 mg/day orally) is recommended for relapse prevention. Patients usually show response to the treatment within two weeks after the treatment with resolution of fever and other symptoms as well as signs of infection.

Prognosis

Patients who develop acute respiratory failure or meningitis have a higher mortality than those who do not.

Prevention

It is difficult to avoid air-borne exposure to the fungus or direct skin contact with contaminated soil in endemic areas.

Malaria

Epidemiology and aetiology

Malaria, a vector-borne disease, is a major communicable disease in tropical rainforest countries. Despite enormous progress in the understanding of the biology of the malarial parasite, there is still a long way to find a solution to the problems of malaria eradication. In Thailand, reported cases of malaria (passive surveillance) is decreasing from 200–250 per 100,000 population during1988–1990 to 100 per 100,000 population during 1995–1997 (69). Endemic areas are located near the Mynmar and Cambodia borders. Human malaria is caused by four species belonging to the genus *Plasmodium* (*Plasmodium falciparum, P. vivax, P. ovale and P. malariae*).

Pathophysiology

The parasite is transmitted to humans following the bite of an infected female anopheline mosquito. The sporozoites thus injected enter the bloodstream briefly and then enter the host liver cells. Exoerythrocytic schizogony ensues and after 12–16 nuclear divisions, 2,000–30,000 merozoites are liberated by rupture of the schizont. Erythrocytic schizogony entails formation and growth of a trophozoite that ingests haemoglobin. Three-five divisions of erythrocytic merozoites are formed and liberated by schizont rupture. *P. falciparum*, by virtue of its capacity to infect red cells of all ages, produces very high levels of parasitaemia and is thus the only parasite associated with the development of severe complicated malaria. The parasitized red blood cells adhere to the endothelial surface and sequester in the microcirculation causing impaired perfusion, nutrition and oxygenation in various tissues especially the brain (cerebral malaria). Pulmonary oedema in malaria, in contrast to cerebral malaria, is not related to sequestration of parasitized red blood cells in the lungs but to capillary leak syndrome.

Clinical features

Pulmonary manifestations occur in 3–10% of

patients infected with falciparum malaria. The clinical picture is varied and ranges from asymptomatic to fatal pulmonary oedema. Even asymptomatic patients may have increased work of breathing, tachypnoea and respiratory alkalosis (70). The incidence of bronchitis is 7.5% in one large report (71). Pleural effusions probably have little clinical significance since they have never been large enough to compromise lung function but are frequently found in autopsied patients (72). The pleural fluid, either a transudate or an exudate, usually contains predominantly lymphocytes (73). Malarial pneumonitis is less common than secondary bacterial pneumonia which is usually found in severe cases having cerebral symptoms of coma, convulsions, vomiting and aspiration. The clinical features of malarial pneumonitis are cough, haemoptysis, chest pain, rales, pleural rub and signs of pulmonary consolidation. Pulmonary oedema is a serious complication with a high fatality rate between 30–70% and commonly occurs in association with severe malaria (20–50%) (74,75). It may develop early in the course of illness and usually is associated with heavy parasitaemia, high level of acidaemia and delayed antimalarial treatment or even a few days after antimalarial therapy has been instituted and the parasitaemia is falling with apparent clinical response (76–78). The contributor for "delayed" pulmonary oedema include prolonged altered capillary permeability in severe malaria. Approximately 40–70% of cases with pulmonary oedema develop features consistent with ARDS (74,76).

Pulmonary oedema is preceded by a sense of chest tightness, a dry cough and an entirely normal chest examination. This is followed within hours by rapidly progressive restlessness and agitation, dyspnoea, orthopnoea, cyanosis and frothy sputum. The lungs then show the characteristic signs of pulmonary oedema. The chest radiograph reveals interstitial and alveolar oedema with a normal size heart. There is no evidence of left ventricular dysfunction but hypoalbuminemia and heavy parasitaemia are risk factors for the development of pulmonary oedema (78,79). These clinical features are nonspecific and may lead to marked delay in diagnosis especially when the pulmonary manifestation is an outstanding feature and the initial blood smear for malaria is overlooked. The first signs of respiratory failure may mimic those of cerebral malaria by prominent clinical features of drowsiness. Irritability, confusion and headache are due to hypoxia from acute lung injury and such a patient may be misdiagnosed as cerebral malaria resulting in delayed treatment of hypoxaemia. As the clinical signs are likely to be misleading, regular monitor of arterial oxygenation and chest radiographs should be done in cases of cerebral malaria. Malarial pulmonary oedema must also be differentiated from aspiration pneumonia, iatrogenic fluid overload pulmonary oedema (especially in the presence of renal failure), left ventricular failure and other causes of ARDS. Pulmonary pathologic appearances are similar to those of ARDS (74). A definite diagnosis of malaria-related ARDS must be based on the demonstration of parasitized red blood cells in the dilated and packed vascular channels. Several mechanisms may contribute to lung injury in falciparum malaria:

1. impaired tissue perfusion and tissue hypoxia in the pulmonary microcirculation
2. abnormal autonomic effects on the lung resulting from reduced blood flow in the central nervous system
3. immunologic injury to alveolar-capillary membrane
4. morphologic changes in the membranes of infected red blood cells leading to sequestration of parasitized red blood cells in vascular beds and pulmonary capillary damage (80).

Clinical investigations

The diagnosis of malarial infection is made by careful examination of well-stained thick and thin film peripheral blood smears by the experienced personnel.

Treatment

The mainstays of treatment, apart from specific antimalarial drugs, are the maintenance of adequate tissue oxygenation with FiO_2 as low as possible to avoid oxygen toxicity and modest fluid balance to avoid fluid overload. These are achieved by the

use of positive airway pressure mechanical ventilation if necessary and the use of central venous pressure or pulmonary wedge pressure monitoring for optimum fluid balance. The use of steroids in cerebral malaria has been shown to be harmful (81) and their role in pulmonary oedema is also not established, so the use of these agents should be avoided. Since bacterial co-infections such as bacterial pneumonia or primary septicaemia are common, empirical antibiotic therapy should be strongly considered in patients with acute lung injury or septic shock (76). The mortality rate of non-ARDS pulmonary oedema patients is much lower than that of ARDS pulmonary oedema patients in recent series (75). Quinine is still the standard drug of choice in the management of severe falciparum malarial infection and is now generally used together with a tetracycline derivative. After an initial loading dose, 20 mg/kg, a slow steady infusion of 10–20 mg/kg at 8 hour intervals provides sustained therapeutic drug levels and administration should be continued for at least 72 hours after asexual forms of the parasite have disappeared from the peripheral blood. A newly developed class of drugs named artesunate combined with a longer-acting antimalarial drug named mefloquine is becoming the treatment of choice for uncomplicated multidrug-resistant malaria in the western and eastern borders of Thailand (82). Exchange transfusion therapy is recommended in the treatment of severely complicated malarial patients who present with heavy parasitaemia (83,84). However, heavy parasitaemia alone, if promptly treated even without exchange, has a very good prognosis (85).

Prognosis

The morbidity and mortality are high in severe complicated malaria, especially in those with ARDS-pulmonary oedema, acute renal failure and cerebral malaria.

Prevention

The most popular public health preventive strategy is using insecticide-treated nets and house spraying with residual insecticides in endemic areas (86). This strategy can reduce the risk of human infection and disease as a cost effective means. Its extended use is then limited by cost /affordability problems and operational issues. Various malarial vaccine are being developed. Chemoprophylaxis is recommended for those who travel to or temporarily living in endemic areas, not for residents of endemic areas. Chloroquine phosphate (500 mg weekly beginning 1 week before exposure and continuing for 4 week after exposure) is widely used in endemic areas of chloroquine-susceptible falciparum malaria. Mefloquine (250 mg weekly beginning 1 week before exposure and continuing for 4 week after exposure) is commonly used in endemic areas of chloroquine-resistant falciparum malaria and doxycycline (100 mg daily beginning 1 day before exposure and continuing for 4 week after exposure) can be used instead of mefloquine in endemic areas of mefloquine-resistant strains.

Amoebiasis

Epidemiology and aetiology

Amoebiasis is a disease caused by the protozoan *Entamoeba histolytica.* The disease is a worldwide parasitic infestation but more prevalent and virulent in tropical countries with poor hygiene and socio-economic situations. Endemic areas are India, South Africa, Southeast Asia, parts of Middle East, and the western portion of South America and Mexico. It is the third leading cause of death due to parasitic infections in the world (87). Approximately 500 million people worldwide are infected with *E. histolytica.*

Pathophysiology

Human is infected by ingestion of the *E. histolytica* cyst, the infective stage of the parasite that is viable in water, dwelling in fecal-contaminated water, food and fingers. After ingestion, the parasitic cyst passes through the gastrointestinal tract where excystation occurs in the small bowel and four trophozoites are released from a cyst. Each trophozoite multiplies and moves to the large bowel where it remains a commensal for years or

becomes a pathogen. In the latter case, it may manifest as intestinal or extraintestinal symptoms. Amoebic colitis and liver abscess are the most common intestinal and extraintestinal manifestations of *E. histolytica* infection. The parasite contaminates the liver by hematogenous spread via portal venous system or direct extension from the colon. Pleuropulmonary amebiasis occurs almost exclusively in individuals with liver abscess. The incidence of pleuropulmonary complications varies widely, but is approximately 15–40% in large series of amoebic liver abscesses (88,89). Most pleuropulmonary complications result from direct extension of an amoebic liver abscess through the diaphragm but haematogenous dissemination occasionally occurs either through the portal circulation or through inferior haemorrhoidal veins and inferior vena cava.

Clinical features

Pleuropulmonary amoebic manifestations are commonly accompanied by clinical features of liver abscess but sometimes there are no clinical signs of associated hepatic involvement and the diagnosis will be delayed (90). The clinical features of liver abscess are usually insidious onset of fever, night sweats, anorexia and pain in the right hypochondriac region. Sometimes, a patient experiences only weight loss for many months or a prolonged fever. Most of the liver abscess manifestations have no concurrent intestinal manifestations and only a minority has experienced colitis in the past. The early signals for pleuropulmonary complications are increase or change in character of pain to pleuritic pain in the right hypochondrium, right shoulder or scapular pain due to diaphragmatic irritation by the liver abscess, hiccups and nonproductive cough (91). These signals may be followed shortly by dyspnoea, haemoptysis, respiratory insufficiency or even collapse. Haemoptysis usually begins with repeated scanty amounts before a massive episode occurs. A patient with a hepatobronchial fistula usually coughs up characteristic chocolate-coloured or anchovy paste contents of the abscess. The most common radiographic findings are the elevation of right hemidiaphragm (in approximately half of the cases) and right-sided pleural effusion (92). A plate-like atelectasis or basal pneumonitis can also be found. The degree of pleural effusion may be small, moderate, or massive and sometimes the subpulmonic effusion may mimic the elevation of right hemidiaphragm. A triangular shadow with its base on the diaphragm (Figure 6) is said to be characteristic in circumstances of known liver abscess (93). Lung abscess formation can be found, usually in the right lower lobe but may be seen in any lobe indicating haematogenous dissemination. Bilateral pulmonary amoebiasis is rare and usually results from erosion of amoebic liver abscess into the hepatic vein or haematogenous spread (94).

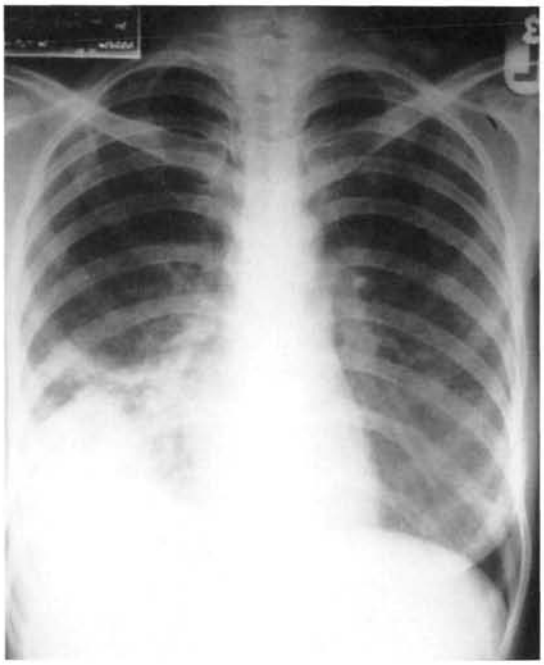


Figure 6. A triangular shadow with its base on the diaphragm in amoebic liver abscess

Clinical investigations

The diagnosis should be strongly considered in a liver abscess patient with right-sided pleural effusion, right lower lobe lung consolidation or abscess. The diagnosis should also be suspected in a patient who has unexplained right-sided pleural effusion, right lower lobe lung consolidation or abscess even though there are no concurrent clinical features of amoebic liver abscess. The

delayed diagnosis by an inexperienced doctor or the patient's delay in seeking medical treatment makes morbidity and mortality higher (95–97). Presentation in many cases mimic bacterial infections, tuberculosis or carcinoma. An elevation of serum alkaline phosphatase may be an important clue for making a diagnosis in the absence of hepatic manifestations. Liver scan or ultrasonography are almost always positive for a large single abscess that is commonly located in the posterosuperior portion of right hepatic lobe or occasionally in the left lobe. Serological tests for amoebiasis (such as IHA, ELISA, CIE, IFA, CF tests) are very helpful diagnostic tools and are positive in over 95% of cases but they do not differentiate between active and previous infections. The indirect haemagglutination test is widely available and highly sensitive but it needs an experienced technician and yields higher false positive rate than other techniques. The latex agglutination test is also highly sensitive and it is positive only in an active phase of the disease, so it is the most useful diagnostic test at present. The diagnosis can also be based on demonstrations of the organisms in clinical specimens such as sputum, bronchoalveolar lavage or pleural fluid but unfortunately the trophozoites are present in less than 20% of patients (98). The pleural fluid may be "sympathetic" or turning into empyema with characteristic chocolate colour of anchovy paste, or green/yellow (93).

Treatment

The current drug of choice is metronidazole at a dosage of 400–800 mg three times a day for 10–14 days (99). For a case with hepatobronchial fistula or lung abscess, postural drainage is required. Sympathetic pleural fluid rarely requires surgical drainage but simple needle aspiration is needed when it becomes symptomatic. The surgical treatment of amoebic empyema is more conservative than in bacterial empyema (100). Repeated needle aspirations can be tried initially in mild to moderate symptomatic cases. Intercostal drainage is indicated in those who fail to respond with repeated aspirations or severe cases. Decortication is rarely required and only in the case with incomplete lung expansion after tube drainage (101). Concurrent drainage of the associated amoebic liver abscess should be considered in those with large abscess cavity (96,97).

Prognosis

Morbidity and mortality of pleuropulmonary amoebiasis are higher than amoebic liver abscess and intestinal amoebiasis. Delayed diagnosis by an inexperienced doctor or the patient's delay in seeking medical treatment makes mortality and morbidity higher than the early treated case.

Prevention

Improved sanitation and public health hygienic measures are important in prevention of infection and epidemics.

Paragonimiasis

Epidemiology and aetiology

Paragonimiasis, a food borne trematode infection that is estimated to affect over 20 million people around the world, is endemic in many Asian countries (such as Japan, Korea, Taiwan, central China, Thailand, Laos, Vietnam, Cambodia, Malaysia, Indonesia, Phillipines, India and Nepal); Africa and central and South America (98). The disease is caused by infection with the lung flukes of the genus Paragonimus containing 16 species all known to be pathogenic to humans. Most human paragonimiasis is due to *Paragonimus westermani.*

Pathophysiology

Humans or other carnivorous animals become infected by eating raw or poorly cooked freshwater crabs, the second intermediate hosts of this parasite, living in or near streams in mountainous areas. Metacercaria are released from cysts and penetrate the small bowel wall through the abdominal cavity, diaphragm and appear in the

pleural cavity about 14 days after infection. Two weeks later, the young worms enter the lungs where they mature into adult worms within several weeks and form parasitic cysts. The flukes lodge near bronchioles where they may begin to lay eggs 5 to 6 weeks after infection; the eggs are then discharged in bronchial secretions and coughed up or passed in the faeces to renew the cycle (103). The flukes may migrate to the brain which is the most common extra-pulmonary site reported (104,105). Paragonimiasis at other sites (such as liver, spleen, kidney, heart and pericardium, eyes, lymph nodes and other unusual sites) are usually symptom free. Eosinophilic infiltration around the sites of egg deposition, as well as peripheral blood eosinophilia and an elevated IgE level, reflecting the activation of the immune system, play a major role in pathogenesis of the disease.

Clinical features

Most humans who become infected remain asymptomatic. In others, symptoms begin with chronic cough and chest pain followed by repeated haemoptysis which is seldom severe. The sputum is characteristically rusty brown or chocolate coloured as seen in pneumococcal pneumonia but the patients are still healthy. The duration of illness varies from less than a month to years (on average 1–3 years) (106,107). Malaise, weight loss and anorexia are commonly present. Extrapulmonary involvement can also be found (such as headache, convulsion, hemiplegia, hepatomegaly and ascites) usually after pulmonary symptoms. There are abnormal breath sounds (rhonchi and crepitations) in a minority of the patients (15–30%). Chest radiographs are normal in 5–21% (108). The abnormalities are frequently bilateral and more extensive lesions correlate well with longer duration of illness and numbers of egg output per day (109). These abnormal radiographic findings can be divided into three stages of the disease (103). Firstly, the stage of larvae migration, is characterized by pleural effusion or pneumothorax which appear during penetration of the flukes into the pleural cavity or the lung. Poorly defined airspace consolidation and long band-like opacities (2–4 mm thick and 2–7 cm long) abutting the pleura are commonly seen. These findings represent haemorrhagic and exudative pneumonia along larvae migration tracts. The airspace consolidation may resolve several weeks later leaving better-delineated nodules (chocolate-coloured fluid filled cysts) or thin-walled cysts (fluid extruded). A CT scan with contrast media or sometimes a plain chest radiograph can demonstrate these cysts within the consolidated lung. Secondly, nodular or cystic lesions characterize the stage of worm maturation. These nodules or cysts occur predominantly in the periphery of mid- and lower lung zones containing the mature worms embedded in fibrous tissue (Figure 7). The cysts may vary in size from 0.5 to 4 cm in diameter with walls less than 3-mm thick. A big cyst containing chocolate-coloured fluid may mimic pyogenic lung abscess. The most characteristic radiographic feature is ring shadows representing thin-walled borders of cystic cavities with a crescent-shaped opacity along one side of the border resembling the corona phase of a solar eclipse which may be found in 8 to 82% of cases (109,110). This corona appearance represents a worm attached to the wall of a cyst and is demonstrable on CT scan. The cystic lesions are usually multiple and aggregate with a soap-bubble appearance. On CT scan, focal bronchiectasis is commonly associated, suggesting inflammatory or mechanical injury by the worms. Burrows or tracts

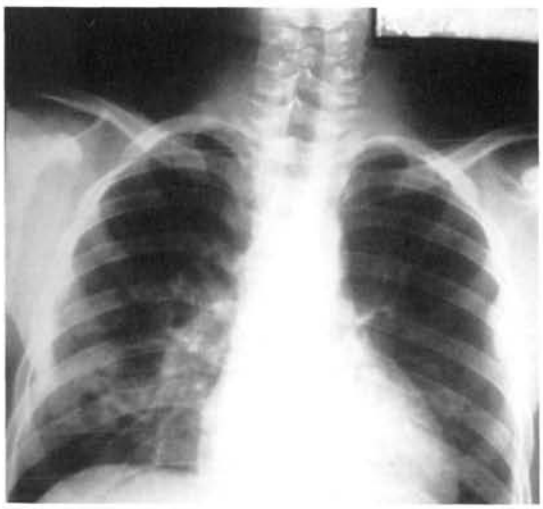


Figure 7. Nodules or cysts occur predominantly in the periphery of mid and lower lung zones in Paragonimiasis

that run an irregular tortuous course in the lung parenchyma and communicate with the adjacent cysts can also be noted. Pleural reactions, thickened pleura or pleural effusion, may also occur at this stage. Thirdly, the stage of recovery, after the death of parasite by treatment, the lesions gradually improve and disappear completely within 3–26 months, in contrast to post-primary tuberculosis (111). It should be noted that pulmonary paragonimiasis can mimic pulmonary tuberculosis in both clinical features and radiological findings, so the sputum examination for confirmation or exclusion is mandatory especially in endemic areas (106).

Clinical investigations

The diagnosis of pulmonary paragonimiasis is to demonstrate the characteristic golden brown oval 90 x 55 mm egg with a flattened operculum at one end in the sputum, BAL fluid, pleural fluid, lung biopsy or in the stool. Sputum eosinophilia in the absence of the characteristic eggs is common and repeated examinations should be carried out in a suspicious case. The characteristic pleural fluid of paragonimiasis is reported to be of diagnostic value even in the absence of positive ova studies by showing a glucose < 10 mg/dl, LDH level > 1,000 IU/L, eosinophilia, a high protein value and low pH (112). Because of the low sensitivity of egg detection and the low specificity of intradermal test, serological tests have been developed. Dot-ELISA and IHA tests are highly sensitive and specific (97–100%) (113,114).

Treatment

Praziquantel (25 mg/kg three times a day for 2 days) is the treatment of choice, giving a cure rate of 90% and haemoptysis stops dramatically within a few days (107).

Prognosis

The clinical course of pulmonary paragonimiasis is usually benign. Many individuals with heavy infections are entirely symptom free. Untreated cases can spontaneously resolve in 5–10 years. Haemoptysis is seldom severe and may continue for years (endemic or benign haemoptysis), but may be occasionally life-threatening (103).

Prevention

Public health education for people living in or travelling to endemic areas to avoid eating poorly cooked or raw freshwater crabs is the best known method for infection prevention.

Strongyloidiasis

Epidemiology and aetiology

Strongyloidiasis is a disease caused by a free living and parasitic nematode named *Strongyloides stercoralis* that is endemic throughout the tropical and subtropical countries (115).

Pathophysiology

After the infective filariform larvae penetrate human skin, they migrate via the bloodstream or lymph through the right heart and lungs where they become adult worms en route to the small intestine. They can re-enter the bloodstream and migrate through the lungs again without soil cycle. Because of their capabilities of autoinfection, the infection may persist for life and extremely heavy infections can be acquired. Fifteen to thirty percent of chronically infected people may be asymptomatic. Most infected patients present with chronic diarrhoea, abdominal pain, cutaneous eruptions and peripheral eosinophilia. Pulmonary symptoms can occur during larvae migration or dissemination.

Clinical features

The most common pulmonary manifestation of *S. stercoralis* infection in normal host is Loeffler's syndrome, presenting as transient cough and wheeze, fever, pneumonitis and eosinophilia during larvae migration through the lungs. In

immunocompromised hosts, severe pulmonary disease caused by disseminated strongyloidiasis is the most common manifestation. These hosts are mostly people receiving prolonged or repeated courses of corticosteroids including those with steroid-dependent asthma or frequent exacerbations of COPD (115–118), occasionally people with severe immunosuppressive states such as renal transplant or chronic debilitating illness. The infection is surprisingly uncommon in HIV/AIDS patients (119). Pulmonary signs and symptoms are cough, shortness of breath, wheezing, haemoptysis that may be massive and ARDS (116,117). These signs and symptoms frequently mimic the underlying disease manifestations (e.g. exacerbation of asthma and COPD especially after corticosteroid therapy) or other pulmonary infections (eg. bacterial pneumonia, disseminated tuberculosis, lung abscess) (118,120,121). Gram negative faecal bacteria, travelling with the larvae, may cause coexistent haematogenous spread of bacterial pneumonia, meningitis or septicaemia. The chest radiogram shows abnormalities in up to 90% of cases including bilateral pulmonary infiltrates (such as patchy lobar or bronchopneumonia; reticulonodular, miliary or reticular infiltrates; large alveolar or diffuse ground-glass appearance) (116,117). More rarely, air-fluid cavity and pleural effusion have been described (121,122).

Clinical investigations

Unfortunately, the diagnosis is frequently delayed until late in the course of the disease which contributes to a high death rate and it is not uncommon for this diagnosis to be made after death (113). The diagnosis requires a high index of suspicious of this disease in high risk patients, concurrent gastrointestinal and cutaneous symptoms, repeated sputum examinations for the larvae that can be demonstrated on fresh sputum specimens or Gram's stained sputa and occasionally bronchoalveolar lavage (Figure 8) (124,125). Duodenal aspirate collected by a string test is usually positive. Stool examination for the larvae is positive in varying degrees depending on the method of testing, with direct smear, concentration technique, filter-paper and agar-plate culture in order of increasing sensitivity levels (126). Eosinophilia is a uniform feature in healthy hosts but may be found in only a minority of immunocompromised hosts on high corticosteroid dosage.

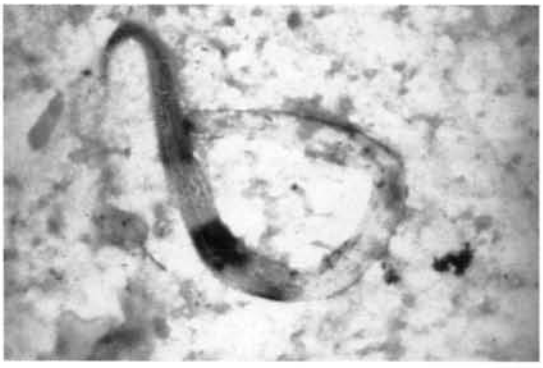


Figure 8. Larvae of *Strongyloides stercoralis* in sputum examination

Treatment

Thiabendazole (1 g twice daily for 5 days) or albendazole (400 mg twice daily for 5 days) is the standard treatment but repeated doses may be necessary if the parasite is not initially eradicated (127). Ivermectin can be used successfully in cases of standard treatment failure.

Prognosis

Loeffler's syndrome is a benign presentation of intestinal strongyloidiasis during transient pulmonary migration phase. In contrast, disseminated strongyloidiasis has a high mortality rate because of many factors such as heavy parasitic pulmonary involvement, concurrent Gram-negative sepsis, poor immune status, delayed diagnosis and treatment.

Prevention

The infection can be prevented by the use of shoes and public health measures emphasizing on proper disposal and treatment of excreta. Patients who

are planned for immunosuppression with corticosteroids or other immunosuppressive drugs, and patients with HIV/AIDS, should be investigated and the intestinal infections treated before starting immunosuppression or the emergence of disseminated infection.

Gnathostomiasis

Epidemiology and aetiology

Gnathostomiasis is a disease in human or animal definitive host caused by a small round worm of the genus *Gnathostoma*. Gnathostomiasis is seen worldwide affecting dogs, cats, tigers, lions, leopards, minks and raccoons (128). The disease affects humans mainly in those countries where raw freshwater fish is frequently ingested. Human gnathostomiasis is almost always caused by *G. spinigerum*. The endemic areas of human gnathostomiasis are in Asia (including Thailand, Korea, Japan, Malaysia, Laos, Cambodia, Mynmar, Vietnam, Philippines, Bangladesh, Indonesia, India, Pakistan and China); the Middle East (Palestine and Israel); Africa (Cameroon); Central America (Mexico); South America (Ecuador) and Australia (129,130).

Pathophysiology

Humans contact the disease by eating raw or poorly-cooked infected freshwater fish, chicken, pork, frog or snake containing third-stage larvae. After ingestion, the larvae penetrate the gastric wall and migrate to the liver and other tissues. Infection through larval penetration of the skin or drinking contaminated water has been proven experimentally but has yet to be established for human cases (129). Transplacental transmission has been reported in neonates (129,130).

The mechanism of pathogenicity of gnathostome is mechanical damage caused by its migration, gnathostome toxin and the host's reaction. Although it tends to remain in the subcutaneous tissues, it can migrate to any visceral organ where it may cause serious damage and even fatality.

Clinical features

Within 24–48 hours after ingestion of *G. spinigerum*, patients may develop nonspecific signs and symptoms such as fever, malaise, anorexia, nausea, vomiting, diarrhoea, epigastric pain and urticaria. Eosinophilia develops in association with larval penetration through the gastric or intestinal wall. Subsequent migration through the liver may be associated with right upper quadrant pain, and further penetration through the diaphragm may produce pleuropulmonary symptoms. As these initial symptoms are mild and nonspecific, they may be overlooked. The most common symptom is intermittent migratory swelling due to subcutaneous migration (cutaneous gnathostomiasis). This often occurs 3–4 weeks after ingestion but may not develop until months or years later. The swelling may vary in size, do not pit on pressure and are often accompanied by itching or irritation and pain, and last for about 1–2 weeks. Less commonly, cutaneous gnatho-stomiasis presents as a creeping eruption, skin abscess or skin nodule. Visceral gnathosomiasis has been reported in many visceral organs including lungs and pleura, gastrointestinal tract, genitourinary tract, central nervous system, eye, ear, nose and throat.

Pleuropulmonary involvement of gnathostomiasis may precede or follow episodes of migratory subcutaneous swelling, or not infrequently present as a solitary manifestation (130). Patients usually present with dry cough, pleuritic pain, haemoptysis and dyspnoea. The worm may be expectorated with resolution of symptoms in some cases. Chest radiographic findings are pleural effusions, pneumothorax, hydro-pneumothorax, lobar consolidation and collapse, or even normal.

Clinical investigations

Peripheral blood eosinophilia is universal, and even the pleural fluid is eosinophilic. The ELISA has replaced the intradermal test for diagnosis of the disease because of its high sensitivity and specificity (131). However, its specificity may be impaired by cross-reactivity with *Angiostrongylus* species and intestinal round worms. The definite diagnosis of gnathostomiasis by isolation of the

parasite from the clinical specimen (such as skin nodule, sputum or pleural fluid) is impossible in most cases. The diagnosis is often presumptive and based on a history of intermittent episodes of subcutaneous migratory swelling, peripheral eosinophilia in people who live in or come from endemic areas, with the ELISA serological test as supportive evidence.

Treatment

Surgical removal of the parasite is the most effective treatment for ocular and cutaneous forms (such as creeping eruption, skin nodule or abscess). Blind surgical exploration of subcutaneous areas of diffuse swelling is not recommended except when it is located in a digit, as the parasite is difficult to find. Albendazole appears to be effective for the treatment of gnathostomiasis in a recent study by administration at a dose of 400–800 mg/day for 21 days (132). Corticosteroids can be used concomitantly to minimize the cutaneous or chest symptoms.

Prognosis

Prognosis depends on the organ that the parasite involves. The parasite can cause blindness in ocular form, neurological sequelae or death in central nervous form or serious morbidity in other visceral forms. It can persist in human body for years with intermittent or recurrent manifestations.

Prevention

Prevention of human gnathostomiasis is sufficiently known, especially the avoidance of raw or poorly cooked animal flesh which may contain the infective larval forms; the consumption of properly treated water in endemic areas; the use of gloves or frequent hand washing during the handling of animal flesh to prevent larval penetration of the skin (129).

Public health education to change people's eating habit of raw or poorly cooked fish, pork, chicken, frog or snake to well cooked meat is important.

Trichinellosis

Epidemiology and aetiology

Trichinellosis is a worldwide food borne nematode infection. The incidence of human trichinellosis in developed countries has declined substantially over the past few decades but outbreaks are still frequent. Most of the outbreaks in developed countries resulted from eating infected wild game meat (133,134). In Asia, Latin America and Mexico, the outbreaks usually result from eating infected pork and most of the outbreaks are due to Trichinella spiralis species.

Pathophysiology

Humans are infected by eating poorly cooked or raw meat infested by encysted larvae. The larvae are released in the stomach and mature into adult over 1–2 days in the small bowel. After mating, the female adult worms release the newborn larvae, which migrate throughout the body via the blood and lymphatic system and penetrate striated muscle to mature within 2 weeks. The encysted larvae generally persist for years before calcification and death occur. During larval migration, other organs may be involved, such as myocardium, central nervous system, lungs, kidney and skin.

Clinical features

The classical clinical manifestations can be described in three stages. The intestinal stage occurs within 24 hours after ingestion of infected meat, characterized by abdominal cramp, vomiting and diarrhoea resembling food poisoning and which disappear in 24–48 hours. The larval migration stage manifests approximately one to two weeks after ingestion, characterized by high fever, myalgia, periorbital oedema, elevation of muscle enzymes and peripheral eosinophilia with occasional involvement of the central nervous system, myocardium, lungs and other organs. Pulmonary manifestations may occur during this stage, manifested by dyspnoea, pain during inspiration and fatigue which are commonly due to involvement of respiratory muscles especially

the diaphragm (135). Respiratory distress can be the presenting feature (136,137). Chest radiographs are usually normal but may reveal increased pulmonary vascular markings, fine nodular or diffuse patchy infiltrations of varying sizes. The pathologic basis consists of pulmonary vascular dilatation and congestion and intrapulmonary haemorrhagic lesions (138). Overt pulmonary oedema results either from cardiac failure (myocarditis) or noncardiogenic pulmonary oedema due to larval pulmonary vascular invasion in severely infected cases. It is rare and is associated with increased morbidity and mortality. After the acute period, convalescence lasting from months to years follows, usually with complete recovery. The muscle larvae are eventually destroyed over the next few years, followed by calcification. The existence of chronic trichinellosis is still a matter of debate (139).

Clinical investigations

The diagnosis can be confirmed by presentation of the larvae in a muscle biopsy (Figure 9) (commonly performed in the gastrocnemius or deltoid muscle). A negative muscle biopsy does not exclude low level infection. Precipitin test, complement fixation, bentonite flocculation, latex agglutination, indirect immunofluorescence and enzyme-linked immunosorbent assay are commonly used for diagnosis, the last being the most sensitive. Immunological and molecular methods for early detection of circulating antigens are being developed (140).

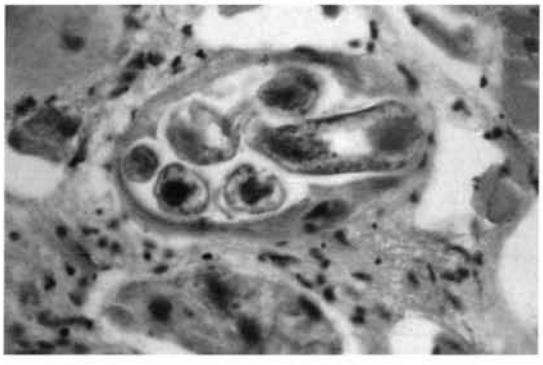


Figure 9. Larvae of *Trichinella spiralis* in a muscle biopsy

Treatment

Treatment during acute phase are mebendazole (200–400 mg thrice a day for three days then 400–500 mg thrice a day for ten days), albendazole (400 mg/day for three days then 800 mg/day for 5 days), thiabendazole (50 mg/kg/day for 3–7 days) (141). The treatment goal is to limit muscle invasion by larvae so as to reduce muscle damage. Corticosteroids (equivalent to prednisolone 0.5–1 mg/kg/day) are recommended for rapid reduction in symptoms especially in severely symptomatic cases.

Prognosis

The disease course is generally benign and recovery is the rule, even though it may take several months or years. The existence of chronic trichinellosis is still a matter of debate. Rarely severe cardiopulmonary complications may occur in severely infected cases and is often associated with increased morbidity and mortality.

Prevention

Prevention of human infection is routine inspection of pork at slaughterhouses for trichnellosis and the practice of cooking pork thoroughly.

Loeffler's Syndrome

Epidemiology and aetiology

Loeffler's syndrome arises from reactions elicited by developing helminthic larvae that pass through the lungs as part of the parasite's initial developmental cycle in the human. For three helminthic intestinal parasites (Ascaris, hookworms and Strongyloides), the larvae pass through the lungs, entering via the bloodstream, penetrating alveoli and then ascending the airway to transit down the oesophagus into the small bowel. The syndrome consists of the triad of pulmonary symptoms, characteristic radiographic evidence of a pulmonary infiltrate and peripheral eosinophilia. It is seen mainly in ascariasis. Typical

cases of Loeffler's syndrome in various locations around the world have been described as occurring seasonally and in adults with prior infection (142). In Switzerland and Southern China, it is associated with the onset of summer. Annual epidemics of pneumonitis with eosinophilia in Saudi Arabia have been reported to occur at the end of the relatively short rainy season (143). In view of the high prevalence of helminthic infections in the tropics, clinical migration through the lungs could be expected to occur frequently and to be reported from these areas. The rarity of such reports is possibly due to the generally benign course of the illness, the inadequacy of diagnostic facilities or the usual heavy workloads of medical personnel. A prospective study conducted over a 1 year period in Columbia confirmed that the incidence of the syndrome was rare despite the high prevalence of infection and year round transmission (142). The findings suggest that frequent and uninterrupted contact between Ascaris lumbricoides and its host results in a high degree of natural tolerance and control.

Pathophysiology

Evidence suggests that the symptoms of pulmonary ascariasis observed in humans are due to a hypersensitivity reaction. An IgE-mediated hypersensitivity reaction can occur even if only 6–45 larvae are in the lungs. This reaction gradually disappears as the larvae move on to the intestine or perish in the tissues.

Clinical features

In most cases the symptoms are mild, lasting 4–6 days. Occasional outbreaks have been observed of which a number of persons have had to be hospitalized (143). In isolated cases it has been near fatal or fatal.

About 1–2 weeks after ingestion of Ascaris eggs, the larvae migrate to the lungs. In symptomatic patients, fever, dyspnoea, irritating paroxysmal dry cough or occasionally mucoid and rusty sputum, a sensation of pressure or pain over the chest and wheezing that mimic asthma develop (144). These last for 4–10 days. A few patients experience severe respiratory distress and die. Chest radiographs show unilateral or bilateral nonsegmental patchy infiltrates with indefinite borders, nodular infiltrates ranging in size from several millimetres to several centimetres or as a miliary pattern. The infiltrates are transient, migratory and spontaneously clear within 2 weeks (145). Peripheral blood eosinophilia is striking and persists for several weeks. Stool examinations for Ascaris or hookworm eggs are negative during pulmonary migration phase, but the larvae can often be seen in sputum or gastric aspirate.

Clinical investigations

The diagnosis should be suspected in any patient with diffuse pneumonitis and peripheral eosinophilia. Ascaris or hookworm ova should be absent from the stool at the time of pneumonitis. The appearance of the parasitic ova in stool later but within 3 months of self-limited eosinophilic pneumonitis suggests this diagnosis. The sputum or BAL may contain eosinophils, Charcot-Leyden crystals, and occasionally, the larvae. The presence of larvae in gastric aspirate, sputum or BAL fluid confirms the diagnosis. Serologic tests have little application and usually fail to distinguish between roundworm infections.

Treatment

Although eradication of these intestinal parasites is relatively easy, there is no known treatment for the migrating larval phase of the disease.

Prognosis

Most cases are benign and self-limited within a few days to one week. Only a few have severe symptoms and need hospitalization. Fatality is rare.

Prevention

Multi-modality approaches to reduce the risk of new or recurrent infection aiming at improving sanitation, education and antihelmintic therapy are

important to reduce the risks of ascaris, hookworm and stongyloides infection in humans.

Visceral Larva Migrans

Epidemiology and aetiology

Visceral larva migrans (VLM) is the syndrome caused by persistent larval migration in the human viscera by animal nematodes, most commonly *Toxocara canis* and *T. cati* in dogs and cats respectively, so the syndrome is also known as toxocariasis. However, other animal round worms, such as Gnathostoma, Angiostrongylus and Anisakis, can also cause the syndrome in certain geographic areas. Therefore, toxocariasis is not synonymous with VLM. Transient larval migration in the life cycle of several parasites, such as Ascaris, Strongyloides, Trichinella, is not considered to be VLM either. Human toxocariasis have been reported worldwide especially in the United States. The prevalence of human toxocariasis in tropical countries is not well known. The infection appears to be common since *T. canis* is commonly found in dogs in the tropics, but it may be overlooked or undiagnosed due to limitations of diagnostic facilities. In a survey in Bangkok in 1998, the prevalence of *T. canis* in stray dogs was 22.5% and its prevalence in young dogs is much higher than adult dogs (37.5% vs 3.4%) (146).

Pathophysiology

Most affected population is young children because of their habit of playing on parasitic ova contaminated soil and placing contaminated fingers in their mouths. Adults can also be infected by ingestion of ova contaminated food or drinking water or uncooked tissues of paratenic hosts with larvae. The hatched larvae that are unable to mature in humans may migrate via bloodstream for months in systemic host tissues before stopping within a visceral organ, such as lung, eye, liver and brain, until death. In the early stage, the lungs show infiltration by eosinophils and oedema in the alveolar septa. In the late stage, the eosinophil-mediated granulomatous responses surrounding the degenerating larvae ensue (147).

Clinical features

Signs and symptoms of allergy characterize pulmonary toxocariasis including rhinorrhea, urticaria and asthma. Wheezing is a common presenting symptom and severe asthma can develop (148). Pulmonary involvement may suggest bronchiolitis, asthma or pneumonia. Approximately half of the patients with pulmonary symptoms have transient infiltrates on chest radiograph and may progress to acute eosinophilic pneumonia or respiratory failure (149,150). Constitutional symptoms such as fever, anorexia, malaise and weight loss can be found. Hepatomegaly is a common finding, although any other organs can be affected.

Clinical investigations

Eosinophilia is a consistent finding and usually striking. The sputum may contain numerous eosinophils, Charcot-Leyden crystals and Curschmann's spirals. Hypergammaglobulinaemia is another consistent but nonspecific laboratory finding. The marked elevation of serum IgE is helpful for diagnosis. The standard serologic test for confirming toxocariasis is an ELISA using larval secretory-excretory antigen. It has a sensitivity of higher than 75% and a specificity of greater than 90% (151). Lung biopsy is rarely helpful because the larvae are too few to be found.

Treatment

Treatment is primarily symptomatic. Most mild to moderately symptomatic patients recover without specific treatment. Corticosteroids and antihistamines are often used to minimize inflammatory reactions. Antihelminthic treatment with adjunctive corticosteroids is recommended in severe cases. The drug of choice is diethylcarbamazine, 6 mg/kg/day devided in 3 doses for 7–10 days. The alternatives are albendazole, 400 mg twice a day for 3–5 days, and mebendazole, 100–200 mg twice daily for 5 days (152).

Prognosis

Although VLM is a benign disease with spontaneous recovery in most cases, deaths from severe pulmonary, myocardial, or cerebral involvement can occur (153).

Prevention

General preventive measures are to avoid playing on suspected parasitic ova-contaminated ground in young children, hand washing before eating, use of spoon and fork or chopsticks for eating, drinking clean water and eating well cooked tissue of paratenic hosts. Animal control measures are also important, including periodically testing and treating roundworm infestations in dogs and cats or using broad-spectrum antihelminthics in stray dogs on a large scale, but such animal control measures are rarely used in tropical countries.

Tropical Pulmonary Eosinophilia

Epidemiology and aetiology

Tropical pulmonary eosinophilia (TPE) or tropical eosinophilia is the pulmonary syndrome that result from a distinct immune hyperresponsiveness against microfilaria in a patient who has an occult microfilariasis. Although lymphatic filariasis are endemic widely in tropical countries (Africa, India, Southeast Asia, the Western Pacific), most cases of tropical pulmonary eosinophilia have been reported in India, Indonesia, Sri Lanka, Pakistan and Southeast Asia where the microfilariae, Wuchereria bancrofti and Brugia malayi, are endemic (154). There is evidence that it is more likely to occur in nonimmune individuals,ie, visitors to endemic regions, than in individuals of endemic populations who have developed immunity to filarial infections (155). The syndrome has the following characteristics: a history of residence in a filarial endemic region; asthma-like symptoms, radiologic evidence of pulmonary infiltrate or increased bronchovascular markings, a striking peripheral eosinophilia (> 3000 cells/mm^3), a high serum level of IgE (> 1000 U/ml); a high titre of filarial antibody and a favorable response to diethylcarbamazine treatment.

Pathophysiology

The current hypothesis is that it begins with an intense eosinophilic lung parenchymal inflammation in persons who are highly sensitized immunologically to filarial parasites (156). The lymphatic-dwelling adult worms release microfilariae into the circulation which are trapped in the pulmonary vasculature, and degenerate to release their antigenic constituents that trigger local inflammatory and immune process.

Clinical features

The patients are residents or immigrants from endemic areas and males are affected more than females (157). Symptoms of a progressive hacking nonproductive cough and wheezing that worsen at night are prominent features. Dyspnoea and occasionally chest pain or tightness accompany these episodes. Coarse rales and rhonchi are found on physical examination, and wheezing may be heard especially during the symptomatic episodes. Mild fever, fatigue, anorexia and weight loss are common. Skin rash, urticaria and generalized lymphadenopathy are occasionally found. These clinical features last for a few weeks or months but may remit spontaneously and then recur months to years later several times. Chest radiographs may be normal or reveal increased bronchovascular markings, diffuse miliary, nodular or reticulonodular infiltrates and patchy consolidations involving primarily the middle and basal regions of the lungs. The upper lung fields are less likely to be involved; hilar adenopathy is not common and pleural effusions are rare. If the disease remains untreated, pulmonary fibrosis with restrictive pulmonary disability may ensue.

Clinical investigations

Eosinophilia is strikingly high (3000–50000 cells/mm^3) and persists for weeks. Serum IgE is higher than 1000 units per millilitre. Complement fixation,

haemagglutination, indirect immunofluorescence and other techniques can invariably detect high titres of antifilarial antibodies. Filarial antigens can also be detected by application of monoclonal antibodies for antigen detection in the blood (158). The findings of elevated polyclonal and antigen-specific IgE with increased parasite-specific IgG4 antibodies are helpful for diagnosis. The microfilariae are never found in the blood. Histopathology of the lungs shows a picture of eosinophilic bronchopneumonia in the early stage, multiple small granulomas with fibrosis and foreign-body giant cells are found in the later stage. Multiple lung sections are required to demonstrate degenerating microfilariae within the lung parenchyma. Biopsy of the affected lung seems unwarranted for routine diagnosis because of low diagnostic yield. Microfilariae are more likely to be found in enlarged lymph nodes. Pulmonary function test reveals restrictive or combined with obstructive defect rather than pure obstructive defect due to mainly interstitial lung pathology rather than asthmatic component (159).

Treatment

Diethylcarbamazine citrate (DEC) is the drug of choice for treatment of filariasis. It kills the adult worms and suppresses microfilariae through stimulation of host defence mechanism. The recommended dose is 6 mg/kg daily in three divided doses for 12 days. The treatment is quite effective and most patients show marked improvement or disappearance of symptoms after 7–10 days of treatment but relapses or re-infections are not uncommon. The total eosinophil count decreases by a mean of 92.5%, 3 months after administration of DEC (160).

Prognosis

Morbidity is mainly related to the chronicity of the disease, the asthma symptom severity and the degree of disability due to interstitial pulmonary fibrosis (155). Fatality is rare. The disease may be symptomatic for several years and then spontaneously disappear in the long run.

Schistosomiasis

Epidemiology and aetiology

Schistosomiasis, also named biharziasis, is caused by *Schistosoma japonicum, S. mansoni and S. haematobium. S. japonicum* is endemic to China, Japan, the Philippines, Taiwan, Thailand, Laos and the Indonesian island of Celebes. *S.mansoni* is endemic in Africa, South America and the Middle East. *S. haematobium* is endemic in Africa and Middle East (161).

Pathophysiology

Snails are the intermediate hosts in which the miracidia develop to the stage of cercaria. The mercurial larvae penetrate the human skin and access portal blood in the liver, then become adult and mate for life. The adults migrate to venous plexus of bladder (*S. haematobium*) or mesenteric venules of bowel (*S. mansoni* and *S. japanicum*), laying eggs that circulate to the liver and are shed in the stool. Host reactions are granulomatous reactions and vasculitic response to parasitic eggs in the tissues (such as intestine, liver and bladder), not the adults themselves. In cardiopulmonary schistosomiasis, the pathologic change is that of granulomatous pulmonary endarteritis. Most people living in endemic areas have acquired immunity and usually are asymptomatic. Visitors are more likely to be symptomatic and sometimes develop severe symptoms when infected for the first time. Most infected persons become symptomatic within 5 years of infection.

Clinical features

In the early stage, cercarial dermatitis can occur at the skin site of cercarial penetration. At the beginning of oviposition, the Katayama syndrome, characterized by fever, cough and general debility with hepatosplenomegaly and lymphadenopathy, can develop especially in non-immune persons. The chest radiograph shows increased bronchovascular markings producing a generalized haziness and hilar adenopathy, and may mimic miliary tuberculosis (162). Eosinophilia is striking.

In the chronic stage, as seen in endemic areas, fibrosis occurs in affected organs due to prolonged repeated tissue injury from host responses to chronic deposition of parasitic eggs in the tissues. Chronic pulmonary schistosomiasis, resulting from parasitic egg deposition in the pulmonary vasculature followed by granuloma formation and obstruction of blood flow, can manifest as pulmonary hypertension and cor pulmonale (145).

Clinical investigations

Finding of viable eggs in the patient's stool is diagnostic, but it is not infrequent that the stool is negative because of the limited number of eggs in the stool in the early course of the disease or periodic shedding of eggs from the bowel wall into the lumen. Biopsy of the affected bowel wall, liver or bladder can confirm the diagnosis. Bronchoalveolar lavage and transbronchial lung biopsy via fiberoptic bronchoscopy is a very fruitful procedure for the diagnosis of pulmonary schistosomiasis (163). The serologic tests using ELISA techniques for screening and the Western blot assay for confirmation are currently used for epidemiological surveys and diagnosis (164).

Treatment

The drug of choice for all forms of schistosomiasis is praziquantel given by a single 40 mg/kg dose orally. Those who fail the single dose treatment can be retreated to achieve a cure rate of 80–100% (165). Patients with cor pulmonale may require decompression surgery.

Prognosis

Infected people, who are the residents of endemic areas, are usually asymptomatic. A patient who develops features of cor pulmonale has a poor prognosis even after receiving medical treatment due to permanent fibrotic damage of pulmonary vascular structures. In acute cases, the clinical manifestations spontaneously subside in a few weeks in most patients though a few have died.

Prevention

Improved sanitation, provision of safe water supplies, continuing healthcare education to limit high risk exposure, elimination of vector snail and snail habitats and drug therapy for egg excretors are the principle measures to control and eliminate the disease (166).

Echinococcosis

Epidemiology and aetiology

Echinococcosis or hydatid disease is caused by the larval stage of the non-human tapeworm of the genus *Echinococcus*. *Echinococcus granulosus* is the most common species responsible for most cases of infection in tropical countries and worldwide. The endemic areas of echinococcosis are the Middle East, India, South America, East Africa, Eastern Europe, the Mediterranean basin, the countries of the former Soviet Union and Australia (167). The definitive hosts are dogs or other carnivores. Sheep are the most common reservoir host for *E. granulosus*. Humans are the intermediate host, carrying the larval tapeworm or hydatid cyst.

Pathophysiology

Humans contract the infection by swallowing the eggs in the excreta of a definitive host through contaminated food, water or hands. The hexacanth embryos, or oncospheres, hatch in the small intestine and migrate via circulation to liver, lung, brain, or elsewhere. Hydatid cysts develop and enlarge as space-occupying lesions over months to years in those organs.

Clinical features

The lungs are the second most common site for hydatid disease after the liver (168,169). The lung can be either the primary site of infection or the secondary site to hepatic echinococcosis (170,171). Most patients present with a solitary lung cyst, sometimes located in the fissure, pleural cavity,

and mediastinum. Patients are commonly asymptomatic for a long period. Clinical manifestations are related to the size of the cyst or its complications including ruptured cyst, secondary bacterial infection, and pneumothorax (172). The most common symptoms are cough, dyspnoea, and chest pain. Fever and haemoptysis may be found in some patients. Cysts may rupture into the pleural space or into a bronchus. In the latter case, the patient may describe cough up "grapeskins", and intrapulmonary spread (secondary hydatidosis), anaphylactic reactions, and ARDS can occur (172,173). Leakage of the cyst causes chest pain, dyspnoea, cough or haemoptysis. Lung abscess and empyema may result from secondary bacterial infection. Physical examination is rarely specific, although a fluid wave (hydatid thrill) on percussion of a large cyst is occasionally found.

Clinical investigations

A cyst like mass in the lung of a man with a history of exposure to sheepdogs in endemic areas is strongly suggestive of the diagnosis of echinococcosis (171,174). It must be differentiated from benign cysts, tuberculosis, mycosis, abscess and bronchogenic carcinoma. Helpful radiographic findings are the water lily sign (ruptured membranes are seen floating on the fluid level of a partially empty cyst) and the crescent or meniscus sign (air trapped between two layers of the ruptured cyst wall). Computed tomography (CT) is highly specific for the identification of a large, low-density cyst containing numerous septae. Ultrasonography is less specific but is helpful for therapeutic monitoring. Serologic tests are useful for confirming a presumptive imaging diagnosis. The ELISA for antibody detection is widely used and being improved in specificity (175). Percutaneous transthoracic needle aspiration under ultrasound or CT guidance with antihelminthic coverage for diagnosis of hepatic echinococcosis with minimal risks of anaphylaxis or secondary hydatidosis may be used in some cases of pulmonary echinococcosis in whom the diagnosis is still uncertain. Eosinophilia is found in only 25% of the patients.

Treatment

The drug of choice is albendazole, 400 mg twice a day for 28 days. The cure rate is only 30%, partial response is 30–50%, and no response is 20–40% (176). Cysts should be surgically removed in those who show partial or no response (177). A lung-conserving operation, cystectomy with capitonnage, is the treatment of choice and offers a good outcome with minimal recurrence rate (172).

Prognosis

Operative mortality and recurrence rate for pulmonary echinococcosis or its complications is nil for a lung-conservative operation, with very good long-term survival rate (171–173).

Prevention

Control measures of proven usefulness are health education, control of commercial and home slaughter of sheep and other livestocks, stray dog control, routine testing and treatment of dogs and the development of adequate surveillance systems.

References

1. Gubler DJ, Clark GG. Dengue/dengue hemorrhagic fever: The emergence of a global health problem. *Emerg Infect Dis* 1955; 1:55–7.
2. Dengue Hemorrhagic Fever: Diagnosis, Treatment and Control. Geneva, World Health Organization, 1986.
3. Eram S, Setyabudi Y, Sadono TI, et al. Epidemic dengue hemorrhagic fever in rural Indonesia. II. Clinical studies. *Am J Trop Med Hyg* 1979; 28:711–7.
4. Torres EM. Lessons from the Cuban experience. Dengue today symposium. Ninth International Congress on Infectious Disease; April 10–13. 2000; Argentina.

5. Chavalittamrong B, Pidetcha P, Pongpipat D, et al. Composition of pleural fluid in dengue hemorragic fever. *J Med Ass Thai* 1979; 27:55–8.
6. Gubbeler DJ. Aedes aegypticud Aedes aegypi-borne disease control in 1990s: Top down or bottom up. *Am J Trop Med Hyg* 1989; 40:571–8.
7. Berman SJ, Kundin WD. Scrub typhus in South Vietnam. *Ann Int Med* 1973; 79:26–30.
8. Sayen JJ, Pond HS, Forrester JS, et al. Scrub typhus in Assam and Burma. Clinical study of 616 cases. *Medicine* 1976; 25:155–214.
9. Supparatpinyo K, Horsin P, Hirunsri P. Scrub typhus at Maharaj Nakorn Chiang Mai Hospital: a study of 60 cases. *Intern Med* 1990; 6:6–10.
10. Brown GW, Shirai A, Jegathesen M, et al. Febrile illness in Malaysia. *J Trop Med Hyg* 1984; 33:311–5.
11. Chayakul P, Panich V, Silpapojakul K. Scrub typhus pneumonitis: an entity which is frequently missed. *Q J Med* 1988; 68:596–602.
12. Editorial. Scrub typhus pneumonia. *Lancet* 1988; 2:1062.
13. Tsay RW, Chang FY. Serious complications in scrub typhus. *Chung Hua Min Kuo Wei Sheng Wu Chi Mien I Hsueh Tsa Chih* 1998; 3:240–4.
14. Division of Epidemiology, Ministry of Public Health, Thailand. Annual epidemiological surveillance report 1997.
15. Frances SP, Watcharapichat P, Phulsuksombati D, et al. Seasonal occurrence of Leptotrobidium deliense (Acari: Trombiculidae) attached to sentinel rodents in an orchard near Bangkok, Thailand. *J Med Entomol* 1999; 36:869–74.
16. Choi YH, Kim SJ, Lee JY, et al. Scrub typhus: radiological and clinical findings. *Clin Radiol* 2000; 55:140–4.
17. Pothirat C. Scrub typhus pneumonia with Adult Respiratory Distress Syndrome: a report of four cases. *J Infect Dis Antimicrob Agent* 1987; 4:68–72.
18. Punyakupta S. Cardiopulmonary complications in an acute febrile patient. *J Infect Dis Antimicrob Agent* 1985; 2:192–7.
19. Weddle JR, Chan TC, Thompson K, et al. Effectiveness of a dot-blot immunoassay of anti-Rickettsia tsutsugamushi antibodies for serologic analysis of scrub typhus. *Am J Trop Med Hyg* 1995; 53:43–6.
20. Suwanabun N, Chouriyagune C, Eamsila C, et al. Evaluation of an enzyme-linked immunosorbent assay in Thai scrub typhus patients. *Am J Trop Med Hyg* 1997; 56:38–43.
21. Watt G, Kantipong P, Jongsakul K, et al. Azithromycin activities against Orientia tsutsugamushi strains isolated in cases of scrub typhus in Northern Thailand. *Antimicrob Agents Chemother* 1999; 43:2817–8.
22. Watt G, Chouriyagune C, Ruangweerayud R, et al. Scrub typhus infections poorly responsive to antibiotics in northern Thailand. *Lancet* 1996; 348:86–9.
23. Watt G, Kantipong P, Jongsakul K, et al. Doxycycline and rifampicin for mild scrub-typhus infections in northern Thailand: a randomized trial. *Lancet* 2000; 356:1057–61.
24. Olson JG, Bourgeois AL, Fang RCY, et al. Prevention of scrub typhus. Prophylactic administration of doxycycline in a randomized double blind trial. *Am J Trop Med Hyg* 1980; 29:989–97.
25. Boonsawat W, Boonma P, Tangdajahiran T, et al. Community-acquired pneumonia in adults at Srinagarind Hospital. *J Med Assoc Thai* 1990; 73:345–52.
26. Chaowagul W, White NJ, Dance AB, et al. Melioidosis: a major cause of community-acquired septicemia in northern Thailand. *J Infect Dis* 1989; 159:890–9.
27. Dhiensiri T, Puapairoj S, Susaengrat W. Pulmonary melioidosis: clinical-radiologic correlation in 183 cases from northeastern Thailand. *Radiology* 1988; 166:711–5.
28. Everett ED, Nelson RA. Pulmonary melioidosis. Observations in thirty-nine cases. *Am Rev Respir Dis* 1975; 112:331–40.
29. Malizia WF, West GA, Brundage WG, Walden DC. Melioidosis-laboratory studies. *Health Lab Sci* 1969; 6:27–39.
30. Patamasucon P, Stead UB, Nelson JD. Medical progress: melioidosis. *J Pediatr* 1982; 10:175–82.
31. Kunakorn M, Boonma P, Khupulsup K, Petchclai B. Enzyme-linked immunosorbent assay for immunoglobulin M specific antibody for the diagnosis of melioidosis. *J Clin Microbiol* 1990; 28:1249–53.
32. Desakorn V, Smith MD, Wuthiekanun V, et al. Detection of Pseudomonas pseudomallei antigen in urine for the diagnosis of melioidosis. *Am J Trop Med Hyg* 1994; 51:627–33.

33. White NJ, Dance DAB, Chaowakul W. et al. Halving of mortality of severe melioidosis by ceftazidime. *Lancet* 1989; 2:697–701.
34. Sookpranee M, Boonma P, Sasaengrat W, et al. Multicenter prospective randomized trial comparing ceftazidime plus co-trimoxazole with chloramphenicol plus doxycycline and co-trimoxazole for treatment of severe melioidosis. Antimicrob Agents *Chemother* 1992; 36:158–62.
35. Rajchanuvong A, Chaowagul W, Suputtamongkol Y, et al. A prospective comparison of co-amoxiclav and the combination of chloramphenicol, doxycycline, and co-trimoxazole for the oral maintenance treatment of melioidosis. *Trans R Soc Trop Med Hyg* 1995; 89:546–9.
36. Maneechotesuwan K. An exotic pulmonary infection in Thailand: melioidosis. *Respirology* 1999; 4:419–22.
37. Hill MK, Sanders CV. Leptospiral pneumonia. *Semin Respir Infect* 1997; 12:44–9.
38. Bethem N, Lemle A, Nelson G. Leptospirosis. *Semin Respir Med* 1991; 12:58–67.
39. Centers for Disease Control and Prevention. Outbreak of acute febrile illness and pulmonary hemorrhage: Nicaragua, 1995. *MMWR* 1995; 44:841–3
40. Tangkanakul W, Kingnate D. Leptospirosis epidemic in northeastern provinces 1997 (a review). *J Health Science* 1998; 7:386–95.
41. Phusuksombat P, Tangkanakul W, Kingnate D, Sangjun N. Reemergence of leptospirosis in Thailand 1998. Ninth Asia Pacific Military Medicine Conference. 7–12 March 1999, Central Grand Plaza Hotel. Bangkok 1999.
42. Waraluk T, Kanjana Y, Noreerat S, et al. Risk factors associated with Leptospirosis infection among Northeastern Thai villagers. *J Health Science* 1999; 8:351–9.
43. World Health Organization, Western Pacific Regional Office, Japan Science and Technology Cooperation, University of the Philippines, Department of Health, the Phillipines. Leptospirosis in Western Pacific and South-East Asia.In: Proceedings of the Regional Seminar-Workshop on leptospirosis, 2000. 21–22 January 2000, Manila, Philippines.
44. Nicodemo AC, Duarte MI, Alves VA, et al. Lung lesions in human leptospirosis: microscopic, immunohistochemical, and ultrastructural features related to thrombocytopenia. *Am J Trop Med* 1997; 56:181–7.
45. Burke BJ, Searl JF, Mattingly D. Leptospirosis presenting with profuse hemoptysis. *BMJ* 1976; 2:982.
46. Edwards CN, Nicholson GD, Hassell TA, et al. Thrombocytopenia in leptospirosis: the absence of evidence for disseminated intravascular coagulation. *Am J Trop Med Hyg* 1986; 79:352–4.
47. Im JG, Yeon KM, Han MC, et al. Leptospirosis of the lung;radiographic findings in 58 patients. *Am J Roengenol* 1989; 152:955–9.
48. Kiatboonsri S, Vathesatogit P, Charoenpan P. Adult respiratory distress syndrome in Thai medical patients. *Southeast Asian J Trop Med Public Health* 1995; 26:774–80.
49. Lee RE, Terry SI, Walker TM, et al. The chest radiograph in leptospirosis in Jamaica. *Br J Radiol* 1981; 54:939–43.
50. Wang CP, Chi CW, Lu FL. Studies on anicteric leptospirosis III. Roentgenologic observations of pulmonary changes. *Chin Med J* 1965; 84:298–306.
51. Faine S. Leptospirosis. In: *Microbiology and Microbial Infections*, 9th ed. Eds. Collier L, Bola's A, Sussman M. New York: Oxford University Press 1998:849–69.
52. Torten M, Shenberg E, Gerichter CB, et al. A new leptospiral vaccine for use in human II. Clinical and serologic evaluation of a field trial with volunteers. *J Infect Dis* 1973; 128:647–51.
53. Takafuji ET, Kirkpatrick JW, Miller RN, et al. An efficacy trial of doxycycline chemoprophylaxis against leptospirosis. *N Engl J Med* 1984; 310:497–500.
54. Hoffman TA, Ruiz CJ, Counts GW, et al. Waterborne typhoid fever in Dade County, Florida: Clinical and therapeutic evaluations of 105 bacteremic patients. *Am J Med* 1975; 59:481–7.
55. Stuart BM, Pullen RJ. Typhoid: Clinical analysis of three hundred and sixty cases. *Arch Intern Med* 1946; 78:629–61.
56. Saphra I, Winter JW. Clinical manifestations of salmonellosis in man. An evaluation of 7779 human infections identified at the New York Salmonella Center. *N Engl J Med* 1957; 256:122–34.
57. Boonsawat V, Apiratkasem P, Boonma P, Sukpranee M. Calcified empyema due to *Salmonella typhymurium*. *Thai J Tuberc Chest Dis* 1987; 8:137–41.

58. Bovornkitti S, Danchaivichit S. Prapasavat D. Salmonella pneumonia. *Sririraj Hosp Gaz* 1978; 30:681–5.
59. Leelarasamee A, Bovornkitti S, Dumavibhat B. Salmonellosis with pleuropulmonary complications. *Siriraj Hosp Gaz* 1983; 35:73–8.
60. Pothirat C, Jiemsripong K, Kiratikanont P, Singhacharoen T. Salmonellosis and the respiratory system infections. *Thai J Tuberc Chest Dis* 1988; 9:71–8.
61. Jacobs JL, Gold JW, Murray HW, et al. Salmonella infection in patients with the acquired immunodeficiency syndrome. *An Intern Med* 1985; 102:186–8.
62. Pang T, Calva E, Punjabi N, Rowley D. Report from an international symposium on typhoid fever. *Asian Pacific J Allergy Immunol* 1992; 10:81–3.
63. Duong TA. Infection due to Penicillium marneffei, an emerging pathogen: review of 155 reported cases. *Clin Infect Dis* 1996; 23:125–30.
64. Supparatpinyo K, Khamwan C, Baosoung V, et al. Disseminated Penicillium marneffei infection in Southeast Asia. *Lancet* 1994; 344:110–3.
65. Pothirat C, Lertprasertsuke N, Tharavichitkul P. Presumptive diagnostic efficacy of Pneumocystosis, Bacteriosis, Mycobacteriosis and Mycosis in HIV infected patients. (Abstract). The ERS Annual Congress, Barcelona, Spain. 16–20 September 1995, p234–5.
66. Pothirat C, Lertprasertsuke N, Tharavichitkul P. Bronchoalveolar lavage of pulmonary infections in HIV seropositive patients. *Thai J Tuberc Chest Dis* 1995; 16:213–20.
67. Pothirat C, Lertprasertsuke N, Tharavichitkul P. Sputum analysis of pulmonary infections in HIV seropositive patients. (Abstract). The 13th Asia Pacific Congress on Diseases of the Chest. Hong Kong 5–8 December 1994, p321.
68. Supparatpinyo K, Nelson KE, Merz WG, e al. Response to antifungal therapy by human immuno-deficiency virus infected patients with disseminated Penicillium marneffei infections and in vitro susceptibilities of isolates from clinical specimens. *Antimicrob Agents Chemother* 1993; 37:2407–11.
69. Division of Epidemiology, Ministry of Public Health, Thailand. Annual Epidemiological Surveillance Report 1997.
70. Tony M, Ballantine T, Youel D. Pulmonary function studies in Plasmodium falciparum malaria. *Am Rev Resp Dis* 1972; 106:23–9.
71. Mehta SR, Naidu G, Chandar V, et al. Falciparum malaria — present day problems. An experience with 425 cases. *J Assoc Physicians India* 1989; 37:264–7.
72. Punyagupta S, Srichaikul T, Nitiyanant P, Petchalai B. Acute pulmonary insufficiency in falciparum malaria; summary of 12 cases with evidence of disseminated intravascular coagulation. *Am J Trop Med Hyg* 1974; 23:551–9.
73. Al-Ibrahim MS, Holzman RS. Bilateral pleural effusions with *Plasmodium falciparum* infection. *Am J Trop Med Hyg* 1975; 24:910–2.
74. Aursudkij B, Wilairatana P, Vannaphan S, et al. Pulmonary edema in cerebral malaria patients in Thailand. *Southeast Asian J Trop Med Health* 1998; 29:541–5.
75. Gachot B, Wolff M, Nissack G, et al. Acute lung injury complicating imported *Plasmodium falciparum* malaria. *Chest* 1995; 108:746–9.
76. Fein LA, Rackow EC, Shapiro L. Acute pulmonary edema in *Plasmodium falciparum* malaria. *Am Rev Respir Dis* 1978; 118:425–9.
77. Goddard JE, Hanson RA. Interstitial pulmonary edema in acute malaria. *Radiology* 1971; 101:523–4
78. Charoenpan P, Indraprasit S, Kiatboonsri S, et al. Pulmonary edema in severe falciparum malaria: haemodynamic study and clinicophysiologic correlation. *Chest* 1990; 97:1190–7.
79. James MF. Pulmonary damage associated with falciparum malaria: a report of ten cases. *Ann Trop Med Parasitol* 1985; 79:123–38.
80. Feldman RM, Singer C. Noncardiogenic pulmonary edema and pulmonary fibrosis in falciparum malaria. *Rev Infect Dis* 1987; 9:134–9.
81. Ware DA. Looareesuwan S, Warell MJ, et al. Dexamethasone proves deteriorious in cerebral malaria: a double-blind trial in 100 comatose patients. *N Engl J Med* 1981; 306:313–9.
82. Looareesuwan S, Wilairatana P, Chokejindachai W, et al. Research on new antimalarial drugs and the use of drugs in combination at the Bangkok Hospital for Tropical Diseases. *Southeast Asian J Trop Med Public Health* 1998; 29:344–54.

83. Pinanong M. Exchange transfusion therapy in severe complicated malaria. *J Med Assoc Thai* 1997; 80:332–7.
84. Gulprasutdilog S, Chongkolwatana V, Buranakitjaroen P, Jaroonvesama N. Exchange transfusion in severe falciparum malaria. *J Med Assoc Thai* 1999; 82:1–8.
85. Mordmuller B, Kremjner PG. Hyperparasitemia and blood exchange transfusion for treatment of children with falciparum malaria. *Clin Infect Dis* 1998; 28:850–3.
86. White GB. Malaria prevention by vector control: effectiveness of insecticidal method. *Parasitologia* 1999; 41:305–7.
87. Lyche KD, Jensen WA. Pleuropulmonary amebiasis. *Semin Respir Infect* 1997; 12:106–12.
88. Shaw RR. Thoracic complications of amebiasis. *Surg Gynecol Obstet* 1949; 88:753–62.
89. Shabot JM, Patterson M. Amebic liver abscess: 1966–1976. *Am J Dig Dis* 1978; 23:110–8.
90. Roudant M, Tiendrebogo H, Condat JM, et al. Pleuropulmonary manifestations in amebiasis. Sixty-one cases seen in Abidjan over a three-year period. *Sem Hop* 1982; 58:85–92.
91. Ibarra-Perez C. Thoracic complications of amebic abscess of the liver: report of 501 cases. *Chest* 1981; 79:85–92.
92. Lyche KD, Jensen WA, Kirsch CM, et al. Pleuropulmonary manifestations of hepatic amebiasis. *West J Med* 1990; 153:275–8.
93. Le Roux BT. Pleuro-pulmonary amebiasis. *Thorax* 1969; 24:91–101.
94. Broeke JE ten, Fred HJ. Bilateral pulmonary amebiasis. *Am Rev Resp Dis* 1964; 9:1233–5.
95. Mbaye PS, Koffi N, Camara P, et al. Pleuropulmonary manifestations of amebiasis. *Rev Pneumo Clin* 1998; 54:346–52.
96. Verghese M, Eggleston FC, Handa AK, Singh CM. Management of thoracic amebiasis. *J Thorac Cardiovas Surg* 1979; 78:757–60.
97. Ragheb MI, Ramadan AA, Khalil MA. Intrathoracic presentation of amebic liver abscess. *Ann Thorac Surg* 1979; 22:483–9.
98. Jain NK, Madan A, Sharma TN, et al. Hepaopulmonary amebiasis. Efficacy of various treatment regimens containing dehydroemetine and/or metronidazole. *J Assoc Physicians India* 1990; 38:269–71.
99. Cameron E. The treatment of pleuropulmonary amebiasis with metronidazole. *Chest* 1978; 73:647–50.
100. Stephen S. Uragoda C. Pleuropulmonary amebiasis. *Br J Dis Chest* 1970; 64:96–106.
101. Raseretnam R, Paul A, Yoganathan M. Pleural empyema due to ruptured amebic liver abscess. *Br J Surg* 1974; 61:713–5.
102. World Health Organization. WHO study group on control of food-borne trematode infections. *WHO Tech Rep Ser* 1993; 849.
103. Im JG, Chang KH, Reeder MM. Current diagnostic imaging of pulmonary and cerebral paragonimiasis, with pathological correlation. *Semin Roengenol* 1997; 32:301–24.
104. Oh SJ. Roentgen findings in cerebral paragonimiasis. *Radiology* 1968; 90:292–9.
105. Higashi K. Cerebral paragonimiasis. *J Neurosurg* 1971; 34:515–27.
106. Belizario V, Guan M, Borja L, et al. Pulmonary paragonimiasis and tuberculosis in Sorsogon, Philippines. *Southeast Asian J Trop Med Public Health* 1997; 28(suppl1):37–45.
107. Benjapong W, Naeypatimanond S, Benjapong K, et al. Studies on paragonimiasis: treatment with mebendazole, emetine with mebendazole and praziquantel. *Southeast Asian J Trop Med Public Health* 1984; 15:354–9.
108. Ogakwu M, Nwokolo C. Radiological findings in pulmonary paragonimiasis as seen in Nigeria: a review based on one hundred cases. *Br J Radiol* 1973; 46:699–705.
109. Vanijanonta S, Bunnag D, Harinasuta T. Radiological findings in pulmonary paragonimiasis heterotremus. *Southeast Asian J Trop Med Public Health* 1984; 15:122–8.
110. Suwanik R, Harinsuta C. Pulmonary paragonimiasis: an evaluation of roentgen findings in 38 positive sputum patients in an endemic area in Thailand. *Am J Roentgenol* 1959; 81:236–44.
111. Vanijanonta S, Bunnag D, Harinasuta T. Praziquantel and niclofolan in the treatment of pulmonary paragonimiasis. In: 10th International congress on tropical medicine and malaria, 9–15 Nov 1980, p183.
112. Romeo DP, Pollock JJ. Pulmonary paragonimiasis: diagnostic value of pleural fluid analysis. *South Med J* 1986; 79:241–3.
113. Maleewong W, Intapan PM, Wongkham C, et al. A dot-ELISA test using monoclonal antibody-purified

antigens for the diagnosis of paragonimiasis caused by *Paragonimus heterotremus*. *Southeast Asian J Trop Med Public Health* 1997; 28:621–3.
114. Maleewong W, Intapan PM, Wongkham C, et al. Indirect haemagglutination test using monoclonal antibody-affinity purified antigens for diagnosis of human paragonimiasis due to Paragonimus heterotremus. *Trop Med Int Health* 1998; 3:57–9.
115. Chu E, Whitlock WL, Dietrich RA. Pulmonary hyperinfection syndrome with *Strongyloides stercoralis*. *Chest* 1990; 97:1475–7.
116. Woodring JH, Halfhill H, Berger R, et al. Clinical and imaging features of pulmonary strongyloidiasis. *South Med J* 1996; 89:10–9.
117. Woodring JH, Halfhill H, Reed JC. Pulmonary strongyloidiasis: clinical and imaging features. *Am J Roengenol* 1994; 162:537–42.
118. Higenbottam TW Heard BE. Opportunistic pulmonary strongyloidiasis complicating asthma treated with steroids. *Thorax* 1976; 31:226–33.
119. Gompels MM, Todd J, Peters BS, et al. Disseminated strongyloidiasis in AIDS: uncommon but important. *AIDS* 1991; 5:329–32.
120. Ossorio MA, Brown PE, Fields CL, Roy TM. Exacerbation of obstructive pulmonary disease due to hyperinfection with *Strongyloides stercoralis*. *J Ky Med Assc* 1990; 88:233–7.
121. Ford J, Reiss-Levy E, Clark E, et al. Pulmonary strongyloidiasis and lung abscess. *Chest* 1981; 79:239–40.
122. Froes HP. Identification of nematode larvae in the exudate of a serohaemorrhagic pleural effusion. *J Trop Med* 30; 33:18–9.
123. Cook GC. *Strongyloides stercoralis* hyperinfection syndrome; how often is it missed? *Q J Med* 1987; 64:625–9.
124. Harris RA, Musher DM, Fainstein V, et al. Disseminated strongyloidiasis. Diagnosis made by sputum examination. *JAMA* 1980; 244:65–6.
125. Williams J, Nunley D, Dralle W, et al. Diagnosis of pulmonary strongyloidiasis by bronchoalveolar lavage. *Chest* 1988; 94:643–4.
126. Jongwutiwes S, Charoenkorn M, Sitthicharoenchai P, et al. Increased sensitivity of routine laboratory detection of Strongyloides stercolaris and hookworm by agar-plate culture. *Trans R Soc Trop Med Hyg* 1999; 93:398–400.
127. Pitisuttithum P, Supanaranond W, Chindanond D. A randomized comparative study of albendazole and thiabendazole in chronic strongyloidiasis. *Southeast Asian J Trop Med Public Health* 1995; 26:735–8.
128. Sun T. Gnthosomiasis. In: *Parasitic Disorders: Pathology, Diagnosis, and Management*, 2nd ed. Eds. Sun T. Baltimore: Williams & Wilkins 1999, 225–31.
129. Daengsvang S. Gnathosomiasis in Southeast Asia. *Southeast Asian J Trop Med Public Health* 1981; 12:319–22.
130. Rusnak JM, Lucky DR. Clinical gnathostomiasis: case report and review of the English-language literature. *Clin Infect Dis* 1993; 16:33–50.
131. Dhamrong-At A, Migasena S, Suntharasamai P, et al. Enzyme-linked immunosorbent assay for detection of antibody to Gnathostoma antigen in patients with intermittent cutaneous migratory swelling. *J Clin Microbiol* 1986; 23:847–51.
132. Kraivichian P, Kulkumthorn M, Yingyourd P, et al. Albendazole for the treatment of human gnathostomiasis. *Trans R Soc Trop Med Hyg* 1992; 86:418–21.
133. Moorhead A, Grunenwald PE, Dietz VJ, Schantz PM. Trichinellsis in the United States, 1991–1996: declining but not gone. *Am J Trop Med Hyg* 1999; 60:66–9.
134. Bruschi F, Murrel KD. Trichinosis. In: *Tropical Infectious Diseases; Principles, Pathogens, & Practice*. Eds. Guerrant RL, Walker DH, Weller PF. Philadelphia: Churchill Livingstone 1999, 917–25.
135. Winter MD, Ball ML, Altringham JD, Lee DL. The effect of Trichinella spiralis and Trichinella pseudospiralis on the mechanical properties of mammalian diaphragm muscle. *Parasitology* 1994; 109:129–34.
136. Compton SJ, Celum CL, Lee C, et al. Trichinosis with ventilatory failure and persistent myocarditis. *Clin Infect Dis* 1993; 16:500–4.
137. Clausen MR, Meyer CN, Krantz T, et al. Trichinella infection and clinical disease. *Q J Med* 1996; 88:631–6.
138. Pu FS. X-ray manifestations of trichinosis on chest radiograph. *Chung Hua Fang She Hsueh Tsa Chih* 1989; 23:21–2.

139. Harms G, Binz P, Feldmeier H, et al. Trichinosis: a prospective controlled study of patients ten years after acute infection. *Clin Infect Dis* 1993; 17:637–43.
140. Ko RC. A brief update on the diagnosis of trichinellosis. *Southeast Asian J Trop Med Public Health* 1997; 28:91–8.
141. Sun T. Trichinosis. In: *Parasitic Disorders: Pathology, Diagnosis, and Management,* 2nd ed. Ed. Sun T. Baltimore: Williams & Wilkins 1999, 179–84.
142. Spillmann RK. Pulmonary ascariasis in tropical communities. *Am J Trop Med Hyg* 1975; 24:791–800.
143. Gelpi AP, Mustafa A. Seasonal pneumonitis with eosinophilia: a study of larval ascariasis in Saudi Arabia. *Am J Trop Med Hyg* 1967; 16:646–57.
144. Phills JA, Harrold AJ, Whiteman GV, et al. Pulmonary infiltrates asthma and eosinophilia due to Ascaris suum infestation in man. *N Engl J Med* 1972; 286:965–70.
145. Barret-Connor E. Parasitic pulmonary disease. *Am Rev Respir Dis* 1982; 126:558–63.
146. Rojekittikhun W, Nuamtanong S, Anantaphruti MT, et al. Toxocara and Gnathostoma among stray canines in Bangkok. *Southeast Asian Trop Med Public Health* 1998; 29:744–7.
147. Sun T. Visceral larva migrans. In: *Parasitic Disorders Pathology, Diagnosis, and Management.* Ed. Sun T. Baltimore: Williams & Wilkins 1999, 245–50.
148. Feldman GJ, Parker HW. Visceral larva migrans associated with the hypereosinophilic syndrome and the onset of severe asthma. *Ann Intern Med* 1992; 116:838–40.
149. Roig J, Romeu J, Riera C, et al. Acute eosinophilic pneumonia due to toxocariasis with bronchoalveolar lavage findings. *Chest* 1992; 102:294–6.
150. Bartelink AK, Korbeek LM, Huidekoper HJ, et al. Acute respiratory failure due to toxocara infection. *Lancet* 1993; 342:1234.
151. Glickman LT, Schwartz P, Dombroski R, et al. Evaluation of serodiagnostic tests for visceral larva migrans. *Am J Trop Med Hyg* 1978; 27:492–8.
152. Abramowicz M, ed. Drugs for parasitic infections. *Med Lett* 1995; 37:99–108.
153. Schantz PM, Glickman LT. Toxocaral visceral larva migrans. *N Engl J Med* 1978; 298:436–9.
154. Neva FA, Ottesen EA. Tropical (filarial) eosinophilia. *N Engl J Med* 1978; 298:1129–31.
155. OngRK,Doyle RL. Tropical pulmonary eosinophilia. *Chest* 1998; 113:1673–9.
156. Pinkston P, Vijayan VK, Nutman TB, et al. Acute tropical pulmonary eosinophilia. *J Clin Invest* 1987; 80:216–25.
157. Udwadia FE. Tropical eosinophilia: a review. *Respir Med* 1993; 87:17–21.
158. McReynolds LA, Poole C, Hong Y, et al. Recent advances in the application of molecular biology in filariasis. *Southeast Asian J Trop Med Public Health* 1993; 24:55–63.
159. Udwadia FE. Tropical eosinophilia: a correlation of clinical, histopathologic and lung function studies. *Dis Chest* 1967; 52:531–8.
160. Cooray JH, Ismail MM. Re-examination of the diagnostic criteria of tropical pulmonary eosinophilia. *Respir Med* 1999; 93:655–9.
161. Sun T. Schistosomiasis. In: *Parasitic Disorders: Pathology, Diagnosis, and Management,* 2nd ed. Ed. Sun T. Baltimore: Williams & Wilkins 1999, 309–22.
162. Schaberg T, Rahn W, Racz P, Lode H. Pulmonary schistosomiasis acute pulmonary tuberculosis. *Eur Respir J* 1991; 4:1023–6.
163. Zhang JX. Bronchofiberosocopy for diagnosis of 6 cases of pulmonary schistosomiasis. *Chung Hua Chieh Ho Ho Hu Hsi Tsa Chih* 1989; 12:232–3,256.
164. Tsang VC, Wilkins PP. Immunodiagnosis of schistosomiasis. *Immunol Invest* 1997; 26:175–88.
165. Abu-Elyazeed RR, Youssef FG, Merrell BR, et al. Praziquantel in the treatment of Schistosoma mansoni infections: *Am J Trop Med Hyg* 1997; 56:404–7.
166. WHO Expert Committee on the control of Schistosomiasis: Public health impact of schistosomiasis: disease and mortality. *Bull World Health Organ* 1993; 71:657–62.
167. Sun T. Echinococcosis. In: *Parasitic Disorders: Pathology, Diagnosis, and Management,* 2nd ed. Ed. Sun T. Baltimore: Williams & Wilkins 1999, 365–75.
168. Arytae A, Yurdakul Y, Ikizler C, et al. Pulmonary hydatid disease: report of 100 patients. *Ann Thorac Surg* 1977; 23:145–51.
169. Bhatia G. Echinococcus. *Semin Respir Infect* 1997; 12:171–86.

170. Todorov T, Boeva V. Echinococcosis in children and adolescents in Bulgaria: a comparative study. *Ann Trop Med Parasitol* 2000; 94:135–44.
171. Burgos R, Varela A, Castedo E, et al. Pulmonary hydatidosis:surgical treatment and follow-up of 240 cases. *Eur J Cardiothorac Surg* 1999; 16:628–34.
172. Safioleas M, Misiakos EP, Dosios T. et al. Surgical treatment for lung hydatid disease. *World J Surg* 1999; 23:1181–5.
173. Michaylova V. Communicating rupture of pulmonary hydatid cysts with resulting acute respiratory distress syndrome. *J Emerg Med* 2000; 18:260.
174. Salih OK, Topcuoglu MS, Celik SK, et al. Surgical treatment of hydatid cysts of the lungs: analysis of 405 patients. *Can J Surg* 1998; 4:131–5.
175. Craig PS. Echinococcus granulosus: immunodiagnosis and vaccination, a perspective. *Parasitologia* 1997; 39:345–7.
176. Horton RJ. Albendazole in the treatment of human cystic echinococcosis: 12 years of experience. *Acta Trop* 1997; 64:79–93.
177. WHO Informal Working Group on Echinococosis. Guidelines for treatment of cystic and alveolar echinococcosis in humans. *Bull World Health Organ* 1996; 15:52–3.

15 Tuberculosis: Epidemiology and Surveillance

Donald Enarson, Li Xing Zhang and Cheuk Ming Tam

Introduction

The International Epidemiological Society has established standardized definitions for epidemiological terms. Epidemiology is defined as the study of the distribution and determinants of health-related states and of the interventions to control them. The epidemiology of tuberculosis has been described in detail in a Monograph published by the International Union Against Tuberculosis and Lung Disease (1). The methods, and their limitations, used in studying the epidemiology of tuberculosis have been outlined in one of a series of monographs published by the European Respiratory Society (2). Surveillance is defined as continuous analysis, interpretation and feedback of systematically collected data, generally distinguished by their practicality, uniformity and rapidity rather than by accuracy or completeness (3). The use of epidemiological methods in the surveillance of tuberculosis have been outlined by Styblo (4).

This chapter will address the epidemiology and surveillance of tuberculosis from the Asian perspective, beginning with a discussion of surveillance which functions, to a large extent, as the source of much of the information that informs the epidemiology. It will proceed by presenting the global picture and then issues related specifically to the countries of Asia. For purposes of this chapter, countries of Asia are those within the World Health Organization Regions of Western Pacific (east Asia), excluding Australia, New Zealand and the Pacific Islands, and South East Asia (southern Asia).

Global surveillance of tuberculosis

The World Health Organization has declared tuberculosis, alone among diseases, a "Global Emergency". An estimated eight million new cases annually and some two to three million deaths are thought to be due to the disease (5). This declaration was based on the impact of tuberculosis as a disease on the expectation of life and the productive capacity of the middle-aged adults primarily affected by the disease.

Comparative information on tuberculosis has been difficult to obtain until recent years. Routine surveillance of tuberculosis (6) has been notably unreliable with the numbers of notified cases grossly underestimating the estimated numbers of existing cases (7). The number of cases estimated in response to the report of existing cases were accepted as "official" estimates of the size of the tuberculosis problem some two decades ago and remained unchallenged (8) until some time later (9), after standardized methods of reporting of cases had been generally adopted in a large number of countries around the world. The striking difference between reported and estimated cases

underscore the limitations of routine notification of cases and the difficulty of accurately estimating the numbers of existing cases. These estimates were flawed by certain assumptions concerning case fatality ratios and, more importantly, estimations of case numbers based on "access" to health facilities which, while possibly reliable for acute illnesses, are clearly less reliable for chronic illnesses primarily affecting adults and males with greater access to family resources.

More recent methods of estimating the burden of disease due to tuberculosis using the measure of "disability-adjusted life years" (10), while much more sophisticated and permitting comparisons among diseases, suffers from the same error in assumptions as the previous estimates of the size of the problem.

This difficulty in adequately estimating the size of the tuberculosis problem has led to the development of several methodological approaches. One, the national tuberculosis prevalence survey used primarily in Asia, will be discussed in the following section. The other, the national tuberculin survey, attempted to measure the prevalence of infection with *Mycobacterium tuberculosis* using the tuberculin skin test, the limitations of which have been outlined (11). From measurement of prevalence of significant reactions to the tuberculin skin test, a mathematical method to estimate annual incidence was developed. This measure, the "average annual risk of infection" (12), has been used widely to demonstrate the trend in tuberculosis, primarily in industrialized countries, and, to a lesser extent, in some low income countries where repeated tuberculin surveys have been undertaken.

In addition to global surveillance of tuberculosis, an international project on global surveillance on anti-tuberculosis drug resistance has been developed (13,14). This project was conceived as a program of periodic surveys and began with a consensus on approaches to surveillance, including a definition of representative sampling methods, standard laboratory techniques and reporting. This was followed by a programme of quality assurance of performance of a group of supra-national reference laboratories who underwent proficiency testing to ensure that their performance was similar and of a high quality. Finally, these supra-national laboratories paired with national laboratories to carry out the surveys on a representative sample of tuberculosis patients in each of the participating countries.

Surveillance of tuberculosis in Asia

The national prevalence survey of tuberculosis has been a method used in some countries of Asia to determine the extent and distribution of tuberculosis (15). The first national survey was undertaken in Japan in 1953 (16), followed by national surveys in Taiwan (1960), Vietnam (1962), Korea (1965), Cambodia (1967–1968), Burma (1972), Singapore (1975), China (1979) and the Philippines (1981–1983) (17). A series of surveys were undertaken in Japan (5-year surveys until 1973), Taiwan (most recent in 1993), Korea (most recent in 1995) (18) and China (most recent in 1999). Repeated surveys have been or will soon be undertaken in Philippines (1999) (19), Cambodia and Vietnam.

The results of these surveys have been used to model the tuberculosis situation and have provided the data that demonstrated that "poor treatment is worse than no treatment" (20), an observation that shifted the priority from case-finding to treatment as an indicator of the quality of tuberculosis control (21), an essential component of the DOTS Strategy. Moreover, these data were also used in a mathematical model that demonstrated the key role of chronic, drug-resistant cases in the maintenance of tuberculosis in the community (22).

More recently, routine notifications of tuberculosis cases, using the standardized information system that is part of the DOTS Strategy, have been obtained covering more than 90% of the country in various countries in Asia. In 2000, such reports were submitted to the World Health Organization from the South East Asia and Western Pacific Regions for Bangladesh, Bhutan, Maldives, Myanmar, Nepal, Sri Lanka, Cambodia, China, Republic of Korea, and Viet Nam (23).

A number of Asian countries participated in the global project on anti-tuberculosis drug resistance surveillance. Supranational laboratories were present in India, Japan and Republic of Korea, the latter becoming the regional

coordinating centre in the second round of surveys. National laboratories collaborating in the surveys were located in China (Henan), India (Delhi), Nepal, Republic of Korea, Thailand and Viet Nam in the first survey with addition of China (Guangdong), China (Hong Kong SAR), China (Shandong), China (Zhejiang), India (Tamil Nadu), Malaysia, and Singapore in the second survey. Table 1 shows the rates of multi-drug resistance from some of the Asian countries.

Table 1. Rate of Multi-Drug Resistance among Some Asian Countries[14]

Countries	*Year*	*Rate of MDR-TB (%)*
China		
Henan Province	1996	15.1
Guangdong Province	1998–99	4.3
Hong Kong SAR	1996	2.6
Shandong Province	1997	6.4
Zhejiang Province	1998–99	9.4
India (Tamil Nadu State)	1997	7.1
Malaysia	1996–97	0.1
Nepal	1999	1.4
Republic of Korea	1998–99	2.7
Singapore	1996	0.8

Because of its relation to the epidemiology of tuberculosis, routine information on the level and trend of human immunodeficiency virus (HIV) infection is essential to understand trends and predictions of tuberculosis in a community (24). Such information is collected and collated by the WHO from sentinel groups in the population in a large number of countries (25).

Global distribution of tuberculosis

In epidemiological terms, distribution of a disease is generally addressed in terms of place, person and time.

The distribution of tuberculosis varies widely according to geographical location. Making precise estimates of geographical distribution is difficult because of widely varying capacity for case detection, completeness of routine reporting, and availability of comparable scientific surveys. An exercise has recently been undertaken by the World Health Organization to estimate the global distribution of tuberculosis, utilizing the best available information, from whatever source, and employing a consensus approach to arrive at the best estimate of the problem in the 212 member-states of the WHO (26). This exercise provides an excellent template upon which to continuously refine estimates and to arrive at reasonable figures for the burden of tuberculosis.

A global total of 7.962 million cases of tuberculosis were estimated to have appeared in 1997, including an estimated 3.521 million sputum smear positive cases. Of this number, the proportions notified to the WHO in that year were 42% and 37% respectively. Twenty-two countries accounted for 80% of these cases (and 63% of the total population). The estimated population, cases of tuberculosis and number of persons living with HIV in 1999 for the 22 most heavily burdened countries are given in table 2. The populations of the 22 countries range from 1,269 million in China to 11 million in Cambodia; the numbers of cases range from 1,885 thousand in India to 62 thousand in Cambodia; the number of persons living with HIV vary from 4.2 million in South Africa to less than 100 in Afghanistan.

Estimates of the geographic distribution of new multidrug resistant cases are possible for only 10 of the 22 countries (Table 2). These range from no cases in Kenya to 134 thousand new cases in India in 1999.

A number of migrant studies have been carried out to determine the impact of geographical relocation on the occurrence of tuberculosis. These studies have clearly shown that not only the occurrence of the disease, but also its clinical characteristics, resemble those of the community from which the migrant originates, provided that the migrant is moving to a community with a relatively low rate of tuberculosis (27). In most of the countries with the lowest reported rates of tuberculosis, a high proportion of all new cases arise from amongst those who have migrated into the community from locations with a much higher rate of the disease.

Table 2. Estimations for 1999 of Population, Tuberculosis (TB) Cases[1], Persons Living with HIV[2] and Occurrence of Multidrug Resistance[3]

	Population	*TB cases*		*Persons living with HIV*	*Multidrug resistance*
		Number	*Rate (per 100,000)*		
India	995,055,506	1,885,295	189	3,700,000	133,856
China	1,268,737,134	1,373,545	108	500,000	109,884
Indonesia	210,498,663	634,364	301	52,000	
Bangladesh	125,948,651	297,414	236	13,000	
Pakistan	151,702,727	275,284	181	74,000	
Nigeria	124,361,431	270,263	217	2,700,000	
Philippines	74,014,717	232,329	314	28,000	
South Africa	44,910,137	183,065	408	4,200,000	4,577
Russian Federation	147,412,732	155,688	106	130,000	20,239
Ethiopia	63,439,840	167,295	264	3,000,000	
Vietnam	79,484,458	150,562	189	100,000	6,022
Democratic Republic Congo	51,362,254	140,233	273	1,100,000	
Brazil	167,731,670	126,849	76	540,000	1,649
United Republic Tanzania	33,360,903	104,429	313	1,300,000	
Kenya	29,910,736	91,883	307	2,100,000	0 (0%)
Thailand	60,348,096	86,651	144	755,000	2,686
Myanmar	47,894,094	83,773	175	530,000	
Afghanistan	24,205,128	80,965	334	100	
Uganda	21,971,596	70,917	323	820,000	567
Peru	25,202,520	60,674	241	48,000	2,609
Zimbabwe	12,106,337	72,583	600	1,500,000	
Cambodia	11,091,530	62,127	560	220,000	

[1] calculated from reference [26]
[2] from reference [24]
[3] new MDR cases in 1999 from references [13] [14]
* estimates from partial surveys of the country

The second and third categories in which distribution is described are person and time. To obtain an accurate picture of the distribution of tuberculosis by age and sex, it is necessary to study the distribution of tuberculosis over time, as the disease characteristics have changed relatively rapidly over time in many locations where the disease has been studied. An accurate picture of the relation of the disease to age and sex is obtained primarily by observing the lifetime experience of a group of individuals (a cohort). This concept was introduced to epidemiology through studies of tuberculosis in Norway (28). This showed clearly that mortality from tuberculosis has two peaks; one in infants and another in young adults, aged 15 to 24. The second peak is characteristically greater in young women than in young men. The excess among cases of older people in many countries where tuberculosis rates are low has been clearly shown to be an effect of much greater rates of infection with *Mycobacterium tuberculosis* in earlier life among persons presently in the older

age groups, with a rapid decline in infection in succeeding birth cohorts. This cohort effect has also been demonstrated for infection with *Mycobacterium tuberculosis* with the greatest occurrence of infection prior to the age of 20 years, no matter what the cumulative life time probability of becoming infected (29). The birth cohort is so powerful a predictor of life-time experience with tuberculosis that any understanding of the epidemiology of this disease must take account of this factor.

Distribution of tuberculosis in Asia

Figure 1 illustrates the trend in prevalence of smear positive pulmonary tuberculosis in China over the 4 prevalence surveys undertaken since 1979.

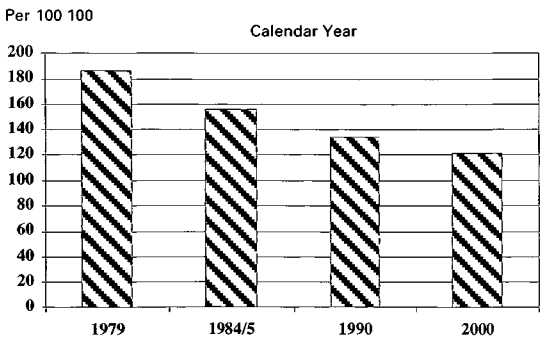


Figure 1. Tuberculosis prevalence — Smear positive cases in China, 1979–2000

The geographical distribution of tuberculosis in Asia, from 'best-estimates' of incidence, has been described in the material previously presented. From the estimated numbers of cases noted in Table 2, 73% of the estimated 6.6 million total cases in 1999 occurred in the countries of East and South Asia. This is, to a large extent, due to the large populations in many of the countries of Asia. For purposes of comparison, and to take into account the variation in population size, it is useful to compare estimated incidence of tuberculosis per unit of population. For this purpose, rates of 100 per 100 000 persons per year or greater are considered to be very high rates (30). This group can be further divided to identify those countries with extremely high rates (250 per 100 000 per year and higher). In 1997, all countries in the region with the exception of Japan, The Republic of Korea and Sri Lanka (with intermediate rates 25–99 per 100 000 per year) were in the group with very high rates with the Philippines, Indonesia, Papua New Guinea and Cambodia having extremely high rates.

The distribution of tuberculosis by age and sex may be different in some countries of Asia than it has been in Europe and North America when the disease was very frequent. Unlike the latter locations, a number of countries in Asia have experienced much higher rates of tuberculosis in men than in women even when the disease was very frequent (31).

The impact of migration on tuberculosis among people born in Asia has been described (31–33). The rates of the disease in those who have migrated to a community with lower levels of the disease are similar, although slightly lower, than those among their compatriots who have remained in the country of origin. The rate of cases discovered on the initial screening examination on arrival in the country are substantially higher and comprise cases with less extensive disease, both radiographically and bacteriologically, reflecting the bias associated with finding prevalence cases on the screening examination. The unique characteristic of having a higher proportion of cases involving the peripheral lymph nodes among those migrating from Asia, as compared with the population in the host country, has been previously noted and remains unexplained.

An example of the distribution of tuberculosis in a single location in Asia, where reliable information exists over a long period of time is that of Hong Kong. Hong Kong is situated in the south part of China with a total land area of 1,098 square kilometres. The territory has a population of 6,711,500 at the end of 2000, the population density being high at 6,112 per square kilometre. It has an ageing population with the median age rising from 30 in 1990 to 36 in 2000. The proportion aged under 15 fell from 21.5% in 1990 to 16.9% in 2000, while the proportion aged 65 and over rose from 8.5% to 10.9% during the same period. There has been a huge amount of population movement, with 144 million people

moving in and out of the territory in 2000, an increase of 11.6% from 129 million in 1999.

In Hong Kong, tuberculosis has been a notifiable disease since 1939. The mortality declined from a peak of 207.9 per 100,000 in 1951 to 4.5 per 100,000 in 2000. The average age at death increased from 25 in 1951 to 73 in 2000. TB, once the top killer disease, is now outside the top 10 causes of death in Hong Kong.

The notification rate of tuberculosis has improved significantly with a continuous decline in the past three to four decades (Figure 2) (34). The notification rate decreased from a peak of 697.2 per 100,000 in 1952 to 101.0 in 1996. However, in the recent decade, this decline has slowed down and the rate became rather stagnant and stayed at around 110 per 100,000. Moreover, there is a concern of possible resurgence of the disease locally. A similar phenomenon of stagnant trend of TB notification in the past decade has also been observed in some neighbouring countries, including Singapore, Japan, and Malaysia. Postulations to explain such observation include: ageing population, increase in population movement, increase in population density, urbanization of districts, strengthened publicity and surveillance of the disease, and the so-called "ageing of the TB epidemic" (35). The term "ageing of the TB epidemic" has been used to describe the epidemiological changes with time characterized by a fall in the proportion of active TB cases arising from progressive primary infection and exogenous reinfection, with an increasing proportion arising from endogenous reactivation. As endogenous reactivation of TB may continue from the large pool of individuals infected in the past, "ageing of the TB epidemic" has been postulated as being one of the important underlying factors for the stagnant trend.

In Hong Kong, there has been an increase in notifications from health care sectors which were previously minor sources of TB notification (36). Although the increase in awareness among those health care sectors of the need to notify TB may have led to an apparent increase in TB notification in Hong Kong, a real increase in the rate of tuberculosis cannot be excluded. The rate of tuberculosis among elderly, especially among those over the age of 70 years, has increased in the past decade in Hong Kong (37). It has been estimated that the increase in number of cases of tuberculosis in those over the age of 60 years could almost account for the total excess number of cases during the past decade (37).

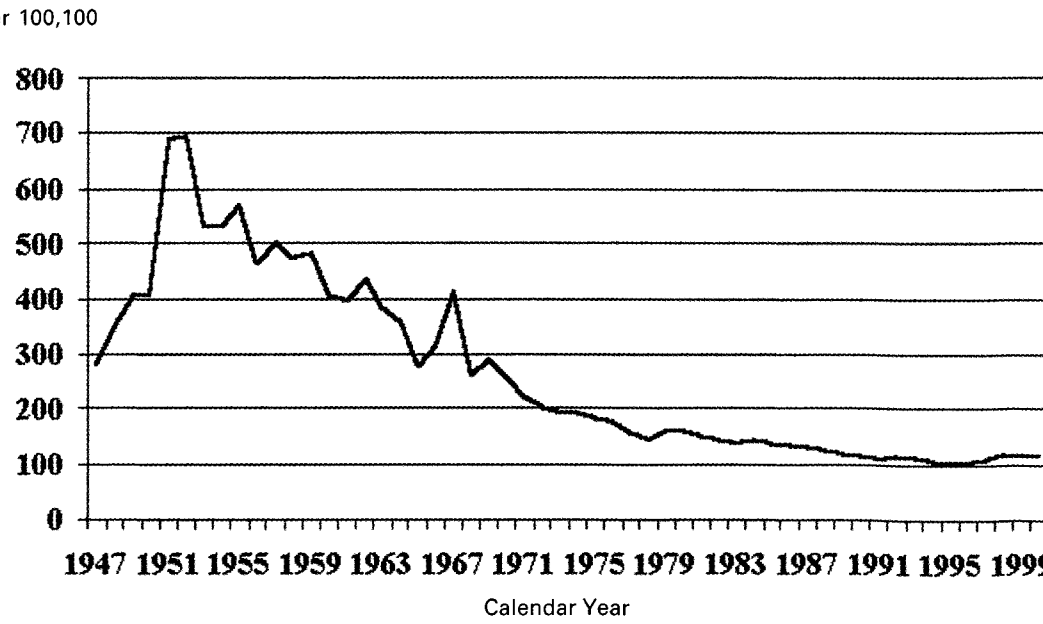


Figure 2. Notification of tuberculosis in Hong Kong, 1947–2000

Among the TB cases, about one third were sputum smear positive pulmonary cases and two thirds were sputum culture positive. The male to female ratio is around 2:1 and about 15% were retreatment cases. Currently, among all notified TB cases, about 77.8% of them were pulmonary, 13.7% were extrapulmonary, and the remaining 8.6% involved both pulmonary and extrapulmonary sites (38). It is interesting that although the trend of pulmonary TB has been decreasing over the past four decades, that of extrapulmonary TB has shown an opposite trend. Notification rate of extrapulmonary TB increased gradually from a rate of 3.4 per 100,000 in 1965 to 13.5 in 2000. The great majority of extrapulmonary TB cases are pleural TB (41.2%), and TB lymphadenopathy (36.5%) (38). Change in notification practice, completeness of reporting, and disease misclassification are the possible underlying reasons. However, they may not explain fully the long-term trend observed.

