THE YEAR IN RESPIRATORY MEDICINE, VOLUME 3

R. Fergusson, et al.
Editors

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Foreword

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The concept of an annual review in respiratory medicine has proven very successful. The design of each chapter is excellent: beginning with an introduction or review of up-to-date information, followed by a concise summary of selected recently published important original articles, each followed by a balanced commentary. At the end of every chapter, the issues brought up in the preceding discussion are then summarized. This format makes the book a real pleasure to read, and the end result is most engaging and didactic.

Inside *The Year in Respiratory Medicine Volume 3*, readers will find that the topics covered include, amongst others, recent developments in asthma, COPD, obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and pulmonary embolism. In all areas, there is critical discussion of new studies to elucidate prevention, prognosis, diagnosis and treatment.

Highlights from the first section on asthma are the studies showing the highly beneficial effects of primary and secondary prevention from a multifaceted approach to improve indoor climate and reduce allergen exposure. The new studies about the value of self-management plans are well summarized and good to know when personal recommendations are given. This section also documents the value of new treatments, and evaluates the importance of stable treatment with inhaled corticosteroids and the safety of topical corticosteroids.

The selected topics in COPD are well chosen and underline the relevant issue that physical performance status is of the utmost importance in evaluating prognosis. The handling of exacerbations with regard to early treatment and the use of antibiotics is also usefully covered. The use of serum procalcitonin as an aid to excluding bacterial aetiology may be proven to be of clinical value. The pharmacological long-term treatments with long-acting anticholinergics or β-agonists reduce dynamic hyperinflation and improve inspiratory capacity and endurance. Inhaled corticosteroids seem able to reduce markers of the systemic inflammatory reaction connected to the disease, and the combination of inhaled corticosteroids and long acting β-agonists improves lung function and reduces exacerbations. The new findings in physical rehabilitation and lung volume reduction surgery are also discussed.

Pulmonary embolism is a difficult area not only in diagnosis and evaluation of prognosis, but also regarding choice and length of treatment. A timely discussion of recent advances in our understanding in this area is presented by Dr John Simpson.

The newly appreciated disease entity of obstructive sleep apnoea/hypopnoea

syndrome (OSAHS) is a story that continues to develop as the understanding of frequent episodes of hypoxaemia on the vasculature is unravelled and the pathogenetic mechanisms are more clearly understood. OSAHS is now clearly associated with severe cardiovascular and cerebrovascular comorbidity, and is increasingly seen to be an underlying factor in cases of systemic hypertension and cardiac failure. These latest findings, and the preventative value of effective treatments, are presented through carefully selected research articles from the recent literature.

If anybody in primary or secondary healthcare is interested in having a sober and quick update of new discoveries and trends in respiratory research, then practitioners should immediately turn to *The Year in Respiratory Medicine*. It is an easily digestible and well-prepared text that allows you, the reader, to relax, enjoy the speciality of respiratory medicine, and at the same time improve your professional insight.

Part I

Asthma

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Asthma

PETER REID

Introduction

This year saw the publication of the *Global Burden of Asthma Report* which has provided important information on the prevalence and impact of this disease. Based on standardized data collected in epidemiology studies in more than 80 countries, the report concludes that an estimated 300 million people now have asthma. This makes it one of the most common chronic diseases in the world. Rather more alarmingly, projected figures suggest that if current trends continue, an additional 100 million people may develop asthma by 2025. In many countries, people with asthma cannot get access to proper medication because of poverty, poor education and poor infrastructure. In countries where medications are widely available, they are often underutilized.

The consequences of poorly controlled asthma include chronic ill health, hospitalization, missed work and school, limitations on physical activity, sleepless nights and, in some cases, death. These represent not only a considerable impact on the quality of life of any individual with asthma but also important economic and social costs to society as a whole. Although a cure for asthma remains elusive, effective management strategies can minimize the impact of asthma and should allow the majority of patients to lead a full and active life. The impact of this message on patients and their health providers needs to be reinforced.

At the turn of this century, asthma therefore poses the medical community a number of challenges. As ever, more research is needed to build on the emerging understanding of the basic mechanisms that lead to the development and persistence of the disease. However, in addition, we should be challenged to apply continued political pressure on governing authorities, by promoting asthma as a priority for the funding of national health programmes and research.

The world of medical publishing has become increasingly competitive. Good studies are meticulously planned and a substantial amount of work is invested in the recruitment and follow-up of the patients. Good researchers are becoming increasingly professional and highly dedicated individuals. Choosing a selection of published work from any year is a largely subjective task and to some extent reflects the bias of the author. As ever, I have tried to give precedence to papers that have been published in leading medical journals. I have used the comments section to distil the

major points made by the authors in the discussion section of their papers, but on occasion I have added my own thoughts. Finally, as always, you will see that good research answers some questions but proposes many others. Enjoy!

1

Epidemiology and disease causation

PETER REID

Introduction

The effective delivery of healthcare requires the collection of reliable information on the incidence and prevalence of illnesses in the community, including their likely impact on the utilization of healthcare resources. Such information is particularly important for asthma, given that it is common, affects all age groups and ethnic backgrounds, and has shown a dramatic increase in incidence and prevalence over the latter part of the last century.

The rapid rise in the prevalence of asthma, particularly over a relatively short time frame, suggests that environmental rather than genetic factors are important in the development and/or persistence of the disease. This has focused a significant body of effort into epidemiological research programmes that may identify causative factors. Given the complexity of the asthma phenotype, it is unlikely that any one factor will emerge; however, it is believed that research of this nature will continue to generate hypotheses that can be tested with the hope that some consistent and potentially modifiable factors can be identified.

Several broad themes have emerged from this research, and the most widely popularized has been the hygiene hypothesis adapted from observations on hay fever |**1**|. This attempts to attribute the rising prevalence of asthma to the increasingly hygienic Western lifestyle. The hygiene hypothesis has been bolstered by an immunological model of asthma suggesting a bias towards T lymphocytes that mediate the immunological reactions that accompany parasitic infections and allergic responses, and a reduction in those that mediate cellular immunity to bacteria and viruses. T helper (Th) cells are thought to orchestrate the asthmatic inflammatory response and are believed to differentiate into two relatively distinct subsets: Th1 and Th2. Th2 lymphocytes predominantly secrete cytokines such as interleukin-4 (IL-4), interleukin-5 (IL-5) and interleukin-13 (IL-13), which direct the immune system towards an allergic type of response. Th1 lymphocytes preferentially secrete interferon-γ and interleukin-2 (IL-2), which are important in fighting viral and bacterial infections. The Th cell polarity of the newborn infant is predominantly skewed to Th2 cell function, but as it matures and encounters a variety of infectious insults in the post-partum period a

shift in polarity of the T cells occurs towards Th1 responses. Thus, by growing up in a more hygienic environment, the infant fails to be exposed to bacterial and viral infections, and the polarity of the Th cells remains skewed towards Th2. The infant is therefore at risk of developing allergic diseases such as asthma. However, although this model has been widely recognized and will be referred to below, it is beginning to be questioned and viewed as an oversimplification |**2**|.

The increasingly cosseted and centrally heated environment of our homes encourages the growth of house dust mites, which are one of the major factors linked to the development of atopy and asthma. Other indoor allergens may also play key roles and a substantial amount of research has been focused on the role of household pets, such as cats and dogs |**3–7**|. Exposures occurring outdoors may also be relevant, previous observations suggesting protection from farming environments |**8–9**|.

The importance of diet has been examined by a number of teams, particularly concentrating on foodstuffs likely to be important in the regulation of the immune system or inflammatory processes. Closely allied to diet is the role of obesity in the developing world |**10–12**|. This is a major public health problem in its own right but may be linked to the appearance of asthma through a number of possible mechanisms |**13–15**|.

Other investigators have examined the role of the diet, with regard to either its impact on the gut microflora or the intake of foods that may influence the immune response. Furthermore, as the increase in asthma has occurred in line with the increase in obesity in Western society, some investigators have focused on possible links between the two. Lastly, the possible contribution of environmental pollutants accompanying the industrialization of society has been examined. Although genetic changes are unlikely to account for the rise in asthma, it is highly probable that genetic factors influence its development through complex interactions with the environment.

Increase in diagnosed asthma but not in symptoms in the European Community Respiratory Health Survey

Chinn S, Jarvis D, Burney P, *et al*. *Thorax* 2004; **59**: 646–51

Background. Reliable information on the change in incidence or prevalence of asthma with age has been difficult to obtain. The authors of this study analysed data from a large international longitudinal study of asthma to examine the change in prevalence of asthma with age in young adults.

Interpretation. The proportion of young adults being treated for asthma increased but there was no change in the proportion reporting symptoms. This may be explained by increased use of effective therapy or greater recognition of mild asthma.

Comment

The authors report findings from the European Community Respiratory Health Survey (ECRHS). In this study a range of centres were selected with a population of

at least 150 000. Random sampling was performed and at least 1500 men and 1500 women aged 20–44 years were enrolled. Participants were divided into age groups according to age: 20–24 years, 25–34 years, and 35 years or older. The first phase of this study was performed between 1991 and 1993 and included 11 168 participants, aged between 20 and 44 years, who completed a self-administered questionnaire. The same participants completed an identical questionnaire 5–11 years later, between 1998 and 2003.

When comparing the two time-points the authors employed the concept of 'net change' in an attempt to correct for possible bias in reporting symptoms in longitudinal studies, although they accepted that this concept has the disadvantage that it is not possible to calculate incidence or remission rates. Thus, the authors report that there was no evidence for either an increase or a decrease in the proportion of subjects reporting symptoms suggestive of asthma. The main findings of this study were the reporting of an increase of 0.8% (95% confidence interval [CI] 0.2–1.4) in the prevalence of asthma attacks in the last 12 months and an increase of 2.1% (95% CI 1.6–2.6) in the use of asthma medications. However, there was no appreciable change in the reporting of the symptoms of asthma. They also reported an increase in nasal allergies, particularly in the youngest age group.

The authors explored whether their results were influenced by possible participation bias but concluded that this was unlikely. They also speculated about whether their results reflected an ageing effect (the increased propensity to report medical illness with age) or a period effect (an enhanced change in the diagnostic awareness of asthma over the period of the study). It was also suggested that the results may be explained by increased use of effective medications for asthma or greater recognition of mild asthma.

Prevalence of asthma and allergy in schoolchildren in Belmont, Australia: three cross-sectional surveys over 20 years

Toelle BG, Ng K, Belousova E, Salome CM, Peat JK, Marks GB. *BMJ* 2004; **328**: 386–7

BACKGROUND. The authors of this study had previously reported an increase in asthma in Australian primary school children between 1982 and 1992. The purpose of this study was to determine whether the prevalence of asthma and allergy has continued to increase during the late 1990s and early 2000s.

INTERPRETATION. The previously reported increase in prevalence of asthma has not continued.

Comment

The authors have previously reported an increasing prevalence of asthma in Australian primary school children between 1982 and 1992 |**16**|. In this study they applied

identical parent-completed questionnaires regarding the symptoms, diagnosis and treatment of asthma and other allergic disorders. They also characterized their population with a histamine challenge test and performed skin prick tests to a range of common allergens

Since their last reported results in 1992, they found that the prevalence of diagnosed asthma had fallen by 7.3% (95% CI 11.8 to 2.8%). They also reported a decrease in the prevalence of wheeze in the past 12 months (4.9%; 95% CI 9.1 to 0.7%) and noted a decrease in the use of asthma medications. There was no significant change in the prevalence of hay fever (4.3%; 95% CI 0.3–8.9%) or positivity for the skin prick test (–3.1% [95% CI –8.1 to 1.9%]). There was also no significant change in the prevalence of current asthma (recent wheeze and airway hyper-reactivity [AHR]) (–1.1%; 95% CI –4.5 to 2.3%).

The results are encouraging and consistent with other reports that the prevalence of asthma is not rising. However, the authors accepted that their results may have been influenced by a lower response rate and it is also notable that they studied a different age range than before.

Trends in prevalence of symptoms of asthma, hay fever, and eczema in 12–14 year olds in the British Isles, 1995–2002: questionnaire survey

Anderson HR, Ruggles R, Strachan DP, *et al*. *BMJ* 2004; **328**: 1052–3

BACKGROUND. The authors employed International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires to examine whether the prevalence of reported symptoms of asthma, hay fever and eczema had changed in 12- to 14-year-old children in the British Isles.

INTERPRETATION. The burden of self-reported asthma and allergic disease has fallen in recent years in the British Isles.

Comment

The authors of this study had previously surveyed the symptoms of atopic disease in England, Scotland, Wales, the Isle of Man and Jersey as part of the ISAAC in 1995 |**17,18**|. In this study the authors studied secondary school children aged 12–14 in Southeast England, Scotland, Wales and the same islands as before. The questionnaire was identical to that used previously and the investigators followed the same procedures in the same period of the year and, mostly, in the same schools.

The authors reported that there was a relative reduction in the prevalence of wheezing (19%), frequent attacks (35%) and speech-limiting attacks (24%). They also reported reductions in symptoms of allergic rhinoconjunctivitis (16%) and atopic eczema (30%). They were also able to report decreases in the proportion of children ever reporting 'asthma' (26%) or 'eczema' (15%) and the lifetime prevalence of hay

fever (8%). The authors point out that their data are consistent with other sources indicating that hospital admissions and general practitioner visits for children in this age group with asthma also fell.

Respiratory symptoms and atopy in children in Aberdeen: questionnaire studies of a defined school population repeated over 35 years

Devenny A, Wassall H, Ninan T, Omran M, Khan SD, Russel G. *BMJ* 2004; **329**: 489–90

BACKGROUND. The authors of this study have previously reported a marked increase in symptoms suggestive of asthma since 1964. In this study they report their experience in 1999.

INTERPRETATION. The prevalence of symptoms of asthma appears to be stable in Aberdeen.

Comment

This study also draws on the strength of previously reported data using the same techniques from the same region in which a marked increase in wheezing children was observed between 1964 and 1989 |**19,20**|. This study sampled 4209 children in 1999 and was able to present data from 3537. Although asthma remains common, the authors found little difference in the prevalence of wheeze in the past 3 years, shortness of breath in the past year and persistent nocturnal cough in the past 3 years, suggesting that the prevalence of asthma symptoms appears to be stable. They draw attention to the fact that the male:female ratio for the diagnosis of asthma has narrowed over the past 35 years, being 1.7:1 in 1964 and 1.1:1 in 1999. In this study the reporting of eczema and hay fever appeared to have increased.

Relationship between socio-economic status and asthma: a longitudinal cohort study

Hancox RJ, Milne BJ, Taylor DR, *et al*. *Thorax* 2004; **59**: 376–80

BACKGROUND. The relationship between asthma and socio-economic status is unclear. The authors of this study set out to evaluate the prevalence of asthma symptoms, lung function, AHR and atopy in relation to socio-economic status in a cohort of patients taken from the Dunedin Multidisciplinary Health and Development Study.

INTERPRETATION. Socio-economic status in childhood had no significant impact on the prevalence of asthma in this New Zealand-born cohort.

Comment

The relationships between socio-economic status and disease are potentially important but studies often reveal conflicting information. Although atopy has been consistently associated with higher socio-economic status, studies investigating links between socio-economic status and asthma have reported variable results |**21–29**|. The Dunedin Multidisciplinary Health and Development Study recruited from children born in Dunedin, New Zealand, between April 1972 and March 1973. Children were classified according to the average of the higher socio-economic status of either parent over repeated measures recorded to age 15. Adult socio-economic status was determined at age 26. The diagnosis of asthma was based on a questionnaire, and lung function, AHR and atopy were evaluated. Potential confounding factors, such as smoking during pregnancy, parental asthma, parental smoking, birth order and breast-feeding, were also recorded.

The main finding of this study was the lack of any consistent relationship between either childhood or adult socio-economic status and asthma prevalence, lung function or AHR at any age. However, consistently with other reports, the authors found a trend between a higher socio-economic status and the reporting of atopy. An important and reassuring finding was that a diagnosis of asthma did not appear to impact on educational achievement or adult socio-economic status.

Factors associated with difference in prevalence of asthma in children from three cities in China: multicentre epidemiological survey

Wong GWK, Ko FWS, Hui DSC, *et al*. *BMJ* 2004; **329**: 486

BACKGROUND. The authors examined the prevalence of asthma in three Chinese cities in order to investigate whether any factor(s) emerged that may assist in explaining the increasing prevalence of asthma.

INTERPRETATION. Differences in the prevalence of asthma may be explained by environmental factors and diet.

Comment

The authors of this study randomly selected primary school children aged 10 years from schools in three Chinese cities: Hong Kong, Guangzhou and Beijing. Information was sought through the use of parent-/guardian-completed questionnaires (based on the phase II protocol of the ISAAC) and a subset of participants were randomly selected to undergo skin prick testing. Asthma was defined as 'asthma ever' if it had ever been diagnosed by a doctor, and 'current asthma' if current wheeze occurred in addition to asthma ever.

The study was impressively large, with 10 902 of a possible 11 608 children participating and a further 3483 undergoing skin testing. The authors reported that the preva-

lence of wheeze in the past year was significantly higher in children from Hong Kong (odds ratio [OR] 1.64; 95% CI 1.35–1.99) compared with Guangzhou and Beijing (OR 0.61; 95% CI 0.49–0.77). After adjustment for the propensity score (a calculation to reduce the chance of bias from differences in distribution of factors between the cities), six factors were related to current wheeze: cooking by gas, foam pillows, cotton quilts, damp housing, consumption of fruit more than once a day, and consumption of raw vegetables once or more than once a week. Of these, the highest risk of wheeze was associated with foam pillows and cooking with gas. Following adjustment for the propensity score and sex, cooking with gas, foam pillows, damp housing and consumption of fruit remained significantly associated with current wheeze. These observations are consistent with other studies that have reported a higher prevalence of asthma in association with household cooking gas exposure |**30–33**|, synthetic bedding |**34**| and the greater occurrence of respiratory disease in those who live in damp housing |**35**|. A reduced risk of wheeze was associated with the frequent consumption of fruit (OR 0.70; 95% CI 0.54–0.89) and raw vegetables (OR 0.81; 95% CI 0.64–1.03), again consistent with data obtained from other studies published recently |**36,37**|.