Several risk groups for tuberculosis have been evaluated in Hong Kong.

Elderly

As mentioned, Hong Kong has an ageing population. However, the proportion of elderly among TB patients has increased at an even faster rate. The percentage of elderly aged over 65 among the general population increased from 6.4% in 1980 to 10.9% in 2000, while that among the notified TB cases increased from 12.3% to 37.8% during the same period (Figure 3). The increase in the rate of tuberculosis with age is greater in men than in women (39).

An analysis of the trend in the rate of tuberculosis for different birth cohorts in Hong Kong (40) has shown the typical pattern seen in all such cohort studies with rates peaking in the 25 to 39-year age groups and gradually declining thereafter. Since 1978, there has been a slight increase in notification rate with advanced age, as has been the case in England and Wales. The data are unlikely to result from a change in reporting accuracy and completeness. They probably represent a true increase in TB burden among the elderly.

A comparison of the notification rates among the elderly group and the young age group shows that the rates among the elderly has become rather stagnant or even shown a slight increase in recent years, while there is apparently a continuous declining trend among the younger age groups. As the younger age groups are in general more representative of new infections, it is likely that reactivation and perhaps re-infection are assuming a greater part in disease development among all the TB cases.

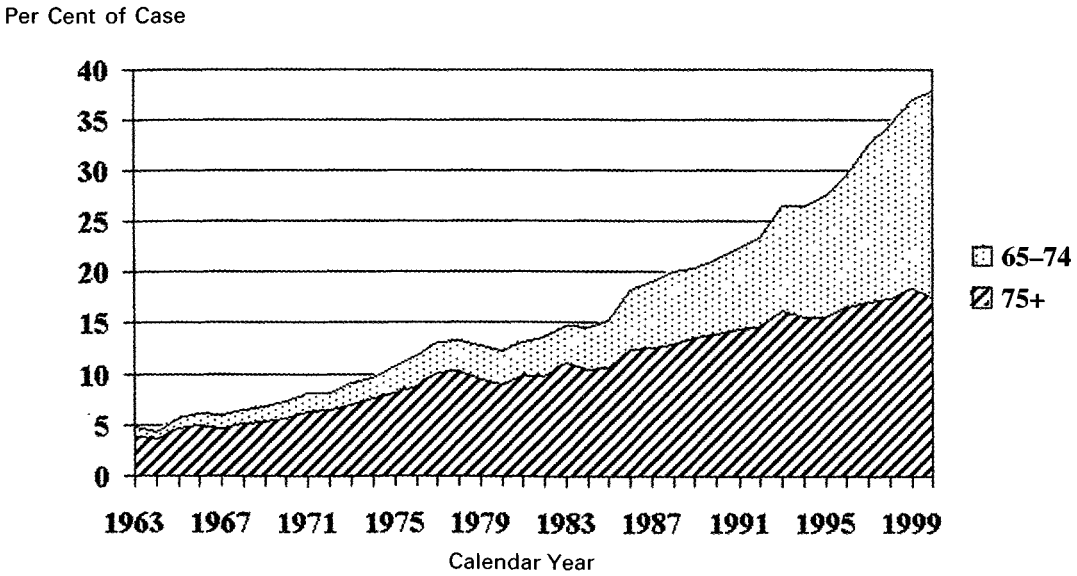


Figure 3. Tuberculosis in the elderly in Hong Kong, 1963–2000

Predisposing medical conditions

A survey has been done for all notified TB cases in the month of August in 1999 in Hong Kong (41). Among the 594 notified TB cases in that month, about one quarter (or 26%) had one or more medical conditions that could predispose to the development of TB. Diabetes mellitus was the commonest (12%) (Table 3). Others include malignancies, chronic renal failure, treatment with cytotoxic drugs and corticosteroids, and silicosis. The advance in clinical medicine has prolonged the survival of patients with medical diseases. It is likely that the number of this group will continue to grow. As they are at a higher risk of progression from TB infection to disease, their impact on the TB epidemiology will continue.

Table 3. Medical Conditions of 594 Consecutive Tuberculosis Patients Notified in August 1999 in Hong Kong

Condition:	*Number*	*%*
Diabetes mellitus	72	12.1
Malignancy	27	4.6
Chronic renal failure	18	3
Alcoholism	10	1.7
Pneumoconiosis	9	1.5
Corticosteroid therapy	8	1.4
Drug addiction	6	1
Leukemia / lymphoma	4	0.7
Cytotoxic medications	1	0.2
Other	20	3.4

HIV patients

The prevalence of HIV infection in Hong Kong is still quite low at present, as shown from unlinked anonymous surveys among various groups (42). Unlinked anonymous testing among TB patients over the years showed that the HIV seropositivity rate among TB patients is also low (Table 4). However, the trend has been rising slowly. Vigilant control of both infections is necessary.

Several other indicators of the trend in tuberculosis in Hong Kong have been evaluated. Over the years, surveys of tuberculin skin testing have been done among primary school children mainly aged between 6 to 10. The percentage of the school children showing a positive reaction has decreased from 79.5% in 1967 to 16.9% in 2000 (Figure 4). Although BCG vaccination has been given to the children at birth in Hong Kong, this is unlikely to have a significant effect on the rate of positive skin tests and affect the observed trend. The most likely explanation is a decreasing prevalence of TB infection over the years. Again, this is in support of the decreasing proportion of TB cases due to new infection.

Table 4. Unlinked Anonymous Screening for HIV in the TB and Chest Service, Hong Kong, 1990–2000

Period From:	*To:*	*Sample*	*Tested number*	*Positive number*
Dec 1990	Jan 1991	blood	1548	
Jun 1991	Aug 1991	blood	485	
Apr 1992	Jun 1992	blood	1469	2
Sep 1995	Nov 1995	blood	1173	
Sep 1996	Nov 1996	urine	895	2
Oct 1997	Jan 1998	urine	1003	2
Oct 1998	Jan 1999	urine	833	4
Sep 1999	Dec 1999	urine	1166	8
Sep 2000	Dec 2000	urine	1018	5

In the 1950s and 1960s in Hong Kong, only about one quarter of the TB patients completed treatment. The rate of drug resistance had been high at that time with the rate of resistance to any one drug (streptomycin, isoniazid, or para-aminosalicylic acid) over 40% (43). The danger of unsupervised treatment became increasingly recognized. Supervised treatment (now known as directly observed treatment) was introduced on a service basis since the 1970s. In 1996, about 80% of patients completed treatment at 12 months, a significant improvement compared to before but still falling slightly below the goal of the WHO goal of 85%. The improved treatment completion rate resulted in a declining trend of the drug resistance rate and a low proportion of retreatment cases (44). In 2000, a survey showed that the rate of drug resistance to any one drug (isoniazid,

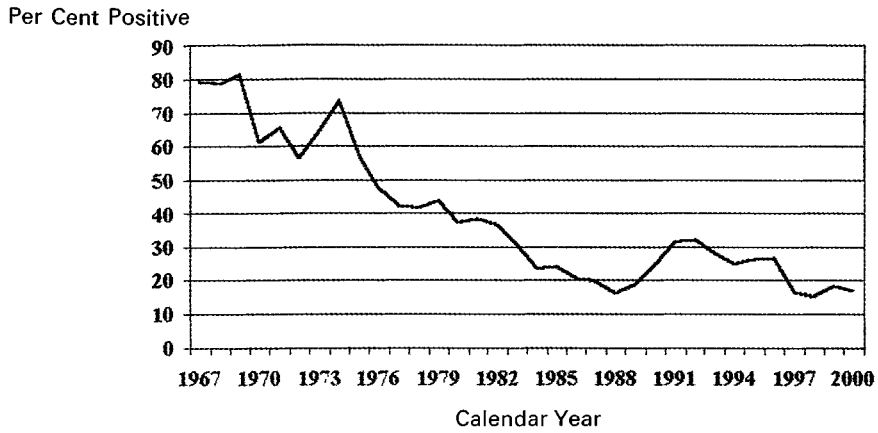


Figure 4. Tuberculin skin reactivity in Hong Kong primary school students.

rifampicin, ethambutol and streptomycin) was 10.0% and the rate of multidrug resistant TB was 1.6%. These rates are about average figures as compared with the Global TB Drug Resistance Surveillance Programme (14).

Hong Kong continues to report a high rate of tuberculosis. Although encouraged by a rapid decline over the past decades, the rate of TB has become rather stagnant in recent years. More effort will be required if the rate of decline is to be resumed as in the past. The results of interventions must be reviewed periodically. The DOTS strategy must remain the top priority and should continued to be delivered with high quality to have the greatest impact.

Determinants of tuberculosis

Key determinants of tuberculosis have been identified as

1. probability and characteristics of exposure to *Mycobacterium tuberculosis* which accounts for much of the probability of becoming infected,
2. the time which has elapsed since infection and the level of immunity of the infected host, which account for a great deal of the risk of developing disease, and
3. bacterial load in the body, which correlates with the extent and course of disease and the probability of recurrence of the disease following its quiescence in the individual.

Characteristics of exposure that are associated with probability of becoming infected with *Mycobacterium tuberculosis* have been studied in a variety of settings where contacts of active cases of tuberculosis have been systematically evaluated. The largest such study was undertaken in Canada (45) and indicated that the concentration of bacteria in expectorated sputum (determined by direct microscopic examination of sputum) and the intensity of exposure, reflected by the amount of time the person in contact shared a closed environment, were the greatest determinants of probability of becoming infected. Other studies have identified the duration of the contact with a person who retains bacteria in the expectorated sputum as an important determinant for infection (46). This is very likely to be a key determinant of the greater probability of chronic, drug resistant cases causing the appearance of new cases in the community (22). The development of molecular techniques, using restriction fragment length polymorphism (47), has further refined the capacity for detecting the "unit of transmission" of infection with *Mycobacterium tuberculosis* by identifying the same genetic strains of the bacillus in different cases within the community.

Infection with HIV is the most potent and extensive factor leading to decline in host immunity and therefore promoting the transition from infection to disease in individuals already infected with *Mycobacterium tuberculosis*. The majority (65%) of those estimated to be living with HIV infection in the 22 heavily burdened

countries (over 15 million persons) are in the countries of Africa (Table 2). For this reason, Africa would be expected to experience the greatest impact of HIV on tuberculosis. This is already the case in many sub Saharan countries where the health services are now stretched to capacity and greater, dealing with persons living with HIV. It is very likely that at least one-third (5 million) of these individuals will develop active tuberculosis in the next several years and they will, in addition, infect many others who are not presently HIV seropositive.

The effect of bacterial load on the recurrence of tuberculosis in those who previously suffered from the disease is well illustrated in migrants (31–33) where the rate of recurrence of the disease in such individuals is multiple times higher than it is in those who have never previously had the disease. This group would be expected to have a role in transmission of infection among those who are in contact with them.

Determinants of tuberculosis specific to Asia

As noted in Table 2, the greatest number of chronic, drug-resistant, cases are in the large countries of Asia. Consequently, these patients might exert a greater influence on transmission of infection in this region than might be the case in a number of other regions. In addition, a substantial minority (from 1 to 6 % of adults) of migrants from Asia are known to have previously had tuberculosis, as reflected by radiographic shadows consistent with the disease. At least half of these individuals had no knowledge of having previously had tuberculosis. Such individuals have a high probability of suffering from recurrent tuberculosis.

The numbers of persons estimated to be living with HIV is proportionately less in Asia as compared with Africa, with on one-quarter of such individuals (just under 6 million) in the 22 most heavily burdened countries living in Asia. The impact of HIV infection on the tuberculosis situation in Asia will depend to a large extent on what happens to the trend in HIV infection in India. Should the prevalence rise dramatically, the impact on tuberculosis could be substantial.

Interventions to control and eliminate tuberculosis

Chemotherapy of tuberculosis is the most powerful planned intervention in reducing transmission of *Mycobacterium tuberculosis*. When applied correctly, it has a substantial impact by reducing the duration of infectiousness of tuberculosis patients who are contagious (21). When chemotherapy is applied in a haphazard fashion, its effect can be the opposite (20,48,49) by saving the life but failing to cure the patient, thus increasing the prevalence of contagious cases in the community. Moreover, chemotherapy poorly applied converts previously curable patients into difficult to treat (and frequently incurable) drug resistant cases.

The importance of standardization of management and careful application of control measurements has recently been recognized through the widely applied "DOTS Strategy" (Directly Observed Treatment, Short-Course). This public health strategy was developed over a decade of technical collaboration of the International Union Against Tuberculosis and Lung Disease (50) and consists of a package of policies designed to deliver high quality health services to ensure the successful treatment of tuberculosis patients (with a priority on those who are most contagious). The overall objective of this strategy is the protection of children from becoming infected with *Mycobacterium tuberculosis*. In the absence of an effective vaccine to prevent infectious cases of tuberculosis, this strategy is the only feasible intervention for primary prevention of tuberculosis.

Aspects of interventions relevant to Asia

The potential negative impact of chemotherapy on the epidemiology of tuberculosis was convincingly demonstrated in countries of Asia (20,49). The application of programmed activities for control of tuberculosis without careful analysis of their impact led to an accumulation of large numbers of badly treated cases of tuberculosis, many of whom were drug resistant, who then became a focus for further transmission of infection. It was this observation that led to the emphasis on evaluation of treatment outcome as a

key indicator of program performance in tuberculosis control within the DOTS Strategy.

While the declared objective of tuberculosis control is the protection of children from becoming infected with *Mycobacterium tuberculosis*, conclusive evidence that this could be accomplished (over and above a natural trend in the disease) in poor countries is very scanty. Most of the countries that were partners in the development of the DOTS Strategy in collaboration with the International Union Against Tuberculosis and Lung Disease have subsequently been heavily impacted by the HIV epidemic with the result that the numbers and rates of cases have steadily risen and, along with the increased numbers of cases, infection in children has also begun to rise.

The most compelling evidence that the DOTS Strategy can be effective in controlling transmission of infection comes from Beijing Municipality. The elements of the DOTS Strategy were systematically introduced into that community (at the time a very poor community) from 1978 and applied regularly since that time (51). Although systematic surveillance of tuberculin skin reactivity was not carried out, surveillance of tuberculous meningitis in children (a reasonable surrogate of infection) was recorded. With the progressive reduction in prevalence of tuberculosis in the community as effective tuberculosis case management was instituted, meningitis regularly declined and virtually disappeared over this period of time (52). Moreover, by the end of the period under study (1995), the average annual risk of infection in children had reached a level less than 0.2% (53), a level similar to that in many Western European countries.

Prediction of the future of global tuberculosis

Taking into account the estimates of the current tuberculosis problem (Table 2), calculating the population growth and estimating the impact of HIV on the trend in tuberculosis (24), it is possible to calculate an estimation of the trend in numbers of tuberculosis cases projected over the decade following 1997 (Figure 5). From this figure, it is

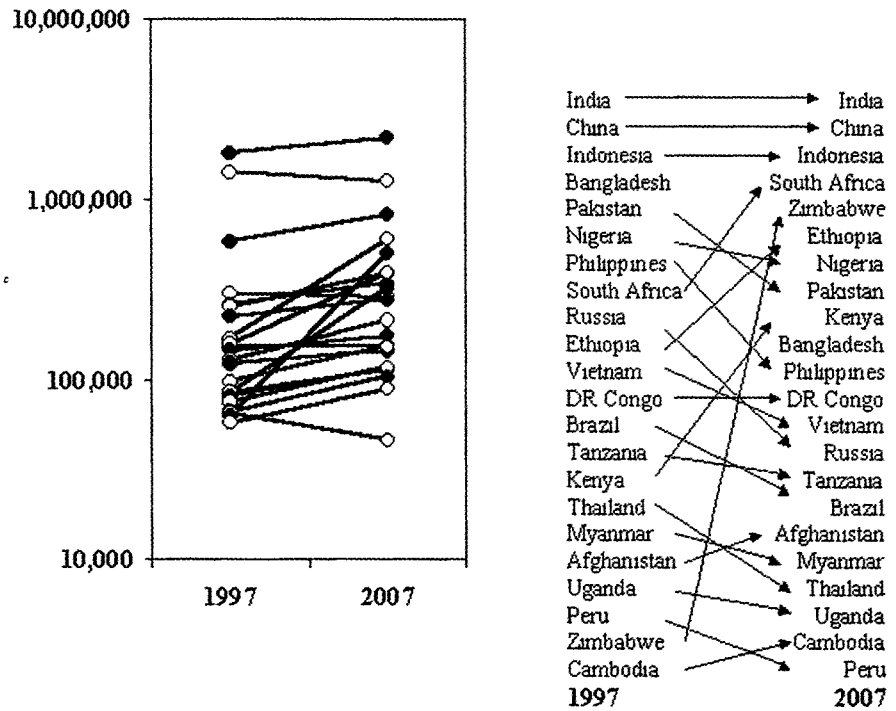


Figure 5. Trend in tuberculosis in 22 heavily burdened countries

clear that the three large countries of India, China and Indonesia will retain their lead in terms of numbers of tuberculosis cases. After these countries, there will be a striking increase in the numbers of tuberculosis cases in some African countries (South Africa, Zimbabwe, Ethiopia, Nigeria and Kenya) to the point where these countries will contribute the next highest numbers of cases in 2007. A number of countries of Asia will lose their position in the list of most heavily burdened countries, most notably Bangladesh, Philippines, Vietnam and Pakistan. These estimated changes will be primarily due to the impact of HIV on the tuberculosis situation and, less importantly, changes in the population size and structure.

References

1. Rieder HL. *Epidemiologic Basis of Tuberculosis Control.* Paris: International Union Against Tuberculosis and Lung Disease. 1999; 162 pages.
2. Enarson DA, Ait Khaled N. Tuberculosis. In: *Respiratory Epidemiology in Europe.* Eds. Annesi-Maesano I, Gulsvik A, Viegi G. Sheffield: European Respiratory Monograph 15, Volume 5, 2000, 67–91.
3. Last JM. *A Dictionary of Epidemiology.* Oxford: Oxford University Press 1995; p 180.
4. Styblo K. Surveillance of tuberculosis. *Int J Epidemiol* 1976; 5:63–8.
5. Dolin PJ, Raviglione MC, Kochi A. Global tuberculosis incidence and mortality during 1990–2000. *Bull Wld Health Org* 1994; 72:213–30.
6. Bulla A. World health statistics report: tuberculosis patients — how many now? *WHO Chronicle* 1977; 31:35–40.
7. Styblo K, Rouillon A. Estimated global incidence of smear-positive pulmonary tuberculosis. Unreliability of officially reported figures on tuberculosis. *Bull Int Union Tuberc* 1981; 56:118–26.
8. Kochi A. The global tuberculosis situation and the new control strategy of the World Health Organization. *Tubercle* 1991; 72:1–6.
9. World Health Organization. *Global Tuberculosis Control. WHO Report 1999.* Geneva: WHO/CDS/CPC/TB/99.259. 1999, p 174.
10. Murray CJL, Styblo K, Rouillon A. Tuberculosis in developing countries: burden, intervention and cost. *Bull Int Union Tuberc Lung Dis* 1990; 65:2–20.
11. International Union Against Tuberculosis and Lung Disease. Guidelines for conducting tuberculin skin test surveys in high prevalence countries. *Tuber Lung Dis* 1996; 77(suppl 1):1–20.
12. Styblo K, Meijer J, Sutherland I. The transmission of tubercle bacilli. Its trend in a human population. *KNCV Selected Papers* 1971; 13:1–104.
13. World Health Organization. *Anti-Tuberculosis Drug Resistance in the World.* Geneva: WHO/TB/97.229. 1997; 227 pages.
14. World Health Organization. *Anti-Tuberculosis Drug Resistance in the World. Report No. 2. Prevalence and Trends.* Geneva: WHO/CDS/TB/2000.278. 2000; 253 pages.
15. Shimao T. Measuring tuberculosis: the role of the Tuberculosis Prevalence Survey as developed in Eastern countries. *Tubercle Lung Dis* 1993; 74:293–4.
16. Yamaguchi M. Survey of tuberculosis prevalence in Japan in 1953. *Bull World Health Org* 1955; 13:1041–73.
17. The National Institute of Tuberculosis. *Report on a National Tuberculosis Prevalence Survey in the Republic of the Philippines (1982–1983).* Manila, Philippines; 1984.
18. Ministry of Health & Social Affairs and the Korean National Tuberculosis Association. *The 7th Tuberculosis Prevalence Survey in Korea* (in Korean). Seoul; 1996.
19. Tupasi TE, Radhakrishna S, Rivera AB, Pascual MLG, Quelapio MID, Co VM, Villa MLA, Beltran G, Legaspi JD, Mangubat NV, Sarol JN Jr, Reyes AC, Sarmiento A, Solon M, Solon FS, Mantala MJ. The 1997 Nationwide Tuberculosis Prevalence Survey in the Philippines. *Int J Tuberc Lung Dis* 1999; 3:471–7.
20. Grzybowski S, Enarson DA. The fate of cases of pulmonary tuberculosis under various treatment programmes. *Bull Int Union Tuberc* 1978; 53:70–5.
21. Rouillon A, Perdrizet S, Parrot R. Transmission of tubercle bacilli: the effects of chemotherapy. *Tubercle* 1976; 57:275–99.

22. Schulzer M, Enarson DA, Grzybowski S, Hong JP, Kim SJ, Lin TP. An analysis of tuberculosis data in Taiwan and Korea. *Int J Epidemiol* 1987; 16:584–9.
23. World Health Organization. *Global Tuberculosis Control. WHO Report 2000.* Geneva: World Health Organization, WHO/CDS/TB/2000–275. 2000; 185 pages.
24. Schulzer M, Fitzgerald JM, Enarson DA, Grzybowski S. An estimate of the future size of the tuberculosis problem in sub-Saharan Africa resulting from HIV infection. *Tuberc Lung Dis* 1992; 73:52–8.
25. UNAIDS / WHO Working Group on Global HIV/AIDS and STI Surveillance. Epidemiological Fact Sheets on HIV / AIDS and sexually transmitted infections. 2000 update. Geneva: 20, Avenue Appia, CH-1211 Geneva 27.
26. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Global Burden of Tuberculosis. Estimated Incidence, Prevalence, and Mortality by Country. *JAMA* 1999; 282:677–86.
27. Enarson D, Ashley MJ, Grzybowski S. Tuberculosis in immigrants to Canada: a study of present-day patterns in relation to immigration trends and birthplace. *Am Rev Respir Dis* 1979; 119:11–8.
28. Andvord KF. Der Verlauf der Tuberculose durch Generationen. *Beitr Klin Tuberk* 1930; 75:552–63.
29. Styblo K. *Epidemiology of Tuberculosis.* The Hague: Royal Netherlands Tuberculosis Association 1991; 102.
30. Enarson DA, Fanning EA, Allen EA. Case-finding in the elimination phase of tuberculosis: high-risk groups in epidemiology and clinical practice. *Bull Int Union Tuberc Lung Dis* 1990; 65:73–4.
31. Lin HT. *Tuberculosis Problem and Its Control in East Asia and South Pacific Area.* Kiyose, Research Institute of Tuberculosis 1984; 11.
32. Enarson DA. Active tuberculosis in Indochinese refugees in British Columbia. *CMAJ* 1984; 131:39–42.
33. Wang JS, Allen EA, Chao CW, Enarson D, Grzybowski S. Tuberculosis in British Columbia among immigrants from five Asian countries. *Tubercle* 1989; 70:179–86.
34. Wang JS, Allen EA, Enarson DA, Grzybowski S. Tuberculosis in recent Asian immigrants to British Columbia, Canada; 1982–1985. *Tubercle* 1991; 72:277–83.
35. Chest Service of the Department of Health of Hong Kong SAR. Annual Report 2000.
36. World Health Organization Western Pacific Regional Office. Epidemiological analysis of possibly stagnated decline of tuberculosis in intermediate burden countries in the Western Pacific Region. Third Meeting of the Technical Advisory Group, Osaka, Japan, February 2002.
37. Chan-Yeung M, Noertjojo K, Tan J, Chan SL, Tam CM. Tuberculosis in the elderly in Hong Kong. *Int J Tuberc Lung Dis* 2002; 6:771–9.
38. Nertjojo K, Tam CM, Chan SL, Chan-Yeung M. Extrapulmonary tuberculosis in Hong Kong. *Int J Tuberc Lung Dis* 2002; 6:879–86.
39. Chan-Yeung M, Noertjojo K, Chan SL, Tam CN. Sex differences of tuberculosis in Hong Kong. *Int J Tuberc Lung Dis* 2002; 6:11–8.
40. Tocque K, Bellis MA, Tam CM, Chan SL, Syed Q, Remmington T, Davies PDO. Long-term trends in tuberculosis. Comparison of Age-cohort Data between Hong Kong and England and Wales. *Am J Respir Crit Care Med* 1998; 158:484–8.
41. Leung ECC, Tam CM. Comorbidities among patients with tuberculosis in Hong Kong. HK Pract 2002; 24:170–8.
42. Advisory Council on AIDS, Hong Kong. Report 1999–2000.
43. Government Chest Service, Hong Kong. Annual Report 1968.
44. Kam KM, Yip CW. Surveillance of Mycobacterium tuberculosis drug resistance in Hong Kong 1986–1999, after implementation of directly observed treatment. *Int J Tuberc Lung Dis* 2001; 5:815–23.
45. Grzybowski S, Barnett GD, Styblo K. Contacts of cases of active pulmonary tuberculosis. Bull Int Union Tuberc 1975; 50:90–106.
46. Aoki M, Mori T, Shimao T. Studies on factors influencing patients', doctors' delay of tuberculosis case detection in Japan. *Bull Int Union Tuberc* 1985; 60:128–30.
47. Glynn JR, Bauer J, de Boer AS, Borgdorff MW, Fine PEM, Godfrey-Faussett P, Vynnycky E, European Concerted Action on Molecular Epidemiology and Control of Tuberculosis. *Int J Tuberc Lung Dis* 1999; 3:1055–60.
48. Crofton J. The contribution of treatment to the prevention of tuberculosis. *Bull Int Union Tuberc* 1962; 32:643–53.

49. Frimodt-Moller J. Changes in tuberculosis prevalence in a south Indian rural community following a tuberculosis control programme over a seven years' period. *Ind J Tuberc* 1962; 9:187–91.
50. Enarson DA. The International Union Against Tuberculosis and Lung Disease model National Tuberculosis Programmes. *Tuber Lung Dis* 1995; 76:95–9.
51. Zhang L-X, Kan G-Q. Tuberculosis control programme in Beijing. *Tuberc Lung Dis* 1992; 73:162–6.
52. Zhang L-X, Tu D-H, Enarson DA. The impact of directly-observed treatment on the epidemiology of tuberculosis in Beijing. *Int J Tuberc Lung Dis* 2000; 4:904–10.
53. Zhang L-X, Tu D-H, He G-X, Ma Z-Q, Nagelkerke NJ, Borgdorff MW, Enarson DA, Broekmans JF. Risk of Tuberculosis Infection and Tuberculous Meningitis after Discontinuation of Bacillus Calmette-Guerin in Beijing. *Am J Respir Crit Care Med* 2000; 162:1314–7.

16 Tuberculosis: Clinical Features in Adults

S K Jindal and V K Vijayan

Introduction

The clinical features with which tuberculosis presents are ubiquitous in nature but vary significantly depending upon the organ system involvement. Historically, spinal tuberculosis is perhaps the most ancient form. It has been recognized in Egyptian wall-paintings showing typical hunch-back deformities, and in skeletons dating back to 4000 – 5000 B.C., recovered from graves in Heidelberg (Germany), Liguria (Italy), Denmark and Jordan Valley (1). Pulmonary tuberculosis was possibly known in Asia some 5000 years ago in Chinese writings, and in Rig Veda of Indo-Aryan civilization (2). The first written description of "Yakshma" (tuberculosis) is available in Ayur-Veda (700 B.C.) such as the statement on clinical symptomatology of early tuberculous disease — "a consumptive who is evidently master of himself, who has a good digestion, is not emaciated and is at the beginning of the disease the physician can cure".

Ever since antiquity, through Biblical and medieval periods, tuberculosis has occupied the centre stage of clinical pulmonology all over the world, but especially so in the developing countries of Asia.

With the advent and wider availability of a more sensitive and specific diagnostic armamentarium, other nontuberculous pulmonary diseases are now being diagnosed with increased confidence and frequency in the developing countries (3), but pulmonary tuberculosis continues to dominate the scene. In most Asian countries, it tops the list of differential diagnosis of most clinical syndromes presenting with respiratory symptoms and signs especially those with radiological shadows. Even in the West, tuberculosis should be considered, especially in high risk populations (4).

There are significant differences in prevalence and manifestations of tuberculosis in different countries of Asia, although the spectrum is largely similar. There are several important points on which tuberculosis in this region differs from that in a Western population (Table 1).

Spectrum of Tuberculosis

The clinical spectrum of pulmonary tuberculosis is widely variable. While at one end of the spectrum is "tuberculosis infection" defined by a positive tuberculin skin test, without presence of any symptoms or signs, at the other end is tubercular disease which presents with different clinical features. The clinical features may also differ in different forms of tuberculosis.

Table 1. Tuberculosis in High Prevalence Countries in Asia versus the Low Prevalence Countries in the West — Clinical Considerations

	High Prevalence Asian Countries	*Low Prevalence Western Countries*
1. Type of TB		
Primary	Mostly Children	Mostly adults
Post-primary	Adults	Adults
2. Age distribution	All ages Mostly < 50 yrs	Mostly adults and elderly (> 50 yrs)
3. Population groups	All populations More common in poor, slum & crowded areas	More common in the "disadvantaged"
4. HIV association	Less common (but increasing)	Very common
5. Clinical presentation		
i. Stage of disease	Mostly advanced	Incidental to moderately advanced
ii. Most common form	Fibrocavitary	Infiltrates/Pneumonia
iii. Other forms	Disseminated miliary Lymph hode	Miliary Pleural
iv. Atypical presentation	Common	Less common
6. Associated disorders	Common	Rare to less common

Primary Tuberculosis

After the mycobacterial infection, commonly by inhalational route, spread is contained in over 90 percent of individuals by the host defence system. Commonly, it happens in children who do not develop any symptom (5). In a minority of subjects, in whom the mycobacteria overcome the defence mechanisms, the infection progresses to primary tubercular disease within a period of a few weeks or months. Primary tuberculosis, therefore, occurs in individuals who are infected for the first time and are not exposed to tuberculosis in the past. In high prevalence countries, most adults have been exposed to mycobacteria during early years of life. Primary tuberculosis, however, can involve previously unexposed tuberculin-negative adults who may contact infection in the presence of immunodeficiency or during old age.

Primary tuberculosis generally involves the regional lymph nodes and spreads to multiple organs through blood stream. It commonly presents in a disseminated form involving lungs, liver, kidney, bone marrow and other organs. Most often, it is seen in the form of miliary disease. Cavitary form of primary pulmonary tuberculosis was described from Mumbai in 75 children below 2 years of age; wide spread haematogenous infection was common with tuberculous meningitis in 28% and miliary nodules in 45.3% (6).

Post-primary or reactivation tuberculosis

Post-primary tuberculosis occurs in previously asymptomatic tuberculin-positive individuals infected earlier during childhood. The latent infection gets reactivated during a period of stress when host defences are compromised. Rarely it can occur as direct progression of a primary lesion (7). Exogenous reinfection in adults confirmed on DNA finger-printing is now described with increasing frequency in the West (8,9).

Post-primary tuberculosis is the most common form seen in adults. The lungs are the most frequently involved organs. It generally presents in the form of a fibrocavitary disease. Extrapulmonary organs are involved in 10 to 15 percent of patients.

Sequelae of tuberculosis

Pulmonary tuberculosis leaves many sequelae in over 50 percent of individuals. Pulmonary scarring due to fibrosis, calcification, pleural thickening, bronchiectasis and lung cavities may persist even after mycobacterial negativity is obtained and tuberculosis as an infection is conceptually cured. Tubercular sequelae are rather common in most Asian countries with poorer populations because of the delayed diagnosis and treatment. Many such patients may remain symptomatic throughout their lives.

Congenital tuberculosis

True congenital tuberculosis satisfying criteria of bacteriological positivity and being present 'in vitro' at birth or within the first few days, is very rare (10). Tuberculosis in a new-born child is more often acquired from a sputum positive mother after, than before, the birth. Rarely, infection in the foetus may occur due to haematogenous spread via the umbilical vein or following aspiration of the infected amniotic fluid.

The disease is generally disseminated in nature and severe respiratory distress may occur. The presence of fever, general ill health, lymphadenopathy, hepatosplenomegaly and jaundice in a premature baby born to a mother suffering from tuberculosis should immediately arouse suspicion of congenital tuberculosis. Diagnosis is confirmed on positive microbiological smears obtained by fine needle aspiration or on biopsy from an involved organ.

Socio-Demographic Characteristics

Several changes seem to have taken place in the socio-demographic pattern and characteristics of patients with tuberculosis over the last several years but it largely continues to be a disease of the poor. In the developed countries of Europe and North America, tuberculosis is recognized more often in foreign-born individuals and in disadvantaged populations such as the homeless, prisoners, drug-users and persons with Human Immunodeficiency Virus (HIV) infection (11). On the other hand, tuberculosis in Africa is closely linked to the HIV pandemic and poor public health infrastructure (12). In most South Asian countries, tuberculosis is rampant even in the non-HIV infected patients. It is widely present in the crowded slums with poor hygienic conditions. An increasing association with HIV infection is now being seen and reported in many studies (13,14).

Preponderance in the poor in no way excludes the diagnosis of tuberculosis in the rich, educated and other well placed people. Tuberculosis in fact is now diagnosed with an increased frequency in all sections of society. Hospital staff members including doctors and nurses and other groups exposed to the mycobacteria while taking care of tuberculosis patients seem to be more vulnerable to infection.

In our recent analysis of tuberculous patients seen at this hospital, the male to female ratio was 2:1 with an average age of 35.6 (+/– 13.7) years (15). Tuberculosis patients compared to patients with nontuberculous chronic respiratory ailments had an increased odds ratio for being younger in age, poorly educated and lower income level. Tuberculosis patients had poor housing, poor water supply and lived in over-crowded houses. There was a progressively increasing odds ratio for tuberculosis patients to have lower socio-economic conditions in a graded manner from the best to the worst category (15).

There is an age-related increase in pulmonary tuberculosis in several Asian countries including India. Such an increase was also shown in Indian, Pakistani and Bangladeshi immigrants in England (16). In another report from UK, tuberculosis in the elderly whites was more advanced and diagnosed with greater difficulty. Its course was complicated by other diseases and the tolerance of therapy was poor (17).

A comparison of hospitalized patients between 1964–66 and 1985–88 in National Sanatorium in Japan revealed that the primary treatment cases with positive bacteriology, atypical mycobacteriosis and those with complications increased while re-treatment cases decreased (18). Further, the disease in 1985–88 more often involved patients of less than 29 and more than 70 years of age (18).

Syndromic Presentation

The clinical picture of post primary pulmonary tuberculosis may vary from the presence of minimal and nonspecific symptoms to that of an end-stage lung and respiratory failure. The different clinical syndromes with which a patient may present may suggest one or the other form of lung-involvement such as the fibrocavitary, endobronchial or miliary tuberculosis; hilar and mediastinal lymphadenopathy; tuberculous pleural disease or post tubercular sequelae. Some of the rarer forms which have been described from time to time include manifestations such as reactive immunological phenomena, vasculitis and acute lung injury.

Symptomatic presentation

General constitutional symptoms

Most patients complain of nonspecific symptoms of ill health such as fever, generalized malaise, fatigue, weakness and anorexia (19). Although weight loss is an important feature, it may not be present in early cases. Tuberculosis is also an important cause of the syndrome of pyrexia of unknown origin (PUO). It was recently reported as responsible in a quarter of 212 patients with prolonged pyrexia in Dhaka (20). Evening rise in temperature and night sweating have been characteristically described in tuberculosis.

Polyarthralgia has been described in both pulmonary and extrapulmonary tuberculosis (21,22). Diagnosis of this form of reactive arthritis or tubercular rheumatism (Poncet's disease) rests on exclusion of a known cause of polyarthritis (such as rheumatoid arthritis, and other connective tissue diseases), and disappearance of symptoms after antituberculosis treatment.

Respiratory symptoms

Cough is present in about 90% of patients, while sputum production and haemoptysis are seen in about a third (23). It has been reported that haemoptysis, fever and cough are more common in young adults compared to the elderly patients (24). Cough, the most common symptom of pulmonary tuberculosis, is initially nonproductive and usually occurs in the morning in the early stages of disease. As the disease progresses, cough becomes continuous throughout the day. Barking cough can occur in endobronchial tuberculosis due to ulceration of bronchial mucosa. Sometimes cough may be paroxysmal. Sputum is initially scanty, mucoid, purulent or blood-tinged. In advanced disease, sputum becomes thick and mucopurulent. It may be yellow or yellowish green in colour. It is rarely foul smelling. Any patient with cough of more than three week duration should have his/her sputum examined for tuberculosis.

Haemoptysis can occur in patients with active tuberculosis as well as those who have received chemotherapy. Bleeding usually occurs in patients with cavitary disease. Massive haemoptysis can lead to death, and in pre-chemotherapeutic era, 7.7% of deaths in tuberculosis were attributed to occurrence of massive haemoptysis. Rupture of Rasmussen aneurysms of vessels passing through the cavity was responsible for massive haemoptysis (25). Aneurysms can also be formed by herniation of adventitia and media of vessel wall into the lumen of the cavity. Rupture of an aneurysm can be precipitated by tuberculous inflammation of the vessel wall. Bronchial arteries supplying the walls of a cavity can also get dilated and form another source of bleeding.

Haemoptysis in patients with inactive disease can occur because of the sequelae such as bronchiectasis, broncholith or a cavernolith. An open healed cavity may be colonized by fungus, leading to the formation of mycetomas. Aspergilloma is not an uncommon condition seen in old tuberculosis cavities and is associated with haemoptysis. Occasionally, an aspergilloma can be diagnosed on endoscopic examination (26,27). Haemoptysis in such a patient can be massive leading to death. Haemoptysis is also common in patients with tracheo-bronchial lesions such as endobronchial tuberculosis.

Chest pain is usually pleuritic in nature. Sudden and severe pain may occur in spontaneous pneumothorax. Hoarseness of voice is associated with laryngeal tuberculosis. If there is extensive disease, shortness of breath can also occur. Endobronchial disease can cause localized wheezing.

Fibrocavitary tuberculosis

Most adult patients with post primary tuberculosis present with typical features of fibrocavitary disease of the lungs with presence of pulmonary infiltrates, fibrosis and cavitation. The disease generally starts in one or both the apices and progresses to other lobes especially if treatment is delayed or inadequate. Significant lung destruction may have already occurred when the patient presents for the first time.

Symptoms of cough, expectoration and haemoptysis are present for a few weeks to months. General physical examination of a patient with chronic fibrocavitary disease shows the appearances of a classical patient traditionally described as a "consumptive"— a wasted, sick individual with contracted thorax, hollow infraclavicular fossae, prominent ribs and narrow intercostal spaces. Chest auscultation reveals the presence of bronchial breathing and fine to coarse crepitations over the site of lesion.

Acute forms of tuberculosis

Occasionally, a tubercular focus may rupture and discharge mycobacteria into either a bronchus or a vessel and cause local spread in the lungs or disseminate widely through circulation. These patients present with pneumonia or miliary tuberculosis.

Tuberculous pneumonia

Onset of symptoms is generally acute with high fever, cough, expectoration and haemoptysis. The consolidation can occasionally cavitate and appear as an abscess. Expectoration is significantly increased and haemoptysis frequent. Tuberculous pneumonia and abscess are commonly mistaken as of pyogenic bacterial origin.

A relatively subacute onset and less severe presentation may suggest tubercular aetiology. Tuberculous pneumonia is frequently patchy and bilateral. Upper lobes and apical segments of lower lobes are the more likely involved sites.

Miliary tuberculosis

Respiratory symptoms of cough, expectoration and haemoptysis are absent or minimal in miliary tuberculosis. Similarly, chest examination may also be normal. Patient will present primarily with fever and other constitutional symptoms (28). Miliary tuberculosis can also present with acute respiratory distress, shock and multi-organ failure (29,30).

Extrapulmonary organs such as liver, spleen and lymph nodes are frequently involved in classical miliary tuberculosis. Eye examination may show the presence of choroid tubercles in over 90% of children with miliary disease. It is the cryptic form which is more likely seen in adults. It is difficult to diagnose because of an apparently normal chest radiograph and negative tuberculin test. Moreover, choroid tubercles are absent and onset is insidious. A significant number are likely to show haematological abnormalities, such as anaemia, neutropenia, pancytopenia, and occasionally polycythaemia or leucoerythroblastic anaemia.

Diagnosis is suspected on chest radiograph or high resolution computed tomographic scan showing presence of diffuse mottling and miliary shadows. Pneumoconioses, bronchopneumonia, fungal infections and occasionally sarcoidosis may present with similar radiological appearances (31,32). Transbronchial lung biopsy and/or biopsy of another organ of involvement may help in the differential diagnosis (32–35).

Tuberculous pleurisy

Tuberculosis presenting as pleural effusion is seen worldwide but more so in Asian Countries (36–38). It is usually a manifestation of primary tuberculosis and occurs more commonly in children and young adults (37,38). Patient generally complains of heaviness or pain in the chest, dry cough and breathlessness with or without fever. Pain may characteristically increase on deep inspiration or coughing. Presentation is generally insidious but may be acute, simulating bacterial pneumonia. Physical signs of effusion such as diminished chest movements, impaired or dull percussion note and diminished to absent breath sounds are easily demonstrable in any effusion of more than mild degree. Pleural rub is easily appreciated in cases of mild to moderate effusion or after tapping of fluid.

Complicated and atypical presentations

Frequently, the clinical presentation of pulmonary tuberculosis is either atypical or complex due to presence of a complication or an associated disease. Complications of pulmonary tuberculosis may be classified as those occurring (1) during active disease and (2) after treatment. In both situations the clinical manifestations can either be thoracic or extrathoracic.

During active disease

Complications in the presence of active infection are attributed to either direct involvement of an extrapulmonary organ by the mycobacteria or due to an immunological insult. Some of the complications can also be caused by the antituberculosis drugs. Infarction occurring secondarily to tubercular vasculitis can occur in the lungs and other organs such as brain, liver and spleen.

Tuberculosis continues to top the list of causes of pleural effusion, pneumothorax and hydropneumothorax in India. Similarly, tuberculosis is an important cause of empyema and pyopneumothorax in this country. Endobronchial tuberculosis can be highly infectious during the acute stage.

General biochemical abnormalities such as a leukemoid reaction, raised sedimentation rate and globulin level can occur in active, especially miliary, tuberculosis. Hyponatraemia occurs due to the syndrome of inappropriate antidiuretic hormone (SIADH) in extensive disease. It may be characterized by lowered serum osmolality, and features of "water-toxicity" such as drowsiness, mental confusion and occasionally convulsions.

Raised liver enzymes can occur during an acute disease before the treatment, although drugs (rifampicin and/or isoniazid) constitute a more common cause of hepatitis, seen in 2–4% of patients on treatment. Occasionally, tubercular hepatitis and liver abscess can also occur. Almost all extrapulmonary sites such as brain and meninges, eyes, heart, bones and joints, gastrointestinal, genitourinary systems can be involved in tuberculosis.

Acute respiratory failure due to adult respiratory distress syndrome (ARDS) can occur in patients with miliary tuberculosis or occasionally in tuberculosis bronchopneumonia. Patients with ARDS present with acute onset of respiratory difficulty, hypoxia and air hunger (39,40). If not treated in time, the condition can be fatal (Figure 1a and 1b).

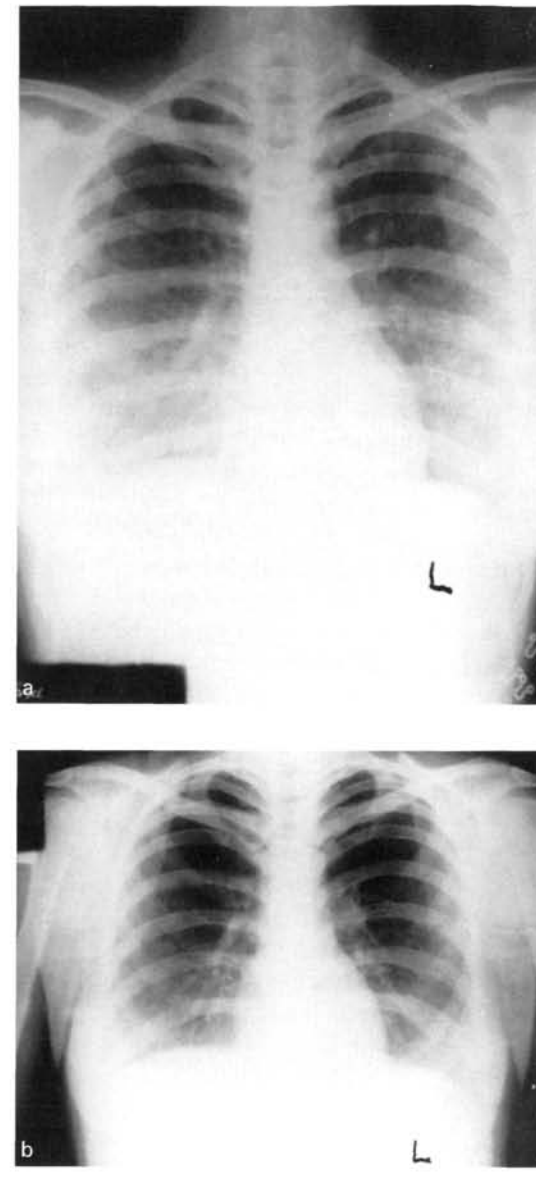


Figure 1. a) Bilateral haziness and ground glass appearances on chest roentgenogram suggesting acute lung injury seen in a young girl with severe distress and acute respiratory failure. b) Chest roentgenogram of the same patient after 72 hours of oxygenation and mechanical ventilation: showing almost clear lung fields.

Post-tuberculous complications

Most complications following completion of treatment are attributed to the residual lung damage. Chronic respiratory disability due to loss of lung tissue is the most common problem in poorly treated patients. The patient continues to complain of breathlessness and cough with or without expectoration. The damaged lung is a site for recurrent bacterial infections causing increased sputum production, fever and haemoptysis. Fungal infection can also supervene and an aspergilloma may form in a chronic, persistent cavity (Figure 2).

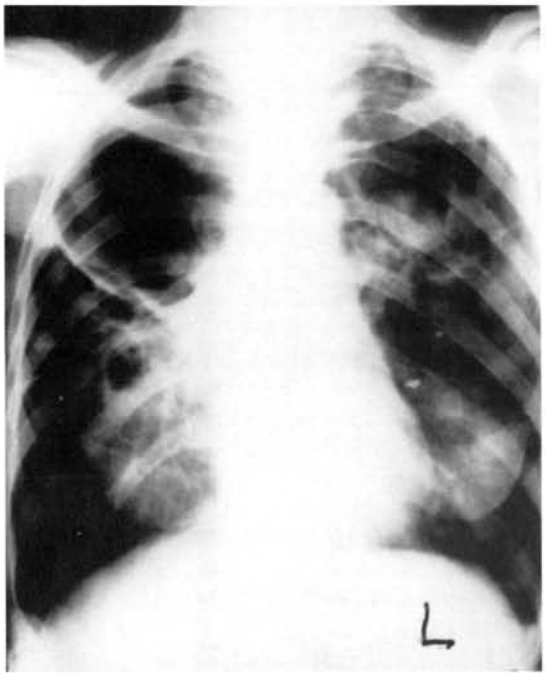


Figure 2. Aspergilloma (left) in a patient with bilateral chronic, fibrocavitary tuberculosis

Endobronchial tuberculosis can cause either bronchial stenosis or bronchiectasis. Localized stenosis of a major bronchus can cause collapse of a lobe or a segment. Bronchiectasis on the other hand, presents with massive, purulent expectoration and haemoptysis. Chronic empyema, bronchopleural fistula, pyopneumothorax and destroyed lung are other sequelae of inadequately treated pulmonary tuberculosis. Systemic amyloidosis can occur because of chronic suppuration.

Post-tuberculous fibrosis and lung destruction are also occasional causes of pulmonary hypertension and chronic cor pulmonale. Malignant transformation of an old tuberculous scar can occur, but is extremely rare (41,42).

Tuberculosis complicating other diseases

Tuberculosis is suspected as a cause of almost any clinical disorder where diagnosis is uncertain or unproven. It also complicates several other medical and surgical disorders either pathogenetically or only incidentally because of a high prevalence.

In India, it is commonly reported in patients with immunosuppression, such as HIV infection, chronic drug abuse, connective tissue orders, malignancies, organ-transplantation patients and others on chronic immunosuppressive treatment (43–46). It is also commoner in patients with diabetes mellitus, silicosis, chronic malabsorption syndrome, hepatic cirrhosis, leprosy and following gastrectomy (47–50). Clinical features in all such patients are attributed to both tuberculosis and the underlying disorders, and the picture is therefore complex.

Patients with respiratory diseases, such as bronchial asthma, bronchopulmonary aspergillosis, pneumoconiosis and other interstitial lung diseases, who require long-term corticosteroid therapy, are liable to develop tuberculosis. Diagnosis in all such patients, especially those with allergic bronchopulmonary aspergillosis, is particularly difficult because of an overlap of clinical features as well as radiographic appearances. A high degree of suspicion is therefore required for an early diagnosis and treatment.

(Tuberculosis in patients with HIV infection is discussed in Chapter 12).

Silicotuberculosis

Tuberculosis complicating silicosis is distinctly common (50–51). In India it has been reported in 18.6% of mica workers and 60% of workers in the pottery and ceramic industries (52).

Presence of the two conditions together poses difficulties in differential diagnosis. Symptoms are generally exaggerated and respiratory disability is

more severe. Both morbidity and mortality are significantly increased due to the development of progressive massive fibrosis (53).

Diabetes mellitus and tuberculosis

Tuberculosis is reported to occur 3 to 4 times more often in diabetic patients. About 6 to 20% of patients with tuberculosis are found to have diabetes mellitus in different clinical reports from India (54–56). Further, severe forms and atypical presentations of tuberculosis are more likely in diabetic patients (48).

Lower lobe tuberculosis

Tuberculosis involving one or both lower lobes in the absence of upper lobe involvement is relatively uncommon. Such presentation however, has been described from time to time (57,58). This is especially so in the elderly patients in whom the disease may present with atypical and unusual features (59,60). This is also likely in patients with diabetes mellitus or an immunosuppressive state. It is largely because of an increased number of such patients that more cases of lower lobe tuberculosis are now being recognized. For example, lower lobe tuberculosis in Japan is reported to have almost doubled in 1985–88 compared to that in 1964–66 (18). Many physicians in other Asian countries including India report similar experience.

References

1. Dubos R, Dubos S. The White Plague: *Tuberculosis, Man and Society.* New Brunswick, NJ: Rutgers University Press 1987.
2. Keers RY. Tuberculosis in antiquity. In: Pulmonary Tuberculosis — A Journey Down the Centuries. London: Bailliere Tindal 1978; 1–5.
3. Jindal SK, Bhaskar BV, Behera D. Respiratory disease pattern in a large referral hospital in India. *Lung India* 1989; 7:119–21.
4. Brandli O. The clinical presentation of tuberculosis. *Respiration* 1998; 65:97–105.
5. Miller-FJW, Seal RME, Taylor MD, et al. *Tuberculosis in Children.* London: Churchill 1963.
6. Maniar BM. Cavitating pulmonary tuberculosis below age of 2 years. *Ind Paediatr* 1994; 31:181–90.
7. Lincoln EM, Gilbert L, Morales SM. Chronic pulmonary tuberculosis in individuals with known previous primary tuberculosis. *Dis Chest* 1960; 38:473.
8. Alland D, Kalkut GE, Moss AR, et al. Transmission of tuberculosis in New York City: an analysis by DNA finger printing and conventional epidemiologic methods. *N Engl J Med* 1994; 330:1710.
9. Small PM, Hopewell PC, Singh SP, et al. The epidemiology of tuberculosis in San Francisco: A population based study using conventional and molecular methods. *N Engl J Med* 1994; 330:1703–9.
10. Snider DE, Blok AB. Congenital tuberculosis. *Tubercle* 1984; 65:81.
11. Chin DP, DeRiemer K, Small PM, DeLeon AP, Steinhart R, Schecter GF, et al. Differences in contributing factors to tuberculosis incidence in US born and foreign born persons. *Am J Respir Crit Care Med* 1998; 158:1797–803.
12. Johnson JL, Ellner JJ. Adult tuberculosis overview: African versus Western perspectives. *Curr Opin Pulm Med* 2000; 6:180–6.
13. Agarwal AK, Singh NY, Devi LB, Shyamkanhai KH, Singh YM, Bhattacharya SK. Clinical features and HIV progression as observed longitudinally in a cohort of injecting drug users in Manipur. *Ind J Med Res* 1998; 108:51–7.
14. Paranjpe RS, Tripathy SP, Menon PA, Mehendale SM, Khatavkar P, Joshi DR, Patil U, Gadkari DA, Rodrigues JJ. Increasing trend of HIV seroprevalence among pulmonary tuberculosis patients in Pune, India. *Ind J Med Res* 1997; 106:207–11.
15. Das K, Gupta D, Jindal SK. Sociodemographic characteristics of patients with pulmonary tuberculosis. Thesis; Postgraduate Institute of Medical Education and Research, Chandigarh, India, 2000.
16. Ormerod LP, Nunn AJ, Byfield SP, Darbyshire JH. Patterns of tuberculosis in Indian and Pakistani/Bangladeshi patients: effects of age, date of first entry and ethnic group. *Respir Med* 1991; 85:275–80.
17. Mackay AD, Cole RB. The problems of tuberculosis in the elderly. Q J Med 1984; 59:497–510.
18. Toyoda T. Studies on the changes in clinical features of tuberculosis (Japanese). *Kekkaku* 1990; 65:619–31.

19. Deshmukh MD. Clinical features of pulmonary tuberculosis. In: *Text Book of Tuberculosis.* Ed. Rao KN. Bombay: The Kothari Book Depot 1972; 155–66.
20. Haq SA, Alam MN, Hossain SM, Dhar UK, Rahim S, Rahman M, Ahmed T, Tahir M. A study of prolonged pyrexia in Dhaka. *Bangladesh Med Res Counc Bull* 1996; 22:33–42.
21. Malik SK, Deodhar SD. Poncet's disease (Tubercular rheumatism). *Tubercle* 1985; 66:152.
22. Sood R, Wali JP, Handa R. Poncet's disease in a north Indian hospital. *Tropical Doctor* 1990; 29:33–6.
23. Dongrey LR, Bhatia JL. Symptomatology. In: *Text Book of Tuberculosis.* Ed. Rao KN. India: The Tuberculosis Association of India 1981; 181–191.
24. Korzeniewska-Kosela M, Krysl J, Muller N, Black W, Allen E, Fitzgerald JM. Tuberculosis in young adults and the elderly. *Chest* 1994; 106:28–32.
25. Plessinger VA, Jolly PN. Rasmussen's aneurysms and fatal haemorrhage in pulmonary tuberculosis. *Am Rev Tuber* 1949; 60:589–603.
26. Guleria R, Gupta D, Jindal SK. Treatment of pulmonary aspergilloma by endoscopic intracavitary instillation of ketoconazole. *Chest* 1993; 103:1301–2.
27. Rohatgi PK, Chasse RT. Endoscopic visualization of aspergilloma. *Respiration* 1991; 58:112–4.
28. Sharma SK, Mohan A, Prasad KL, Gupta AK, Khilnani GC. Clinical profile, laboratory characteristics and outcome in miliary tuberculosis. *Quart J Med* 1995; 88:29–37.
29. Vijayan VK. Disseminated tuberculosis. *J Ind Med Ass* 2000; 98:107–9.
30. Sydow M, Schauer A, Crozier JA, Burchardi H. Multiple organ failure in generalized disseminated tuberculosis. *Respir Med* 1992; 86:517–9.
31. Gupta D, Kumar S, Jindal SK. Bilateral miliary mottling without hilar lymphadenopathy: a rare presentation of sarcoidosis. *Lung India* 1996; 14:87–8.
32. Tong P, Tan WC, Pang M. Sporadic disseminated histoplasmosis simulating miliary tuberculosis. *Br Med J* 1983; 28:822–3.
33. Burk JR, Viroslaw J, Bynum LJ. Miliary tuberculosis diagnosed by fiberoptic bronchoscopy and transbronchial biopsy. *Tubercle* 1978; 59:107–9.
34. Gupta D, Behera D, Joshi K, Jindal SK. Role of fiberoptic bronchoscopy (transbronchial lung biopsy) in diagnosis of parenchymatous lung diseases. *J Ass Phy India* 1997; 45:371–3.
35. Jindal SK, Behera D, Dhand R, Kashyap S, Malik SK. Flexible fiberoptic bronchoscopy in clinical practice — a review of 1000 procedures. *Ind J Chest Dis Allied Sci* 1985; 27:153–8.
36. Al-Alusi F. Pleural effusions in Iraq: A prospective study of 100 cases. *Thorax* 1986; 41:492–3.
37. Aggarwal AN, Gupta D, Jindal SK. Diagnosis of tuberculous pleural effusion. *Ind J Chest Dis Allied Sci* 1999; 41:89–100.
38. Shah A. Tuberculous pleural effusion: a diagnostic problem. *Ind J Chest Dis Allied Sci* 1992; 34:115–6.
39. Liam CK, Lim KH, Wong CM. Tuberculous pleurisy as a manifestation of primary and reactivation disease in a region with a high prevalence of tuberculosis. *Int J Tuberc Lung Dis* 1999; 3:816–22.
40. Mohan A, Sharma SK, Pande JN. Acute respiratory distress syndrome in miliary tuberculosis: a twelve year experience. *Ind J Chest Dis Allied Sci* 1996; 38:157–62.
41. Auerbach O, Garfinkel L. Scar cancer of the lung. *Cancer* 1979; 43:636–42.
42. Jindal SK, Malik SK, Bedi RS, Gupta SK. Risk of lung cancer in patients with old tuberculosis. *Lung India* 1986; 4:59–61.
43. Arora VK, Kumar SV. Pattern of opportunistic pulmonary infections in HIV seropositive subjects: observations from Pondicherry, India. *Ind J Chest Dis Allied Sci* 1999; 41:135–44.
44. Kumar RR, Shafiulla M, Sridhar H. Association of tuberculosis with malignancy at KIMIO — an oncology centre. *Ind J Pathol Microbiol* 1999; 42:339–43.
45. Advani SH, Banavali SD. Pattern of infection in haematologic malignancies: an Indian experience. *Rev Infect Dis* 1989; 11:S1621–8.
46. Jindal SK, Behera D. Clinical spectrum of primary lung cancer— review of Chandigarh experience of 10 years. *Lung India* 1990; 8:94–8.
47. Singh M, Kaur S, Kumar B, Kaur I, Sharma VK. The associated diseases with leprosy. *Ind J Lepr* 1987; 59:315–21.
48. Morris JT, Seaworth BJ, McAllister CK. Pulmonary tuberculosis in diabetes. *Chest* 1992; 102:539–41.
49. Snider DE. Tuberculosis and gastrectomy. *Chest* 1985; 87:414–5.

50. Jindal SK, Whig J. Silicosis in developing countries. In: *Occupational Lung Disease — An International Perspective.* Eds. Banks DE and Parker JE. London, Chapman and Hall Medical 1998; 213–8.
51. Ng TP, Trin TW, O'Kelly FJ, Chan SL. A survey of the respiratory health of silica exposed gem stone workers in Hong Kong. *Am Rev Respir Dis* 1987; 135:1249–54.
52. Kashyap SK. Occupational pneumoconiosis and tuberculosis. *Ind J Tuberc* 1994; 41:73–6.
53. Ng TP, Chan SL. Factors associated with massive fibrosis in silicosis. *Thorax* 1991; 46:229–32.
54. Deshmukh PA, Shaw T. Pulmonary tuberculosis and diabetes mellitus. *Ind J Tuberc* 1984; 31:114–7.
55. Tripathy SR, Kar KP, Chakraborty DC, Mazumdar AK. Diabetes mellitus and pulmonary tuberculosis — a prospective study. *Ind J Tuberc* 1984; 31:122–5.
56. Research Committee of Tuberculosis Association of India. Prevalence of diabetes mellitus amongst patients of pulmonary tuberculosis. *Ind J Tuberc* 1987; 34:91–5.
57. Chang SC, Lee PY, Perng RP. Lower lung field tuberculosis. *Chest* 1987; 91:230–2.
58. Ravindran P, Joshi M, Sundaram P, Jose Raj R, Parameswaran K. Lower lung field tuberculosis. *Ind J Tuberc* 1992; 39:29–31.
59. Alvarez S, Shell C, Berk SL. Pulmonary tuberculosis in elderly men. *Am J Med* 1987; 82:602–6.
60. Ip MS, So SY, Lam WK, Mok CK. Endobronchial tuberculosis revisited. *Chest* 1986; 89:727–30.

17 Tuberculosis: Diagnosis and Drug Treatment

Wing Wai Yew

Diagnosis of Pulmonary Tuberculosis

A high index of suspicion of tuberculosis must be maintained by all clinicians taking care of patients with pulmonary disease in Asia. This would enable early diagnosis and treatment, as well as prompt initiation of public health measures for this communicable disease. Children, elderly and HIV-infected patients especially constitute groups for concern since they may present with atypical clinical and/or radiographic features. Chest radiography and sputum bacteriology are still the key investigations for diagnosing pulmonary tuberculosis. Other investigations are available to complement these time-honoured tools when required.

Clinical presentation of tuberculosis

Primary pulmonary tuberculosis

The majority of cases of primary infection are asymptomatic. Fever and malaise can be non-specific features. Clinical symptoms and signs are usually those pertinent to the complications of progressive primary tuberculosis. These generally include consolidation/collapse, obstructive emphysema, bronchiectasis, and pleural effusion. Other associated phenomena such as erythema nodosum and phlyctenular conjunctivitis can occur.

Miliary tuberculosis

Miliary tuberculosis results from widespread haematogenous dissemination of *Mycobacterium tuberculosis* from a lung focus. This usually occurs following primary infection in a small group of susceptible individuals. The onset in the young adult or child is usually more acute. General symptoms are fever, malaise, weight loss, dry cough and dyspnoea. A pathognomonic sign is the choroidal tubercle found on funduscopic examination. Hepatosplenomegaly and involvement of meninges can occur.

Post-primary pulmonary tuberculosis

The course of post-primary pulmonary tuberculosis varies widely. At one extreme, the patients can have marked clinical symptoms and poor general health. At the other, the patients can have mild symptoms and chronic ill health. A small proportion of patients can even develop sufficient immunity to "cure" the disease. The early stage of the disease can be asymptomatic. Later on, insidious general symptoms occur, namely malaise, weight loss, fever and night sweats. Cough and sputum are usually the most common respiratory symptoms followed by haemoptysis. Other specific symptoms and signs are often related to disease complications. These include pleural effusion, tuberculous empyema, tuberculous laryngitis and tuberculous endobronchitis. Thus, the patient may present with symptoms like dyspnoea, wheezing, chest pain, and dysphonia.

Progressive tuberculosis in organs

This refers especially to lymph nodes, urogenital tract, meninges, bone and gut. The mode of spread is largely by lympho-haematogenous route. The clinical features can be palpable neck masses, haematuria, dysuria, headache, neurological deficit, abdominal pain, malabsorption, pain and deformity of spine.

Cryptic tuberculosis

This is a form of haematogenous disseminated tuberculosis without typical radiographic findings, usually occurring in the elderly. The symptoms are insidious and comprise weight loss, lethargy and intermittent fever. Meningeal involvement is rare. Involvement of bone marrow resulting in pancytopenia or a leukaemoid picture can occur. This condition is often difficult to diagnose.

Chest radiography in pulmonary tuberculosis

The typical features of primary pulmonary tuberculosis comprise infiltrate/consolidation in the middle or lower lobes associated with ipsilateral hilar or paratracheal lymphadenopathy. Atelectasis or obstructive emphysema can occur in the involved lobes. Miliary tuberculosis is denoted by the presence of micronodular opacities, each being usually 1–2 mm in diameter throughout both lung fields. For post-primary pulmonary tuberculosis, the upper lobes and apical segment of lower lobes are the usually involved sites. Cavities may be present. Patchy pneumonic shadows may result from bronchogenic spread, while haematogenous spread gives rise to a micronodular pattern. Endobronchial tuberculosis can lead to obstructive emphysema or collapse of the whole lung or its lobes.

Other investigations for diagnosing pulmonary tuberculosis

Smear microscopy

The detection of acid-fast bacilli (AFB) in stained sputum smear (Ziehl-Neelsen and fluorochrome methods) microscopically provides the first bacteriological evidence of mycobacteria present in the clinical specimen most commonly the sputum. Fluorochrome staining has the advantage of being more sensitive, but it can give rise to false-positive results rarely when blood is present in the specimen. It is estimated that 5,000 to 10,000 organisms per ml is required for producing a positive result on direct microscopy (1). Despite its low sensitivity of about 50% (2), a positive smear for AFB is relatively specific for *M. tuberculosis* (3,4), especially in Asia where the prevalence of tuberculosis is still much higher than the other pulmonary mycobacterioses. A positive smear generally identifies an infectious case of tuberculosis, notwithstanding the caveat of inability of the stains to discriminate the viable from nonviable organisms (3). The first diagnostic upgrade that most mycobacteriology laboratory should implement is correctly performed smear microscopy (4). This includes maintenance of microscopes, training for technicians, and the overall laboratory quality control. Other measures such as enhanced centrifugation and use of a Zwitterion detergent (4) can potentially improve the sensitivity of direct microscopy.

Incremental cost-effectiveness analysis of three consecutive sputum examination in the diagnosis of smear-positive pulmonary tuberculosis has shown that the yields of first, second and third smears are 77.1%, 15%, and 7.9% respectively (5). Thus a policy of examining two samples should be considered in resource-poor settings. Repeated sputum smear examination was also shown to produce a high cumulative yield in HIV-associated tuberculosis (6). Sputum induction has been shown to improve the chance of recovery of mycobacteria on direct microscopy (7). Management algorithms based on clinical symptoms, response to antibiotic trials, smear investigations, and chest radiography have been developed for smear-negative pulmonary tuberculosis, and these have become increasingly important in the context of HIV-associated tuberculosis (8).

Culture

In general, a much lower bacillary load in the specimen is required to produce a positive culture result, i.e. 10–100 organisms (9). The sensitivity of culture is about 70% and the specificity is about 100% (7,10). Three different types of traditional

culture media (two solid and one liquid) are available, being egg based (Lowenstein-Jensen), agar based (Middlebrook 7H10/7H11) and broth (Middlebrook 7H12 and others) in nature (3). The growth of mycocbacteria tends to be better on the egg-based medium, but faster on the agar medium. Growth in liquid media is more rapid than on solid media. There are currently several available commercial broth systems for mycobacterial growth detection. The radiometric technique is gradually being supplanted by non-radiometric ones. The former principally involves the BACTEC 460 system and the latter mainly include BACTEC 9000MB system, Mycobacterial Growth Indicator Tube (MGIT) system, extra sensing power (ESP) Myco-ESP culture system, and BacT/ALERT MB system. Liquid systems allow for more rapid detection of mycobacterial growth within 1–3 weeks compared with solid media where growth usually requires 3–8 weeks (11–17). The agar media possess the advantage of enabling the identification of colony morphology and detection of mixed mycobacterial growth, but the sensitivities are slightly lower than those of the liquid media.

Although these commercial rapid culture systems offer an attractive enhancement (probably not replacement) for culture on Lowenstein-Jensen or other solid media, the cost of these commercial systems is still currently too high for routine use in many communities (4).

Biochemical methods can distinguish mycobacterial species, but are time-consuming and laborious. Two other identification procedures are widely used — nucleic acid hybridization using molecular probes and high performance liquid chromatography (3). The former is only largely restricted to *M. tuberculosis* complex, *M. kansasii*, *M. avium* complex and *M. gordonae*.

Nuclei acid amplification

There are currently 2 commercially available and well-validated nucleic acid amplification systems (NAA) for rapid diagnosis of tuberculosis (18). These are (1) Gen-Probe MTD (*Mycobacterium tuberculosis* direct test) (Gen-Probe Incorporated) and (2) Amplicor *Mycobacterium tuberculosis* test (Roche Diagnostics Systems Incorporated). Both of these have been approved by the Food and Drug Administration (FDA) in the United States of America for clinical use in respiratory specimens.

According to FDA and other data, the sensitivity of the tests for tuberculosis (compared with culture) is approximately 95% in patients with positive smear but only about 50–70% in smear negative patients (19).

The Centers for Disease Control and Prevention (CDC) in the United States now recommends that AFB smear and NAA be performed on the first sputum specimen collected (20). If both smear and NAA are positive, the diagnosis of tuberculosis is almost certain. If the smear is positive and NAA is negative, the authority recommends testing the sputum for inhibitors. If inhibitors are not detected, and the repeated smear and NAA results are consistent, the patient presumably has non-tuberculous mycobacteria. If the smear is negative but NAA positive, CDC recommends sending further sputum samples. If positive, the patient can be presumed to have tuberculosis. If both smear and NAA are negative, an additional specimen should be tested by NAA. If negative, the patient can be presumed to be not having infectious tuberculosis. The recommending statement (20) finally concludes by noting that clinicians must always rely on clinical judgment, and that ultimately definitive diagnosis rests on response to therapy and culture results.

As for the appropriate use of NAA for rapid diagnosis of tuberculosis, one rather logical suggested approach is depicted as follows (21). NAA should be used to confirm that a positive AFB smear does represent *M. tuberculosis*. If sputum smears are negative, but clinical suspicion is strong, NAA should be done on a sputum sample, either expectorated or induced. Even with a sensitivity of about 50%, the added value in diagnosing a sizeable proportion of smear-negative cases is obvious. NAA should not be performed in sputum samples from cases in which the clinical suspicion is low and the AFB smear is negative. Given the significant cost of NAA assay in most laboratories, it might be pertinent to consider its applicability in resource-compromised settings. However, if these are only provided at centralised laboratories with high specimen throughput, then these tests may in fact be economically feasible and clinically useful (22). It would be relevant to acquire more widespread experience on the cost-effectiveness of NAA assay in Asian countries and communities.

Serology

The use of antibody detection in the diagnosis of tuberculosis is of interest and importance particularly in selected patient populations such as children (23). While the quest for a rapid, sensitive, and accurate serological test appears relevant for HIV-infected patients, the anticipated results are unlikely to be promising. Humoral response to new antigens is poor in HIV-infected persons, and a substantial proportion of HIV-attributable tuberculosis arise as a result of exogenous infection rather than reactivation. Furthermore, false positivity may occur from anamnestic responses seen as a result of polyclonal B-cell stimulation seen in the HIV setting.

So far, a number of mycobacterial antigens or epitopes have been identified for use. Some examples include Antigen 60, Antigen 5, Kp90 antigen, 38 Kda antigen, and lipoarabinomannan (24–28). However, the sensitivities and specificities are often ≤80%. As antibody detection appears not to live up to expectation in most studies in the clinical settings, serological tests cannot be generally recommended for rapid diagnosis of tuberculosis. In the event that serological assays have a high negative predictive value, the tests are more useful as a screening test to rule out tuberculosis rather than confirming the presence of disease (29). In HIV-positive individuals, low sensitivities and poor negative predictive values are often encountered, thus compromising the utility of these tests in the HIV settings. The diagnostic values of serological tests theoretically depend on the context of their use (27). While a negative result would be useful in excluding disease in a population with a low prevalence of tuberculosis, a positive result could potentially aid clinical decision making when tested on a group of selected symptomatic patients when there is a moderate to high clinical suspicion of tuberculosis. Much more work needs to be done in the development and evaluation of relevant diagnostic tests in this area.

Histology

Fibreoptic bronchoscopy can be utilized for the rapid diagnosis of smear-negative pulmonary tuberculosis by assessment of direct smear of bronchial aspirate and/or brush, direct smear of postbronchoscopy sputum, and histological and bacteriological examination of tissue obtained by bronchial and transbronchial biopsies. The diagnostic sensitivities of these 3 techniques ranged from 10–67%, 10–73% and 30–58% respectively (30–34). Exclusive diagnosis by tissue examination via fibreoptic bronchoscopy could be achieved in 12–26% of cases (32,33). The yield of fibreoptic bronchoscopy in diagnosis of tuberculosis can be enhanced by performing NAA in the bronchoalveolar lavage fluid (35,36). However, some studies have shown that examination of induced sputum by direct microscopy produced similar sensitivity to fibreoptic bronchoscopy, and thus could considerably simplify the diagnostic approach especially for HIV-positive subjects (37,38). Percutaneous transthoracic needle biopsy is a useful invasive investigational method complementary to the fibreoptic bronchoscopy for diagnosis of pulmonary tuberculosis. It can give a sensitivity of about 50% from histological and direct bacteriological examination of tissue specimen (39,40). It also provided the exclusive means for diagnosing pulmonary tuberculosis in 43% of cases in one report (39). The diagnostic yields of direct microscopy and culture of pleural fluid in tuberculous pleurisy are generally unsatisfactory. In one study, the sensitivities were 1.4% and 16.2% respectively (41). This is in great contradistinction to the much more favourable diagnostic yields of histological examination of tissue obtained from closed pleural biopsy: 55–80% (41–43). Combination of histology and culture of pleural biopsy can give a sensitivity of 90% (43,44), but prolongs the turnaround time as compared with pleural biopsy alone. The use of markers such as adenosine deaminase and cytokines might help in the rapid diagnosis of tuberculous pleural effusion (45,46), but studies on the utility of polymerase chain reaction in the rapid diagnosis of this condition have often yielded discordant results (47,48). Combination of the markers and NAA may be beneficial for the differential diagnosis of pleural tuberculosis (49). Judicious use of lymph node aspiration and early lymph node or pleural biopsy can streamline the diagnosis of HIV-associated tuberculosis (6).

Tuberculin test

Tuberculin skin testing (TST) is a means of detecting infection with *M. tuberculosis* and may

be the only positive test in subjects where infection has not progressed to clinical disease. The immunological basis is a delayed hypersensitivity reaction to intracutaneously injected tuberculin. PPD-RT23 is the most widely used tuberculin in the world including the Asia Pacific region (50). Two tuberculin units of PPD-RT23 has been shown to be bioequivalent to 5 TU of PPD-S, the international tuberculin standard designated by the WHO (51). The Mantoux test refers to the administration of 0.1 ml PPD intradermally on the volar aspect of the forearm and the transverse diameter of induration produced is read between 48 to 72 hours (52). Other methods like the multiple puncture techniques are generally less reliable. A positive result can, however, be due to active tuberculosis disease, inactive tuberculosis disease, latent tuberculosis infection, nontuberculous mycobacterial infection, or even Bacille Calmette-Guerin (BCG) vaccination. Hence, in communities where there is a wide coverage of BCG vaccination, or a high prevalence of nontuberculous mycobacterial infection among the general population, interpretation of TST is often difficult. TST reaction due to BCG usually wanes with time and a strong reaction is more likely due to tuberculosis infection rather than BCG or nontuberculous mycobacterial infection (53). False negative results can occur from malnutrition, immunosuppression, viral infection or recent vaccination with live attenuated virus. Conversion from a negative to a positive TST is indicative of recent tuberculosis infection, but this should be distinguished from the "boosting effect" presumably due to immunological recall, and a two-step test may be required (54). Specific tests of *in vitro* immune-based diagnosis of tuberculosis are currently under development and will be evaluated to supplement the TST to improve its specificity (55). These tests largely involve interferon-gamma release assays.

Drug susceptibility testing in pulmonary tuberculosis

The definite proof of drug-resistant tuberculosis can only be furnished by drug susceptibility testing of sputum or other respiratory materials. Recently, some authorities have recommended performance of drug susceptibility tests for all cases of active tuberculosis based on rising drug resistance globally (56). Others still favour the use of drug susceptibility testing largely for surveillance of the level of drug resistance in the community, reserving the use of testing in selected clinical settings. There are 3 basic methods (56) for assessing drug resistance conventionally on solid media, commonly the Lowenstein-Jensen medium or the Middlebrook agar. These are the (1) absolute-concentration (minimum-inhibitory-concentration), (2) resistance-ratio, and (3) proportion methods. Both the absolute-concentration and resistance-ratio methods require strict standardization of inoculum, and therefore are less reproducible, leaving the proportion method as the more popular one (56). The proportion method utilizing the Middlebrook 7H10 /7H11 agar plates also provides the important opportunity of performing the direct test wherein the sputum specimen after processing is directly inoculated onto drug-containing media (56) with resultant economy of time (21 days in total). However, the direct test can only be performed with smear-positive specimens only. A variant of the proportion method that utilizes the BACTEC radiometric liquid medium (Becton-Dickinson Diagnostic Instrument System) (56) provides a rapid way for assessing drug resistance (10–21 days instead of 42 days required when using the solid agar). Newer liquid media systems under evaluation for drug susceptibility testing include Mycobacteria Growth Indicator Tube (MGIT, Becton-Dickinson Diagnostic Instrument Systems), MB/BacT system (Organon Teknika), and ESP Myco System (Difco-Accu Med International) (56). In these 3 non-radiometric systems, mycobacterial growth detection is based either on the release of carbon dioxide or on oxygen consumption. At the moment the MGIT has the shortest turnaround time among all these: 5–11 days. These 3 systems are rather comparable in performance (57–59). New technologies aim to improve over existing drug susceptibility testing by further cutting the turnaround time. These can be broadly classified into phenotypic and genotypic techniques (56). Phenotypic technologies attempt to use novel indicators that provide information on mycobacterial physiology more rapidly than existing ones. One important example is the phage

system. Mycobacteriophage-based methods include the luciferase reporter phage (60) and the PhaB test (61). Another rapid and inexpensive phenotypic technique for assessing drug susceptibilities was found to rely on a nitrate reductase assay (62) and might be suitable for use in developing countries with high drug resistance rates. Genotypic approaches target at detecting the genetic determinants of drug resistance directly (56). The first step in genotypic analysis is the amplification of mycobacterial DNA containing the genes of interest, largely by polymerase chain reaction. The second step in genotypic testing is the assessment of the amplification products for genetic markers of drug resistance. The most important ones currently are the rpoB genes in which mutations are linked with rifampicin resistance (63,64). The line probe assay, representing a relatively straightforward amplification and reverse hybridization technique, has been available as a commercial kit for several years. Good correlation of this assay with standard drug susceptibility testing in clinical isolates have suggested a wide applicability (65) though it may be too expensive for use in resource-compromised settings. With unraveling of the genome of *M. tuberculosis* before the turn of the century, it now becomes possible to construct DNA microarrays (66) for mapping quickly the DNA sequence of genes that confer drug resistance enabling their more efficient detection.

Aside from focusing on drug susceptibility testing of the conventional or first-line drugs to discover drug-resistant tuberculosis, accurate laboratory susceptibility testing results of second-line drugs will support clinical decision making and guide management of multidrug-resistant tuberculosis. To ensure realization of such goals, only laboratories with experience and well-documented competency in performing first-line drug testing should consider offering testing for second-line drugs. Guidelines for the second-line drug testing have been officially published (67).

Future challenges in diagnosis of tuberculosis

Continuing progress in technology is required to refine and improve the current performance of new diagnostic methods in tuberculosis. Furthermore, it would be of great importance to find out how these new technologies can be used most appropriately. Thus research is needed to enable development of algorithms and protocols optimizing the use of the new diagnostics. The whole process is a lengthy one and must involve stringent evaluation at many junctures. Finally, it should always be borne in mind that exuberant advances in technology cannot replace quality control in the mycobacteriology laboratory and care in the hospital/clinic. In connection with the former, set up of central reference laboratories is both relevant and desirable for many countries or communities in Asia with high prevalences of the disease.

Treatment of Pulmonary Tuberculosis

Background of antituberculosis chemotherapy

Chemotherapy for tuberculosis started only after the discovery of streptomycin in 1944. Sputum bacteriology, clinical and radiographic improvement occurred after 2–3 months of treatment. These good responses were, however, short-lasting and subsequently resistance to streptomycin developed after the monotherapy, with resultant disease deterioration (68). After some time, it was found that combined therapy of streptomycin and para-aminosalicylic acid prevented drug resistance from developing and achieved better results (69). The introduction of isoniazid as a drug in the combination regimen for treating tuberculosis formed the basis of primary chemotherapy from the 1950s to the 1970s (70). The standard regimen then comprised streptomycin, isoniazid and para-aminosalicylic acid for a few months followed by the latter two drugs up to a total period of 18 months. Para-aminosalicylic acid could be substituted by ethambutol or thiacetazone depending on their acceptability and availability in the community.

Aside from adverse drug reactions, patients often absconded treatment prematurely or took drugs irregularly, especially when they became symptom free after a few weeks to months. This

brought about treatment failure and development of drug resistance. In the early 1960s, the experience from Madras and Hong Kong, obtained from collaborative studies with British Medical Research Council, demonstrated the effectiveness and efficacy of ambulatory treatment (71). Prolonged hospitalization in sanatoria became unnecessary. Fully supervised chemotherapy, (later also known as directly observed therapy or DOT), in form of streptomycin and isoniazid given on an intermittent basis twice per week in the continuation phase after the initial few months of the alluded triple therapy was utilized. For patients who failed on this standard regimen, second-line drugs that included pyrazinamide, ethionamide and cycloserine were given for 6 months, followed by 12–18 months of combination therapy with the former two drugs. In 1965, rifampicin was discovered. In the 1970s, short-course chemotherapy primarily based on rifampicin, isoniazid and pyrazinamide was introduced for treatment of tuberculosis (72).

Aims of chemotherapy

The aims of drug treatment of tuberculosis are:

1. To cure the patients of tuberculosis, preferably with minimum interference with their lives, by the shortest duration of drug administration
2. To prevent death or late effects of tuberculosis
3. To prevent relapse of tuberculosis
4. To prevent emergence of drug resistance
5. To reduce transmission of tuberculosis to others within or outside the community

Biological characteristics of Mycobacterium tuberculosis and scientific basis of short-course chemotherapy

Mycobacterium tuberculosis, the causative organism of tuberculosis, is slow-growing and can enter into a phase of dormancy which proves to be drug-refractory. A patient with tuberculosis basically harbours four populations of organisms. The first population is the actively growing extracellular organisms which are usually present in abundance within cavities. The second population consists of slow, intermittently growing organisms in an unstable part of the lesion. The third population includes organisms surviving in a low environmental pH, which can occur in inflammatory lesions or within phagolysosomes of macrophages. The last population refers to the completely dormant organisms surviving under anaerobic condition. The 3 major actions of antituberculosis drugs (73) are:

1. bactericidal action, defined as their ability to kill actively metabolizing bacilli rapidly,
2. sterilizing action, defined as their capacity to kill the semi-dormant organisms and
3. prevention of emergence of acquired resistance.

Isoniazid is the most potent bactericidal drug. Rifampicin is also important as such. Rifampicin and pyrazinamide are the most important drugs for sterilizing the tuberculous lesions and preventing disease relapse. Resistance to an antituberculosis drug is due to spontaneous chromosomal mutation at a frequency of 10^{6} to 10^{8} bacterial replications (74). Because mutations resulting in drug resistance are unlinked, the probability of resistance to 3 drugs used simultaneously becomes 10^{18} to 10^{20} (75). Thus, the chance of drug resistance is practically nil when 3 effective drugs are used in combination for treatment of tuberculosis. Among the first-line antituberculosis drugs, isoniazid and rifampicin are most effective in preventing the emergence of acquired resistance (73). Streptomycin, ethambutol and pyrazinamide are less so. Thiacetazone and para-aminosalicylic acid are the least effective.

Treatment of smear-positive pulmonary tuberculosis

In the past few decades, a number of effective drug regimens have been found, largely through clinical trials, for treating patients with newly diagnosed smear-positive pulmonary tuberculosis. These regimens are summarized in Table 1 (76–83). Most regimens are given for 6 months, this being the shortest duration of treatment required. Regimens that do not contain pyrazinamide in the initial intensive phase must be given for longer

Table 1. Drug Regimens for Treatment of New Cases of Smear-Positive Pulmonary Tuberculosis

	Reference
Standard 6-month regimens	
2 EHRZ/4 HR	(76)
2 SHRZ/4 HR	
Standard 6-month regimens when directly observed, intermittent chemotherapy can be organized	
2 EHRZ/4 H_3R_3	
2 SHRZ/4 H_3R_3	(77)
2 $E_3H_3R_3Z_3$/4 H_3R_3	
2 $S_3H_3R_3Z_3$/4 H_3R_3	(78) (79)
Alternative less active regimens of longer durations	
With a highly active initial 4-drug phase	
2 SHRZ/6 HT	(80)
2 EHRZ/6 HT	
2 SHRZ/6 HE	
2 EHRZ/6 HE	
2 SHRZ/6 $S_2H_2Z_2$	(81)
With a less active or no initial phase	
2 SHR/7 HR	
2 EHR/7 HR	(82)
9 HR	(83)

S = Streptomycin; E = Ethambutol; H = Isoniazid
R = Rifampicin; Z = Pyrazinamide; T = Thiacetazone
X = Daily; X_3 = Thrice per week; X_2 = Twice per week

than 6 months. The relapse rates during 6–30 months after stopping treatment are generally < 5%. In countries or communities with a high level of initial resistance to isoniazid (≥ 4%) (83), as in most Asian countries, a 4-drug regimen followed by 2 drugs is advisable. This is currently the standard regimen recommended by the World Health Organization and International Union Against Tuberculosis and Lung Disease (WHO/IUATLD) (84). The administration of pyrazinamide beyond 2 months has not been shown to be of advantage (85,86). However, for individual cases with extensive disease and slow sputum bacteriological conversion, prolongation of the administration of pyrazinamide ± streptomycin/ethambutol beyond 2 months can be practiced, and so is prolongation of the total duration of treatment (83). The 8-month regimen 2SHRZ/6HT or 6HE combined with hospitalization in the first 2 months has been proven to be effective in controlled clinical trials and programme settings in Africa (80). In confirmed or suspected HIV-infected patients, ethambutol should be used in place of thiacetazone in light of severe reaction, especially cutaneous, to the latter drug. There is indication that thiacetazone should be dropped from the antituberculosis regimens in the developing countries, many of which are experiencing rising HIV infection rates. Regimens based almost entirely on isoniazid and rifampicin are only good for pan-susceptible tuberculosis and has to be given for 9 months (namely 2HRE/7HR or 9HR). These regimens are not usually applicable for use in Asian countries except in patients who cannot tolerate pyrazinamide. Intermittent regimens comprising 2 drugs in the continuation phase following upon an intensive phase of 4 drugs given daily have been proven to be highly effective (SHRZ/H_3R_3 or SHRZ/H_2R_2) (83). The WHO however does not generally recommend twice weekly regimens because of the higher risk of treatment failure when missing doses occur (84). Lately, data from China (including Hong Kong) on $2S_3H_3R_3Z_3/4H_3R_3$ also shows high efficacy in

both study and programme settings (78,79). The advantages of intermittent short-course regimens include lower cost, possibly lower drug toxicity and greater feasibility for ambulatory administration under supervised settings, while the efficacy is equivalent to daily regimens.

For treatment of smear-positive relapse cases of pulmonary tuberculosis as well as retreatment after interruption, a 8-month regimen has been recommended by the WHO/IUATLD, namely 2SHRZE/1HRZE/5HRE or $5H_3R_3E_3$ (84). Bacillary drug susceptibilities *in vitro* can help to guide modification of this regimen as required.

The use of fixed dose drug combination (FDC) comprising 2–3 and even 4 drugs can enhance ease of prescription for physicians and treatment adherence by patients (87). When used properly, FDC tablets should decrease the risk of development of multidrug-resistant tuberculosis caused by bacilli resistant to at least isoniazid and rifampicin *in vitro* (88). While FDC by self-administered therapy can constitute an alternative to DOT when the latter cannot be practised, the delivery of DOT using FDC should be recommended as there is still a theoretical risk of emergence of drug resistance when these FDC are taken irregularly (89). The main concern in using FDC is the quality and bioavailability of its component drugs, particularly rifampicin (90). In 1994, the IUATLD and WHO issued a joint statement advising that only FDC of proven good quality should be used in treatment of tuberculosis (91).

Another important new drug development among the rifamycins is in the discovery of rifapentine, a long-acting cyclopentyl rifamycin which is currently being evaluated for use together with isoniazid on a once-weekly basis in the continuation phase of treatment of smear-positive pulmonary tuberculosis after the initial 2-month intensive phase. The preliminary results are somewhat encouraging although delineation of the optimal dosage is still required (79,92). The distinct advantage of this once-weekly regimen is facilitation of DOT and thus enhancing patient adherence to therapy.

Directly observed therapy, short-course

Drug-resistant tuberculosis usually results from poor patient adherence and other aspects in failure of implementation of an effectively functioning tuberculosis control programme (93). The CDC in the United States estimates that 25% of patients fail to complete their designated chemotherapy. Although some patient characteristics like homelessness, alcohol or substance abuse, behavioural problems, mental retardation, and lack of social or family support are more commonly associated with non-adherence to therapy, it is generally held difficult to identify poorly adherent patients because the underlying reasons for such behaviour are not only multifaceted and complex, but range from characteristics of the individual patients to qualities of the societal and economic environment (94). DOT was in fact shown to be highly efficacious in ensuring patient adherence by experience gained in Madras and Hong Kong many decades ago. In order to facilitate the delivery of DOT, other concomitant strategic interventions must be incorporated. Short-course chemotherapy has been shown to be the most important component. In 1993, the WHO officially announced the new global control strategy for tuberculosis known as Directly Observed Therapy, Short-course (DOTS) (95). The DOTS strategy is certainly more than DOT alone. The 5 key components include (96):

1. a network of trained healthcare or community workers to administer DOT,
2. properly equipped laboratories with personnels trained to perform sputum microscopy diagnosis for tuberculosis,
3. a reliable supply of high-quality drugs (preferably at no cost to patients),
4. an accurate record-keeping and cohort analysis system for monitoring case findings, treatment and outcomes, and
5. sustained political commitment and funding.

To reiterate, the DOTS strategy should be viewed as a comprehensive service, or an integral part thereof, which possesses ingredients also inclusive of enablers, incentives, education and holistic care that are conducive to the success of the treatment programme.

Treatment of mono-resistant pulmonary tuberculosis

For patients who are subsequently known to have organisms resistant to streptomycin, there would obviously be no unfavourable sequelae using the first-line regimens just described for initial treatment. For patients with isoniazid-resistant tuberculosis, one of the following possible approaches can be adopted. Firstly, continuation of rifampicin, ethambutol and pyrazinamide for another 10 months or rifampicin plus ethambutol for 12 months after having administered rifampicin, isoniazid, ethambutol and pyrazinamide for 2 months before drug susceptibilities are known (97,98). Secondly, no modification of the initially administered 4-drug regimen is made and all drugs are given for a total of 6 months (99). Reducing from 4 drugs to 2 drugs after 2 months, as for management of drug-susceptible tuberculosis is also acceptable for programme purpose, except the relapse rate is somewhat higher i.e. 10% versus 3% (86). When patients are already known to have isoniazid-resistant disease at the commencement of therapy, a 9-month regimen comprising streptomycin, rifampicin, pyrazinamide and ethambutol for 2 months, followed by rifampicin and ethambutol for 7 months, has also been shown to be effective (100). On the other hand, for patients with isolated rifampicin-resistant tuberculosis, which is rare in clinical practice, recommendation has been made to treat with isoniazid, pyrazinamide and ethambutol for 18–24 months (101).

Treatment of multidrug-resistant pulmonary tuberculosis

Multidrug-resistant tuberculosis (MDR-TB) is defined as disease caused by bacillary strains resistant to at least isoniazid and rifampicin *in vitro*. DOTS is highly effective in treating drug-susceptible tuberculosis. It can, however, only achieve a cure rate of < 50% in patients with MDR-TB. Further, the possible "amplifier effect" resulting in additional drug resistance by repeated courses of short-course chemotherapy might even endanger future attempts to treat drug-resistant tuberculosis. For established MDR-TB, effective treatment should be an alternative, specific and ideally individualized regimen. Three facts are useful in the design of the regimen. These include 1) results of prior susceptibility tests, 2) prior treatment history and 3) susceptibility patterns in the community. However, the single most important determinant in guiding the formulation of new drug regimen is the current drug susceptibility pattern of the patient's bacilli (102). Unfortunately, the methodology for assessing drug susceptibilities for many second-line agents is far from being standardized and this may account for the discrepancy in the microbiological response of the patient and the bacillary drug susceptibility tests *in vitro*. The treatment success rates of MDR-TB with drugs alone are much lower than those of drug-susceptible disease, namely 55–80% versus ≥90% (103–106). Thus, MDR-TB is a formidable clinical and health problem. Improvement of existing therapy is definitely required. Also, the cost of the reserve regimens comprising second-line and new antimycobacterial drugs is more than 100 times higher than the standard first-line short-course regimen, let alone higher hospitalization need associated with MDR-TB management. In countries with limited healthcare budget in particular, implementation or resurrection of an effective tuberculosis control programme centred on the DOTS strategy is still a more cost-effective way to prevent the development of MDR-TB and should be given top priority.

Patients diagnosed as having MDR-TB should receive a regimen comprising initially at least 4–5 second-line and new antituberculosis drugs (basing largely on results of drug susceptibility testing *in vitro*) under supervised settings. One regimen recommended by the WHO includes ethambutol, ethionamide/prothionamide, ofloxacin/ciprofloxacin, pyrazinamide and aminoglycoside — for 3 months and the first 3 drugs being administered for at least another 18 months (107). Among the drugs utilized in the multidrug regimen, the fluoroquinolones are most likely the pivotal drugs that have the major contribution to the therapeutic efficacy. Indeed, in a retrospective analysis of patients with MDR-TB in Hong Kong, who were treated with ofloxacin/levofloxacin plus similar accompanying drugs, resistance to ofloxacin *in vitro* was found to be an important independent variable significantly associated with

adverse treatment outcomes (106). Aside from efficacy *in vivo* resulting from good bactericidal and reasonable sterilizing activities, ofloxacin/ciprofloxacin also has the following favourable therapeutic characteristics, namely high peak serum concentration: MIC ratio, good tissue penetration, particularly into the lungs and good tolerance by patients during long-term administration. The last attribute is particularly beneficial therapeutically and sets some fluoroquinolones aside from most second-line antituberculosis agents. Fluoroquinolones must, however, be used with great prudence in the management of MDR-TB to prevent emergence of cross-resistance among members of this class of drugs. This cross-resistance has been reported in some communities and might have negative impact on the potential usefulness of new members of the class which have greater antimycobacterial activities (108).

The optimum duration of therapy for patients with MDR-TB is currently unknown. A number of authorities including WHO has recommended a total duration of at least 18 months after sputum smear conversion to negativity, even for human immunodeficiency virus-seronegative subjects (107). However, the retrospective study in Hong Kong alluded has suggested that some HIV-negative patients who managed to achieve sputum culture conversion early in their treatment course could be adequately treated with 12 months of the fluoroquinolone-containing regimens (106). Patients who are immunocompromised or have concomitant diabetes mellitus and silicosis, or extensive disease/drug resistance, or delayed achievement of culture negativity (> 3 months after chemotherapy) would possibly require longer duration of therapy. In formulating the optimum duration of therapy for MDR-TB, the key factors that must be considered include the number of active drugs, their bactericidal capacity, dosage, cost and toxicity as well as anticipated patient adherence. To enhance adherence, DOT is mandatory for these MDR-TB patients.

Aside from the fluoroquinolones with well-documented antimycobacterial activity, there are a number of classes of drugs which are currently under intensive evaluation for their antituberculosis activity. Among the rifamycins, rifabutin has not been shown to have unequivocal clinical efficacy in the MDR-TB setting (109,110). Rifalazil (KRM-1648), a benzoxazinorifamycin more potent than rifampicin and rifabutin but with partial cross-resistance with rifampicin (111) is currently being evaluated under phase II settings. Aminosidine (paromomycin) is an aminoglycoside structurally more related to neomycin and kanamycin rather than streptomycin. It has been shown to have activity against drug-resistant *M. tuberculosis* strains *in vitro* (112). The role of β-lactam-β-lactamase-inhibitor combinations in the treatment of MDR-TB is currently uncertain (113) and so is that of clofazimine and its analogues (114). There are insufficient data on the antimycobacterial activities of drugs such as nitroimidazoles, oxazolidinones and polaxamers (115).

Treatment of smear-negative pulmonary tuberculosis

In many countries, nearly 50% of patients are diagnosed as having active pulmonary tuberculosis on clinical and radiographic grounds, without immediate bacteriological confirmation. In the first smear-negative study in Hong Kong (116), it was subsequently found that 36% of these patients had one or more initial sputum cultures positive for *Mycobacterium tuberculosis*. When patients were observed until radiographic and/or bacteriological evidence for active disease appeared, 57% of this control group of patients required treatment within 60 months. When smear-negative, culture-positive patients were treated with 2–3 months of daily streptomycin, isoniazid, rifampicin and pyrazinamide only, relapses occurred in 32% and 13% respectively over 60 months of follow up. The corresponding relapse rates for culture-negative patients for the 2 durations of therapy were 11% and 7% respectively. In the second smear-negative study in Hong Kong (117), which again included 35% of subjects with sputum cultures initially positive for *M. tuberculosis*, all patients were treated with streptomycin, isoniazid, rifampicin and pyrazinamide, daily or 3 times per week for 3–4 months if culture was negative, and 4–6 months if culture was positive. Over 60 months, the combined relapse rate for the 4-month regimen was < 5%. There was no significant difference between the relapse rates among patients allocated 4-month and 6-month regimens.

However, the WHO recommends, in the latest guidelines, the use of 6-month regimens — daily isoniazid, rifampicin and pyrazinamide for 2 months followed by daily or 3 times per week isoniazid and rifampicin for the treatment of new smear-negative pulmonary tuberculosis (84). For patients living in countries with high levels of initial resistance to isoniazid, or having extensive radiographic disease, streptomycin or ethambutol should be added to the regimen in the initial 2 months.

Dosages and adverse reactions of antituberculosis drugs

The usual dosages of the drugs used in conventional short-course chemotherapy and therapy of MDR-TB are shown in Table 2. The important adverse reactions to these antituberculosis drugs are listed in Table 3. Although 25–60% of a large number of patients in studies reported at least one type of reaction, most of these reactions were mild and required no modification of the treatment regimen. The commonest types of reaction were gastrointestinal and cutaneous (85,86). If a serious reaction such as haematological, circulatory or renal in nature occurs after administration of rifampicin, the drug should be withdrawn and never given again. When a significant hypersensitivity (allergic) cutaneous reaction occurs, all chemotherapy must be stopped until the reaction has subsided. Re-introduction of drugs should follow the suggested protocol (Table 4). The idea of drug challenging is to identify the drug responsible for the reaction. The purpose of starting with a small challenge dose is that if reaction indeed occurs it will not be as severe as to a full dose. The dose is gradually increased over 3 days. There is no evidence that this challenge process invites the development of drug resistance. If the initial cutaneous reaction was severe, smaller initial desensitizing doses should be given (approximately one tenth of the doses shown for day 1). Desensitization is a tedious process. It can be dangerous for HIV-infected patients and therefore not recommended (84). If other effective drugs are available, it is easier to substitute another drug for the one that has caused the reaction except when the tuberculosis is severe and the incriminated drug(s) being the most potent one(s).

Treatment in special settings

Renal impairment

Some antituberculosis drugs are eliminated from the body almost exclusively by non-renal routes particularly via hepatic metabolism or biliary excretion. They can therefore be given in the usual/normal dosages to patients with renal failure. These include isoniazid (daily), rifampicin(daily), pyrazinamide (three times a week), and ethionamide/prothionamide (daily). The 2 most bactericidal drugs, namely isoniazid and rifampicin are still the safest to administer in the face of renal impairment. In severe renal failure, the dosage of isoniazid should be reduced to 200 mg once daily and pyridoxine supplementation is needed to prevent the development of peripheral neuropathy. For patients on regular haemodialysis, it has been suggested that such dosage adjustment may not be always necessary (118,119). Rifampicin has high lipid solubility, protein binding, large volume of distribution and high molecular weight and thus, not significantly removed by haemodialysis (119,120).

Streptomycin and other aminoglycosides, being heavily dependent on renal clearance, must have dosages adjusted in the presence of renal impairment (120,121). Streptomycin should be spaced intermittently to ensure that the trough level of the drug does not exceed 4 mg/l to avoid toxicity (121). For patients on haemodialysis, streptomycin can be given 6–8 hour before dialysis commences or after dialysis ceases (118,120). Ethambutol is excreted predominantly by the kidney. Dosage reduction is mandatory in the presence of renal impairment (122). In patients with creatinine clearances of 50–100 ml/min, 25 mg/kg 3 times a week should be used; for patients with creatinine clearances of 30–50 ml/min, the same dose should be given twice a week. With lower creatinine clearance (10–30 ml/min), a dosage of 15 mg/kg at 48 hours interval has been suggested (123). Patients on thrice-weekly haemodialysis may be given 15–25 mg/kg doses of ethambutol 6 hour before the procedure or after dialysis (118,120). Ethambutol clearance of 50 ml/min has been observed during

Table 2. Usual Dosages of Antituberculosis Drugs

Drug	*Daily dosage*			*Intermittent dosage*		
	Adults and children (mg/kg)	*Adults*		*Adults and children (mg/kg)*	*Adults*	
		Weight (kg)	*Dosage*		*Weight (kg)*	*Dosage*
Drugs commonly used in conventional therapy						
Isoniazid	5	–	300 mg	10 three times/week	–	–
				15 twice/week	–	–
Rifampicin	10	<50	450 mg	10–12 three times/week	–	600 mg
		≥50	600 mg	10–12 twice/week	–	600 mg
Streptomycin	12–15	<50	500–750 mg	12–15	<50	500–750 mg
		≥50	750 mg	thrice or twice/week	≥50	750 mg
Pyrazinamide	20–30	<50	1.0–1.5 g	30–40	<50	2.0 g
		≥50	1.5–2.0 g	three times/week	≥50	2.5 g
				40–60	<50	2.5–3.0 g
				twice/week	≥50	3.0–3.5 g
Ethambutol	15	–		30 three times/week	–	–
				45 twice/week		
Thiacetazone	2.5	–	150 mg	–	–	–
Rifater		per 10 kg >50 kg	1 tablet 5 tablets			
Drugs commonly used in therapy for MDR-TB						
Amikacin	15		750 mg	three to five times/week		
Kanamycin	15		750 mg			
Capreomycin	15		750 mg			
Ofloxacin			600–800 mg			
Levofloxacin			500–600 mg			
Ciprofloxacin†			750–1500 mg			
Ethionamide†	15	<50	500 mg			
Prothionamide†	(adults)	≥50	750 mg			
Cycloserine†	15	<50	500 mg			
	(adults)	≥50	750 mg			
Para-aminosalicylic acid†	2 g/10 kg		8–12 g			

Some authorities recommend higher dosages of isoniazid, rifampicin, streptomycin, and thiacetazone for children

† *May require drug administration as 2 split doses*

Table 3. Adverse Reactions to Antituberculosis Drugs

		Reactions	
Drug	*Common*	*Uncommon*	*Rare*
Drugs commonly used in conventional therapy			
Isoniazid		Hepatitis Cutaneous hypersensitivity Peripheral neuropathy	Giddiness Convulsion Optic neuritis Mental symptoms Haemolytic anaemia Aplastic anaemia Lupoid reactions Arthralgia Gynaecomastia
Rifampicin		Hepatitis Cutaneous hypersensitivity Gastrointestinal reactions Thrombocytopenic purpura Febrile reactions "Flu syndrome"	Shortness of breath Shock Haemolytic anaemia Acute renal failure
Pyrazinamide	Anorexia Nausea Flushing	Hepatitis Vomiting Arthralgia Cutaneous reaction	Sideroblastic anaemia
Ethambutol		Retrobulbar neuritis Arthralgia	Hepatitis Cutaneous reaction Peripheral neuropathy
Streptomycin	Cutaneous hypersensitivity Giddiness Numbness Tinnitus	Vertigo Ataxia Deafness	Renal damage Aplastic anaemia
Thiacetazone	Gastrointestinal reactions Cutaneous hypersensitivity Vertigo Conjunctivitis	Hepatitis Erythema multiforme Exfoliative dermatitis Haemolytic anaemia	Agranulocytosis
Drugs commonly used in therapy for MDR-TB			
Amikacin Kanamycin Capreomycin	Ototoxicity: hearing damage, vestibular disturbance Nephrotoxicity: deranged renal function test	Clinical renal failure	
Ofloxacin Ciprofloxacin	Gastrointestinal reactions Insomnia	Anxiety Dizziness Headache Tremor	Convulsion
Ethionamide Prothionamide	Gastrointestinal reactions	Hepatitis Cutaneous reactions Peripheral neuropathy	Convulsion Mental symptoms Impotence Gynaecomastia
Cycloserine	Dizziness Headache Depression Memory loss	Psychosis Convulsion	Sideroblastic anaemia
Para-aminosalicylic acid	Gastrointestinal reactions	Hepatitis Drug fever	Hypothyroidism Haematological reactions

Table 4. Suggested Protocol for Re-introducing Antituberculosis Drugs after Cutaneous Reaction

Drugs re-introduced	*Challenge doses*		
(in sequence)	*Day 1*	*Day 2*	*Day 3*
Isoniazid	50 mg	300 mg	300 mg
Rifampicin	75 mg	300 mg	Full dose
Pyrazinamide	250 mg	1 gm	Full dose
Ethambutol	100 mg	500 mg	Full dose
Streptomycin	125 mg	500 mg	Full dose

haemodialysis (119). It would be useful to monitor serum concentration of ethambutol to optimize therapy and minimize toxicity. Pyrazinamide can be removed significantly by haemodialysis (124,125). It is still not totally clear whether dosage reduction or spacing intermittently is more advisable for patients on haemodialysis and receiving pyrazinamide.

Thiacetazone and para-aminosalicylic acid are excreted both as unchanged drugs and metabolites in the urine. Both are weak antituberculosis drugs. The toxic-therapeutic ratio of thiacetazone is low and para-aminosalicylic acid administration can worsen the electrolyte and acid-base balance in patients with renal impairment. Both drugs should be avoided. Most fluoroquinolones with good safety profile for long-term use, such as ofloxacin and ciprofloxacin, are dependent on renal handling for clearance to varying extent. Dosage adjustment in the presence of renal impairment must be made accordingly (126,127). However, haemodialysis only removes a limited amount of ofloxacin or ciprofloxacin. Cycloserine clearance also depends on the renal route, and the degree of removal of the drug by haemodialysis is not well known.

The data on the clearance of antituberculosis drugs during continuous ambulatory peritoneal dialysis are scanty (124). It should be further studied before categorical recommendation on dosing can be made.

Liver impairment

Drug-induced hepatotoxicity during administration of standard short-course antituberculosis treatment has been well documented and deaths due to fulminant liver necrosis (though rare) have been reported (128). Preliminary data also suggest that liver transplantation might be a viable option for treating such patients with severe liver failure and dismal prognosis (129).

Patients with underlying liver diseases, particularly alcohol-, hepatitis B-, hepatitis C- and HIV-related disease, appear to be more prone to develop drug-induced liver dysfunction (130,131). The relative risk compared with the general population for these patients with chronic viral hepatitides to develop such liver toxicity is about 3. Other possible predisposing factors include old age (132) and malnourishment. Hepatitis-B chronic carriage is endemic in many South-East Asian countries. In Hong Kong for example, the rate can reach 10% of the overall population (133). Hepatitis-C chronic infection is also gaining importance in some Asian countries like Japan and Thailand (134,135). HIV infection is surging in Asia (136). Although it is apparent that co-administration of rifampicin and isoniazid confers additive, or even synergistic, potential of liver toxicity (137), whenever possible, these 2 drugs should be resumed once the liver chemistry recovers so that the duration of treatment will not be unduly prolonged. The use of streptomycin, isoniazid and ethambutol followed by isoniazid and ethambutol may be an alternative regimen provided that no coagulopathy contraindicates intramuscular injection. It is also important to note that toxicity due to isoniazid alone can occur. The contribution of pyrazinamide to liver toxicity in short-course regimens is not entirely clear, and its toxicity appears to be largely dose-dependent.

The fluoroquinolones, especially ofloxacin can be utilized in conjunction with streptomycin and ethambutol as an interim non-hepatotoxic regimen in the face of extensive tuberculosis and drug-induced hepatic dysfunction (138). This regimen enjoys good tolerance by the majority of such patients. Ofloxacin can also be considered as a component of definitive regimens if co-administration of isoniazid and rifampicin cannot be tolerated in the face of significant liver impairment. However, further evaluation on the optimal dosage of the fluoroquinolone and duration of definitive therapy with these fluoroquinolone-containing regimens is clearly required.

Pregnancy and lactation

Rifampicin, isoniazid, pyrazinamide and ethambutol are commonly used in many parts of the world for treatment for tuberculosis in pregnant women without problems apparently. Streptomycin (and other aminoglycosides) can cause high-frequency hearing loss in the foetus. The quinolones may interfere with foetal cartilage development in-utero and ethionamide has been found to cause foetal damage. Thus, these 3 aforementioned drugs and their allied members should not be used during pregnancy definitely. Breast-feeding, in general, should not be discouraged in mothers receiving antituberculosis medications. Only small, subtherapeutic amounts of drugs are secreted into the milk. If there is concern, the mother may take her medications directly after breast-feeding and then use a formula for the next feeding.

HIV co-infection

For HIV-infected patients with drug-susceptible tuberculosis, the standard 6-month regimen results in rapid sputum bacteriological conversion and low rate of treatment failure. But the relapse rate of tuberculosis is higher than in HIV-negative patients. Prolongation of therapy to 12 months resulted in lower relapse rate but no significant improvement of survival (139). In light of uncertainties, prolongation of therapy has been recommended. The most recent guidelines of the CDC state that the minimum duration of treatment is 6 months, but that if the clinical or bacteriological response is slow, treatment should be offered for a total period of 9 months, or for at least 4 months after achievement of culture negativity (140).

Combination regimens of antiretroviral drugs have improved the prognosis of HIV-infected patients, but have complicated the management of those with concomitant tuberculosis. Rifampicin can be used with nucleoside reverse transcriptase inhibitors (140,141). However, as rifampicin induces the enzymes of the cytochrome P-450 superfamily, this results in lowering of the plasma concentrations of most HIV-protease inhibitors and some non-nucleoside reverse transcriptase inhibitors. Therefore, concomitant administration of rifampicin with these drugs is generally not recommended (142). On the other hand, rifabutin, being a less potent inducer than rifampicin, can be administered in combination with some protease inhibitors like indinavir or nelfinavir. To increase the plasma levels of protease inhibitors so as to decrease the chance of emergence of drug-resistant HIV mutants, the dose of indinavir has to be escalated. Because protease inhibitors inhibit the metabolism of rifabutin and increase the rate of drug-related uveitis, dosage reduction of the latter should be carried out (140,141). The interactions of non-nucleoside reverse transcriptase inhibitors with rifabutin are complex and the use of these drugs together can be very problematic (140,141). Delavirdine cannot be used with rifabutin or rifampicin. Efavirenz may be used with either rifamycin though some increase in dosage of rifabutin is required (142). Further, to reduce the risk of subtherapeutic levels of protease inhibitors, the CDC also recommends, a non-rifamycin containing regimen, namely the administration of isoniazid, pyrazinamide and streptomycin for 9 months together with ethambutol for the first 2 months (140). There is, however, some concern for the clinical efficacy of this regimen. An alternative regimen recommended includes the use of isoniazid, ethambutol and pyrazinamide for 18–24 months (101).

Although the prevalence of drug-resistant tuberculosis among HIV-positive subjects is not widely available in many parts of the world, data from CDC (1993–1996) in the United States showed the risk of drug-resistant tuberculosis was indeed higher among this specific patient group when compared with others (140). The underlying causes are likely multiple and complex. One of

them is clearly nonadherence to therapy. To prevent drug resistance from developing, early and effective treatment of active tuberculosis using the cost-effective DOTS together with prompt drug susceptibility testing are key strategies. HIV-positive patients with MDR-TB should be treated early with appropriate multidrug regimens for 24 months after culture bacteriological conversion (140).

Silicosis

Silicosis is a well-known occupational disease in Asia. Patients with silicosis are at risk of developing active pulmonary tuberculosis. Their tuberculosis is more difficult to treat because of impaired function of lung macrophages and penetration of drugs into areas of conglomerate fibrosis. A study on patients with silico-tuberculosis in Hong Kong (143) showed that a regimen that comprised streptomycin, isoniazid, rifampicin and pyrazinamide given thrice per week (ethambutol being added in the first 3 months if there was a history of previous chemotherapy) was adequate when given for 8 months, but not for 6 months. The 3-year relapse rates were 7% and 22% respectively. One problem is that about 20% of patients experienced adverse reactions to this intensive regimen, with intolerance largely to streptomycin and pyrazinamide. A prospective study for silico-tuberculosis undertaken in Taiwan (144) revealed that a 9-month regimen that comprised streptomycin, isoniazid, rifampicin and pyrazinamide daily for 2 months followed by isoniazid and rifampicin for 7 months yielded an encouraging success rate of 95% and relapse rate of 5% after 18–40 months of follow-up. This regimen apparently was better tolerated by patients than the Hong Kong regimens.

Concluding summary

Directly Observed Therapy, Short Course (DOTS) is currently the most important strategy for control of tuberculosis worldwide. This is especially relevant for many countries in Asia and the Pacific area with high disease burden. However, new challenges need to be met with the surge in HIV infection and antituberculosis drug resistance. Measures in additional to DOTS are required to tackle these problems. Special concerns in the clinical management of tuberculosis in these settings have to be addressed. Ageing of the population and the endemicity of hepatitis B infection in many Asia-Pacific countries would be associated with a higher risk of hepatotoxicity during antituberculosis treatment. Finally, understanding and resolving poverty as part of the DOTS strategy should be reinforced.

References

1. Hobby GL, Holman AP, Iseman MD, Jones JM. Enumeration of tubercle bacilli in sputum of patients with pulmonary tuberculosis. *Antimicrob Agents Chemother* 1973; 4:94–104.
2. Medical Research Council Cardithoracic Epidemiology Group. National Survey of notification of tuberculosis in England and Wales. *Thorax* 1992; 47:770–5.
3. American Thoracic Society/Centers for Disease Control and Prevention. Diagnostic standards and classification of tuberculosis in adults and children. *Am J Respir Crit Care Med* 2000; 161:1376–95.
4. Perkins MD. New diagnostic tools for tuberculosis. *Int J Tuberc Lung Dis* 2000; 4:S182–8.
5. Walker D, McNerney R, Kimankinda Mwembo M, Foster S, Tihon V, Godfrey-Faussett P. An incremental cost-effectiveness analysis of the first. second and third sputum examination in the diagnosis of pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2000; 4:246–51.
6. Hudson CP, Wood R, Maartens G. Diagnosing HIV-associated tuberculosis: reducing costs and diagnostic delay. *Int J Tuberc Lung Dis* 2000; 4:240–5.
7. Al Zahrani K, Al Jahdali H, Poirier L. Rene P, Menzies D. Yield of smear, culture and amplification tests from repeated sputum induction for the diagnosis of pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2001; 5:855–60.
8. Colebunders R, Bastian I. A review of the diagnosis and treatment of smear-negative pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2000; 4:97–107.

9. Yeager HJ Jr, Lacy J, Smith L, LeMaistre C. Quantitative studies of mycobacterial populations in sputum and saliva. *Am Rev Respir Dis* 1967; 95:998–1004.
10. Al Zahrani K, Al Jahdali H, Poirier L, Rene P, Gennaro ML, Menzies D. Accuracy and utility of commercially available amplification and serological tests for the diagnosis of minimal tuberculosis. *Am J Respir Crit Care Med* 2000; 162:1323–9.
11. Morgan MA, Horstmeier CD. De Young DR, Roberts GD. Comparison of a radiometric method (BACTEC) and conventional culture media for recovery of mycobacteria from smear-negative specimens. *J Clin Microbiol* 1983; 18:384–8.
12. Ichiyama S, Shimokata K, Takeuchi J and the AMR Group. Comparative study of a biphasic culture system (Roche MB check system) with conventional egg medium for recovery of mycobacteria. *Tuber Lung Dis* 1993; 74:338–41.
13. Rohner P, Ninet B, Metral C, Emler S, Auckenthaler R. Evaluation of the MB/BacT system and comparison to the BACTEC 460 system and solid media for isolation of mycobacteria from clinical specimens. *J Clin Microbiol* 1997; 35:3127–31.
14. Pfyffer GE, Cieslak C, Welscher HM, Kissling P, Rusch-Gerdes S. Rapid detection of mycobacteria in clinical specimens by using the automated BACTEC 9000 MB system and comparison with radiometric and solid-culture systems. *J Clin Microbiol* 1997; 35:2229–34.
15. Palacios JJ, Ferro J, Ruiz Palma N, Garcia JM, Villar H, Rodriguez J, Macias MD, Prendes P. Fully automated liquid culture system compared with Lowenstein-Jensen solid medium for rapid recovery of mycobacteria from clinical samples. *Eur J Clin Microbiol Infect Dis* 1999; 18:265–73.
16. Sharp SE, Lemes M, Sierra SG, Poniecka A, Poppiti RJ Jr. Lowenstein-Jensen media: no longer necessary for mycobacterial isolation. *Am J Clin Pathol* 2000; 113:770–3.
17. Chien HP, Yu MC, Wu MH, Lin TP, Luh KT. Comparison of the BACTEC MGIT960 with Lowenstein-Jensen medium for recovery of mycobacteria from clinical specimens. *Int J Tuberc Lung Dis* 2000; 4:866–70.
18. Della-Latta P, Whittier S. Comprehensive evaluation of performance, laboratory application, and clinical usefulness of two direct amplification technologies for the detection of *Mycobacterium tuberculosis* complex. *Am J Clin Pathol* 1998; 110:301–10.
19. Dalovisio JR, Montenegro-James S, Kemmerly SA, Genre CF, Chambers R, Greer D, Pankey GA, Failla DM, Haydel KG, Hutchison L, Lindley MF, Nunez BM, Praba A, Eisenach KD, Cooper ES. Comparison of the amplified *Mycobacterium tuberculosis* (MTB) direct test, Amplicor MTB PCR, and IS6110-PCR for detection of MTB in respiratory specimens. *Clin Infect Dis* 1996; 23:1099–106.
20. Centers for Disease Control and Prevention. Update: Nucleic acid amplification tests for tuberculosis. *MMWR* 2000; 49:593–4.
21. Schluger NW. Changing approaches to the diagnosis of tuberculosis. *Am J Respir Crit Care Med* 2001; 164:2020–[202]4.
22. Chedore P, Jamieson FB. Routine use of the Gen-Probe MTD2 amplification test for detection of *Mycobacterium tuberculosis* in clinical specimens in a large public health mycobacteriology laboratory. *Diagn Microbiol Infect Dis* 1999; 35:185–91.
23. Lagrange PH, Simonney N, Wargnier A, Herrmann JL. Usefulness of serological tests in childhood tuberculosis. *Pediatr Pulmonol* 2001; (suppl 23):S61–4.
24. Luh KT, Yu CJ, Yang PC, Lee LN. Tuberculosis antigen A60 serodiagnosis in tuberculous infection: application in extrapulmonary and smear-negative pulmonary tuberculosis. *Respirology* 1996; 1:145–51.
25. Chiang I-H, Suo J, Bai K-J, Lin TP, Luh KT, Yu CJ, Yang PC. Serological diagnosis of tuberculosis. A study comparing three specific mycobacterial antigens. *Am J Respir Crit Care Med* 1997; 156:906–11.
26. Somi GR, O'Brien RJ, Mfinanga GS, Ipuge YA. Evaluation of the Myco-Dot™ test in patients with suspected tuberculosis in a field setting in Tanzania. *Int J Tuberc Lung Dis* 1999; 3:231–8.
27. Pottumarthy S, Wells VC, Morris AJ. A comparison of seven tests for serological diagnosis of tuberculosis. *J Clin Microbiol* 2000; 38:2227–31.
28. Julian B, Matas L, Hernandez A, Alcaide J, Luquin M. Evaluation of a new serodiagnostic tuberculosis test based on immunoglobulin A detection against Kp-90 antigen. *Int J Tuberc Lung Dis* 2000; 4:1082–5.
29. Chan ED, Heifets L, Iseman MD. Immunologic diagnosis of tuberculosis: a review. *Tuber Lung Dis* 2000; 80:131–40.
30. Danek SJ, Bower JS. Diagnosis of pulmonary tuberculosis by flexible fiberoptic bronchoscopy. *Am Rev Respir*

Dis 1979; 119:677–9.
31. Sarkar SK, Sharma GS, Gupta PR, Sharma RK. Fiberoptic bronchoscopy in the diagnosis of pulmonary tuberculosis. *Tubercle* 1980; 61:97–9.
32. Wallace JM, Deutsch AL, Harrell JH, Moser KM. Bronchoscopy and transbronchial biopsy in evaluation of patients with suspected active tuberculosis. *Am J Med* 1981: 70:1189–94.
33. So SY, Lam WK, Yu DYC. Rapid diagnosis of suspected pulmonary tuberculosis by fiberoptic bronchoscopy. *Tubercle* 1982; 63:195–200.
34. Pant K, Chawla R, Mann PS, Jaggi OP. Fiberbronchoscopy in smear-negative miliary tuberculosis. *Chest* 1989; 95:1151–2.
35. Wong CF, Yew WW, Chan CY, Au LY, Cheung SW, Cheng AFB. Rapid diagnosis of smear-negative pulmonary tuberculosis via fibreoptic bronchoscopy: utility of polymerase chain reaction in bronchial aspirates as an adjunct to transbronchial biopsies. *Respir Med* 1998; 92:815–9.
36. Chen N-H, Liu Y-C, Tsao TC-Y, Wu T-L, Hsieh M-J, Chuang M-L, Huang C-C, Kuo A-J, Chen M-C, Yang C-T. Combined bronchoalveolar lavage and polymerase chain reaction in the diagnosis of pulmonary tuberculosis in smear-negative patients. *Int J Tuberc Lung Dis* 2002; 6:350–5.
37. Anderson C, Inhaber N, Menzies D. Comparison of sputum induction with fiberoptic bronchoscopy in the diagnosis of tuberculosis. *Am J Respir Crit Care Med* 1995; 152:1570–4.
38. Conde MB, Soares SL, Mello FC, Rezende VM, Almeida LL, Reingold AL, Daley CL, Kritski AL. Comparison of sputum induction with fiberoptic bronchoscopy in the diagnosis of tuberculosis: experience at an acquired immune deficiency syndrome reference center in Rio de Janeiro, Brazil. *Am J Respir Crit Care Med* 2000; 162: 2238–40.
39. Yew WW, Kwan SYL, Wong PC, Fu KH. Percutaneous transthoracic needle biopsies in the rapid diagnosis of pulmonary tuberculosis. *Lung* 1991; 169:285–9.
40. Das DK, Pant CS, Pant JN, Sodhani P. Transthoracic (percutaneous) fine needle aspiration cytology diagnosis of pulmonary tuberculosis. *Tuber Lung Dis* 1995; 76:84–9.
41. Yew WW, Chan CY, Kwan SYL, Cheung SW, French GL. Diagnosis of tuberculous pleural effusion by the detection of tuberculostearic acid in pleural aspirates. *Chest* 1991; 100:1261–3.
42. Scerbo J, Keltz H, Stone DJ. A prospective study of closed pleural biopsies. *JAMA* 1971; 218:377–80.
43. Berger HW, Mejia E. Tuberculous pleurisy. *Chest* 1973; 63:88–92.
44. Kumar S, Seshadri MS, Koshi G, John TJ. Diagnosing tuberculous pleural effusion: comparative sensitivity of mycobacterial culture and histopathology. *Br Med J* 1981; 283:20.
45. Gorguner M, Cerci M, Gorguner I. Determination of adenosine deaminase activity and its isoenzymes for diagnosis of pleural effusions. *Respirology* 2000; 5:321–4.
46. Xirouchaki N, Tzanakis N, Bouros D, Kyriakou D, Karkavitsas N, Alexandrakis M, Siafakas NM. Diagnostic value of interleukin-1 alpha, interleukin-6, and tumor necrosis factor in pleural effusions. *Chest* 2002; 121:815–20.
47. Reechaipichitkul W, Lulitanond V, Sungkeeree S, Patjanasoontom B. Rapid diagnosis of tuberculous pleural effusion using polymerase chain reaction. *Southeast Asian J Trop Med Public Health* 2000; 31:509–14.
48. Nagesh BS, Sehgal S, Jindal SK, Arora SK. Evaluation of polymerase chain reaction for detection of *Mycobacterium tuberculosis* in pleural fluid. *Chest* 2001; 119:1737–41.
49. Villegas MV, Labrada LA, Saravia NG. Evaluation of polymerase chain reaction, adenosine deaminase, and interferon-gamma in pleural fluid for the differential diagnosis of pleural tuberculosis. *Chest* 2000; 118:1355–64.
50. Arnadottir T, Rieder HL, Trebucq A, Waaler HT. Guidelines for conducting tuberculin skin test surveys in high prevalence countries. *Tuber Lung Dis* 1996; 77(suppl 1):S1–9.
51. Comstock GW, Edwards LB, Philip RN. Winn WA. A comparison in the United States of America of two tuberculins, PPD-S and RT23. *Bull World Health Organ* 1964; 31:161–70.
52. Bouros D, Zeros G, Panaretos C, Vassilatos C, Siafakas N. Palpation vs pen method for the measurement of skin tuberculin reaction (Mantoux test). *Chest* 1991; 99:416–9.
53. Chee CB, Soh CH, Boudville IC, Chor SS, Wang YT. Interpretation of the tuberculin skin test in *Mycobacterium bovis* BCG-vaccinated Singaporean school children. *Am J Respir Crit Care Med* 2001; 164:958–61.
54. Menzies D. Interpretation of repeated tuberculin tests. Boosting, conversion, and reversion. *Am J Respir Crit Care Med* 1999; 159:15–21.

55. Andersen P, Munk ME, Pollock JM, Doherty TM. Specific immune-based diagnosis of tuberculosis. *Lancet* 2000; 356:1099–104.
56. Heifets LB, Cangelosi GA. Drug susceptibility testing of *Mycobacterium tuberculosis*: a neglected problem at the turn of the century. *Int J Tuberc Lung Dis* 1999; 3:564–81.
57. Tortoli E, Mattei R, Savarino A, Bartolini L, Beer J. Comparison of *Mycobacterium tuberculosis* susceptibility testing performed with BACTEC 460 TB (Becton Dickinson) and MB/BacT (Organon Teknika) systems. *Diagn Microbiol Infect Dis* 2000; 38:83–6.
58. Yew WW, Tong SCW, Lui KS, Leung SKF, Chau CH, Wang EP. Comparison of MB/BacT system and agar proportion method in drug susceptibility testing of *Mycobacterium tuberculosis*. *Diagn Microbiol Infect Dis* 2001; 39:229–32.
59. Bemer P, Palicova F, Rusch-Gerdes S, Drugeon HB, Pfyffer GE. Multicenter evaluation of fully automated BACTEC Mycobacteria Growth Indicator Tube 960 system for susceptibility testing of *Mycobacterium tuberculosis*. *J Clin Microbiol* 2002; 40:150–4.
60. Carriere C, Riska PF, Zimhony O, Kriakov J, Bardarov S, Burns J, Chan J, Jacobs WR Jr. Conditionally replicating luciferase reporter phages: improved sensitivity for rapid detection and assessment of drug susceptibility of *Mycobacterium tuberculosis*. *J Clin Microbiol* 1997; 35:3232–9.
61. Albert H, Trollip AP, Mole RJ, Hatch SJB, Blumberg L. Rapid indication of multidrug-resistant tuberculosis from liquid cultures using FAST Plaque TB-RIF™, a manual phage-based test. *Int J Tuberc Lung Dis* 2002; 6:523–8.
62. Angeby KA, Klintz L, Hoffner SE. Rapid and inexpensive drug susceptibility testing of *Mycobacterium tuberculosis* with a nitrate reductase assay. *J Clin Microbiol* 2002; 40:553–5.
63. Whelen AC, Felmlec TA, Hunt JM, Williams DL, Roberts GD, Stockman L, Persing DH. Direct genotypic detection of *Mycobacterium tuberculosis* rifampin resistance in clinical specimens by using single-tube heminested PCR. *J Clin Microbiol* 1995; 33:556–61.
64. Garcia L, Alonso-Sanz M, Rebollo MJ, Tercero JC, Chaves F. Mutations in the rpoB gene of rifampin-resistant *Mycobacterium tuberculosis* isolates in Spain and their rapid detection by PCR-enzyme-linked immunosorbent assay. *J Clin Microbiol* 2001; 39:1813–8.
65. Traore H, Fissette K, Bastian I, Devleeschouwer M, Portaels F. Detection of rifampicin resistance in *Mycobacterium tuberculosis* isolates from diverse countries by a commercial line probe assay as an initial indicator of multidrug resistance. *Int J Tuberc Lung Dis* 2000; 4:481–4.
66. Service RS. Microchip arrays put DNA on the spot. *Science* 1998; 282:396–9.
67. World Health Organization. Guidelines for drug susceptibility testing for second-line anti-tuberculosis drugs for DOTS-PLUS. WHO, Geneva, Switzerland, 2001 WHO/CDS/TB/2001.288.
68. Medical Research Council. A Medical Research Council Investigation. Streptomycin treatment of pulmonary tuberculosis. *BMJ* 1948; ii:769–82.
69. Medical Research Council. A Medical Research Council Investigation. Treatment of pulmonary tuberculosis with streptomycin and para-aminosalicylic acid. *BMJ* 1950; ii:1073–85.
70. Medical Research Council. Various combinations of isoniazid with streptomycin or with PAS in the treatment of pulmonary tuberculosis. *Seventh report to the Medical Research Council by their Tuberculosis Chemotherapy Trials Committee* 1955; i:434–45.
71. Bayer R, Wilkinson D. Directly observed therapy for tuberculosis: History of an idea. *Lancet* 1995; 345:1545–8.
72. Fox W, Mitchison DA. Short course chemotherapy for pulmonary tuberculosis. *Am Rev Respir Dis* 1975; 111:845–8.
73. Mitchison D. Basic mechanisms of chemotherapy. *Chest* 1979; 76 (suppl):771–81.
74. David HL. Drug resistance in *Mycobacterium tuberculosis* and other mycobacteria. *Clin Chest Med* 1980; 1:227–30.
75. Iseman MD, Madsen LA. Drug-resistant tuberculosis. *Clin Chest Med* 1989; 10:341–53.
76. British Thoracic Society. A controlled trial of 6-months' chemotherapy in pulmonary tuberculosis. Final report: Results during the 36-months after the end of chemotherapy and beyond. *Br J Dis Chest* 1984; 78:330–6.
77. Singapore Tuberculosis Service/British Medical Research Council. Five year follow up of a clinical trial of three 6-month regimens of chemotherapy given intermittently in the continuation phase in the treatment of pulmonary tuberculosis. *Am Rev Respir Dis* 1988; 137:1147–50.

78. China tuberculosis control collaboration. Results of directly observed short-course chemotherapy in 112842 Chinese patients with smear-positive tuberculosis. *Lancet* 1996; 347:358–62.
79. Tam CM. Chan SL. Lam CW, Leung CC, Kam KM, Morris JS, Mitchison DA. Rifapentine and isoniazid in the continuation phase of treating pulmonary tuberculosis: Initial report. *Am J Respir Crit Care Med* 1998; 157:1726–33.
80. Third East African/British Medical Research Council Study. Controlled clinical trial of four short-course regimens of chemotherapy for two durations in the treatment of pulmonary tuberculosis. Second Report. *Tubercle* 1980: 61:59–69.
81. Hong Kong Chest Service/British Medical Research Council Study. Controlled trial of 6-month and 8-month regimens in the treatment of pulmonary tuberculosis. The results up to 24 months. *Tubercle* 1979; 60:201–10.
82. Somner AR. Short course chemotherapy in pulmonary tuberculosis. A controlled trial by the British Thoracic Association (third report). *Lancet* 1980; i:1182–3.
83. American Thoracic Society. Treatment of tuberculosis and tuberculosis infection in adults and children. *Am J Respir Crit Care Med* 1994; 149:1359–74.
84. World Health Organization. Treatment of Tuberculosis: Guidelines for National Programmes, 2nd ed. Geneva, Switzerland WHO 1997.
85. Hong Kong Chest Service/British Medical Research Council. Second report: controlled trial of four three-times-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. The results up to 24 months. *Tubercle* 1982; 63:89–98.
86. Hong Kong Chest Service/British Medial Research Council. Controlled trial of 2, 4 and 6 months of pyrazinamide in 6-month three-times-weekly regimens for smear-positive pulmonary tuberculosis, including an assessment of a combined preparation of isoniazid, rifampicin and pyrazinamide. Results at 30 months. *Am Rev Respir Dis* 1991; 143:700–6.
87. Sbarbaro J, Blomberg B, Chaulet P. Fixed-dose combination formulations for tuberculosis treatment. *Int J Tuberc Lung Dis* 1999; 3:S286–8.
88. Moulding T, Dutt AK, Reichman LB. Fixed-dose combinations of antituberculosis medications to prevent drug resistance. *Ann Intern Med* 1995; 122:951–4.
89. Mitchison DA. How drug resistance emerges as a result of poor compliance during short course chemotherapy for tuberculosis. *Int J Tuberc Lung Dis* 1998; 2:10–5.
90. Fox W. Drug combinations and the bioavailability of rifampicin. *Tubercle* 1990; 71:241–5.
91. A joint statement of the International Union Against Tuberculosis and Lung Disease/World Health Organization. The promise and reality of fixed dose combinations with rifampicin. *Tubercle Lung Dis* 1994; 75:180–1.
92. Tam CM, Chan SL, Kam KM, Sim E, Staples D, Sole KM, Al-Ghusein H, Mitchison DA. Rifapentine and isoniazid in the continuation phase of a 6-month regimen. Interim report: no activity of isoniazid in the continuation phase. *Int J Tuberc Lung Dis* 2000; 4:262–7.
93. Yew WW. Directly Observed Therapy, Short-course: The best way to prevent multidrug-resistant tuberculosis. Chemotherapy 1999; 45(suppl 2):S26–33.
94. Sumartojo E. When tuberculosis treatment fails. A social behavioral account of patient adherence. *Am Rev Respir Dis* 1993; 147:1311–20.
95. World Health Organization Global tuberculosis Programme. Global tuberculosis control. WHO/GTB/97.225. Geneva, WHO 1997.
96. Kochi A. Is DOTS the health breakthrough of the 1990s? *World Health Forum. Geneva, WHO* 1997; 18:225–47.
97. Davidson PT. Drug resistance and the selection of therapy for tuberculosis. *Am Rev Respir Dis* 1987; 136:255–7.
98. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; 53:536–48.
99. Hong Kong Chest Service/British Medical Research Council. Five-year follow up of a controlled trial of five 6-month regimens of chemotherapy for pulmonary tuberculosis. *Am Rev Respir Dis* 1987; 136:1339–42.
100. Babu Swai O, Aluoch JA, Githui WA, Thiong'o R, Edwards EA, Darbyshire JH, Nunn AJ. Controlled clinical trial of a regimen of two durations for the treatment of isoniazid resistant pulmonary tuberculosis. *Tubercle* 1988; 69:5–14.

101. Barnes PF, Block AB, Davidson PT, Snider DE Jr. Tuberculosis in patients with human immunodeficiency virus infection. *N Engl J Med* 1991; 324:1644–50.
102. Park MM, Davis AL, Schluger NW, Cohen H, Rom WN. Outcome of MDR-TB patients, 1983–1993: Prolonged survival with appropriate therapy. *Am J Respir Crit Care Med* 1996; 153:317–24.
103. Yew WW, Kwan SY, Ma WK, Khin MA, Chau PY. In-vitro activity of ofloxacin against *Mycobacterium tuberculosis* and its clinical efficacy in multiply resistant pulmonary tuberculosis. *J Antimicrob Chemother* 1990; 26:227–36.
104. Goble M, Iseman MD, Madsen LA, Waite D, Ackerson L, Horsburgh CR Jr. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med* 1993; 328:527–32.
105. Telzak EE, Sepkowitz K, Alpert P, Mannheimer S, Medard F, El-Sadr W, Blum S, Gagliardi A, Salomon N, Turett G. Multidrug-resistant tuberculosis in patients without HIV infection. *N Engl J Med* 1995; 333:907–11.
106. Yew WW, Chan CK, Chau CH, Tam CM, Leung CC, Wong PC, Lee J. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. *Chest* 2000; 117:744–751.
107. Crofton J, Chaulet P, Maher D. Guidelines for the management of drug-resistant tuberculosis WHO/TB/96.210 (Rev 1). World Health Organization, Geneva 1997.
108. Sullivan EA, Kreiswirth BN, Palumbo L, Kapur V, Musser JM, Ebrahimzadeh A, Frieden TR. Emergencce of fluoroquinolone-resistant tuberculosis in New York City. *Lancet* 1995; 345:1148–50.
109. Pretet S, Lebeaut A, Parrot R, Truffot C, Grosset J, Dinh-Xuan AT. (Group for the study and treatment of resistant mycobacterial infection.) Combined chemotherapy including rifabutin, for rifampicin and isoniazid resistant pulmonary tuberculosis. *Eur Respir J* 1992; 5:680–4.
110. Hong Kong Chest Service/British Medical Research Council. A controlled study of rifabutin and an uncontrolled study of ofloxacin in the retreatment of patients with pulmonary tuberculosis resistant to isoniazid, streptomycin and rifampicin. *Tubercle Lung Dis* 1992; 73:59–67.
111. Hirata T, Saito H, Tomioka H, Sato K, Jidoi J, Hosoe K, Hidaka T. *In vitro* and *in vivo* activities of the benzoxazinorifamycin KRM-1648 against Mycobacterium tuberculosis. *Antimicrob Agents Chemother* 1995; 39:2295–303.
112. Kanyok TP, Reddy MV, Chinnaswamy J, Danziger LH, Gangadharam PRJ. *In vivo* activity of paromomycin against susceptible and multidrug-resistant *Mycobacterium tuberculosis* and *Mycobacterium avium* complex strains. *Antimicrob Agents Chemother* 1994; 38:170–3.
113. Yew WW, Wong CF, Lee J, Wong PC, Chau CH. Do b-lactam-b-lactamase inhibitor combinations have a place in the treatment of multidrug-resistant tuberculosis? *Tubercle Lung Dis* 1995; 76:90–2.
114. Jagannath C, Reddy MV, Kailasam S, O'Sullivan JF, Gangadharam PRJ. Chemotherapeutic activity of clofazimine and its analogues against *Mycobacterium tuberculosis*: *In vitro*, intracellular and *in vivo* studies. *Am J Respir Crit Care Med* 1995; 151:1083–6.
115. Schraufnagel DE. Tuberculosis treatment for the beginning of the next century. *Int J Tuberc Lung Dis* 1999; 3:651–2.
116. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A controlled trial of 2-month, 3-month and 12-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis: Results at 60 months. *Am Rev Respir Dis* 1984; 130:23–8.
117. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A controlled trial of 3-month, 4-month and 6-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Results at 5 years. *Am Rev Respir Dis* 1989; 139:871–6.
118. Mitchison DA, Ellard GA. Tuberculosis in patients having dialysis. *Br Med J* 1980; i:1186,1533.
119. Andrew OT, Schoenfeld PY, Hopewell PC, Humphreys MH. Tuberculosis in patients with end-stage renal disease. *Am J Med* 1980; 68:59–65.
120. Swan SK, Bennett WM. Use of drugs in patients with renal failure. In: *Diseases of the Kidney,* 6th ed, Volume 3. Eds. Schrier RW, Gottschalk CW. New York: Little Brown 1997, 2968–3011.
121. Girling DJ. The chemotherapy of tuberculosis. In: *Biology of the Mycobacteria,* Vol 3. Eds. Ratledge C, Standard J. London: Academic Press 1989, 285–323.
122. Varughese A, Brater DC, Benet LZ, Lee CS. Ethambutol kinetics in patients with impaired renal function. *Am Rev Respir Dis* 1986; 134:34–8.

123. McEvoy GK (ed). Antituberculosis agents. In: Drug Information, American Hospital Formulary Service. *American Society of Health System Pharmacists* 1996, 394–423.
124. Woo J, Leung A, Chan K, Lai KN, Teoh R. Pyrazinamide and rifampicin regimens for patients on maintenance dialysis. *Int J Artif Organs* 1988; 11:181–5.
125. Malone RS, Fish DN, Spiegel DM, Childs JM, Peloquin CA. The effect of haemodialysis on isoniazid, rifampin, pyrazinamide and ethambutol. *Am J Respir Crit Care Med* 1999; 159:1580–4.
126. Singlas E, Taburet AM, Landru I, Albin H, Ryckelinck JP. Pharmacokinetics of ciprofloxacin tablets in renal failure; influence of haemodialysis. *Eur J Clin Pharmacol* 1987; 31:589–3.
127. Lameire N, Rosenkranz B, Malerczyk V, Lehr KH, Veys N, Ringoir S. Ofloxacin pharmacokinetics in chronic renal failure and dialysis. *Clin Pharmacokinet* 1991; 21: 357–71.
128. Whittington RM. Fatal hepatotoxicity of antitubercular chemotherapy. *Lancet* 1991; 338:1083–1084.
129. Mitchell I, Wendon J, Fitt S, Williams R. Antituberculous therapy and acute liver failure. *Lancet* 1995; 345:555–6.
130. Ungo JR, Jones D, Ashkin D, Hollender ES, Bernstein D, Albanese AP, Pitchenik AE. Antituberculosis drug-induced hepatotoxicity: The role of Hepatitis C virus and the human immunodeficiency virus. *Am J Respir Crit Care Med* 1998; 157:1871–6.
131. Wong WM, Wu PC, Yuen MF, Cheng CC, Yew WW, Wong PC, Tam CM, Leung CC, Lai CL. Antituberculosis drug-related liver dysfunction in chronic hepatitis B infection. *Hepatology* 2000; 31:201–6.
132. Pande JN, Singh SPN, Khilnani GC, Khilnani S, Tandon RK. Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. *Thorax* 1996; 51:132–6.
133. Yeoh EK, Chang WK, Kwan JPW. Epidemiology of viral hepatitis B infection in Hong Kong. In: *Viral Hepatitis B infection: Vaccine and Control.* Eds. Lam SK, Lai CL, Yeoh EK. Singapore: World Scientific 1984, 33–41.
134. Moriya T, Koyama T, Tanaka J, Mishiro S, Yoshizawa H. Epidemiology of hepatitis C virus in Japan. *Intervirology* 1999; 42:153–8.
135. Songsivilai S, Jinathongthai S, Wongsena W, Tiangpitayakorn C, Dharakul T. High prevalence of hepatitis C infection among blood donors in northeastern Thailand. *Am J Trop Med Hyg* 1997; 57:66–9.
136. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement-Global burden of tuberculosis: Estimated incidence, prevalence and mortality by country: WHO Global Surveillance and Monitoring Project. *JAMA* 1999; 282:677–86.
137. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. *Chest* 1991; 99:465–71.
138. Yew WW, Lee J, Wong PC, Kwan SYL. Tolerance of ofloxacin in the treatment of pulmonary tuberuculosis in presence of hepatic dysfunction. *Int J Clin Pharm Res* 1992; XII:173–8.
139. Perriens JH, St Louis ME, Mukadi YB, Brown C, Prignot J, Pouthier F, Portaels F, Williame JC, Mandala JK, Kaboto M, Ryder RW, Roscigno G, Piot P. Pulmonary tuberculosis in HIV-infected patients in Zaire: a controlled trial of treatment for either 6 or 12 months. *N Engl J Med* 1995; 332:779–84.
140. Centers for Disease Control and Prevention. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. *MMWR* 1998; 47 (RR-20):1–58.
141. Burman WJ, Gallicano K, Peloquin C. Therapeutic implications of drug interactions in the treatment of human immunodeficiency virus-related tuberculosis. *Clin Infect Dis* 1999; 28:419–30.
142. Centers for Disease Control and Prevention. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors. *MMWR* 2000; 49:185–9.
143. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A controlled clinical comparison of 6 and 8 months of antituberculosis chemotherapy in the treatment of patients with silicotuberculosis in Hong Kong. *Am Rev Respir Dis* 1991; 143:262–7.
144. Lin TP, Suo J, Lee CN, Lee JJ, Yang SP. Short-course chemotherapy of pulmonary tuberculosis in pneumoconiotic patients. *Am Rev Respir Dis* 1987; 136:808–10.

18 Severe Acute Respiratory Syndrome

Wah Kit Lam, Kenneth Tsang, Clara Ooi, Mary Ip and Moira Chan-Yeung

Introduction

Severe acute respiratory syndrome (SARS) poses a threat to international health and could potentially become the first severe new disease of the twenty-first century with global epidemic potential. It has spread within one week to 11 countries in 3 continents created by a highly mobile, closely interconnected world. The relatively long incubation period of up to 10 days potentially allows the novel coronavirus to be transported by an asymptomatic air traveller globally.

Although scientists collaborated with lightning speed and identified the culprit virus (1) and broke its genetic code in 5 weeks from the onset of the epidemic in Hong Kong (2), there is still a great deal of unknowns such as the different modes of transmission, the pathogenesis, and the behaviour of the virus. SARS is associated with high morbidity, with 20–25% of patients requiring intensive care management, and 10–15% mortality. In addition, health care workers are at the highest risk, and all affected individuals and contacts require strict isolation. Moreover, one patient can infect many people, and some even exhibit the "super-spreader phenomenon" whereby hundreds of patients could be infected by one single index case. For all these reasons, SARS has created a great deal of anxiety and even within the medical circle as well as in the general public. The economic consequence of the disease to the society is enormous.

History of the outbreak in Asia

China

This disease can be traced to the province of Guangdong in southern China. The first case of SARS was reported on 16 November 2002 in Foshan. There was no further report until one month later when 11 cases, 8 involving health care workers in a hospital, occurred in Huyuen. On December 26, 2002, Zhongshan reported 28 cases (14 health care workers). The linkage between the first cases in Foshan and the outbreaks in the two other cities in Guangdong is not clear (Figure 1). On 31 January 2003, a visitor from Zhongshan arrived at Guangzhou, felt ill and was admitted into the Second Affiliated Hospital where he stayed for less than 24 hours before he was transferred to the Third Affiliated Hospital. During the few hours in the Second Affiliated Hospital he managed to infect 30 hospital staff. In the Third Affiliated Hospital, he infected 26 hospital staff before he was transferred to Guangzhou Infectious Disease Hospital. In addition, this man also infected 19 of his family members. On 11 February 2003, 305 cases were reported in Guangdong and the World Health Organization (WHO) received a report about this illness from China (3). No further information was available until 26 March 2003.

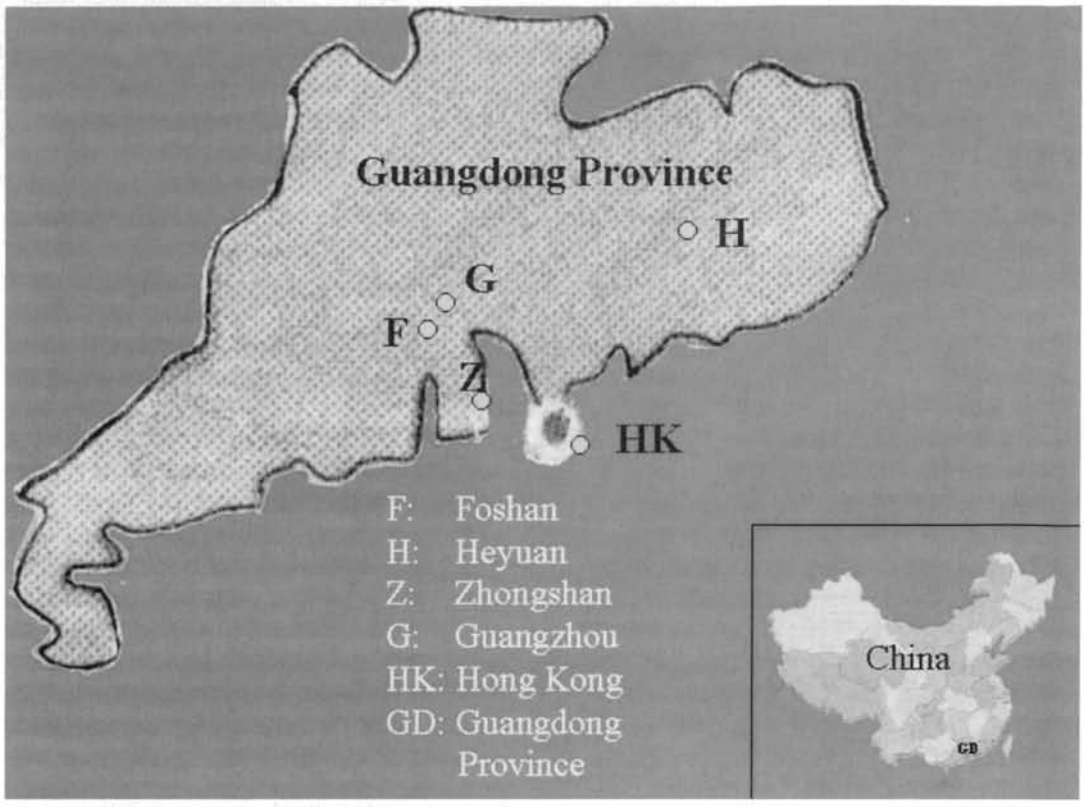


Figure 1. Map of Southern China showing the places where the epidemic originated

Hong Kong

The outbreak in Hong Kong started when a professor of nephrology arrived from Guangzhou, China, on 21 February 2003 to attend a wedding. He was unwell for a few days before the trip. His first day in Hong Kong was spent also on sightseeing and shopping with his brother-in-law, before he was admitted as an emergency to a local hospital with respiratory failure and acute respiratory distress syndrome (4). He died of respiratory failure in a local hospital to which his brother-in-law was also admitted after a few days, and later died. The nephrologist also infected a nurse and a health care assistant in the same hospital, and at least twelve guests who stayed on the same floor of the hotel before his death. Each of the infected hotel guests in turn led to an outbreak in different places around the world (4,5).

One of these hotel guests was admitted to a regional teaching hospital on 4 March 2003 with a history of fever and abnormal chest radiograph. From 11 to 25 March 2003, a total of 138 cases: 69 health staff, 17 medical students and 54 patients and visiting relatives, were identified to be linked to this index case (6). The disease involving health care workers initially has spread very rapidly to the community by visitors to the ward. The second major SARS outbreak occurred in the community, and involved 330 residents (at the time of writing) in a housing estate (Amoy Gardens). This outbreak could in fact be traced back to a patient discharged from the same ward of the above regional teaching hospital. A high proportion of patients with SARS could be linked with the index case in the public hospital as they were patients, or family members and visitors of patients of the hospital, the exact proportion cannot be estimated at present (7). However, there were some patients with a history of travel to Guangdong and contracted the disease there. Thus Hong Kong probably had many index cases instead of one or two.

Singapore

Three guests from the same index hotel in Hong Kong were from Singapore. On their return, they developed the disease and started an outbreak there. The majority of SARS patients in Singapore could be linked to this cluster (8).

Vietnam

The outbreak in Hanoi started with the index case, a 48 year-old Chinese American businessman who stayed in the same index hotel as the professor on 22 February 2003. The number of cases increased rapidly but stabilized on 24 March 2003 at 58 (9). By 29 April 2003, the WHO has removed Hanoi as an "affected area" defined as a region at the first administrative level where the country is reporting level of local transmission of SARS, within the last 20 days (10).

Epidemiology

Cumulative number of cases

Hong Kong reported to the WHO on 12 March 2003 the outbreak of atypical pneumonia in the regional teaching hospital and WHO issued the following day a global alert for this disease (3). WHO called this atypical pneumonia Severe Acute Respiratory Syndrome (SARS) because of the severity of its presentation (11). Within one week, altogether 264 cases (including 150 from Hong Kong) were reported to the WHO (excluding China as none was provided) from 11 countries in 3 continents (12). On 26 March 2003, China released the data and brought the global total to 1485 with 53 deaths since November 2002 (13). By the end of the epidemic in July 2003, the global cumulative total was 8096 cases with 774 deaths (14). Places with most cases include China (5327 cases with 349 deaths), Hong Kong (1755 cases with 299 deaths). The rapidity with which the disease has spread indicated that the causative agent is highly infectious and virulent.

Figure 2 shows the number of cases reported each day in Hong Kong, Singapore, Vietnam, Canada (places where infected hotel guests started the outbreak), together with Taiwan and worldwide during the epidemic.

The age and sex distribution of the 1750 SARS patients in Hong Kong are shown in Figure 3 (15). People of all ages (1–96 years old) were affected. Females and males were equally affected except in those 15 to 54 years old when more females had the disease (15).

Risk factors for infection

Health care workers. Table 1 shows the cumulative number of cases of SARS and number and percentage of health care workers (14). About one fifth of patients with SARS are health care workers in Hong Kong and higher in Canada, 43.4%. Doctors, nurses, health care assistants and cleaners are all at risk of developing SARS from exposure to patients with the disease especially when the diagnosis was unsuspected and the health care worker unprotected (6).

Table 1. Total cumulative number of cases, number and % of health care workers+, number of deaths and case fatality ratio

Country/Region	*Cumulative no of cases*	*No of health care workers (%)*	*Total no of deaths*	*Case-fatality ratio*
Global	8096	1706 (21.1)	774	9.6
China	5327	1002 (18.8)	349	6.6
Hong Kong, SAR, China	1755	386 (22.0)	299	17.0
Singapore	238	97 (40.8)	33	13.9
Vietnam	63	36 (57.1)	5	7.9
Taiwan, China	346	68 (19.7)	37	10.7
Canada	251	109 (43.4)	43	17.1

+ From Communicable Disease Surveillance and Response (CSR), WHO website http //who int/csr/country /table 2004_04_21/en

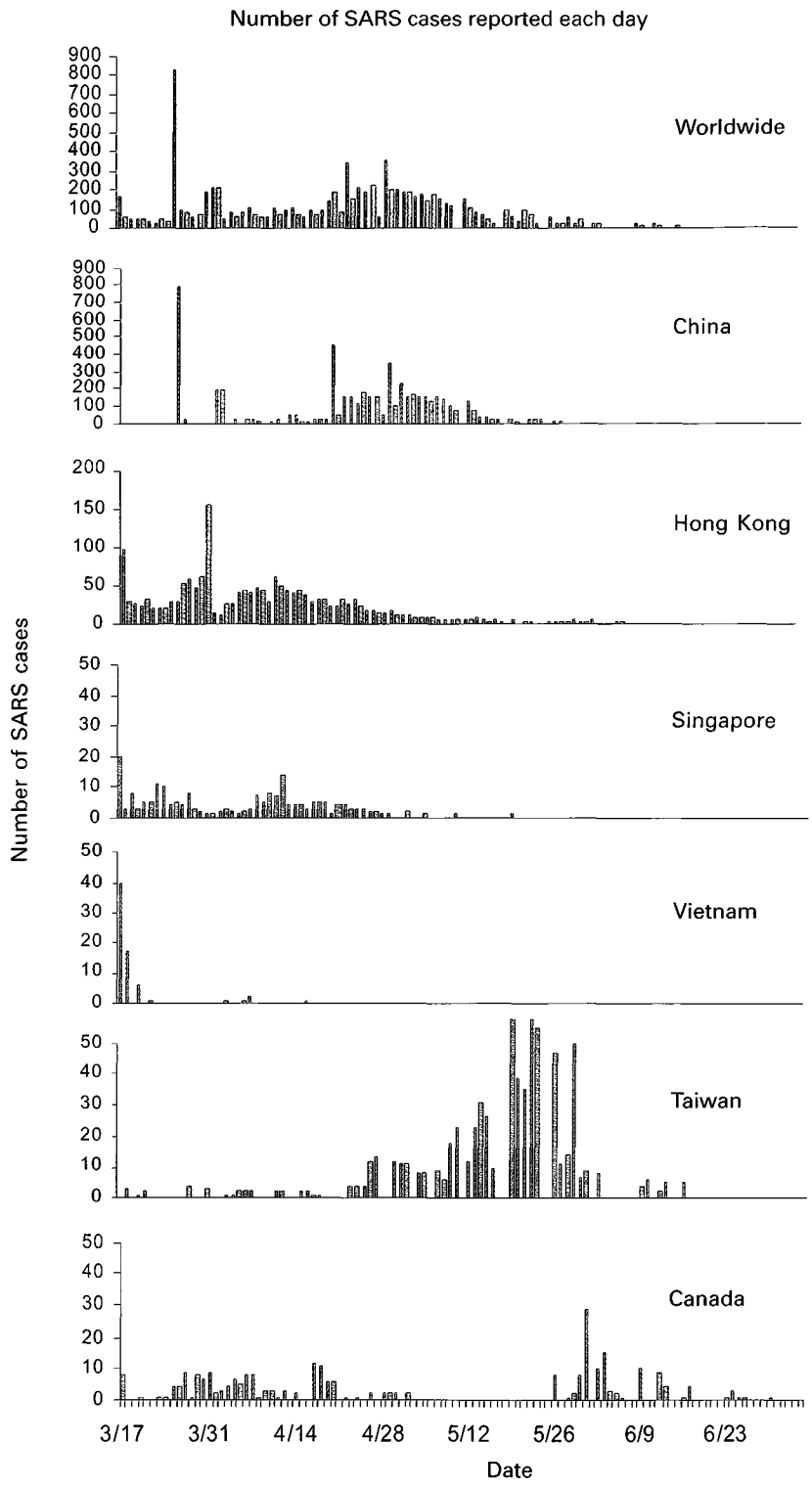
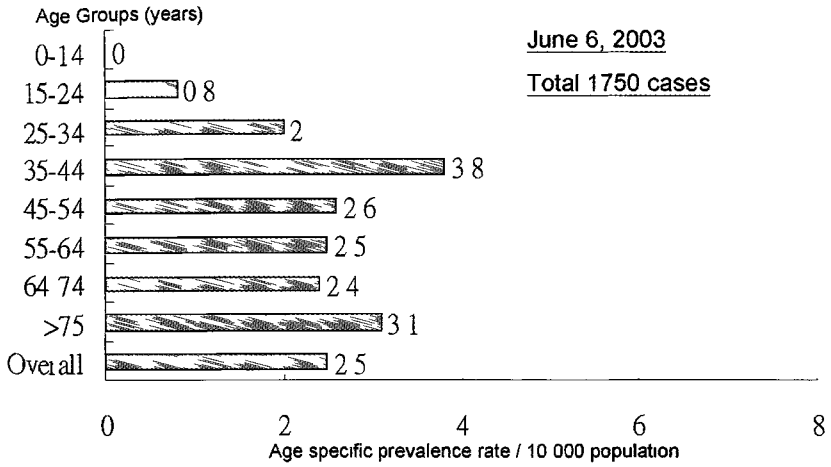
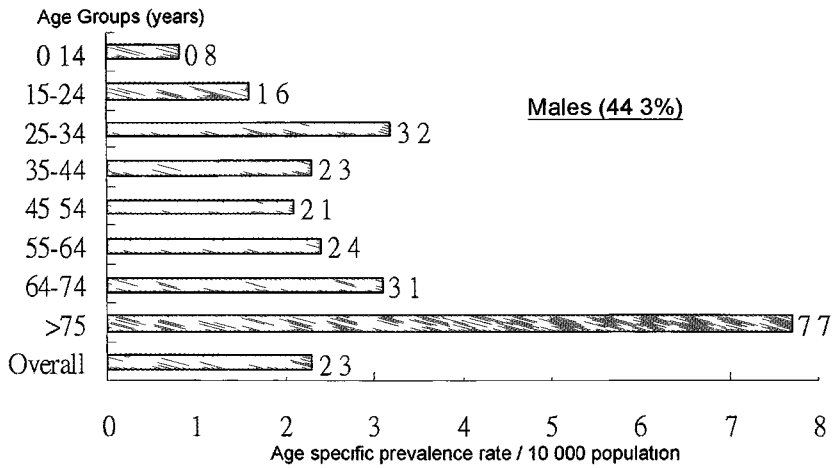


Figure 2. Number of SARS cases reported each day by selected Asian countries and Canada during the 2003 epidemic





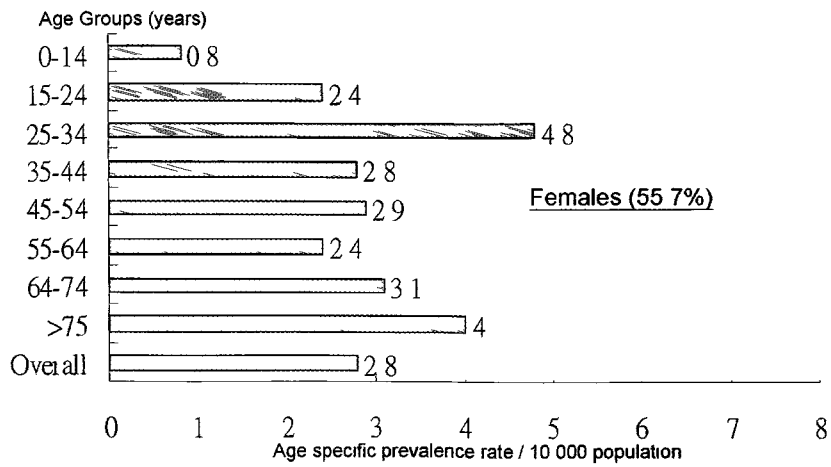


Figure 3 Age and gender specific prevalence rate (number of SARS cases / 10 000 population)

From the Clinical Trial Centre The University of Hong Kong http //www hkuhk/ctc
Source Hospital Authority and Hong Kong SAR Government press release

Close contacts. Family members and close friends are at high risk of developing disease. Use of nebulizer (16) and any procedure that induce cough is associated with increase risk of spread of disease (17). Exposure to unsuspected SARS patients in enclosed space such as aeroplane and small elevators was studied (18). The result showed that passengers sitting on the same row and two in front and two behind a patient with SARS in an aircraft were not at the highest risk of getting infected as suggested by the WHO (19).

Case-fatality rate

Table 1 also shows the cumulative number of deaths in selected countries since the onset of the epidemic (14). The case fatality ratio (calculated as the number of deaths/total number of reported cases) estimated by the WHO at the conclusion of the epidemic varied between regions and countries (mainland China 6.6%, Hong Kong 17%, Singapore 13.9%, Canada 17.1%, many countries, including European countries and the United States 0%). It is estimated to be less than 1% in persons aged 24 years or younger, 6% aged 25 to 44 years, 15% aged 45 to 64 years and greater than 50% aged 65 years and older (20).

In Hong Kong, there were 299 deaths out of 1755 patients with SARS (case fatality 17.0%) (14). The experience in Hong Kong and other areas suggested that deaths are associated with pre-existing illness, age of 65 and over and treatment late in the course of the disease (17). Age and gender specific case fatality of SARS patients in Hong Kong is shown in Figure 4.

Aetiology

When clusters of cases of a severe, highly infectious atypical pneumonia were first reported in Guangdong province in southern China from November 2002 to January 2003, all tests for known pathogens including bacterial, mycoplasma, chlamydial, legionella, fungal, and common respiratory tract viruses have either been negative or unrevealing. The causative organism was not known. Several organisms were implicated in the beginning. Chinese scientists first reported a chlamydia-like organism followed by reports of paramyxovirus (12) and metapneumovirus (5) as likely causative organisms. In early April 2003, Peiris et al from Hong Kong (1), Poutanen et al (5) from Toronto, Ksiazek et al (21) from the Centers for Disease Control and Prevention (CDC) in the United States, and Drosten et al (22) from the European group independently announced identification of a novel coronavirus associated with SARS. The identification process involved a stepwise tissue culture isolation and electron-microscopic identification followed by molecular studies to confirm the identity and characterization of its unique nature. Finally on 16 April 2003, the WHO announced that a coronavirus never before seen in humans has satisfied all the four requirements of Koch's postulates as the etiologic agent responsible for SARS (2). The WHO has named the new virus "SARS virus", and Ksiazek et al has proposed the name "Urbani SARS-associated coronavirus" in memory of Dr Carlo Urbani, a WHO infectious disease expert who drew attention to the world of this new epidemic of atypical pneumonia but who sadly contracted SARS in Hanoi and died in Bangkok on 29 March 2003. The genome for this novel virus has also been sequenced independently by Canadian, CDC (US), Hong Kong and Singaporean scientists (23–26).

Coronaviruses are large enveloped RNA viruses. They are known to be associated with a variety of diseases in humans and domestic animals, including respiratory tract infections (common cold in humans (27)) and gastroenteritis. The genomic sequences of the SARS virus show that it is distinct from all previously described coronaviruses in animals and humans (23–26). It was thought that the SARS virus originated in animals that somehow acquired the ability to infect humans. At this time, the virus genomic sequence does not show obvious evidence of an animal origin, and there is no evidence that SARS virus is a mutant of any known coronavirus or a recombinant of known coronaviruses. A characteristic of RNA viruses is the high rate of genetic mutation. Genotypes have already been linked to geographic and temporal clusters of infectious contacts, and genetic signatures have the potential to trace sources of infection (26). Whether different genotypes will cause different clinical spectra is being studied, particularly the genotype that caused the Hong Kong Amoy

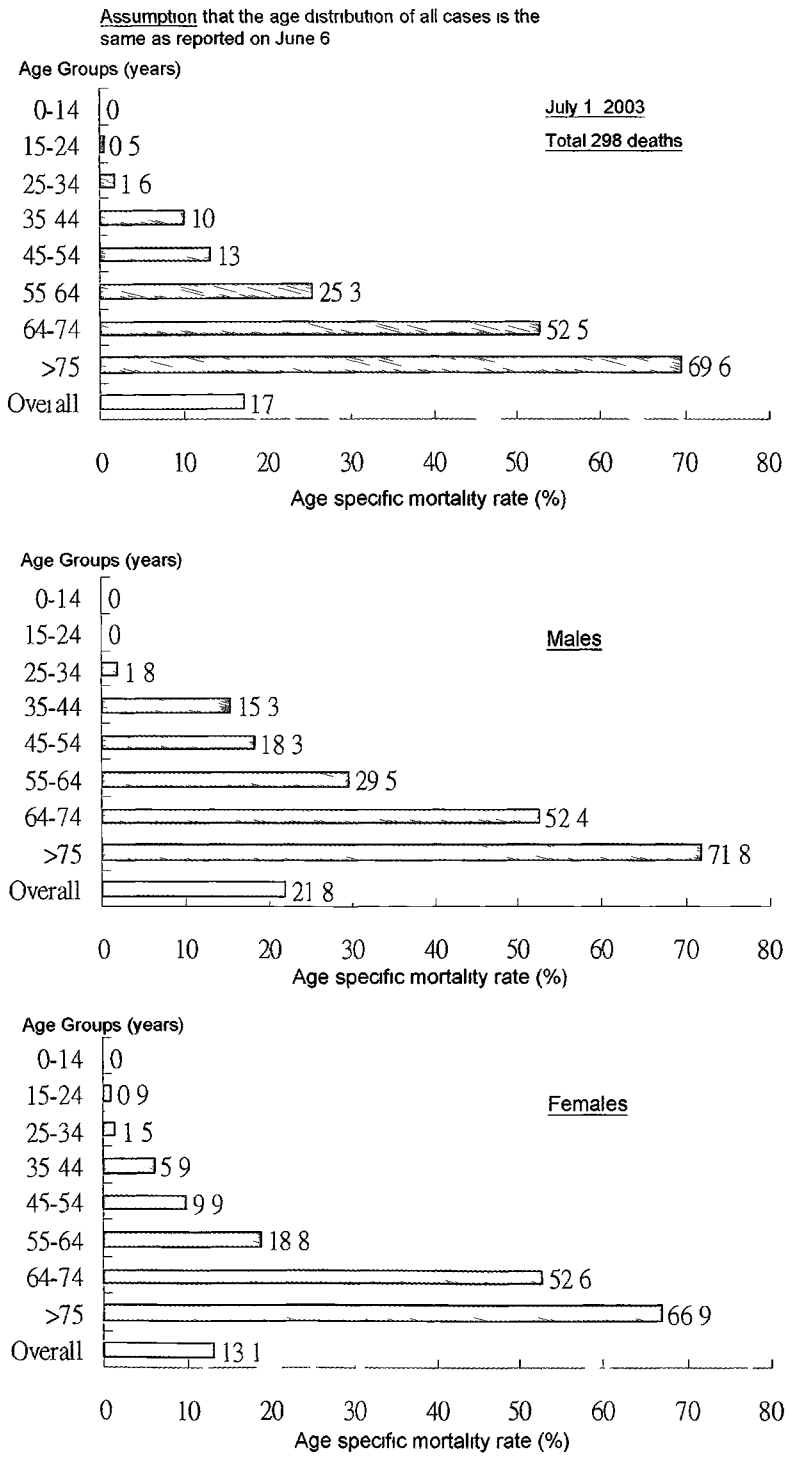


Figure 4 Age and gender specific case fatality rate

From the Clinical Trial Centre The University of Hong Kong http //www hkuhk/ctc
Source Hospital Authority and Hong Kong SAR Government press release

Gardens housing estate outbreak with over 330 patients who presented with more serious disease featuring prominent diarrhoea resulting in 35 deaths up to 14 May 2003.

The demonstration of an antibody in sera of patients to this virus and the identification of its gene sequence allows development of a serological test and a rapid, specific molecular test for SARS using reverse transcription-PCR (RT-PCR) technique.

Mode of transmission

The disease is very likely transmitted from human-to-human by droplets generated by coughing and sneezing and by direct inoculation. The virus can survive in stool and urine at room temperature for at least 2 days and longer in stool from diarrhoeal patients (28). Contact with surface with infected droplets can be a source of infection. A study carried out by an infection control unit locally has shown that the use of surgical or N-95 masks, thorough hand washing (droplet precaution) provided a very high level of protection to health care workers, thus supporting transmission of the virus by droplets (29). The virus loses its infectivity after exposure to several commonly used disinfectants such as Clorox, 75% ethanol and fixatives such as formaldehyde and paraformaldehyde (28).

The large number of residents in Amoy Gardens developing disease within a short period of time raised the suspicion that other modes of transmission such as airborne or oral-fecal route may be responsible. Investigation conducted by the Department of Health, Hong Kong concluded that the virus was carried by droplets into people's bathrooms as a result of contamination of waste drainage pipe and failure of the U-shaped water-seal (30). The contamination could be traced to a patient who had loose stool when he visited his brother in one of the flats in the E Block of Amoy Gardens. The report excluded airborne transmission, but clear evidence has yet to be provided.

Some patients are "super-spreaders" as one of them can infect dozens of people as indicated above. It is not clear why some patients are super-spreaders but it could be that they have very high viral load in their secretion.

Pathology

Pathology of the lungs of fatal cases showed early and organizing phases of diffuse alveolar damage suggestive of adult respiratory distress syndrome (4,17,31). Areas of alveolar oedema with foci of haemorrhage and hyaline membrane formation were seen with scattered foci of alveolar myxoid fibroblastic tissue. Epithelial cell proliferation was evident. The alveolar pneumocytes showed cytomegaly with granular amphophilic cytoplasm. Lymphocytes infiltration and viral cytopathic features were scanty. There was a marked increase in pulmonary macrophages with haemophagocytosis (31). Electron microscopy revealed viral particles in the cytoplasm of epithelial cells corresponding to coronavirus.

Clinical features and diagnosis

Clinical presentation

The incubation period is from two to 10 days, and patients are admitted to hospitals at a mean of 5 days of onset of symptoms. High fever (> 38°C) is present in practically all patients (except a few elderly patients) (1,4,5,17,32). The other prominent presenting features are chills (73–90%), cough, usually dry (57–80%), dyspnoea (42–80%), myalgia (49–61%), headache (56–70%), malaise (50–70%), and dizziness (12–43%) (1,4,5,17). Interestingly, diarrhoea occurs in about 20% of patients, and much more so (60–70%) in the subgroup of patients in the Amoy Gardens housing estate outbreak involving 330 patients. Upper respiratory symptoms such as sore throat and running nose occur in less than 25% of patients. Haemorrhagic-fever-like illness with disseminated intravascular coagulopathy can occur, but is usually mild (33). History of contact (either history of attending to patients or household members of patients), or of visits to hospitals with SARS patients, or of travel to other regions outside Hong Kong affected by SARS is characteristic. Up to 80% of the patients in Hong Kong have identifiable links with known cases and clusters. Physical examination on admission shows a high temperature (> 38°C) in nearly all patients, but rarely rash or lymphadenopathy. Inspiratory crackles, if present, are usually at the base of the lungs.

Laboratory findings

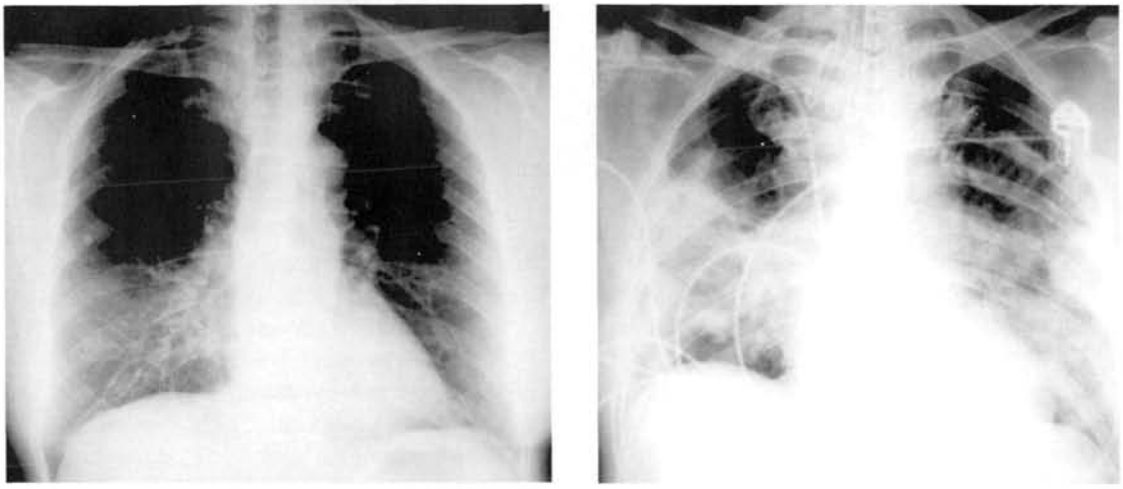
Despite high fever, leucocytosis is rare. Lymphopenia occurs in 68–100% of patients (1,4,17,32). Other common blood tests findings on presentation include thrombocytopenia (40–45%), prolonged activated partial-thromboplastic time (43%), elevated serum alanine aminotransferase (23–100%), elevated lactate dehydrogenase (87%), hypocalcemia (60%), elevated creatine kinase (26–32%, particularly high in patients with significant myalgia), and hyponatremia (20%).

Radiological findings

The most commonly seen chest radiograph abnormalities on presentation are air-space shadowing. At presentation the chest radiograph may initially be normal although ground glass opacities are most commonly encountered. These progress rapidly to focal, patchy or diffuse consolidation with lower lobe predominance (4,17,34) (Figure 5). In one series of 108 patients, 59 (55%) had unilateral focal involvement and 49 (45%) had either unilateral multifocal or bilateral involvement (17). In a smaller cohort (n = 40), initial radiographic abnormalities were confined to one lung in 67.5% of cases but at maximal disease, bilateral involvement was present in 65.5% (35). After treatment, the lung changes continue to increase peaking at 5 days post treatment (35) before showing a decline. Pleural effusions per se and mediastinal lymphadenopathy are not seen, although a trace of pleural fluid can sometimes be found. High-resolution computed tomography (HRCT) scan shows characteristic ground-glass abnormality in a subpleural location in the initial phase, which progresses rapidly to involve other areas of the lungs (4,17,34) (Figure 6). The ground glass opacity is associated with interlobular septal thickening, and nodular or focal areas of consolidation. In the few patients with normal chest radiograph on presentation, HRCT scan will be able to pick up the abnormal ground-glass opacification and small areas of consolidation (4,17,33,34). HRCT will also identify more extensive disease in contralateral or other areas of the lungs not visualized on the chest radiograph. The differential diagnosis for the HRCT appearance will have to include ARDS, CMV pneumonitis, acute interstitial pneumonitis, BOOP and even alveolar proteinosis.

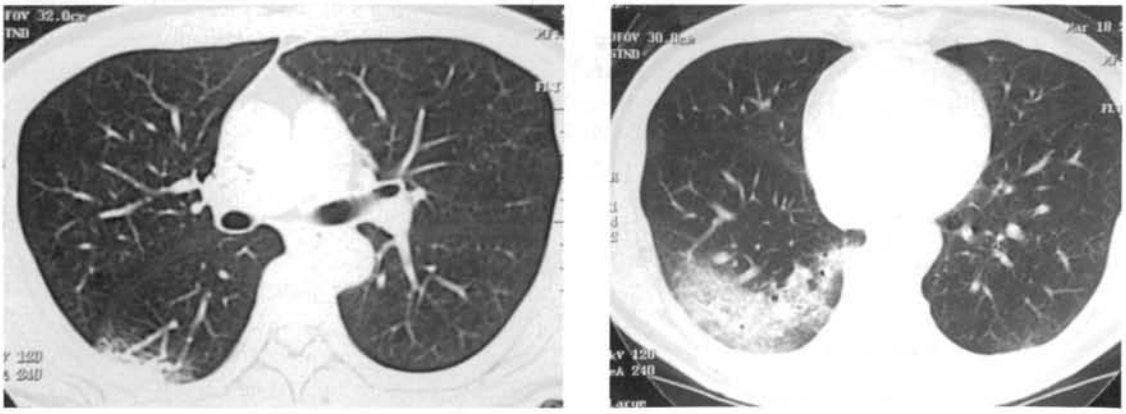
Clinical diagnosis

At present, the diagnosis of SARS remains a clinical one, which is made after excluding background pneumonia and other interstitial lung disease. The WHO defines a suspected case as a person presenting after 1 November 2002 with a history of high fever (> 38°C) AND cough or



a. b.

Figure 5. Chest radiographs of a 45-year old female with SARS showing (a) ground glass opacification in the right lower lobe that progressed to (b) multifocal patchy consolidation within 4 days.



a. b.

Figure 6. CT scans showing progression of disease in a 56 year-old patient with SARS. (a) CT scan at presentation when the chest radiograph was normal. There was a small subpleural area of ground glass opacity and consolidation in the apical segment of the right lower lobe. (b) After 6 days, this had progressed to involve most of the sub pleural regions of the right lower lobe. Note the consolidation with adjacent ground glass opacification.

breathing difficulty AND one or more of the following exposures during the 10 days prior to onset of symptoms: close contact with a person who is a suspect or probable case of SARS, or history of travel to an area with recent local transmission of SARS (11). In Hong Kong, the Hospital Authority's case definition of SARS (36) includes:

1. the presence of new radiological infiltrates compatible with pneumonia;
2. fever > 38°C or history of such any time in the last two days; and
3. at least two of the following: chills any time in the last 2 days, new or increased cough or breathing difficulty, general malaise or myalgia, or known history of exposure.

In practice, known history of contact is the most important, although the existence of numerous pockets of infections in the community has diminished its value as a distinct link to a case may not be evident.

In highly suspected cases with a normal chest radiograph, a HRCT scan is indicated. Blood cells counts, liver function and renal function tests are helpful as lymphopenia, elevated alanine aminotransferase and creatine kinase and hyponatremia are helpful clues to support the diagnosis. All standard microbiological investigations for bacteria, mycoplasma, chlamydiae, fungi, legionella and influenza A and B, parainfluenza types 1, 2 and 3, respiratory syncytial virus and adenovirus are negative.

Virological diagnosis

Serum antibody (IgG) tests have been developed, including enzyme immunoassay (ELISA) and indirect immunofluorescence antibody (IFA) tests. IFA test done on paired acute and convalescent sera in a series of 32 patients showed that all had seroconverted or had more than a four-fold increase in antibody titre (1). Convalescent serum should be collected 21 days or later after the onset of symptoms. This test is very specific as none of the sera from 200 blood donors had antibodies to this new coronavirus.

Viral RNA can also be detected in nasopharyngeal aspirates (NPA) and stools of patients by a RT-PCR assay. In a study of a cohort of 75 patients in a community outbreak, the RT-PCT test was positive in 32% of NPA at presentation, and by day 14, 68% of NPA and 97% of stools were positive (37). Quantitative RT-PCR demonstrated a peak viral load at day 10 of onset of symptoms. It is reported that viral RNA can also be detected in saliva. The RT-PCR assay is a rapid and specific test for SARS, but its overall sensitivity needs to be improved.

In May 2003, The WHO has issued recommendations on the interpretation of laboratory results (38). Apart from virus isolation, SARS diagnostic test findings are considered positive if

1. PCR for SARS virus is confirmed positive by
   a. at least 2 different clinical specimens (e.g. nasopharyngeal and stool), or
   b. the same type of clinical specimen collected on 2 or more days during the course of the illness, or
   c. 2 different assays or repeat PCR using the original clinical sample on each occasion of testing
2. Seroconversion is demonstrated by IFA or ELISA
   a. negative antibody test on acute serum followed by positive antibody test on convalescent serum, or
   b. a four-fold or greater rise in antibody titre between acute and convalescent phase sera tested in parallel

Management

Principles and assumptions

SARS is a completely new infectious disease, and its most efficacious treatment is not known at this time. The management of SARS is based on the following principles, observations and assumptions:

1. The diagnosis of SARS at presentation is a clinical one, and pneumonia due to other microbes must be excluded;
2. SARS is a highly infectious disease. Strict isolation policies and universal precaution measures against droplet spread must be strictly adhered to by all health care workers. Visiting by relatives should be forbidden although critically ill patients must be treated with special understanding;
3. SARS can present without fever or respiratory symptoms, particularly among older patients, in whom the presentation could be general ill-health and anorexia. The severity of the disease also varies greatly for different individuals, with some patients showing hyper-acute presentation progressing to adult respiratory distress syndrome over the course of 2–3 days while others with slowly but partially resolving pneumonia;
4. Anti-viral therapy should be given in the early phase of the disease when viral replication is taking place. A peak viral load has been demonstrated on day 10 of presentation (37). However, ribavirin has been described to be a weak anti-viral agent and there is currently no other more effective anti-viral agent against SARS-virus. It is likely that intensive efforts to search for this mode of therapy will limit the severity of subsequent lung damage.
5. Many patients with SARS have progressive pneumonic changes over the course of their second week of hospitalization, some even occurring in the first 24–48h after presentation. Radiological changes of diffuse confluent shadows in peripheral and subpleural areas of the lung are similar to those of immune mediated lung diseases such as BOOP. The patients may concommittantly develop desaturation. This phase of clinical and radiological deterioration occurs at the time of a fall in viral load (37), and is unlikely to be due to viral replication.. Pathological findings in the lung of serious or fatal cases show relatively little cytopathic effect, but there are features of alveolar macrophage activation with haemophagocytosis and fusion to form giant cells, followed by squamous hyperplasia and hyaline membrane formation and diffuse alveolar damage, features of adult respiratory distress syndrome (4,17,31). All these changes are suggestive of an acute host reaction to a "cytokines storm" triggered by the coronavirus leading to acute and severe host tissue damage. Hence corticosteroid therapy is indicated, pending availability of more specific anti-inflammatory and anti-viral therapy to limit the damage. The recurrence of pneumonic changes with reduction in corticosteroid therapy among some patients with good radiological resolution also circumstantially supports this hypothesis. Unless an appropriate dose corticosteroid therapy is instituted early and judicially, many patients will progress to irreversible lung damage within the span of 1–3 weeks. There is therefore only a limited therapeutic window for steroid therapy, in order to avoid

progression to adult respiratory distress syndrome as well as residual pulmonary fibrosis.

6. SARS appears to be similar to the bronchiolitis obliterans with organizing pneumonia (BOOP) in its radiology as well as response to corticosteroid therapy.

Initial investigations

All health care workers should have a high index of suspicion for SARS. In hospital setting, universal precautions must be taken by all staff. In the Accident and Emergency (A & E) Department, a history of contact or travel must be taken from any patient with fever, chills, with or without chest symptoms or diarrhoea together with a chest radiograph. Patients with suspected or probable SARS must be admitted directly to specially designated wards with designated staff, and not to a general medical ward (6, 39). The relevant blood tests include complete blood counts, liver and renal function tests, clotting profile, creatine kinase and lactate dehydrogenase. These blood tests and chest radiographs are performed daily until fever has subsided for three days (17).

Microbiological screen for bacterial (including blood culture), mycoplasma, chlamydial, legionella and common respiratory viral infections should be performed as in any patient with community acquired pneumonia. Acute and convalescent serum samples should be sent for serological test for SARS virus antibody. Convalescent serum sample taken more than 21 days after symptom onset is needed if earlier samples are negative. Nasopharyngeal aspirate or swab, and stool for RT-PCR test for viral RNA should be performed. As collection of nasopharyngeal aspirate has been associated with infection of nursing staff, this is currently only reserved for difficult diagnostic cases when other viral infections are strongly suspected and when initial RT-PCR for coronavirus is negative. Saliva specimens are being studied as alternative to nasopharyngeal aspirates for the RT-PCR test.

For highly probable cases with normal chest radiograph, a high-resolution CT (HRCT) scan may be ordered to detect the characteristic ground glass consolidation, which may otherwise be missed, especially when the lesion is behind the heart shadow. However, routine HRCT for all cases is strongly discouraged as this imposes unnecessary exposure to all staff and fellow patients. We currently only perform HRCT at baseline if the chest radiograph remains persistently normal and the patient appears to be highly suspicious (e.g. high fever, abnormal liver function and lymphopenia and with history of contact). For patients with persistent parenchymal shadows after commencement of adequate treatment, we also perform HRCT to assess the extent of "reversible" (ground glass) and fibrotic elements, thus to determine the dosage of steroid therapy.

Cohorting and isolation

All suspected or probable cases must be cohorted in designated wards. Staff of any grade should fully comply with isolation and infection control measures. No visitors should be allowed, and no nebulization therapy should be implemented to avoid aerosolized spread of the virus (17). Even high flow oxygen therapy has been implicated in causing infection in health care workers. Non-invasive nasal mask ventilation might also carry the danger of droplet spread, but it has been widely used in mainland China with no significant problem. In Hong Kong, it is only used in negatively pressurized rooms with increased air exchanges (10 to 12 or more air exchanges per hour). The patient's oxygenation status should be monitored by pulse oximetry, and oxygen is given as indicated.

Antibiotics and antiviral therapy

A regimen of potent B-lactam antibiotic (by intravenous route) and macrolide should be given. A quinolone is given for patients sensitive to B-lactams. Patients with traditional community acquired pneumonia should start to show response clinically or radiologically within two to three days. In non-responders, or when the patient deteriorates, one has to consider initiating treatment as for SARS in the appropriate clinical setting.

Antiviral therapy should be implemented in the early viral replication phase. In Hong Kong, Singapore, Taiwan and Toronto, the antiviral drug currently in use is ribavirin (4,17,32,40). Ribavirin is a broad-spectrum antiviral drug against a number of RNA and DNA viruses. It is not very effective against the SARS virus, and a high dose (8 mg/kg every 8 hours) is given by the intravenous route

for at least 3 days or till stable followed by oral route 1200 mg twice daily for a total of 10 to 14 days (40), with the associated increased side effects especially haemolysis of red blood cells and decrease in haemoglobin of up to 2 g/dL (31). It is also teratogenic and is contraindicated in early pregnancy. The US CDC has expressed concern on the lack of activity of ribavirin against the SARS virus. At this time, however, there is no other anti-viral drug with better activity. Moreover, ribavirin has been shown in a mouse coronavirus hepatitis model to decrease the release of tumour necrosis factor from macrophages, indicating that ribarvirin may also act as an immunomodulator (Yuen KY, personal communication). In the US, neuraminidase inhibitor (oseltamivir) has been tried, but its efficacy has yet to be assessed.

Corticosteroids and other immunomodulatory therapy

The timing of the body immune hyperreactivity phase is not known and the best time to start corticosteroid therapy or its appropriate dose is not clear. In Hong Kong, the practice varies although this is likely to unify when experience gathers. Some physicians withheld corticosteroids for several days and then start hydrocortisone 4 mg per kg body weight every 8 hours intravenously while others gave methylprednisolone (including pulse doses) with ribavirin early in the clinical course particularly when the condition is rapidly deteriorating (40). Most patients responded clinically and radiologically, and some patients responded dramatically with resolution of fever and improvement in heart rate within 48 hours (4).

In our institute, we generally give most patients with severe and multilobar disease IV pulse methylprednisolone at a dosage of 500 mg daily for 5 days, and then switch to oral prednisolone at a dosage of around 50 mg twice daily (41). Preliminary results of this regimen indicated that about 60–70% of cases had clinical remission and radiological resolution when assessed at 3 weeks. The remaining patients (some 20–25% of patients requiring admission to ICU) appeared to have a more severe disease that did not completely resolve radiologically despite this treatment. These cases also developed recurrence of pneumonic changes or continued to deteriorate towards the beginning of their second week of illness. For these patients, a second pulse of methylprednisolone often led to radiological and clinical improvement, although some cases continued to deteriorate. Pneumomediastinum is a well-recognized complication in this phase of treatment. A few such patients have responded to other immunomodulating therapies such as intravenous immunoglobulins. Secondary chest infection is a complication at this stage, which may contribute to mortality of the disease.

Lamivudine should be given with high-dose corticosteroid therapy in patients who are chronic hepatitis B carriers to avoid reactivation of the hepatitis.

A recent retrospective study showed that a combination of Kaletra (lopinavir 400 mg and ritonavir 100 mg), an anti-HIV drug, and ribavirin resulted in reduction in steroid usage and nosocomial infection, and these patients had a decreasing viral load and rising peripheral lymphocyte count (42).

Subsequent clinical course and sequelae

The post-recovery clinical course of the disease is not known. In Hong Kong, the patients are discharged after one week of staying afebrile with clinical and radiological improvement. They are asked to monitor their temperatures and other clinical features at home. Of the about 800 patients discharged from hospitals up to 30 April 2003, 12 patients have returned with relapse of fever, often with other symptoms and a few with radiological relapse as well within two weeks of discharge. Some of them have other problems rather than a true relapse of the disease (e.g. secondary chest infection). At the time of writing, they have either been discharged again well or remained stable in hospital. None of them have required intensive care treatment or died.

The radiological, lung function, other systemic and psychological sequelae of SARS in survivors are not known at this present time. Patients surviving intensive care treatment tend to have radiological features of residual pulmonary fibrosis on discharge.

Future treatment and prophylaxis

At present, the most efficacious treatment regimen

for SARS, if any, is unknown. All current treatment regimens are empirical and have not undergone any randomized controlled studies. Many questions remain to be answered, including the choice of anti-viral drugs, the role, dose and timing of corticosteroid treatment or other immunosuppressive drugs, and the role of immunomodulating therapies including immunoglobulins, convalescence serum and anti-cytokines such as anti-TNF-a. There is an ongoing international effort to discover newer, more effective anti-viral drugs and to develop an effective vaccine in the long term. As this new coronavirus is an enveloped RNA virus which carries a surface glycoprotein enabling the virus to find its way to the target tissue, recognizing specific receptors and allowing fusion of the virion with the target cells, strategies of finding new anti-viral drugs include this anti-fusion targeted therapy approach. The viral main proteinase ($3CL^{pro}$) which controls the viral replication process, is another possible target for therapy (43). Similarly, protease inhibitors used against HIV infection are being tested. The efficacy of interferon is also being studied in the laboratory. Antibodies against the viral S glycoprotein or the receptor for the SARS virus are other potential therapeutics. Meanwhile in mainland China, clinical studies on the role of inhaled interferon a-2b and Chinese medicine in prophylaxis against SARS are being initiated in health care workers. Chinese medicines as adjuvant therapy are also being studied in mainland China and Hong Kong.

Prognostic factors

Age is the most important prognostic factor (1,17,20,37,44). In Hong Kong, older age group (> 65 years) accounted for 14% of the cases but 54% of the fatalities. Children under the age of 10 years old tend to run a much milder course (45). Males are more at risk to dying than females. Other prognostic factors include late presentation and delayed therapy, high absolute neutrophil count, severe lymphopenia, high peak level of lactate dehydrogenase, elevated alanine amintransferase and presence of co-morbidities, including chronic hepatitis B infection and diabetes mellitus (1,17,32,37).

Prevention

Infection control in the hospital

One of the major problems in many countries is the lack of training in infectious disease and infection control of the health care profession. This is because major infectious disease such as smallpox and poliomyelitis that plague people during the first part of last century are almost nonexistent.

With a highly infectious disease as SARS, strict hospital isolation is necessary. Isolation facilities should be created not only for confirmed SARS patients but also for suspected SARS patients. All isolation wards should not have visitors. Strict barrier nursing should be carried out. All staff should wear n-95 mask, gowns, face shields, goggles and gloves. They should be taught how to wash hands meticulously before putting their protective devices on and how to take them off and how to wash their hands afterwards.

Public health measures

The classical public health measures for controlling infectious disease should be in place.

1. Vigorous tracing and mandatory quarantine of close contacts for 10 days (the incubation period for SARS) should be instituted as soon as possible supported by invoking the Quarantine and Prevention of Disease Ordinance.
2. Port control. As SARS is spreading very rapidly globally from one country to another by international travel, it is vital to screen individuals to ensure they do not have symptoms of SARS before departure. Measurement of temperature has provided a relatively easy and quick method of screening but its effectiveness is not clear. It is not known at present whether asymptomatic individuals during incubation period is infectious or not.
3. Disinfection of places where a SARS patient lives and works should be carried out.
4. Closure of schools and universities, cancellation of all public events during an epidemic may be necessary to reduce the chance of transmission.

All these measures should be accompanied by an intensive public education campaign on the use of masks in all public places, public transportation, frequent and thorough hand washing, and personal hygiene via newspaper, television, posters and hotlines. The importance of isolation of close contacts and the need for the disease to be treated early to ensure recovery has to be emphasized.

Summary

As a disease SARS is less contagious than influenza and the number of affected individuals globally is small. The cumulative number of cases of SARS globally in the past 5 months is less than 8000. This is insignificant compared to tuberculosis when 8 million people develop the disease and 1.9 million died from the disease each year globally. However, because of its potential of causing a pandemic and its high morbidity, its control from spreading from one place to another is paramount.

Despite the complete lack of knowledge at the onset of the epidemic, very significant advances have been made in a very short period of time. More new information will become available between the time of writing of this chapter and its publication.

This epidemic has taught us a number of lessons:

1. The reporting of an outbreak of infectious disease as early as possible to the WHO is absolutely essential for containment and control. WHO disseminates information and alerts health authorities in other countries, provides international experts to assist investigation of the epidemic and to identify the causative agent.
2. There should be much greater communication between health authorities of neighbouring regions when an outbreak of infectious disease is suspected to alert the medical profession of a potential problem.
3. Health care workers must be trained in infection control measures and be assiduous in applying them at all times.
4. Early institution of appropriate quarantine measures of close contacts is necessary for the control of an epidemic of SARS. To introduce these later so as not to cause public panic is not permissible.

Hong Kong and southern China have been the birthplaces of several viral illnesses in the past such as Hong Kong flu, Asian flu and avian flu. SARS is likely to be followed by others. There has been progressive integration between Hong Kong and Guangdong province, and Hong Kong is one of the most densely populated cities in the world. Hence any new infection is likely to spread much more rapidly than less densely populated areas and consequently much more difficult to control. The whole region has to be prepared against the potential introduction and spread of similar diseases in the future in several ways. It has to strengthen its capacity for disease prevention and control. The environmental conditions that led to the spread of disease have to be dealt with. The public needs education and reminder on personal and public hygiene. It is only when every citizen realizes the importance of personal hygiene and a clean environment that better living conditions can be sustained and the chances of spread of diseases like SARS can be lessened.

References

1. Peiris JSM, Lai ST, Poon LLM, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003; 361:1319–25.
2. World Health Organization. Severe acute respiratory syndrome (SARS). 16 April 2003. www.who.int/csr/2003_04_16/en.
3. World Health Organization. Severe acute respiratory syndrome (SARS). 12 March 2003. www.who.int/csr/2003_03_12/en.
4. Tsang K W, Ho PL, Ooi GC, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. *N Engl J Med* 2003; 348:1977–85.

5. Poutanen SM, Low DE, Henry B, et al. Identification of severe acute respiratory syndrome in Canada. *N Engl J Med* 2003; 348:1995–2005.
6. Chan-Yeung M, Seto WH, Sung JJY. et al Severe acute respiratory syndrome: Patients were epidemiologically linked. *BMJ* 2003; 326:1393
7. Chan-Yeung M, Lai T, Yan WW, Yu WC. Unpublished data.
8. Ministry of Health, Singapore. Severe Acute Respiratory syndrome (SARS). 8 May 2003. www.app.moh.gov.sg/.
9. World Health Organization. Severe acute respiratory syndrome (SARS). 24 March 2003. www.who.int/csr/2003_03_24/en.
10. World Health Organization. Severe acute respiratory syndrome (SARS). 29 April 2003. www.who.int/csr/2003_04_29/en.
11. World Health Organization. Severe acute respiratory syndrome (SARS) definition, 2003. www.who.int/csr/sars/casedefinition/en/.
12. World Health Organization. Severe acute respiratory syndrome (SARS). 19 March 2003. www.who.int/csr/2003_03_19/en.
13. World Health Organization. Severe acute respiratory syndrome (SARS). 26 March 2003. www.who.int/csr/2003_03_26/en.
14. World Health Organization. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. 21 April 2004. www.who.int/csr/sars/country/table_2004–04–21/en.
15. Clinical Trial Centre, The University of Hong Kong. www.hkuhk/ctc. Source: Hospital Authority and Hong Kong SAR Government Press Release on 6 June 2003.
16. Lee N, Hui D, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. *New Engl J Med* 2003; 348:1986–94.
17. Center for Disease Control and Prevention. Severe Acute Respiratory Syndrome (SARS). www.cdc.gov/ncidod/sars/clinicians.htm.
18. Olslen SJ, Chang HL, Cheung TY, Tang AF, Fisk TL, Ooi SP, Kuo HW, Jiang DD, Chen KT, Lando J, Hsu KH, Chen TJ, Dowell SF. Transmission of the severe acute respiratory syndrome on aircraft. *N Engl J Med* 2003; 349:2461–22.
19. World Health Organization. Severe acute respiratory syndrome (SARS). 27 March 2003. www.who.int/csr/2003_03_27/en.
20. World Health Organization. Update 49 — SARS case fatality ratio, incubation period. 7 May 2003. www.who.int/csr/2003_05_07/en.
21. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 2003; 348:1953–66.
22. Drosten C, Gunther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med* 2003; 348:1967–76.
23. CDC Lab sequences genome of new coronavirus. Atlanta, Centers for Diseases Control and Prevention 2003. 16 April 2003. www.cdc.gov/od/oc/media/pressrel/r030414.htm.
24. Rota PA, Oberste MS, Monroe SS, et al. Characterization of a novel coronavirus associated with severe acute respiratory syndrome. *Science* 2003; 300:1394–9.
25. Marra MA, Jones SJM, Astell CR, et al. The genome sequence of the SARS-associated coronavirus. *Science* 2003; 300:1399–404.
26. Ruan YJ, LW Chia, AE Ling et al. Comparative full-length genome sequence analysis of 14 SARS coronavirus isolates and common mutations associated with putative origins of infection. *Lancet* 2003; 361:1779–85.
27. El-Sahly HM, Atmar RL, Glezen WP, Greenberg SB. Spectrum of clinical illness in hospitalised patients with "common cold" virus infection. *Clin Infect Dis* 2000; 31:96–100.
28. World Health Organization. First data on stability and resistance of SARS coronavirus compiled by members of WHP laboratory network. 4 May 2003. www.who.int/csr/sars/survival_2003_05_04/en/index.html.
29. Seto WH, Tsang D, Yung RWH, et al. Effectiveness of precautions against droplets and contact in preventing nosocomial transmission of severe acute respiratory syndrome (SARS). *Lancet* 2003; 361:1519–20.
30. Main findings of an investigation into the outbreak of Severe Acute Respiratory Syndrome at Amoy Gardens. Department of Health, Hong Kong. 17 April 2003. www.info.gov.hk/dh.
31. Nicholls JM, Poon LLM, Lee KC, et al. Lung pathology of fatal severe acute respiratory syndrome. *Lancet* 2003; 361:1773–8.

32. Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term. outcomes of 144 patients with SARS in the Greater Toronto Area. *JAMA* 2003; 289:2801–9.
33. Wu EB, Sung JJY. Haemorrhagic-fever-like changes and normal chest radiograph in a doctor with severe acute respiratory syndrome. *Lancet* 2003; 361:1520–1.
34. Muller NL, Ooi GC, Khong PL, Nicolaou S. Severe acute respiratory syndrome: radiographic and CT findings. *Am J Roentgenol* 2003; 181:3–8.
35. GC Ooi, Pl Khong, B Lam, et al. SARS: Relationship between radiological and clinical parameters. *Radiology* 2003; 229:492–9.
36. Hospital Authority (Hong Kong) Information on Management of SARS: Case definition, 2003; 361:1767–72.
37. Peiris JSM, Chu CM, Cheng VCC et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003; 361:1767–72.
38. World Health Organisation. Use of laboratory methods for SARS diagnosis. 5 May 2003. www.who.int/csr/sars/labmethods/en/.
39. Ho W. Guideline on management of severe acute respiratory syndrome (SARS). *Lancet* 2003; 361:1313–5.
40. So LKY, Lau ACW, Yam LYC et al. Development of a standard treatment protocol for severe acute respiratory syndrome. *Lancet* 2003; 361:1615–7.
41. Tsang KW, Lam WK. Management of SARS: The Hong Kong University experience. *Am J Respir Crit Care Med* 2003; 168:417–24.
42. Chu CM, Cheng VCC, Hung IFN, et al. Role of lopinavir/ritonavir in the treatment of SARS: Initial virological and clinical findings. *Thorax* 2004; 59:252–6.
43. Anand K, Ziebuhr J, Wadhwani P, et al. Coronavirus main proteinase ($3CL^{pro}$) structure: basis for design of anti-SARS drugs. *Science* 2003. www.sciencexpress.org/13 May 2003/Page 1/10.1126/Science.1085658.
44. Donnelly CA, Ghani AC, Leung GM, et al. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. *Lancet* 2003; 361:1761–6.
45. Hon KLE, Leung CW, Cheng WTF, et al. Clinical presentations and outcome of severe acute respiratory syndrome in children. *Lancet* 2003; 361:1701–3.

Part III Environmental and Occupational Lung Diseases

19 Air Pollution and Lung Health

Michael Brauer and Moira Chan-Yeung

Introduction

Exposure to air pollutants

In order to understand the potential health risks associated with air pollution, one must first understand the variables affecting exposure to air contaminants. Exposure may be defined as the intersection of individuals with pollutants over space and time. While much emphasis is placed on the regulation, control and health effects associated with outdoor sources of air pollution, it must be recognized that the majority of exposure to air pollution occurs indoors. This is due to the simple fact that individuals, particularly those in developed countries or in urban areas, spend the majority of their time indoors. Therefore, while the distinction between indoor and outdoor sources is important from a regulatory perspective (outdoor sources are typically subject to regulations while most indoor sources are not), from a health impact perspective both must be considered. Evaluation of the indoor environment and the various sources of air pollutants, including those from outdoors, that affect indoor air quality is an essential component in the evaluation of health effects associated with air pollution.

In one example, which illustrates the relative importance of indoor and outdoor sources of air pollutants, Florig evaluated the health risks of air pollution in China and concluded that, even though China has severely deteriorated urban outdoor air quality that adversely affects the health of the population, the most serious air pollution health risk is from poor indoor air quality. Specifically, residential burning of coal and biomass fuels for cooking and heating are the most important sources of air pollution exposure. Florig estimated that about 1 of every 8 deaths in China can be attributed to air pollution (1). In regions of China and in other countries where indoor biomass and coal burning is not common, however, outdoor air pollution presents a major health concern. For example, a 1997 World Bank report estimated that outdoor air pollution in 11 of China's largest cities was responsible for 50,000 premature deaths and 400,000 new cases of chronic bronchitis each year. The report also estimated annual deaths attributable to air pollution to be 6300 in Jakarta, 2400 in Seoul, 2800 in Bangkok, and 3800 in Manila (2).

Sources of air pollutants (indoor and outdoors)

In addition to natural sources of air pollution such as volcanic eruptions, dust storms and naturally occurring vegetation fires, major human-generated sources of outdoor air pollution can be classified as stationary or mobile sources. Major stationary sources include rural sources such as agricultural production, agricultural burning, mining and

quarrying, industrial sources such as manufacturing and power generation, and community sources such as residential home heating and municipal waste incinerators. In many urban areas, mobile sources are the major contributors to air pollution emissions. These include any form of combustion-engine vehicles such as gasoline and diesel powered cars, trucks, motorcycles and buses, as well as aircraft and marine vessels.

Important indoor sources of air pollution include infiltration of polluted outdoor air, combustion products from unvented indoor combustion devices (stoves for heating and cooking); consumer products such as perfumes, hairsprays and cleaning products; and emissions from building materials such as paints, furniture and carpet. In addition, indoor air may be contaminated with elevated levels of biological pollutants such as dust mites, pet allergens and fungal spores, which propagate on moist or water-damaged surfaces.

How are air pollutants measured?

Many countries develop a network of outdoor air quality monitoring stations as a means of overseeing pollution levels. A typical air quality monitoring station will routinely measure the concentrations of the major outdoor air pollutants based upon the procedures first employed by the U.S. Environmental Protection Agency. These pollutants are ozone (O_3), carbon monoxide (CO), nitrogen dioxide (NO_2), sulphur dioxide (SO_2), lead (Pb) and particulate matter (PM). Specific size classes of PM itself may be measured, including total suspended particles (TSP), inhalable particles (PM_{10}) and fine particles ($PM_{2.5}$). The details of these size classifications are discussed below. Specific monitoring locations may measure one or more of these pollutants at a frequency ranging from one measurement per minute to one per day. Together, multiple monitors may comprise a local monitoring network for a specific municipal area. Typically, the spatial coverage of a monitoring network is more thorough in more populated regions or in areas with specific air pollution concerns. Monitoring in rural areas is rare, except in the context of international monitoring networks to evaluate global atmospheric processes. No routine programs exist for indoor air quality monitoring, except those conducted in industrial occupational environments. Measurements in non-industrial-indoor locations are made in conjunction with research studies or in response to complaints from occupants.

Standards and indices

Air quality guidelines and standards have been adopted to protect public health from the negative effects of environmental pollutants. As one example, the World Health Organization (WHO) has developed guidelines that encompass the routinely measured pollutants indicated above, as well as other pollutants (www.who.int/peh/air/Airqualitygd.htm accessed 11 July 2002). While these guidelines apply to air pollutants indoors or outdoors, standards that are adopted by specific countries are limited to outdoor air. The application of specific indoor air quality standards is rare, and there are numerous examples of indoor air concentrations exceeding levels of outdoor air quality standards. Table 1 lists current outdoor air pollution standards for a number of Asian countries. Outdoor air pollution standards for a number of other Asian countries in available from <www.ipieca.org/activities/OIWG/directories/standards.html> (accessed 11 July 2002). Research is increasingly suggesting that there is little evidence to indicate no-effect thresholds related to the health effects of outdoor air pollution. For example, the most recent version of the WHO Air Quality Guidelines does not set guideline values for particulate matter but instead includes a quantitative relationship between PM concentrations and various health impacts. This is based upon the absence of scientific evidence to support a no-effects threshold concentration for airborne particulate matter. These relationships allow any individual country to manage air pollution by assessing the health effects associated with different levels. On this basis, most standards are not thought to be purely health-based, but are rather an application of scientific information in the political context of any given jurisdiction.