Early prescriptions of antibiotics and the risk of allergic disease in adults: a cohort study

Cullinan P, Harris J, Mills P, *et al*. *Thorax* 2004; **59**: 11–15

BACKGROUND. Overprescription of antibiotics has been cited as a possible contributing factor to the later appearance of asthma. However, it is unclear whether the associations observed between antibiotic use and the appearance of asthma reflect a true relationship or reverse causation—the tendency for prescriptions to be written for the early manifestations of pre-existing asthma. The authors of this study report findings from a UK cohort in which the link between antibiotic prescription and the appearance of self-reported asthma, hay fever and atopy was investigated.

INTERPRETATION. The reported associations between childhood antibiotic use and asthma are most plausibly explained by 'reverse causation'.

Comment

The popularity of the hygiene hypothesis has led to the concern that overuse of antibiotics in childhood may be linked to the appearance of asthma |**38–42**|. However, an alternative explanation for a positive association between antibiotic prescription and the later appearance of asthma may simply reflect the fact that the early presentation of asthma is indistinguishable from a chest infection for which antibiotics would normally be prescribed. The study by Cullinan and colleagues was designed to explore this dilemma.

Two research nurses were employed to undertake a careful review of the medical records, carefully documenting antibiotic prescriptions in the first 5 years of life.

Antibiotic prescriptions were characterized according to whether they were prescribed for respiratory (upper and lower) infections or non-respiratory (ear, skin, eye, urinary and other) infections. They were able to identify an indication for over 99% of prescriptions. Asthma and hay fever were defined by questionnaire and atopy by skin prick testing.

One-fifth of antibiotics were prescribed for lower respiratory tract infections and just over one-third for upper respiratory tract infections. Analyses by indication suggested that significant associations between antibiotic prescribing and asthma were essentially confined to antibiotics issued for lower respiratory tract infections. However, there was an absence of any relationship between early antibiotic prescription and atopy, either for all antibiotic use or for antibiotics prescribed at different ages.

The numbers in this study were relatively small and the authors questioned whether their study had sufficient power to detect a weak association. Whilst this is possible, explanations suggesting a link between antibiotic prescriptions and the appearance of atopy and asthma seemed less plausible. In particular, they suggested that if a true causal relationship between antibiotic prescribing and the appearance of allergic disease were to be the case then this ought to be seen for all indications for antibiotic prescription rather than for respiratory indications only. That any association with asthma was linked to documented lower respiratory tract infections seems more consistent with the view that these prescriptions reflected a protopathic bias (reverse causation), whereby diagnoses of respiratory infection were in reality asthma.

Fatty acid levels and risk of asthma in young adults

Woods RK, Raven JM, Walters EH, Abramson MJ, Thien FCK. *Thorax* 2004; **59**: 105–10

BACKGROUND. There is considerable interest in the potential health benefits of omega-3 fatty acids. The authors of this community-based cross-sectional study were interested to determine whether plasma concentrations of long chain (n-3) fatty acids differed between young adults with and without asthma.

INTERPRETATION. Plasma n-3 fatty acids are not associated with a reduced risk of asthma or atopy among young adults. An association was noted between the n-6 polyunsaturated fatty acid dihomo γ-linolenic acid (DHGLA) and current asthma, asthma, and doctor-diagnosed asthma.

Comment

The omega-3 fatty acids have attracted a substantial amount of interest among the medical profession and the general public with regard to a range of potential health benefits in relation to diseases such as coronary heart disease, hypertension and other inflammatory conditions |**43,44**|. The potential beneficial effect of omega-3 fatty acids on lung health is also attracting interest. |**45**|. Indeed, in last year's *The Year in Respiratory Medicine* |**46**|, I included a paper from the Childhood Asthma Prevention Study

which was designed to test whether interventions promoting dietary supplementation with omega-3 fatty acids, the avoidance of house dust mite allergens, or a combination of the two, could decrease the incidence of allergy and asthma in high-risk children |**47**|. The prevalence of various wheeze outcomes was lower in the active dietary intervention groups than in the control group. A protective association between oily fish consumption and asthma has also been reported in a community-based survey of Australian schoolchildren |**48**|. Interestingly, a recent Cochrane publication has reported on the impact of low and high n-3 diets on asthma outcomes, but found that insufficient evidence existed to report on whether these affected asthma outcomes |**49**|.

The aims of this study were to investigate whether plasma n-3 fatty acids (as a measure of dietary intake) were protective against asthma and atopy in young adults, and to determine whether plasma fatty acid levels differed between individuals with and without asthma and atopy. Subjects were recruited from a computer-generated random sample of 4455 young adults from the electoral roll in Melbourne, Australia. Following an initial screening questionnaire, 1601 young adults (mean [SD] age 34.6 [7.1] years) completed an interviewer-administered European Community Respiratory Health Survey questionnaire and a food frequency questionnaire. They also underwent lung function testing, skin prick testing, methacholine challenge and measurement of plasma fatty acids.

The outcome of the study with regard to the main hypothesis was negative. The authors did not find any association between the n-3 fatty acids or n-6:n-3 ratio and any one of a number of different asthma definitions or atopy. The authors did report an association between the n-6 polyunsaturated fatty acid DHGLA and current asthma (OR 1.30; 95% CI 1.06–1.60), asthma (OR 1.34; 95% CI 1.13–1.60) and doctor-diagnosed asthma (OR 1.25; 95% CI 1.06–1.48). This fatty acid is derived from plant sources and is a precursor of arachidonic acid, which in turn is a precursor of a variety of pro- and anti-inflammatory lipid mediators, including the cysteinyl leukotrienes. The implications of this finding remain unclear.

Breast-feeding reduces the risk of asthma during the first 4 years of life

Kull I, Almqvist C, Lilja G, Pershagen G, Wickman M. *J Allergy Clin Immunol* 2004; **114**: 755–60

BACKGROUND. Whether breast-feeding reduces or increases the risk of asthma remains controversial. The authors of this study have followed up a birth cohort of 4089 children and present results pertaining to the development of asthma and sensitization to airborne allergens during the first 4 years.

INTERPRETATION. Breast-feeding appears to reduce the risk of developing asthma in the first 4 years of life.

Comment

Breast-feeding confers many benefits on the newborn infant and is widely encouraged. However, it remains unclear whether it protects against the development of allergy and asthma. Indeed, in *The Year in Respiratory Medicine 2003* |**50**| I included a paper from a Dunedin birth cohort reporting that children who were breast-fed were more than twice as likely as those who were not to develop wheeze with AHR or current asthma with AHR |**51**|. Other papers have also suggested an increased risk of asthma |**52,53**|, whereas some report either no effect |**54**| or apparent protection from the disease |**55,56**|.

The authors of this study analysed data from a prospective population-based birth cohort recruited in Stockholm, Sweden between February 1994 and November 1996. Data on allergic, hereditary and potentially relevant exposures were obtained when the infants were born, and information on wheezing and the development of other allergic diseases was obtained by questionnaires administered at 1, 2 and 4 years of age. The response rate at year 4 was 90%. Asthma was defined as at least four episodes of wheezing during the last 12 months, or at least one episode of wheezing during the same period if the child was receiving inhaled steroids. Information on breast-feeding was collected at 2 months and 1 year of age, and the total dose of breast milk was estimated by combining periods of exclusive and partial breast-feeding.

The authors found that exclusive breast-feeding for 4 months or more reduced the risk of asthma at age 4 (OR 0.72; 95% CI 0.53–0.97) irrespective of sensitization to common airborne allergens. In recognition that breast-feeding would be unlikely to completely stop following the introduction of other foods, they also analysed the effect of a combination of exclusive and partial breast-feeding and found that 3 months or more of partial breast-feeding appeared to offer further protection; exclusive breast-feeding for 3–4 months combined with partial breast-feeding for 3 or more months reduced the risk of asthma further (OR 0.44; 95% CI 0.21–0.87). The protective effects of breast-feeding appeared to be stronger in children without a family history of allergy.

Presence and timing of cat ownership by age 18 and the effect on atopy and asthma at age 28

de Meer G, Toelle BG, Ng K, Tovey E, Marks GB. *J Allergy Clin Immunol* 2004; **113**: 433–8

BACKGROUND. Sensitization to domestic pets such as cats is a recognized risk factor for both atopy and asthma. However, the literature is confusing, and several reports document that in certain circumstances cat exposure may confer protection against the development of asthma. The aim of this study was to assess the effect of cat ownership during different age periods (<18 only, >18 only, and both periods) on asthma and allergy outcomes at age 28.

INTERPRETATION. Ownership of a cat before 18 years of age appears to provide protection against allergic sensitization and symptoms of asthma.

Comment

Exposure to pets in early life has traditionally been felt to be causally associated with the development of atopy and asthma. However, recent data suggest that exposure to certain pets, particularly cats, and farm animals may protect against the development of atopy and asthma |**57–61**|. The aim of this study was to analyse the effect of cat ownership in different age periods on the expression of asthma and allergy at age 28.

Data were drawn from a random sample of Australian schoolchildren who were recruited in 1982 and continued to participate in follow-up until 2002. The authors were able to analyse data on 224 subjects, 50 of whom had a cat before 18 years only, 14 after the age of 18 years only, and 70 in both age periods. Compared with 90 subjects who had never owned a cat, the authors found that those who had a cat before the age of 18 years were less likely to report current wheeze at age 28 years. Cat ownership during this period also appeared to protect against atopy to outdoor allergens, AHR and asthma. By contrast, the acquisition of a cat after the age of 18 years was associated with cat sensitization, current wheeze and AHR, although these results did not attain statistical significance. Separate analyses for those with and without a parental history of atopy could only be undertaken on a limited number of outcomes, but none of these showed any difference.

This study is interesting in that it provides information on cat ownership from two time periods and suggests that protection in early life appears to persist into adulthood. Interestingly, the authors speculated that their results might reflect selective avoidance of pets by pet-allergic individuals; however, following exclusion of subjects with childhood asthma or those with cat sensitization in surveys prior to 1992, protective effects were actually observed to increase rather than, as might be expected, to decrease. The authors suggested that protection may be mediated by endotoxin or a modification of the Th2 response.

Do farming exposures cause or prevent asthma? Results from a study of adult Norwegian farmers

Eduard W, Douwes J, Omenaas E, Heederik. *Thorax* 2004; **59**: 381–6

BACKGROUND. A number of recent publications have suggested that growing up on a farm confers protection against developing asthma in childhood. The authors of this study wished to determine if exposure to microbial agents or irritant gases encountered on farms increased or decreased the risk of atopy and asthma in adult farmers.

INTERPRETATION. Livestock farmers appeared to be protected against the development of atopic asthma but had a greater prevalence of non-atopic asthma, than farmers without livestock. The effect may be mediated through high levels of endotoxin and fungal spores.

Comment

Several recent studies have suggested that living on a farm in early life can protect against the subsequent development of atopy and asthma |**62–67**|. Braun-Fahrländer and colleagues (reviewed in *The Year in Respiratory Medicine 2003* |**50,68**|) have suggested that protection may be mediated through endotoxin. However, the authors of this paper suggest that other microbial products could be important; these include fungal spores, bacteria, storage mites and other allergens. This study recruited from farmers registered with the Norwegian Government's Register of Farmers. A total of 8482 farmers underwent medical examinations including spirometry and collection of blood samples, and completed a questionnaire (providing information on asthma, work participation and duration, and smoking habits). Exposure to dust, fungal spores, bacteria, endotoxins and ammonia during the performance of certain farming-related tasks was performed on a nested sample.

The prevalence of physician-diagnosed asthma was 3.7% and the prevalence of current asthma was 2.7%. However, the authors suggest that these figures may underestimate the true prevalence as they exclude farmers who had retired or changed production on health grounds. The prevalence of atopy was 14% but the majority (80%) of asthma was non-atopic, in keeping with other observations suggesting that atopy is much less important in the development of adult asthma than it is in the development of childhood asthma. When compared with farmers who did not keep livestock, cattle farmers (OR_{adj} 1.8; 95% CI 1.1–2.8) and pig farmers (OR_{adj} 2.0; 95% CI 1.0–2.5) showed a significantly higher prevalence of asthma.

The authors emphasize that a number of types of exposure that were associated with farming were associated with a decreased risk of atopic asthma but with an increased risk of non-atopic asthma. Non-atopic asthma was significantly higher in pig farmers (OR_{adj} 2.0; 95% CI 1.2–3.3) and in farmers with two or more types of livestock (OR_{adj} 1.9; 95% CI 1.1–3.3), whereas atopic asthma was less common in farmers with two or more types of livestock (OR_{adj} 0.32; 95% CI 0.11–0.97). Exposure to endotoxins, fungal spores and ammonia was positively associated with non-atopic asthma and negatively associated with atopic asthma.

To explain this apparent paradox, they argued that the association with endotoxin and non-atopic asthma may be explained by neutrophilic inflammation and non-immunoglobulin E (IgE)-mediated reversible airflow obstruction |**69,70**|. As regards atopic asthma, they speculated that the same microbial products could inhibit IgE production through inhibition of Th2-driven immune responses |**71**|. However, in arguing this point they accepted that protection from atopy should also have been observed.

The authors prompt speculation on the potential role of fungal spore exposure and asthma. Moulds have previously been associated with current asthma, emergency room attendance for AHR, hospital admission, near-fatal episodes and death |**72–75**|. However, in this paper the authors note an apparent protective effect on non-atopic asthma. Although they also noted associations with ammonia, they believed these were less likely to be causative and more likely to be explained by correlation with other agents.

Asthma and atopy in overweight children

Schachter LM, Peat JK, Salome CM. *Thorax* 2003; **58**: 1031–5

BACKGROUND. The aim of this study was to investigate whether body mass index (BMI) was associated with a higher prevalence of asthma or atopy, or with an increase in airway obstruction or AHR. The authors also investigated whether the association between body weight, atopy and asthma differs between girls and boys.

INTERPRETATION. A high BMI is associated with a higher prevalence of wheeze and cough in children; the strength of the association is greater in girls than boys, and is independent of atopic status. However, a higher BMI does not appear to be a risk factor for asthma or AHR in either sex.

Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP)

Tantisira KG, Litonjua AA, Weiss ST, Fuhlbrigge AL, for the Childhood Asthma Management Research Group. *Thorax* 2003; **58**: 1036–41

BACKGROUND. The authors hypothesized that BMI would be independently associated with measures of asthma severity in a population of children with mild to moderate asthma.

INTERPRETATION. The data from this paper do not support the hypothesis that increasing BMI significantly contributed to overall asthma severity in a large cross-sectional population of children with mild to moderate asthma.

Comment

An increased BMI is an important risk factor for a number of diseases and investigators continue to explore possible associations between obesity and the development of asthma |**76**|. In some individuals the link may be mechanical and associated with the higher incidence of gastro-oesophageal reflux or alterations that may occur in airway smooth muscle operating at low lung volumes. However, interesting theories have been developed exploring the relevance of shared genetic traits, immune modification by diet, or modification of airway responsiveness by changes in hormonal levels. Others have speculated whether the development of obesity favours an indoor lifestyle with a resultant increased exposure to indoor allergens |**1**|. Obesity is best described in terms of the BMI, which links height and weight: BMI = weight (kg) divided by height (m^2). Overweight, or grade 1 obesity, is defined as a BMI of 25.0–29.9, grade 2 obesity by a BMI of 30.0–39.0, and a BMI >40 represents grade 3 obesity.

Indeed, in *The Year in Respiratory Medicine 2003* |**50**| we examined two papers addressing this issue. Celedón and colleagues reported a cross-sectional study in an adult population in which the risk of symptomatic AHR in overweight among women was 2.3 times higher than in those with a normal BMI |**77**|. Castro-Rodriguez and colleagues performed a prospective study that allowed the issue of obesity to be addressed and suggest that asthma is associated with weight gain, particularly in females |**78**|.

Schachter and colleagues report on a cross-sectional study of 5993 Caucasian Australian children (aged 7–12 years) that included children taken from seven large epidemiological studies in seven regions of New South Wales, Australia. Questionnaires were employed to obtain data on physician-diagnosed asthma, wheeze, cough, and medication use. Recent asthma was defined as a physician diagnosis of asthma ever together with wheeze in the last 12 months. As there is no standard for weight distribution in children, they employed BMI percentiles according to sex and age as a measure of standardized weight. AHR was measured by histamine challenge and the dose:response ratio (percentage change in final FEV_1 [forced expiratory volume in 1 s] from baseline divided by the total dose of histamine administered) was calculated. Adjusted ORs were obtained by logistic regression. Following adjustments for atopy, sex, age, smoking and family history, BMI was a significant risk factor for wheeze ever and cough, but not for recent asthma (OR 1.02) or AHR (OR 0.97). In girls, a higher BMI was significantly associated with a higher prevalence of atopy.

This study suggests that a higher BMI in children is associated with a higher prevalence of symptoms that are typical of asthma, but not with a higher prevalence of asthma. The authors measured lung function and recorded AHR with histamine challenge tests, but did not find that obesity was linked to a higher prevalence of airway obstruction or AHR. Indeed, they suggested that these symptoms may be attributed to gastro-oesophageal reflux or obstructive sleep apnoea.

Tantisira and colleagues drew similar conclusions from the CAMP study. The CAMP study is a large randomized controlled trial that recruited children aged between 5 and 12 years who had mild to moderate asthma of at least 6 months' duration and documented AHR to methacholine |**79**|. In this study the authors failed to find any association between BMI and asthma symptoms. They did report a relationship between BMI and the change in FEV1 following bronchodilator and the degree of methacholine sensitivity. However, any association between BMI and AHR disappeared after they adjusted for baseline FEV1, suggesting that this could be explained by an effect of obesity on airway calibre. Neither of the measures of atopy (IgE or eosinophil count) was associated with BMI.

One of the attractions of establishing a link between obesity and the development of asthma lies in the fact that it is a modifiable risk factor. Indeed, randomized controlled trials have demonstrated improvements in asthma symptoms and peak expiratory flow (PEF) following weight loss |**80**,**81**|. However, whether or not obesity is associated with asthma, weight reduction leads to numerous other beneficial health outcomes.