Air quality indices have been developed as a simple way to inform the general public about pollution conditions. There is currently no

Table 1. Ambient Air Quality Standards/Guidelines for United States, World Health Organization and Selected Asian Regions

Pollutant	*Averaging time*	*Hong Kong*	*Thailand*	*Philippines*	*Singapore*	*EPA NAAQS**	*WHO***
SO_2	10 min	–	–	300	–	–	500
	1 hr	800	–	850	–	–	–
	24 hr	350	300	370	365	365	125
	annual	80	100	–	80	80	50
NO_2	30 min	–	–	300	–	–	–
	1 hr	300	320	–	–	–	200
	annual	90	–	–	100	100	40
CO	15 min	–	–	–	–	–	100
	30 min	–	–	–	–	–	60
	1 hr	30	50	35	40	40	30
	8 hr	10	20	10	10	10	10
O_3	30 min	–	–	200	–	–	–
	1 hr	240	200	–	235	–	–
	8 hr 240	–	–	–	–	157	120
Suspended matter (TSP)	24 hr	260	330	180	260	–	–
	annual	80	100	–	75	–	–
Particulate < 10 μm (PM_{10})	24 hr	180	–	–	–	150	No guideline
	annual	55	–	–	–	50	**value** (impact relationship)
Particulate < 2.5 μm (PM2.5)	24 hr	–	–	–	–	65	No guideline
	annual	–	–	–	–	15	**value** (impact relationship)
Pb	24 hr	–	10	–	–	–	–
	3 months	1.5	–	20	1.5	1.5	–
	annual	–	–	–	–	–	0.5

All concentrations in $\mu g/m^3$ except CO in mg/m^3 **

* www.epa.gov/ttn/oarpg/naaqsfin/ accessed 11 July 2002

** www.who.int/peh/air/Airqualitygd.htm accessed 11 July 2002

standardised global air pollutant index, although many countries develop an index based upon the U.S. EPA Pollutant Standards Index (PSI) or the recent revision called the Air Quality Index (AQI) (www.epa.gov/airnow/aqibroch/ accessed 11 July 2002). The PSI and AQI are based on the measurement of five pollutants: carbon monoxide, sulphur dioxide, nitrogen dioxide, ozone and PM_{10}. The values for each pollutant are converted to a scale from 0 to 500, with only the highest value being reported. A value of 100 represents the air quality standard while a value of 500 represents the level of significant harm. At different index levels, precautionary statements are included to advise the public on actions to reduce their risk of health effects associated with air pollution. It is important to note that these indices do not take into account the effects of the combination of pollutants. Further, they are designed as tools to help communicate urban air pollution measurements to the public, and are not meant to be the basis of management strategies. They do

not themselves indicate whether any given individual will experience health effects.

Major Outdoor or Ambient Air Pollutants and Concentrations

Before discussing specific air pollutant concentrations and health impacts, it is important to note that air pollution monitoring methods are not standardized across countries nor is the availability of monitoring data the same in all locations. In an attempt to estimate the global health impacts associated with air pollution the World Resources Institute recently categorized outdoor urban air quality in countries throughout the world on the basis of the limited available air quality data for TSP, SO_2, NO_2 and (where available) PM_{10}. Countries in Asia where data were available are summarized in Table 2. The Table lists the number of cities with measurements of any pollutant that exceeded WHO guideline values and the population living in cities with air quality data exceeding WHO guidelines as a percentage of the total population of all cities for which both air quality and population data were available. The relative ranking of 1 –10 is based on the percentage of population in cities over WHO guidelines. The rankings range from a relatively low percentage (rank of 1) to a relatively high percentage (rank of 10) for developing countries; and from a relatively low percentage (rank of 1) to a relatively high percentage (rank of 27) for developed countries. Countries with the same percent of population in cities over the guidelines were assigned the same rank. Based on this classification system, the potential public health impacts of poor urban air quality in many Asian countries are obvious.

Table 3 lists concentration information reported from a selection of health effects studies conducted in Asian cities. These concentrations may be compared to the Guideline values indicated in Table 1. As is clear from Tables 2 and 3, air quality in many Asian cities is amongst the poorest in the world. In Beijing for example, coal burning for residential heating and power generation results in high concentrations of particles and SO_2 (Table 2 and 3). Further, some regions in Asia may be affected by recurrent regional air pollution episodes

Table 2. Summary Categorization of Urban Air Quality in Asia

Country	*# of cities with air quality data*	*Year*	*# cities > WHO Guidelines*	*% of population in cities > WHO*	*Rank of outdoor air exposures (1 = low 10 = high)*
China	87	1995	85	99	9
India	66	1991–4	62	98	8
Indonesia	1	1990	1	100	10
Korea	7	1994–5	5	89	6
Malaysia	2	1990–3	1	15	4
Philippines	1	1995	1	100	10
Singapore	1	1995	0	0	1
Thailand	1	1995	1	100	10
Japan	5	1995	4	99	26*

For China, and India the table includes all of the major cities, such as Beijing, Tianjin, Chengdu, Guangzhou, Shanghai, Shenyang, Wuhan in China and Bombay, Calcutta, Delhi, Hyderabad, Madras and Bangalore in India Indonesia = Jalkarta, Thailand = Bangkok, Korea = Incheon, Kwanjin, Pusan, Seoul, Taequ, Taejeon, Ulsanx, Malayisa = Kuala Lumpur and Georgetwon, The Philippines = Manilla, Japan = Kanazawa, Kawasaki, Osaka, Tokyo, Yokohama *The ranking for Japan is based on a scale of 1–27 (Source World Resources Institute, Indicators of potential risks to human health from environmental threats Potential exposure to polluted outdoor air www.wri.org/ehi/airranks.html accessed 11 July 2002)

Table 3. Selected Outdoor Air Pollution Epidemiological Studies in Asian Locations

Location	*Study Design*	*Pollutant(s) (Median concentrations)*	*Findings*	*Ref*
Kaohsiung, Pintong Taiwan	Cross-sectional study of 165,000 high school students.	PM_{10} (91) TSP (181) SO2 (34) NO_2 (53) CO (0.9) Ozone (43)	Independent significant association with asthma prevalence and long-term concentrations of all pollutants.	(39)
Taiwan	Cross-sectional study of 331,000 school children stations.	PM_{10} (66) SO2 (18) NO_x (51)@ CO (0.9) Ozone (41)	Traffic-related pollutants (CO, NO2) significantly associated with asthma prevalence.	(40)
1 rural, 2 urban and 3 industrial areas in Taiwan	Cross-sectional study of 5000 school children	#(Rural, Urban, Petrochemical) PM_{10} (72, 53–67, 64–110) SO_2 (8, 24, 42–120) NO_2 (19, 47–58, 38–55) CO (0.5, 1.0–1.5, 0.8–0.9) O_3 (102, 75–82, 102–118)	School children in urban communities had more respiratory symptoms and diseases compared to those in rural communities. Increased nasal symptoms in petrochemical communities compared to rural.	(41)
Hong Kong	Longitudinal study of (quarterly) asthma hospital discharges — all ages.	Concentrations not reported	Correlation found between asthma hospitalization rates and TSP in the 1–4 age group.	(42)
Hong Kong	Daily time series study of emergency hospital admissions in 12 major hospitals	PM_{10} (45) SO_2 (17) NO_2 (51) O_3 (24)	Significant associations between respiratory, cardiovascular, COPD and heart failure admissions with all pollutants. Admissions for asthma, associated with NO_2, O_3, and PM_{10}.	(32)
Hong Kong	Daily time series of mortality (1995–1997)	(warm season/ cool season) PM_{10} (36/59) SO_2 (15/14) O_3 (24/33)	Associations between SO_2, NO_2, O_3 and cardiovascular and respiratory mortality in cool season only; Weak associations between PM10 and respiratory mortality only.	(32)

(to be continued)

Table 3. *(Continued)*

Location	*Study Design*	*Pollutant(s) (Median concentrations)*	*Findings*	*Ref*
Hong Kong	Daily time series of mortality (1995–1998)	PM_{10} (46) SO_2 (14) NO_2 (54) O_3 (30)	In multipollutant models, significant associations between ischaemic heart disease mortality and NO2; significant associations between respiratory mortality and O_3 and SO_2.	(34)
Hong Kong	Daily time series of hospital admissions (1995–1997)	PM_{10} (47) SO_2 (14) NO_2 (53) O_3 (28)	Significant associations between air pollutants and cardiorespiratory hospital admissions. Magnitude of associations were similar to those observed in London, using same methodology.	(36)
Urban and suburban areas of Wuhan, China.	Cross-sectional study of 600 healthy children, ages 7–13.	#(Suburban, Urban) TSP (110, 251) SO_2 (13, 59) NO_x (7, 47) CO (1.1–3.2)	Children from urban area had lower lung function and reduced lung function growth relative to children from suburban area.	(43)
Lanzhou, Wuhan (urban and suburban), and Guangzhou, China	Cross-sectional study of 2800 school children, ages 5–14.	#Guangzhou, Wuhan suburban, Wuhan urban, Langzhou) TSP (296, 191, 406, 1067) SO_2 (110, 19, 92, 121) NO_x (89, 18, 78, 92)	Significant association between TSP and cough, phlegm, pneumonia and respiratory disease hospitalization in urban Wuhan and Lanzhou relative to Guangzhou. Parental smoking and use of coal in the home associated with cough.	(44)
Lanzhou, Wuhan (urban and suburban), and Guangzhou, China	Cross-sectional study of 4100 adults	#Guangzhou, Wuahn suburban, Wuhan urban, Langzhou) TSP (296, 191, 406, 1067) SO_2 (110, 19, 92, 121) NO_x (89, 18, 78, 92)	Significant differences between districts in prevalence rates of respiratory symptoms.	(45)
Shenyang, China	Daily time series study of mortality.	(Summer, Winter) TSP (292, 543) SO_2 (87, 272)	Significant associations between TSP and SO_2 with total (non-trauma) daily mortality.	(52)
Two residential areas of Beijing	Daily time series study of mortality.	TSP (336) SO_2 (40)	Significant association between SO_2 and daily non-trauma mortality. Association of TSP with total daily mortality was positive but not significant. The strongest effects of SO_2 and TSP were consistently seen for respiratory disease in both seasons.	(46)

(to be continued)

Table 3. *(Continued)*

Location	*Study Design*	*Pollutant(s) (Median concentrations)*	*Findings*	*Ref*
Suburban, residential and industrial areas in Beijing	Cross-sectional study of 1500 non-smoking adults ages 40–69.	#(Suburban, Residential, Industrial) TSP (Outdoor) (151, 230, 256) PM_{10} (Indoor) (coal stoves: 41, 90,152) PM_{10} (Indoor) (gas stoves: 25, 60, 99)	Excess risk of all respiratory symptoms for for residents of industrial and residential areas. Increase in symptom prevalence associated with outdoor particulate levels. Increased respiratory symptoms for residents of homes with coal stoves.	(47)
Suburban and residential and industrial areas in Beijing	Cross-sectional study of 3300 smoking and non-smoking adults ages 40–69.	#(Suburban, Residential, Industrial) TSP (261, 389, 449) SO_2 (18, 128, 57)	Air pollution significantly associated with decreased lung function in both smokers and non-smokers. Greater associations in smokers.	(48)
Beijing	Daily time series study of outpatient visits	#(Summer, Winter) TSP (289, 486) SO_2 (17,211)	Significant associations between SO_2 and TSP with total (non-trauma) and non-surgical outpatient visits.	(49)
Beijing	Prospective cohort study of 25,000 pregnant women	Total suspended particles (350) SO_2 (108)	Significant association between gestational age and SO_2 and TSP concentrations.	(50)
Beijing	Prospective cohort study of pregnant women. 75,000 live births.	TSP (320) SO_2 (100) (estimated median)	Exposure to elevated concentrations of TSP and SO_2, especially during the third trimester, significantly associated with low birth weight.	(51)
Inchon, Kwangju, Pusan, Seoul, Taejon, Taegu, Ulsan, Korea	Daily time series study of mortality	#CO (1.5) NO_2 (46) O_3 (46) SO_2 (65) TSP (78)	Association between TSP and SO_2 with daily (all-cause) mortality. In two-pollutant models, SO_2 coefficient was not affected by TSP.	(25)
Bangkok	Daily time series study of mortality	#PM_{10} (63)	Significant associations between PM_{10} concentrations and total (non-trauma), cardiovascular and respiratory daily mortality.	(27)
Delhi	Daily time series study of mortality	#TSP (378) SO_2 (19) NO_x (33)	Significant association between TSP and total (non-trauma), cardiovascular and respiratory daily mortality.	(26)

#Mean concentration. All other concentrations are medians. Concentrations are in units of $\mu g/m^3$ for TSP, PM_{10}, SO_2 and NO_2 and in mg/m^3 CO. @NO_x assumes 40% of total NO_x is in the form of NO_2.

such as the 1997–98 Southeast Asian haze, which resulted from Indonesian vegetation fires that produced high concentrations of particulate matter throughout much of Southeast Asia (3). In the following section we briefly describe the major types of air pollutants and their health impacts. Due to the respiratory health emphasis of this text we will not discuss leaded gasoline and the resulting health impacts, although high lead exposure is still a huge problem in many countries in Asia.

Particulate matter (PM)

Airborne particles are a complex mixture of solid particles and liquid droplets suspended in the air. Particles in outdoor air have numerous sources with varying chemical and physical composition. Typically particles are classified according to their size; particle size affects deposition in the respiratory tract and consequently the potential to cause health effects. "Fine" particles are those with aerodynamic diameters smaller than 2.5 micrometers in diameter ($PM_{2.5}$) and include mainly particles produced in fuel combustion (motor vehicles, power plants, industry), fireplaces and wood stoves and via atmospheric reaction of gases (sulphur dioxide, nitrogen oxides, volatile organic compounds). "Coarse" particles are those larger than 2.5 micrometers and include mainly those originating from soil material such as road and windblown dust and from materials handling, crushing and grinding operations. PM_{10} includes fine particles and a major portion of the suspended coarse particles, and is meant to reflect the proportion of suspended particles that can be inhaled into the respiratory tract. Earlier measurements were made for Total Suspended Particles (TSP) which includes PM_{10} and $PM_{2.5}$ as well as even larger particles which are likely not inhalable and therefore of less relevance for health impacts.

Wei et al (4) describe detailed elemental composition measurements collected in multiple locations in four Chinese cities in conjunction with a series of epidemiological studies (Table 3). In each location urban sites had higher concentrations of all particulate size fractions than the suburban sites. Annual mean PM_{10} concentrations in the urban locations ranges from 115–275 $\mu g/m^3$ and 68–192 $\mu g/m^3$ in the suburban locations. $PM_{2.5}$ comprised 50–75% of the PM_{10} concentration.

Numerous studies have linked particulate matter, especially fine particles with a series of significant effects, including premature death (5–7), cardiac / respiratory hospital admissions (8) (9) and emergency room visits (10), aggravated asthma (10–12), acute respiratory symptoms (13), decreased lung function (14), work and school absences (15), and chronic bronchitis (16). The individuals who appear to be at greatest risk from exposure to ambient fine particles are the elderly and those with individuals with preexisting heart or lung disease as well as children and infants. Two cohort studies conducted in the USA suggest that life expectancy may be 2 to 3 years shorter in communities with high PM than in communities with low PM, consistent with the earlier cross-sectional studies (17).

Although it is clear that high exposures to particulate air pollution occur in developing country cities, there have only been a limited number of studies performed to assess the health impacts. Those studies that have been performed indicate significant associations between urban particle concentrations and daily mortality, as well as other health impacts (Table 3).

Ozone (O_3)

Ozone is a gas that occurs naturally in the stratosphere to filter UV radiation. At ground level it is the prime ingredient of smog in cities and many rural areas. Ozone is a secondary pollutant, meaning that it is formed as the product of atmospheric reactions of primary emissions. Ozone is formed by the reaction of nitrogen oxides and volatile organic compounds in the presence of sunlight, especially during hot weather.

Ozone exposure, even at very low levels, is associated with a range of health adverse effects including increased hospital admissions and emergency visits (18), asthma exacerbation, acute respiratory symptoms (chest tightness, wheeze) in healthy individuals, temporary decreases in lung capacity of 15–20% in healthy individuals, and inflammation of lung tissue (19).

The individuals at greatest risk from ozone

exposure are children, due to the coincidence between peak ozone concentrations and the times of the day when children tend to be outdoors. For the same reasons, healthy adults who work or exercise outdoors are also at increase risk. Even moderately exercising healthy adults can experience 15–20% reductions in lung function from exposure to low levels of ozone over several hours. Asthmatics are also particularly sensitive to the effects of ozone. Ozone can aggravate asthma, causing more asthma attacks, increased use of medication, more medical treatment and more visits to emergency clinics. Animal studies suggest that repeated exposure to high levels of ozone for several months or more can produce permanent structural damage in the lungs (19).

Volatile organic compounds (VOC)

Volatile organic compounds are a variety of compounds including alkanes, alkenes, alkynes, aromatics, aldehydes, ketones, alcohols, esters, benzene, and some chlorinated hydrocarbons. The sources of VOCs are quite diverse and include fossil fuel evaporation and combustion, solvent use and other industrial processes. Natural sources of VOCs are also significant in many areas. Vegetation emits large amounts of VOCs, especially when temperatures are high. Since VOCs are a major precursor to ozone, the importance of natural VOC sources complicates efforts to control ozone production. Benzene is one VOC, which has received much attention due to its carcinogenicity. The main sources of benzene emissions are vehicle fuels, although in some cases exposure may be dominated by indoor sources such as environmental tobacco smoke, stored fuels and paint supplies. In the indoor environment, exposure to low levels of VOCs may result in headache and irritation of the eyes and nose.

Sulphur dioxide (SO_2)

Sulphur dioxide is released into the atmosphere primarily as a result of combustion of sulphur-containing fuels such as coal and oil. The emission rate depends on, among other factors, the sulphur content of the fuel. In urban areas, particularly those with many diesel vehicles, vehicular sources (diesel cars, buses, and trucks) are also a significant source of SO_2. SO_2 was implicated in several of the more significant historical air pollution episodes (the 1952 London fog, for example). Today, the highest concentrations are found in cities in China where coal is burned for residential heating and power generation. SO_2 is an irritant gas and produces bronchoconstriction; individuals with asthma are more sensitive to these effects (19). Sulphur dioxide may be oxidized in the atmosphere to form sulphuric acid and sulphate salts; these are important components of the ambient fine particle burden.

Carbon monoxide (CO)

Carbon monoxide is produced by the incomplete combustion of fossil fuels, mainly from mobile sources. Concentrations in urban areas depend upon traffic density, topography and weather conditions. Accidental indoor exposure is responsible for a significant number of deaths in many countries. Unvented biomass or coal burning for cooking or residential heating results in high levels of CO that may be 5–10 times greater than those measured in pollutant urban areas. The health hazards of CO exposure are related to the binding of this gas to hemoglobin. Carbon monoxide exposures especially affect the developing fetus, infants, and people with anaemia or a history of heart disease (20).

Nitrogen oxides (NO_x)

Oxides of nitrogen are produced by high temperature combustion of fossil fuels for transport, heating and power generation. Nitrogen oxides are formed by oxidation of nitrogen in the air and by oxidation of nitrogenous compounds in the fuels themselves. Initially, almost all of the NOx emission is in the form of nitric oxide (NO). NO is then oxidized to nitrogen dioxide (NO_2) — a more toxic compound and a major precursor of photochemical smog. Experimental exposure studies have produced inconsistent findings for healthy individuals. In asthmatics exposure to 375–950 $\mu g/m^3$ NO_2 has been shown to increase

nonspecific airway hyperresponsiveness (NSBH) (20) and enhance specific airway response to inhaled allergen such as house dust mite (21,22). NO_2 exposure is of particular concern due to exposures indoors from unvented cooking or heating with natural gas. Neas and colleagues reported an odds ratio of 1.45 for lower respiratory symptoms in children for an increase in the annual average NO_2 concentration of 28 $\mu g/m^3$ (23). A meta-analysis of 11 epidemiological studies yielded similar results, suggesting a 20% increase in the odds of a lower respiratory infection for children with a prolonged increase in exposure of 30 $\mu g/m^3$ NO_2 (24).

Health Effects Associated With Outdoor Air Pollutants

In the recent American Thoracic Society Statement on "What constitutes an adverse health effect of air pollution" (17), the following were considered adverse health effects:

- Decreased health-related quality of life
- All reversible loss of lung function in combination with the presence of respiratory symptoms
- Any permanent loss of lung function
- Symptoms related to air pollution associated with diminished quality of life or with a change in clinical status
- Any detectable effects on clinical outcomes such as emergency room visits, hospital admissions and mortality

The evidence for some of the adverse health effects of air pollution is briefly discussed below with particular emphasis on studies that have been conducted in Asia. Table 3 lists many air pollution epidemiological studies conducted in Asia. The results of these studies appear to support those conducted elsewhere in the world and indicate a wide range of health impacts associated with ambient air pollution. These include increased mortality, decreased birth weight, decreased lung function and increased respiratory symptoms and exacerbation of asthma.

A series of studies have been conducted in Beijing and other large cities in China. Many of these studies have used state-of-the-art statistical approaches to evaluate the health impacts of air pollution. Collectively, studies in Beijing indicate associations between air pollution, especially particles and sulphur dioxide, with increased cardiopulmonary mortality, respiratory symptoms, outpatient visits, reduced gestational age and low birth weight (Table 3). Associations between mortality and TSP and SO_2 concentrations have also been observed in Shenyang. A large cross-sectional study conducted in Wuhan, Lanzhou and Guangzhou China has indicated reduced lung function, increased respiratory symptoms and increased prevalence of respiratory illnesses in areas with higher levels of TSP and SO_2, especially in Wuhan where coal burning leads to severely deteriorated air quality. Several cross-sectional studies in Taiwan have indicated associations between air pollution and asthma prevalence as well as respiratory symptoms. Several time series studies conducted in Korea indicated associations between air pollution and daily mortality that were similar to those observed in North America and Western Europe. Recently, a combined analysis of the relationship between air pollution and daily mortality was undertaken in 7 major Korean cities in which 50% of Korea's population lives. Results indicated a consistent between mortality and SO_2, although PM_{10} was not included in the analysis and it is possible that SO_2 serves as a surrogate for particulate matter in this analysis (25).

In Delhi, high particle concentrations result from vehicular traffic, industrial sources and a significant amount of resuspended dust. An analysis of mortality impacts in Delhi indicated significant associations, but less so than in other locations, possibly due to the non-combustion origin of much of the particles (26). In an analysis of particles in Bangkok, a significant association was observed with daily mortality, with an effect estimate similar to those observed in North America and Western Europe. Particulate matter in Bangkok is derived largely from motor vehicles, including a large proportion of diesel vehicles and two-stroke motorcycles (27).

In Hong Kong, a series of studies have been carried out on the effects of air pollution on health. A cross-sectional study comparing respiratory morbidity among school children living in a heavily polluted with those living in a less polluted district found the prevalence of sore throat, cough and

wheeze to be significantly higher among children living in the more polluted district (28). When legislation was implemented to reduce fuel sulphur levels in 1990, there was a significant reduction in sulphur dioxide levels and in the sulphate content of respirable particles. This reduction in pollution was associated with a significant reduction of respiratory symptoms, more so in those living in the more polluted district (29). Moreover, children living in the more polluted district had a significantly higher prevalence of NSBH compared with those living in the less polluted district (30). The degree of NSBH decreased in children living in the polluted areas after the introduction of the fuel legislation in 1990 (31). Recent time series studies have shown significant associations between major air pollutants and hospital admissions and daily mortality for respiratory diseases and cardiovascular diseases (32–34), hospital admissions for asthma in children (35) as well as adults (36) and emergency room visits for asthma in Hong Kong (37). The strength and magnitude of these associations appear to be quite similar to those observed in North America and Western Europe (36).

Nitta and colleagues (38) summarized a series of cross-sectional studies of respiratory symptoms and automobile exhaust in Japan. The studies evaluated approximately 5000 residents living near busy roads. Exposure was assessed by distance from major roads and was supported by NO_2 (and limited PM) monitoring along a transect from each roadway. Collectively, these studies indicated a small increase in respiratory symptom prevalence that is related to vehicle exhaust exposure.

The studies discussed above and listed in Table 3 are mainly focused on acute cardiopulmonary and chronic non-cancer respiratory effects. Known or suspected carcinogens such as benzene and polycyclic aromatic hydrocarbons are detectable in vehicle and industrial emissions (39–52). A limited number of studies have shown a significantly increased mortality risk ratio for lung cancer associated with ambient fine particle levels. (6,53–56). These studies provide reasonable grounds for concern that ambient air pollution may increase lung cancer risk, although specific evidence for Asia is lacking. A more detailed discussion of lung cancer and indoor air pollution from coal burning is discussed below.

Magnitude of adverse health effects of outdoor air pollution

The WHO Guidelines may be used to estimate the percentage increase in adverse health effects corresponding to increases in PM_{10} and $PM_{2.5}$ levels. Similar plots are available in the WHO Guidelines documents for O_3 and SO_2 and selected health outcomes. It is important to realize, however, that these guidelines do not incorporate the effects of mixtures. For example the effects attributed to PM may be enhanced by exposure to other pollutants, or the health effects attributed to PM may in reality be due to multiple compounds in the air pollution mixture that is typically present in urban air. Further, caution should be used when applying these estimates to countries in Asia, as the estimates of effects are based mainly on studies conducted in North America and Western Europe where demographics, health care and the air pollution mixture may be different from Asia.

It should be noted that deaths and hospital admissions are only the "tip of the iceberg" for adverse health effects. Below the "tip of the iceberg" are visits to emergency room for treatment and unscheduled doctor visits, for respiratory and cardiovascular diseases, and increases in usage of medications for acute exacerbation of asthma or chronic obstructive lung disease, loss of productivity due to work and school absences and impaired quality of life. All these parameters should be taken into consideration if one has to calculate the direct and indirect cost of air pollution to health.

Indoor Air Pollutants

Due to the fact that individuals spend the majority of their time indoors, the understanding of environmental impacts on respiratory health must consider the indoor environment. Indoor air quality may be degraded by pollutants originating either outdoors or indoors as well as by the products of reactions between pollutants.

Biomass and coal burning

In many countries in Asia, wood and other biomass as well as coal are used as cooking and heating

fuels. Respirable particulate levels measured in these settings are typically 1000–2000 $\mu g/m^3$ depending upon the specific fuel, ventilation, cooking duration and measurement interval (53). These levels are 10–50 times above those observed in urban areas. Exposures and health effects associated with indoor coal burning in China are summarized in detail elsewhere (1,53). In one example, a series of studies conducted in Xuanwei, China, an area noted for high mortality from respiratory disease and lung cancer, suggested that the high lung cancer rates were strongly associated with the use of using smoky coal, but not wood, for cooking and heating (54–56). Indoor PM_{10} concentrations measured during cooking were extremely high (24, 22 and 1.8 mg/m^3 for smoky coal, wood and smokeless coal, respectively). Mutagenicity tests of particulates collected from the various combustion processes indicated that smoky coal was approximately 5 times more mutagenic than wood. In a recent follow-up study, the impact of household stove improvements from unvented firepits to stoves with chimneys was shown to result in 65% and 85% decreases in PM10 and benzo[a]pyrene concentrations. More importantly, the household stove improvements were associated with a significant long-term reduction in the incidence of lung cancer in the Xuanwei area (57). In terms of exposure, domestic cooking and heating with biomass or coal clearly presents the highest source of exposure to air pollutants since individuals are exposed to high levels of smoke on a daily basis for many years. Exposures of this group are typically 70–85 hour-years of exposure.

The health effects of biomass smoke inhalation have been documented in developing countries where women, and in some cases, children spend many hours cooking over unvented indoor stoves. A number of studies have reported associations of health impacts with use of biomass fuels, and a few have directly measured exposure. These studies have been reviewed in detail (58,59). Exposure to biomass combustion products has been identified as a major risk factor for acute respiratory infections, the leading cause of infant mortality in the developing countries (60). In addition to the risks in infants, women who are cooking are also at risk for chronic respiratory diseases as well as adverse pregnancy outcomes (61,62). Of equal importance is recent research from India (63) and replicated elsewhere (64) in which an association between exposure to biomass smoke and tuberculosis was observed. If this association were causal, the public health impacts of biomass smoke exposure would be even greater than previously thought.

Environmental tobacco smoke

Exposure to environmental tobacco smoke (ETS), also known as "passive smoking," is associated with several well established adverse health effects and is a major public health concern throughout the world. The effects of exposure to environmental tobacco smoke and health have been discussed in the previous chapter on Smoking and Health and will not be repeated here.

Nitrogen oxides

A major source of exposure to nitrogen oxides is from the use of domestic gas stoves for cooking. The association between gas stove use, the resulting emissions of NO_2, the primary nitrogen oxide of concern for respiratory health impacts, and respiratory health has received a great deal of attention and is a major public health concern due to the large numbers of people exposed to stove emissions. In the United Kingdom, women who used gas mainly for cooking had an increased risk of several asthma-like symptoms during the past 12 months (65). Atopic women are more susceptible than nonatopic women.

The use of gas stoves is also common in many Asian countries. In Hong Kong and in other tropical and subtropical areas, gas stoves are used only for cooking and for a short period of time rather than for heating. Windows are opened most of the time; thus indoor levels of nitrogen oxides are not high compared to countries in the temperature climate. Despite this, Koo et al (66) found increased nitrogen oxides levels in homes of women with respiratory symptoms. As discussed above, asthmatics are particularly sensitive to the effects of NO_2; short-term exposure to NO_2 at 1 ppm, a level that can be reached when cooking with gas, has been shown to heighten NSBHs in asthmatics (67).

Volatile organic compounds (VOC)

Volatile organic compounds (VOCs) are often implicated as a contributing factor to poor indoor air quality, especially in modern buildings in developed countries. VOCs are emitted from many furnishings, consumer products and bioeffluents from humans as well as microorganisms (68). In buildings where very high concentrations are found, it is often due to the presence of easily identified strong sources such as VOC-based finish materials, cleaning products, hobby and art materials, reproduction equipment, and newly installed building materials (carpets, paints, sealants, and adhesives). Emissions from most building materials tend to decrease rapidly when materials are new or newly exposed to the environment, and more slowly thereafter. In general, the older the building, the lower the VOC concentrations are likely to be.

In controlled chamber studies, subjects exposed to mixtures of very low levels of VOCs experienced airway and eye irritation as well as attention deficits (68). Other health effects include skin irritation, hypersensitivity reactions, abnormal odour and taste. VOCs have also been implicated in "sick building syndrome" (69). However, associations between VOC levels and symptoms have not been consistently found in epidemiological studies (69). One possible explanation is that the reaction products of VOCs are more important than VOCs themselves. Hydroxyl radicals can be produced from reactions between VOCs and ozone (laser printers, photocopiers) in indoor environments; they then react with other VOCs to produce organic acids and aldehydes which may be more potent irritants than their parent compounds.

Radon

Radon is naturally occurring gaseous radioactivity in soil and is a risk factor for lung cancer in regions with high soil radon concentrations. Radon gas is emitted indoors from the soil and then naturally decays into radioactive radon daughter particles that can be inhaled. Even within areas of high soil radon concentrations there is substantial variability in indoor levels due to the ability of radon gas to penetrate different building designs and their ventilation characteristics. Elevated indoor radon levels have been associated with lung cancer, especially for individuals who smoke. Wang et al, found an association between indoor radon and lung cancer in Gansu Province, China (70).

Allergens

Sensitivity to indoor allergens, such as house dust mite and cat dander, has been found to be a significant risk for asthma (71). In developed countries, the construction of homes that are tightly sealed to conserve heat, the use of wall-to-wall carpeting, cold water detergents for washing, and the change of lifestyle to sedentary living have led to increased exposure to indoor allergens. Unfortunately, with few exceptions, measurements of indoor allergens are rarely carried out in Asian countries. The role of indoor aeroallergens is discussed in Chapter 1 on asthma epidemiology.

Bioaerosols

The indoor environment can be contaminated with a variety of airborne microorganisms such as fungi, bacteria, viruses, and amoeba as a result of high indoor humidity, water-damaged indoor surfaces, reduced ventilation, and HVAC systems containing stagnant water. Epidemiological studies have consistently shown a strong and consistent relationship between dampness in homes and/or the presence of visible mould and respiratory health effects such as wheeze, cough and bronchitis with odds ratios of 1.2–2.1 in children (72,73). Viable airborne mould levels have also been associated with symptom responses in a number of investigations. Residential fungal contamination is associated with chronic stimulation of lymphocytes in children (74). Further, laboratory studies have indicated that spores isolated from mouldy homes stimulate macrophages leading to the production of inflammatory mediators (75). Together these observations support a causal association between indoor fungal contamination and health impacts.

Bacteria and viruses can cause disease but their presence in indoor air is seldom the cause of infection. Notable exceptions are *Legionella,*

Aspergillus and Mycobacteria tuberculosis. Fungi are well known to be capable of causing hypersensitivity pneumonitis, a disease due to a hypersensitivity reaction of the individual to the fungi rather than due to infection.

Endotoxin is produced by gram-negative bacteria and causes inflammation of the airways giving rise to irritation of the eyes, nose and the airways (76). It has been implicated as the cause of humidifier fever or toxic pneumonitis. (1→3)–β-D-glucans are found on the cell wall of plants, bacteria and fungi. These compounds stimulate humoral and cellular immunity in human and animals and have been implicated in hypersensitivity pneumonitis (77,78). The amount of (1→3)–β-D-glucans present may serve as an indicator of fungal exposure. (1→3)–β-D-glucans have also been associated with symptoms in a number of epidemiological studies leading to the hypothesis that (1→3)–β-D-glucans are a causative agent.

Health Effects Associated With Indoor Air Pollution

Specific building-related illnesses

Infection

Legionella pneumophila is responsible for Legionnaires' disease. The organism has been isolated from water sampled from cooling towers and evaporative condensers, devices to cool water for buildings (79). The 1976 epidemic in Philadelphia has been attributed to airborne transmission of the bacterium, although the source has not been identified (80).

Nosocomial infections with Aspergillus species also illustrate the potential for disease transmission through ventilation systems. Patients with defects of cell-mediated immunity are particularly vulnerable to infection with these organisms. Outbreaks of Aspergillus infection have been described in hospitalised patients from airborne spread of the organism from contaminated ventilation system (81). Transmission of tuberculosis to health care workers in hospitals has been attributed to poor ventilation system (82).

Hypersensitivity reactions

Hypersensitivity pneumonitis was first described in 1970 in 4 out of 27 workers in one office developing the disease from exposure to thermophilic actinomycetes contaminating the air-conditioning system (83). Subsequently, hypersensitivity pneumonitis and humidifier fever (an influenza syndrome without prominent pulmonary manifestations) have been described in association with contaminated air conditioning systems in offices, homes, and automobiles (83–85).

A wide range of biologic sources for potentially sensitising antigens has been described in the literature including thermophilic actinomycetes, diverse fungi, bacteria, amoeba and nematodes. In some outbreaks, a specific antigenic exposure underlying the illness could not be identified. The offending antigens have been introduced into the indoor environment through central and room humidifiers, contaminated heating and cooling systems, moisture-damaged building materials and cool mist vaporizers used in the home and automobile air conditioning systems (69).

Nonspecific building-related illnesses or "Sick Building Syndrome"

The terms sick building syndrome, tight building syndrome and non-specific building related illness refer to a heterogeneous group of symptoms related to exposure in primarily mechanically ventilated buildings. Symptoms usually disappear upon exit from the building and the cause of symptoms is not known because conventional air monitoring does not show individual pollutants to be at unsafe levels.

The early conceptualisation of the problem was that there were two distinct populations of buildings — "sick" buildings in which many occupants had symptoms that were attributed to the indoor environment and "healthy" buildings in which few workers had symptoms (69). This concept has proven incorrect and consequently the term "sick building syndrome" is misleading. The term non-specific building related illness has been introduced recently for a group of heterogeneous and non-specific symptoms including irritation of the skin, mucous membranes of the eyes, nose and throat, headache, fatigue, and difficulty concentrating. These symptoms are not associated with objective clinical or laboratory abnormalities and the causative agent(s) have not been identified.

Epidemiologic studies of office buildings selected without regard to occupant health status, has demonstrated that the prevalence of work-related symptoms ranged in a continuum from low to high. No single cut-point or criteria can distinguish problem from non-problem buildings. In cross-sectional surveys of buildings selected without regard to the occupant's health status, up to 60% of workers reported at least one work-related symptom, and 10–25% reported such symptoms occurring twice weekly or more (69).

The aetiology of the symptoms is not known, and in most cases specific agent(s) responsible for the symptoms has not been identified. Several host risk factors have been identified. Young females with atopy are more prone to have symptom complaints, including those associated with psychosocial factors. Accordingly, sick building syndrome is often dismissed as purely psychological. There are building-related factors that have been shown to be associated with "sick building syndrome" including temperature, high and low relative humidity and very low ventilation rates. Fungi and bacteria have also been implicated because microorganisms and/or their toxins have been detected in high concentrations in HVAC systems, cooling coils, filters, duct work, humidifiers, drip pans or air cooling units of buildings with high levels of occupant complaints. Other less well-established factors include exposure to ETS, VOCs, formaldehyde, CO, biological agents.

Preventive Strategies

Using the information described above regarding air pollution exposure and health impacts it is possible to recommend a prioritized series of preventive measures to reduce health impacts. Clearly the most effective measure is to reduce source emissions and to avoid sources wherever possible. This may involve regulatory measures to reduce emissions from stationary sources or motor vehicles, or personal lifestyle changes to reduce exposure to environmental tobacco smoke and VOCs in consumer products or to use alternate transit modes to lower the number of motor vehicles contributing to poor ambient air quality.

In addition to reduced source emissions and avoidance, reduced physical activity, especially during air pollution episodes, will reduce the amount of inhaled pollutant and may therefore reduced the likelihood of an adverse effect. One mitigation measure frequently recommended by governments is to remain indoors. While this may reduce exposure to some outdoor pollutants, it will have the effects of increasing exposure to indoor-source pollutants. Thus, to be effective as a mitigation measure, indoor sources and general indoor air quality must also be considered for those who remain indoors. For outdoor air pollutants such as ozone and other reactive gases such as SO_2 and NO_2, remaining indoors will effectively reduce exposure. Unfortunately for particles and non-reactive gases such as CO, remaining indoors offers very little protection, except for buildings with air conditioning systems with effective filtration. The use of appropriately sized air cleaners and filters indoors may also be effective, especially for particles.

In general, reducing the indoor humidity to below 50% reduces the growth of not only house dust mites but also the growth of moulds indoors. Effective means of reducing house dust mite exposure are now available. The encasement of mattresses, duvets and pillows together with hot water washing of bedding reduces the level of mite allergen significantly. Removal of carpets and upholstered furniture removes reservoirs for house dust mite. The use of chemicals to kill mites has not been found to be useful. The only effective way of reducing exposure to pet allergens is to remove the pet from the home; frequent washing of the pet or application of chemicals to reduce shedding of allergen has not been found to be useful. Meticulous house keeping and the use of insecticides are required to eliminate cockroaches from homes.

Medication such as bronchodilators may reduce, but do not eliminate, acute effects of particles, ozone and allergen exposure and are unlikely to impact chronic effects. Recently several studies have suggested that antioxidants are effective in reducing the acute effects of ozone (86–89). Respirators (and dust masks) may be effective for some pollutants but not practical for non-occupational exposures. One must also consider that effective respirators increase respiratory resistance.

References

1. Florig H. China's air pollution risks. *Environ Sci Technol* 1997; 31:A274–9.
2. Hughes G. *Can the Environment Wait? Priorities for East Asia.* Washington, DC, The World Bank 1997; p 42.
3. Brauer M, Hisham-Hashim J. Indonesian fires: Crisis and reaction. *Env Sci Technol* 1998; 32:A404–7.
4 Wei F, Teng E, Wu G, et al. Ambient concentrations and elemental compositions of PM10 and PM2.5 in four Chinese cities. *Environ Sci Technol* 1999; 33:4188–93.
5. Pope CA, 3rd, Thun MJ, Namboodiri MM, et al. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *Am J Respir Crit Care Med* 1995; 151:669–74.
6 Pope CA, 3rd, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, Thurston GD. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA* 2002 6; 287:1132–41.
7. Dockery DW, Pope AC, Xu X, et al. An association between air pollution and mortality in six U.S. cities. *N Engl J Med* 1993; 329:1753–9.
8. Burnett RT, Dales R, Krewski D, Vincent R, Dann T, Brook JR. Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. *Am J Epidemiol* 1995; 142:15–22.
9. Burnett RT, Cakmak S, Brook JR, Krewski D. The role of particulate size and chemistry in the association between summertime ambient air pollution and hospitalization for cardiorespiratory diseases. *Environ Health Perspect* 1997; 105:614–20.
10. Schwartz J, Slater D, Larson TV, Pierson WE, Koenig JQ. Particulate air pollution and hospital emergency room visits for asthma in Seattle. *Am Rev Respir Dis* 1993; 147:826–31.
11. Delfino RJ, Becklake MR, Hanley JA. The relationship of urgent hospital admissions for respiratory illnesses to photochemical air pollution levels in Montreal. *Environ Res* 1994; 67:1–19.
12. Thurston GD, Ito K, Kinney PL, Lippmann M. A multi-year study of air pollution and respiratory hospital admissions in three New York State metropolitan areas: results for 1988 and 1989 summers. *J Expo Anal Environ Epidemiol* 1992; 2:429–50.
13. Peters A, Goldstein IF, Beyer U, et al. Acute health effects of exposure to high levels of air pollution in eastern Europe. *Am J Epidemiol* 1996; 144:570–81.
14. Pope CA, 3rd, Dockery DW. Acute health effects of PM10 pollution on symptomatic and asymptomatic children. *Am Rev Respir Dis* 1992; 145:1123–8.
15. Pope CA, 3rd. Adverse health effects of air pollutants in a nonsmoking population. *Toxicology* 1996; 111:149–55.
16. Abbey DE, Ostro BE, Petersen F, Burchette RJ. Chronic respiratory symptoms associated with estimated long-term ambient concentrations of fine particulates less than 2.5 microns in aerodynamic diameter (PM2.5) and other air pollutants. *J Expo Anal Environ Epidemiol* 1995; 5:137–59.
17. American Thoracic Society. What constitutes an adverse health effect of air pollution? *Am J Respir Crit Care Med* 2000; 161:665–73.
18. Thurston G, Ito K. Epidemiological studies of ozone exposure effects. In: *Air Pollution and Health.* Eds. Holgate S, Samet J, Koren H, Maynard R. London: Academic Press 1999, 485–510.
19. Health effects of outdoor air pollution. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. *Am J Respir Crit Care Med* 1996; 153:3–50.
20. Health effects of outdoor air pollution. Part 2. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. *Am J Respir Crit Care Med* 1996; 153:477–98.
21. Tunnicliffe WS, Burge PS, Ayres JG. Effect of domestic concentrations of nitrogen dioxide on airway responses to inhaled allergen in asthmatic patients. *Lancet* 1994; 344:1733–6.
22. Devalia JL, Rusznak C, Herdman MJ, Trigg CJ, Tarraf H, Davies RJ. Effect of nitrogen dioxide and sulphur dioxide on airway response of mild asthmatic patients to allergen inhalation. *Lancet* 1994; 344:1668–71.
23. Neas LM, Dockery DW, Ware JH, Spengler JD, Speizer FE, Ferris BG, Jr. Association of indoor nitrogen dioxide with respiratory symptoms and pulmonary function in children. *Am J Epidemiol* 1991; 134:204–19.
24. Hasselbad V, Eddy D. Kotchmar D. Synthesis of environmental evidence: Nitrogen dioxide epidemiology studies. *J Air Waste Manage Assoc* 1992; 42:662–71.
25. Lee JT, Kim H, Hong YC, Kwon HJ, Schwartz J, Christiani DC. Air pollution and daily mortality in seven major cities of Korea, 1991–1997. *Environ Res* 2000; 84:247–54.

26. Cropper M, Simon N, Alberni A, Sharma P. *The Health Effects of Air Pollution in Delhi,* India. India, Policy Research Department. The World Bank 1997.
27. Ostro B, Chestnut L, Vichit-Vadakan N, Laixuthai A. The impact of particulate matter on daily mortality in Bangkok, Thailand. *Journal of the Air and Waste Management Association* 1999; 49:100–7.
28. Ong SG, Liu J, Wong CM, et al. Studies on the respiratory health of primary school children in urban communities of Hong Kong. *Sci Total Environ* 1991; 106:121–35.
29. Tam AY, Wong CM. Lam TH. Ong SG, Peters J, Hedley AJ. Bronchial responsiveness in children exposed to atmospheric pollution in Hong Kong. *Chest* 1994: 106:1056–60.
30. Peters J, Hedley AJ, Wong CM, et al. Effects of an ambient air pollution intervention and environmental tobacco smoke on children's respiratory health in Hong Kong. *Int J Epidemiol* 1996; 25:821–8.
31. Wong CM, Lam TH, Peters J, et al. Comparison between two districts of the effects of an air pollution intervention on bronchial responsiveness in primary school children in Hong Kong. *J Epidemiol Community Health* 1998; 52:571–8.
32. Wong TW, Lau TS, Yu TS, et al. Air pollution and hospital admissions for respiratory and cardiovascular diseases in Hong Kong. *Occup Environ Med* 1999; 56:679–83.
33. Wong CM, Ma S, Hedley AJ, Lam TH. Effect of air pollution on daily mortality in Hong Kong. *Environ Health Perspect* 2001; 109:335–40.
34. Wong TW, Tam WS, Yu TS, Wong AH.Associations between daily mortalities from respiratory and cardiovascular diseases and air pollution in Hong Kong, China. *Occup Environ Med* 2002; 59:530–2.
35. Wong GWK, Ko FWS, Lau TS, Li ST, Hui D, Pang SW, Leung R, Fok TF, Lai CKW. Temporal relationship between air pollution and hospital admission for asthmatic children in Hong Kong. *Clin Exp Allergy* 2001; 31:565–9.
36. Wong CM, Atkinson RW, Anderson HR, Hedley AJ, Ma S, Chau PY, Lam TH. A tale of two cities: effects of air pollution on hospital admissions in Hong Kong and London compared. *Environ Health Perspect* 2002; 110:67–77.
37. Vedal S, Brumm J, Brauer M, Tsui M, Tong HK, Wong YK, Petkau J, Chan-Yeung M Acute effects of air pollution on asthma emergency room visits in Hong Kong. *Am J Respir Crit Care Med* 2001; 161:A562.
38. Nitta H, Sato T, Nakai S, Maeda K, Aoki S, Ono M. Respiratory health associated with exposure to automobile exhaust. I. Results of cross-sectional studies in 1979, 1982, and 1983. *Arch Environ Health* 1993; 48:53–8.
39. Wang TN, Ko YC, Chao YY, Huang CC, Lin RS. Association between indoor and outdoor air pollution and adolescent asthma from 1995 to 1996 in Taiwan. *Environ Res* 1999; 81:239–47.
40. Guo YL, Lin YC, Sung FC, et al. Climate, traffic-related air pollutants, and asthma prevalence in middle-school children in Taiwan. *Environ Health Perspect* 1999; 107:1001–6.
41. Chen PC, Lai YM, Wang JD, et al. Adverse effect of air pollution on respiratory health of primary school children in Taiwan. *Environ Health Perspect* 1998; 106:331–5.
42. Tseng RY, Li CK, Spinks JA. Particulate air pollution and hospitalization for asthma. *Ann Allergy* 1992; 68:425–32.
43. He QC, Lioy PJ, Wilson WE, Chapman RS. Effects of air pollution on children's pulmonary function in urban and suburban areas of Wuhan, People's Republic of China. *Arch Environ Health* 1993; 48:382–91.
44. Qian Z, Chapman RS, Tian Q, Chen Y, Lioy PJ, Zhang J. Effects of air pollution on children's respiratory health in three Chinese cities. *Arch Environ Health* 2000; 55:126–33.
45. Zhang J, Qian Z, Kong L, Zhou L, Yan L, Chapman RS. Effects of air pollution on respiratory health of adults in three Chinese cities. *Arch Environ Health* 1999; 54:373–81.
46. Xu X, Gao J, Dockery DW, Chen Y. Air pollution and daily mortality in residential areas of Beijing, China. *Arch Environ Health* 1994; 49:216–22.
47. Xu X. Wang L. Association of indoor and outdoor particulate level with chronic respiratory illness. *Am Rev Respir Dis* 1993; 148:1516–22.
48. Xu X, Wang L. Synergistic effects of air pollution and personal smoking on adult pulmonary function. *Arch Environ Health* 1998; 53:44–53.
49. Xu X, Dockery DW. Christiani DC, Li B, Huang H. Association of air pollution with hospital outpatient visits in Beijing. *Arch Environ Health* 1995; 50:214–20.
50. Xu X, Ding H, Wang X. Acute effects of total suspended particles and sulfur dioxides on preterm delivery: a community-based cohort study. *Arch Environ Health* 1995; 50:407–15.

51. Wang X, Ding H, Ryan L, Xu X. Association between air pollution and low birth weight: a community-based study. *Environ Health Perspect* 1997; 105:514–20.
52. Xu Z, Yu D, Jing L, Xu X. Air pollution and daily mortality in Shenyang, China. *Arch Environ Health* 2000; 55:115–20.
53. Smith K, Liu Y. Indoor air pollution in developing countries. In: *Epidemiology of Lung Cancer.* Ed. Samet J. New York: Marcel Dekker 1993, 151–84.
54. Mumford J, He XZ, Chapman R, et al. Lung cancer and indoor air pollution in Xuan Wei, China. *Science* 1987; 9:217–20.
55. Mumford J, He X, Chapman R. Human lung cancer risks due to complex organic mixtures of combustion emissions. *Recent Results in Cancer Research* 1990; 120:106–21.
56. Chapman R, Mumford J, He X, Jiang W, Yang R. The Epidemiology of Lung Cancer in Xuan Wei, China: Current Progree, Issues, and Research Strategies. *Arch Environ Health* 1988; 43:180–5.
57. Lan Q, Chapman RS, Schreinemachers DM, Tian L, He X. Household stove improvement and risk of lung cancer in Xuanwei, China. *J Natl Cancer Inst* 2002; 94:826–35.
58. Smith K. Fuel combustion, air pollution exposure and health: The situation in developing countries. *Ann Rev Energy Environ* 1993; 18:529–66.
59. Chen BH, Hong CJ, Pandey MR, Smith KR. Indoor air pollution in developing countries. *World Health Stat Q* 1990; 43:127–38.
60. Smith KR, Samet JM, Romieu I, Bruce N. Indoor air pollution in developing countries and acute lower respiratory infections in children. *Thorax* 2000; 55:518–32.
61. Perez-Padilla R, Regalado J, Vedal S, et al. Exposure to biomass smoke and chronic airway disease in Mexican women. *Am J Respir Crit Care Med* 1996; 154:701–6.
62. Dennis R, Maldonado D, Norman S, Baena E, Martinez G. Woodsmoke exposure and risk for obstructive airways disease among women. *Chest* 1996; 109:115–9.
63. Mishra VK, Retherford RD, Smith KR. Biomass cooking fuels and prevalence of tuberculosis in India. *Int J Infect Dis* 1999; 3:119–29.
64. Perez-Padilla R, Perez-Guzman C, Baez-Saldana R, Torres-Cruz A. Cooking with biomass stoves and tuberculosis: a case control study. *Int J Tuberc Lung Dis* 2001; 5:441–7.
65. Jarvis D, Chinn S, Luczynska C, Burney P. Association of respiratory symptoms and lung function in young adults with use of domestic gas appliance. *Lancet* 1996; 347:426–31.
66. Koo LC, Ho JHC, Ho CY, Matsuki A, Shimizu, Mori T, Tominaga S. Personal exposure to nitrogen dioxide and its association with respiratory illness in Hong Kong. *Am Rev Respir Dis* 1990; 141:1119–26.
67. Samet JM, Marbury MC, Spengler JD. Health effects and sources of indoor air pollution, Part I. *Am Rev Respir Dis* 1987; 136:1486–508.
68. Norback D, Bjornsson E, Janson C, Widstrom J, Bonman G. Asthmatic symptoms and volatile organic compounds, formaldehyde and carbon dioxide in dwellings. *Occup Environ Med* 1995; 52:388–95.
69. Menzies D. Building-related illnesses. In: Bernstein DI. Asthma in the Workplace, 2nd ed. Eds. Bernstein IL, Chan-Yeung M, Malo J-L. New York: Marcel Dekker Inc. 2000, 657–82.
70. Wang Z, Lubin JH, Wang L, Zhang S, Boice JD Jr, Cui H, Zhang S, Conrath S, Xia Y, Shang B, Brenner A, Lei S, Metayer C, Cao J, Chen KW, Lei S, Kleinerman RA. Residential radon and lung cancer risk in a high-exposure area of Gansu Province, China. *Am J Epidemiol* 2002; 155:554–64.
71. Sears MR, Herbison GP, Holdaway MD, Hewitt CJ, Flannery EM, Silver PA. The relative risks of sensitization to grass pollen, house dust mite and cat dander in the development of childhood asthma. *Clin Exp Allergy* 1989; 19:419–24.
72. Husman T. Health effects of indoor-air microorganisms. *Scan J Work Environ Health* 1996; 22:5–13.
73. Pope AM, Patterson R, Burge H. — Institute of Medicine. Indoor Air Allergens: Assessing and Controlling Adverse Health Effects. Washington, DC, National Academy Press 1993.
74. Dales R, Miller D, White J, Dulberg C, Lazarovits AI. Influence of residential fungal contamination on peripheral blood lymphocyte populations in children. *Arch Environ Health* 1998; 53:191–195.
75. Hirvonen MR, Nevalainen A, Makkonen N, Monkkonen J, Savolainen K. Induced production of nitric oxide, tumor necrosis factor and interleukin-6 in RAW 264.7 macrophages by streptomycetes from indoor air of moldy homes. *Arch Environ Health* 1997; 52:426–32.
76. Molina C. The role of endotoxins in humidifier disease. In: Humidifiers and air-conditioners disease. Colloque

INSERM 1986, p377.
77. Rylander R, Lin RH. (1–3)-beta-D-glucan — relation to indoor air-related symptoms, allergy and asthma. *Toxicology* 2000;152:47–52.
78. Lundholm M. Rylander R. Work-related symptoms among sewage workers. *Br J Ind Med* 1983; 40:325–9.
79. Fraser DW, Tsai TR, Orenstein W. Oarkin W, Beecham H, Sharrar R, et al. Legionnaire's disease: description of an epidemic of pneumonia. *N Eng J Med* 1977: 297:1189–97.
80. Dennis PJ, Taylor JA, Fitzgerald RB. Bartlett CLR, Barnow GL. Legionella pneumophilia in water plumbing systems. *Lancet* 1982; 1:949–51.
81. Cornet M, Levy V, Fleury L, Lortholary J, Barquins S, Coureul MH, Deliere E, Zittoun R, Brucker G, Bouvet A. Efficacy of prevention by high efficiency particulate air filtration or laminar airflow against Aspergillus airborne contamination during hospital renovation. *Infect Con Hosp Epidemiol* 1999; 20:508–13.
82. Nardell EA, Keegan J, Cheney SA, Etkind SC. Airborne infection: theoretical limits of protection achievable by building ventilation. *Am Rev Respir Dis* 1991; 144:302–6.
83. Banaszak EF, Thiede WH, Fink JN. Hypersensitivity pneumonitis due to contamination of an air conditioner. *N Eng J Med* 1970; 283:271–6.
84. Woodard ED, Friedlander B, Lesher RJ, Font WF, Kinsey R, Hearne FT. Outbreak of hypersensitivity pneumonitis on an industrial setting. *JAMA* 1988; 259:1965–9.
85. Bernstein RS, Sorenson WG, Garabrant D, Reaux C, Treitman RD. Exposure to respirable airborne penicillium from a contaminated ventilation system: clinical, environmental and epidemiologic aspects. *Am Ind Hyg J* 1983; 44:161–9.
86. Samet JM, Hatch GE, Horstman D, Steck-Scott S, Arab L, Bromberg PA, Levine M, McDonnell WF, Devlin RB. Effect of antioxidant supplementation on ozone-induced lung injury in human subjects. *Am J Respir Crit Care Med* 2001; 164:819–25.
87. Trenga CA, Koenig JQ, Williams PV. Dietary antioxidants and ozone-induced bronchial hyperresponsiveness in adults with asthma. *Arch Environ Health* 2001; 56:242–9.
88. Grievink L, Zijlstra AG, Ke X, Brunekreef B. Double-blind intervention trial on modulation of ozone effects on pulmonary function by antioxidant supplements. *Am J Epidemiol* 1999; 149:306–14.
89. Romieu I, Meneses F, Ramirez M, Ruiz S, Perez Padilla R, Sienra JJ, Gerber M, Grievink L, Dekker R, Walda I, Brunekreef B. Antioxidant supplementation and respiratory functions among workers exposed to high levels of ozone. *Am J Respir Crit Care Med* 1998; 158:226–32.

20 Smoking and Lung Health

Somchai Bovornkitti, Wah Kit Lam and Moira Chan-Yeung

The Origin of Smoking

Tobacco has been smoked for centuries and possibly used for millennia. The tobacco plant is a native of the Americas and Australia; and also of China according to Tso (1,2). The American Indians used tobacco in ceremonials. After contact with American Indians, Christopher Columbus and other early explorers introduced tobacco to Europe. That was around 500 years ago, and now tobacco-smoking is a habit popular worldwide. Tobacco users get their addiction and apparent "relaxation" by absorbing nicotine and related alkaloids in the smoke produced by burning tobacco.

Chemical Components of Tobacco Smoke

Tobacco smoke that is drawn from the mouth that the smoker inhales is called "mainstream smoke", and the smoke released into the air from the burning tip of the cigarette including the material emitted from the mouth end of the cigarette which is not drawn into the mouth is called "sidestream smoke". Volatile chemicals in vapour phase constitute 50% of cigarette smoke components, while others are particulate phase components (3). Many of the components are present in higher concentration in sidestream smoke than in mainstream smoke, but exposure to sidestream smoke is generally less than to mainstream smoke because of dilution with air.

Tables 1 and 2 list some of the constituents in the vapour phase and particulate phase of cigarette smoke, respectively. The contents in the tables represent only major types of components among approximately 4,000 identified compounds. Over 50 cigarette smoke constituents have been identified as carcinogens *(vide infra)*.

The Smoking Epidemic

The World Health Organization (WHO) estimated that there are about 1100 million smokers in the world, representing about one third of the global population aged 15 year and older (4). About 800 millions are in the developing countries and most of them are men. Table 3 shows that about 47% of men and 12% of women in the world are smokers. Smoking prevalence varies substantially among regions, being lowest in Africa and highest in the Western Pacific, which includes China. In China alone, there are about 300 million smokers, 90% men and 10% women.

Table 4 shows the prevalence of smoking in adults and young adults by sex in selected Asian countries and in the United States and the United Kingdom in the 1990s. In both adults and young adults, the prevalence of smoking in men in many

Table 1. Major Constituents of the Vapour Phase in Cigarette Smoke[3]

Compound	*% of total effluent*
Nitrogen	56–64
Oxygen	11–14
Carbon dioxide	9–13
Carbon monoxide	2.8–4.6
Water	1.4–2.4
Argon	
Hydrogen	
Ammonia	
Nitrogen oxides [NOx]	
Hydrogen cyanide	
Hydrogen sulphide	
Methane	
Other volatile alkanes	
Volatile alkenes	
Volatile aromatic hydrocarbons	
Volatile acids	
Volatile aldehydes	
Volatile ketones	
Volatile alcohols	
Volatile nitriles	
Volatile furans	
Volatile pyridines	
Pyrrole	
Pyrrolidine	
N-Methylpyrrolldine	
Volatile pyrazines	
Aliphatic amines	

Table 2. Major Constituents of the Particulate Matter in Cigarette Smoke[3]

Nicotine	Cyclotenes
Nornicotine	Quinones
Anatabine	Solanesol
Anabasine	Terpenes
Other tobacco alkalolds	Palmatic acid
Bipyridyls	Stearic acid
n-Hentriacontaine [n-$C_{31}H_{64}$]	Oleic acid
Total nonvolatile hydrocarbons	Linoleic acid
Naphthalene	Linolenic acid
Naphthalenes	Lactic acid
Phenanthrenes	Indoles
Anthracenes	Aza-arenes
Fluorenes	Benzofurans
Pyrenes	*O*-heterocyclic compounds
Fluoranthenes	Stigmasterol
Carcinogenic polynuclear aromatic hydrocarbons	Sitosterol
Phenols	Campesterol
Catechols	Cholesterol
Dihydroxybenzenes	Aromatic amines
Scopoletin	Tobacco-specific nitrosamines
Polyphenols	Glycerol

Table 3. Estimated Smoking Prevalence for Men and Women, 15 years of Age and Over by WHO Region, Early 1990s[4]

WHO region	*Men (%)*	*Women (%)*
Africa	29	4
The Americas	35	22
Eastern Mediterranean	35	4
Europe	46	26
South-East Asia	44	4
Western Pacific	60	8
More developed countries	**42**	**24**
Less developed countries	**48**	**7**
World	**47**	**12**

Table 4. Prevalence of Smoking in Adults and Young Adults in Selected Asian Countries by Sex, and Cigarette Consumption per Capita Compared with Two Developed Countries

Country/Region year	*Prevalence in adults*			*Prevalence in young adults*			*Cigarette consumption (Unit)*
	Age	*Male*	*Female*	*Age*	*Male*	*Female*	
Cambodia, 1994	15–45	64.7 (ur) 86.3 (ru)	NA	< 21	18.0 (ur) 58.0 (ru)	NA	NA
China, 1996	15–69	63.0	3.8	NA	23.0	5.0	1798 (1998)
Hong Kong, 1998	15+	27.1	2.9	14–15	16.0	18.0	926
India, 1985–6	25–64	45.0	7.0	NA	12.8 (ur)	1.1(ur)	129
Japan, 1998	15+	52.8	13.4	12–19	8.0	1.5	2403
Korea, 1997	NA	NA	NA	13–15	35.3	8.1	2841
Malaysia, 1996	18+	49.2	3.5	16	25.1	0.6	910
Philippines, 1999	20+	75.0	18.0	NA	NA	NA	1688
Singapore, 1998	18–64	26.9	3.1	9–20	3.0	0.2	1230
Taiwan, 1996	18+	55.1	3.3	NA	23.8	8.2	NA
Thailand, 1999	11+	38.9	2.4	11–14	0.4	0	1162
Vietnam, 1995	18–92	72.8	4.3	15	20.0	NA	844
United States, 1997	**18+**	**27.6**	**22.1**	**11–15**	**7.0**	**6.0**	**2255**
United Kingdom, 1996–97	**16+**	**29.0**	**28.0**	**11–15**	**8.0**	**11.0**	**1748**

Source: National Tobacco Information Online system (NATIONS) from http://apps nccd.cdc.gov/nations/
Ur = urban, ru = rural

Asian countries now exceeds those of the US and the UK (5). Compared to the US and the UK, the prevalence of smoking in adult women is lower in Asian countries; however, the prevalence in young women in some Asian countries is higher.

The trends in annual cigarette consumption per adult between 1970–1972 and 1990–1992 in different regions are shown in Figure 1a and in developed and developing countries in Figure 1b (4). Over the 20-year period, cigarette consumption per adult remained about the same in Europe, decreased in the Americas, and increased in all other regions, especially in the Western Pacific. Cigarette consumption has decreased in developed countries since 1980–1982 but increased in developing countries. The increase in consumption in China has been most dramatic because of the vast population. In China, the estimated consumption of cigarettes per adult increased by 260% between 1970–1972 and 1990–1992.

Despite these opposite trends in developed and developing countries, the average cigarette

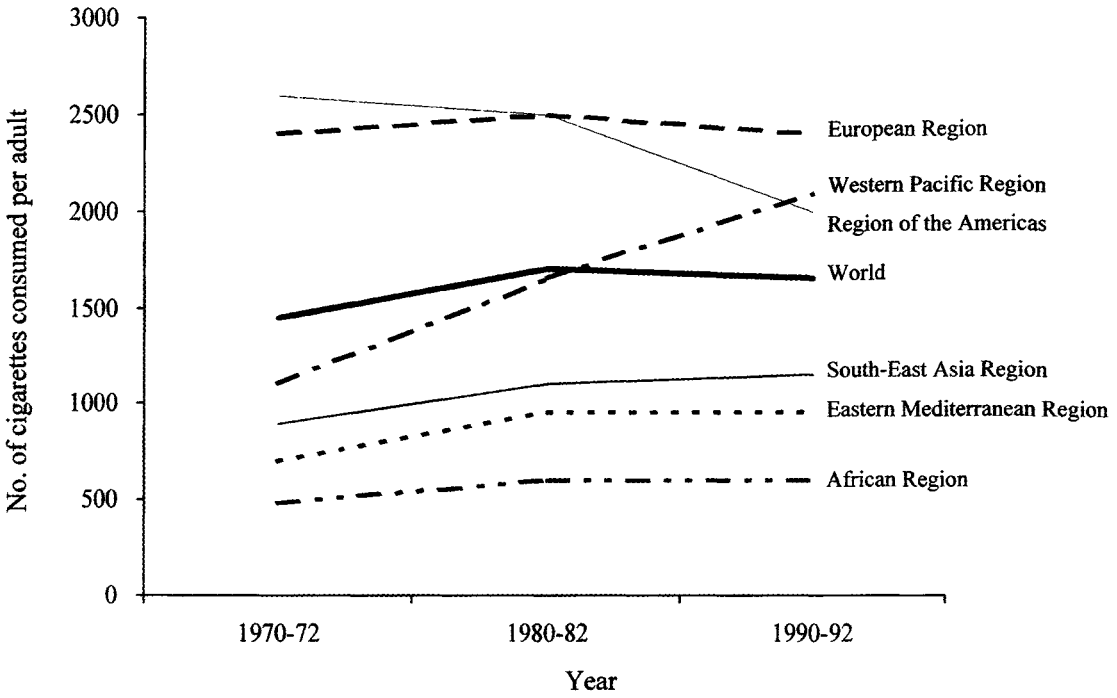


Figure 1a. Trends in annual per adult cigarette consumption in developed and developing countries 1970–1992 (modified from reference 4)

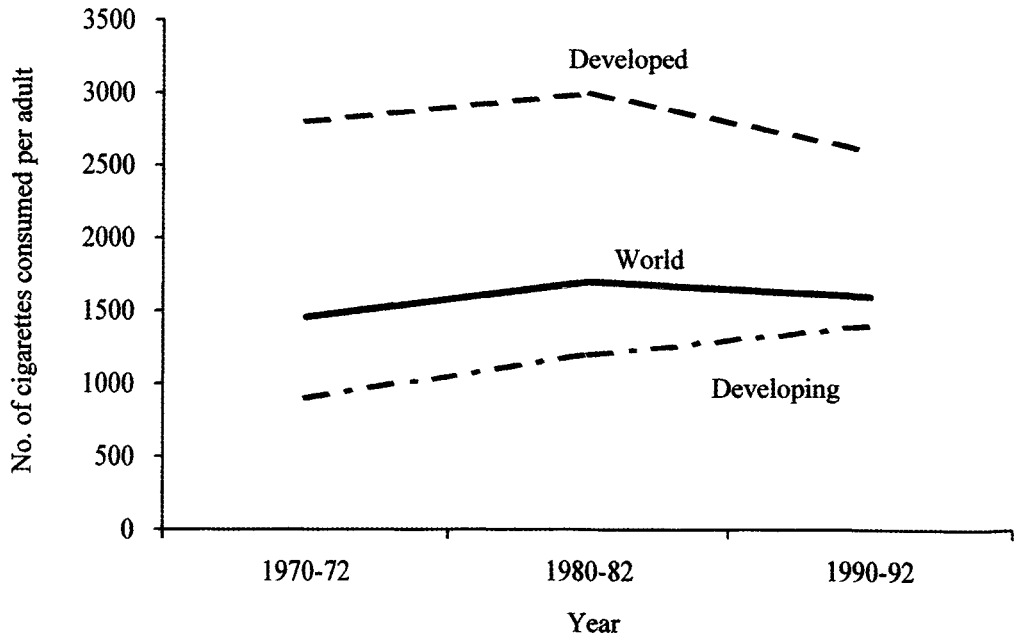


Figure 1b. Trends in annual per adult cigarette consumption, WHO Regions, 1970–1992 (modified from reference 4)

consumption per adult in developed countries remains higher than in developing countries. This is illustrated to a certain extent in Table 4 and in some countries in the Western Pacific, such as Japan and Korea, annual cigarette consumption per capita exceeded those in the US or the UK in late 1990s (5).

Health Hazards of Smoking

Over fifty years have passed since the serious health effects of tobacco smoking were scientifically established (6,7). At present, tobacco use is well known to be the single largest cause of preventable diseases and death in developed countries. "Where there is smoke, there is fire", the old saying goes. To paraphrase it, we would say: "where there are cigarettes, there is ill health" (8). There is substantial evidence that inhalation of tobacco smoke — actively or passively — is a major cause of diseases and ill-health.

Active Smoking

Lung cancer

Cigarette smoking is the leading cause of avoidable cancer death worldwide. The evidence linking smoking and cancer is beyond dispute. In 1950, Wynder and Graham (6) in United States and Doll and Hill (7) in England reported the first large scale studies linking smoking and lung cancer. In 1964, the US Surgeon General concluded that cigarette smoking was the major contributing factor in the development of lung cancer (9).

In the early part of the 20th century, lung cancer was a rare disease globally. The first modern blended cigarette was introduced in 1913 in the US. The prevalence of lung cancer in men and women then slowly increased to follow trends in their uptake of cigarette smoking, with an approximately 20-year delay (3). Lung cancer is now the leading cause of cancer death in both men and women worldwide, including in Asian countries and regions such as Thailand (10), China (in cities) (11), and Hong Kong (12). The relative risk of lung cancer in smokers has been consistently demonstrated by major prospective studies to closely relate in a dose-response manner to the numbers of cigarettes consumed daily and the duration of smoking (13–15). US statistics show that the risk ratios among male smokers who smoke < 19 cigarettes, 20–39 cigarettes and >40 cigarettes a day are 4.6–9.9, 14.7–17.4 and 18.8–23.9 respectively. On the other hand, there is a significant and progressive reduction in the risk after quitting smoking—the risk ratio decreases from 12–19 in the initial one to four years after quitting to about 2 after fifteen years.

Although all the three main types of lung cancer (squamous cell, small cell, and adenocarcinoma) are caused mainly by tobacco smoking, certain issues remain to be solved, for instances, the changing histology of cigarette smoke-induced lung cancer in males from formerly predominantly squamous-cell type toward adenocarcinoma in recent years (16), geographic and ethnic differences, and staple diet and cooking styles as risk factors in certain racial populations (17–19).

The existence of carcinogens has been established in the cigarette smoke (Table 5), and those over 55 compounds have been evaluated by the IARC as carcinogenic in animals. Specific carcinogens of tobacco smoke that play a major role as causative agents in human lung cancer are shown in Table 6.

PAHs, which are formed by the incomplete combustion of tobacco during smoking, are shown to induce tumours of the lung in animals exposed by inhalation (20), intratracheal instillation (21), or implantation in the lung (22). Squamous cell carcinoma is the predominant cell type induced by benzo[*a*]pyrene, and mutational changes in the *p53* gene similar to those observed in smokers' lung cancer also occur (23).

NNK, a tobacco-specific nitrosamine (one of nicotine-derived nitrosamines) formed during the processing of tobacco and during smoking, is an organ-selective lung carcinogen, especially for adenocarcinoma (24).

Polonium-210, which is present in cigarette smoke, is a strong carcinogen. It has been estimated that about 1 per cent of the lung cancer risk in smokers could be ascribed to ^{210}Po.

Chromium, cadmium, and nickel are present in cigarette smoke (Table 5) and may play a role

Table 5. Carcinogens in Tobacco and Cigarette Smoke

Compound	*In processed tobacco (per gram)*	*In mainstream smoke (per cigarette)*	*Evidence of carcinogenicity*	
			In laboratory Animals	*In humans*
PAH				
Benz[*a*] anthracene		20–70 ng	Sufficient	
Benzo[*b*] fluoranthene		4–22 ng	Sufficient	
Benzol[*j*] fluoranthene		6–21 ng	Sufficient	
Benzo [*k*] fluoranthene		6–12 ng	Sufficient	
Benzo [*a*] pyrene	0.1–90 ng	20–40 ng	Sufficient	Probable
Dibenz [*a,i*] anthracene		4 ng	Sufficient	
Dibenzo [*a,i*] pyrene		1.7–3.2 ng	Sufficient	
Dibenzo [*a,l*] pyrene		Present	Sufficient	
Indeno [1,2,3-*cd*] pyrene		4–20 ng	Sufficient	
5-Methylchrysene		0.6 ng	Sufficient	
Aza-arenes				
Quinoline		1–2 μg		
Dibenz[*a,h*] acridine		0.1 ng	Sufficient	
Dibenz [*a,j*] acridine		3–10 ng	Sufficient	
7H-dibenzo[*c,g*] carbanzole		0.7 ng	Sufficient	
Nitrosamines				
N.-Nitrosodimethylamine	ND–215 ng	0.1–180 ng	Sufficient	
N-Nitrosoethylmethylamine		3–13 ng	Sufficient	
N-Nitrosodiethylamine		ND–25 ng	Sufficient	
N-Nitrosopyrrolidine	5–50 ng	3–60 ng	Sufficient	
N-Nitrosodiethanolamine	50–3,000 ng	ND–68 ng	Sufficient	
N-Nitrososarcosine	20–120 ng		Sufficient	
N-Nitrosonornicotine (NNN)	0.3–89 μg	0.12–3.7 μg	Sufficient	
4-(Methylnitrosamino)-1-(3-pyrldyl)-1-butanone (NNK)	0.1–7 μg	0.08–0.77 μg	Sufficient	
N'-Nitrosoanabasine	0.01–1.9 μg	0.14–4.6 μg	Limited	
N-Nitrosomorpholine	ND–690 ng		Sufficient	
Aromatic amines				
2-Toluidine		30–200 ng	Sufficient	Inadequate
2-Naphthylamine		1–22 ng	Sufficient	Sufficient
4-Aminobiphenyl		2–5 ng	Sufficient	Sufficient
Heterocyclic aromatic amines				
AαC		25–260 ng	Sufficient	
MeAαC		2–37 ng	Sufficient	
IQ		0.26 ng	Sufficient	Probable
Trp-P-1		0.29–0.48 ng	Sufficient	
Trp-P-2		0.82–1.1 ng	Sufficient	
Glu-P-1		0.37–0.89 ng	Sufficient	
Glu-P-2		0.25–0.88 ng	Sufficient	
PhIP		11–23 ng	Sufficient	Possible
Aldehydes				
Formaldehyde	1.6–7.4 μg	70–100 μg	Sufficient	Limited
Acetaldehyde	1.4–7.4 μg	18–1400 μg	Sufficient	Inadequate
Miscellaneous organic compounds				
1,3-Butadiene		20–75 μg	Sufficient	Probable
Isoprene		450–1000 μg	Sufficient	Possible
Benzene		12–70 μg	Sufficient	Sufficient
Styrene		10 μg	Limited	Possible

(continued on p. 355)

Table 5. (Continued)

Compound	*In processed tobacco (per gram)*	*In mainstream smoke (per cigarette)*	*Evidence of carcinogenicity*	
			In laboratory Animals	*In humans*
Vinyl chloride		1–16 ng	Sufficient	Sufficient
DDT				
DDT	20–13400 ng	800–1200 ng	Sufficient	
Acrylonitrile	7–960 ng	200–370 ng	Sufficient	Limited
Acrylamide		3.2–15 μg	Sufficient	Probable
1, 1-Dimethylhydrazine		Present	Sufficient	
2-Nitropropane	60–147 μg		Sufficient	
Ethyl carbamate		0.73–1.21 μg	Sufficient	
Ethylene oxide	310–375 ng	20–38 ng	Sufficient	Limited
Di(2-ethylhexyl) phthalate		7 μg	Sufficient	
Furan	Present	20 μg	Sufficient	Inadequate
Miscellaneous organic compounds		18–30 μg		
Benzo [*b*] furan			Sufficient	Inadequate
Inorganic compounds		Present		
Hydrazine			Sufficient	Inadequate
Arsenic	14–15 ng	24–43 ng	Inadequate	Sufficient
Nickel	500–900 ng	40–120 ng	Sufficient	Limited
Chromium	2000–6000 ng	0–600 ng	Sufficient	Sufficient
Cadmium	1000–2000 ng	4–70 ng	Sufficient	Limited
Lead	1300–1600 ng	41–62 ng	Sufficient	Inadequate
Polonium-210	8–10 μg 0.2–1.2 pCi	35–85 ng 0.03–1.0 pCi	Sufficient	Sufficient

[a] Abbreviations for heterocyclic amines: AαC, 2-amino-9H-pyrido (2,3-*b*) indole; MeAαC, 2-amino-3-methyl-9H-pyrido (2,3-*b*) indole; IQ, 2-amino-3-methylimidazo (4,5-*b*) quinoline; Trp-P-1, 3-amino-1, 4-dimethyl-5H-pyrido (4,3-*b*) indole; Trp-P2, 3-amino-1-methyl-5H-pyrido-(4,3-*b*) indole; Glu-P-1, 2-amino-6-methyl (1,2-*a:3', 2'-d*) imidazole; Glu-P-2, 2-aminodipyrido-(1,2-*a:3',2'-d*) imidazole; PhIP, 2-amino-1-methyl-6-phenylimidazol (4,5-*b*) pyridine.

ND = not detected. * Adapted from reference 3

Table 6. Smoking and Lung Cancer: Causative Agents[a]

Carcinogens	*Modifying agents*
Strong evidence	
NNK	Cocarcinogens (catechols)
PAH (benzo[a]pyrene, benzo[*b,j,* and *k*] fluoranthenes, 5-methylchrysene, dibenz[*a,h*] anthracene, indeno[1,2,3-*cd*] pyrene)	Tumor promoters (phenols & others)
	Toxic aldehydes (acrolein)
	Diet
Weak evidence	
Oxidative damage and free radicals	
^{210}Po, Cr, Cd, Ni	
Aldehydes	

NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; PAH = polycyclic aromatic hydrocarbon

in lung cancer induction. Formaldehyde and acetaldehyde are weak respiratory carcinogens.

Cocarcinogens are non-tumorigenic agents by themselves, but can enhance tumorigenicity when present simultaneously with a carcinogen. The major cocarcinogen in cigarette smoke is catechol (1,2-dihydroxybenzene); others include methylcatechol, pyrogallol, decane, undecane, pyrene, and fluoranthene.

Cigarette smoke carcinogens are metabolically activated to reactive electrophiles. The electrophiles react with DNA and the resultant damage leads to permanent mutations. The consequences of such mutations include activated oncogenes or inactivated tumour suppressor genes.

Chronic obstructive pulmonary disease (COPD)

A number of premature deaths attributable to smoking are cases of respiratory failure caused by chronic obstructive pulmonary disease (COPD). The relationship between the loss of lung function (FEV_1) and smoking was shown by Fletcher et al (25) in an elegant study in which they observed the rate of loss of respiratory capacity in smokers and non-smokers over a period of 8 to 10 years and showed that the rapid rate of decline in some smokers was reduced to that in non-smokers when smoking was stopped. Tobacco smoking classified as a type of personal air pollution is the most important cause of COPD.

Impairment of mucociliary clearance in the airways is an important pathogenetic mechanism in COPD caused by cigarette smoking, although other environmental factors such as sulphur dioxide, sulphuric acid and wood dust are also known to slow mucociliary clearance (26). Impaired clearance mechanisms may make respiratory tracts susceptible to infection, which is a well-documented aggravating factor of COPD. Repeated airway infection results in persistent abnormal lung structure and/or function.

Some of the components in the polluted environment may activate pulmonary neutrophils and macrophages. Activated neutrophils and macrophages release elastases, which destroy the collagen framework of the lung parenchyma. The proteolytic enzyme inhibitor, alpha 1- antitrypsin (α1AT), protects the lung from excessive elastolytic damages. Oxidizing agents contained in cigarette smoke suppress the capacity of α1AT to compete with elastase. Activated neutrophils and macrophages are also known to release oxygen radicals, which may enhance the destructive effect of elastases on the lung.

Pulmonary tuberculosis

Gupta et al (27) recently reported results from a case-control study indicating that smoking was significantly associated with risk of active pulmonary tuberculosis, as evident statistically by:

1. more smokers being among cases as compared to controls;
2. higher yields of sputum-smear positive for acid-fast bacilli among smokers; and
3. a strong association between smoking and risk of active pulmonary tuberculosis observed by multiple logistic regression analysis.

Other diseases

Cigarette smoking is also a major cause of coronary artery disease, stroke, peripheral vascular disease, cancers of the mouth, tongue, larynx, oesophagus and urinary bladder, and is associated with an increased risk of invasive pneumococcal disease and male sexual impotence.

Passive Smoking (Environmental Tobacco Smoke, ETS)

In the US, about half of the children under the age of 5 years were exposed to ETS in 1988 (28). In a survey in Hong Kong, about one third of children are living with a smoker at home (29). Exposure to ETS in children is a universal problem.

Comprehensive reviews on the health hazards of passive smoking and ETS have been available since 1986 (28, 30–43). Most studies have been conducted in the US and Western countries, but in the 1992 US Environmental Protection Agency Review on ETS and acute respiratory illnesses in children, three studies were from Shanghai (31).

Effects on the foetus

Pregnant women who smoke are at higher risk of having miscarriages, still-births and premature deliveries. Techniques for assessing lung function in infants have become available in recent years. Healthy infants whose mothers smoked during pregnancy showed reduced FEV_1 shortly after birth (42,44). Increased airway responsiveness was found in normal infants of smoking parents at 4.5 weeks of age were compared with infants of nonsmoking parents (45). These studies suggest that ETS exposure in-utero has deleterious effect on lung growth since airways are fully present before the end of pregnancy while alveolar proliferation continues to about four years of age. The impact of this small deficit in older children is not known but is likely to be more important in children of countries where nutrition and health care are poor. In addition to low birth weight, congenital abnormalities have been reported (46).

Effects on children

Lower respiratory tract infection in early childhood

There is substantial epidemiological evidence on maternal smoking and increased risk for lower respiratory tract illnesses such as pneumonia and bronchitis during infancy and early childhood (34,47–51). The relationship between parental smoking and acute lower respiratory illnesses in infancy is likely to be a causal one (34). While most of the studies showed that maternal rather than paternal smoking increased the risk, the study from China showed that paternal smoking alone also increased the risk of lower respiratory tract infection in children with a dose-dependent relationship (48).

Asthma, allergic sensitization and bronchial hyperresponsiveness

There is consistent evidence that exposure to ETS aggravates asthma in children. Exposure to ETS led to increase in emergency room visits and hospitalization in these children (52,53). Intervention measures by reducing exposure to ETS resulted in decreased health care utilization (54).

There is convincing evidence that parental smoking is associated with increased prevalence of asthma and respiratory symptoms in schoolchildren (36,55–58). While there is general consensus that exposure to ETS increased asthma severity, there is still controversy as to whether ETS exposure leads to the inception of asthma. A meta-analysis has found an increased risk of asthma in children of about two times from maternal smoking (58). However, a more recent meta-analysis has shown that while the incidence and recurrence of wheezing illness in early life is increased if there is smoking in the household, particularly by the mother, the incidence of asthma during the school years is less strongly affected by parental smoking (36). This may be due to the reduced level of exposure to ETS as children grow up. The evidence points to the fact that parental smoking is an important cause of early wheezing than of late onset "asthma".

There is no consistent relationship between parental smoking either before or immediately after birth and the risk of allergic sensitization (positive skin test reactivity, IgE level, hay fever, or eczema) in children (38). On the other hand, a meta-analysis carried out by the same authors found a small but real increase in bronchial hyperresponsiveness in children of smoking mothers (40).

Lung function

There have been more than 30 studies linking ETS exposure at home with decreased lung function in children (32). These studies included not only cross-sectional ones but also longitudinal studies (59–65). The projected reductions of lung function growth for a child because of maternal smoking were 28, 51 and 101 ml in FEV_1 for 1, 2 and 5 years respectively (62).

There are probably 3 different windows of exposure that are biologically relevant: in-utero, the first two years of life when the rates of lower respiratory tract infection are highest and maternal smoking has greatest effects, and the subsequent years of childhood. Maternal smoking during pregnancy appears to have the largest effects on neonatal lung mechanics with smaller effects in school-aged children (42).

Middle ear disease in young children

Nearly 20 studies reported on the association of ETS exposure with middle ear problems in children

(66). A recent meta-analysis was carried out showing significant increased risks of recurrent otitis media and middle ear effusion for children of smoking parents (37). A highly significant positive relationship between the duration of effusion and the number of smokers in the household during the first and the second year of life was found.

Sudden infant death syndrome (SIDS)

Sudden infant death syndrome is characterized by sudden, inexplicable death, usually during sleep, of infants aged from one month to one year. In developed countries, SIDS is the most common cause of post-natal death. Maternal smoking has been consistently shown to be a major risk factor for SIDS independent of low birth weight and other potential confounders (35,67–71). Postnatal exposure to ETS explained the increased risk rather than maternal smoking during pregnancy (35).

Effects on adults

Lung cancer

There is now firm evidence that ETS is a cause of lung cancer in non-smokers (28, 30–33,72–73). A recent weighted analysis of 37 published epidemiological studies showed an increased risk of 24% (95% confidence interval or CI 13% to 36%) among non-smoking wives of smoking husbands compared with controls (72), although reanalysis of the data allowing for publication bias would lower this estimate of relative risk (73). It is notable that of these 37 studies, 17 were from Asia (eight from mainland China, five from Japan and four from Hong Kong). Because of the low prevalence of smoking in Asian women, any misclassification bias should be small, and the Asian evidence for a casual relationship between ETS and lung cancer is particularly strong (74). ETS is now classified as a class A carcinogen, and the US National Research Council concluded that about 20% of lung cancer occurring in non-smoking men and women may be attributable to ETS (30,31).

Asthma and COPD

The effects of ETS exposure on asthma in adults are less well studied compared to children. Recently there have been 4 studies showing that ETS exposure at work or at home or both is associated with increased risk of asthma symptoms, work disability, restricted activity and acute exacerbation of asthma requiring hospitalization (41,75–78). Passive smoking as a risk factor for COPD among nonsmokers has been demonstrated in a number of studies that have used self-reports of doctor diagnosis, physician diagnosis, and mortality data; the magnitude of the association is small (41).

The Burden of Disease From Tobacco Smoke

There is no doubt from scientific evidence that smoking is an important cause of premature mortality and disability worldwide. Table 7 shows cigarette consumption, mortality and disease burden measured by Disability-Adjusted Life Years (DALYs) by WHO regions (79).

Table 7. Cigarette Consumption, Mortality and Disease Burden by WHO Region[79]

WHO region	*Cigarette consumption / capita (1995 estimates)*	*Mortality (000) (1998 estimates)*	*DALYs (000) (1998 estimates)*
Western Pacific	1,945	1,093	11,022
South-East Asia	415	580	7,439
Europe	2,080	1,273	17,084
The Americas	1,530	772	8,867
Eastern Mediterranean	890	182	2,976
Africa	480	125	1,900
World total	1,325	4,023	49,288

Table 8. Deaths and Disability-adjusted Life Years (DALYs) Attributed to Tobacco Use for 1990 and Projected for 2020[79]

Region	*Mortality*		*DALYs*	
	1990	*2020*	*1990*	*2020*
World	3,038 (6.0)	8,383 (12.3)	36,182 (2.6)	123,678 (8.9)
Developed	1,577 (14.5)	2,387 (17.7)	19,410 (12.1)	29,141 (18.2)
Developing	1,460 (3.7)	5,996 (10.9)	16,770 (1.4)	94,537 (7.7)
China	820 (9.2)	2,229 (16.0)	8,078 (3.9)	35,415 (16.1)
India	129 (1.4)	681 (8.8)	2,638 (1.5)	10,061 (6.1)
Other Asia and Islands	223 (4.0)	1,523 (13.3)	1,719 (0.6)	24,024 (10.2)

DALYs is the sum of years of life lost because of premature mortality and years of life lived with disability adjusted for the severity of disability (79). In 1996, the WHO estimated that smoking caused about 4 million deaths annually worldwide (about 1.6 million from Asian countries) and predicted that this number will likely increase dramatically if the current pattern of smoking persists. The magnitude of the effects of tobacco on mortality and DALYs in 1990 and projected for 2020 are shown in Table 8 (79). In 2020, tobacco will become the largest single health problem, causing an estimated 8.4 million deaths annually. Tobacco's contribution to the burden of disease will change between now and 2020 but different for different regions as tobacco use declines in many developed countries but is increasing rapidly in many developing countries. Thus the increase in mortality and DALYs in developed regions are expected to rise 50% from 1.6 million to 2.4 million while those in Asia will increase almost fourfold from 1.1 million in 1990 to an estimated 4.2 million in 2020 (79).

Although these are projections, recent studies from China have validated them to a certain extent. A retrospective study was carried out by Liu et al (80) of one million death during mid 1980s and this was followed by a prospective study set up in 1991 to follow middle aged smokers for the next few decades (80). Data from these two studies concurred with the estimates that 12% of deaths are currently attributable to tobacco, similar to the world's developed regions where 14.9% of deaths in 1990 are attributable to tobacco (3).

In China, the prevalence of smoking is increasing in men and about two thirds become smokers before the age of 25 years and very few quit (81). It can be estimated that the number of male deaths from tobacco is about 3 million annually by mid-2000s, half while middle-aged, thus leading to substantial loss of productive life years (82).

As the effects of tobacco smoke on morbidity and mortality has a long latent period, the full impact of the increase in cigarette consumption and the economic burden to the developing nations will not be realized until some years from now.

Tobacco Control in Asia

As US anti-smoking campaigns and laws have reduced smoking in the US by almost 20% over the past decade, the transnational tobacco companies have expanded into the huge and growing populations of the developing world and increased their exports by 260%, mainly to Asia (83). "No discussion of the tobacco industry in the year 2000 would be complete without addressing what may be the most important feature on the landscape, the China market," said a tobacco executive in 1986. "You know what we want? We want Asia!" said another tobacco executive in an interview with tobacco reporter in 1988. China and the Republic of Korea have been especially targeted for aggressive expansion (84). They have been highly successful in their marketing strategy, and by 1998, the top US tobacco companies sold 57 to 70% of their products overseas.

Concerted efforts by governments, health care

professionals, citizen groups, and tobacco control bodies and organizations (e.g. WHO Regional Office for the Western Pacific, Asian Consultancy on Tobacco Control) in Asian countries are urgently needed to curb the tobacco epidemic and its disastrous consequences in Asia. Joint forces with the International Non-Governmental Coalition Against Tobacco (INGCAT) which currently represents over 1000 non-governmental organization in 160 countries, would help to influence governments and public opinions. Similarly, the International Association for the Study of Lung Cancer has issued the "Tokyo Declaration on Tobacco" during the 9th World Conference on Lung Cancer held in Tokyo in September 2000. Objectives and effective activities would include the following:

1. To develop and implement comprehensive national policies and programmes on tobacco control. Leadership and commitment by the government is essential, and national, concerted action is required. In the Asia Pacific region, Australia, the mainland of China, Hong Kong, New Zealand, Singapore and Thailand are among the countries and regions that had taken significant anti-tobacco programmes starting in the 1980s or before.
2. To support health advocacy, education and information. Health advocacy is important. When there is a strong social consensus against smoking, there is a strong incentive for the smokers to quit. It must be realized that the general awareness of the risks of smoking is relatively low in developing countries especially in low-income groups. A national survey in China, for instance, found that 55% of Chinese non-smokers and 69% of smokers believed that cigarettes "did little or no harm" (85). Similarly, young people would grossly underestimate the risks of addiction and believe that they would be able to easily quit the habit as they wish. Globally, 82,000 to 99,000 young people start smoking every day. Teenagers should be educated not to take up the habit.

   Restrictions on smoking at home, more extensive bans on smoking in public places and enforced bans on smoking at school may further reduce teenage smoking (86). Smokers must be encouraged to quit. There should be increased access to nicotine replacement and other treatments for quitting smoking, which has been shown to roughly double the chances of success. In this regard, health care professionals, particularly doctors, will be in the best position to contribute effectively. All health care providers should receive training in counselling on stopping smoking. The Smokers' Clinic in Thailand is such an example (8,87). "Smokers' Clinic" is not a conventional clinic only for helping people to stop smoking, but it will also help to preserve the health of continuing smokers by delaying the occurrence or emerging of tobacco-related diseases. Ultimately, it will provide appropriate treatment for smokers, if or when they become patients. Thus, the "Smokers' Clinic" is a service for smokers that offers the following:
   (a) To help people break their smoking habit or addiction.
   (b) To prevent the adverse consequences of smoking among people who do not want to stop smoking or cannot do so.
   (c) To give treatment to smokers or exsmokers who are suffering from smoking-related diseases.
3. To implement appropriate legislations and coordinated administrative measures. Legislations should cover licensing of nicotine as an addictive drug, reduction of tar levels in cigarettes, health warnings and banning of sales to minors, smoke-free areas in public places, public transport and workplaces, and a tobacco-advertising ban. Currently, most Asian countries have such legislations, including China and the Republic of Korea, the main targets of transnational tobacco companies. A review of 102 countries and economic analyses in high-income countries showed that comprehensive bans on tobacco advertising can reduce tobacco consumption (88). It should be noted that partial advertising bans have little effect, as the tobacco companies quickly turn to other unbanned forms of media or sports sponsoring. Even specific government agreements with tobacco companies to prohibit tobacco advertising that targets young people have had little effect on cigarette advertising in magazines and on the

exposure of young people to these advertisements (88).

4. To achieve pricing policies that deter tobacco use. Tax increases are the single most effective way to reduce tobacco consumption especially in children/teenagers and in the poor (89). Tax increases that raise the real price of cigarettes by 10% would reduce smoking by 4% in high-income countries and 8% in low income or middle-income countries.

National anti-smoking programmes as described above have been effective in reducing the number of smokers in developed countries. Recently, it was also shown to be effective in the middle-income country as Mauritius (90). In Hong Kong, China, the Hong Kong Council on Smoking and Health was established in the mid 1980s. It has a comprehensive policy of legislation (particularly in banning smoking in public areas and advertising bans), education, publicity, and taxation, and the results have been impressive. The proportion of smokers in the adult population (age >15 years) decreased from 23.3% in 1982 (male 39.7%, female 5.6%) to 16.8% (male 29%, females 2.9%) in the 1990s (91). There are other success stories in Thailand and Singapore. In Thailand, comprehensive tobacco control measures have been launched since 1974 including health warnings, health education, legislation, protection of non-smokers' health, protection of tobacco addiction among youth, prevention of smoking in women, smoking cessation programmes, taxation, tobacco control networking and research. As a result, the incidences of smoking in Thais have decreased steadily from 34.4% (63.3% in men and 5.4% in women) in 1981 to 22.8% (48.5% in men and 2.5% in women) in 1993 (92). The Thai experience is valuable to other Asian countries that have not yet launched or are facing difficulties in their tobacco control programmes. Lessons learned include networking and coalition building both domestically and internationally to add lobbying power to tobacco control advocates, lobbying the government to champion the campaign for tax increases and legislation, stressing to policy makers that the objective is to prevent children from taking up smoking, and to emphasize on health education (92). In Singapore, the government has been fully supportive; cigarette advertising was banned in 1970, followed by progressive banning of smoking in indoor public areas and workplaces, massive health education campaigns, licensing all retailers of tobacco products and other measures (93). In China, tobacco control measures began tentatively in 1979. In 1983, China banned smoking on all domestic air flights, the first country to do so. The Chinese Association on Smoking and Health (CASH) was established as the central coordinating organization on tobacco control in 1993. In 1995, all cigarette advertising in print and electronic media was banned and by 1997, the Ministry of Health has implemented banning of smoking in public places in 71 cities and three provinces (94).

It should be emphasized that even in a country where tobacco is largely self-supplied, the tobacco industry is still unfavourable to the country's overall economy. While the government may derive short-term benefits from income, tobacco always erodes economy by increased medical and health care, lost productivity, deforestation from the use of wood for tobacco curing, misuse of land for growing tobacco rather than crops, and causing fires from careless smoking. The world tobacco market currently produces an annual global loss of US$200 billion, one third of which occurs in developing countries. Comprehensive tobacco control policies will only help and not harm a country's economy (89).

There have been recent successes in litigations against US tobacco companies, including the US$368.5 billion settlement between 40 state attorney generals and the tobacco industry in 1997 and the verdict for the top 5 US tobacco companies to pay US$ 145 billion punitive damages to sick smokers in Florida in 2000. However, any US tobacco settlement in the absence of global controls may actually worsen tobacco problems in developing countries. Indeed, in 1997, tobacco control advocates from 19 countries/regions, including Australia, Hong Kong, India, Japan, Malaysia, Mongolia, New Zealand, the Philippines, Taiwan and Thailand, issued a joint statement that "it is unacceptable to discuss a comprehensive settlement of the US tobacco litigation which does not include measures to control the use of US tobacco products outside of the United States" (83).

References

1. Doll R. The effects of smoking on health. *Siriraj Hosp Gaz* 1993; 45:634–46.
2. Tso TC. In: *Handbook of Tobacco and Tobacco Products.* Eds. Adlkofer F, Scherer G. Hamburg: Beitrage zur Tabakforschung International 1986.
3. Hecht SS. Cigarette smoking and cancer. In: *Environmental & Occupational Medicine,* 3rd ed. Ed. Rom WN. Philadelphia: Lippincott-Raven 1998, 1479–99.
4. World Health Organization. Smoking Prevalence. In: *Tobacco or Health: A Global Status Report.* Geneva: World Health Organization 1997; 10–18.
5. National Tobacco Information Online System (NATIONS). http://apps.nccd.cdc.gov/nations
6. Wynder EL, Graham EA. Tobacco smoking as a possible etiologic factor in bronchogenic carcinoma. *J Am Med Assoc* 1950; 143:329–36.
7. Doll R, Hill AB. Smoking and carcinoma of the lung. *Br Med J* 1950; 2:739–48.
8. Bovornkitti S. Smokers' clinic. *Siriraj Hosp Gaz* 1994; 46:798–807.
9. United States Surgeon General. *Smoking and Health.* USPHS publication no. 1103. Washington, DC: Department of Health, Education and Welfare, 1964.
10. Silarug N, Sawanpanyalert P, Bovornkitti S. Lung cancer prevalence in Thailand. *J Environ Med* 2000; 2:257–61.
11. Li YD, Lu FZ, Chang SW, et al. Analysis of mortality rates of malignant neoplasms in China, 1990–1992 (Chinese). *Chin J Oncology* 1996; 18:403–7.
12. Lam WK, So SY, Yu DYC. Clinical features of bronchogenic carcinoma in Hong Kong — a review of 480 patients. *Cancer* 1983; 52:369–76.
13. International Agency for Research on Cancer. Tobacco smoking. In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans,* vol. 38. Lyon, France International Agency for Research on Cancer 1986.
14. United States Surgeon General. Reducing the health consequences of smoking. Twenty-five years of progress. USPHS publication no. (CDC) 89–8411. Rockville, MD: Department of Health and Human Services, 1989.
15. Shopland DR. Tobacco use and its contribution to early cancer mortality with a special emphasis on cigarette smoking. *Environ Health Perspect* 1995; 103(suppl 8): 131–42.
16. Wynder EL, Hoffmann D. Smoking and lung cancer: scientific challenges and opportunities. *Cancer Research* 1994; 54:5284–95.
17. Supornsilphachai C, Bovornkitti S. Lifestyles and lung cancer. *Siriraj Hosp Gaz* 1997; 49:484–9.
18. Shields PG, Xu GX, Blot WJ, Fraumeni JF Jr, Trivers GE, Pellizzari ED, Qu YH, Gao YT, Harris CC. Mutagens from heated Chinese and US cooking oils. *J Natl Cancer Inst* 1995; 87:836–41.
19. Ko YC, Cheng LS, Lee CH, Huang JJ, Huang MS, Kao EL, Wang HZ, Lin HJ. Chinese food cooking and lung cancer in women non-smokers. *Am J Epidemiol* 2000; 151:140–7.
20. Thyssen J, Althoff J, Kimmerle G, Mohr U. Inhalation studies with bezo[a]pyrene in Syrian gloden hamsters. *J Natl Cancer Inst* 1981; 66:575–7.
21. Woltebeek APM, Schoevers EJ, Rutten AAJL, Feron VJ. A critical appraisal of intratracheal instillation of benzo[a]pyrene to Syrian golden hamsters as a model in respiratory tract carcinogenesis. *Cancer Lett* 1995; 89:107–16.
22. Stanton MF, Miller E, Wrench C, Blackwell R. Experimental induction of epidermoid carcinoma in the lungs of rats by cigarette smoke condensate. *J Natl Cancer Inst* 1972; 49:867–77.
23. Denissenko MF, Pao A, Tang M, Pfeifer GP. Preferential formation of benzo[a]pyrene adducts at lung cancer mutational hotspots in p53. *Science* 1996; 274:430–2.
24. Hecht SS, Hoffmann D. Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. *Carcinogenesis* 1988; 9:875–84.
25. Fletcher C, Peto R, Tinker C, Speizer FE. *The Natural History of Chronic Bronchitis and Emphysema.* Oxford: Oxford University Press 1976.
26. Suzuki N, Takizawa H. The pathogenesis of environmental lung disease. *J Environ Med* 1999; 1:102–21.
27. Gupta D, Aggarwal AN, Kumar S, Jindal SK. Smoking increases risk of pulmonary tuberculosis. *J Environ Med* 2001; 3:41–6.
28. US Department of Health and Human Services. The health consequences of involuntary smoking. A report of the surgeon general. Washington, DC DHHS 1986.

29. Lam TH, Chung SF, Betson CL, Wong CM, Hedley AJ. Respiratory symptoms due to active and passive smoking in junior secondary school students in Hong Kong. *Int J Epidemiol* 1998; 27:41–8.
30. National Research Council. *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects.* Washington, DC: National Academy Press 1986; 209–11.
31. US Environmental Protection Agency. *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders.* Washington, DC: Environmental Protection Agency, Office of Air and Radiation 1992.
32. California Environmental Protection Agency. *Health Effects of Exposure to Environmental Tobacco Smoke.* Sacramento, California: Environmental Protection Agency, Office of Environmental Health Hazard Assessment 1997.
33. Jaakkola MS. Environmental tobacco smoke and health in the elderly. *Eur Respir J* 2002; 19:172–181.
34. Strachan DP, Cook DG. Health effects of passive smoking 1: Parental smoking and lower respiratory illness in infancy and early childhood. *Thorax* 1997; 52:905–14.
35. Anderson HR, Cook DG. Health effects of passive smoking 2. Passive smoking and sudden infant death syndrome: review of the epidemiological evidence. *Thorax* 1997; 52:1003–9.
36. Cook DG, Strachan DP. Health effects of passive smoking 3. Parental smoking and prevalence of respiratory symptoms and asthma in school age children. *Thorax* 1997; 52:1081–94.
37. Strachan DP, Derek DG. Health effects of passive smoking 4. Parental smoking, middle ear and adenotonsillectomy in children. *Thorax* 1998; 53:50–6.
38. Strachan DP, Derek DG. Health effects of passive smoking 5. Parental smoking and allergic sensitization. *Thorax* 1998; 53:117–23.
39. Strachan DP, Derek DG. Health effects of passive smoking 6. Parental smoking and childhood asthma: longitudinal and case-control studies. *Thorax* 1998; 53:204–12.
40. Cook DG, Strachan DP. Health effects of passive smoking 7. Parental smoking, bronchial reactivity and peak flow variability in children. *Thorax* 1998; 53:295–301.
41. Coultas DB. Health effects of passive smoking 8. Passive smoking and risk of adult asthma and COPD: an update. *Thorax* 1998; 53:381–7.
42. Cook DG, Strachan DP, Carey IM. Health effects of passive smoking 9. Parental smoking and spirometric indices in children. *Thorax* 1998; 53:884–93.
43. Cook DG, Strachan DP. Health effects of passive smoking 10. Summary of effects of parental smoking on the respiratory health of children and implications for research. *Thorax* 1999; 54:357–66.
44. Li YF, Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Rappaport ED, et al. Effects of in-utero and environmental tobacco smoke exposure on lung function in boys and girls with and without asthma. *Am J Respir Crit Care Med* 2000; 162:2097–104.
45. Young S, LeSouef PN, Geehoed GC, et al. The influence of a family history of asthma and parental smoking on airway hyperresponsiveness in early infancy. *N Engl J Med* 1991; 324:1168–73.
46. Samet JM, Yang G. Passive smoking, women and children. In: *Women and the Tobacco Epidemic. Challenges for the 21st Century.* Eds. Samet JM, Yoon SY. The World Health Organization in collaboration with the Institute for Global Tobacco Control and the Johns Hopkins School of Public Health 2001.
47. Ferguson DM, Horwood LJ. Parental smoking and respiratory illness during early childhood. *Pediatric Pulmonol* 1985; 1:99–106.
48. Chen Y, Wanxian I, Shunzhang YU. Influence of passive smoking on admissions for respiratory illness in early childhood. *BMJ* 1986; 293:303–6.
49. Taylor B, Wadsworth J. Maternal smoking during pregnancy and lower respiratory tract illness in early life. *Arch Dis Child* 1987; 62:786–91.
50. Pullans CR, Hey CN. Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *BMJ* 1982; 284:1665–9.
51. Strachan DP, Cook DG. Passive smoking and lower respiratory illness in infancy and childhood. *Thorax* 1997; 52:905–14.
52. Evans D, Levison MJ, Feldman CH, et al. The impact of passive smoking on emergency room visits of urban children with asthma. *Am Rev Respir Dis* 1987; 135:567–72.
53. Weitzman M, Gortmaker S, Walker DK, Sobol A. Maternal smoking and childhood asthma. *Pediatrics* 1990; 85:505–11.
54. Wilson SR, Yamada EG, Sudhakar R, Roberto L, Mannino D, Mejia C, Huss N. A controlled trial of an

environmental tobacco reduction intervention in low-income children with asthma. *Chest* 2001; 120:1709–22.
55. Martinez FD, Cline M, Burrows B. Increased incidence of asthma in children of smoking mothers. *Pediatrics* 1992; 89:21–26.
56. Neuspiel DR, Rush D. Butler NR, Golding J, Bijur PE, Kerzon M. Parental smoking and post-infancy wheezing in children: a prospective cohort study. *Am J Public Health* 1989; 79:168–71.
57. Ehrlich RI. Du Toit D, Jordaan E, Zwarenstein M, Potter P, Volmink JA. Weinberg E. Risk factors for childhood asthma and wheezing: importance of maternal and household smoking. *Am J Respir Crit Care Med* 1996; 154:681–8.
58. Cook DG, Strachan DP. Health effects of passive smoking: 3. Parental smoking and prevalence of respiratory symptoms and asthma in school age children. *Thorax* 1997; 52:1081–94.
59. Tager IB. Weiss ST, Rosner B, Speizer FE. Effect of parental cigarette smoking on the pulmonary function of children. *Am J Epidemiol* 1979; 110:15–26.
60. Ware JH, Dockery DW, Spiro A III. Passive smoking, as cooking and respiratory health of children living in six cities. *Am Rev Respir Dis* 1984; 129:366–74.
61. Lebowitz MD, Holberg CJ. Effects of parental smoking and other risk factors on the development of pulmonary function in children and adolescents. *Am J Epidemiol* 1988; 128:589–97
62. Tager I, Munoz A, Rosner B, Weiss S, Carey V. Effect of cigarette smoking on lung function of children and adolescents. *Am Rev Respir Dis* 1985; 131:752–9.
63. Wang X, Wypij D, Gold D, Speizer FE, Ware JH, Ferris BG, Dockery DW. A longitudinal study of the effects of parental smoking on pulmonary function in children 6–18 years. *Am J Respir Crit Care Med* 1994; 149:1420–5.
64. Cunningham J, Dockery DW, Speizer FE. Maternal smoking during pregnancy as a predictor of lung function in children. *Am J Epidemiol* 1994; 139:1139–52.
65. Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Vora H, Rappaport ED, et al. Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. *Thorax* 2000; 55:271–6.
66. Paradise JL , Rockette HE, Colborn DK, et al. Otitis media in 2253 Pittsburgh-area infants: prevalence and risk factors during the first two years of life. *Pediatrics* 1997; 99:318–33.
67. Hoffman HJ, Hillman LS. Epidemiology of the sudden infant death syndrome. Maternal, neonatal and postnatal risk factors. *Clinics in Perinatology* 1992; 19:717–37.
68. Nicoll J, O'Cathain A. Antenatal smoking, postnatal passive smoking, and the Sudden Infant Death Syndrome: In: *Effect of Smoking on the Fetus, Neonate and Child.* Eds. Poswillo D, Alberman E. Oxford: Oxford University Press 1992.
69. Brooke H, Gibson A, Tappin D, et al. Case-control study of sudden infant death syndrome in Scotland, 1992–5. *BMJ* 1997; 314:1516–20.
70. MacDorman MF, Cnattingius S, Hoffman HJ, et al. Sudden infant death syndrome and smoking in the United States and Sweden. *Am J Epidemiol* 1997; 146:249–57.
71. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. *B Med J* 1997; 315:980–8.
72. Zhong L, Goldberg MS, Parent ME, Hanley JA. Exposure to environmental tobacco smoke and the risk of lung cancer: a meta-analysis. *Lung Cancer* 2000; 27:3–18.
73. Copas JB, Shi JQ. Reanalysis of epidemiological evidence on lung cancer and passive smoking. *B Med J* 2000; 320:417–8.
74. Lam TH, Hedley AJ. Environmental tobacco smoke in Asia: slow progress against great barriers. *J Am Med Assoc SEA* 1999; 15:7–9.
75. Jindal SK, Gupta D, Singh A. Indices of morbidity and control of asthma in adult patients exposed to environmental tobacco smoke. *Chest* 1994; 106:75–9.
76. Blanc PD, Ellbjar S, Janson C, et al. Asthma-related work disability in Sweden. *Am J Respir Crit Care Med* 1999; 160:2028–33.
77. Ostro BD, Lipsett MJ, Mann JK, et al. Indoor air pollution and asthma. Results from a panel study. *Am J Respir Crit Care Med* 1994; 149:1400–6.
78. World Health Organization. Combating the Tobacco Epidemic. In: The World Health Report, World Health Organization. 1999. www.who.int

79. Murray CJL, Lopez AD. Assessing the burden of disease that can be attributed to specific risk factors. In: *Ad Hoc Committee on Health Research Relating to Future Intervention Options. Investing in Health Research and Development.* Geneva. World Health Organization, 1996.
80. Liu B-Q. Peto R, Chen Z-M, Boreham J, Wu Y-P, Li J-Y, Campbell TC, Chen J-S. Emerging tobacco hazards in China: I. Retrospective proportional mortality study of one million deaths. *BMJ* 1998: 317:1411–22.
81. Niu S-R, Yang G-H, Chen Z-M, Wang J-L, Wang G-H, He X-Z, Schoepff H, Boreham J, Pan H-C, Peto R. Emerging tobacco hazards in China: 2. Early mortality results from a prospective study. *BMJ* 1998; 317:1423–4.
82. Lam TH, He Y, Li LS, Li LS, He SF, Liang BQ. Mortality attributable to cigarette smoking in China. *JAMA* 1997; 278:1505–8.
83. Mackay J. International aspects of US government tobacco bills. *JAMA* SEA 1998; 14:18–9.
84. Tobacco Markets in Asia. Euromonitor, UK, 1993.
85. Chinese Academy of Preventive Medicine. *Smoking in China: 1996 National Prevalence Survey of Smoking Pattern.* Beijing: China Science and Technology Press 1997.
86. Wakefield MA,Chaloupka FJ, Kaufman NJ, Orleans CT, Barker DC, Ruel EE. Effect of restrictions on smoking at home, at school, and in public places on teenage smoking: cross sectional study. *Br Med J* 2000; 321:333–7.
87. Nana A, Charoenratnakul S, Pushpakom R, Bovornkitti S. Philosophy of anti-smoking campaign. *Siriraj Hosp Gaz* 1991; 43:505–7.
88. King C III, Siegel M. The Master Settlement Agreement with the tobacco industry and cigarette advertising in magazines. *N Engl J Med* 2001; 345:504–11.
89. Jha P, Chaloupka FJ. The economics of global tobacco control. *Br Med J* 2000; 321:358–61.
90. Cox HS, Williams JW, de Courten MP, Chitson P, Tuomilehto J, Zimmet PZ. Decreasing prevalence of cigarette smoking in the middle-income country of Mauritius: questionnaire survey. *Br Med J* 2000; 321:345–9.
91. Lam WK. Lung Cancer: Commentary from Southeast Asia. *Medical Progress* 1990; 17:63–4.
92. Vateesatokit P. Tobacco control in Thailand. *J Environ Med* 2000; 2:165–80.
93. Laracy L. Singapore health ministry gets tough on tobacco. *Asian Medical News* 1998; November, 4.
94. Mackay J. Beyond the clouds — tobacco smoking in China. *JAMA* 1997; 278:1531–2.

21 Occupational Airway Diseases

Moira Chan-Yeung and Tze Pin Ng

Introduction

Airway disease due to occupational exposure has been ignored until recently. During the last two decades, occupational asthma has become the most prevalent occupational lung disease in developed or industrialized countries. "Asthma-like syndrome" used to describe nonallergic, mild, acute, reversible obstruction has been reported in relation to many organic dust exposure, some have been recognized for a long time such as cotton or grain dust exposure while others are recent such as swine or poultry confinement exposure. In addition, chronic airflow obstruction has been demonstrated as a result of exposure to organic and inorganic dust. In this section these various entities or syndromes will be discussed.

Occupational Asthma

Definition

Occupational asthma is defined as a disease characterised by variable airflow obstruction and/or airway hyperresponsiveness due to causes and conditions encountered in the working environment and not due to stimuli outside the workplace (1). This definition excludes aggravation of pre-existing asthma as occupational asthma. However, it should be remembered that individuals with pre-exiting asthma could also develop sensitisation to agents encountered in the workplace.

Epidemiology

Occupational asthma has become the most common occupational lung disease in developed countries (2–5). Table 1 shows estimates of annual incidence of occupational asthma from national and regional statistics. In the United Kingdom (4) and in British Columbia, Canada (5) asthma is the most frequently reported occupational lung disease, accounting for 26% and 52% of such diseases respectively. Such estimates are not available in developing countries where mostly case reports of occupational asthma rather than epidemiological studies are published.

In most countries in Asia, pneumoconiosis is still the major occupational lung disease. In Hong Kong, for example, there are only 1 to 3 cases of occupational asthma each year in the past decade (6). It is very likely that occupational asthma is very much under diagnosed and under recognised in many Asian countries.

The prevalence of asthma is increasing in many developed countries (7). There is a great deal of interest in determining whether occupational exposure could account for the increase. There have been several reports

Table 1. Estimates of Annual Incidence to Occupational Asthma from National and Regional Statistics[11]

Country, year	*Source*	*No of cases*	*Reference population (M)*	*Annual incidence/M*	*Comments*
U.K., 1989	Voluntary by physicians	554	Labour force	22 (10–114)	282/554 receiving compensation
B.C., Canada 1991	Voluntary by physicians	124	Labour force	92	Not all cases proven
Quebec, Canada, 1992–3	Voluntary by physicians	287	N/A	121	
Sweden, 1990–2	Self-reported	1010	4.2 M	80 (22–844)	
Finland, 1993	Registers of occupational asthma	386	Labour force 2.02 M	187	
Finland, 1981–9	Occupational disease register	352	Labour force 2.25	156	2-fold increase

estimating the proportion of adult-onset asthma caused by occupational exposures. The proportion varies considerably from country to country. The earliest report came from Japan indicating that 15% of cases of adult asthma was due to occupational exposure (8). In the United States, Blanc and colleagues (9,10) performed two separate studies, one involving patients from specialist practice and the other one from patients in general practice. Both studies demonstrated that exposure to high risk agents occurred in about 13% of patients with new adult onset asthma similar to Japan (8). Several population studies have shown considerable difference in population attributable risk (PAR) of occupational exposure varying from 3% to 33% (11). Again these studies came from industrialized Western countries with the exception of Singapore which reported a PAR of 33% of occupational exposure for asthma (12). A recent analysis of all published literature from 1966 to 1998 reported a median of 10% on the attributable risk of occupational exposure for adult onset asthma (13). While these differences could be due to variations in study methods, the degree of industrialisation and the type of agents used in the workplace within each country also account for the differences as well.

Agents

There are now over 300 agents shown to be capable of causing occupational asthma (14). Table 2 shows some of the more common agents. Isocyanates are used extensively in the production of flexible and rigid foam, and for finish coatings. They have potent sensitising properties and are common causes of occupational asthma in industrialized countries. Very little information is available from Asian countries as to the most common agents responsible for occupational asthma, but it is likely that isocyanates are also the commonest causes.

Types of occupational asthma

Occupational asthma is usually classified by the pathogenic mechanisms of the inducing agents: immunologically or nonimmunologically mediated. Immunologically-mediated occupational asthma is characterised by a latency period between the onset of exposure and the onset of the first attack of asthma and that exposure to a small amount of the agent after sensitisation can induce an attack. In most cases, specific IgE antibodies could be

Table 2. Major Causes of Occupational Asthma*

High molecular weight agents	*Occupation at risk*
Animal proteins eg. laboratory animals	Laboratory workers, farmers, poultry processors
Plant proteins eg. flour, coffee beans, tobacco dust, tea	Bakers, farmers, food processors
Enzymes eg. papain, bacillus subtilis, pectinase, trypsin	Pharmaceutical workers, food processors, detergent manufacturers
Dyes eg. henna, carmine	Fabric and fur dye, beauticians
Low molecular weight agents	
Isocyanates eg. toluene diisocyanate, dipheylmethane diisocyanate	Polyurethane workers, insulators, spray painters
Anhydrides eg. trimellitic anhydride, phthalate anhydride	Manufacturers of paint, plastic, epoxy resins
Metals eg. platinum salts, chromium, nickel, vanadium	Platers, welders, metal and chemical workers
Drugs eg. beta lactam agents, piperazine derivatives, psyllium, organophosphate	Pharmaceutical workers, farm workers

* from *Medical Progress* 2000, 27:10–14

demonstrated. Most high molecular weight compounds (> 5000 daltons) induce asthma by producing specific IgE antibodies. Some low molecular weight compounds (< 5000 daltons) such as acid anhydride and platinum salts act as haptens and induce specific IgE antibodies by combining with a body protein (15,16). There are some low molecular agents such as diisocyanates that induce asthma with clinical features identical to immunologically mediated asthma but specific IgE antibodies could not be demonstrated or demonstrated in only a small proportion of patients.

Nonimmunologically mediated occupational asthma is characterised by a lack of latency period. The most important example is Reactive Airways Dysfunction Syndrome (RADS), following a single exposure to high concentrations of irritant gases, fumes and chemicals (17).

Diagnosis of occupational asthma

History

Any patient with a history suggestive of asthma, which begins during working life, should raise the suspicion of occupational asthma. The suspicion should be heightened if there was a history of improvement of symptoms during weekends and holidays with worsening of symptoms on returning to work. In many cases, the patient may not be aware of the chemicals or the agents at work. Material Safety Data Sheets nowadays should be available in the workplace by law in many developed countries but probably not in developing countries. The information may be helpful in identifying the presence of a sensitizer in the workplace. Published lists and computerised databases of agents and workplaces should assist clinicians in identifying sensitising agents in any jobs or occupations (14). The absence of an agent on such lists or databases should not rule out the diagnosis. A good occupational history should include a detailed history of specific job duties and work processes for both the patient and his/her co-workers.

Nonallergic bronchial hyperresponsiveness

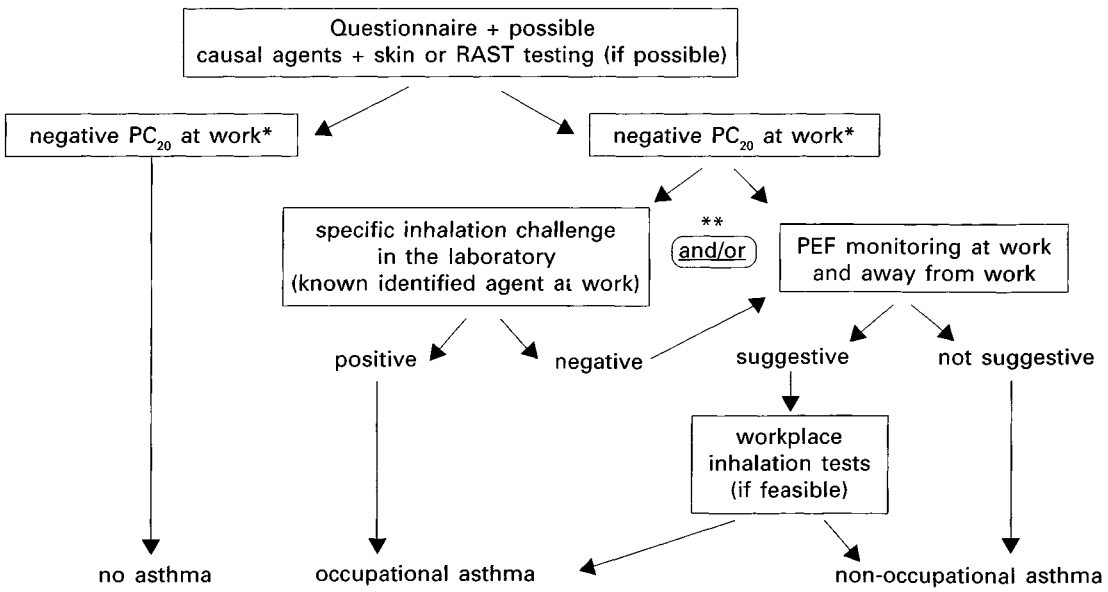
Although a compatible history is a sensitive diagnostic tool, it is far from being specific (18).

If at all possible all cases of occupational asthma should be confirmed by objective testing as the diagnosis of occupational asthma carries important financial and health consequences to the patient (19). The first step is to make a diagnosis of asthma by demonstration of reversible airflow obstruction or presence of nonallergic bronchial hyperresponsiveness to pharmacological agents. The absence of airflow obstruction and nonallergic airway hyperresponsiveness when a patient has symptoms and is still working under his/her usual work conditions virtually excludes the diagnosis of occupational asthma. The presence of reversible airflow obstruction or nonallergic bronchial hyperresponsiveness requires further testing to confirm work-relatedness of asthma. An algorithm for the diagnosis of occupational asthma is shown in Figure 1.

Serial monitoring of peak expiratory flow

The next step is to demonstrate work-relationship. There are very few centres in the world with facilities to carry out specific inhalation challenge testing which is often regarded as the gold standard test for occupational asthma. For centres without facilities for specific challenge tests, monitoring of peak expiratory flow (PEF) for a period of two weeks at work and for a similar period away from work is often used to confirm work-relationship (20). It is important to give careful instructions to the patient when conducting such a test. Medications, if used, should be confined to short acting beta-2-agonist. If inhaled steroids have to be used, the dose should be kept constant throughout the period of monitoring. The patient should be asked to record their peak flow rate for at least 4 times daily and to perform three forced expiratory maneuvours on each occasion.

Although a good association has been found between the results of peak expiratory flow monitoring and specific challenge tests (21,22), such a diagnostic approach has limitations since it depends on the co-operation of the patients and their reliability in performing and recording the correct readings. The interpretation of the serial PEF record has not been standardised and is dependent on the experience of the observer. Moreover, some patients are illiterate and some cannot perform PEF satisfactorily despite extensive coaching. Combining PEF monitoring with serial



* assessed at the end of a working day and after a minimal period of 2 weeks at work
** the choice depends on the facilities of the investigation center

Figure 1. A diagnostic algorithm for workers with suspected occupational asthma[79]

measurements of nonallergic bronchial hyperresponsiveness at and away from work provides a more objective assessment of work-relatedness as illustrated in Figure 2. The use of computerised peak flow meters will ensure that results are accurately recorded and stored but cannot identify poor performance.

Pre and post-shift measurement of FEV_1

Pre- and post-shift spirometry done on one occasion is not sufficiently sensitive to determine work-relatedness.

Specific challenge testing

When facilities are available, specific challenge tests in a laboratory under controlled conditions to reproduce the patient's symptoms can be used to confirm work relationship. Monitoring the level of exposure during testing increases the safety and accuracy of specific challenge tests. Subjects should be exposed to small increments in dose to avoid a severe or an irritant reaction. Specific challenge test can produce false negative reactions if the wrong agent is used or if the person has been away from work for a period of time and his or her bronchial responsiveness has returned to normal. Different types of reaction have been described after specific challenge tests: isolated early, isolated late, biphasic or continuous asthmatic reaction (23). An isolated early asthmatic reaction occurs within a few minutes after inhalation challenge, reaches maximal within half an hour and returns to baseline within one to one-and-a-half hour. An isolated late asthmatic reaction occurs four to six hours after challenge, reaches maximal within eight to ten hours and returns to baseline after 24 to 48 hours. A biphasic reaction is an early reaction with spontaneous recovery followed by a late reaction while a continuous asthmatic reaction has no remission between the early and the late phase. Atypical reactions that start after two hours of challenge lasting for a few hours have also been described (24).

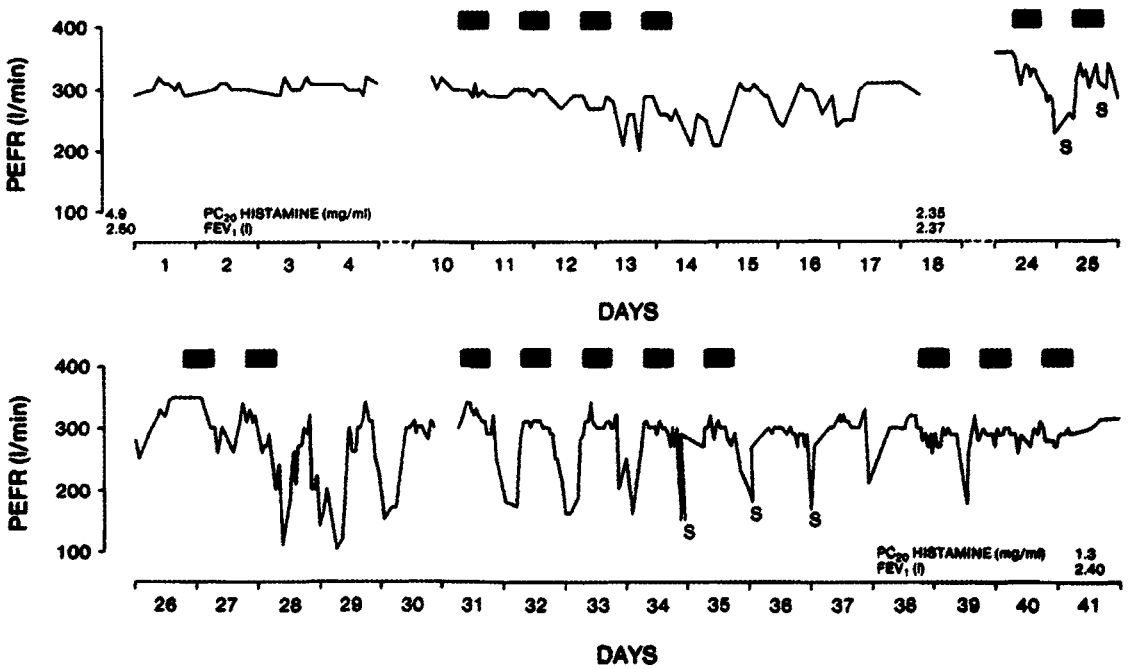


Figure 2. Serial monitoring of peak expiratory flow and nonallergic airway hyperresponsiveness in a patient with occupational asthma showing progressive increase in reduction in peak flow rate during periods at work and improvement during periods away from work. There was a progressive decrease in PC_{20} after the patient returned to work.[80]

Immunologic tests

For IgE dependent agents, skin test or blood test for specific IgE antibodies can be done if appropriate allergens are available. The presence of sensitisation and nonallergic airway hyperresponsiveness are associated with an 80% likelihood of an immediate asthmatic reaction if a person is challenged with the same occupational allergen in the laboratory (25). There are very few standardised occupational allergens available commercially at present.

New techniques

Two new techniques have been evaluated in the diagnosis of occupational asthma: measurement of exhaled nitric oxide and induced sputum analysis before and after inhalation testing (26,27). These techniques still require further assessment.

Outcome

It is well known that the majority of patients with occupational asthma do not recover even after several years away from exposure. They have permanent impairment of lung function and disability (28). The duration of symptoms before removal from exposure is a prognostic indicator irrespective of the type of agent. Early removal from exposure has been shown to increase the likelihood of recovery (28). Thus early diagnosis and prompt removal from exposure are essential in managing patients with occupational asthma.

A recent study has shown that some patients further improved beyond 5 years of removal from exposure to the sensitizer suggesting that permanent impairment rating should be periodically re-evaluated (29). There have been several studies showing that continued exposure to the same agent is associated with worsening of symptoms (28). Fatality from asthma has been reported in those who continued to be exposed (28).

Management

A diagnosis based on objective demonstration of work relationship between exposure and lung function changes is essential for appropriate management of occupational asthma. The ideal management for workers with occupational asthma due to a sensitising agent is removal from exposure. He or she should be transferred to another job without exposure in the same company; unfortunately this is often not possible because the company has no alternative for the patient. Most patients with occupational asthma have to be retrained for a job with another employer in a different field of work.

In some instances, reduction of exposure by improving ventilation or using a respirator may allow a person to return to the same job. Most of the time this may not be possible because such patients tend to react to very low concentrations of the sensitising agent. In addition to the above measures, physicians should counsel patients concerning compensation. The appropriate public health agency such as the workers' compensation board should be notified, which in turn should initiate a surveillance program when a sentinel case has been identified.

Any patient with occupational asthma who returns to the same job should have regular medical follow up examination. Worsening of asthma should lead to immediate removal from exposure. Pharmacological treatment of patients with occupational asthma is similar to patients with other forms of asthma. Monitoring the course of patients after diagnosis is important. Although removal from exposure generally results in improvement of asthma, patients may still require medication and have airflow limitation and/or nonallergic airway hyperresponsiveness for many months or years.

Impairment evaluation

Since patients with occupational asthma may not recover after removal from exposure, they should be evaluated for permanent impairment and disability after two years away from exposure when improvement in asthma has plateaued (29). In the past, all patients with occupational lung disease were being evaluated for respiratory impairment in the same way based on the results of lung function testing. Howerer, patients with asthma have features that are quite different from patients with pneumoconiosis. For example, patients with asthma have variable airflow

obstruction, some patients may be taking medications Most patients with asthma have nonallergic bronchial hyperrepsonsiveness and they are unable to work not only in their current job but also in places with exposure to low dose irritant gases or fumes Guidelines for the impairment and disability evaluation in patients with asthma have been published by the American Thoracic Society (30)

Prevention

Exposure is the most important determinant of occupational asthma, the higher the exposure, the higher the risk of asthma (31) Primary prevention of occupational asthma can be achieved by eliminating the sensitising agent from the workplace and replacing it with a nonsensitising one If this is not possible, one should aim at reducing exposure and limiting the number of workers exposed An excellent example is the success story of disappearance of occupational asthma due to *B subtilis* in detergent enzyme industry after measures were made to reduce exposure by encapsulation of the product Another method is to restrict employment to those with no predisposing host factors The effectiveness of this measure is not known although in the platinum refining industry, employment of nonatopic subjects only, together with reduction of exposure, reduced the incidence of sensitisation effectively (32) There are few known host risk factors For occupational asthma caused by IgE dependent agents, atopy and smoking are important risk factors Smoking is more important than atopy in predispostion to sensitisation to platinum salts (33) The role of smoking has not been as well characterised for other agents In occupational asthma induced by IgE independent agents, both atopy and smoking are not important risk factors (34) Recent studies have shown that HLA class II alleles may be important in isocyanate-induced asthma, or Western red cedar asthma (35,36), these findings need to be confirmed In many countries, civil rights do not allow exclusion of predisposed individuals from the workplace The workplace should be made safe for the workers

Secondary prevention includes periodic screening of workers in high-risk industries So far, the tools are limited to questionnaires, lung function testing and in some instances, performance of skin testing with the appropriate allergen Tertiary prevention involves preventing asthma from getting worse once the diagnosis of occupational asthma has been made as discussed above

Asthma-like Syndrome

The term asthma-like syndrome is used to describe an acute nonallergic airway response arising from inhalation of various agents in the agriculture environment The symptoms consist of chest tightness, wheeze, and/or dyspnoea and may be associated with a cross-shift decline in FEV_1 (usually less than 10%), which is dose-related There may be a transient increase in nonallergic bronchial responsiveness The acute respiratory symptoms or cross-shift declines in lung function occur usually on Monday morning and abate or disappear as the week progresses even though the exposure is the same They usually subside without treatment Healthy subjects may also develop symptoms on first exposure Both atopic and nonatopic subjects are affected, although atopic subjects tend to have a greater cross-shift decline in FEV_1 (37) Specific antigens and antibodies have not been identified

Types of exposures

A number of agents have been shown to give rise to asthma-like syndromes Of these, exposure to grain and cotton dust has been studied most extensively

The term byssinosis is used to describe a symptom complex that occurs among cotton workers The prominent feature is chest tightness, often accompanied by cough and shortness of breath occurring on the first day of the working week after one to two days away from the workplace McKerrow et al (38) was the first to demonstrate that acute cross-shift bronchial obstruction occurred in some workers with the symptoms of byssinosis There have been many studies documenting the prevalence and incidence of byssinosis in the workforce in Britain, the

United States, and in other parts of the world (39,40). The prevalence of byssinosis is directly related to the degree of dust exposure. In Asia, the prevalence of byssinosis varies considerably between different places (Table 3). The prevalence was 1.6% in Hong Kong in 1987 (41) and 22% in Jakarta (42), 9% in Guangzhou (43), 5.6% in Shanghai (44), 4.2% in Beijing (45) and about half of the workforce in India (46). Cross-shift declines in lung function do not always correlate with byssinosis symptoms.

Exposure to grain dust occurs in farms, during transfer at terminals and elevators, and in the vicinity of docks where grain is being loaded. Grain dust is complex and contains a mixture of different types of grain, insect parts, fungi, bacteria, pigeon droppings, pesticides, and silica. Respiratory symptoms such as cough, chest tightness and wheeze during a workshift are reported more frequently among grain workers than controls. At times, these chest symptoms are accompanied by systemic complaints such as fever, flushing of the face, and headache. Cross-shift declines in lung function with a dose-response relationship to the level of dust exposure have been found (47).

Respiratory problems in swine confinement workers have been recognized only in the last two decades. Acute chest symptoms and irritation of the throat occurring over the course of a workshift are common (48). Cross-shift changes in FEV_1 have been observed in several studies (48,49). Systemic symptoms such as fever, headache, and malaise are also common. In addition to dust, swine farmers are also exposed to gases such as ammonia, hydrogen sulphide, carbon monoxide, and carbon dioxide. The dust contains mostly animal feed and aerosolized manure rich gram-negative bacteria. Of these exposures, levels of total dust, endotoxin, and ammonia were found to correlate with chronic respiratory symptoms in swine farmers (50).

Poultry workers (chicken catchers), slaughterhouse workers, and poultry farmers (50-54) also experience similar symptoms. Airborne contaminants in poultry confinement units include mixtures of organic poultry dust, skin debris, feather, insect parts, aerosolized feed, and poultry excreta, as well as a variety of viable bacteria and Gram-negative bacterial endotoxin. High levels of ammonia have also been reported (50).

Table 3. Prevalence of Byssinosis, Cross-Shift Changes in Lung Function in Asian Cities

City	*N*	*Byssinosis (%)*	*Cross-shift decline in FEV (%)*		*Dust level (mg/m³)*	
			> 10%	*> 5%*	*Total*	*Respirable*
Hong Kong (40)	2202	2.7	10.8			Carding 0.12–5.28
Shanghai (43)	887	11.1	NA	NA		Carding 0.48–2.47
						Opening 0.42–2.90
Beijing (44)	289	4.2		Blowing 37	Blowing 14.4	Blowing 3.5
				Carding 36	Carding 3.82	Carding 1.0
				Spinning 1.1	Spinning 1.07	Spinning 0.2
Guangzhou (42)	1320	9.0	4.2	16.8	Blowing 2.94	Blowing 0.63
					Spinning 11.83	Spinning 1.56
Jarkarta (41)	250	Blowing 30	Blowing 2.9			
		Spinning 20	Spinning 3.2			
		Weaving 27	Weaving 3.3			

Pathogenesis

The underlying mechanism of asthma-like symptoms appears to be associated with airway inflammation. Bronchoalveolar lavage studies of healthy subjects after exposure to swine confinement dust and extracts of grain dust have shown intense airway inflammation (55). It is not entirely clear which is the agent causing airway inflammation. Endotoxin has been found in these organic dusts. There is a correlation between acute changes in lung function over a work shift or exposure in a laboratory setting and the endotoxin level. The correlation of changes in lung function with the endotoxin level is at times better than with the total dust concentration (56). Inhalation challenge with endotoxin induced airflow obstruction (57), decrease in diffusing capacity, and leukocytosis similar to inhalation challenge with extract of cotton bract and grain dust (58,59). Airway inflammation has been found after inhalation challenge with endotoxin (59). It is not known, however, whether endotoxin is the sole cause of this syndrome.

Chronic Airflow Obstruction

There is increasing evidence that exposure to inorganic dust or organic dust is associated with chronic airflow obstruction independent of cigarette smoking. The development is insidious after a prolonged period of exposure.

Inorganic dust exposure such as coal mining and hard rock mining activities has been repeatedly shown to be associated with lung function decline and bronchitic symptoms (60-62). A longitudinal study of coal miners employed since 1970, when dust exposure levels were relatively low showed an estimated decline in FEV_1 of 5.7 ml for each mg/m^3 year of exposure over their working life (63). The effects of cumulative gold mining dust exposure have been found to be 10 times greater than those of coal mining dust and were more pronounced among nonsmokers (64). Airflow obstruction and lung function decline has also been found to be associated in a dose-response manner with the level of asbestos exposure (65). Chronic airflow obstruction usually occurs in the presence of pneumoconiosis. At the end stage, both restrictive and obstructive ventilatory patterns are found.

Exposure to organic dusts such as cotton, grain, wood and other agricultural dusts may also lead to the development of chronic obstructive lung disease and associated respiratory disability, independent of the effect of smoking (66).

Whether cotton dust exposure has chronic effects on the lungs has been the subject of debate for many years. While cross-sectional studies of health effects of cotton dust exposure have shown a dose-response relationship between exposure and the prevalence of chronic bronchitis and/or lung function impairment (67,68), the results of longitudinal studies have not been consistent (69–72). Both active and retired U.S. cotton textile workers showed greater declines in FEV_1 than controls, even when stratified by smoking groups (73) suggesting that chronic lung disease is common and may progress after exposure to cotton dust has ended.

The chronic effects of grain dust exposure have been studied quite extensively. Follow-up studies carried out in Canadian grain elevators have shown a greater decline in lung function among grain workers than controls (74–77) as have studies of animal feed workers (78). Retired grain elevator workers (79) had significant reductions in lung function compared to retired civic workers, even among lifetime non-smokers. The retired nonasthmatic grain workers reported significantly greater breathing related impairment in activities of daily living, indicating that grain dust exposure led to chronic respiratory disability in some workers. The specific nature of this chronic lung disease due to grain dust exposure is unclear.

In organic dust exposure, acute cross-shift decline in FEV_1 has been shown to predict the longitudinal decline in lung function (76). Although cross-shift changes in lung function are dose-related, individual susceptibility may also be important. Further studies are required in this area as it has practical implications since longitudinal studies are expensive and difficult to perform.

References

1. Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI. Definition and classification of asthma. In: *Asthma in the Workplace.* Eds. Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI. New York: Marcel Dekker Inc. 1999, 1–4.
2. Reilly MJ, Rosenman KD, Watt FC, et al. Surveillance for occupational asthma — Michigan and New Jersey, 1988–1992. *MMWR* 1994; SS-1:9–17.
3. Keskinen H, Alanko K, Saarinen L. Occupational asthma in Finland. *Clin Allergy* 1978; 8:569–79.
4. Meredith SK, Taylor VM, McDonald JC. Occupational respiratory disease in the United Kingdom 1989: a report to the British Thoracic Society and the Society of Occupational Medicine by the SWORD project group. *Br J Ind Med* 1991; 48:292–8.
5. Contreras G, Rousseau R, Chan-Yeung M. Short Report: Occupational respiratory diseases in British Columbia, Canada. *Occup Environ Med* 1994; 51:710–2.
6. Hong Kong Government Tuberculosis and Chest Service. Annual report. 1997.
7. Burney PG J. Epidemiology Trends. In: *Asthma.* Eds. Barnes PJ; Grunstein MM; Leff AR, Woolcock A. Philadelphia: Lippincott-Raven Publishers 1997; 35–47.
8. Kobayashi S, Yamamura Y, Frick OL, Horiuchi Y, Kishimoto S, Miyamoto T. Occupational asthma due to inhalation of pharmacological dusts and other chemical agents with some reference to other occupational asthmas in Japan. In: *Allergology. Proceedings of the VIII International Congress of Allergology, Tokyo, October 1973.* Eds. Naranjo P, De Weck A. Amsterdam: Excerpta Medica, 1974, 124–32.
9. Blanc P. Occupational asthma in a national disability survey. *Chest* 1987; 92:613–7.
10. Blanc PD, Cisterna M, Smith S, Yelin E. Occupational asthma in a community-based survey of adult asthma. *Chest* 1996; 109:56S–57S.
11. Becklake M. Malo JL, Chan-Yeung M. Epidemiological approaches in occupational asthma. In: *Asthma in the Workplace.* Eds. Bernstein L, Chan-Yeung M, Malo JL, Bernstein D. New York, Marcel Dekker Inc. 1999, 27–66.
12. Ng, TP, Hong CY, Goh LG, Wong ML, Koh KTC, Ling SL. Risk of asthma associated with occupations in a community-based case-control study. *Am J Ind Med* 1994; 25:709–18.
13. Blanc PD, Toren K. How much asthma can be attributed to occupational factors? *Am J Med* 1999; 107:580–7.
14. Chan-Yeung M, Malo J-L. Table of the major inducers of occupational asthma. In: *Asthma in the Workplace.* Eds. Bernstein L, Chan-Yeung M, Malo JL, Bernstein D. New York: Marcel Dekker, Inc. 1993, 595–624.
15. Zeiss CR, Patterson P. Pruzansky JJ, Miller MM, Rosenberg M, Levitz D. Trimellitic anhydride induced airway syndromes: clinical and immunologic studies. *J Allergy Clin Immunol* 1977; 60:96–103.
16. Pepys J, Pickering CAC, Hughes EG. Asthma due to inhaled chemical agents — complex salts of platinum. *Clin Allergy* 1972; 2:391–6.
17. Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposures. *Chest* 1985; 88:376–84.
18. Malo JL, Ghezzo H, L'Archevêque J, Lagier F, Perrin B, Cartier A. Is the clinical history a satisfactory means of diagnosing occupational asthma? *Am Rev Respir Dis* 1991; 143:528–32.
19. Marabini A, Ward H, Kwan S, Kennedy S, Wexler-Morrison N, Chan-Yeung M. Clinical and socio-economical features of subjects with red cedar asthma: a follow up study. *Chest* 1993; 104:821–24.
20. Burge PS. Single and serial measurements of lung function in the diagnosis of occupational asthma. *Eur J Respir Dis* 1982; 63(suppl 123):47–59.
21. Côté J, Kennedy S, Chan-Yeung M. Sensitivity and specificity of PC_{20} and peak expiratory flow rate in cedar asthma. *J Allergy Clin Immunol* 1990; 85:592–8.
22. Perrin B, Lagier F, L'Archevêque J, et al. Occupational asthma: validity of monitoring of peak expiratory flow rates and non-allergic bronchial responsiveness as compared to specific inhalation challenge. *Eur Respir J* 1992; 5:40–8.
23. Pepys J, Hutchcroft BJ. Bronchial provocation tests in etiologic diagnosis and analysis of asthma. *Am Rev Respir Dis* 1975; 112:829–59.
24. Perrin B, Cartier A, Ghezzo H, et al. Reassessment of the temporal patterns of bronchial obstruction after exposure to occupational sensitizing agents. *J Allergy Clin Immunol* 1991; 87:630–9.

25. Grammer LC, Patterson R. Immunologic evaluation of occupational asthma. In: *Asthma in the Workplace.* Eds. Bernstein LI, Chan-Yeung M, Malo JL, Bernstein DI. New York: Marcel Dekker Inc. 1999, 159–72.
26. Obata H, Dittrick M, Chan HC M. Sputum eosinophils and exhaled nitric oxide during late asthmatic reaction in patients with western red cedar asthma. *Eur Respir J* 1999; 13:489–95.
27. Lemiere C, Pizzichini MM M, Balkissoon R, Clelland L, Efthimiadis D, O'Sharughnessy D, Dolovich J, Hargreave FE. Diagnosing occupational asthma: use of induced sputum. *Eur Respir J* 1999; 13:482–8.
28. Cote, J, Kennedy S, Chan-Yeung M. Outcome of patients with cedar asthma with continuous exposure. *Am Rev Respir Dis* 1990: 141:373–6.
29. Perfetti L, Cartier A, Ghezzo H, Gautrin D, Malo J-L. Follow-up of occupational asthma after removal from or diminution of exposure to the responsible agent. *Chest* 1998; 114:398–403.
29. American Thoracic Society. Asthma Ad Hoc Committee on Impairment/Disability Evaluation in Subjects with Asthma. Guidelines for the evaluation of impairment/disability in patients with asthma. *Am Rev Respir Dis* 1993; 147:1056–61.
30. Venables KM. Prevention of occupational asthma. *Eur Respir J* 1994; 7:768–78.
31. Hughes EG. Medical surveillance of platinum refinery workers. *J Soc Occup Med* 1980; 30:27–30.
32. Chan-Yeung M. Occupational asthma. *Chest* 1990; 98 (suppl 5):S148–61.
33. Venables KM, Dally MB, Nunn AJ, et al. Smoking and occupational allergy in workers in a platinum refinery. *Br Med J* 1989; 299:939–42.
34. Chan-Yeung M, Lam S, Koerner S. Clinical features and natural history of occupational asthma due to Western red cedar (Thuja plicata). *Am J Med* 1982; 72:411–5.
35. Bignon JS, Aron Y, Li YJ, et al. HLA class II alleles in isocyanate-induced asthma. *Am J Respir Crit Care Med* 1994; 149:71–5.
36. American Thoracic Society. Respiratory Health Hazards in Agriculture. *Am J Respir Crit Care Med* 1998; 158:S23–4.
37. Mckerrow CB, McDermott M, Gioson JC, Schilling RSF. Respiratory function during the day in cotton makers. A study in byssinosis. *Br J Ind Med* 1958; 15:75–83.
38. Imbus HR, Suh MW. Byssinosis: a study of 10,133 textile workers. *Arch Environ Health* 1973; 26:183–91.
39. Berry G, McKerrow CB, Molyneux MKB, Rossiter CE, Tombleson JBT. A study of the acute and chronic changes in ventilatory capacity of workers in Lancashire cotton mills. *Br J Ind Med* 1973; 30:25–36.
40. Ong SG, Lam TH, Wong CM, Chow WK, Ma PL, Lam SK, O'Kelly FJ. Byssinosis and other respiratory problems in the cotton industry in Hong Kong. *Am J Ind Med* 1987; 12:773–7.
41. Lam TH, Ong SG, Baratawidjaja KG. A study of byssinosis in Hong Kong and Jakarta. *Am J Ind Med* 1987; 12:767–71.
42. Jiang CQ, Lam TH, Kong C, Cui CA, Huang HK, Chen DC, He JM, Xian PZ, Chan YH. Byssinosis in Guangzhou, China. *Occup Environ Med* 1995; 52:268–72.
43. Lu P-L, Christiani D, Ye T-T, Shi N-Y, Gong Z-C, Dai H-L, Zhang W-D, Huang J-W, Liu M-Z. The study of byssinosis in China: A comprehensive report. *Am J Ind Med* 1987; 12:743–53.
44. Liu M-Z. The health investigation of cotton textile workers in Beijing. *Am J Ind Med* 1987; 12:759–64.
45. Gupta S, Gupta BK. A study of byssinosis and associated respiratory disorders in cotton mill workers. *Ind J chest Dis Allied Science* 1988; 28:183–8.
46. Christiani DC, Eisen EA, Wegman DH, Shen Y, Lu PL. Respiratory disease among grain and feed handlers in the People's Republic of China. *Am Rev Respir Dis* 1987; 235:A381.
47. Donham K, Reyolds SJ, Whitten P, Merchant J, Burmeister and Popendorf WJ. Respiratory dysfunction in swine production facility workers in dose-response relationships of environmental exposure and pulmonary function. *Am J Ind Med* 1995; 27:405–18.
48. Schwartz DA, Donham KJ, Olenchuck SA. Burmeister LF, Merchant JA. Determinants of longitudinal changes in spirometric function among swine confinement operators and farmers. *Am J Respir Crit Care Med* 1994; 151:27–33.
49. Clark SR, Rylander R, Larsson L. Airborne bacteria, endotoxin and fungi in poultry and swine confinement buildings *Am Ind Hyg Assoc J* 1983; 44:537–41.
50. Donham K, Haglind Y, Peterson R. Rylander R, Belin L. Environmental and health studies of farm workers in Swiss swine confinement buildings. *Br J Ind Med* 1989; 46:31–7.

51. Thelin AO, Tegler O, Rylander R. Lung reactions during poultry handling related to dust and bacterial endotoxin levels. *Eur J Respir Dis* 1984; 65:266–71.
52. Morris PO, Lenhart SW, Service WS. Respiratory symptoms and pulmonary function in chicken catchers in poultry confinement units. *Am J Ind Med* 1991; 19:195–204.
53. Hagman L, Schultz A, Sjoholm A. Overshift decrease in lung function in poultry slaughterhouse workers. *Am J Ind Med* 1990; 17:77–8.
54. Larsson K, Eklund A, Hansson LO, Isaksson B, Malmberg P. Swine dust causes intense airway inflammation in healthy subjects. *Am J Respir Crit Care Med* 1994; 150:973–7.
55. Rylander R, Morey P. Airborne endotoxin in industries processing vegetable fibres. *Am Ind Hyg Assoc* 1982; 43:811–2.
56. Rylander R, Bakke B, Fischer J, Helander I. Pulmonary function and symptoms after inhalation of endotoxin. *Am Rev Respir Dis* 1989; 140:981–6.
57. Schwartz DA, Thorne PS, Yagla SJ, Burmeister LF, Olenchock SA, Watt JL, Quinn TJ. The role of endotoxin in grain-dust induced airway disease. *Am J Respir Crit Care Med* 1995; 152:603–8.
58. Schwartz DA, Thorne PS, Jagielo PJ, White GE, Bleuer SA, Frees KL. Endotoxin responsiveness and grain dust induced airway inflammation in lower respiratory tract. *Am J Physiol Lung Cell Mol Physiol* 1994; 11:609–17.
59. Oxman AD, Muir DCF, Shannon HS, Stock SR, Hnizdo E, Lange HJ. Occupational dust exposure and chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1993; 148:38–48.
60. Love RG, Miller BG. Longitudinal study of lung function in coal-miners. *Thorax* 1982; 37:193–7.
61. Attfield MD. Longitudinal decline in FEV1 in United States coal miners. *Thorax* 1985; 40:132–7.
62. Seixas NS, Robins TG, Attfield MD, Moulton LH. Longitudinal and cross-sectional analyses of coal mine dust and pulmonary function in new miners. *Br J Ind Med* 1993; 50:929–37.
63. Hnizdo E, Baskind E, Sluis-Cremer GK. Combined effect of silica dust exposure and tobacco smoking on the prevalence of respiratory impairments among gold miners. *Scand J Work Environ Health* 1990; 16:411–22.
64. Siracusa A, Cicioni C, Volpi R, et al. Lung function among asbestos cement factory workers: cross-sectional and longitudinal study. *Am J Ind Med* 1984; 5:315–25.
65. Dimich-Ward H, Kennedy SM, Chan-Yeung M. Occupational exposures and chronic airflow limitation. *Can Respir J* 1996; 3:133–40.
66. Fox A, Tombleson J, Watt A, Wilkie A. A survey of respiratory disease in cotton operatives. Part I. Symptoms and ventilation test results. *Brit J Ind Med* 1973; 30:42–7.
67. Lu P-L, Christiani D, Ye T-T, Shi N-Y, Gong Z-C, Dai H-L, Zhang W-D, Huang J-W, Liu M-Z. The study of byssinosis in China: A comprehensive report. *Am J Ind Med* 1987; 12:743–53.
68. Berry G, McKerrow C, Molyneux M, Rossiter C, Tombleson J. A study of the acute and chronic changes in ventilatory capacity of workers in Lancashire cotton mills. *Brit J Ind Med* 1973; 30:25–36.
69. Zuskin E, Ivankovic D, Schachter E, Witek T. A ten-year follow-up study of cotton textile workers. *Am Rev Respir Dis* 1991; 143:301–5.
70. Glindmeyer HW, Lefante JJ, Jones RN, Rando RJ, Abdel Kader HM, Weill M. Exposure-related declines in the lung function of cotton textile workers. Relationship to current workplace standards. *Am Rev Respir Dis* 1991; 144:675–83.
71. Beck G, Schachter E, Maunder L, Schilling R. A prospective study of chronic lung disease in cotton textile workers. Ann Int Med 1982; 97:645-51.
72. Glindemeyer H, Lefante J, Jones R, Rando R, Weill H. Cotton dust and across-shift change in FEV1 as predictors of annual change in FEV_1. *Am J Respir Crit Care Med* 1994; 149:584–90.
73. Chan-Yeung M, Vedal S, Kennedy S. A longitudinal study of red cedar sawmill workers. *Am Rev Respir Dis* 1990; 141:A80.
74. Broder I, Corey P, Davies G, Hutcheon M, Mintz S, Inouye T, Hyland R, Leznoff A, and Thomas P. Longitudinal study of grain elevator workers and control workers with demonstration of healthy worker effect. *J Occup Med* 1985; 27:873–80
75. Chan-Yeung M, Schulzer M, MacLean L, Dorken E, Tan F, Lam S, Enarson D, and Grzybowski S. A follow up study of the grain elevator workers in the Port of Vancouver. *Arch Environ Health* 1981; 36:75–80.
76. Enarson DA, Vedal S, and Chan-Yeung M. Rapid decline in FEV_1 in grain handlers — Relation to level of dust exposure. *Am Rev Respir Dis* 1985; 132:814–7.

77. Peelen SJM, Heederik D, Dimich-Ward H, Chan-Yeung M, and Kennedy SM. Comparison of dust related respiratory effects in Dutch and Canadian grain handling industries. A pooled analysis. *Occup Environ Med* 1996; 53:559–66.
78. Kennedy SM, Dimich-Ward H, Desjardins A, Kassam A, Vedal S, Chan-Yeung M. Respiratory health among retired grain elevator workers. *Am J Respir Crit Care Med* 1994; 150:59–65.
79. Bernstein DI. Clinical Assessment and Management of Occupational Asthma. In: 2nd Edition Asthma in the Workplace. Eds. Bernstein IL, Chan-Yeung M. Malo JL, Bernstein DI. Marcel Dekker Inc. New York 1999, p145–58.
80. Johnson A, Chan-Yeung M. Nonspecific bronchial hyperresponsiveness. In: 2nd Edition Asthma in the Workplace. Eds. Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI. Marcel Dekker Inc. New York 1999, p173–92.

22 Pneumoconiosis

Moira Chan-Yeung and Tze Pin Ng

Introduction

Occupational lung diseases cover the whole range of respiratory illnesses: diseases of the parenchyma with fibrosis such as silicosis and asbestosis; diseases of the airways such as occupational asthma, asthma-like syndrome and chronic obstructive lung disease diseases; diseases of the pleura such as diffuse pleural fibrosis due to asbestos exposure, and occupational cancers. The clinical features of diffuse lung fibrosis due to asbestos are not much different from idiopathic pulmonary fibrosis; those of occupational asthma are not different from those of common asthma and the same for lung cancer. The only important clue to the diagnosis is the history of exposure, which many of us often fail to elicit. Yet it is important to recognise occupational exposure as the cause of the disease for two reasons: removal from exposure if the disease is diagnosed early may lead to a cure at least in the case of occupational asthma and in some countries, workers' compensation board or similar agencies offer financial assistance and rehabilitation to these patients.

Patients with occupational lung diseases are often difficult to manage since treatment usually consists of removal from exposure. Even in developed countries where social securities are reasonably good, patients with occupational lung diseases suffer financially and their quality of life impaired after the diagnosis. In developing countries, it is often not possible to remove the patient from exposure without taking away their livelihood and those of their families. These patients very often do not wish their employers to learn of their illness nor do they wish their disease to be reported to the workers'compensation boards or similar agencies. Busy physicians may not wish to deal with the hassle of submitting a claim for patients with occupational lung disease. Thus occupational lung diseases are often not reported even though they are notifiable diseases in many countries. It is not easy to obtain good data on the incidence of occupational lung disease through medicolegal statistics or registries or from any source.

During the past two to three decades, there has been a change in the pattern of occupational lung diseases in developed countries. With better recognition and understanding of the disease process, and better exposure control, pneumoconiosis is gradually decreasing while occupational asthma has become the most prevalent occupational lung disease. However, this is not true in developing countries where pneumoconiosis is still very prevalent due to poor working conditions, inadequate control of exposure, and in most cases, lack of worker education on safety issues and recognition of hazardous products.

Within the limited scope of this chapter, common conditions will be discussed only.

Silicosis

Silicosis is an ancient disease. The disease was noted in association with mining in Greek and Roman times (1). Ramazzini published the effects of dusts on the lungs of stonecutters in 1700 (2). The importance of improved ventilation and spraying water onto the rock surface in underground ore mines were well known more than 100 years ago. The clinical features of the disease and the cause of silicosis were well established by the early twentieth century.

Silicosis is a chronic diffuse interstitial fibronodular disease of the lung caused by long-term inhalation of dust containing free crystalline silica. Exposure to silica occurs from inhalation of mineral particles of respirable size of silicon complexed with oxygen (SiO_2). Silica occurs in crystalline forms and in amorphous forms. Quartz is the most abundant crystalline form associated with human disease. The amorphous forms of silica occur in nature as diatomaceous earth and do not cause silicosis as readily.

Exposure settings

Exposure to silica occurs in numerous trades. They can be classified into:

1. Mining — hard rock mining, metal mining
2. Quarrying — stone quarrying, tunnel drilling
3. Foundry work — casting of ferrous or nonferrous metals
4. Sculpting or cutting — stone masonry, granite carving
5. Jobs using abrasives containing silica — tool grinding or sandblasting
6. Jobs involving using powdered silica as a raw material or as an additive in manufacturing — glass, plastics, paint, pottery, ceramic manufacture

Silicosis risk is well recognised in mining, tunnelling and quarrying. The risk in the construction industry, although substantial, is often unrecognised. Quartz dust is created in the drilling, digging and blasting for site preparation; many construction materials, such as cement, produce crystalline silica when cut. Although many industrialised countries severely limited the use of sand for sandblasting, it is still used in the United States (3) and also in developing countries. There are other industries where the risk of silicosis is less well recognised; for example, finely ground silica used in many products such as paints, cosmetics and toothpaste. An increase in the risk of silicosis has been found in silica-milling process (3). In Hong Kong, gemstone workers were found to have silicosis on chest radiograph and abnormal lung function, which was correlated with the duration of employment (4).

Unexpected and serious hazards of silica have also been observed with the use of silica flour as "talc" material in between bales of rubber (5) and in the making of detergents in Singapore (6), and mat-making in Japan (7). In the latter, the cause of the pneumoconiosis is now recognized to be long-term exposure to the dust from "sendo", a clayey soil containing 20–30% free silica, which is smeared onto reaped rush to prevent colour fading. The exposure is reported to give rise to 6–22% prevalence of pneumoconiosis in different districts. 'Biogenic silica' is a significant source of exposure that is under-investigated, and may possibly be the cause of radiological small nodular opacities with or without reticulation observed in Malaysian rice millers (8). Rice is grown on clayey soil and the silica content in rice husk is known to be high. Indeed its abrasive properties have made them useful as detergents and even as cleaning agents for turbo jet engines.

Mild forms of chronic simple silicosis can occur from environmental or domestic exposures to silica dust. Tribal people living in the desert and in villages in the Himalayas exposed to dust storms have been shown to have micronodular densities in the lungs and some may even develop progressive massive fibrosis (9).

Epidemiology

There is no uniform international surveillance and reporting of silicosis. National information on the incidence and trends is difficult to obtain. The number of deaths from silicosis has decreased during the past 25 years in the United States (10). Silicosis mortality rates calculated for various European countries ranged from 0.91 per 100,000 men in the Untied Kingdom to 7.36 per 100,000 men in Belgium from 1985–86 (11).

Few occupational epidemiological studies have been carried out in developing countries. In 1990, Van Sprundel (12) published a survey conducted by the World Health Organization. Table 1 shows the prevalence of silicosis in some Asian countries (13–27). Except for China, the incidence and prevalence of pneumoconiosis were high. Mining and mineral extraction were often the backbone of economic development in these countries. The expansion of these industries increases the number of new workers at risk each year. Dust control measures were often absent or inadequate and workers were exposed to high concentrations of respirable dust. Pneumoconiosis often developed after a short period of exposure and progressed rapidly. As tuberculosis was also prevalent in these countries, silicotuberculosis was a major health hazard.

Clinical presentation

There are four clinical varieties of silicosis:

Simple silicosis

This is the most common variety and is usually identified as radiological abnormalities that develop slowly after 5 to 10 or more years of exposure. Typically fine nodules (< 1 cm in diameter) are found on plain chest radiograph or CT scan, mostly upper lobes (Figure 1). The majority of workers with simple silicosis are asymptomatic. Lung function tests are usually normal or the VC is slightly reduced.

Gross pathologic examination of the lungs of workers with simple silicosis shows discrete nodules that are hard and vary in colour from grey, green, or red, depending on the type of exposure. Microscopically, early lesions are characterised by nodular to stellate aggregates of dust-laden macrophages arranged around a collagenous central region. With time, the central region becomes distinctly whorled and the relative number of inflammatory cells around the periphery decreases. Examination with polarised light usually reveals birefrigent particles, most of which are silicates rather than silica.

Table 1. Prevalence of Silicosis in Developing Countries

Country	*Population*	*Prevalence (%)*	*Ref*
China	Miners	3.48	(13)
	Metallurgy industry workers	5.5	(14)
	Building materials industry workers	1.7	(14)
India	Lead, zinc miner	30.4	(13)
	Slate pencil workers	54.6	(15)
	Stone cutter	35.2	(16)
	Agate workers	18.5	(17)
Korea	Miners	3.5	(13)
Thailand	Ore mill workers	12.5	(18)
	Stone mortar worker	21.0	(19)
	Refractory brick workers	9.3	(20)
Hong Kong	Gemstone workers	27	(21)
	Granite quarry workers	8 (1987)	(22)
	Construction (site development)	12 (1984)	(23)
	Caisson workers	15 (1985)	(24)
Singapore	Granite quarry workers (drillers and crusher workers)	12.5% (1990)	(25)
Malaysia	Granite quarry workers (drillers and crusher workers)	25	(26)
Taiwan	Foundry workers	7.5	(27)
	Furnace	15.4	
	Moulding	8.4	

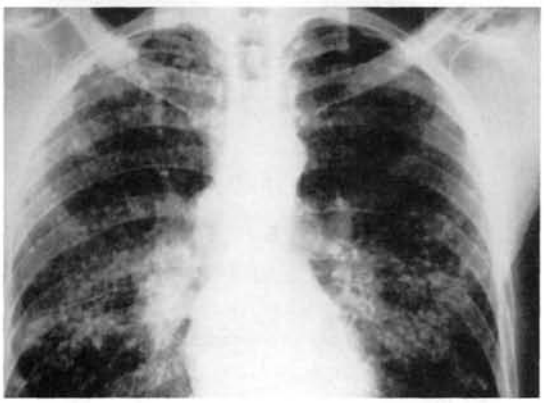


Figure 1. Chest radiograph of a worker with simple silicosis showing diffuse small nodules in both lungs

Complicated silicosis or progressive massive fibrosis

Simple silicosis has a tendency to progress to the complicated form whether or not the subject remains exposed to silica or not. The reason for its progression is not known. There is increasing evidence to suggest that immunologic factors are important. Complicated silicosis or progressive massive fibrosis is characterised by the appearance of one or more areas of confluent nodules, affecting mostly the upper lobes (Figure 2). At this stage, most patients are symptomatic.

Tuberculosis and other mycobacterial infections may accelerate the course of silicosis. There is experimental evidence that the presence of silica potentiate the growth of *M. tuberculosis* in macrophage cultures and that non-pathogenic strains of mycobacteria mixed with finely divided silica will cause progressive lesions in guinea pigs.

Accelerated silicosis

In the accelerated form of silicosis, chest X-ray abnormalities appear within 4 to 8 years of first exposure and the average survival is about 10 years. Several connective tissue diseases have been reported in association with this form of silicosis including scleroderma, rheumatoid arthritis, Caplan's syndrome, and systemic lupus erythematosis.

Acute silicosis or silicoproteinosis

Acute silicosis is due to exposure to very high levels of silica such as those encountered in sandblasting and in caisson work. Patients usually present with rapidly progressive dyspnoea, cough, fever and weight loss. Chest x-rays show diffuse ground glass appearance. Lung function tests show restrictive pattern with reduced diffusing capacity.

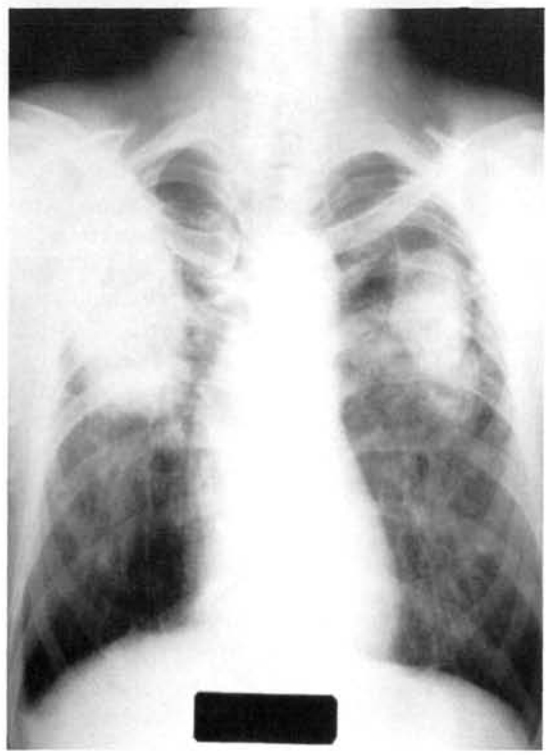


Figure 2a. Chest radiograph of a patient with complicated silicosis, progressive massive fibrosis of both upper lung fields;

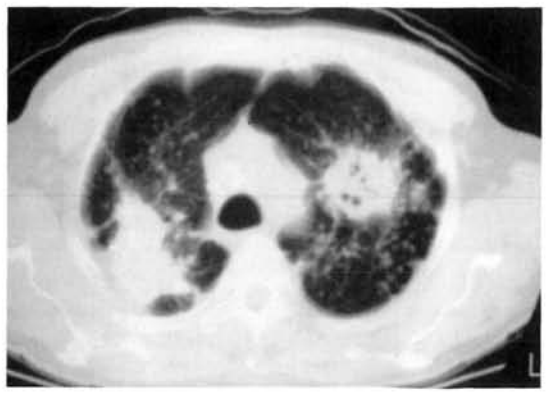


Figure 2b. CT scan of the same patient

The subject usually deteriorates very rapidly. Severe hypoxaemia and heart failure are the terminal events.

Determinants of silicosis

The prevalence of silicosis increases with increasing silica dust exposure. The development of silicosis is dependent on the intensity and the duration of exposure to crystalline silica, the proportion of silica in the dust and the percentage of the particles that are respirable. The US Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) for respirable crystalline silica in general industry is a respirable dust concentration of 10 mg/m^3 divided by (%Sio_2 + 2) or 250 million particles per cubic meter divided by (%Sio_2 + 5) averaged over an 8-h workshift (28).

It is difficult to establish the relationship between the occurrence of silicosis and the level of exposure to silica in the air. This is partly due to the fact that silicosis may develop many years after the worker has left exposure. Higher estimates of risk have been published in studies including retired workers (29). South African goldminers after they had left mining had a 25% cumulative risk of silicosis after 28 years of exposure at a 0.33 mg/m^3 (29). Study of Hong Kong granite quarry workers has shown that cumulative exposure of silica of 1–5 mg/m^3 per year resulted in radiological diagnosis of silicosis in 32% of men 50 years of age and older (30).

The latency is dependent on the level of exposure; extremely high levels of exposure to silica can result in the rapid appearance of silicoproteinosis or accelerated silicosis. The type of silica is also important; crystalline silica is much more fibrogenic than amorphous silica. Co-exposure to other dusts, such as aluminium, was tested in animal studies in the 1930s resulting in less fibrosis in animals receiving aluminium treatment (31). However, a randomized controlled trial of aluminium powder inhalation in pottery workers and miners was carried out with no objective beneficial result (32).

Pathogenesis of silicosis

The pathogenesis of silicosis is dependent not only on the chemical but also on the physical properties of silica. It appears that the mineral surfaces are dynamic and complex and may be modified in the lung after adsorption of proteins and other macromolecules or after being taken up by macrophages. Freshly fractured silica generated during sandblasting is more toxic to alveolar macrophages than aged silica because of its increased redox potential (33).

The fresh surface is highly reactive with hydrogen, oxygen and carbon to generate toxic oxygen radicals. Co-exposure to other minerals decreases the development of silicosis probably because these minerals adhere to or even chemically integrate with the surface of silica particles and reduce the surface area for generating free radicals (33). Once inhaled, silica particles are ingested by pulmonary macrophages. Macrophages are activated and produce chemokines, interleukin-1 (33), macrophage inflammatory proteins, MIP-1, monocyte chemoattractant protein (MCP) and tumour necrosis factor α (TNF-a) (33). These chemokines have been implicated in the inflammatory process in bleomycin-induced lung injury. IL-1 and TNF-a are of critical importance in producing granuloma. These two cytokines together with platelet-derived growth factor (PDGF), fibronectin, and probably other substances appear to be important in inducing granulomatous inflammation and fibrosis in silicosis.

Fibroblasts are responsible for collagen and elastin synthesis and for degradation during the course of normal connective tissue matrix turnover. Production of excess collagen begins almost immediately by fibroblasts after silica exposure and proceeds excessively for at least one-year (33).

Silicosis and mycobacterial disease

The association between tuberculosis and silicosis has long been recognized. The occurrence of tuberculosis in silicosis is related to the underlying prevalence of previous latent infection and the risk of new exposure to tuberculosis of the population at risk for silicosis. Thus the risk of tuberculosis among silicotics in Asian countries is high because of the high prevalence of tuberculosis in these countries. In Hong Kong, 30% of patients with

silicosis developed tuberculosis in 5 years at a constant annual rate (approx 6000/100,000 (34). In countries where atypical mycobacterial infection is high, it is important to consider its infection in patients with silicosis rather than typical mycobacterial infection. A study in the New Orleans area found that 22 out of 83 patients with accelerated silicosis had mycobacterial infection; 45% due to *M. tuberculosis*; 41% *M. kansasii* and *M. intracellulare* 14% (35).

The most effective way to prevent infection by *M. tuberculosis* and atypical organisms is to limit silica exposure. It has been recommended that in countries with low prevalence of tuberculosis, those with silicosis and those with a history of silica exposure for more than 25 years should have a tuberculin test using 5 TU of PPD (36). Those with a 9 mm induration should be offered isoniazid 300 mg daily for 1 year as chemoprophylaxis irrespective of their BCG status. Because of the problems with compliance and the possibility of strains of resistant *M. tuberculosis*, shorter multidrug regimens have been tried with some success (34,37).

Silica exposure, chronic bronchitis and chronic airflow obstruction

Inorganic dust exposure has been traditionally associated with pneumoconiotic changes in the lung parenchyma. There has been increasing evidence of association between exposure and chronic airflow obstruction. Increase frequency of chronic bronchitis has been reported in U.S. coal miners (38), German coal miners (39), South African and Australian gold miners (40,41), Singaporean granite workers (25), Indian agate workers (17), Hong Kong granite workers and other groups (22). In most studies, chronic bronchitis was associated with airflow obstruction.

Becklake first reviewed the association between silica exposure and chronic airflow obstruction in 1985 (42) and selected cross-sectional studies of coalminers and hard rock miners in which the causal hypothesis was addressed: comparison of exposed and non-exposed or heavily exposed compared with lightly exposed group. Most of the studies have shown higher prevalence of bronchitis and lower mean lung function in exposed vs nonexposed and heavily exposed vs less exposed workers. In two of the studies, smoking data were available as well and both demonstrated the effect of dust on airways after adjustment for smoking. A meta-analysis was carried out by Oxman and colleagues in 1993 (43) and 13 studies (from 4 cohorts) satisfied their inclusion criteria: 1) workers exposed to inorganic dust; 2) outcome measurements that included COPD or chronic bronchitis, emphysema, lung function or mortality; 3) exposure measurement. From these studies, a dose-response relationship between cumulative exposure and airflow limitation was found. The percentage of nonsmoking coalminers with 35 years of exposure to mean respirable dust of 2 mg/m^3 had a mean loss of 20% in FEV_1. Goldminers were found to have 3 times the risk of coalminers at 1/5 level of exposure in developing airflow obstruction. The authors concluded that exposure to inorganic dust is an important cause of COPD.

Studies in Asian countries also supported their findings. Granite quarry workers with radiographic progression of simple silicosis in Hong Kong were found to have loss of FEV_1 in excess of vital capacity suggestive of airflow obstruction (44). Small airway disease was described in Singaporean granite workers in the absence of radiographic silicosis or large airway disease (45).

Pathologically, there is evidence of peribronchiolar fibrosis and emphysema in association with progressive massive fibrosis.

Silica, silicosis and lung cancer

The relationship between silica and lung cancer has been the subject of major controversy for more than a decade. This is due to the fact that most of the studies of silicosis and lung cancer did not adjust for a number of confounders such as smoking and exposure to known or suspected carcinogens in the workplace. Known carcinogens in the mining environment include radon daughters, arsenic and its compounds, nickel and nickel compounds, asbestos, and sulphuric acid mists. Suspected carcinogens include polycyclic aromatic hydrocarbons (PAH), oil mists that are either untreated or mildly treated and highly refined, and blasting agents such as nitrosamines.

In foundries, there is exposure to PAHs while in the pottery industry; there may be exposure to talc. In addition, there were either no control groups for comparison or the control groups were not comparable.

A consistent increase in incidence of cancer was found in rats or hamsters after instillation of silica alone or in combination with benzo(a)pyrene through different routes (46). In 1987, a working group of the International Agency of Research on Cancer (IARC) deliberated on all published literature and concluded that there was "sufficient" evidence of carcinogenicity of crystalline silica in experimental animals, but the evidence in man was limited (46). In man, "limited" evidence implies that although a causal interpretation is credible, other explanations such as chance, bias, or confounding cannot be excluded.

The IARC revisited this issue in 1996. After reviewing more recent studies, the committee came to the conclusion that silica should be classified as a Group 1 substance, "carcinogenic to humans" (47). Elevated standardised mortality ratios of about 150 were detected in large population-based studies in the US (48) and in Canada (49). Reports from many countries have identified lung cancer with increased frequency among workers compensated for silicosis with a relative risk from 1.3 to 6.9 (50–56). Slight excess in lung cancer mortality was found in non-smokers in two studies (57,58).

In China, increased lung cancer risk was found in metal ore miners as in other parts of the world (59–63). However, underground miners may be exposed to other carcinogens. Increased lung cancer risk was also found in non-mining industries with exposure to silica in China (61,63), Hong Kong (64), Singapore (65), and in other countries (66–70). Thus the available data support the conclusion that silicosis increase's the risk for lung cancer.

Extrapulmonary disease

After being inhaled or ingested, silica particles can be transported and disseminated. Silicotic nodules have been demonstrated in liver, brain and bone marrow (71). Extrapulmonary effects are plausible. Regional lymph node involvement is the most common form of disease. Association between scleroderma and silicosis has been described since 1914 (72). An increase incidence of progressive systemic sclerosis has been described among South African miners (73). The association between silica exposure and rheumatoid arthritis is less clear. South African miners with rheumatoid arthritis were more likely to have silicosis and more progressive silicosis than were miners without the rheumatoid arthritis (74).

Treatment

Unfortunately there is no specific treatment for silicosis. The clinical approach is directed at prevention of progression, amelioration of symptoms and improvement of overall condition. Silicosis is irreversible. Early identification of disease followed by removal from exposure should lead to more favourable outcome (75) but evidence for this assumption is sparse. However, continued exposure to the causative exposure seems imprudent.

Any treatment is directed at complications of silicosis such as tuberculosis and heart failure. Chemoprophylaxis for tuberculosis has been recommended for silicotics with a positive tuberculin and negative sputum. Other forms of treatment include vaccination against pneumococcal pneumonia and influenza, breathing exercises, home oxygen therapy, and bronchodilator administration.

Corticosteroids may be useful in treating complicating autoimmune diseases. There is no clinical trial to indicate their effectiveness in preventing the progression of the disease.

Whole lung lavage to remove retained dust has been used for subjects with moderate to severe silicosis in China but its use remains experimental (76). Lung transplantation has been done for a few patients with sever advanced disease.

Prevention

The only approach to primary prevention is control of exposure. Exposure controls either through substitution of safer materials or the adoption of

control technologies is the only effective means of prevention of silicosis. The technology to control silica exposure is simple and relatively inexpensive. In mining, cutting and drilling, the addition of water to the cutting surface effectively reduces dust exposure. When a dry process is necessary, enclosures or local exhaust ventilation can be effective in reducing exposure. A follow up study of workers in seven Chinese mines and industrial workers exposed to silica from 1950 to 1980s has demonstrated a significant reduction of cumulative silicosis from 36.1% of workers employed before 1950 to 1.5% in those employed after 1960 when control measures were introduced (77). In developed countries, mortality from silicosis also decreased during the last few decades. Since the technology available for the control of silicosis is inexpensive, it is surprising that the disease still exists in these countries (3). Enforcement of PEL in the workplace and worker health education is other important measures in prevention of silicosis. These measures may help both developed and developing countries in reducing the incidence and mortality of silicosis.

Asbestos and Asbestos-related Diseases

Asbestos has been used since antiquity. World production of asbestos has increased from the late 19th century to the mid 1970s as production reached 5 million metric tonnes per year (78). World consumption has decreased to 2.5 metric tonnes by 1992 as the developed countries reacted to asbestos health catastrophes with a progressive ban on its use. In response, the asbestos industry is progressively transferring its commercial activities and the associated health hazards to the developing world. Conditions of current asbestos use in the developing countries resemble those that existed in the industrialized countries before the dangers of asbestos were widely recognized. The Collegium Ramazzini has called for an international ban on asbestos in 1999 (79). Without an international ban on the substance, one can expect a shift of asbestos-related diseases to developing nations that are much less well equipped to deal with such a problem.

Asbestos fibres and their uses

Asbestos is a silicate, which exists in nature as two groups of fibrous minerals: serpentine and amphiboles. The only member of the serpentine group is chrysotile (white asbestos), a mineral with long thin fibrils. The amphibole group includes crocidolite (blue asbestos), amosite (brown asbestos), tremolite, actinolite and anthophylite, which have shorter and straighter fibrils. As more than 90% of asbestos in use is chrysotile, it is responsible for most cases of asbestos-related diseases. Crocidolite (blue asbestos) has the distinction of being the most carcinogenic. Asbestos possesses unique heat-resistance and fireproofing properties, which make them ideal for use in insulation, fireproofing and acoustics. Asbestos was widely used as asbestos cement, drains, pipes, corrugated roofs, floor tiles, asbestos fabric and paper products, friction materials (eg. brake linings, clutch facings), fillers in rubber, plastic, paints, in the past in developed countries.

Exposure settings

Heavy exposure to asbestos occurs from the mining and milling of asbestos minerals, and in the manufacture and fabrication of asbestos products. Exposure from applications of asbestos in shipyards, powers stations, boilers, incinerators occurs from spraying, lagging and de-lagging of asbestos insulation. By-standing jobs as fitters and electricians also entail significant risks intriguingly for mesotheliomas. It should also be noted that non-industrial and para-exposure to asbestos also arise from residential proximity to mines and factories, or from asbestos brought home to families on worker's garments, which can cause lung cancer and mesotheliomas.

Most of the asbestos in the world is mined from Canada, Russia, Australia and South Africa. Smaller quantities are also mined in Italy, Zimbabwe, Korea and Pakistan.

Long-term inhalation exposure to asbestos causes a number of lung diseases:

- Asbestosis: (diffuse pulmonary fibrosis)
- Pleural plaques
- Pleural fibrosis (diffuse and circumscribed)
- Bronchial carcinoma

- Malignant mesothelioma of the pleura and peritoneum.

Epidemiology

Surveys of current and retired workers exposed to asbestos generally reported the prevalence of pulmonary fibrosis and pleural changes to be between 20 to 30% (80,81). In Japan, the prevalence of asbestosis and pleural plaques in current construction workers exposed to asbestos was 5.7%. There has been few reported prevalence of asbestosis in developing countries. In Brazil (82), 16 to 19% of current asbestos cement workers with over 10 years exposure had asbestosis. Elsewhere in Asia, published prevalence rates are lacking. Epidemiological surveillance data indicate that asbestosis is disappearing as a result of legislative control in most Western industrialized countries (83). Data that are available from some countries in Asia generally showed relatively small numbers of documented cases of asbestosis, as well as lung cancer and mesothelioma in Singapore, Hong Kong, Malaysia, India and China. In India (84) and South Korea (85), studies have shown that workers were exposed to asbestos dust level well above the threshold limit value. In Singapore, the number of cases has begun to decline in recent years, as a result of complete discontinuation of industrial asbestos exposure since the 1980s (86).

Unlike silicosis or coal worker's pneumoconiosis with declining death rates, the death rates from asbestos in the U.S. has increased from about 1 per million in 1968 to 6 per million in 1992 (83). The projected annual excess deaths in the U.S. from all asbestos-related lung cancer increased to a maximum in 1994 and started a downward trend thereafter (87). The situation is the same in Western Europe, where a large number of workers had disease from previous asbestos exposure (88). This finding reflects the effect of an aging cohort of exposed workers who were most highly exposed early in the 1900s, whereas younger cohorts of exposed persons in fact showed a declining trend (89). In most industrialized countries, population surveillance registers of mesothelioma also generally indicate increasing trends over past decades (90).

Pathogenesis

The amount of asbestos fibres deposited and retained in the lung tissue depends on its diameter and to a lesser extent by its length (91). Asbestosis is caused by fibres less than 3 microns in diameter, which can penetrate cell membranes, be translocated to the interstitium and pleural lining to cause fibrosis. Fibres more than 5 microns in length are incompletely phagocytosed or not at all, and are therefore retained in the lung tissue to cause fibrosis. Retained fibres initially cause an inflammatory injury, followed by an accumulation of alveolar macrophages which stimulates fibroblastic proliferation through the release of cytokines (fibronectin, procollagen, platelet-derived growth factors, insulin-like growth factors, and fibroblast growth factors), resulting in the eventual formation of scar tissues around the bronchioles and the interstitium (92).

The cell damage caused by asbestos fibres can lead to cell death, gene mutation, chromosomal aberration, aneuplodies and malignant cell transformation, through the release of oxygen free radical and resultant molecular injuries. The breakdown of bonds between atoms on the fibre surface provides active sites for adsorption of carcinogens such as polycyclic aromatic amines present in tobacco smoke.

Asbestosis

Long-term inhalation exposure to asbestos typically over 15 to 30 years most commonly results in diffuse interstitial fibrosis, predominantly in the lower lobes.

Clinical features

Patients with asbestosis typically present with clinical symptoms and signs of a chronic progressive restrictive airflow disorder: increasing exertional dypsnoea, restricted chest expansion, fine basal crepitations, and finger clubbing. Late inspiratory crackles may be present over the posterior basal regions of the lungs.

Radiological changes

Diffuse interstitial fibrosis is clearly indicated radiologically by irregular small opacities which

predominate in the lower lung fields bilaterally; fine linear opacities in early disease may present as increased vascular markings, fine horizontal striations (Kerly B lines) or reticular shadows in the costophrenic angles, and 'ground-glass veiling'. Such early parenchymal changes are more readily apparent with high-resolution computerized tomography (CT). With more extensive fibrosis, this may manifest as 'honeycomb' changes. Pleural thickenings and plaques (with or without calcifications) involving the visceral layers commonly accompany parenchymal fibrosis, and are radiological detectable often on the diaphragmatic and pericardial surfaces ('shaggy heart') (Figure 3).

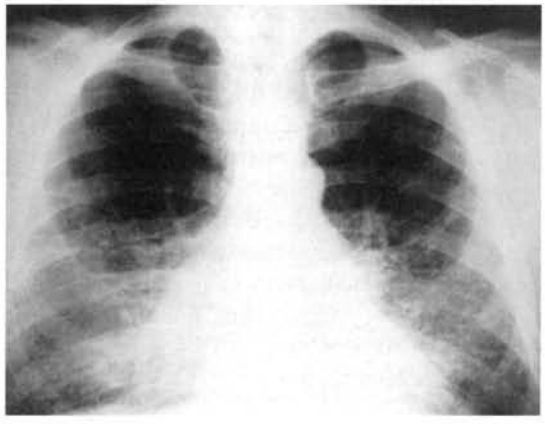


Figure 3. Chest radiograph of a patient with asbestosis showing diffuse linear reticular shadows in both lower zone and shaggy heart border

Lung function tests

Pulmonary function tests typically indicate a restrictive ventilatory function and alveolar-capillary diffusion defects: reduced forced expiratory volume in one second (FEV_1) as well as forced expiratory volume (FVC), with normal FEV_1/FVC ratio, and reduced diffusing capacity (DL_{CO}).

Diagnosis

The diagnosis of asbestosis is based on:

1. an occupational history of long term exposure to asbestos;
2. an appropriate time interval between exposure and detection;
3. radiographic changes suggestive of diffuse lung fibrosis on chest radiograph or CT scan;
4. a restrictive changes in lung function;
5. inspiratory basal crackles.

Asbestos (ferruginous) bodies may be found in the sputum. Histologic diagnosis of asbestosis is the best and most sensitive and specific method particularly when mineral assessment can be included.

Natural history

Most cases of asbestosis do not progress after cessation of exposure. Those whose disease progress are more likely to be those exposed to the amphiboles, particularly crocidolite, those who smoke, and those with a short latency period. A 10 year follow-up study of 2609 insulators from a North American cohort showed that the mortality due to asbestosis increased sharply with increasing interstitial fibrosis as identified on the baseline chest radiograph from 0.9% to 2.4%, 10.8% and 35.4% for profusion categories 0, 1, 2, and 3 respectively (93). Progression after ceasing exposure is likely to be present in the first 5 years; after that, if the disease remains unchanged for 10 years, progression is unlikely for the rest of the patient's life.

Pleural plaques

Pleural plaques are focal, irregular thickenings of the parietal pleura; they may be circumscribed or diffuse. Pleural plaques are the most frequent manifestation of asbestos exposure. Parietal plaque is a marker of environmental asbestos exposure, and may occur in those who are not heavily exposed to asbestos and are seen in a small proportion of the residential population. Pleural plaques are usually asymptomatic in the absence of asbestosis. They have a latency period of around 20 years and have a limited progression and are often found in the absence of asbestosis.

Plaques are thin and have sharp margins. They may be smooth or may have an uneven surface. Oblique films of the chest increase the visibility of plaques on radiographs. CT scan can detect pleural plaques early especially those in the

paravertebral and pericardial area. It can also differentiate plaques from extrapleural fat pads.

In general, pleural plaques do not affect lung function. However when there are multiple plaques, a restrictive ventilatory pattern can be found even in the absence of interstitial lung fibrosis. Pleural plaques can become calcified. It has been suggested that mesothelioma may develop at the edge of the plaques.

Pachypleuritis or diffuse pleural fibrosis

Pachypleuritis or diffuse pleural fibrosis is a disease of the visceral pleura. It could arise from 1) confluence of large pleural plaques; 2) the extension of subpleural fibrosis to the visceral pleura and 3) previous exudative benign pleural effusion. The last one is the most common occurrence and can cause significant restriction even in the absence of interstitial lung fibrosis. Diffuse pleural fibrosis is associated with dyspnoea of exertion and dry cough. Physical examination of the lungs can be normal except for reduction of chest expansion. Most often, however, diffuse pleural fibrosis occurs in the presence of diffuse interstitial lung fibrosis.

Diffuse pleural thickening is a continuous pleural opacity extending on > 25% of the pleural surface with blunting of the costodiaphragmatic angle and with or without blunting of the costophrenic angle. Pachypleuritis is defined as a pleural thickening > 5 cm in width, > 8 cm in length and > 3 mm in thickness by CT scan. Diffuse pleural fibrosis may extend to involve interlobar and interlobular spaces and may sometimes produce a rounded atelectasis on chest radiograph.

Bronchial carcinoma

Exposure to asbestos is associated with significantly increased risk of lung cancer (94–96). Asbestos acts as a promoter (co-carcinogen) in the development of cancer in exposed workers. There is no particular histological type of cancer that is associated with asbestos exposure. The risk of developing lung cancer and meosthelioma is related to the cumulative amount of fibres inhaled over a working life, the type of asbestos fibre (with crocidolite carrying the greatest risk, and chrysotile being the least carcinogenic), smoking and lung fibrosis. Occupationally, the risk varies with the type of work exposure, being highest for textile workers and lowest for miners, and is related in dose-response fashion to the amount of fibres inhaled over a working lifespan. The cumulated evidence suggests that the risk of lung cancer is not increased when exposure to chrysotile is kept below 1 fibre per ml over an entire working life (96). The risk of lung cancer is multiplicative when interaction with smoking is taken into account (95). The risk of lung cancer in a smoker exposed to asbestos is more than the sum of the risks from either factor alone. As the risk of lung cancer is related to increasing profusion of radiological asbestosis, it has been suggested that lung fibrosis is a pre-condition for lung cancer to develop in asbestos workers (97). Can lung cancer be attributed to asbestos exposure in the absence of asbestosis? The question is being debated. A recent review of the available epidemiologic and pathologic evidence suggests that lung cancer can occur as a result of asbestos exposure, in the absence of clinical or histologic asbestosis (97–105).

Pleural and peritoneal mesothelioma

Mesothelioma is a rare tumour that has been found to be associated with asbestos exposure by Wagner (106) and this observation has been repeatedly confirmed by others. About 80% of malignant mesotheliomas are caused by asbestos. Even in women in whom the incidence is 2 to 10 times less common than in men, tissue analysis of mineral fibres has shown that 98% of cases in the U.K. had amphobile fibres in the lungs in greater amounts than controls (107). The risk of mesotheliomas is least with exposure to chrysotile, and greatest with amphiboles, particularly crocidolite and amosite, but not anthophylite.

Mesothelioma appears as small greyish nodules on the visceral and parietal pleura, which coalesce and form large masses of tumour. The tumour grows by direct extension invading the adjacent structures. Malignant mesothelioma may be of peritoneal in origin.

The incidence of mesothelioma in the general population is 2.5 to 13 cases / million per year in men. In asbestos exposed populations, the rates are 5 to 20 times higher.

There is a prolonged period of latency of about 20 to 50 years between exposure and the development of mesothelioma. The patient usually presents with chest pain increasing in severity. With the development of pleural effusion, the patient complains of dyspnoea and cough. There are also systemic symptoms of weight loss, fever and malaise in the late stage. The disease is invariably fatal within 2 years.

Pleural mesothelioma may appear as solid pleural abnormalities, diffuse with irregular surface or multiple pleural nodules or masses with pleural effusion. As the disease progresses, there may be involvement of the adjacent lung tissue, chest wall, pericardium and other mediastinal structures.

Asbestos fibres in the lungs

The current standard in the U.S. for asbestos is 1 fibre per ml of air for chrysotile and 0.2 fibres per ml of air for amphiboles as in most industrialized countries. For clinical diagnosis, workers' compensation and medicolegal purposes, the search for asbestos fibres in biological samples is increasingly utilized to document past exposure to asbestos. Control populations with no occupational exposure to asbestos should not have asbestos bodies in the sputum, < 1 asbestos body/ml in the lavage fluid and < 0.1 asbestos body per mg lung tissue. Patients with pleural plaques have 1.7 asbestos bodies per mg lung tissue, long-term asbestos worker with grade 0 asbestosis have up to 1300 asbestos bodies per mg and those with grade 2 asbestosis have over 70,000 asbestos bodies per mg lung tissue (108). In terms of optical microscopy, the general population has < 250 fibres/mg lung tissue; exposed persons with grade 0 asbestosis 2400 fibres/mg while those with grade 2 asbestosis 14,000–200,000 fibres/mg lung tissue (108).

Treatment and prevention

There is no curative treatment for asbestos-related diseases. Enforced legislation, environmental control of workplace exposures of asbestos fibres to below permissible accepted levels, and health surveillance through periodic medical examination are the most important measures for primary prevention of the disease. Even with the strictest control, there is still excess disease. An international ban is the only way of eliminating these diseases.

Coalworkers' Pneumoconiosis (CWP)

CWP is a well-known disease of coal miners. Although it could develop together with silicosis (anthracosilicosis), it is a clinically distinct entity induced by coal dust and pure carbon. Like silicosis, it can exist as a "simple" CWP or complicated with progressive massive fibrosis. The disease is generally of slower onset and more slowly progressive than silicosis and restrictive ventilatory impairment is generally only observable in those with category 2 profusion or more. CWP complicated by progressive massive fibrosis is clearly associated with disablement and reduced life expectancy. Rapid progression of disease is uncommon and is usually associated with concomitant exposure to silica.

In developing countries in Asia, the reported prevalence of CWP was 6% in China, 9.3% in Korea, and 12% in India (109). In China and Korea, coal workers' pneumoconiosis is associated with a high prevalence of silicosis and tuberculosis (anthraco-silicotuberculosis) (110,111). In these countries, comprehensive control measures have been introduced, and indeed in one major coal mining region in China, this has been reported to result in a remarkable decline in incidence of the disease over three decades (112).

Extensive research in the West has shown that prevention of PMF could be reasonably achieved by keeping the dust exposure down to a level that prevent the development of category 1 small opacities over a lifetime. This is based on the evidence that there is an increasing risk of PMF with higher background level of small opacities. Extensive research has also been reported in the Chinese literature that generally supports this basis, although the Chinese system of radiological

classification differs somewhat from the ILO Classification and the maximal allowable concentration rather than the threshold limit value was used.

Other Pneumoconiosis

Graphite is mined in Sri Lanka and Madagascar. High prevalence of graphite pneumoconiosis has been found in surveys of graphite miners in Sri Lanka, who have worked an average of twenty years (113). The slowly progressing nature of the disease and the relative freedom from symptoms except in those with massive fibrosis indicate this pneumoconiosis as one resembling coal worker's pneumoconiosis rather than silicosis, although workers are also exposed to low concentrations of silica.

Pneumoconiosis is also known to occur from worker's exposure to other mineral dusts such as talc, kaolin, mica, and vermiculite, as well as to metals and their alloys, such as aluminium, beryllium, tungsten carbide, and tin. Polyvinyl chloride pneumoconiosis has also been described in polyvinyl chloride workers in Singapore (114).

Extrinsic Allergic Alveolitis

Extrinsic allergic alveolitis is a disease characterized by immunologically-mediated response of the bronchioles and alveoli to the inhalational exposures to organic dusts and vapours (115). The same allergenic agents (e.g. isocyanates) themselves may also cause concurrently a response at the bronchial level (asthma). It is also frequently associated with an acute self-limiting febrile illness similar to 'metal fume fever', or 'organic toxic dust syndrome' (116). Collectively, they are termed 'hypersensitivity pneumonitis'.

The immunological mechanisms of allergic alveolitis are complex and controversial, but involve at least both a Type III (immune-complexed mediated) and Type IV hypersensitivity injury. The clinical features range over a wide spectrum and include the acute, subacute and chronic form of illness.

The acute form is most characteristic and usually follows a high exposure. The patient suffers from repeated episodes of mild or severe febrile illness associated with dry cough and dyspnoea 3 to 9 hours after exposure. Basal crackles could be heard. The chest radiograph may show diffuse alveolitis with "ground glass" appearance.

The chronic form presents as an insidious progressive dyspnoea without systemic symptoms although weight loss can be present because of progressive pulmonary fibrosis and hypoxaemia. Chest radiographs may show progressive diffuse fibrosis with honeycombing. In between the two spectra is the subacute form when the patient presents with recurrent febrile illness with malaise superimposed on a background of more chronic progressive disease.

Lung function ranges from normal to a progressive restrictive pattern, but air trapping due to bronchiolitis is also found. Diffusing capacity is reduced and hypoxia becomes progressive worse.

The typical pathology in the lung during the acute illness is a nonspecific diffuse pneumonitis with inflammatory cell infiltration of the bronchioles, alveoli and interstitium. With ongoing continuous or intermittent exposure, a lymphocytic alveolitis develops. Noncaseating epitheliod granulomata are present but usually resolve on cessation of exposure (Figure 4). With further exposure, cellular infiltration with monocytes, lymphocytes and plasma cells together with progressive fibrosis occur.

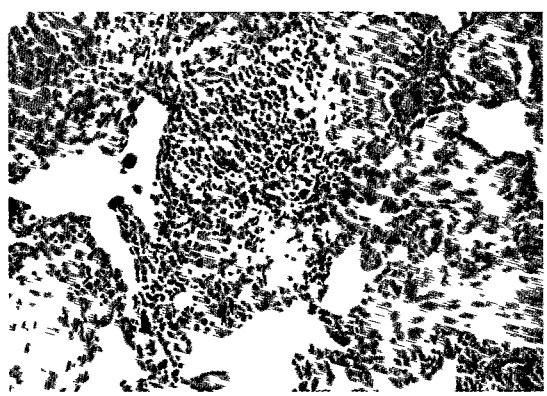


Figure 4. Open lung biopsy of a patient with Farmer's lung showing diffuse cellular infiltration with mononuclear cells in the alveoli and bronchioles and presence of noncaseating epitheliod granulomat

The diagnosis of extrinsic allergic alveolitis is dependent on the history of periodic or continuous exposure to a relevant antigen, the appropriate changes in lung function and pathology and evidence of sensitization to the suspected agent.

Depending on the causative agents (fungi, bacteria, animal materials, and low molecular weight chemicals), extrinsic allergic alveolitis are variously described as 'farmer's lung, bagassosis (sugar cane), mushroom grower's lung, malt worker's lung, cheese worker's lung, maple bark stripper's disease, sequeolosis (redwood dust), woodworker's disease, dry rot lung (house fungus), bird breeder's lung, isocyanate alveolitis, alveolitis due to proteolytic enzymes of Bacillus subtilis in detergent workers. The presence of allergen-specific precipitating antibodies is a strong aid to diagnosis.

In developing countries, acute irritant and allergic respiratory disorders associated with exposure to a wide variety of organic vegetable dusts, has been described. These included disorders seen in Sri Lankan workers (117–122) exposed to spices (chill, paprika, cinnamon), vegetable fibres (kapok, or tree cotton, coir) tea. In rice miller's syndrome reported in Malaysia (123), radiological small nodular opacities with or without reticulation, which is strongly suggestive of extrinsic allergic alveolitis were found. Acute and chronic irritation of the eyes, skin, and respiratory tract as well as nasal catarrh are part of the syndrome.

Assessment of Impairment/ Disability

It is important to make a distinction between "impairment" and "disability" (124). Impairment is a purely medical condition and is the result of a functional abnormality. In conceptual terms, quantitation of impairment is straightforward. It assumes that there is a normal status, taking into account known anthropomorphic determinants. Deviation from the normal value for the individual reflects the functional impairment. Disability, however, indicates the total effect of impairment on a person's life. It is affected by diverse factors such as age, gender, education, economic and social environment, and the requirements of the occupation. Thus two people with identical impairment may be differently affected in their life situations. For example, a person who develops exercise-induced asthma may become disabled from a job that requires considerable physical work but the same person would not have become disabled from a more sedentary work.

Rating of respiratory impairment is usually carried out by physicians, while the determination of disability is an administrative decision that requires consideration of nonmedical as well as medical factors.

General principles for evaluation of respiratory impairment

Impairment assessment of respiratory diseases requires the establishment of a medical diagnosis and the evaluation of the degree of impairment arising from the disease. The following procedures for evaluation of respiratory impairment have been recommended mainly for patients with pneumoconiosis with irreversible lung damage (125).

History and physical examination

The assessment of respiratory impairment should be guided by objective physiologic tests and not determined only by symptoms and physical findings. Dyspnoea should not be used as the sole criterion for evaluation of impairment since individual response to a given degree of physiological abnormalities varies and is influenced by factors unrelated to the extent of lung disease, such as preoccupation with health, socioeconomic status, educational background and physical fitness of the individual.

Chest radiograph

Chest radiographs are usually performed as part of the diagnostic procedure in patients with pneumoconiosis and to exclude other chest conditions in subjects with asthma. Chest radiographic findings in patients with pneumoconiosis correlate poorly with physiologic changes. Chest radiographs should be read according to the International Labour Organization Classification for Pneumoconiosis. Computed tomography (CT) is not routinely justified for the diagnosis of pneumoconiosis or for evaluation of respiratory impairment.

Physiologic measurements

Lung function tests are pivotal in determining the nature and the degree of the physiologic abnormality. They are essential in assessing the presence and the severity of impairment.

Spirometry Spirometry is a well-standardized and simple test. Comprehensive guidelines for spirometry including recommendations for equipment, quality control, techniques of testing procedure and strategies for interpretation for spirometric measurement have been published (126,127). All lung function laboratories should follow these guidelines. For impairment evaluation, only two parameters are used: forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) and their ratio.

Measurement of the diffusing capacity Measurement of the diffusing capacity of the lung for carbon monoxide (DL_{CO}) is a useful test in impairment evaluation in subjects with pneumoconiosis or chronic irreversible obstructive lung diseases, but not in subjects with asthma. The test requires careful attention to detail standardization (128). The test result is dependent on haemoglobin concentration and should be adjusted if the subject is anaemic (129). Smokers should be told to refrain from smoking for 12 hours before the test otherwise adjustment has to be made for back diffusion because of high levels of carbon monoxide in the blood.

Arterial blood gas Measurements of oxygen and carbon dioxide tensions and pH level in arterial blood at rest are sometimes used in impairment evaluation (130).

Exercise tests The majority of patients do not require exercise testing in impairment evaluation (125) since there are well-documented relationships between FEV_1, DL_{CO}, oxygen consumption and work capacity. Exercise testing is indicated only when there is a reason to believe that routine lung function tests may have underestimated impairment. Exercise testing in such cases is used to determine whether a person is impaired and whether the impairment is due to a respiratory disorder.

Normality of lung function measurements

The decision as to where and how to draw the line between "normal" and "abnormal" pulmonary function has been the subject of controversy.

Results of lung function tests are dependent on certain demographic characteristics, such as gender, age, height and race. There are also several means of comparing individual results with those of the reference population. Lung function values may be expressed either as a percentage of the reference value, or as deviations from the reference values in terms of standard deviation or standard error. The use of 80% of the reference value as the demarcation between normal and abnormal lung function has been widely accepted. This method tends to overestimate the prevalence of abnormalities in older individuals (127). The most recent recommendation is to define abnormality as values outside 95% confidence limits (127). Prediction equations vary due to several reasons including instrument and technical differences, differences in population (such as age and race) selected for the comparison and in the mathematical model used to study the relationship between the predictors and lung function. Certain ethnic/racial groups such as the Hispanic, Asians and blacks may have smaller lung volumes than the whites of the same age and height. Frequently a 10 to 15% correction factor is applied, but there is no standard formula in this regard (127). Thus it is best for each laboratory to establish its own reference values rather than using those generated by others.

Grading impairment

Respiratory impairment refers to a functional deficit. Such deficits can be quantified in numerical terms as they are deviations from expected normal physiologic values. The American Medical Association (AMA) Guidelines for Evaluation of Permanent Impairment are often employed by practitioners as a primary source of guidance in matters related to impairment classification for patients with irreversible lung disease (Table 2) (131).

Table 2. Classes of Respiratory Impairment in AMA Guidelines

	Class I 0%	*Class II 10–25%*	*Class III 30–45%*	*Class IV 50–100%*
FVC % predicted	≥ 80	60–79	51–59	< 50
FEV_1 % predicted	≥ 80	60–79	41–59	< 40
FEV/FVC %	≥ 70	60–69	41–59	< 40
DLco % predicted	≥ 80	60–79	41–59	< 40
VO_2 max (ml/kg/min)	≥ 26	20–25	15–20	< 15

FVC is Forced Vital Capacity, FEV_1 is Forced Expiratory Volume in the first second, DL_{co} is diffusing capacity of carbon monoxide. The DL_{co} is primarily of value for persons with restrictive lung disease in Classes II and III. If the FVC, FEV_1 and FEV_1/FVC ratio are normal and the DL_{co} is between 41% and 79%, then an exercise test is required.

VO_2 Max, or measured exercise capacity, is useful in assessing whether a person's complaint of dyspnoea is a result of respiratory or other conditions. A person's cardiac and conditioning status must be considered in performing the test and in interpreting the results.

References

1. Corn JK. Historical aspects of industrial hygiene II Silicosis. *Am Ind Hyg Assoc J* 1980; 41:125–33.
2. Ramazzini B. De morbis artificum (diseases of workers). New York: Hefner 1964.
3. Wagner G. Asbestosis and Silicosis. *Lancet* 1997; 349:1311–5.
4. Bar Ziv J and Goldberg GM. Simple siliceous pneumoconiosis in Negev Bedouins. *Arch Environ Health* 1974; 29:121–6.
5. Poh SC, Chew PK (1976). Silicosis in "rubber powder" workers in Singapore. Proceedings of the 10th Asian Conference on Occupational Health, September 1982, Singapore.
6. Lee HS, Chan OY, Lim Tan SK, Tan TH, Kwok R, Chan YK. Silicosis in the manufacture of scouring powder. *Singapore Med J* 1986; 27:496–506.
7. Ueda A, Futasuka M, Nomura S. Follow up Study on pneumconiosis of farmers engaged in cultivating rush (Igusa) and weaving into tatami mat process. Proceedings of the 10th Asian Conference on Occupational Health, September 1982, Singapore.
8. Lim HH, Domala Z, Joginder S, Lee SH, Lim CS, Abu Bakar CM. Rice miller's syndrome: a preliminary report. *Br J Ind Med* 1984; 41:445–9.
9. Norboo T. Silicosis in a Himalayan village population: role of environmental dust. *Thorax* 1991; 46:341–3.
10. NIOSH Work-related respiratory disease Surveillance Program. www.niosh.gov.
11. Merler E, Biggeri A, Olmastorni L, Arfaioli C, Buiatti E. Pneumoconiosis mortality in Italy. Tenth International Symposium Epidemiology in Occupational Health, ISEOH 1994, Sept 20–23, 1994 Villa Erba, Como, Italy: A200.
12. Van Sprundel MPM. Pneumoconioses: The situation in developing countries. *Exp Lung Res* 1990; 16:5–13.
13. El Batawi MA. The third Theodore F Hatch Symposium Lecture. *Ann Am Con Gov Ind Hyg* 1986; 14:3–15.
14. Qi G. Radiographic studies and pathology of various kinds of pneumoconiosis in China. In: *Inhaled Particles IV.* Eds. Dodgson J, McCallum RI, Baily MR, Fisher DR. Oxford: Pergamon 1988, 1192–4.
15. Saiyed HN, Parikh DJ, Ghodasara NB, Sharma YK, Patel GC, Chatterjee SK, Chatterjee BB. Silicosis in slate pencil workers: I. An environmental and medical study. *Am J Ind Med* 1986; 16:253–63.
16. Parkes WR. Occupational Lung Disorders. London, Butterworths, 1982.
17. Clerck SH. Respiratory morbidity in agate workers. In: Abstract of Communications, VIIth International Pneumoconiosis Conference; Pittsburgh, PA; Aug 23–26, 1988, 190.