Effects of gas and other fume emitting heaters on the development of asthma during childhood

Phoa LL, Toelle BG, Ng K, Marks GB. *Thorax* 2004; **59**: 741–5

BACKGROUND. The aim of this study was to explore whether there was any relationship between exposure to fume-emitting heaters, currently and during the first year of life, and the risk of various asthma outcomes.

INTERPRETATION. Exposure to fume-emitting heaters in the first year of life was associated with an increased risk of AHR, recent wheeze and recent wheeze plus AHR.

Comment

The authors of this study were interested in potential relationships between the quality of indoor air and a number of different asthma outcomes. They performed a cross-sectional study of schoolchildren aged 8–11 years and collected information on respiratory symptoms and heating types by the use of parent-completed questionnaires. In addition, they assessed atopy by the use of skin prick tests and measured AHR by histamine challenge testing.

The main finding of the study was a strong association between the use of fume-emitting heaters during the first year of life and the presence of AHR, recent wheeze and current asthma. However, they did not find any association with physician-diagnosed asthma or atopy. They speculate about possible specific agents, including nitrogen dioxide and sulphur dioxide, and particulate matter from wood smoke. They did not report an association between the current use of fume-emitting heaters and any asthma outcomes.

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2

Clinical expression of asthma

PETER REID

Introduction

Asthma does not represent a distinct disease entity but rather a heterogeneous group of conditions that are characterized by a similar clinical presentation, airway hyperreactivity (AHR) and reversible airflow obstruction. Thus it is not surprising that the clinical expression and course of asthma are also heterogeneous. Nevertheless, important research continues to focus on the ability to detect disease patterns and factors that influence the presentation and likely prognosis. Closely allied to this is research that focuses on the control of asthma.

Influence of early life exposures on incidence and remission of asthma throughout life

de Marco R, Pattaro C, Locatelli F, Svanes C, for the ECRHS Study Group. *J Allergy Clin Immunol* 2004; **113**: 845–52

BACKGROUND. In this study the authors have sought to examine whether early life exposures influence the incidence and remission of asthma or allergy in childhood, adolescence and adulthood, and to explore whether these associations vary according to the age at onset of asthma.

INTERPRETATION. Both genetic factors and the microbial environment play a role in either promoting or preventing asthma throughout life. Exposure to older children early in life was associated with a reduced risk of developing asthma at any time during a person's life, with an increased rate of remission in childhood asthma. Early respiratory infections were a strong risk factor for asthma starting at any time during a person's life. A parental history of asthma and allergy was associated with a higher risk of developing asthma throughout life and worsened the prognosis of both childhood and adult asthma.

Comment

In this study the authors performed a retrospective analysis of data from a large, multinational general population sample that had been collected during the clinical stage of the European Community Respiratory Health Survey (ECRHS). These data

had been collected in discrete time windows using the same highly standardized methods.

Consistent with previously published observations, the authors found that females had a significantly lower risk of developing asthma during childhood than males (hazard ratio [HR] 0.62; 95% confidence interval [CI] 0.52–0.75), whereas the opposite was found for adult-onset asthma (HR 2.01; 95% CI 1.61–2.51). The rate of asthma remission was higher in males and the incidence of asthma decreased with age in males but remained stable in females. A family history of asthma and allergy was positively associated with a higher risk of asthma at all ages (pooled HR 1.89; 95% CI 1.67–2.13), and was also related to lower remission rates.

In keeping with the hygiene hypothesis, the authors reported that subjects in contact with older children in family or day care acquired permanent protection against asthma, displaying a consistent negative association with the onset of asthma and a higher rate of remission of childhood onset asthma. However, they also found that the presence of respiratory infections in childhood showed a consistent positive association with the incidence of asthma (pooled HR 3.19; 95% CI 2.75–3.69). This finding has been described by other authors |**1**,**2**|, prompting the investigators of this study to suggest that the influence of childhood infections on the development of asthma was likely to be bidirectional, and could be influenced by certain host factors, the severity of the infection, the organs involved, the type of microbe, and the length and type of exposure. They suggested that these effects may be explained by the regulation of anti-inflammatory cytokines such as interleukin (IL)-10, thereby predisposing to a persistent T-helper cell (Th2) response |**3**|.

The impact of childhood pets and the development of asthma continues to be a controversial and complex field |**4**|. In this study the authors found that early exposure to cats and/or dogs conferred protection against childhood asthma, but not adolescent or adult asthma. The importance of a parental history of asthma was underlined by a reduced probability of remission in both childhood and adulthood, whereas maternal smoking was not significantly associated with the incidence of asthma.

Childhood factors that predict asthma in young adulthood

Toelle BG, Xuan W, Peat JK, Marks GB. *Eur Respir J* 2004; **23**: 66–70

BACKGROUND. The aim of this study was to test whether it is possible to develop an algorithm for predicting, on the basis of childhood characteristics, whether asthma will persist into adulthood.

INTERPRETATION. The presence of obstructive spirometry, airway hyper-responsiveness and atopy in childhood identifies individuals with an increased likelihood of adult asthma.

Comment

Cohort studies following asthma from childhood to adulthood provide invaluable information on the natural history of the disease. The subjects of this cohort were recruited from randomly selected primary schoolchildren in the Belmont region of New South Wales |**5**|. The authors were able to study 718 children aged 8–10 years who were followed up each second year until 1992 and then again in 1997–1999. Information regarding symptoms, family history, asthma management and morbidity was collected by questionnaire, atopy was defined by the use of skin prick tests to common allergens, and measurements of lung function and airway hyperresponsiveness were made by standard methods. Subjects were classified as having asthma symptoms if they reported wheeze, sleep disturbance due to asthma, or the use of inhaled steroids in the 12 months prior to the study. A history of a hospital admission, an urgent doctor visit, activity limitation or sleep disturbance in the 12 months prior to the study was used to define those with 'troublesome asthma'. Likelihood ratios (LRs) were calculated for the presence of either asthma symptoms or troublesome asthma, as the ratio of the prevalence of the characteristic among those with the disease outcome to the prevalence of the characteristic among those who did not have the disease outcome.

Two hundred subjects (34.7%) of the cohort reported asthma symptoms in adulthood, and 14.3% were defined as suffering from troublesome asthma. The strongest, independent positive predictors of the presence of asthma symptoms in adulthood were the presence of obstructive spirometry (adjusted LR 2.6; 95% CI 1.3–6.5) and the presence of AHR in childhood (adjusted LR 2.6; 95% CI 1.8–3.7), and atopy (adjusted LR 2.0; 95% CI 1.5–2.7), recent wheeze (adjusted LR 1.9; 95% CI 1.5–2.5), and being female (adjusted LR 1.29; 95% CI 0.8–2.1). The strongest predictors for troublesome asthma were the presence of obstructive spirometry and atopy in childhood. The overall LR of either of the outcomes could be calculated by multiplying the independent LRs. The authors quoted an example of a young atopic female, with AHR, recent wheeze and obstructive spirometry, with a multivariate LR of 36.9 for having asthma symptoms in adulthood, whereas the LR for a young male with none of these characteristics was 0.48. Interestingly, although the authors found that the presence of atopy, recent wheeze, AHR and obstructive spirometry increased the likelihood of developing asthma, the absence of these parameters had a much smaller impact on reducing the risk.

Childhood factors associated with asthma remission after 30 years follow-up

Vonk JM, Postma DS, Boezen HM, *et al*. *Thorax* 2004; **59**: 925–9

BACKGROUND. The authors of this study re-examined a cohort of 119 allergic asthmatic children that had been assessed by a paediatric pulmonology department between 1966 and 1969 in order to determine what childhood and early adulthood

factors contribute to the best attainable outcome from asthma. They defined 'complete remission' as the absence of symptoms, no requirement for inhaled corticosteroids, normal lung function and no airway hyper-responsiveness (provocation concentration$_{10}$ [PC$_{10}$] >16 mg/ml). Clinical remission was defined as no asthma symptoms and no requirement for inhaled corticosteroids.

INTERPRETATION. Complete remission was observed in one-fifth of patients and clinical remission in a further third. Complete and clinical remission was associated with a higher level of lung function in childhood and a higher subsequent increase in FEV$_1$. The absence of asthma symptoms was not associated with any of the childhood risk factors. Thus, it does not appear possible that childhood asthma status can predict whether symptoms will persist into adulthood.

Comment

The aim of this paper was to focus on characteristics that may be associated with asthma remission. The authors re-examined a cohort of 119 allergic asthmatic children who were recruited from a university hospital paediatric outpatient clinic between 1966 and 1969 when they were aged between 5 and 14 years. Further studies were conducted between 1983–86 and 1995–96. Complete remission of asthma was defined as the complete absence of asthma symptoms, no use of inhaled corticosteroids, normal lung function (forced expiratory volume in 1 s [FEV$_1$] >90%), and no airway hyper-responsiveness (PC$_{20}$ >16 mg/ml). Clinical remission was defined as the absence of asthma symptoms and no use of inhaled corticosteroids. A total of 20 subjects (22%) were in complete remission of asthma at age 32–42 and a further 27 (30%; total of 52%) were in clinical remission. Symptoms were reported by around 30% of patients (half of whom did not use inhaled corticosteroids), and 20% used inhaled corticosteroids and did not report symptoms.

The main finding of the study was that the presence of better lung function in childhood is associated with a better outcome. Logistic regression analyses showed that a higher FEV$_1$ in childhood and a greater improvement in FEV$_1$ between ages 5–14 and 21–33 were associated with both complete and clinical remission of asthma at age 32–42. Consistent with other reports, the authors found that 57% of those in apparent clinical remission still had evidence of AHR and/or reduced lung function |**6–8**|. However, it remains unclear whether this represents an ongoing inflammatory response or the presence of airway remodelling. In *The Year in Respiratory Medicine 2003* I included a cross-sectional study comparing bronchial biopsy specimens of subjects with a long-standing clinical remission of atopic asthma with subjects currently symptomatic with asthma and healthy controls. Compared with healthy control subjects, subjects in clinical remission of atopic asthma have evidence of persistent airway inflammation and airway wall remodelling, and this has been replicated by other authors |**9,10**|.

Interestingly, in this study smokers with a higher number of pack years were more likely to be in clinical remission, which the authors explained by suggesting a 'healthy smoker' effect. However, other studies highlight the dangers of continued smoking in asthma; a study by Sears and colleagues showed that smoking at 21 years of age was

associated with both persistent wheezing and relapse of wheezing |**11**|. The authors caution about generalization of their results as they acknowledge that this group predominantly comprised patients with moderate to severe asthma who were referred to and managed by a specialist clinic. They therefore constitute a relatively small sample that may be quite different from a general population cohort.

Progression of asthma measured by lung function in the Childhood Asthma Management Program

Covar RA, Spahn JD, Murphy JR, Szefler SJ; Childhood Asthma Management Program Research Group. *Am J Respir Crit Care Med* 2004: **170**: 234–41

BACKGROUND. One of the major concerns regarding the progression of asthma is associated with potential loss of lung function. The aim of this study was to compare the characteristics of children who displayed loss of lung function with the characteristics of those who did not over the 4–6 years of the Childhood Asthma Management Program (CAMP) study.

INTERPRETATION. Around one-quarter of children showed a significant reduction in post-bronchodilator FEV_1% predicted (SRP), which was associated with asthma at a younger age, male sex and a higher post-bronchodilator FEV_1% predicted. A similar proportion of SRP was found in each treatment arm of the study.

Comment

The National Heart Lung and Blood Institute CAMP study has been the largest controlled study of mild to moderate asthma in children and was designed to test the effects of inhaled therapy: budesonide, nedocromil and placebo |**12**|. As a group, the CAMP cohort did not show a significant decline in lung function; however, the authors found that around one-quarter of children demonstrated a reduction of 1% or more in post-bronchodilator FEV_1% predicted. They found that factors associated with this rapid decline included a younger age at entry, male sex, study site, and the presence of a higher post-bronchodilator FEV_1% predicted at baseline

The data on age are consistent with those obtained from the Tucson Children's Respiratory Study, which also reported a decline in lung function from infancy to 6 years in those who reported persistent wheeze, compared with those with transient wheeze, late-onset wheeze or those who had never wheezed |**13,14**|. The data on sex are also consistent with studies that I included in the last two volumes of this book. Both Rasmussen and colleagues and Sears and colleagues reported that the presence of persistent asthma in males was associated with lower lung function in adulthood |**11,15**|. The finding that higher initial lung function appeared to predict accelerated decline may be explained by regression to the mean; however, the authors felt that this did not provide a complete explanation and speculated that it may actually reflect difficulty interpreting lung function in this age group coupled with the inherent variability of the measurements required. Indeed, in an accompanying editorial

Pedersen points out that during puberty the relationship between height and lung function is more complex than at other periods of life, and assessment of FEV_1% predicted may not be as suitable a measure |**16**|.

Although it might be expected that those with SRP would have more severe disease, the authors were unable to find any evidence for this. Nevertheless, concern continues that SRP will eventually lead to severe asthma, given that losses of 1–2% per annum would be expected to result in severe airflow limitation by mid-adult life. A further potentially unexpected finding was that a similar proportion of subjects on budesonide and placebo displayed SRP, with no difference between treatment groups in the rate of reduction in post-bronchodilator FEV_1% predicted. In *The Year in Respiratory Medicine 2004* I included the Inhaled Steroid Treatment as Regular Therapy In Early Asthma (START) study, which examined the potential impact of regular inhaled corticosteroid early in the course of asthma |**17**|. In this study, patients taking regular inhaled corticosteroids appeared to lose lung function but to a lesser extent than those on placebo, although the differences became less apparent at later timepoints. This may reflect an anomaly of intention-to-treat analysis; however, here the authors suggest that decline in lung function may reflect corticosteroid-independent mechanisms, such as the presence of neurogenic inflammation or structural changes in the airways |**18,19**|. However, adherence may be an alternative explanation. Interestingly, in the START study, the decline in post-bronchodilator FEV_1 in both treatment groups was more marked for males, active smokers and patients over 18 years ($P < 0.001$ for all) and the smallest treatment effect of budesonide was seen in adolescents, when compared with children or adults.

At one of the centres, investigators performed induced sputum analysis and reported that SRP was associated with a more prominent eosinophilic inflammatory response during washout. This is consistent with data from a group of severe asthmatics showing that persistent airflow limitation occurred more frequently in patients with sputum eosinophilia |**20**|.

In summary, decline in lung function does not appear to be an issue in the majority of children with asthma. However, a decline may be observed in around one-quarter of children with mild to moderate asthma. The reasons are poorly understood and decline does not appear to be influenced by corticosteroid therapy. This has important consequences for those in whom it declines. The CAMP Continuation Study will collect data from an additional 8 years of follow-up.

Airway inflammation in children with difficult asthma: relationships with airflow limitation and persistent symptoms

Payne DNR, Qiu Y, Zhu J, *et al*. *Thorax* 2004; **59**: 862–9

BACKGROUND. The aim of this study was to describe the nature of the inflammatory cell infiltrate in endobronchial biopsy specimens from children with difficult asthma, following treatment with corticosteroids.

Interpretation. Persistent airflow limitation in children with difficult asthma treated with systemic corticosteroids is associated with an increased density of $CD4^+$ T lymphocytes.

Comment

A limited amount of research has been undertaken in children with difficult asthma. The authors of this study were interested to investigate the inflammatory infiltrate in the airways of such children and determine if there was any relationship between this and measurements of lung function. They studied 36 children with difficult asthma that was defined by the presence of symptoms requiring rescue bronchodilator on at least 3 days per week, despite treatment with $\geq$1600 μg/day inhaled budesonide or equivalent, and regular long-acting β_2 agonist (or a previous unsuccessful trial of long-acting β_2 agonist) and/or regular prednisolone. Two weeks of systemic corticosteroids were then administered (32 patients). Patients were instructed to record the number of symptom-free days over 2 weeks, and then underwent spirometry, measurements of exhaled nitric oxide (FE_{N0}) and bronchoscopy and endobronchial biopsy. A control group of non-asthmatic children who were undergoing bronchoscopy for investigation of respiratory symptoms were enrolled.

In keeping with previously published observations, the authors found that the thickness of the reticular basement membrane was greater in the asthmatic children than in the non-asthmatic control group |**21**|.

The main finding of the study was that patients with persistent airflow limitation had a higher density of $CD4^+$ T lymphocytes than those without persistent airflow limitation. Indeed, a significant negative correlation between $CD4^+$ T lymphocytes and FEV_1 and FEV_1/FVC (forced vital capacity) vital capacity existed for the asthmatic group as a whole. Therefore they suggested that failure to achieve normal lung function following corticosteroid therapy could reflect an inability to suppress this cell type. Following systemic corticosteroids, 11 of the subjects became asymptomatic, but the authors did not find any difference in the inflammatory cell infiltrate between those who became asymptomatic and those who did not.

The authors acknowledged several weaknesses in their study. Ideally, they would have wished to perform bronchoscopy both before and after the administration of systemic corticosteroids. They also acknowledged the lack of a health control group and accept that the lack of difference in inflammatory cell population between their asthmatic children and the control group was probably explained by this. They also would have wished to include a comparator group of mild asthmatic children. However, despite these weaknesses this study is to be commended as it is likely to stimulate further research in this difficult area.

Persistence of asthma symptoms during adolescence: role of obesity and age at the onset of puberty

Guerra S, Wright AL, Morgan WJ, Sherrill DL, Holberg J, Martinez FD. *Am J Respir Crit Care Med* 2004; **170**: 78–85

BACKGROUND. The longitudinal birth cohort of the Tucson Children's Respiratory Study has been followed up consistently with frequent follow-up surveys, and is now approaching its third decade. The authors of this study have examined data from this cohort up to the age of 16 to study the factors influencing persistence and remission of childhood asthma after the onset of puberty.

INTERPRETATION. Thirty per cent of children with infrequent wheezing and 60% of children with asthma in the prepubertal period continue to experience wheezing episodes in the first 4 years after onset of puberty.