18. Metadilogkul O, Siriwattananukul P. Occupational silicosis among workers in an ore mill. In: Abstract of Communications, VIIth International Pneumoconiosis Conference, Pittsburgh, PA; Aug 23–26, 1988, 45.
19. Metadilogkul O. Ithiraviwong A. Silicosis among stone mortar workers in Northern Thailand in 1986. In: Abstract of Communications, VIIth International Pneumoconiosis Conference, Pittsburgh, PA; Aug 23–26, 1988, 147.
20. Metadilogkul O, Supunnachart P. Silicosis among workers in refractory brick factory. Thailand. In: Abstract of Communications, VIIth International Pneumoconiosis Conference, Pittsburgh, PA; Aug 23–26, 1988, 147.
21. Ng T, Tsin T, O'Kelly F, Chan S. A survey of the respiratory health of silica-exposed gemstone workers in Hong Kong. *Am Rev Respir Dis* 1987; 135:1249–54.
22. Ng TP, Chan SL. Quantitative relations between silica exposure and development of radiological opacities in granite workers. Inhaled particles VII. *Ann Occup Hygiene* 1994; 38(suppl 1):857–63.
23. Ng TP, O'Kelly FJ. Silicosis prevalence in granite quarry and construction workers in Hong Kong. *J Hong Kong Med Assoc* 1987; 3:160–2.
24. Ng TP, Yeung KH, O'Kelly FJ. Silica hazard of caisson construction in Hong Kong. *J Soc Occup Med* 1987; 37:62–5.
25. Ng TP, Phoon WH, Lee HS, Ng YL, Tan KT. An epidemiological survey of respiratory morbidity among granite quarry workers in Singapore: chronic bronchitis and lung function impairment. *Ann Acad Med Singapore* 1992; 21:312–7.
26. Singh A. The prevalence of silicosis among granite workers of the government sector in Peninsular Malaysia. *Med J Malaysia* 1977; 31:277–80.
27. Kuo HW, Chang CL, lai JS, Lee FC, Chung BC, Chen CJ. Prevalence of and factors related to pneumoconiosis among foundry workers in central Taiwan. *Sci Total Environ* 1998; 27:133–9.
28. Office of the Federal Register. 29 CFR (United States Code of Federal Regulations) 1910.1000. Office of the Federal Register, National Archives and Records Administration. U.S. Government Printing Office, Washington, DC. 1994.
29. Hnizdo E, Sluis-Cremer GK. Risk of silicosis in a cohort of white South African goldminers. *Am J Ind Med* 1993; 24:447–57.
30. Ng TP, Chan SL, Lam KP. Radiological progression and lung function in silicosis: a ten-year follow up study. *BMJ* 1987; 295:164–8.
31. Begin R. Aluminum inhalation in sheep silicosis. *Int J Exp Pathol* 1993; 74:299–307.
32. Kennedy MCS. Aluminum powder in the treatment of silicosis of pottery workers and pneumoconiosis of coal-miners. *Br J Ind Med* 1956; 13:85–101.
33. Davis GS. Silica. In: Occupational and Environmental Respiratory Disease. Eds. Schenker M, Balmes J, Harber P. New York: Mosby 1996; 373–99.
34. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Centre. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. *Am Rev Respir Dis* 1992; 145:36–41.
35. Bailey WC, Brown M, Buechner HA, Weill H, Ichinose H, Ziskind M. Silicomycobacterial disease in sandblasters. *Am Rev Respir Dis* 1974; 110:115–25.
36. American Thoracic Society. Adverse effects of crystalline silica exposure. *Am J Respir Crit Care Med* 1997; 155:761–5.
37. Cowie RL. Chemoprophylaxis with rifampin, isoniazid, and pyrazinmide for tuberculosis evaluated in gold miners with silicosis: a double blind placebo controlled trial. *Tuberc Lung Dis* 1996; 77:239–43.
38. Morgan W, Lapp N. Respiratory disease in coal-miners. *Am Rev Respir Dis* 1976; 113:531–57.
39. Ulmer WT, Reichel G. Epidemiological problems of coal workers' bronchitis in comparison with the general population. *Ann NY Acad Sci* 1972; 200:211–9.
40. Hnizdo E, Sluis-Cremer GK, Abramowitz JA. Emphysema type in relation to silica dust exposure in South Africa gold miners. *Am Rev Respir Dis* 1991; 143:1241–7.
41. Holman CD, Psaila-Savona P, Rpberts M, NcNulty JC. Determinants of chronic bronchitis and lung dysfunction in Western Australian gold miners. *Br J Ind Med* 1987; 44:810–8.
42. Becklake M. Chronic airflow limitation: Its relationship to work in dusty occupation. *Chest* 1985; 88:608–17.
43. Oxman A, Muir D, Sgannon H, Stock S, Hnizdo E, Lange H. Occupational dust exposure and chronic obstructive pulmonary disease: A systemic overview of the evidence. *Am Rev Respir Dis* 1993; 148:38–48.

44. Ng TP, Chan SL. Lung Function in relation to silicosis and silica exposure in granite workers. *Eur Respir J* 1992; 5:986–91.
45. Chia KS, Ng TP, Jeyaratnam J. Small airways function of silica-exposed workers. *Am J Ind Med* 1992; 22:55–162.
46. Internatioinal Agency for Research on Cancer. Silica and some silicates. IARC Monograph Eval Carcinog Risk Chem Hum 1987; 42:39–143.
47. Internatioinal Agency for Research on Cancer. Silica and some silicates. IARC Monograph Eval Carcinog Risk Chem Hum 1996.
48. Dubrow R, Wegman DH. Cancer and occupation in Massachusetts: a death certificate study. *Am J Ind Med* 1984; 1984:207–30.
49. Siemiatycki J, Gerin M, Dewar R, Lakhani R, Begin D, Richardson L. Silica and cancer associations from a multicentre occupational exposure case-referent study. *IARC Scientific Publications, Lyons* 1990; 97:29–42.
50. Carta P, Cocco P, Casula D. Mortality from lung cancer among Sardinian patients with silicosis. *Brit J Ind Med* 1991; 48:122–9.
51. Finkelstein M, Kusiak R, Suranyi G. Mortality among miners receiving workers' compensation for silicosis in Ontario: 1940–1975. *JOM* 1982; 24:663–8.
52. Infante-Rivard C, Armstrong B, Petitclerc M, Cloutier L, Theriault G. Lung cancer mortality and silicosis in Quebec. *Lancet* 1989; 2:1504–6.
53. Merlo F, Doria M, Fontana L, Ceppi M, Chesi E, Santi L. Mortality from specific causes among silicotic subjects: a historical prospective study. *IARC Scientific Publications, Lyons* 1990; 97:105–12.
54. Finkelstein MM. Radiographic abnormalities and the risk of lung cancer among workers exposed to silica dust in Ontario. *CMAJ* 1995; 152:37–43.
55. Zambon P, Simonato L, Mastrangelo G, Winkelmann R, Sala B, Crepet M. Mortality of workers compensated for silicosis during the period 1959–1963 in the Veneto region of Italy. *Scan J Work Environ Health* 1987; 13:118–123.
56. Chiyotani K, Saito K, Okubo T, Takahashi K. Lung cancer risk among pneumoconiosis patients in Japan, with special reference to silicotics. *IARC Scientific Publications, Lyons* 1990; 97:95–104.
57. Hnizdo E, Sluis-Cremer G. Silica exposure, silicosis, and lung cancer: a mortality study of South African gold miners. *Brit J Ind Med* 1991; 48:53–60.
58. Hodgson J, Jones R. Mortality of a cohort of tin miners 1941–86. *Brit J Ind Med* 1990; 47:665–76.
59. Chen J, McLaughlin J, Zhang J, Luo J, Dosemeci M, Wu Z, Hearl F, McCawley M, Blot W. Mortality among dust-exposed Chinese mine and pottery workers. *JOM* 1992; 34:311–6.
60. Chen S, Hayes R, Liang S, Li Q, Stewart P, Blair A. Mortality experience of haematite mine workers in China. *Brit J Ind Med* 1990; 47:175–81.
61. Wang Z, Dong D, Liang X, QU G, Wu J, Xinmei X. Cancer mortality among silicotics in China's metallurgical industry. *Int J Epidemiol* 1996; 25:913–7.
62. McLaughlin J, Chen J, Dosemeci M, Chen R, Rexing SH, Wu Z, Hearl F, McCawley M, Blot W. A nested case-control study of lung cancer among silica exposed workers in China. *Brit J Ind Med* 1992; 49:167–71.
63. Dong D, Xu G, Sub Y, Hu P. Lung cancer among workers exposed to silica dust in Chinese refractory plants. *Scand J Work Environ Health* 1995; 21(suppl 2):69–72.
64. Ng TP, Chan SL. Mortality of a cohort of men in a silicosis register: further evidence of an association with lung cancer. *Am J Ind Med* 1990; 17:163–71.
65. Chia S, Chia K, Phoon W, Lee H. Silicosis and lung cancer among Chinese granite workers. *Scand J Work Environ Health* 1991; 17:170–4.
66. Mehnert W, Staneczek W, Mohner M, Konetzke G, Muller W, Ahlendorf W, Beck B, Winkelmann R, Simonata L. A mortality study of a cohort of slate quarry workers in the German Democratic Republic. *IARC Scientific Publications, Lyons* 1990; 97:55–64.
67. Costello J, Graham W. Vermont granite workers' mortality study. *Am J Ind Med* 1988; 13:483–97
68. Amandus H, Shy C, Wing S, Blair A, Heineman E. Silicosis and lung cancer in North Carolina dusty trade workers. *Am J Ind Med* 1991; 20:57–70.
69. Tornling G, Hogstedt C, Westerholm P. Lung cancer incidence among Swedish ceramic workers with silicosis. *IARC Scientific Publications, Lyons.* 1990; 97:113–20.
70. Lagorio S, Forastiere F, Michelozzi P, Cavariani F, Perucci C, Axelson O. A case-referent study on lung cancer

mortality among ceramic workers. *IARC Scientific Publications. Lyons* 1990; 97:21–8.
71. Silicosis and silicates Disease Committee. Diseases associated with exposure to silica and nonfibrous silicate minerals. *Arch Pathol Lab Med* 1988; 112:673–720.
72. Bramwell B. Diffuse scleroderma: its frequency; its occurrence in stone masons: its treatment by fibrolysin; elevations to temperature due to fibrolysin injections. *Edinburgh Med J* 1914: 12:387–401.
73. Cowie RL Silica-dust exposed mine workers with scleroderma (systemic sclerosis). *Chest* 1987; 92:260–2.
74. Klockars MR, Koskela RS, Jarvinen E, Kolari PJ. Rossi A. Silica exposure and rheumatoid arthritis: a follow up study of granite workers 1940–81. 1987; 294:997–1000.
75. Banks DE, et al. Strategies for the treatment of pneumoconiosis. *Occup Med* 1993; 8:105–232.
76. Wilt JL, Banks DE, Wegman DN, et al. Reduction of lung dust burden in pneumoconiosis by whole lung lavage. *J Occup Environ Med* 1996; 38:619–24.
77. Lou J, Zhou C. The prevention of silicosis and prediction of its future prevalence in China. *Am J Pub Health* 1989: 79:1613–6.
78. Wagner G. Asbestosis and silicosis. *Lancet* 1997; 349:1311–5.
79. Collegium Ramazzini. Call for an international ban on asbestos. *Am J Ind Med* 1999; 36:2279.
80. Kogan FM. Asbestos-related diseases in Russia. In: *Occupational lung disease.* Eds. Banks DE and Parker JE. London: Chapman & Hall 1998.
81. Koskinen K. Zitting A. Tossavainen A. Rinne JP. Roto P. Kivekas J. Reijula K. Huuskonen MS. Radiographic abnormalities among Finnish construction, shipyard and asbestos industry workers. *Scand J Work, Environ Health* 1998; 24:109–17.
82. Agranti E. Occupational lung diseases in Brazil. In: *Occupational Lung Disease, An International Perspective.* Eds. Banks DE and Parker JE. London: Chapman & Hall 1998.
83. Work-related lung disease surveillance report (1996). U.S. Department of Health and Human Services. October 1996. Cincinnati, OH, DHHS (NIOSH) Publication No.96–134.
84. Mukherjee AK, Rajmonhan HR, Davd SK, Rajan BK, Kakde Y, Rao P. An environmental survey in the chrysotile asbestos milling production. *Am J Ind Med* 1992; 22:543–51.
85. Johanning E, Goldberg M, Kim R. Asbestos hazard evaluation in South Korean textile production. *In J Health Serv* 1994; 24:131–44.
86. Lee HS, Phoon WH, Wang SY, Tan KP. Occupational respiratory diseases in Singapore. *Singapore Med J* 1996; 37:160–4.
87. Work-related lung disease surveillance report. U.S. Department of Health and Human Services. October 1999. Cincinnati, OH, DHHS (NIOSH) Publication No.99.
88. Peto J, Decarli A, La Vecchia C, Levi F, Negri E. The European mesothelioma epidemic. *Brit J Cancer* 1999; 79:566–672.
89. Bang KM. Althouse RB. Kim JH. Game SR. Recent trends of age-specific pneumoconiosis mortality rates in the United States, 1985–1996: coal workers' pneumoconiosis, asbestosis, and silicosis. *Int J Occup Environ Health* 1999; 5:251–5.
90. McDonald AD and McDonald JC. Epidemiology of malignant mesothelioma. In: *Asbestos Related Malignancy.* Eds. Antman K, and Aisner J. Orlando, FL: Grune & Stratton 1987, 31.
91. Begin R and Sabestian P. Alveolar dust clearance capacity as determinant of individual susceptibility to asbestosis: experimental observations. *An Occup Hyg* 1989; 33:279–82.
92. Rom WN, Travis WD, Brody AR. Cellular and molecular basis of the asbestos-related diseases. *Am Rev Respir Dis* 1991; 143:408–22.
93. Markowitz SB, Morabia A, Lilis R, Miller A, Nicholson WJ, Levin S. Clinical predictors of mortality from asbestos in the North American insulator cohort 1981 to 1991. *Am J Respir Crit Care Med* 1997; 156:101–8.
94. Doll R and Peto J. Asbestos: Effects on health of exposure to asbestos. Health and Safety Commission, London, Her Majesty's Stationery Office 1985.
95. Hammond EC, Sellikoff IJ, Seidman H, et al. Asbestos exposure, cigarette smoking and death rates. N Y Acad Sci 1979; 330:473–7.
96. McDonald JC, Liddell FDK, Dufesne A, and McDonald AD. The 1891–1920 birth cohort of Quebec chysotile miners and millers: mortality 1970–88. *Br J Ind Med* 1993; 50:1073–9.

97. Weiss W. Asbestosis: a marker for the increased risk of lung cancer among workers exposed to asbestos. *Chest* 1999; 115:536–49.
98. Banks DE, Wang ML. Parker JE. Asbestos exposure, asbestosis, and lung cancer. *Chest* 1999; 115:320–2.
99. Case BW, Dufresne A. Asbestos, asbestosis, and lung cancer: observations in Quebec chrysotile workers. *Environ Health Perspect* 1997: 105(suppl 5):1113–9.
100. Finkelstein MM. Radiographic asbestosis is not a prerequisite for asbestos-associated lung cancer in Ontario asbestos-cement workers. *Am J Ind Med* 1997; 32:341–8.
101. Egilman D, Reinert A. Lung cancer and asbestos exposure: asbestosis is not necessary. *Am J Ind Med* 1996; 30:398–406.
102. Jones RN, Hughes JM, Weill H. Asbestos exposure, asbestosis, and asbestos-attributable lung cancer. *Thorax* 1996; 51(suppl 2):S9–15.
103. Wilkinson P, Hansell DM, Janssens J, Rubens M, Rudd RM, Taylor AN, McDonald C. Is lung cancer associated with asbestos exposure when there are no small opacities on the chest radiograph? *Lancet* 1995; 345:1074–8.
104. Hughes JM, Weill H. Asbestosis as a precursor of asbestos related lung cancer: results of a prospective mortality study. *Br J Ind Me* 1991; 48:229–33.
105. Browne K. Is asbestos or asbestosis the cause of the increased risk of lung cancer in asbestos workers? *Br J Ind Med* 1989; 43:145–9.
106. Wagner JC. Ed. Biological effects of mineral fibres. Lyons, France. WHO, IARC No 30, 1980.
107. Dawson A, Gibbs AR, Pooley FD. Malignant mesothelioma in women. *Thorax* 1993; 48:269–74.
108. Begin R. Asbestos-related diseases. In: Occupational Lung Disorders. *Eur Respir J* 1999; monograph 11:158–77.
109. Van Sprungel M. Pneumoconiosis: the situation in developing countries. *Exp Lung Research* 1990; 16:5–13.
110. Gu XQ. The role of early detection in the prevention of occupational disease -a review of work in the People's Republic of China. *Scand J Work Environ Health* 1985; (suppl 4):7–9.
111. Yun IG. Recent trends of pneumoconiosis prevalence in Korean coal mines. Proceedings of the 10th Asian Conference on Occupational health, September 1982, Singapore.
112. Yang MD, Wang JD, Wang YL, et al. Changes in health conditions in the Huianan coal mine in the past three decades. *Scand J Work Environ Health* 1985; 11(suppl 4):64–7.
113. Ranasingha KW, Uragoda CG. Graphite pneumoconiosis. *Br J Ind Med* 1972; 29:178–83.
114. Ng TP, Lee HS, Low YM, Phoon WH, Ng YL. Pulmonary effects of polyvinyl chloride dust exposure on compounding workers. *Scand J Work Environ Health* 1991; 17:53–9.
115. Pepys J. Hypersensitivity diseases of the lungs due to fungi and organic dusts. *Monograph Allergy* 1969; 4:1–147.
116. Rylander R. Lung diseases caused by organic dusts in the farm environment. *Am J Ind Med* 1986; 10:221–4.
117. Uragoda CG. Symptoms among chili grinders. *Br J Ind Med* 1967; 24:162–4.
118. Uragoda CG. Asthma and other symptoms in cinnamon workers. *Br J Ind Med* 1984; 41:224–7.
119. Uragoda CG. A compararive study of chilli grinders and and paprika splitters. *J Soc Occup Med* 1983; 33:145–7.
120. Uragoda CG. A clinical and radiological study of coir workers. *Br J Ind Med* 1975; 32:66–71.
121. Uragoda CG. An investigation into the health of kapok workers. *Br J Ind Med* 1977; 342:181–5.
122. Uragoda CG. Respiratory diseases in tea workers in Sri Lanka. *Thorax* 1980; 35:144–7.
123. Lim HH, Domala Z, Joginder S, Lee SH, Lim CS, Abu Bakar CM. Rice miller's syndrome: a preliminary report. *Br J Ind Med* 1984; 41:445–9.
124. American Thoracic Society. Evaluation of impairment/disability secondary to respiratory disease. *Am Rev Respir Dis* 1982; 126:945–51.
125. American Thoracic Society. Evaluation of impairment/disability secondary to respiratory disorders. *Am Rev Respir Dis* 1986; 133:1205–09.
126. American Thoracic Society. Standardization of spirometry — 1987 update. *Am Rev Respir Dis* 1987; 136:1285–98.
127. American Thoracic Society. Lung function testing: selection of reference values and interpretation strategies. *Am Rev Respir Dis* 1991; 144:1202–18.

128. American Thoracic Society. Single breath carbon monoxide diffusing capacity (transfer factor): recommendations for a standard technique. *Am Rev Respir Dis* 1987; 136: 1299–307.
129. Dinakara P, Blumental WS, Johnston RF, Kauffman LA, and Solnick PB. The effects of anaemia on pulmonary diffusing capacity with derivation of a corrected equation. *Am Rev Respir Dis* 1970; 102:965–9.
130. Morgan WKC, and Zaldivar GL. Blood gas analysis as determinant of occupationally related disability. *J Occup Med* 1990; 135:440–3.
131. Doege TC, Houston TP. Guides to the evaluation of permanent impairment. American Medical Association, 4th edition. Eds. Doege TC, Houston TP. Chicago IL 1993, p153–67.

Part IV Neoplasms

23 Lung Cancer: Epidemiology and Risk Factors

Wah Kit Lam and Mei Lin Liao

Epidemiology

From being an uncommon disease before the 1920s, lung cancer has now emerged as an important health problem. Statistics in 1990 showed that worldwide, lung cancer is the most common cause of cancer deaths followed by gastric cancer, colorectal and liver cancers (1). In the United States, lung cancer has been the leading cause of cancer deaths in men in the past four decades, and in women has replaced breast cancer as the leading cause of cancer deaths in the past 17 years. It currently accounts for 28 percent of all cancer deaths each year, which is more than breast, prostate and colorectal cancers combined deaths. In Europe, particularly in eastern European countries, the United Kingdom, Belgium and the Netherlands, lung cancer is also the leading cause of cancer mortality, accounting for about 21% of all cancer cases in men (2).

In Asia, the mortality rates of lung cancer are still generally lower than those in Western countries. However, there has been a significant increase in the death rate from lung cancer in both sexes in many Asian countries and regions over the past few decades. During the periods 1952 to 1960 and 1983 to 1985, the lung cancer mortality rate per 100,000 population increased from 1.8 to 20 in males and 0.9 to 8.5 in females in Taiwan, 7.3 to 32 in males and 3 to 11.5 in females in Japan, and 21 to 50 in males 11.4 to 28.5 in females in Hong Kong (3). Indeed, lung cancer has been the top cancer killer in both sexes in Hong Kong since the 1960s (4), and in Japan since 1998. In South Korea, the age-adjusted mortality rate per 100,000 population increased in men from 3.7 in 1980 to 17.8 in 1994, and in women from 1.4 to 7.0 in the same period (5). The projected rate for the years 2000–2004 will be 65.4 for men and 15.1 for women, corresponding to 17.7 — and 10.7-fold increases over the 1980 mortality rates in men and women respectively. Lung cancer is currently the third most common cancer in South Korea. In Thailand, there has been an abrupt rise since the 1980s, as the total incidence rate (men and women combined) rose from 3.96 per 100,000 population in 1989 to 14.2 per 100,000 population in 1997, and the rise has been especially notable in the northern region (6).

In mainland China, lung cancer is the third commonest cause of cancer deaths nationwide; it is the top cause of cancer deaths in major cities, and accounted for 27% and 19% of cancer deaths in men and women respectively in 1990 to 1992 (7). The age-standardised incidence rates for lung cancer for selected Asian populations in the period 1988 to 1992 are summarized in Table 1 (8).

Differences between ethnic groups within the same population can be great as exemplified by data from Singapore, US Hawaii and San Francisco. The uniformly high rates in Chinese women as compared to other Asian women,

Table 1. Age — Standardised Incidence Rates (per 100,000 population) of Lung Cancer in Selected Asian Populations, 1988–1992, Compared with Some Western Populations[8]

Population	*Male*	*Female*
China, Qidong	35.0	11.0
China, Shanghai	56.1	18.2
China, Tianjin	55.9	37.0
China, Hong Kong	74.7	30.7
India, Bombay	14.5	3.7
India, Madras	12.6	2.4
Japan, Nagasaki	41.7	12.1
Japan, Osaka	43.5	12.4
Japan, Yamagata	35.9	8.3
Korea, Kangwha	33.8	8.4
Philippines, Manila	58.7	16.8
Singapore, Chinese	62.7	19.6
Singapore, Malay	37.2	9.6
Singapore, Indian	14.3	3.5
Thailand, Chiang Mai	36.0	30.3
Thailand, Khon Kaen	17.0	5.3
Viet Nam, Hanoi	34.9	6.3
US, Hawaii : White	59.6	37.9
US, Hawaii : Hawaiian	72.3	35.0
US, Hawaii : Chinese	37.6	18.9
US, Hawaii : Filipino	40.6	17.7
US, Hawaii : Japanese	34.0	11.1
US, San Francisco : Non-Hisp. White	58.6	40.4
US, San Francisco : Hispanic White	37.2	22.9
US, San Francisco : Black	101.5	44.3
US, San Francisco : Chinese	39.4	24.0
US, San Francisco : Filipino	46.8	15.9
US, San Francisco : Japanese	35.7	15.1
Australia, New South Wales	46.6	14.9
Australia, Victoria	46.0	15.8
UK, England and Wales	62.4	22.8
UK, Scotland	79.8	33.7

whether in the mainland of China, Hong Kong, Singapore or US, is noteworthy. Also, incidence rates between regions within a country can also vary greatly as in China and Thailand, and this may be due to differences in lifestyles and environmental factors. These will be further discussed in the Chapter.

Cell Types

The most widely accepted histologic classification of lung cancer is the World Health Organization classification which has been revised in 1999 in collaboration with the International Association for the Study of Lung Cancer (9). Before 1980, the predominant cell type in lung cancer worldwide was squamous cell carcinoma. Since the 1980s, there has been a gradual increase in the incidences of adenocarcinoma with a corresponding decrease in squamous cell cancer in many countries. In the US, the age-adjusted incidence rates per 100,000 person years for both sexes for squamous cell carcinoma for the three periods of 1973–77, 1978–83 and 1983–87 were 33.2, 31.6 and 29.4, and the respective figures for adenocarcinoma were 26, 29.5 and 31.5 (10).

The same changing pattern is observed in Asia. In Taiwan, a study of over 10,000 cases over the period 1970 to 1993 showed that the incidence of squamous cell carcinoma decreased from 46.4% to 36.2% in men, whereas adenocarcinoma increased from 30% to 36% in men and from 50.7% to 64.8% in women, such that adenocarcinoma now becomes the most common cell type (11). In Singapore, Seow et al (12) showed that the proportion of adenocarcinoma of the lung in Chinese female patients increased significantly from 25.8% in 1968 to 1972 to 51.3% in 1988 to 1992. Choi et al (13) also reported that while squamous cell cancer decreased in Korea over the period 1981 — 1990 from 54.3% to 44.3%, adenocarcinoma showed a gradual increase from 17% to 28.3% over the same period. Similarly, in Hong Kong, over the period 1960 — 1972 and 1983–1990, the proportions of squamous cell cancer decreased from 43.6% to 38.9% in men and from 22.7% to 15.7% in women, whereas that of adenocarcinoma increased from 15.6% to 30.7% in men and from 34.3% to 58.5% in women (14). In Japan, a nationwide autopsy study showed that over the periods 1978–87 and 1988–97, adenocarcinoma increased from 35% to 37% in men ($p < 0.001$) and from 57% to 62% in women ($p < 0.005$) whereas squamous cell carcinoma decreased from 32% to 30% in men and from 16% to 14% in women (15).

This changing histologic pattern is ill-understood, and is probably multifactorial due to an increased use of adenocarcinoma specific-stains for diagnosis, the changing composition and filtering of cigarettes resulting in an increase of volatile nitrosoamines depositing in the more distal bronchioles as against the older make of cigarette emitting particulates containing polycyclic aromatic hydrocarbons depositing on proximal bronchi associated with squamous cell cancers, and possibly other changes in environmental factors (16,17).

It is also a common observation that adenocarcinoma is the predominant cell types in young patients, particularly females (13,18,19,20). Comparing younger (40 years or younger) with older patients, Sekine et al (18) found that in Japan, adenocarcinoma was found in 71% and 92% of the younger male and female patients versus 42% and 73% of the older male and female patients respectively. Similarly, Kuo et al (19), and Lam et al (20) showed that there were significantly more female patients and adenocarcinoma in the forty-year or younger age group of lung cancer patients in Taiwan and Hong Kong respectively.

Lifestyle and Environmental Risk Factors

Active tobacco smoking

The evidence linking tobacco smoking and lung cancer is beyond dispute. Tobacco smoke is a complex mixture of over 4000 different chemical of which over 40 compounds have been evaluated by the International Agency for Research on Cancer in animals as carcinogens (Table 2). Polycyclic aromatic hydrocarbons in tobacco smoke have been shown to induce tumours of the lung in animals exposed by inhalation (21), intratracheal instillation (22) or implantation in the lung (23). It should be noted that some locally

Table 2. Carcinogenic Compounds in Tobacco and Tobacco Smoke

Class	*Examples*
Polycyclic Aromatic Hydrocarbons	Benzo(a)pyrene Benz(a)anthracene Benzo(b)fluoranthene Benzo(j)fluoranthene Benzo(k)fluoranthene Dibenz(a,i)pyrene Dibenzo(a,l)pyrene Dibenz(a,h)anthracene 5-Methylchrysene Indeno(1,2,3 c,d)pyrene
Aza-arenes	Dibenz(a,h)acridine Dibenz(a,j)acridine N-Nitrosamines N-Nitrosodimethylamine N-Nitrosopyrrolidine N-Nitrosodiethanolamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
Aromatic amines	2-naphthylamine 4-Aminobiophenyl
Aldehydes	Formaldehyde Acetaldehyde
Miscellaneous organic compounds	Benzene 1,1-Dimethylhydrazine Ethylcarbamate Vinyl chloride
Inorganic compounds	Arsenic Nickel Chromium Cadmium Lead Polonium 210

manufactured cigarettes in Asia contain carcinogens in higher concentrations than light and blended western cigarettes. A study analysing the concentration of volatile nitrosoamines and tobacco-specific nitrosamines in mainstream smoke of nine leading brands of local Thai cigarettes (representing 85% of the market share) showed that the observed ranges (ng/cigarette) were exceptionally high for nitrosodimethylamine (8.5–31.9), nitrosopyrrolidine (8.8–49.6), nitrosodi-n-butylamine (4.2–18.9), nitrosonornicotine (28–730) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butamone (16–370) (24). Interestingly, these nitrosamines, especially the tobacco-specific ones, are also associated with primary liver cancer in Thai people who smoke cigarettes and also carry liver fluke infestation. Squamous cell carcinoma is the predominant cell type induced by benzo(a)pyrene, and mutational changes in the *p53* gene similar to those observed in smokers' lung cancer also occur (25). 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a tobacco-specific nitrosamine, is an organ-specific lung carcinogen, especially for adenocarcinoma (26). It is thought that these carcinogens cause biological damage including damage to DNA through free radicals and nonradical oxidants (27), resulting in multiple genetic aberrations and malignant transformation

of the normal lung epithelial cell. The common genes involve in lung cancer include the *ras* and *erb*-B2 oncogenes and the *p53* tumor suppressor gene.

The current epidemic of lung cancer, first in men and then in women, paralleled the epidemic of cigarette smoking with a lag time of about twenty to thirty years. The first epidemiologic evidence appeared in 1950 when Wynder and Graham (28) in the US and Doll and Hill in the UK (29) reported the first large scale studies linking smoking and lung cancer. In 1964, the US Surgeon General concluded that tobacco smoking was the major contributing factor in the development of lung cancer (30).

Major prospective studies have consistently demonstrated that the relative risk of lung cancer in smokers is closely related to the numbers of cigarettes smoked daily and the duration of smoking in a dose-response manner, such that the risk ratios in male smokers who smoke < 19 cigarettes, 20–39 cigarettes and > 40 cigarettes a day are 4.6–9.9, 14.7–17.4 and 18.8–23.9 respectively (31–33). On the other hand, there is a progressive reduction in the risk after stopping smoking — the risk ratio would decrease from 12–19 in the initial one to four years after quitting to about 2 after fifteen years.

There is evidence that women are at higher risk of lung cancer than males, given equal smoking. Tang et al (34) carried out a molecular epidemiologic case-control study, and found that the glutathione S-transferase M1 (GSTM1) null genotype, a potential marker of susceptibility, was significantly associated with lung cancer (odd ratio = 2.04, 95% confidence interval = 1.13–3.68), and that the effect of this GSTM1 null genotype is greatest in female smokers. This finding is consistent with the observation that women are at higher risk of lung cancer due to smoking than men.

Lung cancer is now the leading cause of cancer death worldwide including many Asian countries and regions, and most of the cases are related to active cigarette smoking, particularly in men (please refer to Tables 3 and 4, and Chapter 20). Overall, about 80% of all lung cancer cases are due to cigarette smoking. In mainland China, tobacco now causes 13% of deaths in men (35). In Taiwan, tobacco (active and passive smoking) attributed to 19% of the total number of deaths in 1990 (36). More men died from smoking-related causes than from all cancer deaths combined, and 91% of lung cancer were due to smoking. In Japan, 84% of the younger (40 years or less) and 95% of the older male patients are chronic smokers (18). In India, smoking was the risk factor in 81.6% of the male patients (37), and in Hong Kong, 91% of the male and 53.6% of the female patients (and 39% of the adenocarcinoma female patients) were smokers (4). The high incidence of lung cancer not related to active smoking in women in Hong Kong and other Chinese populations will be further discussed in later sections in the Chapter.

With the decreasing smoking incidence in the west but increasing smoking incidence in both sexes in Asia, particularly in the young, Asian countries will be the main victim of the tobacco epidemic in the new millennium (please refer to Chapter 20).

Passive tobacco smoking (Environmental tobacco smoke, ETS)

Cigarette smoke that the smoker inhales is called mainstream smoke, and that released from the burning ends of cigarettes is sidestream smoke. Environmental tobacco smoke (ETS) consists of sidestream smoke and the exhaled smoke of the smoker. The two differ in composition, and some carcinogens such as benzo(a)pyrene, nitrosamine and ^{210}Po are present in higher concentration in sidestream smoke (38). Also, it is possible that because sidestream smoke with its appreciable amount of gaseous components would penetrate into the peripheral parts of the lung better, passive smoking might cause an increase in peripheral lung cancers, particularly adenocarcinoma, which is common among non-smokers (39).

The first major epidemiologic study on passive smoking or ETS and lung cancer was reported in 1981 from Japan (40) which found that age-adjusted lung cancer mortality rates were lowest for wives of nonsmokers, intermediate for wives of light or ex-smokers and highest for wives of heavy smokers. Since then, numerous studies have confirm this association. A recent weighted analysis of 37 published epidemiologic studies

showed an increased risk of 24% (95% confidence interval (CI) 13–36%) among non-smoking wives of smoking husbands compared with controls (41). Another meta-analysis of 35 case-control (17 hospital-based and 18 population-based) and five cohort studies showed that the relative risk of lung cancer among non-smoking women ever exposed to ETS from their husbands was 1.20 (95% CI: 1.13–1.92), and the relative risk for ever exposed to ETS at work was 1.16 (95%CI: 1.05–1.28) (42). It is notable that of these 40 studies, 17 were from Asia (7 from mainland China, 5 from Japan, 4 from Hong Kong, and 1 from Taiwan). There have been three additional studies recently from Asia. Rapiti from India reported a case-control study of ETS exposure in childhood and adulthood at home and at the workplace (43). Exposure to ETS during childhood was strongly associated with lung cancer (odd ratio (OR) = 3.0, 95% CI = 1.9–8.2). An increased risk was also found with exposure to cigarette smoking of a smoking spouse (OR = 5.1, 95% CI = 1.5–17). Similarly, Lee et al investigated the effects of cumulative ETS during childhood and adult life on lung cancer risk among non-smoking women in Taiwan (44). The risks of having lung cancer in women exposed to the highest levels of ETS in childhood (> 20 smoker-years) and in adult life (> 40 smoker-years) were 1.8-fold and 2.2-fold higher than those never exposed, and it was estimated that these two exposures accounted for about 37% of lung cancers in the non-smoking female population. Jee et al also reported the effects of spousal smoking in over 160,000 Korean women (45). The risk ratio (RR) of lung cancer in non-smoking wives was 1.9 (95% CI: 1.0–3.5) in current smoking husbands, and the RR rose to 3.1 in wives exposed to husbands' smoke for over 30 years. Thus a dose-response relationship appears to exist. Because of the low prevalence of smoking in Asian women, any misclassification bias should be small, and the Asian evidence for a casual relationship between ETS and lung cancer is particularly strong (46).

ETS is now classified as a class A carcinogen, and the US National Research Council concluded that about 20% of lung cancer occurring in non-smokers may be attributable to ETS (47,48).

Other indoor pollutions

Cooking oil vapours

The high incidence of lung cancer in Chinese women, whether they are in mainland China, Hong Kong, Taiwan, Singapore or the US, is noteworthy (see Table 1). The majority of them (about 90% in Taiwan, 75% in Shanghai and 60% in Shenyang and Hong Kong) cannot be attributed to active smoking. This is different from the high incidence of lung cancer in white women in the US and the UK which is related to cigarette smoking. A number of environmental factors other than ETS including cooking oil vapours, indoor coal burning, and diet, and many genetic factors have been studied (49–55). These will be discussed in this and the sections following.

Volatile substances generated from some vegetable oils during Chinese wok cooking at high temperatures have been suspected as likely risk factors for lung cancer in non-smoking Chinese housewives. Genotoxicity of fumes from heated cooking oils have been reported in Shanghai (rapeseed oil) (56) and Taiwan (lard and soybean oil) (57). In addition, it was shown that linolinic acid in the rapeseed oil is probably the cause of mutagenicity at high temperature when it is oxidized to produced pyrolysates (58). Extracts of fumes from safflower oil, vegetable oil, and corn oil were found to contain benzo(a)pyrene, benzo(a)anthracene and dibenz(a,h)anthracene (59).

Large epidemiologic studies from Shanghai (60), Gansu (61), Shenyang (62) and Taiwan (63) have all confirmed that exposure to cooking oil fumes at high temperature wok cooking with inadequate fumes extractors is a significant risk factor for lung cancer in non-smoking Chinese housewives, with risk ratios of 1.4, 1.67, 3.79 and 3.2–12.2 respectively in the four studies.

Indoor coal burning

It is known that carcinogens such as polycyclic aromatic hydrocarbons are present in high concentrations after coal combustion. Burning of smoky coal for heating and cooking in unvented homes in China has been implicated as a risk factor particularly for nonsmoking housewives who stay indoor for most of the time. A pioneer study in Xuanwei rural county (where lung cancer is

unusually common in women and where severe indoor air pollution due to burning smoky coal is known to exist) showed a good correlation between indoor air benzo(a)pyrene concentration (as an index of indoor coal burning pollution) and high lung cancer mortality rates ($r = 0.778$, $P < 0.01$), particularly from adenocarcinoma (64). Subsequent studies from Guangzhou in southern China (coal burning for cooking) and Harbin and Shenyang in northeast China (coal burning for cooking and heating) all confirmed that household coal burning is a significant risk factor with a risk ratio of 1.5 to 2.2 (55), increasing to 18.7 when exposure was more than 30 years. The frequent use of coal-burning stoves in Shenyang was estimated to contribute to 10 to 20% of the lung cancer cases there (65).

The molecular mechanism of indoor coal smoke-related adenocarcinoma has recently been studied in Xuanwei county in China (66–67). *p53* protein accumulation was detected by immunohistochemistry in 73% (22/30) of lung adenocarcinoma and in 54% (13/24) of tumor cells in sputum from female patients exposed to coal emissions, significantly higher than the control cases. These findings suggest that *p53* abnormalities is important in the pathogenesis of Xuanwei lung cancer. The *p53* mutation spectra in these cancers are being investigated by the same group to further characterize the alterations in this protein. Similarly, *GST* M1 null genotype has been found to be a risk factor for lung cancer in subjects exposed to indoor coal burning in this county in China (67).

With progressive affluence in China, coal burning at home is replaced by electricity, coal gas and others. Indoor coal burning as a risk factor for lung cancer is expected to decrease in importance in the future.

Indoor radon

Uranium in the earth's crust gives rise to decay chain products through radium^{226} to the gas radon^{222} which in turn gives rise to three isotopes termed "radon daughters" (poloniums). Radon and the radon daughters are important α-particles emitters, and are found in soil, rock and building materials, and are dispersed in the atmosphere to attach to water vapor and dust. Thus, indoor radon comes from the soil, building materials and also groundwater from drilled wells.

Inhaling radon and radon daughters has been shown to cause lung cancer among underground miners and in experimental animals. Whether they pose a hazard to the general population in houses is less certain, although the risk can be estimated using risk assessment based on data from a study of miners (68). The risk is compounded by cigarette smoking. In the US, it has been estimated, basing on extrapolations from studies of miners, that indoor radon may cause between 6,000 to 36,000 lung cancer deaths per year (68). The US Environmental Protection Agency has recommended that the annual average concentration for houses should not exceed 4pCi/l (148 Bq/m^3) (69). A number of case-control studies have been performed, with conflicting results. A recent meta-analysis of eight epidemiologic studies from 5 countries (each enrolling a minimum of 200 case subjects and measuring houses for radon concentrations) gave an estimated relative risk of 1.14 (95% confidence interval = 1.0–1.3) at 150 Bq/m^3 (70). This meta-analysis also supported the use of the linear non-threshold model-based extrapolations from miners for risk assessment in households.

Asian Pacific countries and regions have become concerned about the health and environmental issues regarding indoor radon, and a number of surveys have been conducted (38,71) (Table 3). Case-control studies have also been performed, and the results have been variable. In China, The High Background Radiation Research Group (72) and Blot et al (73) did not find a correlation between radiation level and lung cancer, but a third Chinese study in Geijiu area in Yunnan Province demonstrated a positive correlation between lung cancer mortality and indoor radon levels above 100 Bq/m^3 in a dose-response fashion (74). In three case-control studies in women in the three cities of Stockholm (Sweden), New Jersey (US) and Shenyang (China), no excess lung cancer was found (75). A study in three towns of Rajasthan in India estimated that the lifetime risk of lung cancer due to indoor radon exposure for the total population of study area was 0.67%, and the mean relative loss of life expectancy were between 0.12% to 0.20% in the three towns respectively (76). A recent case-control study in Saraphi district of northern Thailand confirmed the enhancing effect of high indoor radon

Table 3. Asian Pacific Surveys of Indoor Radon (Based on Reference 71, except **)

Country/Region	*Average (unless marked *) activity concentration of indoor ^{222} Rn (Bq/m^3)*	*Other findings*
Australia	10.9 some > 100	
China . Beijing	25.9 (detached houses) 15.5 (high-rise buildings)	
. Yunnan	*15–1146 (only 7/143 buildings < 148)	Correlation between lung cancer and ^{222}Rn level (+)ve
. Hong Kong	45	About 13% of lung cancer attributable to radon exposure (1973–86)
India	23	
Japan	Hiroshima 56.8 } Nagasaki 28.5 } **	A soil-based plaster for filling walls in wooden house is a main source of indoor thoron
Korea	59	
Philippines	16.4	
Thailand . northern	50 (hot season) 154 (cool season)	Life time risk of lung cancer 3.2–3.5%
. countryside	1–1974	Soil radium-rich + modern houses will floors in contact with or even underground
Vietnam	27	

** Yonehara H, Aoyama T, Radford EP, Kato H, Sakanoue M. Radon concentration in residential housing in Hiroshima and Nagasaki. Health Phys 1995; 68:683–688.

concentration on smoking in causing lung cancer (77).

Awareness of the health issues regarding indoor radon has only recently begun to grow in Asian countries. More surveys and studies are needed to look into the impact of the problem.

Others

Burning of incense at home by housewives is commonplace in Chinese families especially in older generations and in rural areas. Chinese incense smoke contains carcinogens, including 3,4-benzopyrene (78). Studies in Hong Kong (79,80), however, did not show any association between lung cancer and incense smoke in non-smoking housewives. In fact, both Hong Kong and Taiwan studies have found that incense burning was associated with a reduced risk for lung cancer (80,81). This apparent paradox is thought to be due to the confounding effect of dietary factor (80). Since incense burning among Chinese is done for the purpose of worshipping gods or ancestors, it is representative of a traditional lifestyle that may be correlated with other traditional behaviours such as a more vegetarian diet and less meat and chili consumption, which is a protective factor for lung cancer (*vide infra*).

Other indoor pollutions such as exposure to mosquito coil smoke and kerosene stove cooking have also been studied in Chinese (53,82,83), and the results have all been negative.

A very interesting study from Thailand implicated chronic benign respiratory disease, possibly caused by the infection of a fungus

Microsporum canis which is commonly found inside houses, as a compounding factor to tobacco (khiyo) smoking in lung cancer in northern Thai women in Sarapee (84). This study was performed because lung cancer incidence among northern Thai women is one of the highest in Asia, but the incidence rate differs significantly by geographical regions. Two close areas with similar cultures were studied: the Sarapee area (lung cancer crude incidence rate 40.9), and the Chom Tong area (rate 8.5). Lifestyle factors and diet were studied as well as chemical examination of drinking water and mutagenicity test of urine samples. The most distinct finding was the high incidence of chronic benign respiratory diseases among women in Sarapee, who had a raised serum antigen concentration of a fungus *Microsporum canis* commonly found in air inside the houses in Sarapee.

Outdoor air pollution

Pollution of outdoor air by vehicles, industry and power plants has long been suspected of causing lung cancer. Known carcinogens are detected in ambient air particularly urban air, including gaseous and particulate organic compounds (e.g. benzo(a)pyrene, benzene, dimethynitrosamine), inorganic particles, (e.g. arsenic, asbestos, cadmium, chromium, nickel) and radionuclides (e.g. radium, radon, thoron). A number of case-control and cohort studies have examined the relationship between air pollution, particularly diesel exhaust exposure and lung cancer (85). While some studies showed no correlation, most showed a risk ratio ranging from 1.2 to 1.8. Cigarette smoking is a compounder not adjusted in all studies. A recent study reported the relationship between long-term ambient concentration of inhalable particles < 10 μm in diameter (PM10) and other air pollutants and lung cancer in a cohort of over 6,000 nonsmoking California Seventh-day Adventists (86). The results showed that ozone (> 100 ppb), PM10 (> 100 $\mu g/m^3$) and sulfur dioxide exposure in men and sulfur dioxide exposure in women were associated with lung cancer mortality. The World Health Organization International Agency for Research on Cancer has categorized diesel engine exhaust as a *probable carcinogen* (87).

There are only a few studies on outdoor air pollution and lung cancer in Asia. A large five-year cohort study in 3 residential areas of Shanghai with different levels of air pollution did not show any effect of ambient air pollution on the risk of lung cancer among nonsmokers (88,89). On the other hand, women living within 200 m of factories in Shenyang, China, had a significantly higher risk of lung cancer after adjusting for smoking and other risk factors (90). A study from Japan examined the relationship between regional lung cancer mortality and air pollution and/or temperature (91), and provided the first evidence of a possible synergistic interaction between air pollution (mainly nitrogen dioxide) and high temperature on lung cancer mortality in the southern geographical block of Japan. Another recent case-control study among women from Taiwan showed that women living in municipalities with high levels of petrochemical industrial pollution had a significantly higher risk of having lung cancer than women living in municipalities with low levels of petrochemical pollution (92). The linear trend was also statistically significant ($P < 0.05$).

Non-occupational exposure to talc and amosite/crocidolite in women in urban areas of Japan has been studied by Yamada et al (93) who analysed the correlation between asbestos lung burden (by phase-contrast microscopy) and lung cancer in women in rural areas. The results revealed a significantly higher level of ferruginous and uncoated fibres in urban lung cancer cases than urban non-lung cancer cases. These fibres are mainly amosite/crocidolite with some fibrous talc. Thus fibrous talc in urban environments may be another carcinogenic or cocarcinogenic factor for female lung cancer. With industrialization and modernization of Asia, the problem of outdoor air pollution and lung cancer should be closely monitored.

The carcinogenic mechanism of outdoor air pollution have been studied. Exposure of pulmonary epithelial cells to nontoxic concentrations of airborne particulate matter in vitro resulted in increase in *c-jun* kinase activity and initiation of a cell signalling cascade which was related causally to aberrant cell proliferation and carcinogenesis (94). Tsurudome et al (95) have also demonstrated that the carcinogenesis of diesel

exhaust particules was related to generation of reactive oxygen species.

Diet

Epidemiologic studies from the West have suggested that a higher intake of vitamin A or β-carotene and vegetables would be protective against the risk of lung cancer probably because of their antioxidant effect. On the other hand, dietary fat, particularly saturated fat consumption, is associated with an increased risk of lung cancer.

Case-control studies in Chinese women in Shanghai (96) and Harbin (97) in the mainland of China, Hong Kong (98) and Taiwan (52) have all shown similar findings, namely a protective effect associated with consumption of fruits, leafy green vegetables and food sources rich in vitamin A. The protective effect is especially seen against lung cancer of the adenocarcinoma type (98). On the other hand, cured meats (Chinese sausage, pressed duck and cured pork, all specialties of Cantonese cuisine), deep fried cooking, chili and alcohol increased the risk of lung cancer. In the Taiwan study (52), only 9.4% of the female patients were smokers, and the three factors of exposure to cooking fumes in a kitchen without fume extractor, history of pulmonary tuberculosis and low consumption of fresh vegetables explained 78% of the summary attributable risks for non-smoking women in a multivariate logistic regression model.

In Chiang Mai Province of northern Thailand, the diets among elderly females were compared at two suburban districts which are distinguished by very high and low incidence rates of lung cancer (99). In the low-risk district, in contrast to the high-risk district, the dietary habits were characterized by higher consumption of fruits, green and yellow vegetables, potatoes and confectionery. Similarly, a study in Kerala, south India showed that green vegetables and bananas had a protective effect against lung cancer (100), with pumpkins and onions being the most consistently significant protective factors. On the other hand, the same study found that animal protein foods and dairy products had a predisposing effect on lung cancer.

In Japan, preserved foods formed a large part of the diet before refrigerators were widely used, and they contain N-nitroso compounds or their precursors and show mutgenicity. On the other hand, Japanese diet contains a lot of soyfoods rich in isoflavones which may inhibit carcinogenesis (101). A case-control study was carried out in Okinawa, Japan, to examine the association of dietary intake of preserved foods and soyfoods with lung cancer risk (102). Miso (preserved, fermented soybean paste) soup and pickles (excluding salted fish) was associated with an increased risk, whereas frequent intake of soybeans and tofu (soybean curd) gave a decreased risk (tofu being especially protective against squamous cell cancer). These findings confirmed the deleterious effects of preserved foods and protective effects of soyfoods rich in isoflavones.

A recent study of the relationship between isothiocyanates and lung cancer in a cohort of Chinese men in Shanghai is of special interest (103). Experimental animal studies have shown that isothiocyanates inhibit lung carcinogenesis, and Chinese diet is rich in isothiocyanate-containing cruciferous vegetables (including broccoli, cabbage and bok choi). London et al (103) investigated whether chemopreventive effects of isothiocyanates might be enhanced when glutathione S-transferases (GST) (which increase their elimination) are lacking. They examined the relation between total isothiocyanate concentration in urine, collected before diagnosis, and the subsequent risk of lung cancer among incident cases of lung cancer and matched controls in a cohort of over 18,000 men in Shanghai, China, followed from 1986 to 1997. Homozygous deletion of the GSTMI and GSTT1 genes were determined. At follow up, they found that isothiocyanates reduced lung cancer risk in this cohort of Chinese men, and the risk reduction was strongest among persons genetically deficient in GST, enzymes that eliminate these chemopreventive compounds. Similarly, a study from Singapore showed that in a Chinese female population, the risk of lung cancer is inversely related to dietary isothiocyanates mainly in non-smokers who had homozygous deletion of GSTMI and/or GSTT1 (104).

Occupation

Occupational exposure to many agents is known to cause lung cancers, particularly in smokers. The importance of identifying these industrial carcinogens lies in the fact that the cancer is potentially preventable by appropriate control measures. Also, studies of industrial exposures in relation to high incidences of occupation related cancers have for a long time been an important means for identifying carcinogens in humans.

In the United States, lung cancer is ranked second only to bladder cancer in the proportion of cancers thought to be due to occupational exposures to carcinogens (105). About 9,000 to 10,000 men and 900 to 1,900 women develop lung cancer every year in the U.S. due to past exposure to occupational carcinogens, and more than half of these are due to asbestos, which is classified as Group 1 carcinogen by the International Agency for Research on Cancer (IARC). Worldwide, occupational exposures to various carcinogens have been estimated to account for 5% to 20% of lung cancers in men and women of different cultures and countries (106).

Asbestos and silica

In Asia, details of statistics and studies on occupational lung cancer are less available. Most studies are on asbestos and silica exposure. A historical cohort mortality study on ship repair workers in a single U.S. Navy shipyard in Japan was performed (107), and the follow-up period was from 1947 till 1996. The laggers, who had handled asbestos materials directly, had a significantly raised standardized mortality rate (SMR) of 2.75 for lung cancer, whereas the boiler repairers who had less direct exposure showed no elevation of the SMR of lung cancer overall. A retrospective cohort study (1972–81) of occupational lung cancer in asbestos (chrysotile) factories in China recorded 67 lung cancers among 494 deaths (108). Compared with controls, the risk ratio of lung cancer in these factory workers was significantly raised to 5.32 with a dose-response relationship and a synergistic effect with cigarette smoking. Another study in a Chinese asbestos plant using only chrysotile and employing mainly female workers showed an excess lung cancer mortality, including many cases among non-smoking women compared to local city data (109). In Hong Kong, asbestosis-related diseases are uncommon (110).

Although crystalline silica was recently classified as a human carcinogen by the IARC, controversy still exists over this issue partly because of the difficulty of resolving the confounding factors of smoking and exposure to mixed dust and background irradiation in workers. In Asia, a number of studies examining the association between occupational silica exposure and lung cancer have been performed, with conflicting results. Studies suggesting a positive association included those from Japan (111,112) and China (113,114), which showed an overall excess risk of about two-fold and was dose-related. Honma et al (111) also found that squamous cell carcinoma and small cell carcinoma were especially common in silicotic lungs with massive fibrosis. On the other hand, studies from Shanghai (115) and Hong Kong (116) concluded that smoking was the main factor for lung cancer in these workers, and silica did not contribute independently.

An interesting type of silica exposure among sugar cane farmers in India has been described (117). Sugar cane farmers and sugar mill workers were exposed to fibres of biogenic amorphous silica (BAS) formed from silica absorbed from the soil and deposited in the leaves of the sugar cane crop or crystalline silica formed as a result of conversion of BAS to cristobalite at high temperatures. These farmers had an increased risk of lung cancer (odds ratio = 1.92).

Despite the controversy, silica as an occupational carcinogen should be taken seriously (and silicosis is such an important factor for respiratory impairment and tuberculosis). In Asia, database should be better established, and dust control and exposure prevention measures should be strictly implemented.

A recent Beijing study examined the carcinogenic effect of silica dust at the DNA molecular level (118). *p53* and *K-ras* gene mutations in lung cancer in workers with silicosis were studied. The mutation frequency of *p53* gene were high, but the mutation distributions in exons and among the histological types of lung cancer in silica-exposed workers differed from those of non-silica exposed lung cancer.

In China, collaborative research is now abundant, and cohorts of occupationally-exposed workers with an extensive biologic specimen repository has been established to simultaneously study the etiology and early detection of lung cancer (119). Studies of occupational lung diseases have come of age in many countries in Asia.

Others

In India, a comprehensive study of occupational cancer was carried out in 1991 to 1992 in Trivandrum, south India, in collaboration with the National Cancer Registry Programme (120,121). It appeared that there was an increased risk of lung cancer among textile workers, welders and woodworkers, although this increase in risk was not statistically significant. Another study from Bombay also found an increased risk of lung cancer in textile and wood workers (122).

A large cohort study of over 74,000 benzene-exposed workers (in coating applications, rubber, chemical and shoe production) in 12 cities in China showed that these workers had a significant dose-related increase in death from lung cancer and hematopoietic malignancies (123).

Occupational exposure to other known carcinogens such as arsenic, nickel and chromium will not be discussed here as the Asian scenario is unlikely to be different from the west.

Infections and Host-related Factors

Tuberculosis

In Shanghai, a retrospective cohort study (124) showed a significant increase in the incidence of lung cancer among tuberculosis patients which was independent of smoking. Likewise, a case-control study (125) showed a significant 50% increase in the risk of lung cancer (adjusted for smoking) among patients with a history of tuberculosis. The contribution of tuberculosis to total risk for lung cancer may therefore be significant.

Scar cancer has long been recognised, and adenocarcinoma is reported to the predominant cell type. The causal relationship between tuberculosis scar and lung cancer was therefore studied in Hong Kong (126). Forty-nine surgical or autopsy specimens of lung cancer were studied, of which 22 fitted the description of a scar cancer (i.e. a tumour with pleural puckering and central pigmentation). The scarred appearance of the tumours was found to be the result of localised pulmonary atelectasis owing to small airway obstruction by tumour. Tuberculosis was present in 10 specimens, and in only 1 specimen was the tuberculosis lesion anatomically associated with the tumour. This tuberculosis lesion was however found at the periphery of the tumour and was untouched by the tumour though partly surrounded by it. A causal relationship between tuberculosis scar and lung cancer cannot be confirmed by this pathological study.

Human papillomavirus infection

Human papillomavirus (HPV) has been implicated in human neoplasm including uterine cervix, anus, penis, vulva, skin, esophagus, head and neck (127). HPV 16/18 are the commonest types implicated. HPV infection has also been associated with lung carcinoma in Japanese and Scandinavian studies (128–131).

More recently, Lee's group in Taiwan studied HPV 16/18 DNA in lung tumour and normal tissues by nested polymerase chain reaction (nested PCR) and *in situ* hybridization (ISH), and found that 77 of 141 lung tumours (54.6%) had HPV 16/18 DNA compared to 16 of 60 non-cancer controls (26.7%, $p = 0.0005$) (132). The odds ratio of HPV 16/18 infection in non-smoking female lung cancer patients was 10.12 (95% CI, 3.88–26.88), which is significantly higher than an odds ration of 1.98 (95% CI, 0.84–4.76) in non-smoking male lung cancer patients. This result strongly suggests that HPV infection is associated with lung cancer development of non-smoking female lung cancer patients in Taiwan.

Hormonal factors

Oestrogen may be a factor in the development of lung cancer, particularly adenocarcinoma, in women (133,134). To investigate the relationship between female lung cancer and female sex hormonal changes, Liao et al compared data on

menstrual history among female lung adenocarcinoma and squamous cell carcinoma cases with controls (135). Progesterone and estrogen receptor expression was also measured in surgical specimens of adenocarcinoma. It was found that adenocarcinoma cases had shorter menstrual periods than controls, and a positive estrogen and progesterone receptor expression in cancer cells was correlated with later menarche and earlier menopause. Though preliminary, these results suggest that sex hormones as well as levels of estrogen and progesterone receptors may be involved in controlling the growth of lung cells.

Genetic factors

Lung cancer, like other cancers, is now thought to be due to deregulation of normal gene expression. In this section, emphasis is placed on studies to detect genetic changes in lung cancer of non-smoking female patients of Chinese origin. Studies of genetic changes to investigate the carcinogenic mechanisms for tobacco smoke, coal smoke, airborne particulate matter and silicosis have been mentioned in the relevant sections above, and will not be repeated here.

The high incidence of lung cancer, particularly adenocarcinoma, in non-smoking Chinese women, whether in the mainland of China, Hong Kong, Taiwan, Singapore, or US, is noteworthy (see Table 1). This is thought to be due to the interaction between environmental and specific genetic factors (53,54). Both HLA antigens and other genetic changes have been studied.

HLA antigens are known to be associated with human malignant diseases with a high incidence in specific ethnic groups. However, no difference was found in antigen frequencies compared with controls when a group of Chinese female non-smoking patients with adenocarcinoma of the lung were studied for HLA A and B antigens (136).

K-ras oncogene activation by point mutation occurs in about 30% of adenocarcinoma of the lung in Caucasians. However, K-ras gene mutation was not found in female patients with bronchial adenocarcinoma in studies from Taiwan (137) and Hong Kong (138). This is not surprising as it is now known that point mutation in the *K-ras* oncogene occurs as a result of exposure to cigarette smoking, and our female patients are mostly non-smokers.

The *p53* tumour suppressor gene is another commonly involved gene, and a mutation incidence (most commonly in exons 5 to 8) of over 50% has been reported in the west. Studies in Chinese showed contradicting results. Gao et al in Guangzhou reported an overall mutation rate of 67%, with comparable rates between smokers (70%) and non-smokers (65%) (139). Wang et al from Taiwan (140) found a *p53* mutation rate of 18% in their lung cancer patients irrespective of their smoking habits. Interestingly, 82% of the mutations in their series were nonmissense mutations, i.e. deletions and nonsense mutations in contrast to the frequent occurrence of missense mutations in the *p53* gene reported in the literature. In addition, mutation was most common with squamous cell carcinoma (29%). Similarly, a study of Hong Kong female lung cancer patients showed that a high proportion of the mutations observed were deletions (141), suggesting the possible involvement of a distinct mutagenic factor(s) in Chinese female lung cancer patients. Another study from Hong Kong (142) found 16% mutation rate in the region of exon 5 to exon 8, but abnormal protein expression was present in 46% of patients, indicating possibly other genetic aberrations outside the hot spot region of exons 5 to 8 (143). *p53* polymorphisms have also been studied (144,145). The Pro allele of the *p53* codon 72 polymorphism was found to increase the risk of lung cancer (especially adenocarcinoma) among female Chinese patients in Taiwan (145). Similarly, Ge et al (143) from Hong Kong found that the A1 allelic frequency (of the *p53* intron 2 polymorphism) was increased in adenocarcinoma of the lung.

Two other genetic studies in Chinese female patients are also of interest. In one study, the frequency of genetic alterations on chromosome 11 (146) in females was nearly double that for the males (45.5% vs 23.7%). The second study showed that the N-acetyltransferase (NAT2) slow acetylator genotype was associated with an increased risk of lung cancer, especially adenocarcinoma among non-smoking Chinese women in Singapore (147). As NAT2 activity is known to modify the risk of arylamine-induced carcinogenesis, the results of this study suggest that exposure to arylamines in the environment may play a role in development

of lung cancer among non-smokers. More recently, the same group showed that Chinese women with slow NAT2 and rapid CYP1A2 activity were at highest risk for lung adenocarcinoma (adjusted OR 6.9) relative to those with rapid NAT2 and slow CYP1A2 activity (148).

The mu (*GST* M1) and theta (*GST* T1) members of the glutathione-S-transferase multigene family are known to be detoxifiers of carcinogens. Deletion of these genes results in null *GST* M1 and *GST* T1 genotypes associated with a lack of enzymes action. A recent study in Hong Kong showed a significantly higher prevalence of null T1 genotype among female Chinese lung cancer patients especially among non-smokers, suggesting that lack of this detoxifying enzyme action may be associated with increased susceptibility to lung cancer (149).

CYP2E1 is involved in metabolic activation of nitrosamines, benzene and other carcinogens. CYP2E1 *Rsa* I polymorphism but not *Dra* I polymorphism was found to be associated with the development of lung cancer in Taiwan (150). The homozygote variants of *Rsa* I genotypes were more common in controls (6.9%) than in lung cancer patients (0.8%) (adjusted odds ratio 0.12). This is the first observation of a positive association between this locus and lung cancer in an Asian population.

A great deal of work is still needed to solve the mystery of the very high incidence of lung cancer, especially adenocarcinoma, in non-smoking Chinese females. Newer molecular technology such as comparative genomic hybridization and microarrays will be able to facilitate identification of new, putative tumour suppressor genes or oncogenes or genes clusters relevant to Chinese women. For example, genome-wide screening by microsatellite analysis (151) and comparative genomic hybridization (152) have identified target foci of frequent genetic aberration in 16p, 16q, 17q and 19q in adenocarcinoma of lung in non-smoking Chinese patients in Hong Kong which are non-overlapping with those of smokers. Finally, the interaction between genetic alterations and environmental exposures should be delineated.

References

1. Pisani P, Parkin DM, Bray F, Ferlay J. Estimates of the worldwide mortality from 25 cancers in 1990. *Int J Cancer* 1999; 83:18–29.
2. Schottenfeld D. Etiology and epidemiology of lung cancer. In: *Principles and Practice,* 2nd ed. Eds. Pass HI, Mitchell JB, Johnson DH, Turrisi AT, Minna JD. Lung Cancer: Chapter 20. Philadelphia: Lippincott Williams & Wilkins 2000, 367–88.
3. Yang SP, Luh KT. Primary lung cancer in Asia. *Bronchus* 1986; 2:6–8.
4. Lam WK, So SY, Yu DYC. Clinical features of bronchogenic carcinoma in Hong Kong — a review of 480 patients. *Cancer* 1983; 52:369–76.
5. Jee SH, Kim IS, Suh I, Shin D, Appel LJ. Projected mortality from lung cancer in South Korea, 1980–2004. *Int J Epidemiol* 1998; 27:365–9.
6. Silarug N, Sawanpanyalert P, Bovornkitti S. Lung cancer prevalence in Thailand. *J Environ Med* 2000; 2:257–61.
7. Li YD, Lu FZ, Chang SW, et al. Analysis of mortality rates of malignant neoplasms in China, 1990–1992 (Chinese). *Chin J Oncol* 1996; 18:403–7.
8. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J (eds). Cancer Incidence in Five Continents. Volume VII, IARC Scientific Publications No. 143, Lyon, International Agency for Research on Cancer 1997, 842–3.
9. Travis WD, Colby TV, Corrin B, et al. *Histological Typing of Lung and Pleural Tumours,* 3rd ed. Berlin: Springer Verlag 1999.
10. Travis WD, Travis LB, Devesa SS. Lung cancer. *Cancer* 1995; 75:191.
11. Perng DW, Perng RP, Kuo BI, Chiang SC. The variation of cell type distribution in lung cancer: a study of 10,910 cases at a medical center in Taiwan between 1970 and 1993. *Jpn J Clin Oncol* 1996; 26:229–33.
12. Seow A, Duffy SW, Ng TP, McGee MA, Lee HP. Lung cancer among Chinese females in Singapore 1968–1992: time trends, dialect group differences and implications for aetiology. *Int J Epidemiol* 1998; 27:167–72.

13. Choi JH, Chung HC, Yoo NC, Lee HR, Lee KH, Choi W, Lim HY, Koh EH, Kim JH, Roh JK, et al. Changing trends in histologic types of lung cancer during the last decade (1981–1990) in Korea: a hospital-based study. *Lung Cancer* 1994; 10:287–96.
14. Lam KY, Fu KH, Wong MP, Wang EP. Significant changes in the distribution of histologic types of lung cancer in Hong Kong. *Pathology* 1993; 25:103–5.
15. Morita T. Statistical study of lung cancer cases in the Annual of Pathological autopsy cases in Japan (1958–1997). *Lung Cancer* 2000; 29(suppl 1):232.
16. Devesa SS, Shaw GL, Blot WJ. Changing patterns of lung cancer incidence by histologic type. *Cancer Epidemiol Biomarkers Prev* 1991; 1:29.
17. Charloux A, Quoix E, Wolkove N, et al. The increasing incidence of lung adenocarcinoma: reality or artifact? A review of the epidemiology of lung adenocarcinoma. *Int J Epidemiol* 1997; 26:14.
18. Sekine I, Nishiwaki Y, Yokose T, Nagai K, Suzuki K, Kodama T. Young lung cancer patients in Japan: different characteristics between the sexes. *Ann Thorac Surg* 1999; 67:1451–5.
19. Kuo CW, Chen YM, Chao JY, Tsai CM, Perng RP. Non-small cell lung cancer in very young and very old patients. *Chest* 2000; 117:354–7.
20. Lam CL, Lam WK, Tsang KWT, Ip MSM. Characteristics of young Chinese patients (less than 40 years of age) with carcinoma of lung compared to patients of older age group. *Lung Cancer* 2000; 29(suppl 1): 237.
21. Thyssen J, Althoff J, Kimmerle G, Mohr U. Inhalation studies with bezo[a]pyrene in Syrian gloden hamsters. *J Natl Cancer Inst* 1981; 66:575–7.
22. Woltebeek APM, Schoevers EJ, Rutten AAJL, Feron VJ. A critical appraisal of intratracheal instillation of benzo[a]pyrene to Syrian golden hamsters as a model in respiratory tract carcinogenesis. *Cancer Lett* 1995; 89:107–16.
23. Stanton MF, Miller E, Wrench C, Blackwell R. Experimental induction of epidermoid carcinoma in the lungs of rats by cigarette smoke condensate. *J Natl Cancer Inst* 1972; 49:867–77.
24. Mitacek EJ, Brunnemann KD, Hoffman D, Limsila T, Suttajit M, Martin N, Caplan LS. Volatile nitrosamines and tobacco-specific nitrosamines in the smoke of Thai cigarettes: a risk factor for lung cancer and a suspected risk factor for liver cancer in Thailand. *Carcinogenesis* 1999; 2:133–7.
25. Denissenko MF, Pao A, Tang M, Pfeifer GP. Preferential formation of benzo[a]pyrene adducts at lung cancer mutational hotspots in p53. *Science* 1996; 274:430–2.
26. Hecht SS, Hoffmann D. Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. *Carcinogenesis* 1988; 9:875–84.
27. Kodama M, Kaneko M, Aida M, et al. Free radical chemistry of cigarette smoke and its implication in human cancer. *Anticancer Res* 1997; 17:433.
28. Wynder EL, Graham EA. Tobacco smoking as a possible etiologic factor in bronchogenic carcinoma. *JAMA* 1950; 143:329–36.
29. Doll R, Hill AB. Smoking and carcinoma of the lung. *Br Med J* 1950; 2:739–48.
30. United States Surgeon General. Smoking and health. USPHS publication no. 1103. Washington, DC: Department of health, Education and Welfare, 1964.
31. International Agency for Research on Cancer. Tobacco smoking. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, vol. 38. Lyon, France: International Agency for Research on cancer, 1986.
32. United States Surgeon General. Reducing the health consequences of smoking. Twenty-five years of progress. USPHS publication no. (CDC) 89–8411. Rockville, MD: Department of Health and Human Services, 1989.
33. Shopland DR. Tobacco use and its contribution to early cancer mortality with a special emphasis on cigarette smoking. Environ Health Perspect 1995; 103(suppl 8):131–42.
34. Tang DL, Rundle A, Warburton D, Santella RM, Tsai WY, Chiamprasert S, Hsu YZ, Perera FP. Associations between both genetic and environmental biomarkers and lung cancer: evidence of a greater risk of lung cancer in women smokers. *Carcinogenesis* 1998; 19:1949–53.
35. Liu BQ, Peto R, Chen ZM, Boreham J, Wu YP, Li JY, Campbell TC, Chen JS. Emerging tobacco hazards in China: 1. Retrospective proportional mortality study of one million deaths. *Br Med J* 1998; 317:1411–22.
36. Wen CP, Tsai SP, Yen DD. The health impact of cigarette smoking in Taiwan. *Asia-Pac J Public Health* 1994; 7:206–13.

37. Gupta RC, Purohit SD, Sharma MP, Bhardwaj S. Primary bronchogenic carcinoma: clinical profile of 279 cases from mid-west Rajasthan. *Indian J Chest Dis Allied Sci* 1998; 40:109–16.
38. Lam WK, Du YX. Environmental inhaled agents and their relation to lung cancer. In: *Pathophysiology and Treatment of Inhalation Injuries, Lung Biology in Human and Diseases* Vol 34, Chapter 10. Ed. Loke J. New York: Marcel Dekker 1988, 423–51.
39. Wynder EL, Goodman MC. Smoking and lung cancer: some unresolved issues. *Epidemiol Rev* 1983; 5:177–207.
40. Hirayama T. Nonsmoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. *Br Med J* 1981; 282:183–5.
41. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. *Br Med J* 1997; 315:980–8.
42. Zhong L, Goldberg MS, Parent ME, Hanley JA. Exposure to environmental tobacco smoke and the risk of lung cancer: a meta-analysis. *Lung Cancer* 2000; 27:3–18.
43. Rapiti E, Jindal SK, Gupta D, Boffetta P. Passive smoking and lung cancer in Chandigarh, India. *Lung Cancer* 1999; 23:183–9.
44. Lee CH, Ko YC, Goggins W, Huang JJ, Huang MS, Kao EL, Wang HZ. Lifetime environmental exposure to tobacco smoke and primary lung cancer of non-smoking Taiwanese women. *Int J Epidemiol* 2000; 29:224–31.
45. Jee SH, Ohrr H, Kim IS. Effects of husbands' smoking on the incidence of lung cancer in Korean women. *Int J Epidemiol* 1999; 28:824–8.
46. Lam TH, Hedley AJ. Environmental tobacco smoke in Asia: slow progress against great barriers. *JAMA SEA* 1999; 15:7–9.
47. National Research Council. *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects.* Washington, DC: National Academy Press 1986, 209–11.
48. US Environmental Protection Agency. *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders.* Washington, DC: Environmental Protection Agency, Office of Air and Radiation; 1992.
49. Wu JM, Du YX. Summary of papers and research recommendations presented at the International Symposium on Lifestyle Factors and Human Lung Cancer, Guangzhou, China. *Lung Cancer* 1996; 14(suppl 1):S223–34.
50. Gao YT. Risk factors for lung cancer among nonsmokers with emphasis on lifestyle factors. *Lung Cancer* 1996; 14(suppl 1):S3–45.
51. Liao ML. Environmental lung cancer in China. *J Environ Med* 1999; 1:131–7.
52. Ko YC, Lee CH, Chen MJ, Huang CC, Chang WY, Lin HJ, Wang HZ, Chang PY. Risk factors for primary lung cancer among non-smoking women in Taiwan. *Int J Epidemiol* 1997; 26:24–31.
53. Lam WK. Carcinoma of the lung in women of Chinese origin. *JAMA SEA* 1995; 11:5–6.
54. Lam WK. Why is lung cancer common in non-smoking women in Hong Kong: from epidemiologic to molecular studies. *Chin Med J* 1997; 110:420–4.
55. Lam WK. Lung cancer in non-smoking Chinese women: environmental factors. *J Environ Med* 1999; 1:429–37.
56. Qu YH, Xu GX, Zhou JZ, et al. Genotoxicity of heated cooking oil vapors. *Mutat Res* 1992; 298:105–11.
57. Wu PF, Chiang TA, Ko YC, Lee H. Genotoxicity of fumes fromheated cooking oils produced in Taiwan. *Environ Res* 1999; 80:122–6.
58. Shields PG, Xu GX, Blot WJ, Fraumeni JF Jr, Trivers GE, Pellizzari ED, Qu YH, Gao YT, Harris CC. Mutagens from heated Chinese and US cooking oils. *J Natl Cancer Inst* 1995; 87:836–41.
59. Chiang TA, Wu PF, Ko YC. Identification of carcinogens in cooking oil fumes. *Environ Res* 1999; 81:18–22.
60. Gao YT, Blot WJ, Zheng W, et al. Lung cancer among Chinese women. *Int J Cancer* 1987; 40:604–9.
61. Metayer C, Wang Z, Kleinerman RA, Wang L, Brenner AV, Cui H, Cao J, Lubin JH. Cooking oil fumes and risk of lung cancer in women in rural Gansu, China. *Lung Cancer* 2002; 35:111–7.
62. Wang TJ, Zhou BS, Shi JP. Lung cancer in non-smoking Chinese women: a case-control study. *Lung Cancer* 1996; 14(suppl 1):S93–8.
63. Ko YC, Cheng LS, Lee CH, Huang JJ, Huang MS Kao EL, Wang HZ, Lin HJ. Chinese food cooking and lung cancer in women nonsmokers. *Am J Epidemiol* 2000; 151:140–7.
64. Mumford JL, He XZ, Chapman RS, et al. Lung cancer and indoor air pollution in Xuanwei, China. *Science* 1987; 235:217–20.

65. Xu ZY, Blot WJ, Ziao HP, et al. Smoking. air pollution and the high rates of lung cancer in Shenyang, China. *J Natl Cancer Inst* 1989; 81:1800–9.
66. Mumford JL. Tian D, Younes M. Hu F, Lan Q, Ostrowski ML, He X Feng Z. Detection of p53 protein accumulation in sputum and lung adenocarcinoma associated with indoor exposure to unvented coal smoke in China. *Anticancer Res* 1999; 19:951–8.
67. Lan Q, Hx X, Costa DJ, et al. Indoor coal combustion emission, GST M1 and GSTT, genotypes and lung cancer risk: a case-control study in Xuan Wei. China. *Cancer Epidemiol Biomarkers Prev* 2000; 9:605–8.
68. Lubin JH, Boice JD Jr, Edling C, et al. lung cancer in radon-exposed miners and estimation of risk from indoor exposure. *J Natl Cancer Inst* 1995; 87:817.
69. US Environmental Protection Agency. A citizens' guide to radon. What it is and what to do about it. Washington, DC: US Government Printing Office, 1986 (Publication No.EPA-86–004).
70. Lubin JH, Boice JD. Lung cancer risk from residential radon: meta-analysis of eight epidemiologic studies. *J Natl Cancer Inst* 1997; 89:49–57.
71. Bovornkitti S, Polpong P, Silarug N. Indoor radon — Asian perspective. *J Environ Med* 1999; 1:332–42.
72. High Background Radiation Research Group, China. Health survey in high background radiation areas in China. *Science* 1980; 209:877–80.
73. Blot WJ, Xu ZY, Boice JD, et al. Indoor radon and lung cancer in China. *J Natl Cancer Inst.* 1990; 82:1025–30.
74. Lu W, An S, Wang R, Ye Z. Radon, lung cancer risk and environmental geology in Geijiu area. Paper presented at the 30th International Geological Congress in Beijing, 1995.
75. Lubin JH, Liang Z, Hrubec Z, Pershagen G, Schoenberg JB, Blot WJ, Klotz JB, Xu ZY, Boice JD. Radon exposure in residence and lung cancer among women: combined analysis of three studies. *Cancer Causes Control* 1994; 5:114–28.
76. Singh AK, Prasad R, Khan AJ. Study of ^{222}Rn concentration in some dwellings of Rajasthan. *Health Phys* 1999; 76:306–10.
77. Bovornkitti S. Prevalence of lung cancer and indoor radon in Thailand. *Intern Med J Thai* 2001; 17:241–2.
78. Schoental R, Gibbard S. Carcinogens in Chinese incense smoke. *Nature* 1967; 216:612.
79. Lam WK. Bronchial carcinoma in Chinese women in Hong Kong. Chronicle, Proceedings of the Royal College of Physicians, Edinburgh. 1985; 15:268–9.
80. Koo LC, Ho JHC. Diet as a confounder of the association between air pollution and female lung cancer: Hong Kong studies on exposures to environmental tobacco smoke incense, and cooking fumes as examples. *Lung Cancer* 1996; 14(suppl 1):S47–61.
81. Ger LP, Hsu WL, Chen KT, Chen CJ. Risk factors for lung cancer by histologic category in Taiwan. *Anticancer Res* 1993; 13:1491–500.
82. Koo LC, Lee N, Ho JHC. Do cooking fuels pose a risk for lung cancer? A case-control study of women in Hong Kong. *Ecol Dis* 1984; 2:255–65.
83. Koo LC, Ho JHC. Mosquito coil smoke and respiratory health among Hong Kong Chinese: results of three epidemiological studies. *Indoor Environ* 1994; 3:304–10.
84. Nakachi K, Limtrakul P, Sonklin P, Sonklin O, Jarern CT, Lipigorngoson S, Arai K, Sone Y, Imai K, Suga K, Matsuyama S, Shimizu H, Takahashi T, Suttajit M. Risk factors for lung cancer among Northern Thai women: epidemiological, nutritional, serological, and bacteriological surveys of residents in high and low incidence areas. *Jpn J Cancer Res* 1999; 90:1187–95.
85. Speizer FE, Samet JM. Air pollution and lung cancer. In: *Epidemiology of Lung Cancer, Lung Biology in Human and Diseases* vol 74, Chapter 6. Ed. Samet JM. New York: Marcel Dekker 1994, 31–150.
86. Abbey DE, Nishino N, McDonnell WF, Burchette RJ, Knutsen SF, Beeson WL, Yang JX. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. *Am J Respir Crit Care Med* 1999; 159:373–82.
87. IARC. Diesel and gasoline exhausts and some nitroarenes. In: Evaluation of carcinogenic risk of chemicals to men. Vol. 46, Lyon: International Agency for Research on Cancer, 1989.
88. Gao YT. Risk factors for lung cancer among non-smokers with emphasis on lifestyle factors. *Lung Cancer* 1996; 14(suppl 1):S39–45.
89. Deng J, Gao YT, Wang ZX, et al. Smoking, general air pollution and lung cancer. A prospective cohort study among 210,000 adult residents (in Chinese). *Shanghai Tumor* 1992; 12:258–60.

90. Xu ZY, Blot WJ, Xiao HP, et al. Smoking, air pollution and the high rates of lung cancer in Shenyang, China. *J Natl Cancer Inst* 1989; 81:1800–6.
91. Choi KS, Inoue S, Shinozaki R. Air pollution, temperature and regional difference in lung cancer mortality in Japan. *Arch Environ Health* 1997; 52:160–8.
92. Yang CY, Cheng MF, Chiu JF, Tsai SS. Female lung cancer and petrochemical air pollution in Taiwan. *Arch Environ Health* 1999; 54:180–5.
93. Yamada H, Hashimoto H, Akiyama M, Kawabata Y, Iwai K. Talc and amosite/crocidolite preferentially deposited in the lungs of non occupational female lung cancer cases in urban areas of Japan. *Environ Health Perspect* 1997; 105:504–8.
94. Timblin C, BeruBe K, Churg A, Driscoli K, Gordon T, Hemenway D, Walsh E, Cummins AB, Vacek P, Mossman B. Ambient particulate matter causes activation of the c-jun kinase/stress-activated protein kinase cascade and DNA synthesis in lung epithelial cells. *Cancer Res* 1998; 58:4543–7.
95. Tsurudome Y, Hirano T, Yamato H, Tanaka I, Sagai M, Hirano H, Nagata N, Itoh H, Kasai H. Changes in levels of 8-hydroxyguanine in DNA, its repair and OGG1 mRNA in rat lungs after intratracheal administration of diesel exhaust particles. *Carcinogenesis* 1999; 20:1573–6.
96. Zhong LJ, Gao YT, Jin F, et al. A case-control study of the relation between diet and lung cancer (in Chinese). *Shanghai Tumor* 1995; 15:438–43.
97. Dai XD, Lin CY, Sun XW, Shi YB, Lin YJ. The etiology of lung cancer in non-smoking females in Harbin, China. *Lung Cancer* 1996; 14(suppl 1):S85–91.
98. Koo LC. Dietary habits and lung cancer risk among Chinese females in Hong Kong who never smoked. *Nut Cancer* 1988; 11:155–72.
99. Sone Y, Sakamoto N, Suga K, Imai K, Nakache, Sonklin P, Soklin O, Lipigorngoson S, Limtrakul PN, Suttajit M. Comparison of diets among elderly female residents in two suburban districts in Chiang Mai Province, Thailand, in dry season — survey on high- and low-risk districts of lung cancer incidence. *Appl Human Sci* 1998; 17:49–56.
100. Sankaranarayanan R, Varghese C, Duffy SW, Padmakumary G, Day NE, Nair MK. A case-control study of diet and lung cancer in Kerala, South India. *Int J Cancer* 1994; 58:644–9.
101. Messina MJ, Persky V, Setchell KDR, Barnes S. Soy intake and cancer risk: a review of the in vitro and in vivo data. *Nutr Cancer* 1994; 21:113–31.
102. Wakai K, Ohno Y, Genka K, Ohmine K, Kawamura T, Tamakoshi A, Lin Y, Nakayama T, Aoki K, Fukuma S. Risk modification in lung cancer by a dietary intake of preserved foods and soyfoods: findings from a case-control study in Okinawa, Japan. *Lung Cancer* 1999; 25:147–59.
103. London SJ, Yuan JM, Chung FL, Gao YT, Coetzee GA, Ross RK, Yu MC. Isothiocyanates, glutathione S-transferase M1 and T1 polymorphisms, and lung cancer risk: a prospective study of men in Shanghai, China. *Lancet* 2000; 356:724–9.
104. Zhao B, Seow A, Lee EJ, Poh WT, Teh M, Eng P, Wang YT, Tan WC, Yu MC, Lee HP. Dietary isothiocyanates, glutathione S-transferase -M1, -T1 polymorphisms and lung cancer risk among Chinese women in Singapore. *Cancer Epidemiol Biomarkers Prev* 2001; 10:1063–7.
105. Steenland K, Loomis D, Shy C, Simonsen N. Review of occupational lung carcinogens. *Am J Ind Med* 1996; 29:474–90.
106. Samet JM, Lerchen ML. Proportion of lung cancer caused by occupation: a critical review. In: *Occupational Lung Disease.* Eds. Gee JBL, Morgan WKC, Brooks SM. New York: Raven Press 1984, 55.
107. Kurumatani N, Natori Y, Mizutani R, Kumagai S, Haruta M, Miura H, Yonemasu K. A historical cohort mortality study of workers exposed to asbestos in a refitting shipyard. *Ind Health* 1999; 37:9–17.
108. Zhu H, Wang Z. Study of occupational lung cancer in asbestos factories in China. *Br J Ind Med* 1993; 50:1039–42.
109. Pang ZC, Zhang Z, Wang Y, Zhang H. Mortality from a Chinese asbestos plant:overall cancer mortality. *Am J Ind Med* 1997; 32:442–4.
110. Lam WK, Kung TM, Ma PL, So SY, Mok CK. First report of asbestos-related diseases in Hong Kong. *Trop Geogr Med* 1983; 35:225–9.
111. Honma K, Chiyotani K, Kimura K. Silicosis, mixed dust pneumoconiosis, and lung cancer. *Am J Ind Med.* 1997; 32:595–9.
112. Nakagawa H, Nishijo M, Tabata M, Morikawa Y, Miura K, Okumura Y, Handa K. Dust exposure and lung

cancer mortality in tunnel workers. *J Environ Path Toxicol Oncol* 2000; 19:99–101.
113. Wang Z, Dong D, Liang X, Qu G, Wu J, Xu X. Cancer mortality among silicotics in China's metallurgical industry. *Int J Epidemiol* 1996; 25:913–7.
114. Dong D, Xu G, Sun Y, Hu P. Lung cancer among workers exposed to silica dust in Chinese refractory plants. *Scand J Work Environ Health* 1995; 21(suppl 2):69–72.
115. Fu H, Gu X, Jin X, Yu S, Wu K, Guidotti TL. Lung cancer among tin miners in southeast China: silica exposure, silicosis and cigarette smoking. *Am J Ind Med* 1994; 26:373–81.
116. Chan CK, Leung CC, Tam CM, Yu TS, Wong TW. Lung cancer mortality among a cohort of men in a silicotic register. J Occup Environ Med 2000; 42:69–75.
117. Amre DK, Infante RC, Dufresne A, Durgawale PM, Ernst P. Case-control study of lung cancer among sugar cane farmers in India. *Occup Environ Med* 1999; 56:548–52.
118. Liu B, Guan R, Zhou P, Miao Q, Wang H, Fu D, You B. A distinct mutational spectrum of p53 and K-ras genes in lung cancer of workers with silicosis. *J Environ Pathol Toxicol Oncol* 2000; 19:1–7.
119. Qiao YL, Taylor PR. Yao SX, Erozan YS, Luo XC, Barrett MJ, Yan QY, Giffen CA, Huang SQ, Maher MM, Forman MR, Tockman MS. Risk factors and early detection of lung cancer in a cohort of Chinese tin miners. *Ann Epidemiol* 1997; 7:533–41.
120. Kashyap SK, Chattospadhyay P, Venkiah K. Occupational cancer. Annual Report, National Institue of Occupational Health, Ahmedabad. 1993–1994.
121. Udwadia FE, Kharas RJ. Occupational and environmental respiratory diseases in India (Part II). *J Environ Med* 2000; 2:297–322.
122. Notani PN, Shah P, Jayant K, Balakrishnan V. Occupation and cancers of the lung and bladder. *Int J Epidemiol* 1993; 22:185–91.
123. Hayes RB, Yin SN, Dosemeci M, Li GL, Wacholder S, Chow WH, Rothman N, et al. Mortality among benzene-exposed workers in China. *Environ Health Perspec* 1996; 104(suppl 6):1349–52.
124. Gao YT, Zheng W, Jin F, et al. Retrospective cohort study on the association of lung cancer with pulmonary tuberculosis. J Epidemiol (Jpn Epidemiol Assoc) 1992; 2(suppl):S82–8.
125. Zheng W, Blot WJ, Liao ML, et al. Lung cancer and prior tuberculosis infection in Shanghai. *Br J Cancer* 1987; 56:501–4.
126. Kung ITM, Lui IOL, Loke SL, Aung Khin M, Mok CK, Lam WK, So SY. Pulmonary scar cancer: a pathologic reappraisal. *Am J Surg Path* 1985; 9:391–400.
127. zur Hausen H. Papillomaviruses in human cancers. *Proc Assoc Am Physicians* 1999; 111:581–7.
128. Soini Y, Nuorva K, Kamel D, Pollanen R, Vahakangas K, Lehto VP, Paakko P. Presence of human papillomavirus DNA and abnormal p53 protein accumulation in lung carcinoma. *Thorax* 1996; 51:887–93.
129. Hirayasu T, Iwamasa T, Kamada Y. Koyanagi Y, Usuda H, Genka K. Human papillomavirus DNA in squamous cell carcinoma of the lung. *J Clin Pathol* 1996; 49:810–7.
130. Tsuhako K, Nakazato I, Hirayasu T, Sunakawa H, Iwamasa T. Human papillomavirus DNA in adenosquamous carcinoma of the lung. *J Clin Pathol* 1998; 51:741–9.
131. Hennig EM, Suo Z, Karlsen F, Hol R, Thoresen S, Nesland JM. HPV positive bronchopulmonary carcinomas in women with previous high-grade cervical intraepithelial neoplasia (CIN III). *Acta Oncol* 1999; 38:639–47.
132. Cheng YW, Chiou HL, Sheu GT, Hsieh LL, Chen JT, Chen CY, Su JM, Lee H. The association of human papillomavirus 16/18 infection with lung cancer among non-smoking Taiwanese women. *Cancer Research* 2001; 61:2799–803.
133. Taioli E, Wynder EL. Endocrine factors and adenocarcinoma of the lung in women. *J Natl Cancer Inst* 1994; 84:869–70.
134. Siegfried JM. Women and lung cancer: does oestrogen play a role? *Lancet* Oncol 2001; 2:506–13.
135. Liao ML, Wang JH, Wang HM, Ou AQ, Wang XJ, You WQ. A study of the association between squamous cell carcinoma and adenocarcinoma in the lung, and history of menstruaton in Shanghai women, China. *Lung Cancer* 1996; 14(Suppl 1):S215–21.
136. Lam WK, Hawkins BR, Kung ITM, So SY. No association between HLA antigens and adenocarcinoma of the lung in non-smoking Chinese women in Hong Kong. *Br J Dis Chest* 1986; 80:370–4.
137. Wang YC, Lee HS, Chen SK, Yang SC, Chen CY. Analysis of K-ras gene mutations in lung carcinomas:correlation with gender, histological subtypes and clinical outcome. *J Cancer Res Clin Oncol* 1998; 124:517–22.

138. Lung M, Wong M, Lam WK, Lau KS, Kwan S, Fu KH, Cheung H, Yew WW. Incidence of ras oncogene activation in lung carcinoma in Hong Kong. *Cancer* 1992; 70:760–3.
139. Gao HG, Chen JK, Stewart J, Song B, Rayappa C, Whong WZ, Ong T. Distribution of p53 and K-ras mutations in human lung cancer tissues. *Carcinogenesis* 1997; 18:473–8.
140. Wang YC, Chen CY, Chen SK, Cherng SH, Ho WL, Lee H. High frequency of deletion mutations in p53 gene from squamous cell lung cancer patients in Taiwan. *Cancer Res* 1998; 58:328–33.
141. Takagi Y, Koo LC, Osada H, et al. Distinct mutational spectrum of the p53 gene in lung cancers from Chinese women in Hong Kong. *Cancer Res* 1995; 55:5354–7.
142. Lung ML, Wong MP, Skaanild MT, Fok CL, Lam WK, Yew WW. p53 gene mutations in non-small cell lung carcinomas in Hong Kong. *Chest* 1996; 109:718–26.
143. Ge H, Wong MP, Lam WK, Lee J, Fu KH, Yew WW, Lung ML. p53 intron 2 genotypes detected in normal specimens and lung carcinomas in Hong Kong. *Oncology Reports* 1998; 5:1265–7.
144. Ge H, Lam WK, Lee J, Wong MP, Fu KH, Yew WW, Lung ML. Detection and evaluation of p53 intron 2 polymorphisms in lung carcinomas in Hong Kong. *International Journal of Cancer (Pred Oncol)* 1996; 69:120–4.
145. Wang YC, Chen CY, Chen SK, Chang YY, Lin P. p53 codon 72 polymorphism in Taiwanese lung cancer patients: association with lung cancer susceptibility and prognosis. *Clin Cancer Res* 1999; 5:129–34.
146. Chan ASK, Lam WK, Wong MP, Fu KH, Lee J, Yew WW, Chiu SW, Lung MP. Chromosome 11 alterations in non-small cell lung carcinomas in Hong Kong. *Lung Cancer* 1996; 15:51–65.
147. Seow A, Zhao B, Poh WT, The M, Eng P, Wang YT, Tan WC, Lee EJ, Lee HP. NAT2 slow acetylator genotype is associated with increased risk of lung cancer among non-smoking Chinese women in Singapore. *Carcinogenesis* 1999; 20:1877–81.
148. Seow A, Zhao B, Lee EJ, Poh WT, Teh M, Eng P, Wang YT, Tan WC, Lee HP. Cytochrome P4501A2 (CYP1A2) activity and lung cancer risk: a preliminary study among Chinese women in Singapore. *Carcinogenesis* 2001; 22:673–7.
149. Tan-Un KC, Chan H, Lam WK, Tsang KWT, Ip MS, Chan-Yeung M. GSTT1 null genotype is associated with lung cancer in females in Hong Kong. *Am J Respir Crit Care Med* 2002; 165:A367.
150. Wang SL, Lee H, Chen KW, Tsai KJ, Chen CY, Lin P. Cytochrome P4502E1 genetic polymorphisms and lung cancer in a Taiwanese population. *Lung Cancer* 1999; 26:27–34.
151. Wong MP, Lam WK, Wang E, Chiu SW, Lam CL, Chung LP. Primary adenocarcinoma of the lung in nonsmokers show a distinct pattern of allelic imbalance. *Cancer Research* 2002; 62:4464–8.
152. Wong MP, Fung LF, Wang E, Chow WS, Chiu SW, Lam WK, Ho KK, Ma ESK, Wan TSK, Chung LP. Chromosomal aberrations of primary lung adenocarcinomas in nonsmokers. *Cancer* 2003; 97:1263–70.

24 Lung Cancer: Diagnosis and Staging

Wah Kit Lam and Pan Chyr Yang

DIAGNOSIS

Cell types

The work-up of a patient with suspected lung cancer usually starts with a plain chest radiograph. Confirmation of the diagnosis and classification by histologic cell types is important for prognosis and planning of further investigations and management.

Histologic classification of lung cancer is based on the World Health Organisation classification which has been revised in 1999 in collaboration with the International Association for the Study of Lung Cancer (1). The four major cell types are squamous cell carcinoma, adenocarcinoma, large cell carcinoma and small cell carcinoma. Small cell carcinoma has biologic and clinical features that are distinct from the other types: the fastest growth rate, greatest propensity for early widespread metastasis and production of polypeptide hormones and enzymes, consistent chromosomal abnormalities with loss of a portion of one of the two short arms of chromosome 3 (3p), and more chemo- and radio-sensitive (2). The other three cell types are clinically and biologically more alike, particularly in their response to chemotherapy and radiotherapy, and are therefore conveniently grouped together under the name 'non-small cell lung cancer'.

A changing pattern of cell types has been observed worldwide including in Asia, and is reviewed in Chapter 23. With the increasing incidence of adenocarcinoma and a corresponding decrease in squamous cell carcinoma, adenocarcinoma has become the predominant cell type especially in women (who are usually non-smokers) in many countries (Table 1). Small cell carcinoma accounts for about 13% of all cases.

Plain chest radiograph

Standard postero-anterior and lateral chest radiographs are the usual first investigation for suspected lung cancer. Radiologic abnormalities to detect include hilar shadows, pulmonary parenchymal abnormalities (mass/masses, collapse, lymphangitis carcinomatosis), paratracheal and other mediastinal masses, pleural effusion, cardiomegaly due to pericardial effusion, elevation of diaphragm, and ribs/vertebrae erosion.

A peripheral mass lesion is usually detectable by a plain chest radiograph when its diameter exceeds 1 cm. It is often difficult to differentiate between a malignant and a benign mass lesion ("solitary pulmonary nodule") from chest radiographs alone, but useful radiologic clues suggesting malignancy include the following: speculated or indistinct margin, ground-glass opacity of the lung parenchyma adjacent to the pulmonary nodule, size greater than 3 cm, and doubling time of between 1 and 18 months (13,14).

Table 1. Cell Types Distributions in Selected Asian Populations (%)

		Squamous cell carcinoma	*Adeno-carcinoma*	*Large cell carcinoma*	*Small cell carcinoma*	*Reference*
Guangzhou	men	57.6	23.9	1.9	7.2	(3)
	women	29.1	48.4	0.7	8.3	
Shanghai	men	48.2	32.7			(4)
	women	22.0	60.5			
Hong Kong	men	38.9	30.7	15.8	13.8	(5)
	women	15.7	58.5	11.1	13.4	
India		42	20	18	14	(6)
Japan	men	30	37	8	20	(7)
	women	14	62	6	14	
Korea	men	54.6	24.9	1.9	18.6	(8)
	women	22.9	60.8	0.5	15.8	
Singapore	women	19.5	51.3		10.2	(9)
Taiwan	men	40.1	34.2	8.9	13.1	(10)
	women	19.8	61.4	7.1	7.2	
Thailand		29	29*	24	13	(11)
		30	39	20	11	(12)

* female non-smokers 58% adenocarcinoma

Sputum cytology

Sputum cytology is the simplest, non-invasive way of making the diagnosis of lung cancer. Expectoration of sputum for cytologic examination can be spontaneous or induced by nebulized hypertonic saline or propylene glycol. The yield depends on the location of the tumour and the number of specimens examined. Examination of three adequate specimens for malignant cells will be able to confirm the diagnosis of lung cancer in about 80% of central tumours and 50% of peripheral tumours (15). An experienced cytopathologist can accurately determine the cell types in over 85% of cases. It is noteworthy that unlike squamous cell carcinoma, the bulk of tumour in small cell carcinoma is often in the bronchial submucosa with less exfoliation of malignant cells so that the yield of sputum examination in the diagnosis of small cell carcinoma is lower (16,17).

Bronchoscopy

Bronchoscopy, usually by a flexible fibreoptic instrument, is an extremely valuable investigation for diagnosis and staging of lung cancer. It enables direct visualization of central lesions in the airway down to the level of subsegmental divisions with biopsy specimens obtained under direct vision, and with fluoroscopy, transbronchial lung biopsies can also be performed for peripheral lesions.

In central, bronchoscopically visible tumours, forceps biopsy alone would give a diagnostic yield of 55% to 85% (18). Cytologic examination of specimens of bronchial washing and bronchial brushing both produce diagnostic yields of 62% to 79%. Two studies from Hong Kong showed that for bronchoscopically visible tumours, biopsies, washing and brushing gave diagnostic yields of 82%, 76% and 74% respectively, giving a combined yield of 94% to 95% (19,20). Bronchial washing and brushing provided the exclusive diagnosis in 12% of the cases.

In performing bronchial brushing, some

bronchoscopists withdraw the bronchial brush together with the bronchoscope to increase the yield. However, Parker et al (21) and Kinnear et al (22) have shown that withdrawing the brush through the bronchoscope would not affect the diagnostic yield.

In peripheral, bronchoscopically nonvisible tumours, transbronchial biopsy with fluoroscopy, washing and brushing give diagnostic yields of 15% to 46%, 42% to 46% and 29% to 50% respectively, which are lower than the yield in central tumours (18). The combined yield is 40% to 80%. When a computed tomography shows a bronchus leading to the lesion (the "bronchus sign"), the diagnostic yield with the procedures is higher (23). The Hong Kong experience compared favourably with the world literature, with corresponding yields of 61%, 52% and 52% for individual procedure and 86% for the three procedures combined (19). In this study, bronchial washing and brushing were found to be important complementary procedures to biopsy and provided the exclusive diagnosis in 25% of the cases, which was double that for central tumours. Another important finding was the good cytologic cell typing accuracy (except for large cell carcinoma) in experienced hands — the cytologic cell typing accuracy was 92% for squamous cell carcinoma, 87% for small cell carcinoma, 83% for adenocarcinoma, but only 38% for large cell carcinoma (19). A more recent Japanese study showed a diagnostic yield of 84.1% using all three procedures in peripheral tumours, and 74.1% using transbronchial lung biopsy alone (24).

Transbronchial needle aspiration (TBNA) under fluoroscopic guidance (25,26) and bronchoalveolar lavage (BAL) (27,28) are other procedures for sampling peripheral lesions. TBNA is particularly useful for lesions not penetrable by forceps, and can increase the yield over that of transbronchial biopsy especially in large lesions. Similarly, BAL has been found to give an impressive yield of 65% (27). The most cost effective combination of procedures has yet to be defined.

In Japan, transbronchial curettage after localization of the tumour by selective peripheral bronchogram has been used for small peripheral lesions with a good yield of 76% to 97% (29,30). The procedure was done two weeks after bronchogram which otherwise would affect cytologic results. This method however has not gained widespread use.

Transthoracic needle biopsy (TNB)

Percutaneous transthoracic needle biopsy with ultrasound or CT guidance is a useful procedure for diagnosing lung cancer presenting as a pulmonary nodule or mass including a mediastinal mass. It is also performed for staging patients with suspected tumour extension to the mediastinum or chest wall. In experienced hands, the diagnostic accuracy of TNB in detecting lung cancer is 80% to 95% (31).

Ultrasonography has been shown to be more accurate than CT scan for determining tumour invasion of the chest wall (32). Another advantage for using ultrasound guiding biopsy of malignant lung masses with necrotic centres is that ultrasound can clearly define the large necrotic area within the tumour, thus guiding biopsy from the viable tumour wall precisely (33). Transthoracic needle aspiration biopsy by colour Doppler ultrasound puncture guiding device and amplitude ultrasound angiography have been studied in Taiwan (Figures 1 and 2) (34,35,36). This method has the distinct advantage of being able to identify blood vessels surrounding or within the target tumour (37). It provides a safe and precise approach for transthoracic tissue sampling of lesions, and is particularly useful for guiding biopsies of mediastinal tumours where puncturing of vascular structures is a potential complication. Real-time ultrasound imaging allows for dynamic evaluation and localization of target lesions that move with respiration; during transthoracic biopsy, the tip of the needle can be monitored continuously and fine adjustments made quickly and precisely. This is especially useful for biopsy of small pulmonary nodules (36).

Endobronchial ultrasonograph (38) and transoesophageal endoscopic ultrasound guided fine needle aspiration biopsy (39,40) have also been shown to be safe, sensitive and minimally invasive methods for evaluating patients with mediastinal masses and have a major impact on patient management.

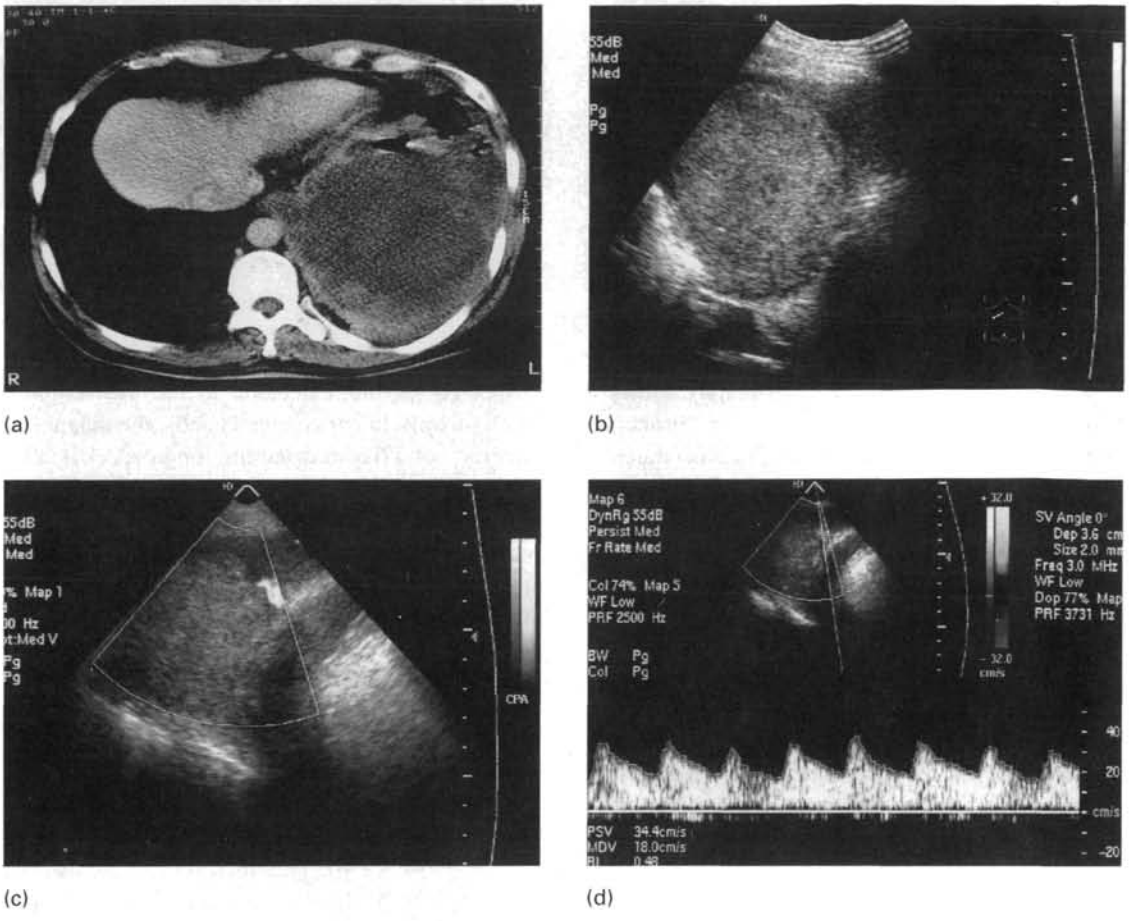


Figure 1. A 42 year old man with "unresolving pneumonia"

(a) Chest CT revealed a huge left lower lobe mass with central cavitation, irregular inner wall with air-fluid level and peripheral obstructive pneumonia.

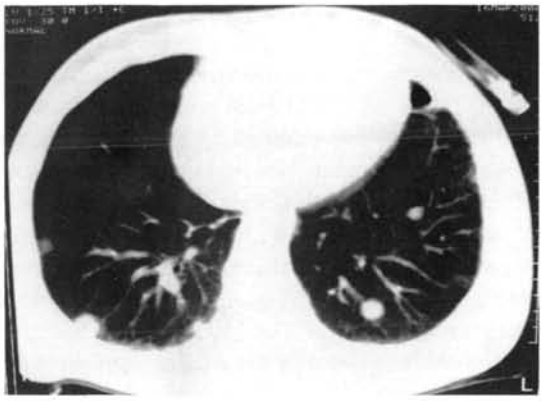
(b) Chest echo revealed huge left lower lobe mass with moderate amount pleural effusion.

- The left lower lung mass was 10 x 9 cm in size
- Well-encapsulated with smooth margin
- Obstructive pneumonitis peripheral to the huge mass
- Heterogeneous echogenicity of the mass with central necrosis

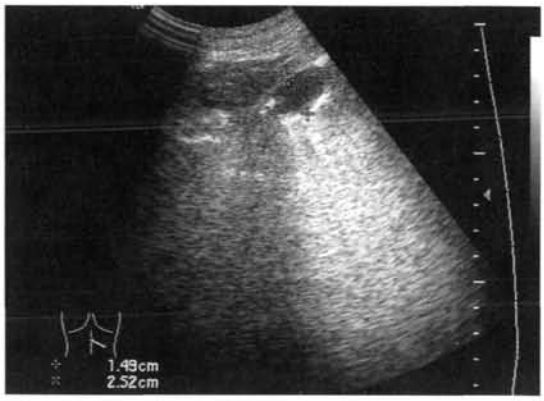
(c) Feeding artery entering the mass was noted by power Doppler image

(d) Colour Doppler study of feeding artery revealed resistance index (RI) : 0.48

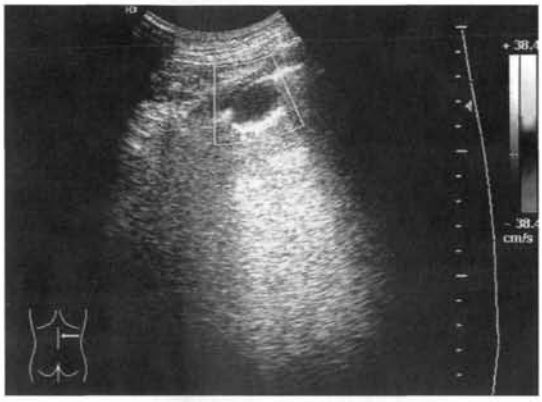
Echo-guided lung biopsy was done smoothly, and confirmed squamous cell carcinoma



(a)



(b)



(c)

Figure 2. A 71 year old man with gingival mass confirmed to be T-cell malignant lymphoma
(a) Chest CT revealed multiple lung nodules
(b) Chest echo revealed right infrascapular subpleural nodule
- 2.5 x 1.6 cm in size
- Located over right B6 segment
- Well-defined margin with posterior echo enhancement
- Hypoechoic internal echo pattern

(c) No flow detected by colour Doppler study
Echo-guided lung biopsy was done smoothly, and confirmed T-cell lymphoma

Thoracoscopy (Video-assisted thoracic surgery, VATS)

VATS, by insertion of a thoracoscope and endoscopic dissecting instruments and clip appliers through the intercostal spaces, enables direct visualization and biopsy of the involved areas of the pleural, lung and mediastinum. It usually requires general anaesthesia, and is most helpful for difficult cases of pleural effusion, lung and mediastinal masses. It permits precise pleural biopsy, mediastinal exploration and lymph nodes sampling, biopsy or wedge resection of pulmonary nodules, and even lobectomy, bilobectomy or pneumonectomy (41,42). For assessment of mediastinal masses and lymph nodes, it gives the same diagnostic yield as cervical mediastinoscopy (91.9% versus 94.3%) (43). It has also been shown to be more effective than bronchoscopy in diagnosing small peripheral lung cancers (i.e. T1 tumours, see *Staging*) (44).

For indeterminate pulmonary nodules and

pleural lesions, a Japanese study has shown that video-assisted thoracoscopy using a miniaturized 4-mm endoscope (mini-VAT) and local anaesthesia is possible with 91% and 100% diagnostic yields for pulmonary nodule and pleural lesion respectively (45).

Staging

Staging systems

The prognosis and treatment of lung cancer depends on the cell type, anatomic extent of the cancer, and the general well-being (performance status) of the patient. The anatomic extent is described in a standardized way by the International System for Staging Lung Cancer basing on the stage grouping of the TNM subsets (T = primary tumour, N = regional lymph nodes, M = distant metastasis). This staging system has recently been revised and accepted by the American Joint Committee on Cancer and the International Union Against Cancer (Table 2) (46). Stage groupings would define groups of patients with generally similar treatment options and prognosis, and allows for valid comparison of clinical outcomes. That prognosis is closely related

Table 2. 1997 International TNM Staging for Lung Cancer (Based on Mountain (46) with Permission)

Primary tumour (T)	
T_{is}	Carcinoma in situ
T_1	Size ≤ 3.0 cm, in lobar bronchus or distal airways, surrounding by lung or visceral pleura
T_2	Size ≥ 3.0 cm; any size that either invades the visceral pleura or with lobar atelectasis / obstructive pneumonitis / invading main bronchus but ≥ 2 cm distal to carina
T_3	Any size, invading chest wall (including superior sulcus tumours) / diaphragm / mediastinal pleura / pericardium; or a tumour in the main bronchus within 2 cm of the carina without involving the carina
T_4	Any size, invading mediastinum / heart / great vessels / trachea / oesophagus / vertebral body / carina; malignant pleural effusion; or satellite tumour nodule(s) within the same lobe
Nodal involvement (N)	
N_0	No demonstrable lymph nodes
N_1	Ipsilateral or peribronchial hilar lymph nodes
N_2	Ipsilateral mediastinal / subcarinal lymph nodes
N_3	Contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph nodes
Distant metastasis (M)	
M_0	No (known) distant metastasis
M_1	Metastasis present — specify site(s); or tumour nodule in non 1° tumour lobe
Staging Grouping — TNM Subsets	
Stage 0	(TisN0M0)
Stage 1A	(T1N0M0)
Stage 1B	(T2N0M0)
Stage 11A	(T1N1M0)
Stage11B	(T2N1M0, T3N0M0)
Stage 111A	(T3N1M0), (T(1–3)N2M0)
Stage 111B	(T4, Any N, M0) (Any T, N3M0)
Stage IV	(Any T, Any N, M1)

to staging is shown by the 5-year survivals after treatment, which are about 60%, 34%, 13% and 1% for stages 1A, IIA, IIIA and IV of non-small cell lung cancer respectively (46).

While this staging system is entirely relevant for the non-small cell lung cancers especially for consideration of surgical treatment (stages I to IIIA) versus non-surgical treatment (stages IIIB and IV), its application to small cell carcinoma is less clear. This is because over 90% of patients with small cell carcinoma present with advanced disease (stages III and IV), and hence a simple two-staged system developed by the Veteran's Administration Lung Cancer Study Group and revised by the International Association for the Study of Lung Cancer (47) has been widely used instead. This system simply classifies patients into *limited disease* (LD) and *extensive disease* (ED) groups. LD indicates that the tumour is confined to one hemithorax and its regional lymph nodes (including ipsilateral and contralateral hilar, mediastinal and supraclavicular nodes, and ipsilateral pleural effusion). In practice, LD is localized tumour that can be encompassed within an acceptable radiotherapy portal. ED indicates presence of more widespread mediastinal disease (e.g. pericardial involvement) and distant metastasis. However, with improved therapy and much better survival in small subsets of patients, many oncologists now believe that the TNM staging system should also be used for small cell carcinoma.

Despite controversies and deficiencies (48), the 1997 TNM staging system of lung cancer is, in general, a valid and reproducible prognostic tool (49). The next revision is scheduled to take place in 2007.

Thoracic staging imagings

Chest computed tomography

Computed tomography (CT) is extremely useful in assessing primary tumour location and extension (hence technical feasibility of tumour resection), and mediastinal lymph nodes location and size.

For assessment of a solitary pulmonary nodule (SPN), thin-section CT densitometry with or without a reference phantom (comparison standard) helps the detection of calcification that could otherwise be missed in a plain chest radiograph. The use of time-enhancement curves after IV injection of contrast material for the characterization of SPN has been found to be highly sensitive (100%) and accurate (93%) in detecting malignant SPN which is more vascular (50).

Mediastinal structure invasion (T4) assessment by CT is generally not very reliable. CT however can be used to differentiate between tumour and adjacent atelectasis or pneumonia, pleural invasion and chest wall invasion with bone destruction (51). For evaluation of pleural dissemination, thin-section CT (2-mm collimation) is both more sensitive and more accurate than thick-section CT (10-mm collimation) (sensitivity 90% vs 50%, accuracy 93% vs. 78%) (52).

CT is useful in evaluation of mediastinal lymph nodes. Although lymph nodes enlargement can be due to reactive hyperplasia, inflammation or infection, a uniform 10 mm size cutoff is generally used to define a malignant node. Some workers prefer to use individual size thresholds for each individual nodal station. Pooled data showed that CT sensitivity and specificity in diagnosing mediastinal lymph nodes metastasis were 0.57 and 0.82 respectively (53).

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has the advantage over CT of being able to image in any desired plane and to directly image vascular structures without intravascular contrast material. It is superior to CT in defining chest wall invasion, Pancoast's tumour (superior sulcus tumour), nerve tissue, bone and vascular invasion (54). MRI of the brain is also indicated in patients with high suspicion for brain metastasis despite negative CT brain.

Positron emission tomography

Whereas CT scanning and MRI give anatomical information, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) gives information on increased tumour glucose metabolism. It is thus a 'functional' or 'metabolic' scan. It has shown great potentials in the differential diagnosis of SPN and small (< 1 cm) mediastinal lymph nodes, in staging of lung cancer, and in assessing intrathoracic recurrence after

surgery or radiotherapy or in assessing mediastinal lymph node downstaging after induction chemotherapy, situations where CT or MRI are inaccurate (50,55,56).

In the assessment of SPN, the degree of FDG uptake one hour after injection is used. A *standard uptake value* (SUV) > 2.5 is likely to represent a malignant lesion, giving sensitivities and specificities of > 80% (50) and indeed > 90% in some studies (57,58). Most false positive results are due to increased FDG uptake in inflammatory conditions such as granulomas, and in these situations, a SUV threshold of 3.8 has been suggested. This is highly relevant in many Asian countries where pulmonary tuberculosis is endemic.

In mediastinal lymph node staging, PET has been found in several studies to be significantly more accurate than CT. In a Belgian study of 50 patients with NSCLC (59), CT was 67% sensitive, 59% specific and 64% accurate in staging mediastinal nodes, whereas PET blinded to CT was significantly better giving 67%, 97% and 88% respectively (increasing to 93%, 97% and 96% respectively for PET visually correlated with CT). Also, PET imaging has been shown to be equally reliable and accurate for detecting disease in small (< 1 cm) and large (> 3 cm) lymph nodes with better efficacy than CT (60). PET imaging has a sensitivity, specificity and accuracy of about 90% in the staging of mediastinal lymph nodes (61). A meta-analysis to compare the ability of PET with that of CT to stage the mediastinum showed that PET was significantly more accurate than CT for identifying nodal metastases (62). The mean sensitivity and specificity were 79% and 91% respectively for PET as compared to 60% and 77% respectively for CT.

The use of PET-CT fusion scan is likely to further enhance the use of these imaging techniques in lung cancer.

Single-photon emission CT

High-affinity somatostatin receptors have been demonstrated *in vitro* in many human tumours. Single-photon emission CT (SPECT) is an imaging method that makes use of the affinity of tumours, including lung cancer, for peptide analogs of somatostatin such as depreotide. In a recent multicenter trial using SPECT with ^{99m}Tc depreotide in the evaluation of solitary pulmonary nodules in 114 patients, this scintigraphic technique gave a sensitivity of 96.6% and a specificity of 73.1%, which is comparable to that of PET (63). Because of its lower projected cost, SPECT with ^{99m}Tc depreotide holds great promise to be a safe, useful, and affordable technique in the evaluation of solitary pulmonary nodules.

Staging procedures: guidelines

Staging of patients with confirmed lung cancer is performed for decision making in treatment options and stratification for prognosis. Staging always starts with a complete history and physical examination with particular attention to symptoms and signs of intrathoracic spread and metastasis. Haematology and biochemistry is also part of the initial assessment and can give the first clue to metastasis (e.g. elevated serum calcium and alkaline phosphatase in bone metastasis and abnormal liver function tests in liver metastasis) or paraneoplastic syndromes (e.g. hyponatraemia in inappropriate secretion of antidiuretic hormone).

Subsequent staging investigations should be logical, evidence-based and cost-effective. For small cell lung cancer with the two-stage system, further imaging should be done to determine if the patient has limited or extensive disease. Imaging test should be directed to the site where symptoms or signs are present. In the absence of any specific or guiding findings, then either bone scan or abdominal imaging (ultrasound or CT) may be performed basing on the equal chance of metastasis in bone or liver (64). The less expensive test (e.g. bone scan vs. CT abdomen) should be performed first. In the non-protocol setting, extensive imaging investigations are not necessary once a site of metastatic disease has been confirmed and the disease is designated 'extensive' (64).

For non-small cell lung cancer, the importance of staging investigations is to determine if the patient is a potential candidate for surgical treatment (stages I to IIIA). Again, the sequence and choice of investigations should be logical, evidence-based, and cost-effective. The American Society of Clinical Oncology (ASCO) has published clinical practice guidelines for staging

investigations in 1997 (65). After history taking, complete physical examination and haematology and biochemistry tests, in patients without evidence of extrathoracic disease, a chest radiograph and chest CT scan (with contrast) extending to include the liver and adrenal glands are recommended to stage locoregional disease. For patients with clinically operable cancer, biopsy of mediastinal lymph nodes found on CT to be greater than 1 cm in shortest transverse axis is recommended. Bone scan or CT of the brain are done only if signs or symptoms of disease are present. The finding of an isolated liver or adrenal mass on abdominal imaging would require a biopsy to rule out metastatic disease if the patient is otherwise considered to be potentially operable (65).

The role of PET scan has not been discussed in the ASCO 1997 guideline. Despite its documented roles in the investigations of pulmonary nodules and mediastinal lymph nodes (see above), its lack of general availability in many Asian countries and high cost would mean that the technique would not be widely used in the near future in this part of the world. In Hong Kong, each test would cost about US$1,200. Even in affluent countries like Japan, the chest CT plus PET strategy (cost of one PET scan about US$700) in patients with lung cancer is not found to be cost-effective compared with chest CT alone in a preliminary study (66). Other studies, however, have found PET to be cost-effective as unnecessary invasive procedures were eliminated and management changed in many cases (67,68). Further studies on cost-effectiveness in Asia are awaited with interest.

A more recent study of 102 patients showed great promise for metabolic staging by PET to simplify and improve the current staging procedures of non-small cell lung cancer (69). The sensitivity and specificity of PET for the detection of mediastinal metastasis were superior to those of CT (91% vs 75% and 86% vs 66% respectively). PET identified distant metastasis that had not been found by standard methods in 11 of 102 patients. The use of PET to stage the disease resulted in a different stage from the one determined by standard methods in 62 out of 102 patients (stage was lowered in 20 and raised in 42). It was concluded that whole-body PET, a single test, as compared to multiple standard staging procedures, simplifies and improves the rate of detection of local and distant metastasis in patients with non-small cell lung cancer (69). Another recent randomized controlled study further showed that PET did improve clinical practice in that additional PET to conventional preoperative workup prevented unnecessary surgery in 20 percent of patients with suspected non-small cell lung cancer (70).

SPECT scintigraphy with ^{99m}Tc depreotide (63), which has similar accuracy as PET in differentiating between malignant and benign pulmonary nodules, should be further studied as it is less costly than PET (*vide supra*).

Performance status

As mentioned above, the prognosis and treatment of patients with lung cancer depends on the cell type, anatomic extent of the disease (staging) and general condition of the patient.

The general ability of the patient to carry on with his/her personal life and work is described by the performance status or performance index. There are two scales of performance status that are used internationally, namely the Karnofsky (K) Performance Status Scale (Table 3) and the Eastern Cooperative Oncology Group (ECOG) or Zubrod Performance Scale (Table 4). It should be noted that the two scales are broadly equivalent as follows: K 90 – 100 = ECOG 0, K 70 – 80 = ECOG 1, K 50 – 60 = ECOG 2, K 30 – 40 = ECOG 3 and K 10 – 20 = ECOG 4. The performance status of the patient correlates well with survival.

Table 3. Karnofsky's Scale of Performance Status

A.	Able to carry on normal activity and to work; no special care is needed.	
	100	Normal; no complaints, no evidence of disease
	90	Able to carry on normal ability; minor signs or symptoms of disease
	80	Normal activity with effect; some signs or symptoms of disease
B.	Unable to work; able to live at home; cares for most personal needs; a varying amount of assistance is needed.	
	70	Cares for self, unable to carry on normal activity or do active work
	60	Requires occasional assistance, but is able to care for most of needs
	50	Requires considerable assistance and frequent medical care
C.	Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	
	40	Disabled; requires special care and assistance
	30	Severely disabled, hospitalization is indicated, although death may not be imminent
	20	Very sick; hospitalization necessary, active supportive treatment necessary
	10	Moribund; fatal process progressing rapidly
	0	Dead

Table 4. Eastern Cooperative Oncology Group (ECOG) (Zubrod) Performance Scale

Grade	*Definition*
0	Fully active, able to carry on all predisease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair

References

1. Travis WD, Colby TV, Corrin B, et al. Histological typing of lung and pleural tumours. In: *World Health Organization International Classification of Tumours,* 3rd ed. Ed. Sobin LH. Berlin: Springer Verlag 1999.
2. Johnson BE, Kelley MJ. Biology of small cell lung cancer. *Lung Cancer* 1995; 12(suppl 3):S5–16.
3. Du YX, Cha Q, Chen XW, Chen YZ, Huang LF, Feng ZZ, Wu XF, Wu JM. An epidemiological study of risk factors for lung cancer in Guangzhou, China. *Lung Cancer* 1996; 14(suppl 1):S9–37.
4. Gao YI, Blot WJ, Zheng W, et al. Lung cancer and smoking in Shanghai. *Int J Epidemiol* 1988; 17:277–80.
5. Lam KY, Fu KH, Wong MP, Wang EP. Significant changes in the distribution of histologic types of lung cancer in Hong Kong. *Pathology* 1993; 25:103–5.
6. Gupta RC, Purohit SD, Sharma MP, Bhardwaj S. Primary bronchogenic carcinoma: clinical profile of 279 cases from mid-west Rajasthan. *Indian J Chest Dis Allied Sci* 1998; 40:109–16.
7. Morita T. Statistical study of lung cancer cases in the Annual of Pathological Autopsy Cases in Japan (1958–1997). *Lung Cancer* 2000; 29(suppl 1):232.
8. Lee CT, Kang KH, Koh Y, Chang J, Chung HS, Park SK, Yoo KY, Song JS. Characteristics of lung cancer in Korea, 1997. *Lung Cancer* 2000; 30:15–22.

9. Seow A, Duffy SW, Ng TP, McGee MA, Lee HP. Lung cancer among Chinese females in Singapore 1968–1992: time trends, dialect group differences and implications for aetiology. *Int J Epidemiol* 1998; 27:167–72.
10. Perng DW, Perng RP, Kuo BI, Chiang SC. The variation of cell type distribution in lung cancer: a study of 10,910 cases at a medical centre in Taiwan between 1970 and 1993. *Jpn J Clin Oncol* 1996; 26:229–33.
11. Limsila T, Mitacek EJ, Caplan LS, Brunnemann KD. History and smoking history of lung cancer cases and implications for prevention in Thailand. *Prev Med* 1994; 23:249–52.
12. Riantawan P, Tungsagunwattana S, Subhannachart P, Yodtasurodom C. Histologic types, staging, resectability and smoking among Thai patients with lung cancer. *J Med Assoc Thai* 1999; 82:121–5.
13. White CS, Templeton PA. Radiologic manifestations of bronchogenic cancer. *Clin Chest Med* 1993; 14:55–67.
14. Seemann MD, Seemann O, Luboldt W, Bonel H, Sittek H, Dienemann H, Staebler A. Differentiation of malignant from benign solitary pulmonary lesions using chest radiography, spiral CT and HRCT. *Lung Cancer* 2000; 29:105–24.
15. Tanaka T, Yamamoto M, Tamura T, et al. Cytologic and histologic correlation in primary lung cancer. A study of 154 cases with resectable tumors. *Acta Cytol* 1985; 29:49–56.
16. Jay SJ, Wehr K, Nicholson DP, Smith AL. Diagnostic sensitivity and specificity of pulmonary cytology: comparison of techniques used in conjunction with flexible fibreoptic bronchoscopy. *Acta Cytol* 1980; 24:304–12.
17. Mehta AC, Lee FYW. Lung Cancer: Sputum cytology. *Clin Chest Med* 1993; 14:69–85.
18. Arroliga AC, Matthay RA. The role of bronchoscopy in lung cancer. *Clin Chest Med* 1993; 14:87–98.
19. Lam WK, So SY, Hsu C, Yu DYC. Fibreoptic bronchoscopy in the diagnosis of bronchial cancer: comparisons of washings, brushings and biopsies in central and peripheral tumours. *Clin Oncol* 1983; 9:35–42.
20. Wong PC, Lee J, Lam FM, Wong CF, Chau CH, Yew WW. Fibreoptic bronchoscopy in the diagnosis of lung cancer. *Monaldi Arch Chest Dis* 1999; 54:394–8.
21. Parker RL, Haesaert SP, Kovnat DM, et al. Bronchial brushing in bronchogenic carcinoma: factors influencing cellular yield and diagnostic accuracy. *Chest* 1977; 71:341–5.
22. Kinnear WJM, Wilkinson MJ, James PD, et al. Comparison of the diagnostic yields of disposable and reusable cytology brushes in fibreoptic bronchoscopy. *Thorax* 1991; 46:667–8.
23. Bilaceroglu S, Kumcuoglu Z, Alper H, et al. CT bronchus sign-guided bronchoscopic multiple diagnostic procedures in carcinomatous solitary pulmonary nodules and masses. *Respiration* 1998; 65:49.
24. Obara M, Satoh H, Ishikawa H, Yamashita YT, Tanaka N, Ohtsuka M, Hasegawa S. Diagnostic procedures in obtaining pathologic materials for pulmonary nodules due to primary lung cancer. *Oncol Rep* 1998; 5:1237–9.
25. Shure D, Fedullo PF. Transbronchial needle aspiration of peripheral masses. *Am Rev Respir Dis* 1983; 128:1090.
26. Wang KP, Haponik EF, Britt EJ, et al. Transbronchial needle aspiration of peripheral pulmonary nodules. *Chest* 1984; 86:819.
27. Pirozynski M. Bronchoalveolar lavage in the diagnosis of peripheral, primary lung cancer. *Chest* 1992; 102:372.
28. Shure D, Conforti JF. Tissue Procurement:bronchoscopic techniques. In: *Lung Cancer: Principles and Practice,* Chapter 31. Eds. Pass HI, Mitchell JB, Johnson DH, Turrisi AT, Minna JD. Philadelphia: Lippincott Williams & Wilkins 2000, 579–90.
29. Ono R, Loke J, Ikeda S. Bronchofiberscopy with curette biopsy and bronchography in the evaluation of peripheral lung lesions. *Chest* 1981; 79:162–6.
30. Mori K, Yanase N, Kaneko M, et al. Diagnosis of peripheral lung cancer in cases of tumors 2 cm or less in size. *Chest* 1989; 95:304–8.
31. Salazar AM, Westcott JL. The role of transthoracic needle biopsy for the diagnosis and staging of lung cancer. *Clin Chest Med* 1993; 14:110.
32. Suzuki N, Saitoh T, Kitamura S. Tumour invasion of the chest wall in lung cancer: Diagnosis with US. *Radiology* 1993; 187:39–42.
33. Pan JF, Yang PC, Chang DB, Lee YC, Kuo SH, Luh KT. Needle aspiration biopsy of malignant lung masses with necrotic centers. *Chest* 1993; 103:1452–6.
34. Wang HC, Yu CJ, Chang DB, Yuan A, Lee YC, Yang PC, Kuo SH, Luh KT. Transthoracic needle biopsy of thoracic tumours by a colour Doppler ultrasound puncture guiding device. *Thorax* 1995; 50:1258–63.
35. Yang PC. Ultrasound-guided transthoracic biopsy of the chest. *Radiol Clin North Am* 2000; 38:323–43.

36. Yang PC. Ultrasonography-guided transthoracic biopsy for peripheral pulmonary nodules. *Lung Cancer* 2000; 29(suppl 2):101.
37. Hsu WH, Ikezoe J, Chen CY, Kwan PC, Hsu CP, Hsu NY, Chiang CD, Ho WL. Color Doppler ultrasound signals of thoracic lesions. Correlation with resected histologic specimens. *Am J Respir Crit Care Med* 1996; 153:1938–51.
38. Okamoto H, Watanabe K, Nagatomo A. Kunikane H, Aono H, Yamagata T, Kase M. Endobronchial ultrasonography for mediastinal and hilar lymph node metastases of lung cancer. *Chest* 2002; 121:1498–506.
39. Larsen SS, Krasnik M, Vilmann P, Jacobsen GK, Pedersen JH, Faurschou P, Folke K. Endoscopic ultrasound guided biopsy of mediastinal lesions has a major impact on patient management. *Thorax* 2002; 57:90–103.
40. Fritscher-Ravens A, Petrasch S, Reinacher-Schick A, Graeven U, Konig M, Schmiegel W. Diagnostic value of endoscopic ultrasonography-guided fine-needle aspiration cytology of mediastinal masses in patients with intrapulmonary lesions and non-diagnostic bronchoscopy. *Respiration* 1999; 66:150–5.
41. Kaseda S, Hangai N, Yamamoto S, et al. Lobectomy with extended lymph node dissection by video-assisted thoracic surgery for lung cancer. *Surg Endosc* 1997; 11:703.
42. Yim AP, Izzat MB, Liu HP, Ma CC. Thoracoscopic major lung resections: an Asian perspective. *Semin Thorac Cardiovasc Surg* 1998; 10:326–31.
43. Gossot D, Toledo L, Fritsch S, Celerier M. Mediastinoscopy vs thoracoscopy for mediastinal biopsy. Results of a prospective nonrandomized study. *Chest* 1996; 110:1328–31.
44. Nomori H, Horio H, Fuyuno G, Kobayashi R, Morinaga S, Suemasu K. Lung adenocarcinoma diagnosed by open lung or thoracoscopic vs bronchoscopic biopsy. *Chest* 1998; 114:40–4.
45. Nakamoto K, Maeda M, Okamoto T, Kameyama K, Sugita A, Haysahi E. Preoperative diagnosis with video-assisted thoracoscopy with miniaturized endoscopes in general thoracic surgery: a preliminary study. *Chest* 1998; 114:1749–55.
46. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest* 1997; 111:1710–7.
47. Stahel R, Aisner J, Ginsberg R, et al. Staging and prognostic factors in small cell lung cancer. *Lung Cancer* 1989; 5:111.
48. Ginsberg RJ. Continuing controversies in staging NSCLC: an analysis of the revised 1997 staging system. *Oncology* 1998; 12(suppl 2):51–4.
49. Lopez-Encuentra A, Bulzebruck H, Feinstein AR. Tumour staging and classification in lung cancer : Summary of the International Symposium. *Lung Cancer* 2000; 29:79–83.
50. Maki DD, Gefter WB, Alavi A. Recent advances in pulmonary imaging. *Chest* 1999; 116:1388–402.
51. Quint LE, Francis IR, Wahl RL, Gross BH. Imaging. In: *Lung Cancer: Principles and Practice.* Eds. Pass HI, Mitchell JB, Johnson DH, Turrisi AT, Minna JD. Philadelphia, Lippincott Williams & Wilkins 2000, 535–78.
52. Mori K, Hirose T, Machida S, Yokoi K, Tominaga K, Moriyama N, Sasagawa M. Helical computed tomography diagnosis of pleural dissemination in lung cancer: comparison of thick-section and thin-section helical computed tomography. *J Thorac Imaging* 1998; 13:211–8.
53. Toloza EM, Harpole L, McCrory DC. Noninvasive staging of non-small cell lung cancer. *Chest* 2003; 123:S137–46.
54. Deslauriers J, Gregoire J. Clinical and surgical staging of non-small cell lung cancer. *Chest* 2000; 117:S96–103.
55. Vansteenkiste JF, Stroobants SG, De Leyn PR, Dupont PJ, Verbeken EK. Potential use of FDG-PET scan after induction chemotherapy in surgically staged IIIA-N2 non-small cell lung cancer: a prospective pilot study. *Ann Oncol* 1998; 9:1193–8.
56. Marom EM, Erasmus JJ, Patz EF Jr. Lung cancer and positron emission tomography with fluorodeoxyglucose. *Lung Cancer* 2000; 28:187–202.
57. Dewan N, Shehan C, Reeb S, et al. Likelihood of malignancy in a solitary pulmonary nodule:comparison of Bayesian analysis and results of FDG-PET scan. *Chest* 1997; 112:416–22.
58. Lowe V, Fletcher J, Gobar L, et al. Prospective investigation of positron emission tomography in lung nodues. *J Clin Oncol* 1998; 16:1075–84.
59. Vansteenkiste JF, Stroobants SG, De-Leyn PR, Dupont PJ, Verschakelen JA, Nackaerts KL, Mortelmans LA. Mediastinal lymph node staging with FDG-PET scan in patients with potentially operable non-small cell lung cancer: a prospective analysis of 50 cases. *Chest* 1997; 112:1480–6.

60. Gupta NC, Graeber GM, Bishop HA. Comparative efficacy of positron emission tomography with fluorodeoxyglucose in evaluation of small (< 1 cm), intermediate (1 to 3 cm), and large (> 3 cm) lymph node lesions. *Chest* 2000; 117:773–8.
61. Vansteenkiste JF. Stroobants SG. The role of positron emission tomography with ^{18}F-fluoro-2-deoxy-D-glucose in respiratory oncology. *Eur Respir J* 2001; 17:802–20.
62. Dwamena BA, Sonnad SS, Angobaldo JO. Wahl RL. Metastases from non-small cell lung cancer: mediastinal staging in the 1990s — meta-analytic comparison of PET and CT. *Radiology* 1999; 213:530–6.
63. Blum J, Handmaker H, Lister-James J, Rinne N. A multicenter trial with a somatostatin analog ^{99m}Tc depreotide in the evaluation of solitary pulmonary nodules. *Chest* 2000; 117:1232–8.
64. Darling GE. Staging of the patient with small cell lung cancer. Chest Surg Clin N Am 1997; 7:81–94.
65. American Society of Clinical Oncology. Clinical practice guidelines for the treatment of unreseactable non-small cell lung cancer. *J Clin Oncol* 1997; 15:2996–3018.
66. Kosuda S, Ichihara K, Watanabe M, Kobayashi H, Kusano S. Decision-tree sensitivity analysis for cost-effectiveness of chest 2-fluoro-2-D-(^{18}F)fluorodeoxyglucose positron emission tomography in patients with pulmonary nodues (non-small cell lung carcinoma) in Japan. *Chest* 2000; 117:346–53.
67. Gambir SS, Hoh CK, Phelps ME, Madar I, Maddahi J. Decision tree sensitivity analysis for cost-effectiveness in FDG-PET in the staging and management of non-small cell lung carcinoma. *J Nucl Med* 1996; 37:1428–36.
68. Valk PE, Pounds TR, Tesa RD, Hopkins DM, Haseman MK. Cost-effectiveness of PET imaging in clinical oncology. *Nucl Med Biol* 1996; 23:737–43.
69. Pieterman RM, van Putten JW, Meuzelaar JJ, Mooyaart EL, Vaalburg W, Koeter GH, Fidler V, Pruim J, Groen HJ. Preoperative staging of non-small cell lung cancer with positron-emission tomography. *N Engl J Med* 2000; 343:254–61.
70. van Tinteren H, Hoekstra OS, Smit EF, van den Bergh JHAM, Schreurs AJM, Stallaert RALM, van Velthoven PCM, Comans EFI, Diepenhorst FW, Verboom P, van Mourik JC, Postmus PE, Boers M, Teule GJJ, and the PLUS study group. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small cell lung cancer: the PLUS multicentre randomized trial. *Lancet* 2002; 359:88–1392.

25 Lung Cancer: Treatment

Reury-Perng Perng and Yuh Min Chen

Introduction

Lung cancer is the leading cause of cancer death in the world, including the Asia region. Approximately one fifth of lung cancer is small-cell lung cancer (SCLC) and the remaining lung cancers are non-small-cell lung cancer (NSCLC). Three predominant histologic types of NSCLC are squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. The biological behaviour, clinical presentation and natural course between SCLC and NSCLC are quite different. The treatment principle of SCLC is thus different from NSCLC and will be discussed separately. The treatment principle of different cell types among NSCLC is the same and will be discussed together.

Small-Cell Lung Cancer

More than half of small-cell lung cancer (SCLC) patients present with overt evidence of distant metastases, and most of those with seemingly localized disease are presumed to have occult metastasis (1). The potential for early metastatic involvement and its high sensitivity to cytotoxic agents has made chemotherapy the foundation for treatment of this disease. For patients with limited disease, the treatment of choice is chemotherapy in combination with radiotherapy. For patients with extensive disease, the treatment of choice is chemotherapy. Prophylactic cranial irradiation can be performed in those patients with a complete response to treatment. Surgical treatment is still not the treatment of choice at this time, and systemic chemotherapy should be given if patients are found to suffer from SCLC after the operation, even in the early stage.

Single-agent chemotherapy

Small-cell lung cancer exhibits sensitivity to a variety of chemotherapy agents (Table 1) (2). Many single agents have yielded objective response rates

Table 1. Active Single Agent Against Small-Cell Lung Cancer

Conventional Agents	*New Agents*
methotrexate	paclitaxel
cyclophosphamide	docetaxel
ifosfamide	irinotecan
doxorubicin	topotecan
vincristine	vinorelbine
vindesine	gemcitabine
etoposide	
teniposide	
cisplatin	
carboplatin	
nitrosoureas	

ranging from 15% to 50% in patients, whether previously treated or not, and a more than 30% response rate in previously untreated patients. Conventional active agents include methotrexate, cyclophosphamide, ifosfamide, doxorubicin, vincristine, vindesine, etoposide, teniposide, cisplatin, carboplatin, and nitrosoureas. The activity of these different agents appears to be highly dependent on whether there was prior therapy or not. For example, short-course intravenous etoposide showed a response rate of less than 20% in patients with prior chemotherapy and a response rate of 40% to 60% in chemo-naïve patients (3). In the past decade, several new agents have been found to possess activity against SCLC, including paclitaxel, docetaxel, irinotecan, topotecan, vinorelbine, and gemcitabine (4). These new agents are appealing because of their novel mechanisms of action.

In clinical practice, however, single-agent chemotherapy for chemo-naive SCLC patients is rarely applied because complete remissions are relatively infrequent and the remission duration tends to be brief. In general, combination chemotherapy is used to treat these patients in clinical practice.

Combination chemotherapy

Combination chemotherapy is the cornerstone of treatment for SCLC. After the diagnosis and staging of SCLC, induction chemotherapy should be given in extensive-stage, and induction chemotherapy plus radiotherapy (concurrent, sequential, or alternating) be given in limited-stage SCLC, as soon as possible. Commonly-used combination chemotherapies for SCLC include etoposide plus cisplatin (with or without a third drug, such as ifosfamide or paclitaxel), cyclophosphamide plus doxorubicin plus vincrisitne (CAV), cyclophosphamide plus etoposide plus vincrisitine (CEV), and cisplatin plus oral etoposide. The treatment usually consists of 4 to 6 cycles, unless early progression is noted. In randomized trials conducted in the 1970s, combination therapy was shown to produce higher overall and more complete response rates and superior survival compared to single-agent treatment. In addition, the simultaneous administration of multiple agents has been found to be more effective than the sequential administration of the same agents. Consequently, combination chemotherapy has been the mainstay of treatment for more than 20 years. When considering the therapeutic efficacy of any given combination regimen, the activity of the cytotoxic agents used was more important than the dose. A randomized trial comparing high-dose versus conventional-dose cyclophosphamide, doxorubicin, and vincristine(5), and another randomized trial of high-dose versus standard-dose cisplatin and etoposide (6), both performed in extensive-stage SCLC patients, failed to show any evidence of superior efficacy or prolonged survival in patients receiving the higher dose.

Several chemotherapy combination regimens have demonstrated acceptable and similar activity against SCLC. In general, active combination regimens yield objective response rates in the range of 70% to 90%, with complete remissions occurring in 20% to 50% of patients, depending on the stage at presentation. Median survival could be up to 18–20 months in patients with a limited stage, and was around 7 to 9 months in extensive-stage patients (2,7–9). The best survival was achieved in patients with a good performance status who presented with limited-stage disease and who received a combined modality treatment with chemotherapy plus thoracic radiotherapy (7,8). No induction combination chemotherapy regimen has been found to be suitable for all patients. Prior to the identification of etoposide as an active agent, cyclophosphamide, doxorubicin, and vincristine (CAV) was one of the most commonly used regimens. However, the cardiac and mucosal toxicities of doxorubicin caused problems in patients, especially when thoracic radiotherapy was used in combination. The substitution of etoposide for doxorubicin in the CAV combination was proven more effective and less toxic in a later randomized trial (10) and since the early 1980s, an etoposide-based treatment, or etoposide in combination with cisplatin, has replaced doxorubicin-based treatment.

The high effectiveness of etoposide plus cisplatin (EP) was first identified in relapsed disease, where it produced a 40% to 50% objective response rate with minimal toxicity (11). This combination has then been tested widely as a first-

line therapy. It was found to be very active and well-tolerated if no other chemotherapeutic agent was added (2,12,13). In addition, an etoposide plus cisplatin regimen can be safely administered with concurrent thoracic radiotherapy, due to its lack of significant mucosal toxicity, and is effective at less myelosuppressive dose levels. In direct comparisons to the CAV regimen, however, EP failed to demonstrate a clear survival advantage in patients with extensive-stage disease (14). Thus, the choice of combination chemotherapeutic agents is usually affected by the patient's coexisting medical problems. For example, cisplatin is contraindicated in patients with pre-existing renal dysfunction, heart failure, and neuropathy. Likewise, doxorubicin is contraindicated in patients with preexisting heart failure.

Despite the high response rate to first-line chemotherapy, most patients suffered from a relapse of drug-resistant disease within months. Several approaches have been explored to prevent this disappointing outcome, including alternating and/or sequential strategies, such as EP plus CAV, but the results have been controversial, so the approaches are not recommended until more active and significantly non-cross-resistant agents and regimens can be found (14). Another strategy is to increase the dose intensity of therapy (increase the number of chemotherapeutic agents, decrease cycle duration, or change to a weekly schedule; with or without colony-simulating factor and/or stem cell support), but these results have also been controversial (6,15,16). It is reasonable to conclude that chemotherapy dose intensification is likely to be harmful and not beneficial to extensive-stage patients. Further large-scale randomized studies or meta-analyses are needed before high dose chemotherapy can be recommended to patients with SCLC, especially those with limited-stage disease. Clinical trials involving new anti-cancer drugs against SCLC performed in Asian region were mainly in Japan, such as irinotecan plus cisplatin in previously untreated SCLC that had promising results, and phase III study comparing cisplatin plus irinotecan or etoposide had been on-going (17).

The optimal duration of induction chemotherapy for SCLC is not currently well-defined. Although there have been few trials addressing the optimal duration of therapy, most doctors administer first-line therapy for 4 to 6 cycles. A prolonged treatment is usually considered unnecessary because a survival benefit has not been demonstrated in many randomized trials of either limited-or extensive-stage SCLC (18,19). Based on these randomized studies, the appropriate duration of induction chemotherapy for SCLC is 4 to 6 cycles of a standard chemotherapy regimen in both limited- and extensive-stage disease. Maintenance chemotherapy beyond 6 cycles is unnecessary and more likely to produce treatment-related toxicity than to extend survival or improve life quality, provided that salvage treatment is re-instituted at the time of relapse.

Salvage chemotherapy

A majority of chemotherapy-treated patients eventually suffer from disease relapse. There are relatively few drugs capable of effecting tumour regression in this setting, and there is no established standard salvage chemotherapy. The results of salvage chemotherapy after the failure of EP or comparable first-line regimens have been dismal. One study found that patients who relapsed 3 months or more after completion of induction therapy, with more than 9 months' response duration to induction therapy, and those with a previous complete response to induction therapy, had a better response to salvage therapy (20). As mentioned above, the EP regimen has been shown to be effective in patients with relapse who were treated initially with CAV, with response rates approaching 50%, whereas CAV is relatively ineffective as a second-line regimen. Oral etoposide given over a protracted course has produced response rates of 23% to 45% in studies of relapsed small-cell lung cancer patients, including patients previously treated with intravenous etoposide. However, response was rarely found in the absence of a 3-month drug-free interval.

New chemotherapeutic agents have demonstrated a response rate of more than 20%, with possible relief symptoms and prolonged survival in many phase II studies of salvage chemotherapy, such as topotecan (response rate 24.3%, median survival 25 weeks) (21), paclitaxel plus carboplatin (response rate 73.5%; median

survival 31 weeks) (22), and irinotecan plus etoposide (response rate 71%; median survival 38.7 weeks) (23). However, none of these available salvage therapies is adequate, and the patients should be considered for clinical trials of new therapeutic agents.

Thoracic irradiation

The chest is the commonest site of relapse in patients with limited-stage small-cell lung cancer after chemotherapy-induced complete remission. A meta-analysis documented that the addition of radiotherapy to combination chemotherapy increased the complete response rate by 10% to 40%, reduced the incidence of chest relapses by 10% to 20%, and increased the long-term survival rate by 5% to 15% (24). The recognition of the benefit of thoracic radiotherapy, when properly combined with chemotherapy (especially etoposide plus cisplatin, which decreases the haematological and mucosal toxicities induced by doxorubicin-based chemotherapy), can be viewed as one of the major advances in the treatment of limited-stage SCLC in the past two decades.

There are still controversies and a lack of agreement about the issues of dose, volume of irradiation, fractionation, and timing with chemotherapy, for limited-stage SCLC. A radiation dose of 45 to 50 Gy was associated with a 50% to 75% local failure rate when administered in once-daily treatments for 5 weeks (25,26). Recent trials have all adopted a higher dose of 60 to 63 Gy, or even higher, because of one previous study which used a dose of 60 Gy with a local recurrence rate of 3% (27). The issue of volume of irradiation is integrally related to the timing of modalities. If radiotherapy accompanies the first cycle of chemotherapy, the choice is the initial tumour volume irradiation. On the other hand, the advantage of the post-chemotherapy manoeuver is a smaller target that exposes less normal tissue. On the issue of fractionation, twice-daily fractionation providing 45 Gy for 3 weeks yielded a better survival than the same dose administered conventionally over 5 weeks; however, there was a significantly worse toxicity, especially oesophagitis (26). The timing of thoracic irradiation in the combined modality treatment of limited-stage SCLC is very crucial. Studies have shown that early administration of radiotherapy is superior to late treatment (7). Results from another two randomized trials also support the contention that early dose-intense radiation can improve loco-regional control with an impact on long-term survival and the pattern of recurrence (26,28). The early addition of thoracic irradiation to chemotherapy appears to yield the best results, but maintaining the dose intensity of both modalities is also critical (29). However, late intensification of chemotherapy was associated with unacceptable toxicity and did not appear to have a favourable impact on survival (29). There was no report of large randomized trial of chemoradiotherapy in Asian countries. A Japanese small phase II study showed effectiveness of this kind of treatment in patients with limited disease (30).

Palliative irradiation to the chest, as well as to the sites of distant metastases, such as the brain and bone, plays an important role in the relieving the symptoms of patients with extensive disease. Still, it is not associated with a survival benefit in this setting.

Prophylactic cranial irradiation

CNS metastases are an important cause of morbidity and mortality in small-cell lung cancer patients. Approximately 20% of these patients at the time of diagnosis, and up to 50% of patients surviving 2 years, have brain metastases, and postmortem evidence of tumour involvement of the brain was found in more than 80% of all SCLC patients (1). Furthermore, the brain is the first and often the only site of failure in more than half of these patients (1). Hence, the concept of using elective brain irradiation to treat occult micrometastatic disease was developed.

At the beginning of clinical trials involving prophylactic cranial irradiation, several trials demonstrated a significant reduction in brain relapse rates in SCLC, from an average of 22% without prophylactic brain irradiation to an average of 8%. However, none of the randomized trials have demonstrated an improvement in overall survival, even in patients with complete remission of systemic disease (31). In addition, late-

developing toxic effects of elective brain irradiation, particularly cognitive impairment and ataxic gait, have become apparent when patients have long-term disease-free survival. Factors influencing the risk of late brain toxicity include the total cranial irradiation dose, the dose per fraction, the temporal relationship of radiotherapy to chemotherapy, and possibly the specific chemotherapeutic agents given. The failure to demonstrate improved survival and concerns about toxicity positioned prophylactic cranial irradiation as a controversial and optional treatment. However, a new wave of randomized trials began in the early 1990's have been completed (32,33). After a review of these studies, clinicians can conclude that prophylactic cranial irradiation halves the lifetime risk of cerebral metastases in SCLC patients and is associated with a significant survival benefit. There is no detectable association between prophylactic cranial irradiation and neuropsychometric impairment, and no evidence of impairment of quality of life. Therefore, prophylactic cranial irradiation should become a part of the standard treatment for patients with a complete response to chemotherapy treatment (34).

Surgery pre- or post-chemotherapy

Less than 10% of patients with small-cell lung cancer are eligible for curative surgical resection at the time of presentation because of the tumour cell's early spreading to regional lymph nodes and haematogenous metastases. Even among this highly select subgroup of SCLC patients, surgery alone seldom results in long-term survival, with a 5-year survival rate of 10% or less. However, if surgery is performed before chemotherapy or in an adjuvant setting, it results in improved local control. The patients who appear to benefit most from combined-modality therapy are those without nodal involvement (stage I disease). The survival rate is significantly shorter when lymph nodes are involved, especially in the mediastinum. Therefore, surgical resection is usually not indicated in SCLC patients unless they are without nodal involvement, and adjuvant chemotherapy is needed even if curative resection is performed (35).

Non-Small-Cell Lung Cancer

Non-small-cell lung cancer (NSCLC) remains one of the most devastating illnesses in the world in terms of the number of patients and the overall mortality. Surgery offers the potential for significant long-term survival in those patients diagnosed with early, local disease. Unfortunately, 75% of all NSCLC patients have regional, nodal, or metastatic involvement at the time of presentation. The treatment of NSCLC is based on the stage of the disease at presentation. Stages I and II patients are good candidates for surgical resection. However, the majority of NSCLC patients have advanced disease at presentation. Multi-modality treatment for locally advanced disease (stage III), involving combinations of chemotherapy, surgery, and radiotherapy, are being actively studied with encouraging results. Stage IV patients with a good performance status can be treated with cisplatin-based chemotherapy, especially in combination with new anti-cancer drugs.

Stages I and II non-small-cell lung cancer

Surgical resection is the preferred form of therapy when feasible, including stage I and stage II patients. Surgical resection is also the treatment of choice in some stage IIIa NSCLC patients (those mostly in need of multi-modality treatment). Unfortunately, only a minority of all patients (20% to 30%) are considered potentially resectable at the time of diagnosis. However, despite a thorough investigation prior to surgery, patients frequently are found to have more extensive disease at the time of thoracotomy. On the basis of clinical findings, only 65% of patients who are deemed to have stage I disease prior to thoracotomy are classified as having stage I disease postoperatively.

Prior to a curative surgery, a complete evaluation of the patient's condition, especially cardiopulmonary functioning, is required. Recent myocardial infarction (within 6 months), a forced expiratory volume in the first second (FEV1) of less than 1.5 L before operation, or a predicted post-operative FEV1 of less than 0.8 L are often contraindications to surgery.

There is no definitive conclusion regarding the extent of resection necessary (pneumonectomy, lobectomy, wedge, or segmental resection) as long as all of the local tumour is clearly removed (pathologically negative margins). However, local recurrence is probably greater in those having wedge or segmental resections. Overall mortality for patients receiving curative surgery ranges between 5% and 10%. Video-assisted lobectomy with radical lymphadenectomy for primary lung cancer is another surgical procedure under investigation, especially in Japan (36).

Peribronchial, hilar, subcarinal, and mediastinal lymph-node sampling during definitive resection are needed to provide the surgical pathologic staging information that would help determine the therapeutic and prognostic implications. Overall, 30% to 40% of patients who receive "curative" surgery for NSCLC survive 5 years. Those with stage I disease experience a 5-year survival rate ranging from 54% to 85%, largely depending on the size of the tumour and the histological type. Five-year survival in stage II and highly selective IIIa patients is approximately 40% and 25%, respectively. In general, surgical staging I and II patients have a 5-year survival of approximately 65% and 40%, respectively (37).

Although surgery is the standard treatment for stage I and II disease, curative radiotherapy is the treatment of choice when patients cannot undergo surgery due to inadequate cardio-pulmonary reserve or other severe systemic disease. Several studies have reported five-year survival rates of 15% to 20% when potentially curative radiotherapy is used in medically inoperable patients. The decreased survival is probably due, in part, to the lack of pathological staging and co-existing severe systemic disease in this population.

Photodynamic therapy for early stage lung cancer have been performed in several phase II trials. Since 1980 at the Tokyo Medical College, 240 patients have had 283 lung cancers treated with photodynamic therapy. These data led to the approval of photodynamic therapy for early-stage lung cancer in Japan in 1994 (38). Among 95 early stage lesions, complete remission was obtained in 83.2% and 71 cases were disease-free at 3 to 176 months (38).

The major causes of mortality in patients with stage I and II disease are distant metastasis or second primary tumours. This has led to current studies aimed at identifying prognostic factors that may indicate those patients at risk for relapse and to trials of neoadjuvant chemotherapy. At present, there is no evidence to support the use of adjuvant chemotherapy or radiotherapy in stage I patients. However, since these patients are at increased risk for second primary tumours or disease recurrence, close follow-up is indicated. A Japanese study using non-specific immunotherapy after surgery in stage I patients showed better survival than those without immunotherapy (39). However, immunotherapy after surgical treatment did not have constant benefit to the patients and need further studies. Neoadjuvant chemotherapy for stage II disease is still controversial and requires more randomized studies to reach a conclusion.

Stage III non-small-cell lung cancer

The use of combined-modality therapy in stage III NSCLC has been an area of intensive investigation in the past two decades. Such intensive research, in turn, has led to the subdivision of stage III disease into stage IIIa (potentially resectable) and stage IIIb (not resectable), based on the difference in outcomes following surgical resection. Stage IIIa patients have a 5-year survival rate approaching 15% with surgery, whereas stage IIIb patients have a 5-year survival rate less than 5% (37). At the present time, the proper treatment for patients with stage IIIa disease might be neoadjuvant chemotherapy, followed by surgery and adjuvant chemotherapy and/or radiotherapy. For patients with stage IIIb without malignant pleural or pericardial effusion, chemotherapy in combination with radiotherapy is the proper choice of treatment. For patients with stage IIIb with malignant pleural or pericardial effusion, chemotherapy is the treatment of choice.

Surgery

The efficacy of surgery varies with the subset of stage III disease. For instance, patients whose stage III classification is based on T3N0Mo disease have the most favourable outcome, and now have been moved from stage IIIa to stage IIb according to

the new staging criteria. However, patients whose stage III classification is based on N2 disease have a less favourable outcome. In a large series of patients seen at Memorial-Sloan Kettering Cancer Center (40) the 5-year survival rate for patients with N2 disease was 30%. However, the majority of survivors consisted of patients who were clinically N0 or N1 and were found to have N2 disease at surgery. Among those patients with clinically evident N2 disease, the 5-year survival rate was only 9%.

Radiotherapy

Radiotherapy has long been considered standard for patients with locally unresectable tumour who show no demonstrable distant metastasis (stage IIIb and some stage IIIa). Early reports established a small survival advantage for radiotherapy over no therapy in such patients. The 1990s standard therapy was 50 to 60 Gy in 0.2 Gy fractions five times weekly for 5 to 6 weeks, based on a Radiation Oncology Study Group trial which found improved local control and a non-significant trend toward improved survival at 2 years among patients receiving 50 to 60 Gy versus 40 Gy (19% survival versus 11%, respectively) (41). A retrospective study performed in China found that overall treatment time should be kept as short as possible for better local control (42). To study the relationship between radiotherapy and survival in detail, a study performed by the Southeastern Oncology Group randomized patients with locally advanced, unresectable NSCLC to receive either radiotherapy (60 Gy), chemotherapy (vindesine), or a combination of radiotherapy and vindesine. Median survival times with the three treatment regimens were 8.6, 10.1, and 9.4 months, respectively. The study concluded that radiotherapy alone did not improve survival in patients with locally advanced NSCLC (43). However, treatment with the single agent vindesine at 3 mg/m^2 is currently considered sub-optimal chemotherapy and would not be expected to have a significant impact on survival. Thus, this arm somewhat more likely represents a control arm rather than a chemotherapy arm. Second, the vindesine-only patients were crossed over to radiotherapy if they became symptomatic, which occurred in 37% of the patients initially assigned to this treatment. Therefore, a conclusion of this study may be that early radiotherapy has no benefit over late thoracic radiotherapy. In other words, there was no disadvantage in delaying radiotherapy if the patients had received chemotherapy initially, followed by radiotherapy, if needed. The radiation dose has been increased to 60–70 Gy in recent years, with the addition of the 3-dimensional method.

The RTOG reported that a subset of patients with locally advanced, unresectable stage III disease, who had a good performance status, no supraclavicular nodes, and less than 6% weight loss, demonstrated increased survival with a twice-daily radiation treatment dose escalating from 60 to 79.2 Gy (44). Patients in this subset who received 69.6 Gy or higher were found to have a longer median survival (13 months) than patients receiving 60 Gy, who had a median survival of 10 months. The improved median survival seen with higher doses of radiotherapy implied that improvements in local therapy could possibly increase survival in locally advanced disease. Because the overall survival of stage III patients remains poor after radiotherapy or surgery alone, the role of multi-modality therapy has become an area of intensive investigation.

Combined-modality approaches

Adjuvant chemotherapy The role of adjuvant chemotherapy after surgical resection in stage IIIa non-small-cell lung carcinoma is still controversial and requires further randomized studies. Generally, chemotherapy can increase patients' disease-free survival, but with only a non-significant trend of increase in overall survival. The Lung Cancer Study Group (45) randomized 141 patients with resected stage II or III adenocarcinoma or large-cell carcinoma (pathology staging) to receive either cyclophosphamide, doxorubicin, and cisplatin (CAP), or a control-like regimen of intrapleural immunotherapy with BCG and levamisole. Disease-free survival increased by 7 months ($p = 0.018$) in the group receiving chemotherapy, and overall survival was also increased by 7 months ($p = 0.08$). Furthermore, in another Lung Cancer Study Group trial (46) of squamous-cell carcinoma patients with positive margins or involved high paratracheal nodes, those patients who received concurrent chemotherapy (CAP) and radiotherapy showed improved disease-free

survival, compared with those who received radiotherapy alone (14 *vs* 8 months, p ≤ 004). However, overall survival was not significantly improved. A randomized study performed in Korea of stage II patients showed lower metastatic rate and marginal survival benefit in patients receiving adjuvant chemotherapy than post-operative radiotherapy alone (47). In contrast, a large randomized trial performed in Japan showed significant survival benefit in stage I-III patients receiving adjuvant chemotherapy after surgery compared to surgery alone (48). In summary, conventional chemotherapy adjuvant to surgery in stage II or stage III patients has produced a marginally significant increase in disease-free survival and a non-significant trend toward improved overall survival.

Neo-adjuvant chemotherapy The role of neo-adjuvant chemotherapy before surgical resection in stage II or stage IIIa non-small-cell lung carcinoma is more important today than before, as evidenced by the published data of many clinical trials in the past decade. Patients with locally advanced NSCLC tend to respond to chemotherapy much better than those with more extensive disease. Chemotherapy has therefore been tried preoperatively to produce tumour shrinkage so that a curative resection can be attempted. The use of chemotherapy prior to surgery in cases of stage IIIa disease has been investigated in several single-arm trials. Several of these studies demonstrated response rates of 50% to 70% with chemotherapy, about half of the patients were able to undergo resection, 9%–11% of patients were found to have no viable tumour at resection, and long-term, disease-free survival was reached in 20% to 30% of patients with stage IIIa disease, which appears to be an improvement over the 10% survival rate seen in historical controls. However, since locally advanced NSCLC has such a variable prognosis, we still need more randomized trials to clearly demonstrate the benefit of neo-adjuvant chemotherapy. Rosell R et al conducted a randomized trial to examine the possible benefit of preoperative chemotherapy and surgery for the treatment of patients with NSCLC (49). Sixty patients with stage IIIa non-small-cell lung cancer were enrolled and randomly assigned to receive either surgery alone or three courses of chemotherapy (mitomycin, ifosfamide, cisplatin) given intravenously at three-week intervals, followed by surgery. All patients received mediastinal radiation after surgery. The median period of survival was 26 months in the patients treated with chemotherapy plus surgery, as compared with 8 months in the patients treated with surgery alone (P < 0.001); the median period of disease-free survival was 20 months in the former group, as compared with 5 months in the latter (P < 0.001). The investigators concluded that preoperative chemotherapy increases the median survival in stage IIIa patients with NSCLC. However, these encouraging data require confirmation with more patient studies and further follow-up before neo-adjuvant chemotherapy can be recommended routinely.

Preoperative radiotherapy Preoperative radiotherapy is usually not considered because of it is a form of local treatment and the resection is more difficult in those receiving high-dose radiotherapy. Superior sulcus tumours represent a unique subset of the disease among stage III patients. Some small studies performed more than 20 years before have demonstrated improved survival in patients with superior sulcus tumours who received preoperative radiotherapy, when compared to historical controls. However, randomized trials are still needed to confirm this finding.

Adjuvant radiotherapy An improvement in overall survival had been reported, two decades before, in several retrospective studies of radiotherapy following resection of stage II or III NSCLC. However, the Lung Cancer Study Group (50) conducted a large randomized trial and failed to demonstrate a survival benefit of postoperative radiotherapy in patients with resected stage II or III squamous-cell carcinoma, although a significant decrease in local recurrence was found. The recurrence rate also decreased in patients with N2 disease, though survival was not improved.

Chemoradiotherapy The combination of chemotherapy and radiotherapy in the treatment of locally advanced NSCLC has been an active area of research in the past two decades. In patients with locally advanced unresectable NSCLC (stages

IIIa and IIIb), several trials comparing radiotherapy alone versus radiotherapy plus chemotherapy have been conducted. While the results have been variable, the majority of studies demonstrate a statistically significant improvement in response rate and/or survival in those receiving combined modality therapy. A small phase II trial conducted in Thailand involving 15 stage IIIa/b patients also showed promising effect of combining chemotherapy (paclitaxel, carboplatin) and radiotherapy (51). A phase II study involving induction chemotherapy followed by concurrent chemoradiotherapy also yielded promising results in Singapore (52). Of the large randomized trials performed to date, those conducted by three different groups all have shown improved survival, albeit modest, in patients receiving chemotherapy plus radiotherapy. However, these trials have used two different approaches in combining of chemotherapy and radiotherapy, including sequential and concurrent chemoradiotherapy (53,54). The American Society of Clinical Oncology guideline for the chemotherapy of unresectable stage III NSCLC patients suggests that chemotherapy plus radiotherapy prolongs patient survival as compared to radiotherapy alone, and is appropriate for patients with a performance status (Zubrod scale) of 0 and 1, and possibly 2 (55).

On the other hand, Mattson et al found no benefit in chemotherapy alternated with radiotherapy versus radiotherapy alone; however, the chemotherapy was given during the interval between two courses of radiotherapy (56). The presence of a gap during radiotherapy has been considered sub-optimal in radiotherapy-only trials. In addition, if only locally advanced patients are evaluated, a strong trend toward improved survival is found in the chemotherapy-plus-radiotherapy arm. A Japanese phase III randomized study also revealed that concurrent approach yielded a significantly increased response rate and longer median survival than sequential approach in selected unresectable stage III patients (57).

The studies reported by Le Chevalier et al involved cisplatin-based chemotherapy prior to radiotherapy. The patients receiving chemotherapy had a significant survival advantage. Of particular interest, Le Chevalier et al found significantly less metastatic disease failure in patients given chemotherapy. Chemoradiotherapy, however, failed to demonstrate improved survival when sub-optimal chemotherapy and/or sub-optimal radiation therapy was given (58).

Another approach involved the use of concurrent chemoradiotherapy to take advantage of the radiosensitizing effects of cisplatin in patients with inoperable tumours. Soresi et al found a trend toward improved survival in a group of patients receiving cisplatin (15 mg/m^2/week) in addition to radiotherapy (59). Furthermore, a significant decrease in the rate of intrathoracic relapses was noted in the chemoradiotherapy arm versus the radiotherapy-only arm (48% versus 59%). Schaake-Konning et al also found a statistically significant survival advantage for patients receiving daily cisplatin (6 mg/m^2) combined with radiotherapy, compared with patients who had received radiotherapy alone [54]. This study also showed a decrease in the local recurrence rate with the combination of chemotherapy and radiotherapy.

While these studies together suggest a benefit for the addition of chemotherapy to radiotherapy, the best way of combining the two is still undetermined for stage III NSCLC patients.

Stage IV non-small-cell lung cancer

Chemotherapy

The most important objectives of chemotherapy in NSCLC are to prolong survival and/or improve quality of life. The drug most often used in the treatment of NSCLC is cisplatin, which constitutes a major component of any combination chemotherapy in stages III and IV disease (55). Conventional cisplatin-based chemotherapy regimens have been shown to prolong survival, relieve symptoms, be cost-effective, and improve the quality of life in advanced NSCLC patients with a good performance status (60,61). Meta-analyses showed that the cisplatin-containing regimen could prolong NSCLC patients' median survival for 6 weeks as compared to the best supportive care alone (60,61). Cisplatin-based combination chemotherapy has also been shown to reduce the risk of death by 27%, equivalent to an absolute improvement in survival from 5% to 15% a year (62). A prospective randomized

study performed in Thailand and studies in Hong Kong also revealed combination chemotherapy improved patient's quality of life and/or survival (63,64).

The response rates from phase II trials of combination chemotherapy containing platinum for NSCLC ranges widely from 10% to 50%, but has been approximately 25% in large phase III randomized trials for NSCLC in recent years, a response rate which is higher than that of a decade ago (65). Despite these improvements, gastrointestinal and bone marrow toxicity induced by the cisplatin-containing regimen is still a major concern in the treatment of cancer patients when the patients' quality of life, in addition to the prolonging of patients' limited life span, is taken into account during treatment. Multiple single agents (> 50) have been tested in the past 30 years, but only a few have produced response rates > 15%. Among conventional drugs, cisplatin, ifosfamide, and mitomycin C are the most active single agents, while vindesine, vinblastine, etoposide, and epirubicin also appear to have modest activity. The active single agents used in NSCLC are listed in Table 2. Use of a single new anti-cancer agent alone has been demonstrated to have similar effects on the median survival of patients treated with conventional cisplatin-based agents in randomized trials (66).

Table 2. Effective Chemotherapeutic Agents for Non-Small-Cell Lung Cancer

Conventional drugs	*New anti-cancer drugs*
> 20% response rates	>20% response rates
cisplatin	paclitaxel
ifosfamide	docetaxel
mitomycin C	vinorelbine
10–20% response rates	gemcitabine
etoposide	topotecan
vinblastine	irinotecan
vindesine	
epirubicin	

There are many prognostic factors that have been identified to help determine whether chemotherapy is potentially beneficial in a specific patient. Patients with bulky disease experience response rates and survival inferior to those with less bulky disease. In addition, those with locally advanced disease have superior response rates and survival compared to those with metastatic disease. A poor performance status (Zubrod score ≥ 3) is the single most important predictor of a poor response to and poor tolerance (increased toxicity) of chemotherapy. The American Society of Clinical Oncology guideline for the chemotherapy of metastatic NSCLC patients suggests that chemotherapy prolongs patient survival, and that patients with a performance status of 0, 1 (and perhaps 2) should receive chemotherapy as soon as the disease and staging is confirmed (55). Platinum-based chemotherapy should be used unless the patient takes part in a well-designed clinical trial in which non-platinum combination chemotherapy is given. In patients with unresectable stage III NSCLC who are candidates for combined chemotherapy and radiotherapy, and in stage IV patients, the chemotherapy should be no more than 8 cycles (55).

New anti-cancer agents In the early 1990s, six new chemotherapy agents with activity in lung cancer were discovered. These agents included the taxanes (paclitaxel and docetaxel), vinorelbine, gemcitabine, and the topoisomerase I inhibitors (irinotecan and topotecan). During the ensuing 10 years, clinical trials with these agents alone or in combination with a platinum agent have been conducted to determine their superiority over currently used agents. These newer agents effectively prolonged patient survival with less toxicity than that of older agents. All these new agents had response rates of more than 20% in phase II studies of NSCLC. Randomized trials also revealed that the efficacy of a single new anti-cancer agent almost equals that of conventional cisplatin-based chemotherapy, with less toxicity (66,67). Vinorelbine plus cisplatin, gemcitabine plus cisplatin, and paclitaxel plus cisplatin, all showed superior response rates, a better quality of life, and/or better survival than conventional cisplatin-based chemotherapy (cisplatin plus etoposide) and/or cisplatin alone (66,68,69). Thus, a novel new agent plus platinum has become the standard treatment for patients

with advanced-stage NSCLC. In general, new anti-cancer drugs in combination with cisplatin prolong patient median survival about 2–3 months, as compared to conventional cisplatin-based chemotherapy. On the other hand, conventional cisplatin-based chemotherapy prolonged patients' median survival about 2–3 months as compared to the best supportive care alone. So, we can assume that new anti-cancer drugs in combination with cisplatin prolong patient median survival about 4–6 months as compared to the best supportive care alone. This hypothesis still requires randomized trials to reach conclusive proof. However, it is very difficult to perform such randomized trials because of ethical concerns. There were also many reported clinical trials using these new anti-cancer drugs in Asian region, including vinorelbine plus cisplatin study in Taiwan (70), paclitaxel plus carboplatin study in Thailand (71), irinotecan plus cisplatin and granulocyte colony-stimulating factor in Japan (72) and a multicentre study of docetaxel plus cisplatin reported from Hong Kong (73).

Choosing a particular platinum-containing regimen became a dilemma because it implied that one combination was superior to another. The first completed randomized trial that compared two new regimens was conducted by the South-West Oncology Group (SWOG) (74). Patients were randomized to receive either vinorelbine plus cisplatin or paclitaxel plus carboplatin. There was no significant difference in response rates, median survival, or 1-year survival rates between the two arms. Modest differences in toxicity were observed, with leucopenia, nausea, and vomiting occurring more often in the vinorelbine arm and peripheral neuropathy occurring more often in the paclitaxel arm. The SWOG recommended either regimen for the treatment of advanced-stage NSCLC. The definitive answer to questions regarding the similarities and differences between the new regimens came from the Eastern Cooperative Oncology Group four-arm trial that compared paclitaxel and cisplatin to gemcitabine plus cisplatin, docetaxel plus cisplatin, and paclitaxel plus carboplatin (75). There seemed to be no major differences in survival rates among the different arms, and only some minor differences in toxicities were found. However, this randomized trial did not include vinorelbine treatment.

In addition to using a new anti-cancer agent in combination with cisplatin, non-platinum-based chemotherapy and triplet therapy have played a relatively more active role in clinical trials in recent years (76–78). Although three-drug (triplet) regimens have not been shown to be superior to two-drug regimens in lung cancer, the reevaluating of this approach with the inclusion of new agents deserves to be investigated, especially because of the milder toxicity profiles of these new agents. Vinorelbine plus gemcitabine is the non-platinum regimen most frequently studied, and has been well tolerated (78,79). Paclitaxel plus gemcitabine treatment has also been tolerated well with minimal myelosuppression (79). On the other hand, docetaxel plus vinorelbine was toxic without any additional benefit over current regimens (79). Triplet therapy containing one or two new anti-cancer agents, or non-cisplatin based new anti-cancer drug therapy, has been found to be at least as effective as doublet therapy containing cisplatin and a new anti-cancer agent, with less toxicity (non-cisplatin regimens) or comparable toxicities (triplet regimens). Determining the optimal dose and schedule of these new agents is an ongoing task. For example, a recent study of a weekly schedule of paclitaxel has produced promising results (80). Akerley et al showed that paclitaxel 100 to 200 mg/m^2 given weekly for 6 of 8 weeks resulted in less toxicity, enhanced dose-intensity, and marked activity in untreated NSCLC patients (80). The results of their further phase II study suggest that weekly paclitaxel is highly active in NSCLC, with results comparable to those of two-drug regimens but with less toxicity (81). Studies that evaluate a weekly schedule of docetaxel are also showing efficacy with reduced toxicity.

Questions remain regarding the new anti-cancer agents' optimal potential, including their role as single agents, and in doublet and, possibly, three-drug regimens. Is any one new agent superior to another? Is the value of platinum compounds jeopardized by these new agents? At present, it is acceptable, and ethical, to give patients platinum plus new anti-cancer agents (doublet or triplet), or two non-cisplatin-based new anti-cancer agents.

Salvage chemotherapy In 1997, the American Society of Clinical Oncology published clinical

practice guidelines for the treatment of unresectable non-small-cell lung cancer. The guidelines mentioned that there is no evidence that either confirms or refutes whether or not second-line chemotherapy improves survival in non-responding or progressing patients with advanced NSCLC (55). Second-line chemotherapy may be appropriate for good-performance-status patients or for patients who respond to initial chemotherapy with a long progression-free interval off-treatment (55). Since then, there have been many reports of clinical trials dealing with salvage chemotherapy, especially docetaxel (82,83). Among the many new anti-cancer drugs which are active in chemo-naive NSCLC patients, very few have shown any major activity in second-line treatment. Docetaxel was the one that constantly showed activity in the salvage setting, including randomized trials which compared the best supportive care or other chemotherapeutic agents (82,83). Gemcitabine and paclitaxel also had some activity in second-line treatment in phase II studies (84,85).

Target therapies Increasing understanding of the molecular biology of NSCLC has led to the development of a wide range of novel treatment strategies, molecular target therapies. These included signal transduction pathways inhibitors, anti-angiogenesis, gene therapy, immunotherapy, etc.

The epidermal growth factor receptor (EGFR) is expressed or highly expressed in most NSCLC and mediates signalling associated with increased cell proliferation, increased angiogenesis, reduced apoptosis, and increased metastases. Several compounds have been developed to inhibit EGFR signalling. Gefitinib (Iressa, ZD1839) is a small molecule EGFR tyrosine kinase inhibitor (TKI) that had been demonstrated clinically having high efficacy in second line or third line treatment of NSCLC (86,87). Main studies of the gefitinib in second line and subsequent therapy were IDEAL 1 and IDEAL 2 study, respectively (86,87). Response rates of 18% to 19% were seen in IDEAL 1 and 9% to 12% in IDEAL 2 study, which compare favourably with the response rate of 7% for docetaxel as a second-line therapy (83). Gefitinib also demonstrated significant improvement in disease-related symptoms and quality of life in IDEAL 1 and 2 studies. Gefitinib has launched in Japan for treatment of NSCLC and for third line treatment (previously treated with platinum agent and docetaxel) against NSCLC in USA. There were many other EGFR-TKIs in development or under clinical trials, such as erlotinib (Tarceva, OSI-774) (88).

Angiogenesis, formation of new blood vessels from existing capillaries, is important in the growth and metastases of solid tumours. Current antiangiogenic approaches include the inhibition of angiogenesis stimulators (eg, vascular endothelial growth factor [VEGF]) or their receptors and blockade of endothelial cell proliferation. There are many drugs included in this category, such as ZD6474, avastin (rhuMab-VEGF), endostatin, BMS-275291, and thalidomide (89).

Other therapies When an isolated adrenal or hepatic mass is found on the sonogram or CT scan of NSCLC patients whose staging is otherwise operable if the adrenal or hepatic lesions are not considered, a biopsy of this solitary adrenal or hepatic lesion should be performed to rule out metastases. In patients with a metachronous solitary brain metastasis, surgical resection of the metastatic lesion may improve survival in those patients whose primary lesion is adequately controlled. Radiotherapy is an effective palliative modality for selected stage IV patients. Radiotherapy to the chest may help relieve pain, haemoptysis, superior vena cava syndrome, or obstructive symptoms. Furthermore, radiotherapy of bone metastases may help prevent pathological fractures and relieve pain. In addition, proximal bronchial obstructive lesions may be relieved with bronchoscopic laser treatment or with brachytherapy, both of which are highly effective as short-term (2 to 4 months) palliative measures, even in patients who have had previous radiotherapy.

References

1. Kraut M, Wozniak A. Clinical Presentation. In: *Lung Cancer: Principles and Practice,* 2nd ed. Eds. Pass HI, Michell JB, Johnson DH, Turrisi AT, Minna JD. Philadelphia: Lippincott Williams & Wilkins 2000, 521–34.
2. Ihde DC. Chemotherapy of lung cancer. *New England Journal of Medicine* 1992; 327:1434–41.
3. Pederson AG, Hansen HH. Etoposide (VP-16) in the treatment of lung cancer. *Cancer Treatment Review* 1983; 10:245–64.
4. Ettinger DS. New drugs for treating small cell lung cancer. *Lung Cancer* 1995; 12(suppl 3):S53–61.
5. Johnson DH, Einhorn LH, Birch R, et al. A randomized comparison of high-dose versus conventional dose cyclophospamide, doxorubicin, and vincristine for extensive-stage small cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. *Journal of Clinical Oncology* 1987; 5:1731–8.
6. Ihde DC, Mulshine JL, Kramer BS, et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. *Journal of Clinical Oncology* 1994; 12:2022–34.
7. Murray N, Coy P, Peter JL, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. *Journal of Clinical Oncology* 1993; 11:336–44.
8. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *New England Journal of Medicine* 1999; 340:265–71.
9. Chute JP, Chen T, Feigal E, Simon R, Johnson BE. Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: perceptible progress. *Journal of Clinical Oncology* 1999; 17:1794–801.
10. Hong WK, Nicaise C, Lawson R, et al. Etoposide combined with cyclophosphamide plus vincristine compared with doxorubicin plus cyclophosphamide plus vincristine and with high-dose cyclophosphamide plus vincristine in the treatment of small-cell carcinoma of the lung: a randomized trial of the Bristol. *Journal of Clinical Oncology* 1989; 7:450–6.
11. Evans WK, Osoba D, Feld R, et al. Etoposide (VP-16) and cisplatin: an effective treatment for relapse in small cell lung cancer. *Journal of Clinical Oncology* 1985; 3:65–71.
12. Glisson BS, Kurie JM, Perez-Soler R, et al. Cisplatin, etoposide, and paclitaxel in the treatment of patients with extensive small-cell lung carcinoma. *Journal of Clinical Oncology* 1999; 17:2309–15.
13. Loehrer PJ Sr, Ansari R, Gonin R, et al. Cisplatin plus etoposide with and without ifosfamide in extensive small-cell lung cancer: a Hoosier Oncology Group study. *Journal of Clinical Oncology* 1995; 13:2594–9.
14. Roth BJ, Johnson DH, Einhorn LH, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: phase III trial of Southeastern Cancer Society Group. *Journal of Clinical Oncology* 1992; 10:282–91.
15. Thatcher N, Girling DJ, Hopwood P, Sambrook RJ, Qian W, Stephens RJ. Improving survival without reducing quality of life in small-cell lung cancer patients by increasing the dose-intensity of chemotherapy with granulocyte colony-stimulating factor support: results of a British Medical Research Council Multicenter Randomized Trial. *Journal of Clinical Oncology* 2000; 18:395–404.
16. Furuse K, Fukuoka M, Nishiwaki Y, et al. Phase III study of intensive weekly chemotherapy with recombinant human granulocyte colony-stimulating factor versus standard chemotherapy in extensive-disease small-cell lung cancer. *Journal of Clinical Oncology* 1998; 16:2126–32.
17. Kudoh S, Fujiwara Y, Takada Y, et al. Phase II study of irinotecan combined with cisplatin in patients with previously untreated small-cell lung cancer. *Journal of Clinical Oncology* 1998; 16:1068–74.
18. Sculier JP, Paesmans M, Bureau G, et al. Randomized trial comparing induction chemotherapy versus induction chemotherapy followed by maintenance chemotherapy in small-cell lung cancer. *Journal of Clinical Oncology* 1996; 14:2337–44.
19. Beith JM, Clarke SJ, Woods RL. Bell DR, Levi JA. Long-term follow-up of a randomised trial of combined chemoradiotherapy induction treatment, with and without maintenance chemotherapy in patients with small cell carcinoma of the lung. *European Journal of Cancer* 1996; 32A:438–43.
20. Ebi N, Kubota K, Nishiwaki Y, et al. Second-line chemotherapy for relapsed small cell lung cancer. Japanese *Journal of Clinical Oncology* 1997; 27:166–9.
21. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *Journal of Clinical Oncology* 1999; 17:658–67.

22. Groen HJ, Fokkema E, Biesma B. et al. Paclitaxel and carboplatin in the treatment of small-cell lung cancer patients resistant to cyclophosphamide. doxorubicin. and etoposide: a non-cross-resistant schedule. *Journal of Clinical Oncology* 1999; 17:927–32.
23. Masuda N, Matsui K. Negoro S. et al. Combination of irinotecan and etoposide for treatment of refractory or relapsed small-cell lung cancer. *Journal of Clinical Oncology* 1998; 16:3329–34.
24. Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. *Journal of Clinical Oncology* 1992; 10:890–5.
25. Work E, Nielsen OS, Bentzen SM, et al. Randomized trial of initial versus late irradiation combined with chemotherapy in limited-stage small-cell lung cancer. *Journal of Clinical Oncology* 1997; 15:3030–7.
26. Turrisi AT, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *New England Journal of Medicine* 1999; 340:265–71.
27. Papac RJ, Son Y, Bien R, et al. Improved local control of thoracic disease in small-cell lung cancer with higher dose thoracic irradiation and cyclic chemotherapy. *International Journal of Radiation Oncology Biologic Physics* 1987; 13:993–8.
28. Bonner JA, Sloan JA, Shanahan TG, et al. Phase III comparison of twice-daily split-course irradiation versus once-daily irradiation for patients with limited stage small-cell lung carcinoma. *Journal of Clinical Oncology* 1999; 17:2681–91.
29. Johnson DH, Turrisi AT, Chang AY, et al. Alternating chemotherapy and twice-daily thoracic radiotherapy in limited-stage small-cell lung cancer: a pilot study of the Eastern Cooperative Oncology Group. *Journal of Clinical Oncology* 1993; 11:879–84.
30. Ishihara S, Tsuchiya S, Minato K, et al. A phase II study of combined chemoradiotherapy for limited disease-small-cell lung cancer. American *Journal of Clinical Oncology* 2000; 23:197–202.
31. Turrisi AT. Brain irradiation and systemic chemotherapy for small-cell lung cancer: dangerous liaisons? *Journal of Clinical Oncology* 1990; 8:196–9.
32. Arriagada R, Le Chevalier T, Borie F, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *Journal of the National Cancer Institute* 1995; 87:183–90.
33. Gregor A, Cull A, Stephens RJ, et al. Prophylactic cranial irradiation as indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. *European Journal of Cancer* 1997; 33(suppl 11):1752–8.
34. Gregor A. Small-cell lung cancer: advances in management of limited disease – prophylactic cranial irradiation. *ASCO Educational Book* Spring 2000:672–7.
35. Lassen U, Hansen HH. Surgery in limited stage small cell lung cancer. *Cancer Treatment Review* 1999; 25:67–92.
36. Morikawa T, Katoh H, Takeuchi E, et al. Technical feasibility of video-assisted lobectomy with radical lymphadenectomy for primary lung cancer. *Surgical Laparoscopy, Endoscopy & Percutaneous Techniques* 1998; 8:466–73.
37. Mountain CF. Revisions in the international system for staging lung cancer. *Chest* 1997; 111:1710–17.
38. Kato H, Okunaka T, Shimatani H. Photodynamic therapy for early stage bronchogenic carcinoma. *Journal of Clinical Laser Medicine & Surgery* 1996; 14:235–8.
39. Fujisawa T, Yamaguchi Y. Postoperative immunostimulation after complete resection improves survival of patients with stage I non-small cell lung carcinoma. *Cancer* 1996; 78:1892–8.
40. Burt ME, Pomerantz AH, Bains MS, et al. Results of surgical treatment of stage III lung cancer invading the mediastinum. *Surgical Clinics of North America* 1987; 67:987–99.
41. Perez CA, Stanley K, Grundy G, et al. Input of irradiation technique and tumor extent in tumor control and survival of patients with unresectable non-oat-cell carcinoma of the lung. *Cancer* 1982; 50:1091–9.
42. Chen M, Jiang GL, Fu XL, et al. The impact of overall treatment time on outcomes in radiation therapy for non-small cell lung cancer. *Lung Cancer* 2000; 28:11–9.
43. Johnson DH, Einhorn LH, Bartolucci A, et al. Thoracic radiotherapy does not prolong survival in patients with locally advanced unresectable non-small-cell lung cancer. *Annals of Internal Medicine* 1990; 113:33–8.
44. Cox JD, Azarnia N, Byhardt RW, et al. A randomzied phase I/II trial of hyperfractionated radiation therapy with total doses of 60.0 Gy to 79.2 Gy: possible survival benefit with ≥ 69.6 Gy in favorable patients wit stage III non-small-cell lung carcinoma: Report of Radiation Therapy Oncology Group 83–11. *Journal of Clinical Oncology* 1990; 8:1543–55.

45. Holmes E, Gail M, Lung Cancer Study Group. Surgical adjuvant therapy stage II and III adenocarcinoma and large-cell undifferentiated carcinoma. *Journal of Clinical Oncology* 1986; 4:710–5.
46. Lad T, Rubinstein L, Sadagh A, et al. The benefit of adjuvant treatment for resected locally advanced non-small-cell lung cancer. *Journal of Clinical Oncology* 1988; 6:9–17.
47. Park JH, Shim YM, Baek HJ, et al. Postoperative adjuvant therapy for stage II non-small-cell lung cancer. *Annals of Thoracic Surgery* 1999; 68:1821–6.
48. Wada H, Hitomi S, Teramatsu T. Adjuvant chemotherapy after complete resection in non-small-cell lung cancer. *Journal of Clinical Oncology* 1996; 14:1048–54.
49. Rosell R, Gomez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *New England Journal of Medicine* 1994; 330:153–8.
50. Weisenburger TH, Gail M, The lung cancer study group. Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid carcinoma of the lung. *New England Journal of Medicine* 1986; 315:1377–81.
51. Lertsanguansinchai P. Phase II study of concurrent chemoradiotherapy for inoperable (bulky) stage III (A/B) non-small cell lung cancer (NSCLC): a preliminary report. *Journal of Medical Association of Thailand* 2000; 83:85–92.
52. Tan EH, Wee J, Ang PT, et al. Induction chemotherapy followed by concurrent chemoradiotherapy in stage III unresectable non-small cell lung cancer. *Acta Oncologica* 1999; 38:1005–9.
53. LeChevalier T, Arriagada R, Quoix E, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in non-resectable non-small cell lung cancer: first analysis of a randomized trial in 353 patients. *Journal of the National Cancer Institute* 1991; 83:417–23.
54. Schaake-Koning C, Vanden Bogaert W, Dalesio O, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *New England Journal of Medicine* 1992; 326:524–30.
55. American Society of Clinical Oncology. Clinical practice guidelines for the treatment of unresectable non-small-cell lung cancer. *Journal of Clinical Oncology* 1997; 15:2996–3018.
56. Mattson K, Holsti LR, Holsti P, et al. Inoperable non-small-cell lung cancer: radiation with or without chemotherapy. *European Journal of Cancer of Clinical Oncology* 1988; 24:477–82.
57. Furuse K, Kukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *Journal of Clinical Oncology* 1999; 17:2692–9.
58. Trovo MG, Minatel E, Veronesi A, et al. Combined radiotherapy and chemotherapy vs radiotherapy alone in locally advanced bronchogenic carcinoma: a randomized study. *Cancer* 1990; 65:400–4.
59. Soresi E, Clerici M, Grilli R, et al. A randomized clinical trial comparing radiation therapy vs radiation therapy plus cis-dichlorodiammine platinum (II) in the treatment of locally advanced non-small-cell lung cancer. *Seminar in Oncology* 1988; 15(suppl 7):20–5.
60. Bunn PA Jr, Kelly K. New chemotherapeutic agents prolong survival and improve quality of life in non-small cell lung cancer: a review of the literature and future directions. Clinical Cancer Research 1998; 4:1087–100.
61. Souquet PJ, Chauvin F, Boissel JP, et al. Polychemotherapy in advanced non small cell lung cancer: a meta-analysis. *Lancet* 1993; 342:19–21.
62. Non-small cell lung cancer collaborative group. Chemotherapy in non-small cell lung cancer, a meta-analysis using updated data in individual patients from 52 randomized trials. *British Medical Journal* 1995; 311:899–909.
63. Thongprasert S, Sanguannitra P, Juthapan W, et al. Relationship between quality of life and clinical outcomes in advanced non-small cell lung cancer: best supportive care (BSC) versus BSC plus chemotherapy. *Lung Cancer* 1999; 24:17–24.
64. Lam WK, Tsang KW, Ip MS. Chemotherapy for advanced (stage IIIB and stage IV) non-small cell lung cancer: the Hong Kong perspective. *Respirology* 1998; 3:145–9.
65. Rajkumar SV, Adjei AA. A review of the pharmacology and clinical activity of new chemotherapeutic agents in lung cancer. *Cancer Treatment Review* 1998; 24:35–53.
66. Le Chevalier T, Brisgand D, Douillard JY, et al. Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small cell lung cancer: results of a European multicenter trial including 612 patients. *Journal of Clinical Oncology* 1994; 12:360–7.

67. Perng RP, Chen YM, Liu JM, et al. Gemcitabine versus the combination of cisplatin and etoposide in patients with inoperable non-small-cell lung cancer in a phase II randomized study. *Journal of Clinical Oncology* 1997; 15:2097–102.
68. Sandler AB, Nemunaitis J, Denham C, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. *Journal of Clinical Oncology* 2000; 18:122–30.
69. Bonomi P, Kim K, Fairclough D. et al. Comparison of survival and quality of life in advanced non-small-cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin: results of an Eastern Cooperative Oncology Group Trial. *Journal of Clinical Oncology* 2000; 18:623–31.
70. Perng RP, Shih JF, Chen YM, et al. A phase II trial of vinorelbine and cisplatin in previously untreated inoperable non-small-cell lung cancer. American *Journal of Clinical Oncology* 2000; 23:60–4.
71. Laohavinij S, Maoleekoonpairoj S, Cheirsilpa A, et al. Phase II study of paclitaxel and carboplatin for advanced non-small-cell lung cancer. *Lung Cancer* 1999; 26:175–85.
72. Mori K, Machida S, Yoshida T, et al. A phase II study of irinotecan and infusional cisplatin with recombinant human granulocyte colony-stimulating factor support for advanced non-small-cell lung cancer. *Cancer Chemotherapy & Pharmacology* 1999; 43:467–70.
73. Ho JCM, Tan EH, Leong SS, et al. A multicenter phase II study of the efficacy and safety of docetaxel plus cisplatin in Asian chemonaive patients with metastatic of locally advanced non-small cell lung cancer. *Respiratory Medicine* 2003; 97:796–803.
74. Kelly K, Crowley J, Bunn PA, et al. A randomized phase III trial of paclitaxel plus carboplatin (PC) versus vinorelbine plus cisplatin (VC) in untreated advanced non-small cell lung cancer (NSCLC): A Southwest Oncology Group (SWOG) trial. *Proceedings of American Society of Clinical Oncology* 1999; 18:461a (abstr 1777).
75. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. *New England Journal of Medicine* 2002; 346:92–8.
76. Comella P, Frasci G, Panza N, et al. Cisplatin, gemcitabine, and vinorelbine combination therapy in advanced non-small-cell lung cancer: a phase II randomized study of the Southern Italy Cooperative Oncology Group. *Journal of Clinical Oncology* 1999; 17:1526–34.
77. Comella P, Frasci G, Panza N, et al. Randomized trial comparing cisplatin, gemcitabine, and vinorelbine with either cisplatin and gemcitabine or cisplatin and vinorelbine in advanced non-small-cell lung cancer: interim analysis of a phase III trial of the Southern Italy Cooperative Oncology Group. *Journal of Clinical Oncology* 2000; 18:1451–7.
78. Chen YM, Perng RP, Yang KY, et al. A multicenter phase II trial of vinorelbine plus gemcitabine in previously untreated inoperable (stage IIIB/IV) non-small cell lung cancer. *Chest* 2000; 117:1583–9.
79. Kelly K. Future directions for new cytotoxic agents in the treatment of advanced-stage non-small-cell lung cancer. *ASCO Educational Book Spring* 2000:357–67.
80. Akerley W, Glantz M, Choy H, et al. Phase I trial of weekly paclitaxel in advanced lung cancer. *Journal of Clinical Oncology* 1998; 16:153–8.
81. Akerley W, Herndon J, Egorin MJ, et al. CALGB 9731: phase II trial of weekly paclitaxel for advanced non-small cell lung cancer (NSCLC). *Proceedings of American Society of Clinical Oncology* 1999; 18:462a (abstr 1783).
82. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. *Journal of Clinical Oncology* 2000; 18:2354–62.
83. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *Journal of Clinical Oncology* 2000; 18:2095–103.
84. Kelly K. The role of single-agent gemcitabine in the treatment of non-small-cell lung cancer. *Annals of Oncology* 1999; 10(suppl 5):S53–6.
85. Androulakis N, Kouroussis C, Kakolyris S, et al. Salvage treatment with paclitaxel and gemcitabine for patients with non-small-cell lung cancer after cisplatin- or docetaxel-based chemotherapy: a multicenter phase II study. *Annals of Oncology* 1998; 9:1127–30.

86. Fukuoka M, Yano S, Giaccone G, et al. A multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small cell lung cancer (the IDEAL 1 trial). *Journal of Clinical Oncology* 2003; 21:2237–46.
87. Kris M, Natale RB, Herbst R, et al. Efficacy of gefinitib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer. A randomised trial (IDEAL 2). *JAMA* 2003; 290:2149–58.
88. Perez-Soler R, Chachoua A, Huberman M, et al. A phase II trial of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor OSI-774, following platinum-based chemotherapy, in patients (pts) with advanced, EGFR-expressing, non-small cell lung cancer (NSCLC). *Proceedings of American Society of Clinical Oncology* 2001; 20:310a (abstract 1235).
89. Shepherd FA. Angiogenesis inhibitors in the treatment of lung cancer. *Lung Cancer* 2001; 34(suppl 3):S81–S89.

Part V Procedures

26 Lung Transplantation

Pantpis Sakornpant and Shui Wah Chiu

Introduction

Hardy et al performed the first human lung transplantation in 1963 (1). The patient survived for 18 days and died of renal failure. The main indications for lung transplantation are certain types of pulmonary vascular and parenchymal disease. Currently, there are four types of operations, namely, heart-lung (HLT), single lung (SLT), double-lung (DLT) and bilateral sequential single-lung transplantation (BSSLT). The choice of each procedure depends on the specific type of lung disease and the experience of individual centres.

Since the long-term survival for all lung transplantation is less than 40% at 10 years (2), selection of candidates for lung transplantation must be strictly observed and specific types of lung disease will be discussed separately.

Guidelines for Selection of Candidates

The International Society for Heart and Lung Transplantation (ISHLT) has proposed guidelines for the selection of lung transplant candidates (3) and these have been accepted internationally.

In general, the patients should be at the end-stage of the disease, having had maximal or optimal medical therapy for the disease but nevertheless declining function. It is important to proceed with lung transplantation prior to multiorgan system failure and severe malnutrition. According to the registry of the ISHLT, patients aged 55 and older had a significantly lower survival than younger patients (2). Currently it is suggested that the upper age limit for HLT is 55 years, SLT 65 years and BSSLT 60 years.

Current contraindications are listed in Table 1. Hepatitis B (HBV) carrier status is an important problem in Asia as 5–10% of the population are chronic carriers. The emergence of anti-HBV drugs have allowed organ transplantation to take place in such carriers.

Table 1. Current Contraindications

1)	Other major organ dysfunction, particularly renal dysfunction with creatinine clearance of < 50 mg/ml/min
2)	Infection with human immunodeficiency virus
3)	Hepatitis B antigen positivity (relative contraindication)
4)	Biopsy-proven histologic evidence of Hepatitis C liver disease (relative contraindication)
5)	Active malignancy
6)	Psychosis
7)	Drug addiction

Necessary Investigations Before Referral

Necessary investigations before referral are listed in Table 2. Patients with end-stage lung disease may have disorders that lead to progressive deterioration in lung function, limitation of physical activity and inability to perform basic tasks of daily living. These comorbidities may be due to pulmonary, cardiovascular and therapy-related complications (4). Regarding pulmonary complications, infections account for the majority, especially in chronic obstructive airway disease (COPD) and bronchiectasis. The most common form of therapy-related complications is steroid-induced side effects. Substantial adverse effects include osteoporosis, diabetes mellitus, hypertension and psychosis. It is recommended that if use of steroids is necessary before transplantation, it must be used at the lowest dosage.

Table 2. Necessary Investigations before Referral

1)	6-minute walk test
2)	Full lung function tests
3)	High resolution computed tomography of the thorax
4)	Echocardiogram
5)	Electrocardiogram
6)	Cardiac catheterization in patients with pulmonary vascular disease

Disease-Specific Guidelines

Idiopathic pulmonary fibrosis (Cryptogenic fibrosing alveolitis)

Generally the disease is progressive with deterioration of lung function in spite of medical treatment with steroids or other immunosuppressive drugs. The patients are symptomatic with $FEV_1 < 30\%$ predicted and $VC < 60\%$. A number of patients will have oxygen desaturation at rest or even after oxygen supplement. Because of rapid progression with high mortality of the disease, early referral is mandatory (5). Patients with age < 60 years who receive intensive treatment acquire a survival advantage. Available data suggest that deaths in patients over 60 years are often confounded by comorbidity (6).

Bronchiectatic diseases

Cystic fibrosis, which is common in the Western countries, is rare in Asian population. However, chronic lung infection with bronchiectasis is quite common among Asian populations. The patients generally are symptomatic and may require increasing numbers of hospitalizations. Patients with resting arterial $pCO_2 > 6.66$ kPa and $pO_2 < 7.33$ kPa must be considered for transplantation if FEV_1 rapidly falls to 25% of predicted value. FEV_1 criteria is a better guide for candidacy of transplantation, even if the patients are not yet obviously hypercapnic or hypoxaemic.

Chronic obstructive lung disease (COPD)

The most common are emphysema, chronic bronchitis and bronchiolitis obliterans. High chances of pre-transplant death are noted for patients with pulmonary fibrosis, while low chances are seen in emphysema (7). It is controversial whether survival is improved in terms of transplant outcome in COPD though some of these patients may experience improved functional capacity (8,9). Preference of candidate selection for lung transplantation should therefore be given to those patients who require long-term oxygen treatment with $FEV_1 < 25\%$ of predicted value and $pCO_2 > 7.33$ kPa or with evidence of cor pulmonale.

Pulmonary hypertension

Pulmonary hypertension occurs as a primary process (primary pulmonary hypertension) or as a secondary manifestation of another disease.

Secondary pulmonary hypertension could be due to thromboembolic disease, collagen disease, pulmonary obstructive airways disease, restrictive lung disease, congenital heart disease (Eisenmenger's syndrome) and others. Pulmonary hypertension secondary to congenital heart disease has better prognosis than other types of pulmonary hypertension (10).

A nationwide survey was conducted in Japan from 1980–1990 on 223 patients with primary pulmonary hypertension. The mean pulmonary arterial pressure was 7.66 ± 2.29 kPa and the overall median survival time was 32.5 months since the first diagnostic catheterization. Comparison between the patients who died within one year of catheterization and those who survived one year or more revealed significant differences in pulmonary artery pressure, right atrial pressure, stroke volume index, pulmonary vascular resistance and partial pressure of carbon dioxide (11).

Useful criteria for lung transplantation in patients with primary pulmonary hypertension include New York Class III or IV, low cardiac index of less than 2 L/min/m^2, right atrial pressure of more than 2.00 kPa and mean pulmonary artery pressure greater than 7.33 kPa. For pulmonary hypertension secondary to congenital heart disease (Eisenmenger's syndrome), the patients must have progressive symptoms and Functional Class IV.

Choice of Procedure

Pulmonary vascular disease

Patients with primary pulmonary hypertension can be considered for heart-lung, single, double or bilateral sequential single-lung transplantation.

SLT, though performed in many centers for primary pulmonary hypertension (12), carries a higher risk of severe pulmonary oedema in the perioperative period. This is due to ventilation/perfusion mismatch because the remaining diseased lung accepts about half of the ventilation with hardly any perfusion. The situation becomes worse during episodes of transplant dysfunction such as reperfusion oedema, rejection, and infection. DLT, BSSLT and HLT is now preferable because of better survival (13). There is also some report that secondary pulmonary hypertension does not adversely affect outcome after SLT (14). For patients with Eisenmenger's syndrome with complex cardiac anomalies, HLT is the best option.

Parenchymal lung disease

In Asia, cystic fibrosis is rare. The common lung diseases requiring transplantation are pulmonary fibrosis, emphysema and bronchiectasis.

DLT or BSSLT is required for bronchiectasis. HLT also gives similar result for patients with end-stage suppurative lung disease (15).

SLT can be applied equally for emphysema and pulmonary fibrosis.

Immunosuppression and Rejection

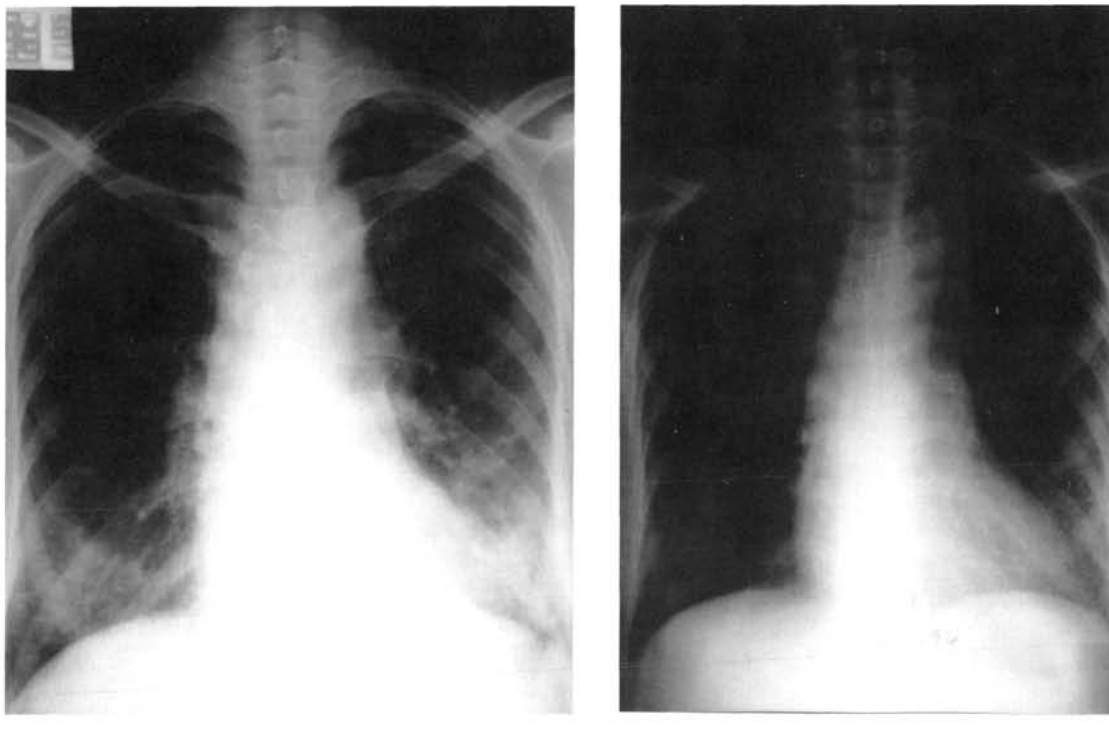
We have used cyclosporin A and azathioprine starting at the time of operation, and after the second week oral steroid is given. The concept of delayed steroid administration is to prevent dehiscence of bronchial anastomosis. We have not routinely practiced cytolytic induction therapy using anti-thymocyte globulin or monoclonal antibodies. We try to maintain cyclosporin A blood level (bioassay) at around 300 ng/ml for the first year and 150–200 ng/ml for the following years. Azathioprine is given at 1 mg/Kg or less to maintain the white blood cell count of 4000 cell/mm^3 or greater. Prednisolone is maintained orally at 0.05–0.1 mg/Kg/day and this is usually stopped after 2–3 years. Currently, tacrolimus and mycofenolic acid are on trial for replacement of cyclosporin and azathioprine.

Monitoring for Acute Rejection

Some patients have low grade fever and malaise during acute lung rejection, but some may not show any clinical symptoms and signs though they may have some X-ray findings of pulmonary infiltration usually at lung bases (Figure 1). A patient who develops hypoxaemia after lung transplantation must be suspected of acute lung

rejection, irrespective of presence or absence of dyspnoea. In asymptomatic patients after lung transplant, regular follow-up of lung function test is very helpful in identifying acute as well as chronic rejection. A progressive decrease in vital capacity and FEV_1 with an obstructive airflow pattern, compared with previous tests, warrants investigations for acute rejection.

Transbronchial lung biopsy (TBB) is the gold standard for diagnosis of acute rejection and it is performed routinely within 2–4 weeks after transplantation or in conjunction with other methods of diagnosis. Acute lung rejection is graded according to the Working Formulation for the Diagnosis of Lung Rejection (16). This formulation was developed to provide a consistent system for patient management and therapy. This scheme is divided into five classes: (A) acute rejection, (B) acute airway damage without scarring, (C) chronic airway rejection (OB), (D) chronic vascular rejection, and (E) vasculitis. Acute rejection may be graded as minimal, mild, moderate and severe, primarily by assessing the perivascular, interstitial and air space components. Each grade is further divided by assessing the presence or absence of airway inflammation. Mild acute rejection or grade 2 show a dense, thick perivascular infiltrate of five to seven layers with accompanying features of endothelialitis and airway inflammation. Minimal acute rejection of grade 1 is mostly asymptomatic and requires no treatment. The mild acute rejection, grade 2 and beyond, deserves treatment. The initial treatment is 1 gram of methylprednisolone intravenously daily for 3 consecutive days (pulse therapy). This is followed by TBB a week after therapy. Unless the histology demonstrates less than mild rejection, the patient should be given another pulse therapy and another TBB is to be repeated a week thereafter. If there is persistent acute rejection of grade 2 or beyond, a course of monoclonal antibodies is given. Most of the patients will



(a) (b)

Figure 1. a) Chest X-ray showing acute rejection with pulmonary infiltration at base of both lungs, b) Chest X-ray of the same patient 4 days after pulse therapy

respond effectively to the monoclonal antibodies. Otherwise newer drugs such as Tacrolimus (17,18) and Mycophenolate mofetil (19) may be tried.