Comment

The Tucson Children's Respiratory Study, Tucson, Arizona, was established as a long-term, longitudinal, prospective study of the risk factors for acute lower respiratory tract illnesses in early childhood and for chronic obstructive airways disease in later life. A total of 1246 newborns were enrolled into the study between May 1980 and January 1984 |**22**|. In this study the authors analysed data from 781 subjects collected at ages 6, 8, 11, 13 and 16 years and obtained information on wheezing both before and after the onset of puberty. Puberty was defined as the age at which the first signs of puberty were reported by the parents and subjects were followed for a period of 4.2 ± 1 years after the onset of puberty. The majority of children (51%) did not report wheezing attacks. Incident asthma (asthma occurring following puberty) was reported in 11%.

The outcome of prepubertal symptoms was different for those children with infrequent wheeze and those with asthma. The majority of children (70%) with infrequent wheeze experienced remission, whereas 58% of those with asthma continued to experience wheezing episodes after the onset of puberty. The proportion of boys was higher in the remitting and unremitting wheezing and asthma groups. The proportion of girls was higher in the unremitting groups than in the corresponding unremitting groups, but the association did not reach statistical significance.

The authors found that both an early onset of puberty and an elevated body mass index (BMI) were associated with persistence of asthma symptoms in adolescence. The association with an elevated BMI has been demonstrated previously, particularly in females; indeed, in *The Year in Respiratory Medicine 2003* I included a longitudinal study by Castro-Rodriguez and colleagues showing that women with a BMI of 30 had approximately double the risk of developing asthma compared with those with a normal BMI |**23**|. The link between obesity and early menarche may be shared |**24**|; however, the authors also speculated that asthma may be linked to an early menarche

by a shared propensity to a common risk factor or a real biological phenomenon acting though hormonal mechanisms.

Worldwide severity and control of asthma in children and adults: the global Asthma Insights and Reality (AIR) surveys

Rabe KF, Adachi M, Lai CKW, *et al*. *J Allergy Clin Immunol* 2004; **114**: 40–7

BACKGROUND. The Global Initiative for Asthma (GINA) severity classification is a first-step population-screening tool based on symptoms and the use of healthcare services and, in those already under care, the use of drug therapy and symptom severity. The aim of this study was to assess actual variations in symptom severity and the control of asthma and the current state of asthma management with respect to the GINA guidelines.

INTERPRETATION. Despite the availability of effective therapy, asthma remains poorly controlled in many patients worldwide. The long-term management goals of GINA are not being met.

Comment

The GINA guidelines specify eight goals for the long-term management of asthma: minimal chronic symptoms, minimal exacerbations, no emergency visits, minimum need for as-required β_2-agonists, no limitations on daily activities, near-normal peak expiratory flow, a peak expiratory flow circadian rhythm of less than 20%, and minimal adverse effects from asthma medication. The Asthma Insights and Reality (AIR) surveys represent the first large-scale international assessment of the effects and management of asthma in children and adults. The authors reported data on 10 939 patients with asthma (3153 children and 7786 adults) from 29 countries. All surveys used the same standard protocol. Patients with current asthma were identified as those with physician-diagnosed asthma who were currently taking asthma therapy, or had experienced asthma attacks or symptoms within the past year. A further random sample of 7786 adults and 3153 children completed a symptom questionnaire, allowing a combined symptom severity index (based on the GINA severity classification) to be defined.

The most striking finding of this study was that in all participating regions asthmatic patients performed equally poorly against different GINA goals, a consistently high proportion of subjects reporting daytime, night-time and exercise-induced symptoms. In addition, asthma limited normal activities in a considerable proportion of patients, ranging from 17% in Japan to 68% across Central and Eastern Europe. The use of lung function was low: ownership of a peak flow meter was highest in the UK (40%), but was rarely used. The frequencies of hospital admissions and emergency visits were similarly high in all regions, as were the overall level of school-days and work-days lost. All patients with persistent asthma, regardless of the severity,

reported low use of preventative medication and high use of quick relief medication. Interestingly, Sweden reported the highest use of preventative medication and performed best with regard to the level of asthma control. It is also important to note that 32–49% of patients who actually reported severe symptoms and 39–70% of patients who reported moderate symptoms described their current level of control as either 'well' or 'complete', highlighting a consistent tendency for patients with asthma to overestimate control and underestimate severity.

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3

Management of asthma

PETER REID

Introduction

The management of asthma is multifaceted and, at its best, involves a number of different healthcare professionals working together with the patient. Increased understanding of the development of asthma in the earliest years of life has led to optimism that primary prevention may be realistic, and there have been a number of studies on the utility of primary preventative measures that are focused on the pre- and perinatal periods in high-risk children. Secondary prevention focuses on the period following sensitization but preceding the clinical appearance of the disease with the aim of reducing the burden of chronic persistent illness, and tertiary prevention examines the role of reducing exposure to allergens with the aim of improving asthma control. The most popular attempts at tertiary prevention have involved the examination of methods to reduce exposure to the house dust mite |**1–6**|. However, it has proved difficult to achieve significant and sustained reductions in levels of exposure and definitive evidence of benefit is lacking |**7**|.

The majority of patients presenting to their physician with symptoms of asthma will require pharmacological intervention. The recognition of the central role of inflammation in the pathogenesis of asthma has led to emphasis on the administration of regular inhaled corticosteroids as anti-inflammatory therapy. Their pre-eminent position in the management of asthma is based on the recognition that regular administration is associated with reduced symptoms, improvements in lung function, a reduction in airway hyper-responsiveness, fewer hospitalizations and the prevention of death. Their use in patients with mild disease has not been fully established. Furthermore, an increasing body of evidence suggests that the maximum therapeutic effect may be attained, for the majority of patients, with low to moderate doses of these agents; higher doses add little and potentially contribute to unwanted systemic effects |**8–10**|. The role of short-acting β_2-agonists is directed towards the relief of symptoms (or the prevention of exercise-induced symptoms) and these agents should be prescribed on an as-required basis. Long-acting β_2-agonists have emerged as useful add-on therapy to inhaled corticosteroids and appear to confer additional benefit in patients with asthma of all levels of severity, including those with mild disease.

Although there is a clear need for the development of new therapies, such as a monoclonal antibody directed against immunoglobulin E (IgE), the expectation of most physicians is that the majority of patients with asthma can achieve control with currently available therapies |**11–13**|. However, this is at variance with the experience of many patients, suggesting that tight control of asthma may be unrealistic and raising the challenge to the asthma community that we may need to reset our expectations of asthma care.

The Canadian asthma primary prevention study: outcomes at 2 years of age

Becker A, Watson W, Ferguson A, Dimich-Ward H, Chan-Yeung M. *J Allergy Clin Immunol* 2004; **113**: 650–6

BACKGROUND. The authors of this study designed a prospective, randomized, controlled study in order to address the important question of whether a multifaceted intervention to reduce allergen load that is focused on infants at high risk of developing asthma can prevent the emergence of sensitization and disease.

INTERPRETATION. A multifaceted intervention in children at high risk of asthma was associated with a significant reduction in the prevalence of asthma at age 2 years.

Comment

As our understanding of the importance of early development on the propensity to develop asthma grows, there is interest in researching whether certain interventions focused on high-risk infants will prevent the emergence of sensitization and disease. The authors identified high-risk infants (during the third trimester of pregnancy) as those with at least one first-degree relative with asthma or two first-degree relatives with other classic IgE-mediated allergic diseases. Study participants were then randomized either to a control group, who did not receive any specific information about intervention measures and were assigned to the usual care recommended by their primary care physicians, or to an active group, who were subjected to a multifaceted intervention including avoidance of house dust mite (encasement of the infant's and parents' bedding, instructions to wash weekly, and chemical measures for carpets and upholstered furniture). Parents were instructed to remove cats and dogs from the home or, if this was not possible, to keep any pets outside the home or away from the infant's bedroom. They also received counselling on smoking cessation and were instructed to keep the home smoke-free. They were encouraged to avoid day-care until after the first year of life and mothers were encouraged to breastfeed for at least 4 months of the first year. When breastfeeding was not possible, partially hydrolysed whey formula was supplied for supplementation until 12 months of age.

Although this study was ambitious, the authors reported good concordance with study interventions in the active group, with successful reduction of house dust

mite exposure, longer breast-feeding and delayed introduction of solid food, and less environmental tobacco smoke (ETS) exposure. The prevalence of pets did not decrease but there was significantly less cat exposure at 2 weeks and 4 months. There was no difference in the prevalence of atopy in the control (13.7%) and intervention (15.6%) groups. The presence of asthma was assessed by a paediatric expert blinded to the arm of the study to which the child had been assigned. At 2 years, 19.5% of the children had asthma and 14.5% had atopy (defined as a positive skin test to one or more common allergens). The authors found a decreased number of children with possible or probable asthma in the intervention group compared with the control group (23.0%; odds ratio [OR] 0.60; 95% confidence interval [CI] 0.37–0.95), and a substantial reduction in persistent asthma (defined as asthma present at both year 1 and year 2) in the intervention group (4.9 vs 11.3%; OR 0.36; 95% CI 0.17–0.73). There was no difference in reporting of recurrent wheeze.

Exposure to house dust mite or cat allergen at ≥ 2 μg/g dust did not influence the incidence of asthma at 2 years, although the authors postulate that this may not hold at later time-points. Breast-feeding for more than 4 months was not associated with either a decreased or an increased risk of asthma by age 2. Day-care at any time during the first 12 months did not affect the incidence of asthma at 2 years. However, it was associated with less atopy. Atopy at 12 months was predictive of asthma at 24 months.

Although controversy exists regarding the diagnosis of asthma in pre-school children, this study and others will continue to provide fascinating data |**1–4**|.

Three-year outcomes of dietary fatty acid modification and house dust mite reduction in the Childhood Asthma Prevention Study

Peat JK, Mihrshahi S, Kemp AS, *et al*. *J Allergy Clin Immunol* 2004; **114**: 807–13

Background. The aim of this study was to assess the potential of omega-3 fatty acids and/or house dust mite allergen avoidance in the primary prevention of allergic disease in children with a family history of asthma. This study reports the results pertaining to atopy and respiratory symptoms at age 3.

Interpretation. Dietary intervention by omega-3 supplementation and omega-6 restriction significantly reduced atopic cough, and allergen avoidance significantly reduced house dust mite atopy. There was no effect of either intervention on wheeze.

Comment

The Childhood Asthma Prevention Study (established in 1997 in Sydney, Australia) was designed to test whether interventions promoting dietary supplementation with omega-3 fatty acids, the avoidance of house dust mite allergens, or a combination of

the two, could decrease the incidence of allergy and asthma in high-risk children. In *The Year in Respiratory Medicine 2004* I included the results of this study, reporting that increasing dietary omega-3 fatty acids had no effect on serum IgE, atopy or doctor's diagnosis of asthma but reduced the prevalence of any wheeze and wheeze of more than 1 week. Prompted by observational studies suggesting that subjects who eat more fish report less wheeze, the authors of this study designed a randomized controlled trial to investigate the effect of dietary supplementation with omega-3 fatty acids on the development of disease. As with the Canadian Asthma Primary Prevention Study, the authors enrolled children at high risk of the development of asthma by selecting families in which one parent or sibling had reported symptoms of asthma. Compliance with intervention was assessed by measuring plasma omega-3 fatty acids and the proportion was found to be higher in the active group.

At age 3, dietary intervention by omega-3 supplementation and omega-6 restriction significantly reduced atopic cough. The absolute reduction of mild cough by dietary intervention was 7.1% and that of moderate cough was 4.1%. However, when stratified by atopy, there was a significant reduction in atopic cough. The authors calculated that the number needed to treat was only 10. Allergen avoidance reduced house dust mite atopy by 7.2% (number needed to treat, 14). However, there was no significant effect of either intervention on wheeze.

As with other studies in childhood, it is difficult to understand the importance of these findings, given that the relationship between cough and other asthmatic features remains uncertain |**14–17**|. Nevertheless, the authors speculate that omega-3 fatty acids may alter airway mediators that are particularly important in cough, such as arachidonic acid-derived prostaglandins and thromboxanes that may be important in determining the threshold for cough |**18,19**|. Interestingly, the Prevention and Incidence of Asthma and Mite Allergy study (PIAMA) also affected cough but not wheeze |**20**|.

Results of a home-based environmental intervention among urban children with asthma

Morgan WJ, Crain EF, Gruchalla RS, *et al*., for the Inner-City Asthma Study Group. *N Engl J Med* 2004; **351**: 1068–80

BACKGROUND. Environmental control measures have been recommended by asthma management guidelines but have not been studied in great detail. The Inner City Asthma Study was designed to assess the efficacy of a multifaceted, home-based, environmental intervention for inner-city children with asthma. Interventions were tailored to each child's sensitization and risk profile.

INTERPRETATION. A multifaceted intervention programme was effective in reducing allergen levels within homes and improved outcome in inner-city children with atopic asthma.

Comment

Asthma guidelines emphasize allergen reduction as an integral component of the management. However, there is minimal evidence on which to base such recommendations. Indeed, in both the *The Year in Respiratory Medicine 2003* and *2004* I included papers that have contributed to some of the pessimism that surrounds this area |**7,21**|. This suggests that, as a single intervention, reducing exposure to house dust mite has no significant effect on asthma control. However, one of the problems with studies such as these is the potential for continued aggravation of asthma by numerous other allergens to which the patient may be sensitized. The aim of this study was to evaluate a multifaceted environmental allergen intervention targeting house dust mite, passive smoking, cockroaches, pets, rodents and mould.

A total of 937 children, with a mean age of 7.7 years, were enrolled. To be eligible, children had to have physician-diagnosed atopic asthma and at least one asthma-related hospitalization or two unscheduled asthma-related visits to the clinic or emergency department during the previous 6 months. The intervention arm of the study lasted 12 months. Home environmental exposures were assessed every 6 months, and asthma-related complications were assessed every 2 months during the intervention and for 1 year following the intervention.

Levels of cockroach allergen (Bla g1) and dust mite allergens (Der f1 and Der p1) in the bedroom decreased in both groups but to a greater extent in the intervention arm. This persisted into the second year of the study. Cat allergen (Fel d1) increased in the bed and on the bedroom floor of the control group but decreased in the intervention group. Whether houses were carpeted or not did not appear to make any difference to the level of allergen reduction achieved. There were no significant changes within or between the groups during the study in the number of homes with current smokers, signs of water damage, cats, dogs or visual signs of cockroach infestation.

During the intervention period the authors reported that for every 2-week period the intervention group had fewer symptoms than the control group. This also held in the year following the intervention. The maximum number of days with symptoms was lower in the intervention group by 0.82 per 2-week period in the first year and 0.60 days per 2-week period in the second year. The authors calculated that this meant that this translated into 34 fewer days with reported wheeze during the 2 years of the study among children in the intervention group compared with the control group. The number of unscheduled healthcare visits was reduced such that, during the first year, for every 2.85 children treated there was one fewer unscheduled visit for asthma.

Within both the intervention and the control group there was a significant relationship between the reduction in the levels of dust aeroallergens and improvements in reported asthma-associated morbidity. The correlation between the levels of cockroach allergen on the bedroom floor and reduction in asthma-related morbidity was particularly strong. The estimated cost of the intervention was US$1500–2000 per child.

The authors acknowledged some weaknesses in the study, including the lack of data on allergen levels in other rooms and the absence of sham interventions in the control arm, with more frequent visits to the intervention homes. Nevertheless, this

important study demonstrated that significant reductions in allergen levels are possible and can be associated with important improvements in asthma control.

Clinical dose–response relationship of fluticasone propionate in adults with asthma

Masoli M, Weatherall M, Holt S, Beasley R. *Thorax* 2004; **59**: 16–20

BACKGROUND. In *The Year in Respiratory Medicine 2003* I included a meta-analysis from the same authors examining the dose–response relationship of fluticasone propionate in adults and adolescents, which found that the dose–response curve begins to plateau around 200 μg/day, with the maximum achievable benefit at 500 μg/day. However, the interpretation was limited by the small number of studies that included doses of more than 500 μg/day because of the requirement for the studies to be placebo-controlled.

INTERPRETATION. The majority of the therapeutic effect from fluticasone is achieved at a total daily dose of 200 μg/day in adolescents and adults with asthma. However, the response to inhaled corticosteroids is characterized by considerable individual variability and some patients are likely to obtain greater clinical benefit at higher doses.

Dose–response relationship of inhaled budesonide in adult asthma: a meta-analysis

Masoli M, Weatherall M, Holt S, Beasley R. *Eur Respir J* 2004; **23**: 552–8

BACKGROUND. The same authors applied a similar study design to the use of budesonide.

INTERPRETATION. The majority of the therapeutic benefit of budesonide in mild to moderate asthma is achieved with a dose of approximately 400 μg/day and the maximum effect is achieved at approximately 1000 μg/day. However, considerable individual variability in the response to inhaled corticosteroids exists.

Comment

Dose–response studies with inhaled corticosteroids are difficult to perform but are very important, given the propensity for higher doses of inhaled corticosteroids to be associated with systemic side effects. The authors of this study had previously reported a meta-analysis (included in *The Year in Respiratory Medicine 2003*) reporting measures of clinical efficacy of inhaled fluticasone propionate in adolescents and adults with asthma and found that the majority of the therapeutic benefit from inhaled fluticasone is achieved with a total daily dose of 100–250 μg/day, and the maximum effect is achieved at a dose of 500 μg/day |**22**|. However, they wished to

repeat this exercise to provide more information on the likely dose response above 500 μg/day.

The authors included all double-blind, randomized controlled trials on fluticasone in adolescents or adults with asthma published after August 2002 that included two or more doses of fluticasone of at least 200 μg/day administered twice daily. Studies were of at least 6 weeks' duration and reported measures of clinical efficacy: in all, a total of seven studies fulfilled these criteria and four studies examined a dose of greater than 500 μg/day. Extraction of data was based on summary statistics for the intention-to-treat population. Outcome measures included forced expiratory volume in 1 s (FEV_1), morning peak expiratory flow (PEF), use of β-agonists, total withdrawals, and exacerbations of asthma leading to withdrawal.