Monitoring for Chronic Rejection

Chronic rejection is manifested histologically as bronchiolitis obliterans (obliterative bronchiolitis, OB). Some patients may not have histology typical of bronchiolitis obliterans, but features of decline in lung function. Bronchiolitis Obliterans Syndrome (BOS) is defined as progressive lung dysfunction characterized by major decline in lung function test parameters of small airway physiology, specifically decline in mid-expiratory flow rate to less than 30% of predicted regardless of whether pathologic OB had been shown on transbronchial biopsy (20). According to the ISHLT for clinical staging (21), BOS is graded from stage 0 with 20% decline of FEV_1 to stage 3 with 50% reduction of FEV_1 and this can happen with or without pathologic evidence. Transbronchial biopsies, though very useful in the diagnosis of OB, have a sensitivity of only 87%, while their specificity is 99% (22). In cases with high suspicion, wedge biopsy of lung may demonstrate the histological diagnosis. We have used FVC and FEV_1 for early detection of BOS. Our protocol is to have all patients who survive after hospital discharge to have routine chest radiograph and lung function test every 1–2 months (Figure 2) and to have high resolution CT scan of the chest at least once yearly. The CT scan usually can demonstrate peribronchial muscular thickening (Figure 3) in most of our patients, whether they exhibit symptoms or not. The early symptoms of BOS are shortness of breath and easy fatigue. The course can last many years and complications such as pneumonia occur and finally lead to death.

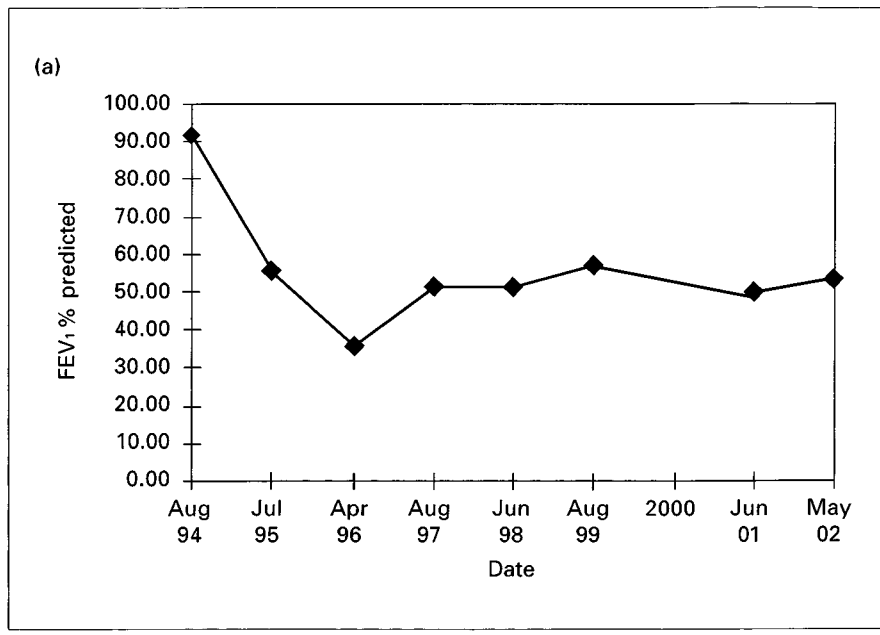
Clinical Lung Transplantation

In 1982 the first HLT was performed with long-term success at Stanford (23). The next two decades saw rapid developments in lung transplantation. The Registry of ISHLT (25) shows there is no significant difference in actuarial survival among all procedures of lung transplantation. The overall 1-, 2-, and 3-year actuarial survival rates for lung transplantation are 45%, 37%, and 31%, respectively. For HLT, the actuarial survival is approximately 60% at one year, whereas the survival rate is 21% at 11 years.

Asian Experience

Thailand experience

The lung transplant programme was started in 1989. One surgeon operated on all patients. Between June 1989 and August 2000, 32 patients underwent 32 first-time lung transplantation and 3 re-transplantation. Among the first-time transplantation, 21 patients had HLT, 7 SLT and 4 BSSLT. The most common indication for HLT was pulmonary vascular disease, mainly Eisenmenger's syndrome while the most common indication for either SLT or BSSLT was parenchymal lung disease (Figure 4). Three patients required re-transplantation. One with HLT developed OB 2 years after operation. She had superimposed pulmonary nocardiosis that was refractory to medical treatment, and received SLT. She then developed non-nocardia infection of both lungs which led to death 4 months after re-transplantation. The second patient developed OB after 7 years of HLT which rapidly progressed to grade IV two years later. He therefore underwent re-transplantation for both lungs but he died after operation. The other re-transplantation had previous left lung transplantation for emphysema at 63 years of age. Almost three years after transplantation the remaining lung which also had previous pleurodesis operation started having hyperinflation and herniated across the mediastinum to encroach upon the transplanted lung. The over-expanded lung compressed the new lung so that it developed atelectasis and repeated infection. Attempt to replace the overexpanded lung failed, therefore both lungs required transplantation. Unfortunately the patient died of myocardial infarction postoperatively. Graft survival for HLT is shown in Figure 5. The 5-year survival was 25%, and the longest survival to date was 9 years after HLT. Our results demonstrate that the causes of death after operation and in the



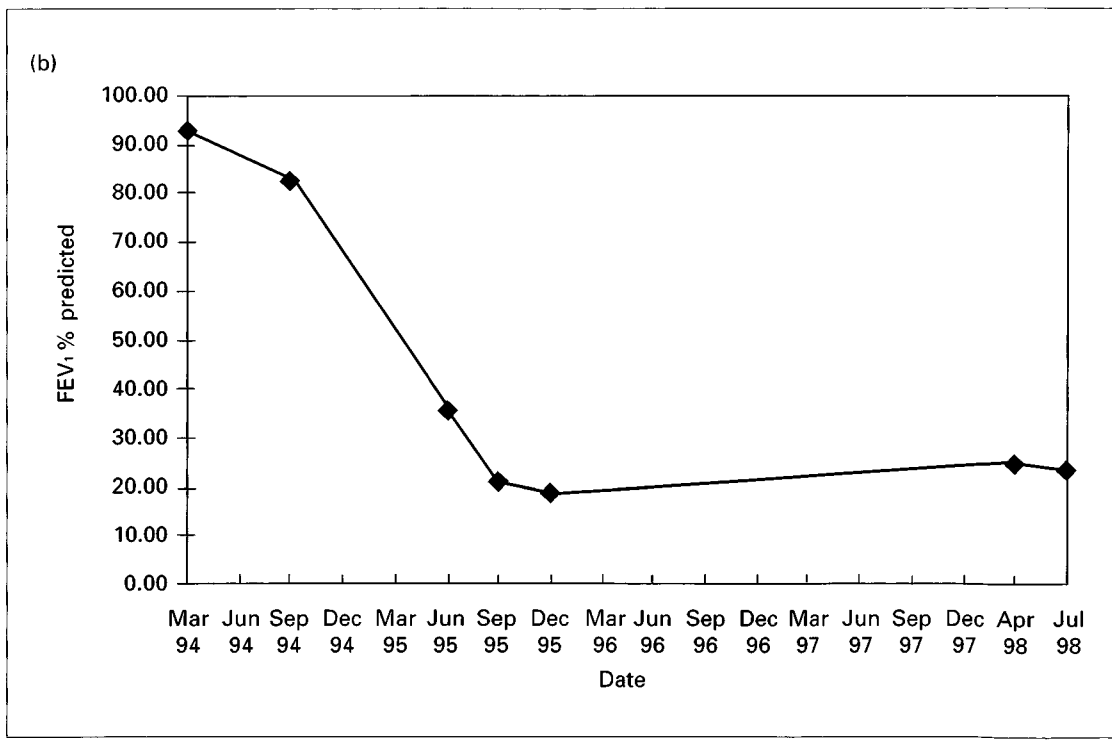


Figure 2. Decline of pulmonary function due to bronchiolitis obliterans in
(a) A patient showing FEV_1 % predicted several years after heart-lung transplantation in July 1991
(b) Another patient showing FEV_1 % predicted several years after heart-lung transplantation in September 1989. Patient died in April, 1999

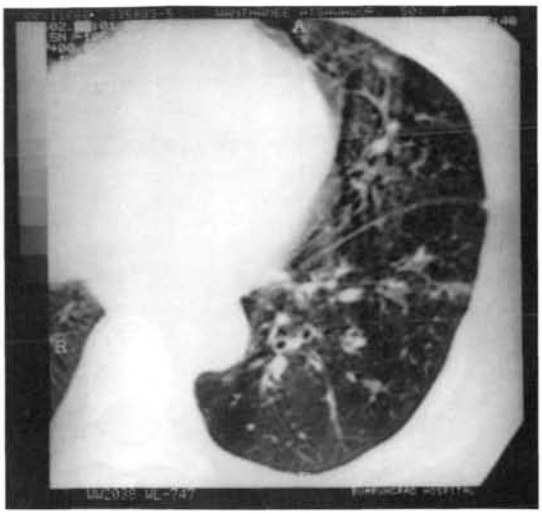


Figure 3. High resolution CT scan of the chest showing peribronchial thickening in bronchiolitis obliterans

first year were due to graft failure, infection and technical problems such as haemorrhage. In the intermediate and late stage, infection and bronchiolitis obliterans account for most of the deaths. The causes of death were similar in all types of transplantation procedures.

The longest survivor lived for almost 3 years after SLT and six months after BSSLT. One patient who had a BSSLT died of lymphoproliferative disease.

Our results are comparable to that reported in the ISHLT registry. We strictly observe the policy that lung transplantation is to be performed only in patients who cannot be treated by other means, and the indications for transplantation are observed strictly according to the guidelines given by the ISHLT.

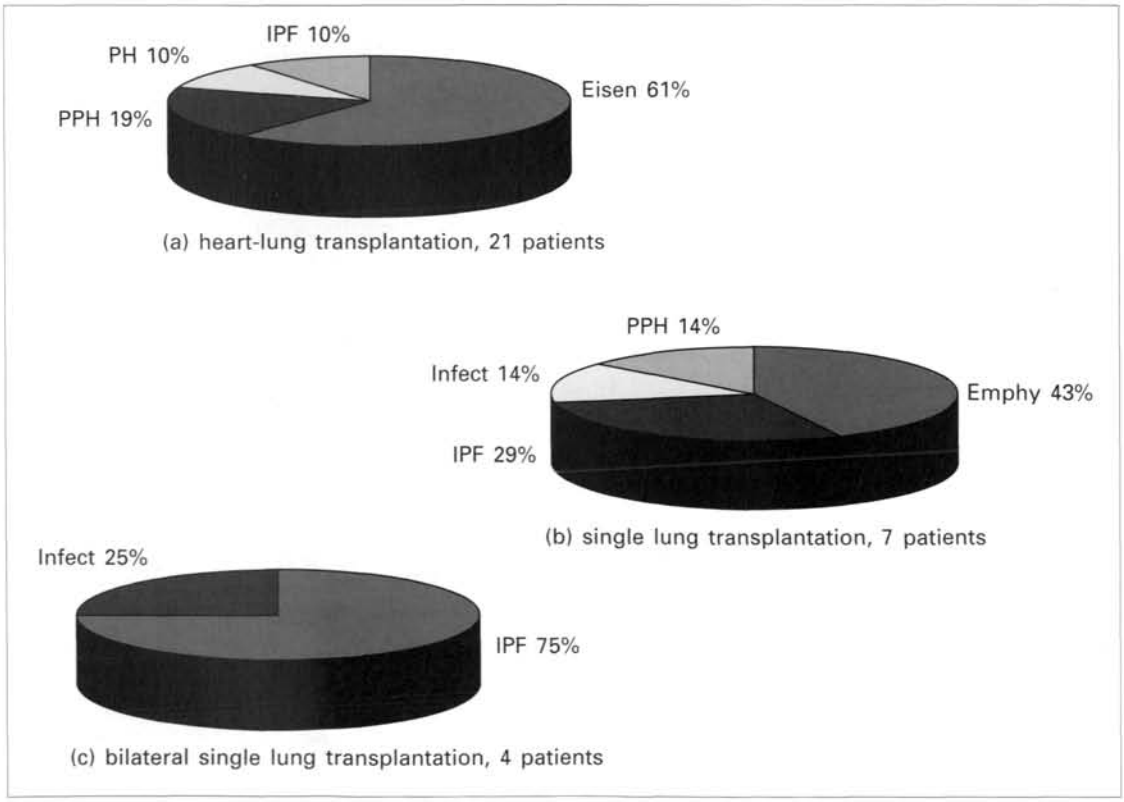


Figure 4. Indications for lung transplantation in Thailand (Eisen, Eisenmenger; PPH, primary pulmonary hypertension; PH, secondary pulmonary hypertension; IPF, idiopathic pulmonary fibrosis; Emphy, emphysema; Infect, infective)

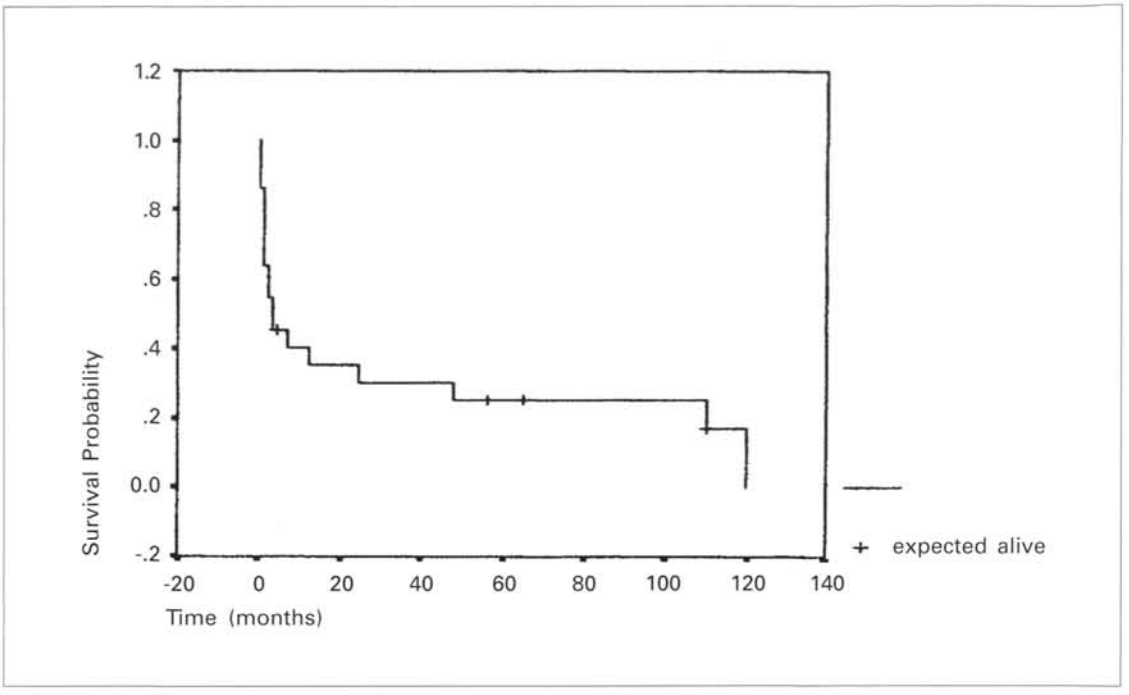


Figure 5. Actuarial survival after heart-lung transplantation in Thailand

Hong Kong experience

In Hong Kong, Grantham Hospital is the only centre for heart and lung transplantation. The lung transplantation programme started in 1995. Up to December 2002, a total of 2 HLT, 2 SLT and 6 BSSLT were performed. There were 8 females and 2 males with mean age of 38.3 years (27–53 years). The mean follow-up period was 28 months (3–67 months). The preoperative diagnosis and types of transplantation are summarised in Table 3. Six out of 8 lung transplant recipients had previous chemical or surgical pleurodesis for recurrent pneumothorax. There was one early mortality in a HLT recipient who developed graft-versus-host disease in the early postoperative period and died of fulminating infection (24). There was no early mortality for lung transplant recipients. Two patients developed bronchomalacia at the anastomotic sites requiring endobronchial stenting. One patient died from OB at 56 months following SLT. All surviving patients are asymptomatic.

Lung transplantation in Asia

At present, there is no official registry of heart-lung and lung transplantation in Asia. The data and information to be presented was by no means complete or representing the whole Asia. In general, lung transplant programme started late in Asia: Thailand started in 1989, Taiwan in 1991, Hong Kong in 1995, Korea in 1996 and Japan in 1998 (25). The numbers of heart-lung and lung transplant in some Asian countries are listed in Table 4.

The reasons for late development of lung transplantation in Asia are likely attributed to the cultural background, late legislation of organ transplant regulations and brain death criteria in some countries. Shortage of donors remains a major obstacle for future development of lung transplantation in Asia.

Table 3. Preoperative Diagnosis and Type of Lung Transplantation in Hong Kong

Diagnosis	*No. of patients*	*Transplantation*
Eisenmenger's syndrome	2 (VSD, ASD)	HLT
Lymphangioleiomyomatosis	2	SLT, BSSLT
Tuberose sclerosis	2	SLT, BSSLT
Bronchiectasis	1	BSSLT
Emphysema	1	BSSLT
Pulmonary fibrosis	1	BSSLT
Primary pulmonary hypertension	1	BSSLT

Note: HLT: heart-lung transplantation
SLT: single lung transplantation
BSSLT: bilateral sequential single lung transplantation

Table 4. Lung Transplantation in Some Asian Countries

Country	*No. of lung transplants*	*Time*
China (25)	8 SLT, 1 BSSLT	Up to 1999
Hong Kong SAR	2 SLT, 6 BSSLT, 2 HLT	Up to 2002
Thailand	7 SLT, 4 BSSLT, 21 HLT	Up to 2000
Taiwan (25)	24 SLT, 1 BSSLT, 3 HLT	Up to 1998
Korea (25)	1 SLT, 1 BSSLT, 3 HLT	Up to 1999
Japan (26)	7 lung transplant (4 from living donors)	Up to 2001

References

1. Hardy JD, Webb WR, Dalton ML, et al. Lung homotransplantation in man. *JAMA* 1963; 186:1065–74.
2. The Registry of the International Society for Heart and Lung Transplantation: Sixteenth Official Report-1999. *J Heart Lung Transplantation* 1999; 18:611–26.
3. International Guidelines for the selection of lung transplant candidate. *J Heart Lung Transplantation* 1998; 17:703–9.
4. Minai OA, Maurer JR, Keston S. Comorbidities in end-stage lung disease. *J Heart Lung Transplantation* 1999; 18:891–903.
5. Hanson D, Winterbaurer KH, Kirkland SH, et al. Changes in pulmonary function test result, after one year of therapy as predictor of survival in patients with idiopathic pulmonary fibrosis. *Chest* 1995; 108:305–10.
6. Lok SS. Interstitial lung disease clinic for the management of idiopathic pulmonary fibrosis: a potential advantage to patients. *J Heart Lung Transplantation* 1999; 18:884–90.
7. Meester JD, Smits JMA, Persijin GG, et al. Lung transplant waiting list: differential outcome of type of end-stage lung disease, one year after registration. *J Heart Lung Transplantation* 1999; 18:563–71.
8. Anthonisen NR. Prognosis in chronic obstructive pulmonary disease: results from multicenter clinical trials. *Am Rev Resp Dis* 1989; 140:S95–9.
9. Bando K, Paradis IL, Keenan RJ, et al. Comparison outcomes after single and bilateral lung transplantation for obstructive lung disease. *J Heart Lung Transplantation* 1995; 14:692–8.
10. D'Armini AM, Callegari G, Vitulo P, et al. Risk factors for early death in patients awaiting heart-lung or lung transplantation, experience at a single European center. *Transplantation* 1998; 66:123–7.
11. Okada O, Tanabe N. Yasuda J. et al. Prediction of life expectancy in patients with primary pulmonary hypertension. A retrospective nationwide survey from 1980–1990. *Intern Med* 1999; 38:12–6.
12. Keck BM, Bennett E, Fid BS, et al. Worldwide thoracic organ transplantation: a report from the UNOS/ISHLT international registry for thoracic organ transplantation. *Clin Transpl* 1997:29–43.

13. Harringer W, Wiebe K, Struber H, et al. Lung transplantation, 10-year experience. *Eur J Cardiothoracic Surg* 1999; 16:546–54.
14. Huerd SS, Hodges TN, Grover FL, et al. Secondary pulmonary hypertension does not adversely affect outcome after single lung transplantation. *J Thorac Cardiovasc Surg* 2000; 119:458–65.
15. Barlow OW, Robbin RC. Moon MR, et al. Heart-Lung versus double-lung transplantation for suppurative lung disease. *J Thorac Cardiovasc Surg* 2000: 119:466–76.
16. Yousem SA, Berry GJ, Cagle PT, et al. Revision of the 1990 working formulation for the classification of pulmonary allograft rejection: Lung Rejection Study Group. *J Heart Lung Transplant* 1996; 15:1–15.
17. Horning NR, Lynch JP, Sundaresan SR, et al. Tracolimus therapy for persistent or recurrent acute rejection after lung transplantation. *J Heart Lung Transplant* 1998; 17:761–7.
18. Onsager DR, Canver CC, Jahania MS, et al. Efficacy of Tracolimus in the treatment of refractory rejection in heart and lung transplant recipients. *J Heart Lung Transplant* 1999; 18:448–55.
19. Ross DJ, Waters PF, Levine M, et al. Mycophenolate Mofetil versus azathioprine immunosuppressive regimens after lung transplantation: preliminary experience. *J Heart Lung Transplant* 1998; 17:768–74.
20. Sarris GE, Smith JA, Shumway NE, et al. Long-term results of combined heart-lung transplantation: the Stanford experience. *J Heart Lung Transplant* 1994; 13:940–9.
21. Cooper JD, Billingham M, Egan T, et al. A working formulation for the standardization of nomenclature and for clinical staging of chronic dysfunction in lung allograft, International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 1993; 12:713–6.
22. Yousem SA. Can transbronchial biopsy aid in the diagnosis of bronchiolitis obliterans in lung transplant recipients? *Transplantation* 1994; 57:151–3.
23. Reitz BA, Wallwork J, Hunt SA, et al. Heart-Lung transplantation: successful therapy for patients with pulmonary vascular disease. New Engl J Med 1982; 306:557–64.
24. Chau EMC, Lee J, Yew WW, Chiu SW, Wang EP, et al. Mediastinal irradiation for graft-versus-host-disease in a heart-lung transplant recipient. *J Heart Lung Transplant* 1997; 16:974–9.
25. *The Journal of the Japanese Association for Chest Surgery.* 16th Annual Scientific Meeting 1999, Abstract 1S 1–4, p 96–99.
26. Date H. Current status and future of lung transplantation. Intern Med 2001 Feb; 40(2):87–95.

27 Minimal Access Thoracic Surgery

Anthony P C Yim, C Peter Clarke and Hui Ping Liu

Minimal access thoracic surgery is a term we choose to use to include both video-assisted thoracic surgery (VATS) and video-assisted interventional bronchoscopy. This chapter is intended to give an overview of these two surgical approaches with special attention to their applications in our localities.

Video-assisted Thoracic Surgery

Introduction

Thoracoscopy was first introduced in the early 1900s by HC Jacobaeus, a European physician who used a cystoscope to examine the thoracic cavity under local anaesthesia (1). Modern video-assisted thoracosocpy was made possible by three advances. Improved endoscopic lens systems coupled with the development of solid state systems and microcameras in the early 1980s allowed a panoramic view of the hemithorax instead of the previous tunnel view (2). Secondly, improved anaesthetic technique with one-lung ventilation gave greater manoeuvrability of the telescope and instruments (3). Lastly, the development of endoscopic surgical instruments, such as the linear staple cutter, opened up new vistas for a spectrum of diagnostic and therapeutic thoracoscopic procedures (4).

Posterolateral thoracotomy, being the conventional mode of access to the chest is arguably the most painful incision even to be encountered by our patients. This is not only because of the length of incision or the transection of chest wall muscles, but mainly because ribs have to be forcefully spread in order to gain access into the chest. Post thoracotomy pain is often chronic and could be felt years and even decades after the operation, often precipitated by changes in weather. Hence, it is hardly surprising that within the last few years, video-assisted thoracic surgery (VATS) has rapidly become an established technique in thoracic surgery. A survey conducted on North American thoracic surgeons in 1995 showed VATS has become the preferred or accepted approach over a wide range of thoracic procedures (5). Recently, we conducted a similar questionnaire survey of thoracic surgeons outside North America. A questionnaire was sent to thoracic surgeons from Australia, Asia, Europe and South America asking the role of VATS in their practice and their opinions regarding appropriate applications, and limitations of the approach (6). Compared to the study conducted in North America 3 years ago, this survey showed increased acceptance of VATS for the more complicated procedures like thymectomy and lobectomy. This may represent an increased acceptance of the VATS approach with time and experience. Considerable concern however, exists

over cost and the use of VATS as a therapy for oncological diseases

Contraindications to VATS are relatively few (Table 1). In addition to the general contraindications like recent myocardial infarction, severe coagulopathy, specific contraindications include pleural symphysis and inability to tolerate selective one lung ventiliation. The former is relatively uncommon and moderate adhesions could usually be taken down using a combination of sharp and blunt dissection under videoscopic vision. Prior operation in the ipsilateal chest should not be regarded as a contraindication (7).

Table 1. Some Common Indications and Contraindications for Video-Assisted Thoracic Surgery Indications

Diagnostic
Pleural biopsies
Staging of intrathoracic tumours
Wedge resections of diffuse pulmonary infiltrate
Mediastinal mass biopsies
Therapeutics
Empysema and Haemothorax
Spontaneous pneumothorax
Sympathectomy / Splanchnicectomy
Pericardial windown
Benign oesophageal disorders
Resection of benign mediastinal masses
Anatomical lung resection (for benign pathology or stage I lung cancer)
Lung volume reduction surgery
Thymectomy
Contraindications
Pleural symphysis
Inability to tolerate single-lung ventilation
Locally advanced lung cancer
Established mediastinal malignancy (for resection)

While there is now a wealth of literature on VATS, there are relatively few publications comparing a VATS procedure with its conventional (thoracotomy) counterpart in a randomized, prospective manner (8,9). Nonetheless, because of their low morbidity, good short and long term results, many VATS procedures are now well accepted as the approach of choice by the thoracic surgical community (9). Detailed discussion of each procedure is beyond the scope of this article and the readers are referred to our specialized textbook on this subject (10).

Diagnostic modality

The use of VATS as a diagnostic modality is well established and this includes biopsy of the pleura, lung mass, diffuse lung infiltrate, mediastinal mass, pericardium and vertebral body (11). For simple procedures, the use of miniaturized instruments ("needlescopic" instruments of 2mm or less in diameter) provides an attractive option which could further reduce postoperative discomfort (12). However, diminished illumination, reduced resolution as well as flexibility of the equipment render it difficult to control fine movements. VATS is a useful adjunct to mediastinoscopy in the biopsy of several lymph node stations not accessible to the latter approach (like the aortopulmonary, para-oesphageal and inferior ligament nodes) for patients with primary lung cancer. However, mediastinoscopy should remain the principle diagnostic modality as VATS would not be able to provide information on contalateral mediastinal node involvement (N3 disease or Stage IIIB). Nonetheless, VATS plays an important role in excluding patients with pleural metastasis for an unnecessary thoracotomy. It is now our routine to perform VATS exploration in all patients with intrathoracic malignancy, even before a planned thoracotomy. VATS exploration could also provide information regarding chest wall invasion to help proper planning of subsequent thoracotomy (13). VATS also plays a role in the secondary staging of lung cancer i.e. patients with Stage IIIA disease who underwent a course of neoadjuvant chemotherapy in whom repeat mediastinoscopy may be technically difficult and potentially hazardous.

Therapeutic modality

Pneumothorax

The tremendous success of VATS in the treatment of primary spontaneous pneumothorax has led to earlier referral by physicians and increased acceptance by patients for surgery (14). Stapled-resection of apical bullae followed by mechanical pleurodesis remains the most frequently used technique, although more cost-effective means of eliminating the bullae (like suturing or looping) have been developed (15). While primary spontaneous pneumothorax cases are easily approachable by VATS, treatment of secondary spontaneous pneumothorax (with established lung pathology like emphysema or pneumoconiosis) requires more clinical judgment (16). Patients with difficult adhesions to take down may be more suitable for thoracotomy, while those who are elderly with multiple co-morbidities may benefit more from a chemical pleurodesis (we prefer talc slurry) if the lung could be fully re-expanded.

Pleural effusion

For therapeutic procedures, the role of VATS in the drainage of loculated effusion (including empyema and hemothorax) and pleural debridement is well established (17). It is important to remember that if simple drainage is inadequate, VATS exploration should be recommended early before the empyema progresses from a fibrinopurulent phase to an organized fibrotic phase, resulting in restricted pulmonary function from encasement or fibrothorax. The use of VATS to guide the proper placement of a chest drain should not be under-rated (18). For malignant pleural effusions, we believe that patients who do not have trapped lungs are better treated with talc slurry than thoracoscopic talc insufflation as the former is simple, could be performed by bedside and does not require general anaesthesia (13).

Sympathectomy and splanchnicectomy

Thoracodorsal sympathectomy is indicated for patient with palmar and axillary hyperhidrosis, and selected patients with reflex sympathetic dystrophy, and vasculopathies like Raynaud's or Buerger's disease (19). A segment of the sympathetic chain could be excised or ablated (for example with electrocautery) and the extent of intervention is dependent on the patient. For example, for palmar hyperhidrosis alone, only the T2 segment needs to be excised but if axillary hyperhidrosis is also a problem, the level of resection (or ablation) should be extended to include T4. Success rate of this procedure for hyperhidrosis is high and ranges from 85 to 95 percent in large series from Taiwan (20,21). The possibility of compensatory truncal hyperhidrosis should be fully explained to the patients before surgery.

Splanchnicectomy is indicated for patients with intractable visceral pain arising from the upper abdomen. The greater splanchnic nerve arises from T5 to T10 and lesser splanchnic nerve from T10 to T11 of the sympathetic chain. In over half the patients, unilateral approach alone from the left is effective and should be tried first before resorting to a bilateral approach (22).

Mediastinal cysts

Benign mediastinal cysts like demoid cyst, oesophageal duplication cyst, thymic cyst and pericardial cysts are often surprisingly easy to resect using VATS. Decompression of the cyst with a needle may be necessary to facilitate mobilization. The phrenic nerve should be identified and carefully preserved. For oesophageal duplication cysts, a fibreoptic light source (from a bronchoscope) placed in the oesophagus could help identify this structure thoracoscopically during dissection. As a rule, for benign cysts, the tissue plane is fairly well preserved. In fact, any suspicion of tissue plane invasion by tumour should call for conversion to a full thoracotomy for further dissection (22).

Thymectomy

Thymectomy is now an established therapy, in conjunction with medical treatment for generalized myasthenia gravis (MG). However, which technique to use continues to be a subject of controversy. Several surgical approaches are currently being used and these include transternal, transcervical, a combination of the two (for "maximal thymectomy") and recently VATS (23). Our own results as well as the collective data with other centres showed that there is little difference in symptomatic improvement to thymectomy regardless of which surgical approach was used (24).

VATS thymectomy definitely has several distinct advantages over the other approaches. It is much less painful than the transternal approach and recovery is much quicker. The thymus is essentially an anterior mediastinal structure and therefore, it is more direct to approach it from the chest than from the neck. The transcervical approach has the disadvantage of instrument crowding through a small, single access. Cosmesis, following VATS is excellent. Although this, on its own should only be regarded as a bonus rather than the main reason for choosing a particular surgical approach, the majority of MG patients are young females who care a lot about the surgical scars. As there is evidence that the sooner the patients with generalized MG have surgery, the better is the long term outcome, it follows that the VATS approach could encourage earlier acceptance of thymectomy by the patients and earlier referral of these patients by their neurologists (25).

Pericardial window

VATS provides a safe and effective approach to the drainage of pericardial effusion of both benign and malignant aetiology. Large pericardial windows could be created both anterior and posterior to the phrenic nerve for drainage (26). When pericardial effusion is associated with pleural effusion, the pericardium should be approached from the side with the pleural effusion (or with more effusion in bilateral disease), otherwise a right approach is usually preferred as the right hemithorax is larger than the left, giving a better perspective for VATS evaluation. Subxiphoid drainage remains a viable alternative approach which could be performed under local anaesthesia in patients who are very ill and debilitated as well as those with a history of bilateral chest surgery or pneumonia when troublesome adhesions could be anticipated. Video-assisted subxiphoid approach using a videomediastinoscope is a recent refinement of the old procedure (27).

Anatomical lung resection

The application of VATS to anatomical lung resections continues to be a subject of considerable controversy. Even among surgeons practising VATS, only a few use this approach for lobectomy (28). Anatomical dissection performed through a minithoracotomy in an essentially closed chest raised questions on the safety of the technique; resection for intrathoracic malignancy casts doubt on adequate clearance; the long term benefits of VATS over conventional thoracotomy approach are uncertain (8,29) and the high cost of the consumables and endoscopic equipment questions the cost effectiveness of this approach in the current era of cost containment.

However, despite all the scepticism, intermediate term results from several centres performing VATS lobectomy have been very encouraging (28). The survival figures for lung carcinoma following VATS resection are at least as good, if not better than a similar group of patients following resection through a conventional thoracotomy. The reason for the improved survival remains unclear at present but there is circumstantial evidence that by minimizing chest wall trauma, the body inflammatory response is dampened and immune function better preserved (30,31).

Regardless of the exact technique used (32–35), it is generally agreed that careful patient selection is essential. Our own patient selection criteria for tumour resection include stage I non-small cell lung cancer (without evidence of endobronchial or chest wall involvement), tumour size less than 4 cm, complete or near complete fissures (a thoracoscopic assessment (28).

We believe that VATS lobectomy is a feasible and safe procedure in experienced hands and may be of particular benefit to the elderly and patients with multiple co-morbidity who are otherwise poor risk candidates for conventional thoracotomy (28).

Other applications of VATS

Many thoracic procedures are being rediscovered through the thoracoscope, some of these also involve the other surgical subspecialties. Thoracoscopic spinal surgery is receiving increasing attention by the orthopaedic community. For spinal deformity, anterior spinal release as well as instrumentation are now feasible (35). VATS is also playing an important role in minimal access cardiac surgery. The left internal mammary artery (LIMA) could be harvested with thoracoscopic assistance through an anterior minithoracotomy (36). This incision is subsequently used for the

anastomosis of LIMA to the left anterior decending (LAD) coronary artery in a procedure now referred to as minimally invasive direct coronary artery bypass grafting (MIDCABG). The thoracoscope has also found use in minimal access mitral valve surgery and a totally endoscopic approach to valve replacement and coronary revascularization (port access approach (37)).

Cost containment

The high cost of the endoscopic surgical consumables has deterred many Asian hospitals from widely applying the VATS technique. To ensure that VATS would benefit patients widely in Asia, the basic cost of equipments and of the procedure as a whole must be kept to the barest minimum. In order to reduce cost, we have endeavoured to keep our VATS technique as simple as possible by using all types of conventional instruments whenever possible. For example, filmsy adhesions often can be easily separated with light pressure using conventional ring forceps. A standard electrocautery with malleable extender works as well as any coagulator or argon beam device. In our hands, this is at least as effective as the endoscopic surgical hook for dissection and haemostasis without the additional expense. The blunt tip of a conventional sucker is an excellent instrument for dissection. In patients with clotted hemothorax or loculated empyema, conventional instruments like a long-handled clamp and a large-bore wall suction tube are frequently used to evacuate the blood clots or the empyema content. The fibrous pleural "peel" can be decorticated and removed by interchanging the positions of conventional instruments through different incisions. Lung nodules in patients who are not willing or cannot afford to pay for the expensive endostapling device, can be wedge resected under video guidance through a small extended incision (4–6 cm) using standard suturing technique. This approach has been found to be as effective as endostapling without requiring extra payment from the patient. The argument commonly used in the United States that the shortened hospital stay conferred by VATS would counterbalance the high cost of the consumables cannot be applied in Asia. Hospital charges are generally cheaper and the cost of hospital stay is only a fraction of the total expenditure when compared to the cost of the endoscopic consumables (14,15). This situation is entirely different in the West where reduction in hospital stay could produce major savings. We believe that only stringent use of endo-equipments, especially the endo-stapling device will bring the operative cost to a minimum. With the combined use of conventional instruments directly through incisions, grasping, suturing, and other means of manipulation manoeuvers become easier. For patients requiring complicated procedures like lobectomy, the extended 4–6 cm utility incision accommodates almost every conventional instrument and aids in expediting the procedure. There is no doubt that VATS could be significantly more costly than the equivalent open procedure if disposable items such as trocar and endoscopic staplers are injudiciously used. Since an airtight system is unnecessary in performing VATS, we strongly advise stringent use of endoscopic instruments to contain cost. This is of paramount importance in achieving a truly cost-effective VATS procedure and to ensure that VATS would have a wider acceptance among Asian countries.

Future prospects

Cardiothoracic surgery is undergoing a rapid flux of evolution as the development of videothoracoscopy revolutionized its practice. The question now is, does VATS, as we currently practice it, represent an end point that only requires minor refinements or is it an intermediate step to an even less invasive approach? We believe that both views may be correct. VATS represents a spectrum with a purely endoscopic approach at one end and a video-assisted approach (with a utility minithoracotomy) at the other end. For the purely endoscopic procedures, there have been attempts to modify further the surgical access and mode of anaesthesia. The former resulted in the development of 2 mm "needlescopic" instrument (38) and the latter in therapeutic thoracoscopy under local anaesthesia. It is entirely possible that in the near future, simple thoracoscopic procedures could be performed under local anaesthesia via an essentially percutaneous route with miniaturized instruments as an outpatient procedure.

To summarize, VATS provides a much more patient-friendly surgical approach to the management of a wide variety of intrathoracic conditions. In many situations, the morbidity associated with a painful thoracotomy can now be avoided.

Interventional Bronchoscopy

Introduction

Bronchoscopy as a therapeutic manoeuver was first introduced by Killian in 1897 when he used an oesophagoscope in the trachea to remove an inhaled piece of pork bone. He went on to develop a purpose built bronchoscope with lateral openings to prevent respiratory obstruction during its use. Chevalier Jackson refined the instrument by adding distal lighting and popularized its use for diagnosis. Both surgeons reported manual removal of tumour occluding the tracheobronchial tree for relief of dyspnoea.

The flexible bronchoscope was introduced by Ikeda in the 1960s (39) and rapidly became the instrument of choice for diagnostic procedures. There are still some occasions however where maintenance of an adequate airway is critical, such as investigation of massive haemoptysis, when the rigid bronchoscope is still preferred.

Laser

Manual removal of tumour occluding the airways has been practiced since the time of Killian but as most centrally placed tumours only cause symptoms in the later stage of the disease because more than 75% of the lumen needs to be obstructed before local symptoms occur, it can prove to be a messy and dangerous procedure. The use of lasers in conjunction with the bronchoscope allows for a more refined method of removing lesions blocking the airways. The first successful operational laser was produced by Maimon in 1960 (40). Laser light is produced by stimulating a crystal source then concentrating the resultant beam and transmitting it to the target where manipulation of its strength can produce cutting coagulation or vaporization (Figure 2). Because of its capability for coagulation and its ability to be transmitted through a fibre, the neodymium yttrium aluminium garnett (Nd-YAG) laser had become the work-horse for endoscopic work. It is most commonly used in conjunction with the rigid bronchoscope to allow safe maintenance of the airway and manual extraction of bulky tissue after it has been coagulated.

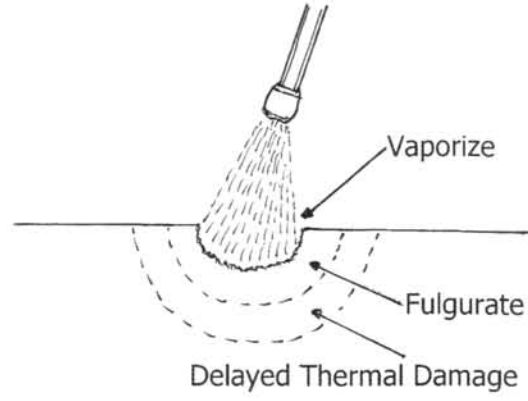


Figure 1. Effect of Nd-YAG Laser on tissues

Our practice is to use the rigid bronchoscope with total intravenous anaesthesia and Venturi jet ventilation (41) and the fibre-optic bronchoscope for direction of the fibre and to aid in clearance of secretions (Figure 3). The Nd-YAG laser is invisible but is dangerous to the retina, so all personnel in the theatre including the patient, wear safety spectacles which give a green tinge to the view and means the patient has to be carefully monitored with an oximeter. The oxygen

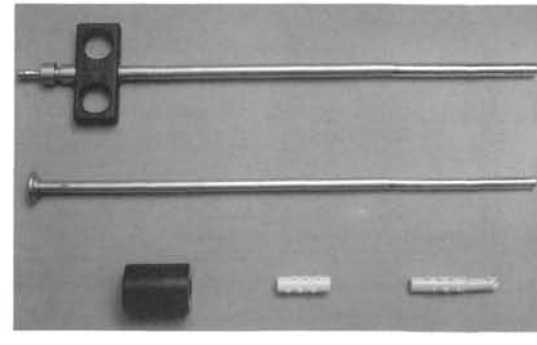


Figure 2. Dumon Endoxane Stents and the introducer

concentration of the entrained gases is kept as low as possible to diminish the likelihood of debris catching fire. This is particularly important if the laser is being used with a Silicone stent in place (42).

Our total experience since 1986 is now over 1,000 cases with a 1% mortality rate and 15% morbidity rate. The main cause of mortality has been post procedural respiratory insufficiency, we have also had a fatal fire with a Silastic stent and exsanguination following perforation of the pulmonary artery on two occasions. The leading causes of morbidity have been cardiac arrhythmias, respiratory problems, and significant bleeding (over 200 cc).

The majority of patients have had bronchogenic carcinoma and the commonest variety has been squamous cell carcinoma as it most often starts centrally. Approximately 17% of patients have had obstruction due to secondary tumour and in ascending order of frequency they have originated from kidney, large bowel, breast and oesophagus.

When the primary tumour is well controlled or slowly growing the results of resection of endobronchial secondaries can be most gratifying (43). A small number of patients have had benign lesions such as congenital or post tuberculous webs, granulomas, sarcoid lesions or angiomas causing haemoptysis.

The majority of patients suffer from dyspnoea but a significant number had intractable cough or haemoptysis as the main symptom. While there is little evidence that life is prolonged in patients with bronchogenic cancer having laser treatment, there is certainly good evidence that there is useful relief of symptoms in over 75% of cases (44). The tumours tend to recur and we found it preferable to perform a check bronchoscopy six weeks after laser resection rather than rely on serial pulmonary function tests or chest X-rays which only change when the obstruction is critical. Depending on the rate of regrowth then further inspections can be planned appropriately. The rate of regrowth can be slowed by further radiotherapy or chemotherapy and if a full course of external beam radiotherapy has been given by a boost with endoluminal brachytherapy.

Approximately 25% of patients will require repeat laser bronchoscopy. Unfortunately repeat laser bronchoscopies tend to become less effective over time as the tumour extends more distally and causes extrinsic compression. Serial ventilation perfusion studies have proven useful in identifying which patients will benefit from further resection as if there is no perfusion in the lung at all, then there will be no useful return of function (44). The mean survival time from the time of first laser resection is of the order of 6.9 months and it is only a minority of patients who require more than two retreatments.

Lasers have also been used for detection of tumour in the bronchial tree and activation of chemicals which then have a local cytotoxic affect. In the first instance a photosensitizer is given which is taken up by tumour and fluoresces when a laser beam with appropriate wave-length is used. In the latter instance the photosensitizer is taken up preferentially by the tumour and when activated by light breaks down to give a local cytotoxic effect (45). Unfortunately the skin also takes up some of the compound which sensitizes it and means that patients need to avoid direct sunlight for up to six weeks. For phototherapy the Nd-YAG laser can be used as a driver using the beam to activate a dye chamber in order to produce light of the required wave length. This has proven useful in cases with widespread carcinoma *in situ*. It is not so useful in patients with obstructing tumour as a second bronchoscopy is necessary to remove the detritus.

Lasers have been widely used as they do not require contact with the tumour and can be easily applied anywhere in the main tracheobronchial tree, but alternative treatments in electrocautery (46) and cryotherapy (47) have been available for some years. Both techniques have suffered in that contact is needed which is messy and cryotherapy also shares the disadvantage with lasers in that the equipment is expensive. There has been a resurgence of interest in electrocautery recently (48,49) as the equipment has been refined to pass down a fibre-optic bronchoscope which allows a proportion of cases to be done on an out-patient basis with the attendant saving in costs.

Brachytherapy

Another technique which is most suitable when

there is a combination of intrinsic tumour and extrinsic compression is brachytherapy whereby a fine tube is placed in the bronchus and a radioactive wire introduced from a protected source to give local irradiation. If high dose rate brachytherapy is used, the time of exposure is short and this lends itself to being used as an outpatient procedure or as an adjunct after laser resection. Mobile shielded remote control units are available and along with local shielding, can be used in an ordinary operating theatre (50).

Tracheobronchial stenting

When the obstruction is mainly due to extrinsic compression but there is still a reasonable distal airway stents are used. The terms stent derives from Charles Stent, a British Dentist in the late 19th Century who developed dental impression material that was then used for a variety of templates. Stents made from Silastic provoke minimal tissue reaction and can be made smooth so secretions are not retained and were popularized by Montgomery who devised a T-tube stent as an aid to tracheal resection (51). More specific bronchial stents incorporating external nodes to prevent migration were introduced by Dumon (52) (Figure 2). These are easily introduced with a special introducer (Figure 2) and can be moved using grasping forceps in a rotary action. Very tight stenoses may need to be dilated before a stent can be introduced and this can be done with gum-elastic bougies or balloons on the end of catheters. The stents tend to provoke granulation tissue at their ends and may become occluded with retained secretions. They can also migrate despite the external nodes and this is particularly likely to occur if radiotherapy is given after their insertion.

If recurrent tumour or distal granulation tissue becomes a problem then the safest course is to remove the stent, resect the tumour with the laser and then replace the stent. Occasionally it is inconvenient to remove the stent such as when it covers a fistula in which case the laser can be used through the stent with care and provided the entrained oxygen level is kept low (42).

The Gianturco metal expandable stent was originally developed by Cesare Gianturco at the animal laboratory at the M. D. Anderson Cancer Centre in the 1980s and was initially used for biliary strictures. The stents have been adapted for use in other areas including the tracheobronchial tree (53). Similar stents are the Wall stent and the Palmanz stents. The latter stent is designed to be expanded fully using a catheter with a balloon and this principle can be used for all the stents.

Metal stents are rather rigid and particularly when placed peripherally are liable to penetrate the bronchial wall into an adjacent vessel with fatal results (54). This occurred in one of our patients only 14 days after insertion of the stent into the left main bronchus. The metal stents are also difficult to remove which really makes them unsuitable for patients with non malignant conditions, although a retrievable Ninotol stent has recently been described (55).

They can also be covered with plastic which helps prevent regrowth of tumour through the interstices of the stent and this is particularly useful when a fistula requires occlusion but does have the disadvantage that it makes lasering through the stent somewhat dangerous. When a tracheo-oesophageal fistula occurs, which most often happens after radiotherapy for an upper oesophageal cancer, then stents are often required both in the oesophagus and the trachea or left main bronchus. Even if the oesophageal stent will occlude the fistula, it often does so at the expense of compression of the tracheobronchial tree which then requires stenting just to keep the lumen open.

Conclusion

In summary bronchial obstruction leads to atelectasis of the distal lung with secondary shunting of blood and hypoxia causing dyspnoea and setting the stage for pulmonary infection.

While relieving the obstruction may not prolong life significantly in patients with bronchogenic cancer it certainly makes them more comfortable and relieves distressing symptoms. A small number of patients with benign conditions may be cured. A therapeutic pulmonary endoscopist needs to be familiar with a range of techniques for relieving tracheobronchial obstruction and use them appropriately.

References

1. Jacobaeus HC. The practical importance of thoracoscopy in surgery of the chest. *Surg Gynecol Obstet* 1992; 34:280–96.
2. Lewis RJ, Kunderman PJ, Sisler GE, et al. Direct diagnostic thoracosocpy. *Ann Thorac Surg* 1976; 21:536–9.
3. Husnain J, Krasna M.J. Anesthetic considerations of thoracoscopy. *J Card Vasc Anesth* 1992; 6:624–7.
4. Landreneau RJ, Hazelrigg SR. Ferson PF, et al. Thoracosocpic resection of 85 pulmonary lesions. *Ann Thorac Surg* 1992; 54:415–20.
5. Mack MJ, Scruggs GR, Kelly KM, Shennib H, Landreneau RJ. Video-assisted thoracic surgery: has technology found its place? *Ann Thorac Surg* 1997; 64:211–5.
6. Yim APC, Izzat MB, Wan S, and the International VATS Study Group (1998). Video assisted thoracic surgery: its role in current thoracic surgical practice worldwide. The XIX World Congress on Diseases of the Chest and the 64th Annual International Scientific Assembly of the American College of Chest Physicians, November 8–12 1998, Toronto, Ontario, Canada. *Chest* 1998; 114:390S.
7. Yim APC, Liu HP, Hazelrigg SR, Izzat MB, Fung ALK, Boley TM, Magee MJ. Thoracoscopic operations on reoperated chests. *Ann Thorac Surg* 1998; 65:328–30.
8. Kirby TJ, Mack MJ, Landreneau RJ, Rice TW. Lobectomy: video-assisted thoracic surgery versus muscle-sparing thoracotomy. A randomized trial. *J Thorac Cardiovasc Surg* 1995; 109:997–1002.
9. Yim APC, Chan TC, Lee TW, Wan YP, Ho JKS. Thoracoscopic talc insufflation versus talc slurry in the treatment of symptomatic malignant pleural effusion. *Ann Thorac Surg* 1996; 62:1655–8.
10. Yim APC, Hazelrigg SR, Izzat MB, Landreneau RJ, Mack MJ, Naunheim KS (eds). *Minimal Access Cardiothoracic Surgery*. Philadelphia: Saunders 1999.
11. Yim APC, Liu HP. Complications and failures from video assisted thoracic surgery: experience from two centers in Asia. *Ann Thorac Sur* 1996; 61:538–541.
12. Yim APC, Izzat MB. Is less better? (Editorial) *Chest* 1998; 113:270–1.
13. Yim APC. Routine video-assisted thoracoscopy prior to thoracotomy. *Chest* 1996; 109:1099–100.
14. Yim APC. Video assisted thoracoscopic surgery (VATS) in Asia — its impact and implications. *Aust N Z J Med* 1997; 27:156–9.
15. Yim APC. Cost containment strategies in video assisted thoracoscopic surgery — an Asian perspective. *Surg Endosc Ultras* 1996; 10:1198–200.
16. Waller DA, Forty J, Morritt G.N. Video-assisted thoracoscopic surgery versus thoracotomy for spontaneous pneumothorax. *Ann Thorac Surg* 1994; 58:372–7.
17. Angelillo Mackinlay TA, Lyons G, Chimondegwy DJ, et al. VATS debridement versus thoracotomy in the treatment of loculated postpneumonia empyema. *Ann Thorac Surg* 1996; 61:1626–30.
18. Yim APC, Ho JKS, Lee TW, Chung SS. Thoracoscopic management of pleural effusion revisited. *Aust N Z J Surg* 1995; 65:308–11.
19. Kohno T, Takamoto S. Thoracoscopic thoracic sympathectomy. In: *Minimal Access Cardiothoracic Surgery*. Eds. Yim APC, Hazelrigg SR, Izzat MB, Landreneau RJ, Mack MJ, Naunheim KS. Philadelphia: Saunders 1999, 232–8.
20. Lin CC. A new method of thoracoscopic sympathectomy in hyperhidrosis palmaris. *Surg Endosc* 1990; 4:224–6.
21. Kao MC. Video endoscopic sympathectomy using a fibreoptic CO_2 laser to treat palmar hyperhidrosis. *Neurosurgery* 1992; 30:131–5.
22. Yim APC. Video assisted thoracoscopic resection of anterior mediastinal masses. *Int J Surg* 1996; 81:350–3.
23. Yim APC, Kay RLC, Ho JKS. Video assisted thoracoscopic thymectomy for myasthenia gravis. *Chest* 1995; 108:1440–3.
24. Mack MJ, Landreneau RJ, Yim APC, Hazelrigg SR, Scruggs GR. Results of VATS thymectomy in patients with myasthenia gravis. *J Thorac Cardiovasc Surg* 1996; 112:1352–60.
25. Yim APC, Kay R, Kay R, Izzat MB, Ng SK. Video-assisted thoracoscopic thymectomy for myasthenia gravis. *Sem Thorac Cardiovasc Surg* 1999; 11:65–73.
26. Liu HP. Chang CH, Lin PJ, Hsieh HC, Chang JP, Hsieh MJ. Thoracoscopic management of effusive pericardial disease: indications and technique. *Ann Thorac Surg* 1994; 58:1695–7.
27. Yim APC, Ho JKS. Video assisted subxiphoid pericardiectomy. *J Laparoendosc Surg* 1995; 5:193–8.

28. Yim APC, Izzat MB, Liu HP. Ma CC. Thoracoscopic major lung resection — the Asian perspective. *Sem Thorac Cardiovasc Surg* 1998; 10:326–31.
29. Landreneau RJ, Mack MJ, Hazelrigg SR, et al. Prevalence of chronic pain after pulmonary resection by thoracotomy or video-assisted thoracic surgery. *J Thorac Cardiovasc Surg* 1994; 107:1079–86.
30. Walker WSA, Leaver HA, Craig SR. Yap PL. Thoracoscopic lobectomy and body immune function. In: *Minimal Access Cardiothoracic Surgery.* Eds. Yim APC, Hazelrigg SR, Izzat MB, Landreneau RJ, Mack MJ. Naunheim KS. Philadelphia: Saunders 1999, 127–34.
31. Yim APC, Wan S, Lee TW, Arifi AA. VATS lobectomy reduces cytokine responses compared to conventional surgery. *Ann Thorac Surg* (In press).
32. Lewis RJ. The role of video-assisted thoracic surgery for carcinoma of the lung: wedge resection to lobectomy by simultaneous individual stapling. *Ann Thorac Surg* 1993; 56:762–728.
33. Yim APC. Minimizing chest wall trauma in video assisted thoracic surgery. *J Thorac Cardiovasc Surg* 1995; 109:1255–6.
34. Yim APC, Landreneau RJ, Izzat MB, Fung ALK. Is video assisted thoracoscopic lobectomy a unified approach? *Ann Thorac Surg* 1998; 66:1155–8.
35. Crawford AH, Wolf RK. Spinal deformities. In: *Minimal Access Cardiothoracic Surgery.* Eds. Yim APC, Hazelrigg SR, Izzat MB, Landreneau RJ, Mack MJ, Naunheim KS. Philadelphia: Saunders 1999, 316–27.
36. Izzat MB, Yim APC. Video-assisted internal mammary artery mobilization for minimally invasive direct coronary artery bypass. *Eur J Cardio-thoracic Surg* 1997; 12:811–2.
37. Yim APC, Izzat MB. Thoracoscopy and video assisted thoracic surgery. In: *Oxford Textbook of Surgery* 2nd ed. Oxford: Oxford University Press (In press).
38. Yim APC, Liu HP, Lee TW, Wan S, Arifi AA. "Needlescopic" VATS for palmar hyperhidrosis. *Eur J Cardio-thorac Surg* 2000; 17:697–701.
39. Sackner MA. Bronchofiberoscopy. *Am Rev Respir Dis* 1975; 111:62–8.
40. Maiman TH. Stimulated radiation in ruby. *Nature* 1960; 187:493–4.
41. Jackson KA, Morland MH. Anaesthesia for resection of the trachea and main bronchi using the neodymium-yttrium alumimum garnett (Nd-YAG) lasers: a report of 75 lasers in 52 patients. *Anaesth Investive care* 1990; 18:69–75.
42. Scherer TA. Nd-YAG laser ignition of Silicone Endobronchial Stents. *Chest* 2000; 117:1449–54.
43. Yim APC, Abdullah V, Chan HS. A case of bronchial obstruction by renal cell carcinoma. *Surg Endosc* 1996; 10:855–56.
44. Clarke CP, Ball DL, Sephton R. Follow-up of patients having Nd-YAG laser resection of bronchostenotic lesions. *J of Bronch* 1994; 1:19–22.
45. Okanaka T, Kato H, Konaka C, Kawate N, Bonaminio A, Yamamato H, Ikeda N, Tolentino H, Eckhauser MC, Hayata Y. Photodynamic therapy for multiple bronchogenic carcinoma. *Cancer* 1991; 68:253–8.
46. Hooper RG, Jackson F. N. Endobronchial electrocautery. *Chest* 1985; 87:712:4.
47. Marasso A, Galla E, Massagla GM, Onoscuri M., Bernardi V. Cryosurgery in bronchoscopic treatment of tracheobronchial stenosis: Indications, limits, personal experience. *Chest* 1993; 103:472–4.
48. Van Boxen T, Muller M, Venmans B, Postmos P, Sutedja T. Nd-YAG laser vs bronchoscopic electrocautery for palliation of symptomatic airway obstruction: A cost-effective study. *Chest* 1999; 116:1108–12.
49. Coulter TD, Mehta AC. The heat is on: impact of endobronchial electrosurgery on the need for Nd-YAG laser photoresection. *Chest* 2000; 118:516–521.
50. Sephton R, Das KR, Coles J, Toye W, Pinder P. Local shielding of high dose rate brachytherapy in an operating theatre. *Austalas Phys and Engineer Scien in Med* 1999; 22:113–7.
51. Montgomery WW. T-tube tracheal stent. *Arch Otolaryngol* 1965; 82:320–1.
52. Dumon JF. A dedicated tracheo-bronchial stent. *Chest* 1990; 97:328–32.
53. Wallace MJ, Charnsangauej C, Ogawa K, Carruso CH, Wright KC, McMurtney M. Expandable metallic stents used in experimental and clinical applications. Work in progress. *Radiology* 1986; 158:309–12.
54. Puma F, Farabi R, Urbani M, Santoprete S, Dadd N, Di Meo A, Gialletti R, Tocchi A, Dadd G. Long term safety and tolerance of silicone and self-expanding airway stents: an experimental study. *Ann Thorac Surg* 2000; 69:1030–4.
55. Song HY, Shim TS, Kang SG, Jung GS, Lee DY, Kim TH, Park S, Ahn YM, Kim WS. Tracheo-bronchial strictures: treatment with a polyurethane covered retrievable expandable ninitol stent — initial experience. *Radiology* 1999; 213:905–12.

28

Pulmonary Function Testing in Asians

Jin Ping Zheng and Nan Shan Zhong

Introduction

Pulmonary function testing, as chest radiography, has become an integral part of the clinical assessment of pulmonary disease (1). The application of pulmonary function testing is increasing in many areas of clinical medicine, including diagnosis of airflow obstruction and lung restriction, evaluation of pulmonary impairment, preoperative assessment, assessment of environmental and occupational lung diseases, epidemiological surveys, and sports, high altitude, space and diving medicine, as well as public health screening (2). Without the assessment of pulmonary function, the diagnosis of bronchial asthma, chronic obstructive lung disease, idiopathic pulmonary fibrosis, and other lung diseases cannot be made adequately.

Pulmonary function measurements are subjected to variations:

1. technical variation related to instrument, procedure, operator and the subject being tested and their interactions;
2. biologic variation between subjects (host factors) and
3. variation due to diseases states (1,3).

It is important to minimize variation due to technical factors and to take biological variations into consideration so that changes due to disease states can be appropriately evaluated (3).

Sources of technical variation can be reduced by performing testing in a standardized manner according to guidelines that have been published by various professional societies and using instruments that satisfy the criteria set forth by these guidelines (4,5). Readers should consult these references for detailed recommendations. The largest source of variation is improper performance of the test (3). The results of spirometry, for example, are dependent on the efforts of the subject to be tested and his/her understanding of how the test is to be performed, which in turn depends on how well instructions are being given by the technician. Technicians conducting pulmonary function testing should ideally be trained for a period of 6 months and longer if troubleshooting is required. Some training manuals for performing pulmonary function testing are available (6).

In common practice, the results of pulmonary function tests should be interpreted in relation to reference values, and in terms of whether or not they are considered to be within the "normal" range. The results of tests cannot be interpreted appropriately without reference to predicted values. Many factors contribute to the between-individual variation in pulmonary function, including host factors such as age, height (or standing height, sitting height, arm span), gender, and race; and environmental factors such as exposure to environmental and workplace pollution, smoking, and socioeconomic status (1–3). The proportions

of between-individual variations due to various factors for forced expiratory volume in one second (FEV_1) or forced vital capacity (FVC) have been estimated as follows: sex 30%, age and height 30%, ethnic differences 10% and the rest unexplained even when the tests are well performed. Ethnic difference has been consistently shown to be an important determinant of pulmonary function and should be taken into account when interpreting these tests in Asians, especially when predicted values are based on populations of European descent.

Ethnic differences in lung function in adults

Many studies have shown that Asians (such as Chinese, Indian, Bhutanese, Japanese, Sri Lankan, Malaysian, Bangladeshi and Pakistani) have smaller lung volumes than Caucasians. To avoid incorrect interpretation of results by using Caucasian prediction equations, many lung function laboratories or institutions in Asian countries have established their own reference values for their own population (Table 1).

Udupihille (7) established reference values for dynamic lung volumes and forced expiratory flows for the Singhalese ethnic group in Sri Lanka by performing pulmonary function testing on 367 and 328 healthy non-smoking Singhalese females and males respectively, age ranged 17–65 years. When standardized for height and age, forced expiratory volumes of Singhalese were smaller than Europeans. By performing spirometry in 333 healthy Bhutanese males and females and comparing with the data of Europeans, Giri et al (8) concluded that Bhutanese have lower ventilatory parameters than Europeans and North Indians. Korotzer and colleagues (9) investigated ethnic differences in pulmonary function in healthy nonsmoking Asian- and European-Americans. They divided the subjects into four groups, European males and females, Asian males and females. The results showed that FVC, FEV_1 and alveolar volume (V_A) were significantly lower in Asians than Europeans. Wu and Yang (10) examined spirometry and maximal expiratory flow-volume curves in 180 healthy nonsmoking subjects aged 60 years and over in Taiwan. They found that spirometric values were lower in elderly Chinese than in elderly Caucasians even after adjustment for height and age.

Table 1. Lung Function Testing in Asian Ethnic Groups

				Lung function testing						
Country	*Ethnic groups*	*Subject No.*	*Age range (years)*	*Spiro*	*Peak Flow Meter*	*Lung subdi-visions*	*DLco*	*Predicted equation*	*Published year*	*First author Reference*
Mainland China	Chinese	4773	15~78	X		X	X	X	2002	Zheng (24)
Mainland China	Chinese	3415	16~75		X			X	1985	Zhong (11)
Srilanka	Srilankans	695	17~65	X				X	1995	Udupihille (7)
Taiwan, China	Chinese	436	20~70				X	X	1993	Yang (40)
Taiwan, China	Chinese	180	60 and over				X	X	1990	Wu (10)
Singapore	Chinese/ Malaysian/ Indonesian	406	20~79	X		X		X	1997	Chin (26)

In a survey of 5082 healthy Chinese aged 8 to 85 years, Zhong et al (11) have shown that the peak expiratory flow (PEF) curves according to age for healthy Chinese men and women did not fit the 'standard' curves for Caucasians generated from the data of Gregg and Nunn (12) (Figure 1). The PEF values of Chinese adults are lower than those of the Caucasians for the same age and height. The maximal PEF in Chinese women occur in those 20–25 years and not 30–35 years of age as in Caucasians and the decline in PEF is more rapid after the age of 60 in Chinese compared to Caucasians.

We have summarized lung function prediction equations derived from our laboratory (13) and other laboratories in China (14–18) and have compared them with those of overseas Chinese (19,20), European Respiratory Society (ERS) and European Coal and Steel Commission (ECSC) for Caucasians (4), and other commonly used prediction equations for Caucasians (21–23). The regression equations for Chinese selected here were from the nationwide normal lung function study that was organized and sponsored by the Public Health Ministry of China (2). The study was carried out in six large areas in Mainland China: south China (Guangzhou) (13), north China (Beijing) (14), northeast China (Shenyang) (15), northwest China (Xi-an) (16), east China (Shanghai) (17), and southwest China (Chongqin) (18), with the participation of twenty-six hospitals and institutions. A total of 4773 healthy Chinese (male: 2560, female: 2213), aged 15 to 78 years, were included in the study. The predicted FVC and FEV_1 derived from different regression equations for an average Chinese male (height 170 cm, weight 65 kg at ages 20, 40 or 60 yr) and female (height 160 cm, weight 55 kg at ages 20, 40 or 60 yr) compared with those derived from prediction equations of ECSC are shown in Tables 2 and 3. On the average, the predicted values of FVC and FEV_1 in Chinese are 6.2% lower in males, and 3.8% lower in females than those derived using predicted values of the ECSC.

Figures 2 and 3 show the FVC and FEV_1 of males (standing height 150 to 190 cm, weight 64 kg) and females (standing height 140 to 180 cm, weight 55 kg) of ages 20, 40 and 60 years, derived from the Chinese and the ECSC regression equations. The data demonstrated that the younger and the taller the subjects, the larger the differences in FVC and FEV_1 between the Chinese and

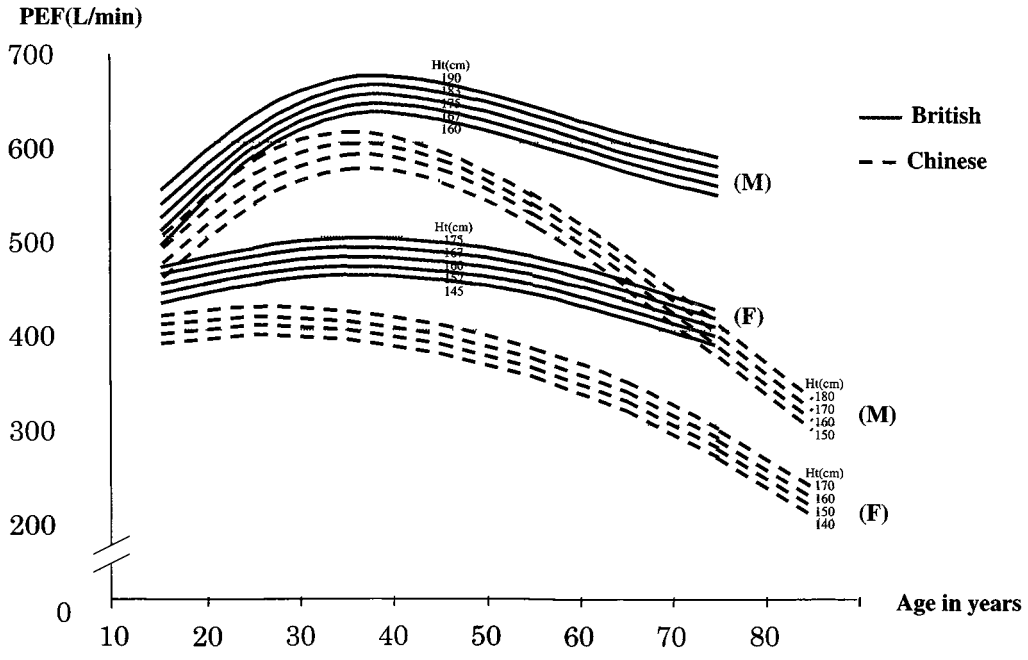


Figure 1. Normal prediction values of peak expiratory flow (PEF) in Chinese and British adults

Table 2. Comparison of Predicted FVC and FEV_1 Values from Different Regression Equations in Male (Height 170 cm, Weight 65 kg)

	Age (yrs)	*ECSC [4]*	*South China [13]*	*North China [14]*	*Northeast China [15]*	*Northwest China [16]*	*Southwest China [17]*	*East China [18]*	*Average# Chinese*
FVC (L)	20	4.87	4.42	4.69	4.48	4.80	4.64	4.49	4.59
			-9.2%@	-3.6%	-8.0%	-1.4%	-4.7%	-7.7%	-5.8%
	40	4.48	3.94	4.25	4.08	4.26	4.20	4.23	4.16
			-12.1%	-5.0%	-9.0%	-4.8%	-6.2%	-5.5%	-7.1%
	60	3.96	3.46	3.81	3.68	3.72	3.76	3.97	3.74
			-12.6%	-3.7%	-7.1%	-6.0%	-5.0%	0.4%	-5.7%
Mean*			-11.3%	-4.1%	-8.0%	-4.0%	-5.3%	-4.3%	-6.2%
FEV_1(L)	20	4.10	3.94	4.13	3.98	N/A	3.92	3.86	3.97
			-3.7%	0.9%	-2.8%		-4.3%	-5.7%	-3.1%
	40	3.66	3.36	3.63	3.44	N/A	3.34	3.48	3.45
			-8.1%	-0.7%	-6.0%		-8.8%	-4.9%	-5.7%
	60	3.08	2.78	3.13	2.90	N/A	2.76	3.10	2.94
			-9.6%	1.7%	-5.8%		-10.4%	0.6%	-4.7%
Mean*			-7.2%	0.6%	-4.9%		-7.8%	-3.3%	-4.5%
Average**			-9.2%	-1.7%	-6.5%	-4.0%	-6.6%	-3.8%	-5.3%

@ percentage represents the difference between predictions from ECSC [4] and from the Chinese authors [13–18] = [(Values(Chinese authors)-Values(ECSC))/Values(ECSC)]x100

* Mean represents the average percentage difference

** Average represents the average percentage difference for both FVC and FEV_1

\# Average represents the average values from the Chinese authors [13–18]

N/A: Not available

Table 3. Comparison of Predicted FVC and FEV_1 Values from Different Regression Equations in Female (Height 160 cm, Weight 55 kg)

	Age (yrs)	*ECSC [4]*	*South China [13]*	*North China [14]*	*Northeast China [15]*	*Northwest China [16]*	*Southwest China [17]*	*East China [18]*	*Average#*
FVC (L)	20	3.50	3.28	3.46	3.23	3.38	3.47	3.40	3.37
			-6.4%@	-1.1%	-7.7%	-3.5%	-0.8%	-2.8%	-3.7%
	40	3.11	2.94	3.18	2.95	3.00	3.13	3.14	3.06
			-5.6%	2.3%	-5.2%	-3.7%	-0.7%	1.0%	-2.0%
	60	2.59	2.60	2.90	2.67	2.62	2.79	2.88	2.74
			0.2%	12.0%	3.1%	1.0%	7.8%	11.3%	5.9%
Mean*			-4.0%	4.4%	-3.3%	-2.1%	2.1%	3.2%	0.1%
FEV_1(L)	20	3.18	2.97	3.07	2.96	N/A	2.94	2.95	2.98
			-6.6%	-3.3%	-6.8%		-7.5%	-7.2%	-6.3%
	40	2.80	2.53	2.73	2.54	N/A	2.50	2.57	2.57
			-9.8%	-2.5%	-9.4%		-10.9%	-8.4%	-8.2%
	60	2.30	2.09	2.39	2.12	N/A	2.06	2.19	2.17
			-9.3%	3.9%	-7.9%		-10.6%	-5.0%	-5.8%
Mean*			-8.5%	-0.6%	-8.0%		-9.7%	-6.9%	-6.7%
Average**			-6.2%	1.9%	-5.7%	-2.1%	-3.8%	-1.8%	-3.3%

@ percentage represents the difference between predictions from ECSC [4] and from the Chinese authors [13–18] = [(Values(Chinese authors)-Values(ECSC))/Values(ECSC)]x100

* Mean represents the average percentage difference

** Average represents the average percentage difference for both FVC and FEV_1

\# Average represents the average values from the Chinese authors [13–18]

N/A: Not available

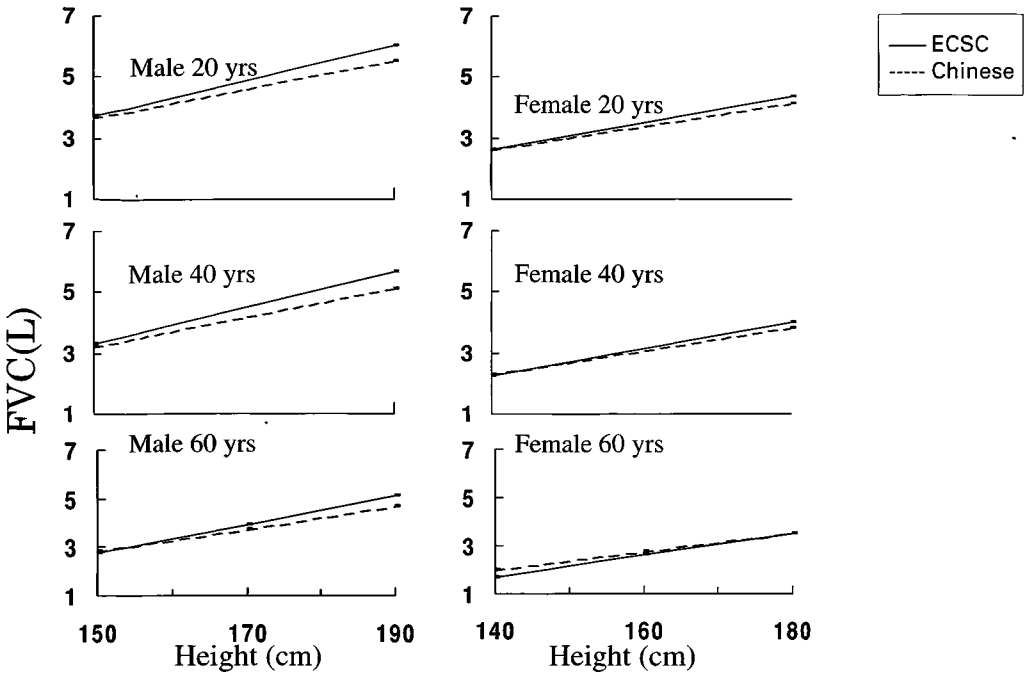


Figure 2. Predicted forced vital capacity (FVC) in Caucasian and Chinese male (height 150 to 190 cm, weight 65 kg) and female (height 140 to 180 cm, weight 55 kg) at the age of 20, 40, 60 years old.

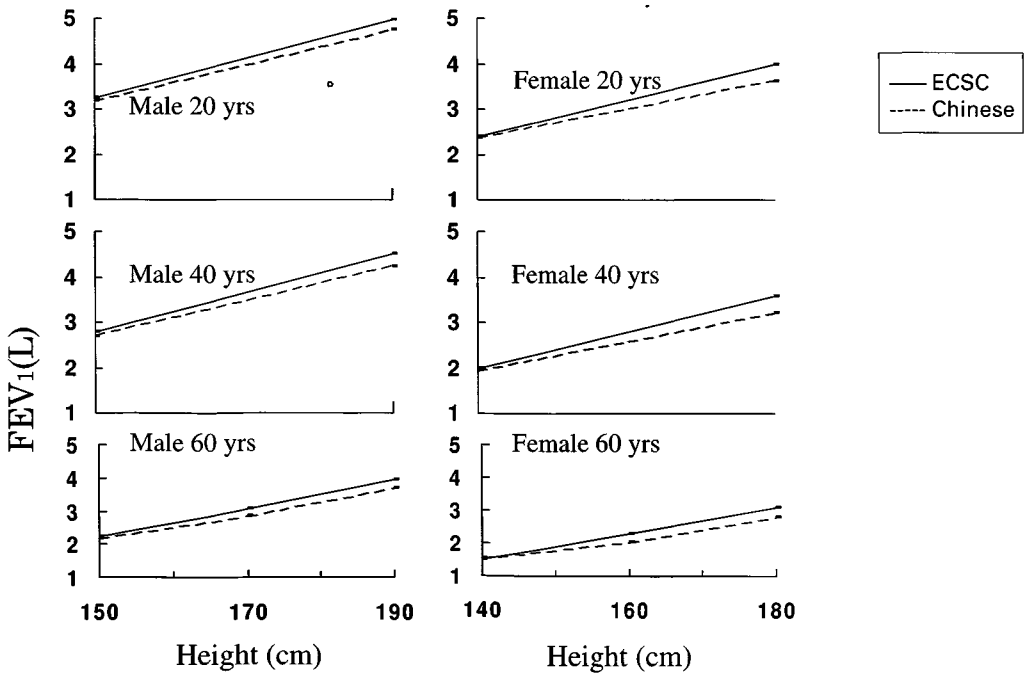


Figure 3. Predicted forced expiratory volume in one second (FEV_1) in Caucasian and Chinese male (height 150 to 190 cm, weight 65 kg) and female (height 140 to 180 cm, weight 55 kg) at the age of 20, 40, 60 years old.

Caucasians in both sexes. The differences in FVC, but not in FEV_1, between the two ethnic groups were larger in males than in females.

Table 4 shows the predicted FVC and FEV_1 from different regression equations in male and female standardized for age, height and weight (male: height 170 cm, weight 65 kg; female: height 160 cm, weight 55 kg). Although prediction equations for overseas Chinese are available (19,20), the differences in FVC and FEV_1 for males and females using these prediction equations when compared with those derived from the ECSC prediction equations are much larger than those derived from prediction equations for Mainland Chinese. For instance, the predicted FVC for a male, standardized for age, height and weight, derived from the prediction equations of Ching (19) and da Costa et al (20) are approximately 14% and 18% lower than those derived from the ECSC prediction equations; it was only 6% lower when the Mainland Chinese prediction equation was used. Thus the prediction equations of overseas Chinese should not be applied to Chinese in the Mainland (24).

Race differences exist within Asian countries. Chia and colleagues (25) demonstrated the ethnic differences by comparing Chinese, Malay and Indians who lived in Singapore. The Chinese have the largest lung volumes and flow rates, followed by the Malays then the Indians. Chin and coworkers confirmed this finding in their study (26).

Table 5 shows that the residual volumes (RV) in Chinese males and females were 4.8% and 8.7% respectively lower than those in Caucasians, and the total lung capacity (TLC) in Chinese males and females were 5.5% and 6.0% lower respectively.

Although lung volumes are smaller in Asians, the diffusing capacity appears to be similar between different ethnic groups. Yang et al (27) investigated the single-breath carbon monoxide diffusing capacity (DL_{coSB}) in 306 Chinese healthy adults who had technically acceptable test results. They found that DL_{co} was lower in Chinese than Caucasians when adjusted for alveolar volume (DL_{co}/V_A).

In addition to ethnicity, latitude position may account for some of the variations in lung function. For instance, the predicted lung volumes of people in northern China are larger than those in southern China. Differences between lung volumes derived from ECSC prediction equations and those derived from southern China were greatest (-9.2% in males and -6.2% in females) while differences in lung volumes derived from ECSC prediction equations and those derived from northern China were lowest (-1.7% in males and +1.9% in females) (23). Lung volumes were also found to be larger in people living in the northern than those in southern part of India (28).

Ethnic differences in lung function in children

The differences between Caucasians and Asians in pulmonary function parameters were not only seen in the adults, but in children and adolescents as well. Table 6 showed lung function testing in Asian children. Ismail (29) conducted a study to measure the PEF, FVC and FEV_1 in a group of Malay primary school children aged 7 to 12 years. PEF was measured in 920 children (482 boys and 438 girls) while FVC and FEV_1 were measured in 292 children (168 boys and 124 girls). The lung function values of Malay children were lower than those of Caucasian children given the same sex, age and height.

To characterize lung function in relation to growth in children and to establish the normal lung function prediction equations for southern Chinese children, a survey of 385 healthy school children (200 boys, 185 girls) aged 6 to 14 years old was carried out by Zheng and colleagues (30). The authors compared the predicted values derived from their prediction equations with that of Knudson et al (23) and found large differences. The average forced expiratory time was 3.1 seconds in the Chinese children, less than the 6 seconds considered by the American Thoracic Society as a satisfactory performance. As the flow-time curve showed that expiratory flow had reached a plateau and that the curve was considered both acceptable and reproducible in these children, the authors concluded that the forced expiratory time might be shorter than 6 seconds in children. The PEF in Chinese boys and girls has been studied by Zhong and his colleagues (11) and are shown in Figure 4.

Table 4. Comparison of Predicted FVC and FEV_1 Values from Different Regression Equations in Male (Height 170 cm, Weight 65 kg) and female (Height 160 cm, Weight 55 kg)

		Male						*Female*					
	Age (yrs)	*ECSC [4]*	*Da Costa [20]*	*Ching B [19]*	*Morris JF [21]*	*Crapo RO [22]*	*Knudson [23]*	*ECSC [4]*	*Da Costa [20]*	*Ching B [19]*	*Morris JF [21]*	*Crapo RO [22]*	*Knudson [23]*
FVC (L)	20	4.87	3.989	4.195	5.119	5.13	4.90	3.50	3.01	2.93	3.87	3.81	3.64
			-18.1%@	-13.9%	5.1%	5.3%	0.6%		-14.1%	-16.4%	10.5%	8.9%	4.0%
	40	4.48	3.769	3.695	4.619	4.71	4.30	3.11	2.71	2.73	3.39	3.37	3.3
			-15.9%	-17.5%	3.1%	5.1%	-4.1%		-13.0%	-12.3%	8.9%	8.4%	6.1%
	60	3.96	3.549	3.195	4.119	4.29	3.70	2.59	2.41	2.53	2.91	2.93	2.96
			-10.4%	-19.3%	4.0%	8.3%	-6.6%		-7.1%	-2.4%	12.3%	13.1%	14.3%
Mean*			-14.8%	-16.9%	4.1%	6.3%	-3.4%		-11.4%	-10.4%	10.6%	10.1%	8.1%
FEV1(L)	20	4.10	3.44	3.65	4.22	4.30	4.30	3.18	2.59	2.52	3.17	3.34	3.155
			-16.1%	-11.0%	3.1%	5.0%	4.9%		-18.4%	-20.7%	-0.2%	5.3%	-0.6%
	40	3.66	3.06	2.95	3.58	3.82	3.72	2.80	2.23	2.10	2.67	2.82	2.755
			-16.5%	-19.5%	-2.2%	4.4%	1.5%		-20.3%	-25.1%	-4.7%	0.8%	-1.6%
	60	3.08	2.68	2.25	2.94	3.34	3.14	2.30	2.04	1.93	2.52	2.64	2.355
			-13.1%	-27.1%	-4.5%	8.4%	1.8%		-18.6%	-27.0%	-5.7%	0.1%	2.4%
Mean*			-15.2%	-19.2%	-1.2%	5.9%	2.7%		-19.1%	-24.3%	-3.6%	2.0%	0.1%
Average**			-15.0%	-18.1%	1.4%	6.1%	-0.3%		-15.2%	-17.3%	3.5%	6.1%	4.1%

@ percentage difference between predictions from ECSC [4] and the authors [19–23] = [(Values(other authors)-Values(ECSC))/Values(ECSC)]x100

* Mean represents the average percentage difference

** Average represents the average percentage difference for both FVC and FEV_1

Table 5. Comparison of Predicted Values of TLC and RV According to ECSC and China Nationwide Study

		TLC		*RV*	
	age (yrs)	*values of ECSC [4]*	*mean values of China**	*values of ECSC [4]*	*means values of China**
male	20	6.52	6.135 -5.9%@	1.42	1.42 -0.4%
	40	6.52	6.159 -5.50%	1.86	1.76 -5.4%
	60	6.52	6.182 -5.20%	2.30	2.10 -8.5%
	average		-5.5%		-4.8%
female	20	4.77	4.48 -6.2%	1.22	1.14 -6.2%
	40	4.77	4.49 -6.0%	1.54	1.39 -9.4%
	60	4.77	4.50 -5.7%	1.86	1.66 -10.6%
	average		-6.0%		-8.7%

* mean values from six equations for Chinese [13–18]
@ percentage indicates the difference between predictions for Chinese and Caucasians

Table 6. Lung Function Testing in Asian Children

				Lung function testing						
Country	*Ethnic groups*	*Subject No.*	*Age range (years)*	*Spiro*	*Peak Flow Meter*	*Lung subdi-visions*	*DLco*	*Predicted equation*	*Published year*	*First author Reference*
Bangladesh	Bangladeshi	588	children	X	X			X	1990	Rahman (34)
Mainland China	Chinese	382	6~14	X				X	2002	Zheng (24)
Mainland China	Chinese	1867	5~15		X			X	1985	Zhong (11)
Hongkong China	Chinese	852	7~19	X			X	X	2001	Ip (31)
Hongkong China	Chinese	551	8~19				X	X	2001	Ip (32)
Malaysia	Malay	920	7~12	X	X			X	1993	Ismail (29)
Japan	Japanese	1375	6~14	X				X	1990	Miyazawa (43)
India	Indian	410	10~15	X				X	1997	Sharma (47)

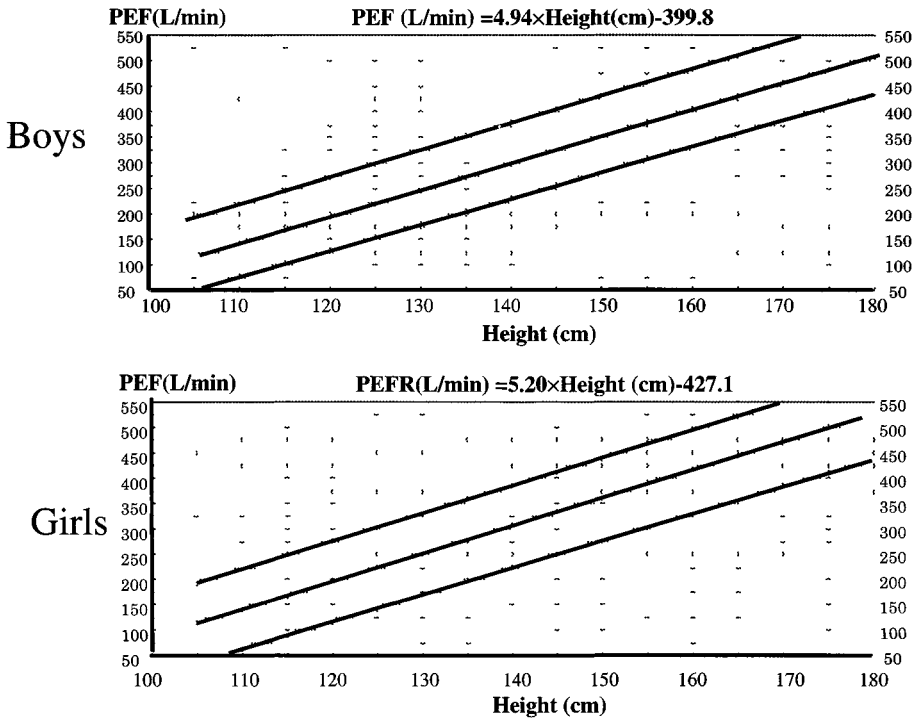


Figure 4. Normal peak flow (PEF) values (mean ± standard deviation) in Chinese boys and girls aged 5~14 years old

Ip and coworkers (31) conducted a spirometry study on 852 (392 male, 460 female) healthy students, aged 7 to 19 years, measurements of subdivisions of lung volume were tested on a subset of students using body plethysmography (32) FVC in boys were 8 to 10% lower than the Caucasians, derived from Rosenthal et al (33) and the differences increased to 12% for those who were taller than 165 cm while FVC in Chinese girls had similar or only slightly lower predicted values FEV_1 values showed a similar pattern with lesser difference between the two ethnic groups. Rahman et al (34) measured FVC, FEV_1 and PEF in a group of 588 healthy and well-nourished (but not obese) Bangladeshi teenagers and found that lung function values were lower than those of the Caucasians of the same age, height and sex.

Differences in lung volumes attributable to race within the same country have been reported in children Neukirch and colleagues (35) showed that Caucasian teenagers had higher lung function values than Chinese teenagers living in the same country

Studies in Asian countries have shown that Chinese children have higher FEV_1, FVC and $FEF_{25\ 75\%}$ than Malay or Indian children of the same sex, age and height (36) while Bangladeshi children have lower lung function values than Jordanians or Chinese, but not different from Libyans (34). Udupihille (7) also found that forced expiratory volumes of Singhalese children were smaller than that of Pakistanis Ismail et al (37) measured PEF, FVC and FEV_1 in 920 normal Malay primary school children aged 7 to 12 years Prediction equations for these lung function indices for Malay boys and girls were formulated and lower lung function values were found in Malay children compared with Caucasian or Chinese children.

It is necessary to choose the normative values for children carefully. Zheng (38) discovered that only 12 out of 71 lung function laboratories that performed test on children used prediction equations for children (aged less than 14 years old) The rest used prediction equations for adults leading to gross errors in interpretation

Possible reasons for ethnic differences

The reasons for ethnic differences in lung function are not entirely clear. There have been studies attempting to address this issue. Donnelly and coworkers (39) found that Caucasians have higher fat free masses, generate higher inspiratory and expiratory muscle pressures and have a wider diameter of the chest cavity than Chinese but the alveolar distensibility and diffusion coefficient were not different. They suggested that the larger lung volume in Caucasians might be due to increased numbers of alveoli and physically larger chest cavities. Chest dimensions, together with height and ethnicity explained 90% of the variation in FVC and 86% of the variations in total lung capacity (20). Yang and colleagues (40) further suggested that Caucasians might be able to stretch their lung mass to a greater volume because of greater inspiratory muscle strength, which in turn may be determined by the shape of the chest wall. Observed differences between races may also be due to genetic factors leading to the formation of airways of different size or with different elastic recoil (41).

Environmental factors may influence ethnic differences. Nutrition and exercise can improve health, enhance muscle strength, and increase lung volume and respiratory flow (even after height adjustment). In 2000, Ip and colleagues (31) reported a significant increase in height-corrected FVC and FEV_1 in both boys and girls in Hong Kong over the whole height range compared to those obtained in 1985. Their findings supported that environmental factors may contribute significantly to differences in lung function values among ethnic groups and that it is important to study normative values for secular trends.

Ethnic differences in lung function within a country may decrease with time. Lung volumes of the second or third generation Japanese-Americans are larger than those of the first generation. Massey and Fournier-Massey evaluated lung function of Japanese-American in Hawaii compared with Caucasians in the same place (42). They found that lung function was lowest in Japanese, highest among Caucasians, with Japanese-American in the middle; and the extent of difference depends on age. Miyazawa and coworkers (43) analyzed spirometric data obtained from 1375 healthy Japanese children (6~14 years old) and found that children of the same sex, age and height had higher spirometric values than those reported in previous studies. The better lung function in the second generation Japanese-Americans may be due to the improvement in the body size.

Why is correction for ethnic differences important?

Most instruments for measurement of lung function are produced by Western countries with recommended reference equations derived from Caucasians. Prediction equations of Morris and colleagues (21), Crapo and colleagues (22) or Knudson and coworkers (23) are widely used in the United States and Canada. Reference values of Quanjer et al (4) have been recommended by the European Respiratory Society and the ECSC for use in Europe. Using Caucasian prediction equations to generate predicted values for Asians underestimates the lung function for Asians. This is important in the following situations: 1) over diagnosing diseases with restrictive ventilatory defects; 2) overestimating the degree of disability due to lung disease, for example, in pneumoconiosis.

Recently, we conducted a questionnaire survey on the practice of pulmonary function testing in 212 hospitals or institutes covering 29 provinces of China with a response rate of 81.6% (38). 69.2% of the responses were from large (provincial or municipal) hospitals. Only 12.4% of lung function equipment used was produced locally while the rest were manufactured in the United States or Europe. Normal predictions for Caucasians are included with imported instruments. If these reference values were applied to Asians without ethnic adjustment, improper interpretations would result. Only 21.4% of the pulmonary function laboratories indicated the reference values they used and the age range which the equations covered. The knowledge and understanding of the importance of race adjustment need to be strengthened.

The need for ethnic corrected values is not of minor importance for Asians. In 1971, an inexperienced industrial physician refused a

Chinese cook employment because of "low" lung function. In 1989, this physician continued his practice of not using race-corrected values for lung function and refusing healthy, unimpaired men for employment or advancement (44). Ghio et al (45) surveyed lung function laboratories in institutions with training programs in adult respiratory disease in United States and Canada to determine which prediction equations were used and whether race correction was applied. They discovered that about half of the laboratories did not make ethnic corrections. Ignoring the race adjustment is not only found in Western countries, but is also prevalent in Asian countries. Zheng reported (38) that race adjustment was applied in only 2 out of 159 hospitals (1.3%) in his national questionnaire survey on pulmonary function testing.

Which prediction equation to use?

Ideally each lung function laboratory should establish its own set of reference values, but it is not feasible for many laboratories. When it is not feasible, one should select reference values according to the following criteria: 1) the study was carried out by trained operators using equipment and techniques that met the ATS or other guidelines and similar to those used by the lung function laboratory; and 2) the population used to establish the prediction equations is similar with respect to ethnic origin (3). If such reference values are not available, one alternative is to apply a conversion factor to the Caucasian prediction equations. A conversion factor of -15% has been suggested (3). The ECSC has suggested a similar conversion factor for Hong Kong Chinese when using European reference values (4). In a review of racial differences in lung function, Yang and colleagues (42) demonstrated that TLC in Chinese was 15~20% lower than that in Caucasians, and RV was 6% and 14% respectively lower in Chinese males and females. The prediction equations they used for Chinese were from Singapore and Guangzhou (South China); these may not be applicable to the other parts of China, or the current generation of Chinese.

Based on our findings, we suggest that the conversion factors of 0.95 in males and 0.97 in females should be applied to predicted values of FVC and FEV_1 derived from European data for adult Mainland Chinese. The conversion factor for adjusting TLC is 0.94 for both sexes. These conversion factors are summarized in Table 7 (23).

Table 7. Conversion Factors for Ethnic Adjustment (from Caucasian Predicted Equations for Chinese)

	Male	*Female*	*Whole population*
FVC	0.94	0	0.97
FEV_1	0.95	0.93	0.94
Mean FVC and FEV_1	0.95	0.97	0.96
RV	0.95	0.91	0.93
TLC	0.94	0.94	0.94
Average	0.95	0.93	0.94

Though normal prediction equations have been developed in many pulmonary function laboratories, some of them are linear regression equations. They are good for adults but not for teenage or children. FEV_1 increases with age for those under the age of 25 years, and decreases gradually after that. Therefore, it is better to establish a nonlinear equation for all individuals over 14 years of age, or to have separate equations for the two age groups, under 25, and 25 and over. Non-linear predicted equations for children are superior to linear equations, as demonstrated by Zheng et al (30) and Hanamoto et al (46).

Summary

Although pulmonary function testing has been practiced for decades in Asia, it is still not widely used in clinical settings due to limited medical resources in many countries. The importance of pulmonary function testing is not fully recognized in many hospital and clinics, especially in those located in the countryside or rural areas. In China where pulmonary function testing are performed in hospitals, spirometric measurement is the most commonly performed test (100%), followed by

reversibility after bronchodilator testing (74 2%) and bronchial provocation test (65 4%) Measurements of subdivisions of lung volume, diffusion capacity and airway resistance are being carried out in 60 0% 58 2%, and 42 7% respectively, in large hospitals while exercise tests in only 16 4% Pulmonary function testing has not been used for general health screening in most of the hospitals

Many sources of variation are involved in performing and interpreting pulmonary function tests Ethnic differences in lung function have been found in many studies in children and adults and should be taken into consideration in interpretation of results It is ideal for each pulmonary function laboratory to establish its own reference values Alternatively, the published reference equations carried out on a similar population and using similar equipment can be used If prediction equations from Caucasians must be used, update correction factors are needed to avoid underestimating lung function Greater efforts should be made to popularize and standardize pulmonary function testing in Asia

References

1 Becklake MR Concepts of normality applied to the measurement of lung function *Am J Med* 1986, 80 1158–61

2 Mu KJ, and Liu SW Nationwide normal values of lung function Beijing, PUMC & Beijing Medical University Publication 1990, 1–86

3 American Thoracic Society Lung function testing selection of reference values and interpretative strategies *Am Rev Respir Dis* 1991, 144 1202–19

4 Quanjer PH , Tammeling CJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC Lung volumes and forced ventilatory flows Report Working Party 'Standardization of lung function tests' of ECSC *Eur Respir J* 1993, 29(suppl 6) 5–40

5 American Thoracic Society Standardization of spirometry 1994 update *Am J Respir Crit Care Med* 1995, 152 1107–36

6 Clausen JL, ed *Pulmonary Function Testing Guidelines and Controversies* New York Academic Press 1982

7 Udupihille M Spirometric and flow standards for healthy adult non smoking Sri Lankans belonging to the Singhalese ethnic group *Ann Hum Biol* 1995, 22 321–36

8 Giri BR, Sharma BK, Jindal SK Normal spirometry in healthy natives of Bhutan *J Assoc Physicians India* 1996, 44 320–2

9 Korotzer B Ong S, Hansen JE Ethnic differences in pulmonary function in healthy nonsmoking Asian Americans and European Americans *Am J Respir Crit Care Med* 2000, 161(4 Pt 1) 1101–8

10 Wu HD and Yang SC Maximal expiratory flow and volume in Chinese aged 60 years and over *J Formosa Med Assoc* 1990, 89 749–55

11 Zhong NS, Zhan YG, Yu MJ, et al Normal value of peak expiratory flow rate and its application in the management of bronchial asthma *Chinese J Tuberc Respir Dis* 1985, 8 183–6

12 Gregg I and Nunn AJ Expiratory flow in normal subjects *BMJ* 1973, 3 282–3

13 Hou S, Zhan YG, Guo SC, He J Normal values of lung function in the population of Guangdong In Eds Mu KJ, and Liu SW Nationwide normal values of lung function Beijing, PUMC & Beijing Medical University Publication 1990, 67–80

14 Lin SW, Sun KS, Kou YS Normal values of lung function in the population of North China In Eds Mu KJ, and Liu SW Nationwide normal values of lung function Beijing, PUMC & Beijing Medical University Publication 1990, 1–23

15 Liu GH, Ma XQ Normal values of lung function in the population of the North East China In Eds Mu KJ, and Liu SW Nationwide normal values of lung function Beijing, PUMC & Beijing Medical University Publication 1990, 24–30

16 Sun B, Li RH, Zhao SH, Jia DH Normal values of lung function in the population of North West China In Eds Mu KJ, and Liu SW Nationwide normal values of lung function Beijing, PUMC & Beijing Medical University Publication 1990, 31–7

17 Jia JQ, Mo BL, Guo XJ, Wang JP Normal values of lung function in the population of South West China In

Eds. Mu KJ, and Liu SW. Nationwide normal values of lung function. Beijing, PUMC & Beijing Medical University Publication 1990. 38–48.
18. Zhu X, Li WD. Neu SF, Cai YY. DongHJ. Zhang ZF, Yu JD. Normal values of lung function in the population of Shanghai. In: Eds. Mu KJ, and Liu SW. Nationwide normal values of lung function. Beijing, PUMC & Beijing Medical University Publication 1990, 57–66.
19. Ching B, and Horsfall PAL. Lung volumes in normal Cantonese subjects: preliminary studies. *Thorax* 1977; 32:352–5.
20. Da Costa JL. Pulmonary function studies in healthy Chinese adults in Singapore. *Am Rev Respir Dis* 1971; 104:128–31.
21. Morris JF, Koski A and Johnson LC. Spirometric standards for healthy nonsmoking adults. *Am Rev Respir Dis* 1971; 103:57–67.
22. Crapo RO, Morris AH, and Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 1981; 123:659–64.
23. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983; 127:725–34.
24. Zheng JP, Zhong NS. Normative values for pulmonary function testing in Chinese adults. *Chinese Med J* 2002; 115:50–4.
25. Chia SE, Wang YT, Chan OY, Poh SC. Pulmonary function in healthy Chinese, Malay and Indian adults in Singapore. *Ann Acad Med Singapore* 1993; 22:878–84.
26. Chin NK, Ng TP, Hui KP, Tan WC. Population based standards for pulmonary function in non-smoking adults in Singapore. *Respirology* 1997; 2:143–9.
27. Yang SC, Yang SP, Lin PJ. Prediction equations for single-breath carbon monoxide diffusing capacity from a Chinese population. *Am Rev Respir Dis* 1993; 147:599–606.
28. Nair RH, Kesavachandran C, Sanil R, Sreekumar R, Shashidhar S. Prediction equation for lung functions in South Indian children. *Ind J Physiol Pharmacol* 1997; 41:390–6.
29. Ismail Y, Azmi NN, Zurkurnain Y. Lung function in Malay children. *Med J Malaysia* 1993; 48:171–4.
30. Zheng JP, Li MR, An JY, et al. Reference values and predicted equations of lung function in southern Chinese children. *Chinese J Pediat* 2002; 4:103–6.
31. Ip MS, Karlberg EM, Karlberg JP, Luk KD, Leong JC. Lung function reference values in Chinese children and adolescents in Hong Kong. I. Spirometric values and comparison with other populations. *Am J Respir Crit Care Med* 2000; 162:424–9.
32. Ip MS, Karlberg EM, Chan KN, Karlberg JP, Luk KD, Leong JC. Lung function reference values in Chinese children and adolescents in Hong Kong. II. Prediction equations for plethysmographic lung volumes. *Am J Respir Crit Care Med* 2000; 162:430–5.
33. Rosenthal M, Bain SH, Cramer D, Helms P, Denison D, Bush A, Warner JO. Lung function in white children aged 4 to 19 years: I — Spirometry. *Thorax* 1993; 48:794–802.
34. Rahman MA, Ullah MB, Begum A. Lung function in teenage Bangladeshi boys and girls. *Respir Med* 1990; 84:47–55.
35. Neukirch, Chansin R, Liard R, Levallois M, Leproux P. Spirometry and maximal expiratory flow-volume curve reference standards for Polynesian, European and Chinese teenagers. *Chest* 1988; 94:792–8.
36. Azizi BH, Henry RL. Ethnic differences in normal spirometric lung function in Malaysian children. *Respir Med* 1994; 88:349–56.
37. Ismail Y, Azmi NN, Zurkurnan Y. Lung function in Malay children. Med J Malaysia 1993; 48:171–4.
38. Zheng JP. A nationwide questionnaire survey on clinical application of pulmonary function testing in China. *Chinese J Tuber Respir Dis* 2002; 25:69–73.
39. Donnelly PM, Yang TS, Peat JK, and Woolcock AJ. What factors explain racial differences in lung volumes? *Eur Respir J* 1991; 4:829–36.
40. Yang TS, Peat J, Keena V, Donnelly P, Unger W, Woolcock A. A review of the racial differences in the lung function of normal Caucasian, Chinese and Indian subjects. *Eur Respir J* 1991; 4:872–80.
41. Huang SY, White DP, Douglas NJ, Morre LG. McCullough RE, Weil JV, Reeves JT. Respiratory function in normal Chinese: comparison with Caucasians. *Respiration* 1984; 46:265–71.
42. Massey DG, Fournier-Massey G. Japanese-American pulmonary reference values: Influence of environment on anthropology and physiology. *Am J Respir Crit Care Med* 1994; 150:1150–3.

43. Miyazawa M, Nakazawa K, Katabami J, Minegishi F, Hasegawa S, Sunaoshi K, Mori M. Studies of normal values and prediction equations for pulmonary function — spirometry and flow-volume measurements in health Japanese children 6 to 14 years of age. *Rinsho Byori* 1990; 38:1182–92.
44. Aelony Y. Ethnic norms for pulmonary function tests. *Chest* 1991; 99:1051–2.
45. Ghio AJ, Crapo RO, Elliott CG. Reference Equations used to predict pulmonary function. – Survey at Institutions with respiratory disease training programs in the United States and Canada. *Chest* 1990; 97:400–3.
46. Hanamoto S, Ohsuji T, Tsuyuguchi I, Kawabata S, Kimura K. Prediction formulas for pulmonary function tests expressed in linear and exponential form for healthy Japanese adults. *Nihon Kyobu Shikkan Gakkai Zasshi* 1992; 30:2051–60.
47. Sharma PP, Gupta P, Deshpande R, Gupta P. Lung function values in healthy children (10~15 years). *Ind J Pediatr* 1997; 64:85–91.

Index