For all outcome measures, there were no statistically significant differences between doses of 200 and 500 μg/day, between 500 and 1000 μg/day, and between 200 and ≥500 μg/day, although the point estimates favoured the higher doses. The mean improvement in FEV_1 and morning PEF resulting from an increase in dose from 200 to ≥500 μg/day was 0.07 litres (95% CI –0.01 to 0.14) and 5.9 litres/min (95% CI –3.0 to 15.3), respectively. These changes are not clinically relevant, even at the maximum change anticipated from the 95% confidence intervals. The odds ratio for withdrawals at doses of 200 μg/day compared with ≥500 μg/day was 1.27 (95% CI 0.78 to 2.07). Thus, the authors concluded that whilst significant individual variability exists with regard to response to inhaled corticosteroids, it is likely that for the majority of adolescents and adults with asthma the maximum clinical benefit will be obtained at doses of 200 μg/day.

The study on budesonide followed a similar design, examining the dose–response relationship for inhaled budesonide in adolescents and adults with mild to moderate asthma. A meta-analysis was performed on placebo-controlled, randomized clinical trials. This provided data on at least one outcome measure of asthma using at least two doses of budesonide, delivered using a Turbuhaler or metered-dose inhaler with a spacer twice daily. They entered a total of six studies, comprising a final population of 1435 adolescents and adults with mild to moderately severe asthma. Using a negative exponential model, they found that approximately 80% of the benefit obtained by delivering 1600 μg/day was achieved at doses of approximately 200–400 μg/day and 90% at 300–600 μg/day. The maximum effectiveness of budesonide was achieved at doses of approximately 1000 μg/day.

Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomized controlled trial

Harrison TW, Oborne J, Newton S, Tattersfield A. *Lancet* 2004; **363**: 271–5

Background. Doubling the dose of inhaled corticosteroids is widely advocated as a means of preventing an impending exacerbation of asthma in national guidelines and self-management plans. The authors of this study undertook a randomized controlled trial to investigate the effect of doubling the dose of inhaled

corticosteroid when asthma deteriorates. The primary end-point was the proportion of individuals in each group who required prednisolone.

INTERPRETATION. Doubling the dose of corticosteroid did not affect the natural history of an exacerbation of asthma.

Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations

FitzGerald JM, Becker A, Sears MR, Mink S, Chung K, Lee J, and the Canadian Asthma Exacerbation Study Group. *Thorax* 2004; **59**: 550–6

BACKGROUND. Motivated by the same question as Harrison and colleagues, the authors of this study performed a double-blind, randomized, placebo-controlled, parallel-group, multicentre trial to determine whether doubling the dose of inhaled corticosteroid prevents worsening and the need for systemic corticosteroids.

INTERPRETATION. In patients currently compliant with regular inhaled corticosteroids, doubling the dose within 48 h of the onset of an exacerbation does not change the outcome and need for further intervention compared with patients who continue on their usual dose.

Comment

In the face of deteriorating asthma control, most guidelines recommend that the dose of inhaled corticosteroid should be doubled to prevent or reduce the severity of an impending exacerbation. However, there is little evidence to support this and the authors of these studies are to be commended for tackling a difficult area of asthma management.

Harrison and colleagues set out to determine if, when asthma control starts to deteriorate, doubling the dose of inhaled corticosteroid reduces the number of patients needing prednisolone, or whether there is any effect on the severity and duration of an exacerbation. They recruited 390 subjects with asthma who had either suffered an exacerbation or temporarily doubled the dose of their inhaled corticosteroids in the last 12 months to treat or prevent an exacerbation. Patients were stratified into low- to moderate- and high-dose groups depending on the dose of inhaled corticosteroid at study entry, and then instructed to commence a study drug (either an equivalent dose of inhaled corticosteroid or placebo) if their morning peak flow fell by more than 15% or if their daytime symptom score increased by 1 point from the mean peak flow and median symptoms score recorded during the run-in period.

During the study period (12 months), 207 (53%) subjects initiated therapy with their study inhaler and 46 (12%) started prednisolone. However, there was no difference between the two groups in the proportion of subjects using prednisolone in either group. The authors therefore found no evidence to support guidelines advocating doubling inhaled corticosteroids in the face of deteriorating asthma. There

was also no difference in the proportion of patients who visited their general practitioner or the proportion prescribed antibiotics.

Doubling the dose led to a small reduction in the mean maximum fall in peak flow. However, compared with patients remaining on the same dose of inhaled corticosteroid, there was no difference in the lowest peak flow recorded, the rise in symptom scores or the highest recorded symptom score. In addition, doubling the dose of inhaled corticosteroids had no effect on the time taken for peak flow or the symptom score to return to baseline values.

The authors draw attention to the problems inherent in studying infrequent outcomes such as asthma exacerbations. Despite selecting patients deemed to be at greater risk of exacerbation, only 12% controls started prednisolone. This point was taken up in correspondence in the *Lancet* by Fardon and colleagues, who calculated that 1640 patients would have been required in order to achieve 90% power with an error of 0.025 in a one-sided test |**23**|.

The study by FitzGerald and colleagues was undertaken by the Canadian Asthma Exacerbation Study Group. They recruited 290 patients with asthma who had experienced an exacerbation (defined as an increase in symptoms and the need for a change in medication) not more than 12 months and not less than 1 month prior to the run-in period. Patients were assigned their usual dose of inhaled corticosteroid but converted to budesonide for purposes of uniformity, and were then monitored to demonstrate stability. Patients were then randomized to either a maintenance arm, in which they were assigned to an additional placebo inhaler, or a double-dose arm, in which they were assigned additional inhaled corticosteroid. During the run-in period the mean baseline PEF and median symptom score was determined for each patient. PEF was measured with a Vitalograph 2110 computerized peak flow meter, which assigned a colour zone to each PEF reading. An alert asthma symptom score was defined by three ordinal values above the mean baseline total symptom score on two consecutive days. Inputting both the PEF colour code and the asthma symptom score allowed an electronic diary called MiniDoc to alert the patient to an impending asthma exacerbation. A study nurse then instructed the patient on when to commence the study inhaler. In this study the primary outcome measure was the proportion of patients who failed to regain control after developing symptoms of an impending exacerbation, and no difference was found between the two treatment arms.

Taking these two studies together provides good evidence that the current advice to double the dose of inhaled corticosteroids in the face of an impending exacerbation is unlikely to be effective. However, one randomized, double-blind, multicentre Italian study of 220 adult patients with perennial asthma showed that quadrupling the dose of inhaled corticosteroid at the start of exacerbation was associated with improved outcomes |**24**|. It is also important to remember the study by Green and colleagues reviewed in *The Year in Respiratory Medicine 2003*, in which the authors showed that adjusting the dose of inhaled corticosteroid in response to the level of sputum eosinophilia reduced the frequency of exacerbations compared with a group of patients whose dose of inhaled corticosteroids was adjusted in accordance with the

British Thoracic Society guidelines [25]. In an accompanying editorial in *Thorax*, Busse and Lemanske speculate that as most asthma exacerbations are caused by viruses they are likely to be accompanied by an influx of airway neutrophils, which are characteristically steroid-unresponsive [26–29].

Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study

Bateman ED, Boushey HA, Bousquet J, *et al*., for the GOAL Investigators Group.
Am J Respir Crit Care Med 2004; **170**: 836–44

BACKGROUND. The authors of the Gaining Optimal Asthma Control (GOAL) study set out to address whether asthma control, as defined by guideline statements on the management of asthma, can be achieved using currently available therapies. They designed a 1-year prospective trial to compare the efficacy of two recommended control therapies – an increasing dose of fluticasone propionate alone or in combination with the long-acting β_2-agonist salmeterol – in achieving asthma control as defined in the Global Initiative for Asthma (GINA)/National Institutes of Health guidelines.

INTERPRETATION. Guideline-defined control is attainable in the majority of patients with asthma.

Comment

Many studies have shown that asthma control in day-to-day life is suboptimal. In addition, the expectation of many patients and respiratory specialists that a high level of asthma control can be achieved is low. This contrasts with the messages to patients and physicians dealing with other chronic diseases, such as diabetes mellitus or hypertension, for which tight control is advocated and clear targets are provided. The authors therefore designed a 1-year, randomized, stratified, double-blind, parallel-group study of 3421 patients with uncontrolled asthma with the aim of determining whether asthma control, as aspired to in guideline documents, could be achieved.

Patients were considered eligible for randomization if they did not achieve at least two well-controlled weeks during the 4-week run-in period. Then, based on their inhaled corticosteroid dose, they were randomized to one of three strata: stratum 1 (no inhaled corticosteroid); stratum 2 (500 μg or less of beclomethasone dipropionate (BDP) daily or equivalent); and stratum 3 (500–1000 μg or less of BDP daily or equivalent). Within each stratum, patients were then randomized to treatment with either fluticasone or fluticasone plus salmeterol. If total control was achieved they remained on this treatment until the completion of the study, but if they reported suboptimal control the dose of fluticasone or fluticasone plus salmeterol was increased until either total control was achieved or the highest drug dose was reached.

The authors aspired to a very high level of asthma control, defined by the use of a composite measure that comprised PEF, rescue medication use, symptoms, nighttime awakenings, exacerbations, emergency visits and adverse events. Total control was defined by the absence of exacerbations, emergency room criteria, or medication-related adverse event criteria for each day of the week on 7 consecutive weeks out of 8, and subjects were defined as well controlled if they recorded 7 of 8 well-controlled weeks. It is noteworthy that the standards set to fulfil the definition of well controlled were also very high, given that being well controlled implied that there had been failure to achieve only one of the parameters of control.

Despite the very stringent definitions of control, total control was achieved across all strata, showing that this is a realistic goal no matter what the severity of the disease. The percentages of patients achieving both well controlled and totally controlled asthma are seen in Table 3.1.

The results seen for patients in stratum 1 reinforce the widely accepted recommendation that inhaled corticosteroids represent the first step in the management of persistent asthma. The use of fluticasone resulted in 40% of patients becoming well controlled and 58% became well controlled following dose escalation to 500 μg/day. The study also reinforces the utility of long-acting β_2-agonists as a therapy complementary to ICS. Patients randomized to receive combined fluticasone and salmeterol achieved asthma control more rapidly even when using a lower dose of inhaled corticosteroid compared to those patients randomized to fluticasone alone.

The aspiration to aim for high levels of control was rewarded by improvements in a range of parameters known to impair the quality of life of patients with asthma. In particular, patients who achieved control recorded low rates of exacerbations and near-maximal health status scores. Indeed, stepping-up therapy in those who were suboptimally controlled was associated with improvements in health status and a reduction in exacerbations, even in patients who did not achieve control. In a well-informed commentary in the same issue of the journal, Dr Neil Barnes points out that the study also shows that there is no single dose of inhaled corticosteroid at which long acting β_2-agonists should be added |**30**|.

Table 3.1 Percentages of patients achieving well controlled and totally controlled asthma

	Well controlled	Total control
Stratum 1		
FP	65%	31%
FP/SAM	71%	42%
Stratum 2		
FP	52%	20%
FP/SAM	69%	32%
Stratum 3		
FP	33%	8%
FP/SAM	51%	19%

As the study progressed, the authors reported a gradual increase in the percentage of patients who achieved total control and well-controlled status. During sustained treatment a further 8–12% achieved total control, and further improvements in FEV_1, exacerbation rates and quality of life were reported.

One of the concerns regarding the use of higher doses of corticosteroids in patients with asthma is the risk of local and systemic adverse events. In this study the authors reported very low rates of local side effects and minimal effects on adrenocortical function. In common with many studies in asthma, smokers of more than 10 pack-years of cigarettes were excluded. Therefore, it is not clear whether patients who smoke can achieve the same levels of control. We are certainly aware that cigarette smoking can reduce the efficacy of inhaled corticosteroids |**31**|. It will also be important to determine whether the same level of control can be maintained if, once optimal control is reached, the level of therapy is stepped down.

Inhaled and nasal corticosteroid use and the risk of fracture

Suissa S, Baltzan M, Kremer R, Ernst P. *Am J Respir Crit Care Med* 2004; **169**: 83–8

BACKGROUND. Inhaled corticosteroids remain the most effective anti-inflammatory therapy for the management of asthma. However, concern exists regarding the risk of accelerated loss of bone mineral density. If this does occur, one of the most important consequences would be an increased risk of fracture, particularly in the elderly. The authors of this study undertook a population-based cohort design with a nested case–control analysis to assess whether, and at what dose, long-term inhaled and nasal corticosteroid use increased the risk of fracture in the elderly.

INTERPRETATION. When used at doses below 2000 μg per day, regular inhaled corticosteroid therapy does not appear to be associated with an increased risk of fracture in older patients.

Comment

Results from four observational studies examining the possibility of an association between regular use of inhaled corticosteroids and the occurrence of fractures have been inconclusive.

Inconclusive results from four observational studies had attempted to define the link between inhaled corticosteroids and fracture |**32–35**|. In an attempt to clarify this area, the authors of this study employed a cohort design with a nested case–control analysis. The source population included all subjects over the age of 65 years who were dispensed at least one respiratory medication during a 3-year period and a cohort formed from this population by identifying all subjects receiving three or more prescriptions for any of these medications in any 1-year period and on at least two different dates. Data were obtained by using the Régie de l'Assurance Maladie du

Québec database. Cohort entry was taken as the date of the third prescription. A case was defined as the first fracture of the hip or upper extremities occurring after 4 years of follow-up. Vertebral fractures were excluded on the grounds that they do not always come to medical attention. Up to 20 age-matched control subjects were selected for each case. The study was impressive in size, with over 9500 cases and 191 000 controls.

The results of this study were largely reassuring, suggesting that for the majority of patients taking inhaled corticosteroids there is no increased risk of fracture of the hip or upper extremities. There was a small increased risk of rate of fracture (relative risk [RR] 1.06; 95% CI 1.01–1.12) for every 1000-μg increase in the daily dose of inhaled corticosteroid, and this was largely due to an increased risk of upper extremity fracture. There was no increased risk of fractures observed for patients taking nasal corticosteroids.

The RRs were similar among users and non-users of oral corticosteroids. The fracture risk increases by 2% (RR 1.02; 95% CI 1.01–1.03) for each gram of oral prednisolone equivalents dispensed over 4 years. Slightly higher RRs for fracture of the upper extremity were reported, with a 12% RR 1.12 (95% CI 1.04–1.19) for every 1000-μg increase in the daily dose of inhaled corticosteroid (beclomethasone equivalent).

As the study was observational the authors considered some potential causes of bias. A suggestion that fractures outside the province could have been missed was felt to be unlikely as the insurance scheme reimburses in part healthcare costs incurred in other provinces. Furthermore, given that sustaining a fracture is usually unforgettable, it seemed unlikely that participants would fail to recall such an event. They also recognized that using prescription data as a measure of exposure did not necessarily equate to actual use of the medication. However, they quite reasonably suggested that it would be unlikely that individuals who were dispensed high quantities of inhaled corticosteroids over a 4-year period would not be regular users. Use of oral steroids before the age of 65 could have affected bone mass and as it was not possible to obtain this information the authors made adjustments for the severity of respiratory disease. They also accepted that they were unable to correct for other important potential confounding factors, such as smoking, physical activity and obesity. However, again they felt that these would have been unlikely to have a strong influence on the results.

Five year study of etidronate and/or calcium as prevention and treatment for osteoporosis and fractures in patients with asthma receiving long term oral and/or inhaled glucocorticoids

Campbell IA, Douglas JD, Francis RM, Prescott RJ, Reid DM, on behalf of the Research Committee of the British Thoracic Society. *Thorax* 2004; **59**: 761–8

Background. This study was designed to determine whether treatment with cyclical etidronate and/or calcium for 5 years would prevent fractures or reverse/reduce the anticipated bone loss in patients receiving glucocorticoid treatment for asthma.

Interpretation. Five years of etidronate therapy significantly increased bone mineral density in the lumbar spine but not at the hip. Convincing evidence of fracture prevention was not demonstrated. Calcium, either as a sole agent or in combination with etidronate, was ineffective.

Comment

Following the introduction of cyclical etidronate therapy (with calcium) to the UK in 1992, the British Thoracic Society initiated a long-term, multicentre, randomized trial of etidronate therapy in patients with asthma. The study recruited 352 patients from 40 UK centres who had been taking oral and/or inhaled glucocorticoids for at least 1 year, including those with pre-existing osteoporosis and with vertebral and non-vertebral fractures. Post-menopausal women aged 50–70 years were eligible unless they had had a hysterectomy. Data were analysed on 349 patients.

Patients were stratified according to their use of glucocorticoids. Stratum A included patients on continuous oral prednisolone and inhaled glucocorticoids ($n = 171$), stratum B included patients on continuous inhaled glucocorticoids and intermittent prednisolone (more than 30 days ever) ($n = 137$), and stratum C included patients on continuous inhaled glucocorticoids but who had received no more than 30 days of prednisolone ever ($n = 41$). Patients received one of the following regimens: (1) etidronate + calcium; (2) etidronate only; (3) calcium only; (4) no treatment.

Although this study represents the largest and longest randomized controlled trial of the prevention and treatment of glucocorticoid-induced osteoporosis, it unfortunately provides a good example of the potential negative impact of health politics on research. The creation of Trust hospitals in the UK and the introduction of fundholding to general practice made it necessary for the investigators to obtain ethical approval from a proliferation of local ethical committees, with a consequent negative impact on recruitment. Indeed, although the study showed a statistically significant reduction in fracture rate in women, the result could not confidently exclude a chance effect as the statistical power of the study was limited by failure to achieve the recruitment target.

No overall effect of cyclical etidronate on the incidence of fracture was shown but there was a significant increase in lumbar spine bone mineral density and a trend towards prevention of bone loss from the proximal femur. This was most prominent in the first 2 years but was maintained for the remaining 3 years of the study, suggesting that the effect of bisphosphonate therapy will be maintained with longer treatment. The authors showed that there was no additional benefit from the addition of calcium to cyclical etidronate, which is important as patients taking additional calcium therapy reported more side effects. There was also no beneficial effect of taking calcium alone on bone mineral density or fracture incidence.

Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma

Holgate ST, Chuchalin AG, Hebert J, *et al*., on behalf of the Omalizumab 011 International Study Group. *Clin Exp Allergy* 2004; **34**: 632–8

BACKGROUND. The aim of this study was to examine the impact of omalizumab on patients with severe atopic asthma. The primary end-point was the percentage reduction from baseline in fluticasone dose following the 32-week treatment period.

INTERPRETATION. Omalizumab improves asthma control in severe allergic asthma patients and facilitates dose reduction in inhaled corticosteroid therapy without worsening the symptoms or increasing the requirement for rescue medication.

Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR

Vignola AM, Humbert M, Bousquet J, *et al*. *Allergy* 2004; **59**: 709–17

BACKGROUND. Patients with allergic asthma frequently experience concomitant allergic rhinitis and IgE appears to be important in both diseases. The authors of this study evaluated the efficacy and tolerability of omalizumab in patients with concomitant moderate to severe asthma and persistent allergic rhinitis.

INTERPRETATION. Omalizumab reduces asthma exacerbations and improves quality of life in patients with concomitant asthma and persistent allergic rhinitis.

The effects of treatment with anti-IgE (omalizumab) on airway inflammation in allergic asthma

Djukanovic R, Wilson SJ, Kraft M, *et al*. *Am J Respir Crit Care Med* 2004; **170**: 583–93

BACKGROUND. The mechanisms underlying the clinical efficacy of omalizumab are unknown. Hence the authors set out to determine whether omalizumab has anti-inflammatory effects in the airways of patients with allergic asthma. The primary outcome variable was sputum eosinophilia.

INTERPRETATION. This study provides a potential mechanism at the level of the airway for the anti-inflammatory effects of omalizumab treatment and provides clues for mechanisms whereby omalizumab reduces asthma exacerbations and improves other asthma outcomes in more severe asthma.

Comment

The formation of circulating IgE antibodies to allergens appears to be crucial to the expression of the asthmatic phenotype and is consistent with our current understanding of the immunological model of asthma, with activation of Th2 lymphocytes leading to the production of inflammatory cytokines that promote the manufacture of IgE antibodies by B lymphocytes |**36,37**|. The recruitment of inflammatory cells such as mast cells and basophils, which express high-affinity receptors for IgE, provides an environment in which allergen exposure leads to activation and the release of key inflammatory mediators, including histamine, prostaglandins and leukotrienes. These and other mediators orchestrate the early and late asthmatic response. Thus, targeting IgE binding should provide an opportunity to intervene in the pathophysiological processes involved in the asthmatic response, regardless of the precipitant.

Omalizumab is a highly specific monoclonal antibody that binds to circulating IgE and prevents receptor binding on effector cells. It is non-anaphylactogenic. To date, omalizumab has been shown to reduce dermal wheal and flare reactions, effectively attenuate allergen-induced early and late asthmatic responses, reduce sputum eosinophilia, and increase the dose of allergen required to provoke an early response to allergen challenge |**38–41**|. In *The Year in Respiratory Medicine 2003* I reviewed papers illustrating that the use of omalizumab could reduce the percentage of patients experiencing an asthma exacerbation and achieve significant dose reductions in maintenance inhaled corticosteroids despite reductions in the rescue use of β-agonists |**42–44**|.

This year Holgate and colleagues report a multicentre, randomized, double-blind, placebo-controlled study of the use of omalizumab in patients with severe asthma (defined by the requirement for daily treatment with high doses of inhaled corticosteroids (≥1000 μg fluticasone per day), with or without long-acting β_2-agonists. The authors took particular care to find the optimum dose of inhaled fluticasone that maintained asthma control. Following an optimization phase with fluticasone, the dose was gradually reduced until a pre-determined level of symptoms was reached. The patient was then stabilized on 1000–2000 μg of fluticasone per day. If stable on this dose over a further 4-week period, participants then entered the study and were randomized to either placebo or omalizumab. The study involved a 32-week treatment period: in the first 16 weeks either omalizumab or placebo was added to fluticasone, and in the second 16-week period the dose of corticosteroid was reduced.

Consistent with an anticipated trial effect, patients randomized to placebo were able to reduce their dose of fluticasone. However, patients receiving omalizumab achieved a 57.2% reduction compared with 43.3% in the placebo arm, and 74% of patients treated with omalizumab were able to reduce their fluticasone dose by at least half compared with 51% of patients treated with placebo. Patients treated with omalizumab had 35–45% fewer exacerbations than patients on placebo, but this did not attain statistical significance.

The paper by Vignola and colleagues is important as they investigated the potential of omalizumab in patients with concomitant asthma and allergic rhinitis. These

diseases frequently coexist and IgE is believed to be important in both [45]. Omalizumab has been shown to improve the control of seasonal allergic and persistent rhinitis [46–48]. Most of the patients in this study had severe persistent asthma and were receiving add-on therapy including long-acting β-agonists and topical nasal steroids as appropriate. Thus, in addition to these treatments, the use of omalizumab reduced the frequency of asthma exacerbations and led to significant improvements in quality of life scores that reflected both asthma and rhinitis.

The study by Djukanovic and colleagues provides important information on the modulation of the cellular inflammatory response by omalizumab. This multicentre, 4-month, randomized, double-blind, placebo-controlled, parallel-group study was conducted in patients with mild to moderate asthma, who were randomized to either 16 weeks of treatment with omalizumab or placebo. Markers of inflammation were assessed by the use of induced sputum and bronchial biopsies before and after treatment. Airway hyper-reactivity was measured by methacholine challenge.

This paper adds to our understanding of the mechanisms of action of omalizumab as it demonstrates that, in addition to circulating IgE, the levels of airway IgE are also decreased. This was accompanied by a reduction in the mean percentage of induced sputum eosinophils and a significant decrease in the number of eosinophils in both the epithelial and the submucosal compartment compared with placebo. Additional effects were noted on the numbers of epithelial and submucosal $CD3^+$ T-lymphocytes, submucosal $CD4^+$ T-lymphocytes, submucosal $CD8^+$ T-lymphocytes and submucosal B-lymphocytes. Omalizumab also reduced the level of the Th2 cytokine interleukin 4, which is known to be an important proinflammatory cytokine in patients with asthma.

The effect of omalizumab on airway eosinophils provides some explanation of the efficacy of omalizumab in reducing asthma exacerbations. As shown by Green and colleagues, targeting therapy to reduce airway eosinophilia appears to reduce the frequency of asthma exacerbations [25]. It is interesting that airway hyper-reactivity did not improve; this is consistent with the idea that there is dissociation between airway inflammation and airway hyper-responsiveness .

Peak flow monitoring for guided self-management in childhood asthma: a randomised controlled trial

Wensley D, Silverman M. *Am J Respir Crit Care Med* 2004; **170**: 606–12

BACKGROUND. It remains unclear whether peak flow is a useful component of guided self-management programmes in children. The authors of this study designed an open, randomized, parallel-group, controlled trial to investigate whether the addition of the peak flow monitoring to a symptom-based action plan resulted in improved outcome.

INTERPRETATION. The addition of peak flow monitoring does not appear to improve the outcome of guided self-management protocols in children.

Comment

Peak flow meters are inexpensive, widely available and straightforward to use, and provide a robust measure of airflow obstruction, and their use is widely advocated as part of self-management programmes in asthma. However, the evidence for this is lacking and a recent review has found no difference in outcome measures from plans based on PEF compared with those based on symptoms in adults |**49**|. The authors of this study explore the utility of PEF as part of guided self-management plans in children.

The authors recruited 90 children in an open-randomized, parallel-group, controlled trial in which participants were randomized to receive either PEF plus symptom-based management or symptom-based management alone for 12 weeks. Participants were aged 7–14 years, had physician-diagnosed asthma, on at least Step 2 of the British Thoracic Society guidelines, and were judged to have been clinically stable for 1 month prior to entry. Children and their care-givers were taught self-management at a training session which included training in spirometry and symptom recording. A colour-coded printed plan incorporating the child's own medication regime was then issued in which the PEF levels for action were based on the child's previous PEF. A written symptom diary was completed each morning and spirometry was performed twice daily. Children were visited approximately monthly to download spirometric data, exchange the diary, and obtain data on quality of life and the use of health services.

The main finding of this study was that, as with adults, the use of PEF did not provide any additional benefits in terms of the primary outcome measure of symptom scores and a range of secondary outcome measures, including lung function, quality of life and the use of health services.

As the result of the study was negative the authors analysed a number of potential areas for bias. Perhaps the most important of these related to recruitment. Of 511 eligible children only 89 were included, raising issues regarding the applicability to the results to the greater population. That said, this anomaly would be more likely to bias the trial to a positive rather than a negative outcome, as those who were entered might be reasonably expected to be more likely to comply with instructions. This is also pertinent to their assessment of the power of the study: they calculate that approximately 800 children would need to be studied to enable statistical significance to be reported with confidence.

At 12 weeks, the study was also rather short; however, the authors chose this period as they believed that it would be long enough for at least half the children to experience an exacerbation but short enough to promote compliance. Interestingly, compliance with PEF monitoring declined rapidly over the 12-week period, suggesting that PEF monitoring would be exceptionally difficult to maintain in the real world. Compliance with the symptom-based diary cards was also low, calling into question the reliability of this measurement as one on which to base clinical results. However, the authors also assessed quality of life in the final week of each month of the trial and also reported negative outcomes.

Action points were defined by thresholds of 70% and 50% of the best PEF recorded in the run-in period. When the PEF fell between 50 and 70% of the best PEF, children were advised to double the dose of inhaled corticosteroid, and if PEF fell to less than 50% of best PEF oral prednisolone was recommended. The authors questioned whether the negative result of the study reflected inappropriate thresholds. However, this also appeared to be unlikely. The overall mean PEF during the study was 83% of best, suggesting that a higher threshold would have led to overtreatment. Most children (or their carers) had enacted changes in treatment based on symptoms before PEF fell to less than 70%. They also found no evidence that using FEV_1, rather than PEF, would have been more helpful.

Although the authors conclude that the utility of PEF is probably best when making decisions in the setting of acute episodes |**50,51**|, this study does not support the use of PEF as a routine component of guided self-management plans in children.

Written action plans for asthma: an evidence-based review of the key components

Gibson PG, Howell H. *Thorax* 2004; **59**: 94–9

BACKGROUND. Guideline statements on asthma encourage the use of action plans as a means of promoting the early recognition and treatment of exacerbations. A variety of different action plans have been proposed but the key components of a successful plan remain unclear. The aim of this study was to determine the impact of individual components within action plans on asthma health outcomes.

INTERPRETATION. Individualized written action plans based on knowledge of personal best peak flow, using two to four action points and recommending both inhaled corticosteroids and oral corticosteroids for the treatment of exacerbations, consistently improve asthma health outcomes.

Comment

The authors were prompted to undertake this study following the publication of a systematic review of 17 randomized controlled trials that evaluated written action plans with usual care in adult asthmatics |**52**|. This suggested that the risk of hospitalization fell by 40% and the risk of presentation to the emergency department fell by 20%. Nevertheless, there was wide variation in the structure and content of the plans used. The authors of this study therefore undertook to determine which components were of greatest importance.

The authors defined three types of action plan: individualized complete written action plans that provided an action point prompting a change in treatment, with instructions on how to change treatment, and for how long, and when to seek medical attention; incomplete individualized action plans which were both individualized and provided instructions on when to increase treatment, but did not specify the

early use of inhaled corticosteroids; and non-specific action plans that provided general information regarding the management of deteriorating asthma.

Interestingly action plans based on the predicted or personal best PEF were associated with improved outcomes, such as reduced hospital admissions and emergency room visits and improvements in PEF. However, those based on the percentage predicted PEF were not associated with improved outcomes. When examining the number of action points, the authors found that for individualized action plans the use of two or three action points was probably optimal. The use of four action points allowed more precise instructions to be given but the authors felt that any potential benefits were likely to have been offset by the complexity of the plan. There was no difference if action points were based on symptoms or PEF. The study also endorsed the use of both inhaled and oral corticosteroids; it found that advocating their use consistently improved asthma outcomes.

Thus, the authors recommended that the provision of written action plans can be based on either symptoms or personal best PEF and should use two or three action points. Action points should advocate the use of inhaled or oral corticosteroids.

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Part II

Chronic obstructive pulmonary disease (COPD)

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4

Management of COPD

ADAM HILL

Introduction

Throughout the world chronic obstructive pulmonary disease (COPD) remains a major cause of chronic morbidity and mortality and is currently the fourth leading cause of death in the world.

Patients with COPD develop progressive and predominantly fixed airflow obstruction that leads to a history of progressive worsening breathlessness. This can affect daily activities and health-related quality of life. Frequent exacerbations can further impair health-related quality of life and have a major impact on health cure utilization.

There have been 1746 articles published on COPD from the beginning of November 2003 until the end of December 2004. Twenty-five articles of clinical relevance have been selected for this chapter.

Diagnosis of COPD

The diagnosis of COPD is normally made on the basis of history, clinical examination, radiology and lung function tests. The first paper evaluates whether an alternative approach can be adopted and whether asthma and COPD can be distinguished by pathological examination of endobronchial biopsy specimens.

Can endobronchial biopsy analysis be recommended to discriminate between asthma and COPD in routine practice?

Bourdin A, Serre I, Flamme H, *et al*. *Thorax* 2004; **59**: 488–93

Background. The aim of this study was to determine whether asthma and COPD could be distinguished by pathological examination of endobronchial biopsy specimens. Endobronchial biopsy specimens were taken from patients with a clear clinical diagnosis of asthma and COPD (50 per group) and examined by three

pathologists in a double-blind manner. The authors proposed a pathological diagnosis of either asthma or COPD and analysed qualitatively the most frequent abnormalities reported in the literature.

INTERPRETATION. There were no significant differences between asthma and COPD in endobronchial biopsies (Fig. 4.1). This is despite the careful selection of patients who had pure asthma and COPD, from their history and physiology. Patients with asthma had a mean age of 33 years (95% confidence interval [CI] 26–49.8), mean forced expiratory volume in 1 s (FEV_1) of 94.5% (79.3–100%) of predicted and a mean of 0 (0–0.75) smoking pack-years. Patients with COPD were older ($P < 0.0001$) with a mean age of 60 years (95% CI 51.5–66.8), a lower mean FEV_1 (59.0% of predicted; 95% CI 45.6–67.8%; $P < 0.0001$) and a higher mean number of smoking pack-years (40; 95% CI 40–50; $P < 0.0001$).

Comment

This study revealed that histopathological features from endobronchial biopsies were not sufficiently discriminatory to distinguish asthma and COPD. This reinforces that the gold standard for the diagnosis of COPD is based on history, examination, pulmonary physiology and radiology.

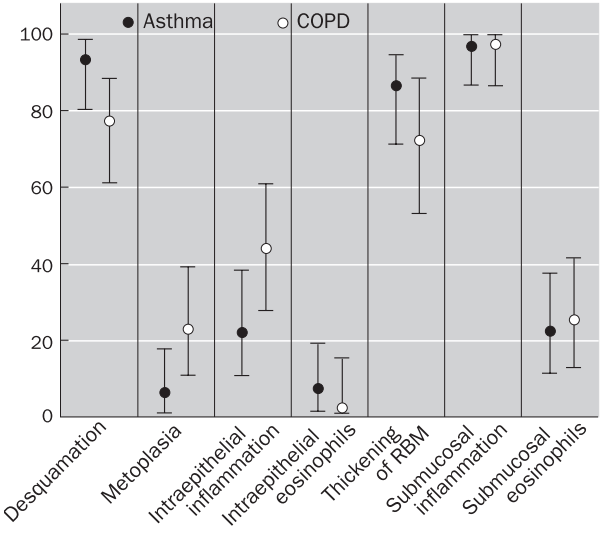

Fig. 4.1 Comparative prevalence in asthma and COPD of all criteria studied. Data are means with 95% CI calculated according to the binomial law. No significant differences were seen between the two groups. Source: Bourdin *et al*. (2004).

Assessing the severity of COPD

International guidelines |**1,2**| have stratified the severity of COPD based on the measurement of FEV_1 and forced vital capacity (FVC). Other complementary tests, such as the 6-minute walk test, may be helpful in addition in stratifying the severity of COPD. The next paper evaluated the role of changes over time in the 6-min walk test distance and its correlation with changes in spirometry and survival.

The 6-min walk distance: change over time and value as a predictor of survival in severe COPD

Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. *Eur Respir J* 2004; **23**: 28–33

BACKGROUND. The 6-min walk distance (6MWD) is used to evaluate the functional capacity of patients with COPD. The aim of this study was to assess the change in 6MWD over time and its correlation with changes in spirometry and survival. Patients (n = 198) with severe COPD (mean ± SD FEV_1 1.04 ± 0.39 l) and 41 age-matched controls (mean ± SD FEV_1 2.54 ± 0.63 l) were followed for 2 years, and anthropometrics, spirometry, 6MWD and comorbidities were measured. Eighty-six per cent of the COPD patients were severely affected, with an FEV_1 less than 50% of predicted.

INTERPRETATION. The 6MWD decreased in the COPD group from 238 ± 107 to 218 ± 112m (–26 ± 37 m per year) and increased in the control group from 532 ± 82 to 549 ± 86 m (12 ± 25 m per year). There was no significant correlation between changes in FEV_1 per year and change in 6MWD per year (r = 0.09; P >0.1). The COPD group was divided into survivors (n = 114) and non-survivors (n = 84). Non-survivors in the COPD group (42%) had a more pronounced change in the 6MWD (–40 versus –22 m per year) but a similar decrease in FEV_1 (118 versus 102 ml per year) to survivors. The 6MWD independently predicted survival after accounting for age, body mass index (BMI), FEV_1 and comorbidities (Fig. 4.2). A log-rank test showed that the categories had significantly different survival times (P <0.001), with longer times to death observed in categories of longer 6MWD. In a Cox proportional hazards regression model accounting for age, BMI, FEV_1 and comorbidities, 6MWD was a significant predictor of survival, with a risk ratio of death of 0.82 per 50 m increase in 6MWD (95% CI 0.72–0.94; P <0.003).

Comment

The 6-min walk test is a useful test in the comprehensive evaluation of patients with severe COPD, as the distance walked in the test will depend not only on respiratory function but also on the cardiopulmonary, nutritional and peripheral muscle status of the individual. In severe COPD, this study revealed that the 6MWD predicted mortality better than traditional markers of disease severity, such as FEV_1.

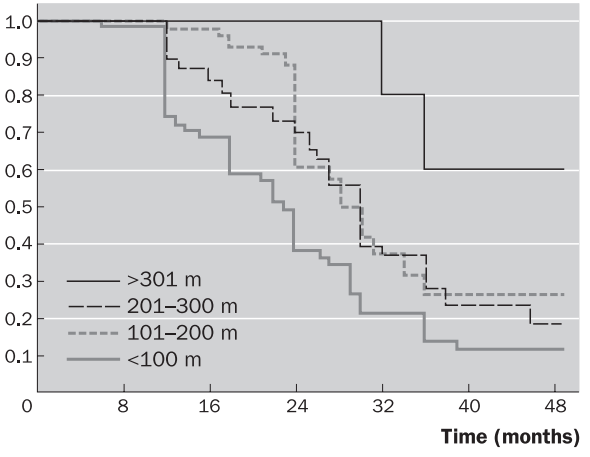

Fig. 4.2 Kaplan–Meier curves comparing survival with four different walked distances. Source: Pinto-Plata *et al*. (2004).

The next three papers evaluated the risk factors for relapse following treatment of COPD exacerbation in an emergency department, the effects of a comprehensive self-management programme and the importance of early treatment for exacerbations of COPD.

Prospective multicenter study of relapse following emergency department treatment of COPD exacerbation

Kim S, Emerman CL, Cydulka RK, Rowe BH, Clark S, Camargo CA; MARC Investigators. *Chest* 2004; **125**: 473–81

BACKGROUND. The aim of this study was to determine the incidence and risk factors for relapse after an emergency department visit for COPD exacerbation. This was a prospective cohort study in 29 North American emergency departments. Patients studied were COPD patients aged 55 years or older who had been discharged from the emergency departments directly to home. Eligible patients underwent a structured interview to assess their demographic characteristics, COPD history, and details of the current COPD exacerbation. Data on medical management in the emergency department and disposition were obtained by chart review. Patients were contacted by telephone 2 weeks later regarding incident relapse events (i.e. urgent clinic or emergency department visits for worsening COPD).

INTERPRETATION. There were 140 patients. At 2 weeks the relapse rate was 21% (95% CI 15–29%). The mean ± SD age was 68 ± 9.6 years. In a multivariate model, the significant risk factors for relapse were the number of urgent clinic or visits to the emergency

department for COPD exacerbation in the past year (per ≥5 visits), self-reported activity limitation during the past 24 h and respiratory rate at presentation to the emergency department (Table 4.1).

Comment

This was an interesting small study of relapses ($n = 30$) following treatment for COPD exacerbation in the emergency department. There was no long-term follow-up of these patients, making the diagnosis and assessment of severity of COPD difficult (indeed, 63% were labelled as having both COPD and asthma and there were no FEV_1 data when the patients were clinically stable).

In this study among patients discharged home after emergency department treatment of a COPD exacerbation, one in five patients experienced an urgent/emergency relapse event during the next 2 weeks. Both chronic COPD severity (exacerbation frequency in the last 12 months) and acute COPD exacerbation (self-reported activity limitations and initial respiratory rate) were associated with increased risk of relapse.

Further larger prospective studies are needed to address reasons for relapse in COPD patients from the emergency department. Follow-up will also be required to stratify patients correctly and assess the severity of COPD, as often this has not been previously assessed.

Table 4.1 Multivariate model of relapse 2 weeks after emergency department visit for COPD exacerbation

Variables	Odds ratio	95% CI	*P*-value
Age (per year)	1.00	0.95–1.05	0.94
Women (vs men)	0.43	0.16–1.11	0.08
Urgent clinic or ED visits in past 12 months (per ≥5 visits) No.	1.49	1.05–2.12	0.03
Activity limitations in past 24 h (per unit)*	2.93	1.35–6.36	0.007
Respiratory rate at presentation†	1.76	1.07–2.90	0.03

* Based on 4-point scale (1, none; 4, severe). Odds ratio is for each 1-point increase from a baseline of 1.
† Odds ratio is for each 5 breaths/min increase from a baseline of 16 breaths/min, with the minimum value reported.
ED, emergency department.
Source: Kim *et al*. (2004).

Effects of a comprehensive self-management programme in patients with chronic obstructive pulmonary disease

Monninkhof E, van der Valk P, van der Palen J, van Herwaarden C, Zielhuis G. *Eur Respir J* 2003; **22**: 815–20

Background. The aim of this study was to assess the effects of a comprehensive self-management intervention on health-related quality of life, symptoms and

walking distance in patients with stable moderate to severe COPD. The authors conducted a large, randomized, controlled single-centre trial over 1 year. Prior to the initiation of the trial all patients received inhaler instruction in small group sessions, COPD medication was optimized, and current smokers were offered a smoking cessation programme. Patients were randomized to a self-management and a control group. The self-management intervention consisted of a skill-oriented patient education programme and a near-home fitness programme (once weekly), in addition to usual care. The control group received usual care by the treating chest physician. Health-related quality of life was measured with the St George's Respiratory Questionnaire (SGRQ) and walking distance with the 6-min walking test. Patients recorded their symptoms in diaries and graded their health status from 1 to 10 in a weekly report.

INTERPRETATION. Altogether, 248 COPD patients were randomly allocated to either an intervention group ($n = 127$; mean ± SD FEV_1 56.1 ± 15.4% predicted) or control group ($n = 121$; mean FEV_1 58.4 ± 14.5% predicted). No differences in the SGRQ scores within and between the two groups were observed over 1 year. Similarly, no differences in symptom scores and 6MWD were found within or between groups. The intervention group had a median of 2 exacerbations (range 0–12) compared with 1 (range 0–9) in the control group. Most (69%) of the exacerbations in the intervention group were self-treated at home.

Comment

This study failed to show positive effects of a self-management programme over 1 year among patients with moderate to severe COPD. It would be interesting to repeat the study in patients with more severe COPD (a group that would be more likely to benefit from a self-management programme) and to look at other outcome measures, such as anxiety, depression and coping strategies.

Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease

Wilkinson TM, Donaldson GC, Hurst JR, Seemungal TA, Wedzicha JA. *Am J Respir Crit Care Med* 2004; **169**: 1298–303

BACKGROUND. Treatment of COPD exacerbations improves outcomes but responses to treatment are variable, and patients with COPD often delay presentation or fail to seek therapy. The impact of delaying or failing to seek treatment on exacerbation outcomes, hospitalization and health status is poorly understood. The study evaluated, between 1996 and 2002, a cohort of 128 patients with COPD. Their mean ± SD FEV_1 was 40.8 ± 15.6% predicted. Patients recorded respiratory symptoms daily and reported exacerbations to the outpatient-based study team or to their primary care physician.

INTERPRETATION. The patients recorded a total of 1099 exacerbations, of which 658 were reported to a physician. The time between exacerbation onset and treatment (median and interquartile range) was 3.69 (2.0–5.57) days and the exacerbation recovery

time was 10.7 (7.0–14.0) days. Earlier treatment was associated with faster recovery (regression coefficient 0.42 days/day delay; 95% CI 0.19–0.65; $P < 0.001$). This remained significant if allowance was made for both symptom severity and treatment with oral steroids (0.57 days/day delay; 95% CI 0.34–0.79; $P < 0.001$). Patients who reported a higher proportion of exacerbations for treatment had better health-related quality of life than patients with more untreated exacerbations ($\rho = -0.22$; $P = 0.018$). Failure to report exacerbations was associated with an increased risk of emergency hospitalization ($\rho = 0.21$; $P = 0.04$).

Comment

This study highlights the importance of early treatment of exacerbations of COPD. Patients who receive prompt therapy after the onset of the exacerbation are likely to recover sooner than those who delay reporting and thus initiation of treatment. Patients who fail to seek treatment for their exacerbations had a poorer health-related quality of life and were more likely to be hospitalized for their exacerbation. Patient education will be a key component in implementing change.

Management of COPD

The next section covers the medical management of COPD, including the role of antibiotics in exacerbations of COPD, bronchodilator therapy, inhaled corticosteroid therapy, influenza vaccination, and mechanical and nasal intermittent positive pressure ventilation.

Short-term and long-term outcomes of moxifloxacin compared to standard antibiotic treatment in acute exacerbations of chronic bronchitis

Wilson R, Allegra L, Huchon G, *et al*.; MOSAIC Study Group. *Chest* 2004; **125**: 953–64

BACKGROUND. The aim of this study was to compare the effectiveness of oral moxifloxacin with that of standard antibiotic therapy in acute exacerbation of chronic bronchitis. This was a multicentre, randomized, double-blind study of two parallel treatment arms. Outpatients aged 45 years or older with stable chronic bronchitis, a smoking history of at least 20 pack-years, two or more acute exacerbations of chronic bronchitis in the previous year and FEV_1 <85% of predicted value were enrolled when clinically stable, and patients with exacerbations within 12 months of enrolment were randomized. Patients with increased dyspnoea, sputum volume and purulence were randomized between moxifloxacin (400 mg once daily for 5 days) and standard therapy preselected by the investigator (amoxicillin [500 mg three times daily for 7 days], clarithromycin [500 mg twice daily for 7 days] or cefuroxime axetil [250 mg twice daily for 7 days]). Patients were assessed at enrolment,

randomization, 7–10 days after treatment and monthly until their next acute exacerbation of chronic bronchitis or up to 9 months. The primary efficacy variable was clinical success (sufficient improvement and no alternative antimicrobial therapy required) 7–10 days after therapy. Secondary predefined end-points were clinical cure (return to pre-exacerbation status), further antimicrobial use, time to the next acute exacerbation of chronic bronchitis and bacteriological success (eradication or presumed eradication 7–10 days after antibiotic treatment).

INTERPRETATION. The results are shown in Table 4.2 for the per-protocol population. A lower percentage (31.8%) than predicted (around 50–60%) had organisms isolated at the randomization visit (at the start of the acute exacerbation). *Haemophilus influenzae* (38%), *Streptococcus pneumoniae* (16%) and *Moraxella catarrhalis* (15%) were most frequently isolated. There was no significant difference in the primary end-point (clinical success) between patients randomized to moxifloxacin or standard therapy. For the secondary end-points, moxifloxacin treatment had superior clinical cure rates ($P < 0.05$) and higher bacteriological success only in microbiologically valid patients in the per-protocol population ($P < 0.05$). The time to next exacerbation was longer with moxifloxacin ($P = 0.03$). The frequency of adverse effects were not significantly different between groups.

Table 4.2 Outcomes for the per protocol population receiving moxifloxacin or standard therapy

Mean ± SD therapy	Moxifloxacin	Standard
Age (years)	64.5 ± 9.7	62.5 ± 9.8
Number	274	298
FEV_1 <50% predicted	43.4%	43.7%
Clinical success	87.2%	84.2%
Clinical cure	69.7%*	62.1%
Bacteriological success in patients with baseline causative organisms	91.5%*	81.0%
Mean time to next exacerbation	132.8 days*	118.0 days
Adverse effects	7.1%	4.8%

* $P < 0.05$; otherwise there were no significant differences between the groups that received moxifloxacin and standard therapy.
Source: Wilson *et al*. (2004).

Levofloxacin versus clarithromycin in COPD exacerbation: focus on exacerbation-free interval

Lode H, Eller J, Linnhoff A, Ioanas M; Evaluation of Therapy-Free Interval in COPD Patients Study Group. *Eur Respir J* 2004; **24**: 947–53

BACKGROUND. The aim of this study was to compare levofloxacin against clarithromycin in exacerbations of COPD with a focus on the exacerbation-free interval (EFI). Five hundred and eleven patients were enrolled in a randomized,

double-blind, multicentre study comparing EFI, efficacy and safety between 7 days of treatment with levofloxacin (500 mg once daily) and 10 days of treatment with clarithromycin (250 mg twice daily) in patients with COPD exacerbation. COPD patients recruited in this study had an FEV_1 35–75% of predicted and at least two exacerbations per year, and presented with an exacerbation with two or more of increased dyspnoea, sputum volume and purulence. Patients were monitored over a 1-year period.

Interpretation. A total of 434 patients (per-protocol population) received the medication for 5 or more days. In the levofloxacin group 223 patients had a mean FEV_1 57.7 ± 11.1% predicted and in the clarithromycin group 211 had a mean of 58.5 ± 12.6% predicted. Potentially pathogenic organisms were isolated in 50% in the levofloxacin group and 51.6% in the clarithromycin group. *Haemophilus influenzae* was isolated in 31%, *Streptococcus pneumoniae* in 20%, *Moraxella catarrhalis* in 15% and *Staphylococcus aureus* in 9%. The median EFI in the per-protocol population was 300 days for levofloxacin and was not significantly different (350 days; $P = 0.6$) in the clarithromycin group. For patients with a new documented exacerbation during follow-up ($n = 223$), the median EFI was 100.5 days in the levofloxacin group and was not significantly different (95 days; $P = 0.6$) in the clarithromycin group. No significant differences in EFI between groups was observed when stratifying the study population according to microbial aetiology and the severity of airways obstruction. The bacteriological success rate was significantly higher in the levofloxacin group (96.8%, versus 83.1% in the clarithromycin group; 13.7% difference; 95% CI 3.7–23.8; $P = 0.01$). Levofloxacin and clarithromycin showed similar clinical success rates (86.1 and 84.8% respectively; 1.3% difference; 95% CI –6.0 to 8.5; $P = 0.7$). Levofloxacin and clarithromycin showed similar frequencies of adverse events (9.5% and 9.7% respectively). The most common type of side effect for both drugs was gastrointestinal.

Comment

Bacteria were implicated in 31.8% of patients in the study by Wilson and colleagues and in about 50% in the study by Lode *et al*. Previous studies have implicated bacteria in 50–60% of acute exacerbations of COPD that present with increased symptoms, increased sputum volume and increased sputum purulence.

Moxifloxacin was equivalent to standard therapy for the primary end-point: clinical success. Moxifloxacin improved secondary predefined end-points of bacteriological success, clinical cure (return to pre-exacerbation status) and time to next exacerbation, although the changes were small.

Compared with clarithromycin, levofloxacin was associated with a significantly higher bacteriological eradication rate but had similar clinical success rates and exacerbation-free interval in patients with COPD exacerbation.

Overall, the importance of antibiotics in acute exacerbations is in hastening recovery. Clinicians choosing an antibiotic will base their choice on local resistance patterns, cost and efficacy. Preference may be given to antibiotics that increase the time to the next exacerbation. The Global Obstructive Lung Disease (GOLD) guidelines |**1**| advise that the choice of antibiotic agents should reflect local patterns of antibiotic sensitivity among *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. The National Clinical Guideline |**2**| advises an aminopenicillin, a macrolide or tetracycline.

In the UK a 7-day course of amoxicillin (500 mg three times daily) costs £1.08, a 7-day course of co-amoxiclav (375 mg three times daily) costs £9.74, a 7-day course of clarithromycin (250 mg twice daily) costs £11.76, a 5-day course of moxifloxacin (400 mg once daily) costs £10.95 and a 7-day course of levofloxacin 500 mg once daily costs £19.46 |**3**|.

Overall, amoxicillin as first-line therapy in acute exacerbations of COPD is a cheap and effective option. In patients who have not responded, alternative antibiotics will be chosen, and the choice is usually based on sputum microbiology and sensitivity testing. The data from moxifloxacin look promising in that treatment is once daily for 5 days only, it has high bacterial eradication rates, achieves clinical success in most patients, and can lengthen the time to next exacerbation.

The next paper evaluated the measurement of serum procalcitonin as a guide in helping the clinician to decide whether to prescribe antibiotics for lower respiratory tract infections.

Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial

Christ-Crain M, Jaccard-Stolz D, Bingisser R, *et al*. *Lancet* 2004; **363**: 600–7

BACKGROUND. Lower respiratory tract infections are often treated with antibiotics without evidence of clinically relevant bacterial disease. Serum concentrations of calcitonin precursors, including procalcitonin, are raised in severe bacterial infections. The aim of this study was to assess a procalcitonin-based therapeutic strategy to reduce antibiotic use in lower respiratory tract infections, with a new rapid and sensitive assay. Two hundred and forty-three patients admitted with suspected lower respiratory tract infections were randomly assigned standard care (standard group; *n* = 119) or procalcitonin-guided treatment (procalcitonin group; *n* = 124). The authors judged that a serum procalcitonin concentration less than 0.1 μg/l indicated the absence of bacterial infection, 0.1–0.25 μg/l indicated bacterial infection was unlikely, 0.25–0.5 μg/l indicated a possible bacterial infection and >0.5 μg/l indicated that a bacterial infection was likely. On the basis of serum procalcitonin concentrations, the use of antibiotics was more or less discouraged (<0.1 μg/l or <0.25 μg/l) or encouraged (≥0.5 μg/l or ≥0.25 μg/l), respectively. The final decision to initiate antimicrobial treatment was left to the discretion of the treating doctor. Re-evaluation was possible after 6–24 h in both groups. The primary end-point was the use of antibiotics and analysis was by intention to treat.

INTERPRETATION. Final diagnoses were pneumonia (*n* = 87; 36%), acute exacerbation of COPD (*n* = 60; 25%), acute bronchitis (*n* = 59; 24%), asthma (13; 5%) and other respiratory infections (*n* = 24; 10%). Serological evidence of viral infection was recorded in 141 of 175 tested patients (81%). Bacterial cultures were positive from sputum in 51 (21%) and from blood in 16 (7%). The foreseen antibiotic prescription was 83% in the standard

group and similar (80%; $P = 0.5$) in the procalcitonin group. Antibiotics were prescribed in 83% in the standard group but significantly less (44%; $P < 0.0001$) in the procalcitonin group. In the procalcitonin group, the adjusted relative risk of antibiotic exposure was 0.49 (95% CI 0.44–0.55; $P < 0.0001$) compared with the standard group. In the procalcitonin group, antibiotic use was significantly reduced in all diagnostic subgroups, including patients with COPD (Fig. 4.3). In the procalcitonin group, the mean antimicrobial cost per patient was reduced by 52% ($P < 0.0001$) in all patients with lower respiratory tract infections and by 36% ($P = 0.01$) in patients with acute exacerbations of COPD. Clinical and laboratory outcomes were similar in the two groups and favourable in 235 out of 243 studied (97%).

Comment

In this study procalcitonin guidance substantially reduced antibiotic use in lower respiratory tract infections and withholding antimicrobial treatment did not compromise outcome. In view of the current overuse of antimicrobial therapy in often self-limiting acute respiratory tract infections, treatment based on procalcitonin measurement could have important clinical and financial implications.

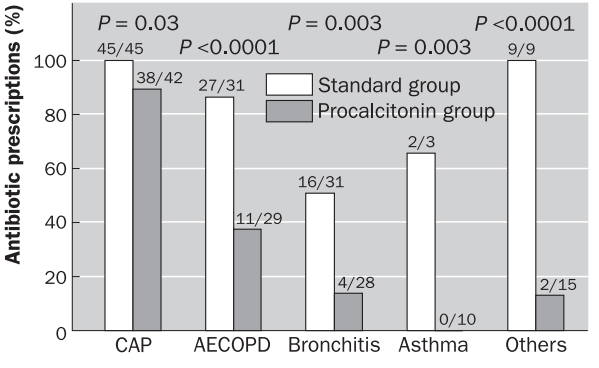

Fig. 4.3 Antibiotic prescriptions in different subgroups of lower respiratory tract infection comparing the standard and procalcitonin groups. CAP, community-acquired pneumonia; AECOPD, acute exacerbations of COPD. Source: Christ-Crain *et al*. (2004).

Long-acting bronchodilators

In the GOLD guidelines |**1**|, long-acting bronchodilators are recommended in patients with moderate and severe COPD (FEV_1 <80% predicted), which can prolong the time to the next exacerbation and improve health status |**4,5**|. The two commonly used long-acting β_2-agonists used are salmeterol and formoterol fumarate, which are both administered twice daily and have the advantage over short-acting bronchodilators

in being more effective and convenient than treatment with short-acting bronchodilators, but are more costly. Tiotropium is a long-acting anticholinergic and has been found to be a useful long-acting bronchodilator in patients with severe COPD (mean FEV_1 <40% predicted) with improved lung function, symptoms, health-related quality of life and a reduced number of COPD exacerbations |**6**|. Its long half-life allows once-daily prescription, which should improve compliance.

For an individual patient the effects of any agent can be very variable. There certainly seems justification that long-acting bronchodilators should be tried in patients with severe COPD (FEV_1 <50% predicted) for a trial of 3–6 months. At the end of the trial period there should be a look at both subjective and objective improvements, along with the side effects. If overall there is a positive effect, then consideration can be given to using the agent in the long term. There may be added efficacy in combining a long-acting anticholinergic with long-acting β_2-agonists, but further studies are needed in order to address this.

The next two papers evaluate the mechanisms for the benefit of these long-acting bronchodilators and look at their effect on lung hyperinflation. The final paper in this section explores whether long-acting inhaled anticholinergic therapy improves sleep oxygen saturation in patients with COPD.

Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD

O'Donnell DE, Fluge T, Gerken F, *et al*. *Eur Respir J* 2004; **23**: 832–40

BACKGROUND. The aim of this study was to test the hypothesis that the use of tiotropium, a long-acting anti-cholinergic bronchodilator, would be associated with sustained reduction in lung hyperinflation and would thereby improve exertional dyspnoea and exercise performance in patients with COPD. A randomized, double-blind, placebo-controlled, parallel group study was conducted in 187 patients (mean ± SE FEV_1 44 ± 13% predicted). Ninety-six patients received 18 μg tiotropium and 91 patients received placebo once daily for 42 days. Spirometry, plethysmographic lung volumes, cycle exercise endurance and exertional dyspnoea intensity at 75% of each patient's maximal work capacity were compared.

INTERPRETATION. On day 42 the use of tiotropium was associated with the following effects at pre-dose (trough response) and post-dose measurements (peak response), compared with placebo: FEV_1 increased (trough response 0.12 l ± 0.03, P <0.001; peak response 0.22 l ± 0.04, P <0.0001); FVC increased (trough response 0.25 l ± 0.06, P <0.001; peak response 0.43 l ± 0.06, P <0.001); inspiratory capacity (IC) increased (trough response 0.10 l ± 0.05, P <0.05; peak response 0.24 l ± 0.06, P <0.001); residual volume decreased (trough response –0.36 l ± 0.09, P <0.001; peak response –0.56 l ± 0.10, P <0.0001); functional residual capacity decreased (trough response –0.30 l ± 0.08, P <0.001; peak response –0.45 l ± 0.08, P <0.0001). Tiotropium increased post-dose exercise endurance time by 105 ± 40 s (21% difference; P <0.001) compared with placebo on day 42 (Fig. 4.4). At a standardized time near the end of exercise

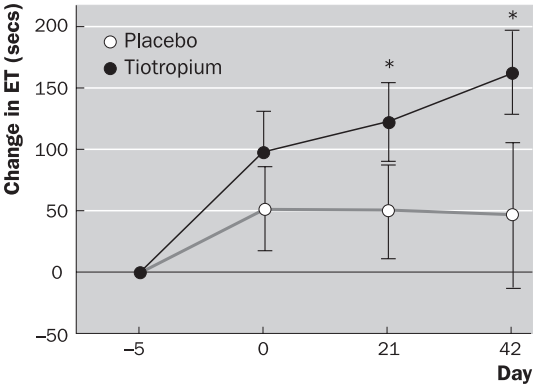

Fig. 4.4 Changes in constant load exercise endurance time (ET) from baseline (day –5) for placebo and tiotropium. Data are presented as means ± SEM. * $P < 0.05$ between groups. ET is in seconds. Source: O'Donnell *et al*. (2004).

(isotime) at day 42 IC increased (0.18 l ± 0.05; $P < 0.001$), tidal volume increased (0.11 l ± 0.03; $P < 0.001$) and minute ventilation increased (3.0 l/min ± 0.8; $P < 0.001$), whilst dyspnoea decreased by 0.9 ± 0.3 Borg scale units ($P < 0.01$).

Comment

Tiotropium is a once-daily anticholinergic and has its effect through prolonged M3 muscarinic receptor antagonism. The use of tiotropium in this study was associated with sustained reductions in lung hyperinflation at rest and during exercise. The resultant increases in IC permitted greater expansion of tidal volume and contributed to improvements in both exertional dyspnoea and exercise endurance.

Another, smaller study by Celli and colleagues |**7**| evaluated the improvement in resting IC and hyperinflation with tiotropium in COPD patients with increased static lung volumes. Eighty-one patients with stable COPD were randomized to tiotropium or placebo in a 4-week randomized, double-blind study. The mean baseline FEV_1 was 1.12 l (43% predicted). The mean differences (tiotropium–placebo) in FEV_1 trough (morning before drug), peak and area under the curve over 3-h values at week 4 were 0.16, 0.22 and 0.22 l respectively ($P < 0.01$ for all); IC 0.22, 0.35 and 0.30 l respectively ($P < 0.01$ for all), and a reduction in thoracic gas volume 0.54, 0.60 and 0.70 l respectively ($P < 0.01$ for all). Like the previous study, tiotropium led to improvements in IC and reductions in thoracic gas volume, which may be one of the mechanisms for improvement in dyspnoea and exercise capacity.

Effect of salmeterol on respiratory muscle activity during exercise in poorly reversible COPD

Man WD, Mustfa N, Nikoletou D, *et al*. *Thorax* 2004; **59**: 471–6

BACKGROUND. Some patients with irreversible COPD experience subjective benefit from long-acting bronchodilators without change in FEV_1. Dynamic hyperinflation is an important determinant of exercise-induced dyspnoea in COPD. The authors hypothesized that long-acting bronchodilators could improve symptoms by reducing dynamic hyperinflation to reduce the work of the respiratory muscles. Sixteen patients with COPD (mean FEV_1 ± SD, 31.1% ± 3.9 predicted) with fixed airflow obstruction (<10% improvement in FEV_1 following a bronchodilator challenge) were recruited into a randomized, double-blind, placebo-controlled crossover study of salmeterol (50 μg twice a day). Treatment periods were 2 weeks with a 2-week washout period. Primary outcome measures were end-exercise isotime transdiaphragmatic pressure–time product and dynamic hyperinflation as measured by IC.

INTERPRETATION. Salmeterol had no significant effect on FEV_1, vital capacity (VC) or FEV_1/VC. Resting hyperinflation was reduced, as evidenced by a reduced residual volume/total lung capacity (RV/TLC) ratio (%), with a mean difference of –2.6 (95% CI –4.9 to –0.3; $P = 0.03$) and an increased IC, with a mean difference of 0.16 l (95% CI 0.02 to 0.32; $P = 0.03$). Salmeterol versus placebo significantly reduced the transdiaphragmatic pressure–time product (294.5 versus 348.6 cm H_2O/s per min; $P = 0.03$), dynamic hyperinflation (0.22 versus 0.33 l; $P = 0.002$) and Borg scores during the endurance treadmill walk (3.78 versus 4.62; $P = 0.02$). There was no significant change in exercise endurance time. Improvements in isotime Borg score were significantly correlated to changes in tidal volume/oesophageal pressure swings ($r = 0.6$; $P = 0.01$), end-expiratory lung volume ($r = 0.58$; $P = 0.02$) and IC ($r = 0.56$; $P = 0.02$), but not pressure–time products.

Comment

Dynamic hyperinflation is an important determinant of exertional breathlessness. During exercise, increased airway resistance and expiratory airflow limitation increases end-expiratory lung volume, which results in intrinsic positive end-expiratory pressure. This leads to an increase in the amount of work needed for breathing and places the diaphragm and other inspiratory muscles at a mechanical disadvantage. The aim with bronchodilator therapy is to reduce airway resistance and dynamic hyperinflation in order to unload the respiratory muscles by reducing the inspiratory load and work of breathing.

This study shows that, despite the non-reversibility of spirometric parameters, long-acting bronchodilators can cause both symptomatic and physiological improvement during exercise in severe COPD by reducing dynamic hyperinflation and respiratory muscle activity.

Long-acting inhaled anticholinergic therapy improves sleeping oxygen saturation in COPD

McNicholas WT, Calverley PM, Lee A, Edwards JC; Tiotropium Sleep Study in COPD Investigators. *Eur Respir J* 2004; **23**: 825–31

BACKGROUND. Oxygen desaturation occurs during sleep in severe COPD, especially during rapid eye movement (REM) sleep, due to hypoventilation and ventilation–perfusion mismatching, but the possible contribution of airflow limitation is unclear. In a randomized, placebo-controlled, double-blind study of severe stable COPD patients, the authors compared 4 weeks of treatment with a long-acting inhaled anticholinergic agent (tiotropium) taken in the morning (tiotropium-AM) or in the evening (tiotropium-PM) on sleeping arterial oxygen saturation (SaO_2) and sleep quality. Overnight polysomnography was performed at baseline and after 4 weeks of treatment.

INTERPRETATION. Ninety-five patients with awake resting arterial oxygen tension 9.98 kPa (75 mmHg) or less were randomized; their mean age was 66.4 years and mean ± SD FEV_1 was 32 ± 12% predicted. Eighty patients completed the study, of whom 56 fulfilled the polysomnographic criterion of at least 2 h of sleep in both sleep study nights. Analysis of data for the pooled tiotropium group revealed that tiotropium improved pre-sleep FEV_1 (190 ml; 95% CI 70–310; $P = 0.002$), pre-sleep FVC (310 ml; 95% CI 40–580; $P = 0.03$) and post-sleep FEV_1 (170 ml; 95% CI 90–260; $P = 0.0001$) and post-sleep FVC (360 ml; 95% CI 150–570; $P = 0.001$). The tiotropium-AM and tiotropium-PM groups both had higher SaO_2 during REM sleep than subjects receiving placebo (tiotropium-AM, +2.41%; 95% CI 0.48–4.33; $P = 0.02$; tiotropium-PM, +2.42%; 95% CI 0.41–4.43; $P = 0.02$). Both pooled and tiotropium-PM groups had higher SaO_2 during total sleep time (pooled, +2.49%; 95% CI 0.02–4.93; $P < 0.05$; tiotropium-PM, +3.06%; 95% CI 0.23–5.91; $P < 0.05$). End-of-treatment FEV_1 correlated with SaO_2 during REM sleep, but tiotropium did not change sleep quality.

Comment

Sustained anticholinergic blockade with tiotropium improved oxygen saturation during sleep in patients with severe COPD independently of whether tiotropium was taken in the morning or evening. These effects were accompanied by improvements in pre- and post-sleep spirometry but there was no significant change in subjective or objective sleep quality.

Overall, tiotropium has been found to be a useful long-acting bronchodilator in patients with severe COPD (mean FEV_1 <40% predicted), giving improvement in lung function, symptoms and health-related quality of life and a reduced number of COPD exacerbations. Its long half-life allows once-daily prescription, which should improve compliance. From these studies, the improvements with tiotropium include bronchodilatation, a reduction in lung hyperinflation and perhaps a contribution from the improvement in nocturnal oxygenation.

Inhaled corticosteroids

Inhaled corticosteroids are recommended in patients with severe COPD with an FEV_1 less than 50% of predicted that have recurrent exacerbations, with the aim of reducing exacerbation frequency and attenuating the decline in health status |**1,8,9**|. The next two papers review the role of inhaled corticosteroids in systemic inflammation in COPD and their role in exacerbations and health-related quality of life.

Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease

Sin DD, Lacy P, York E, Man SF. *Am J Respir Crit Care Med* 2004; **170**: 760–5

BACKGROUND. Systemic inflammation is present in COPD, and this has been linked to cardiovascular morbidity and mortality. The aim of this study was to determine the effects of oral and inhaled corticosteroids on serum markers of inflammation in patients with stable COPD. Forty-one patients with mild to moderate COPD were recruited. After 4 weeks during which inhaled corticosteroids were discontinued if the patient was previously taking them, patients were assigned to fluticasone (500 μg twice a day), oral prednisolone (30 mg/day) or placebo over 2 weeks, followed by 8 weeks of fluticasone at 500 μg twice a day and another 8 weeks of fluticasone at 1000 μg twice a day.

INTERPRETATION. There were 15 patients in the fluticasone group (mean ± SD FEV_1 of 56 ± 20% predicted), 14 in the oral prednisolone group (mean FEV_1 of 47 ± 16% predicted) and 12 in the placebo group (mean FEV_1 of 61 ± 17% predicted). C-reactive protein (CRP) levels increased by 24.8% (95% CI 1.7–44.4%) from visit 1 to 2 (Fig. 4.5). This is when the inhaled steroids were withdrawn, if the patient was previously taking them, prior to starting the 2-week trial of fluticasone, oral prednisolone or placebo. CRP increased by 71% (95% CI 16–152%) in patients previously on inhaled steroids, whereas there was no significant change in CRP in those not on inhaled steroids from visit 1 to 2. At the time of randomization (visit 2), the serum CRP and cytokines (monocyte chemoattractant protein [MCP-1] and interleukin 6 [IL-6]) were similar across the three groups. Two weeks of treatment with inhaled fluticasone reduced CRP levels by 50% (95% CI 9–73%) and prednisolone reduced it by 63% (95% CI 29–81%); no significant changes were observed with the placebo (Fig. 4.5). Two weeks of treatment with inhaled fluticasone reduced IL-6 levels by 26% (95% CI 3–44%; $P < 0.05$) but had no effect on MCP-1, and both prednisolone and placebo had no significant effect on IL-6 or MCP-1. In the open-label phase of the study, an additional 4 and 8 weeks of fluticasone were both associated with CRP levels that were lower than those at baseline (a 29% reduction [95% CI 7–46%] at 8 weeks; $P < 0.05$).

Comment

In this study withdrawal of inhaled corticosteroids led to an increase in serum CRP, whereas reintroduction led to a significant reduction in CRP levels and the reductions

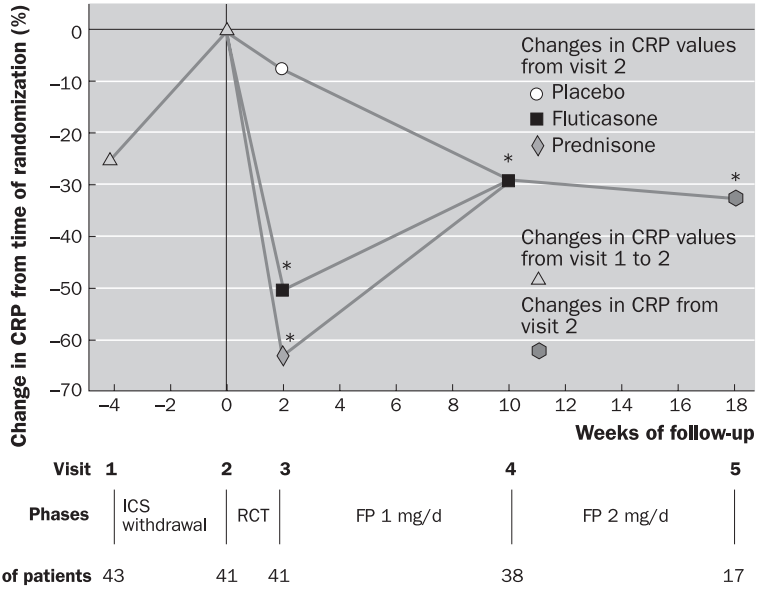

Fig. 4.5 Changes in C-reactive protein (CRP) levels across the study period. *Circles* represent changes in CRP values from visit 2 (i.e. time of randomization) in those assigned to placebo. *Squares* represent changes in CRP values from visit 2 in those assigned to fluticasone. *Diamonds* represent changes in CRP values from visit 2 in those assigned to prednisone. *Triangles* represent changes in CRP values from visit 1 to visit 2. *Hexagons* represent changes in CRP from visit 2. $*P < 0.05$ compared with visit 2 values. FP, fluticasone propionate; ICS, inhaled corticosteroid; RCT, randomized controlled trial. Source: Sin *et al*. (2004).

could be mainly sustained over a 4-month period. Oral prednisolone also reduced CRP levels.

The source of circulating CRP is the liver. The downregulation of IL-6 may be one of the mechanisms of the downregulation of CRP, but this is not the complete answer as oral prednisolone had no effect on IL-6 levels. IL-6 is a major signalling cytokine for CRP expression by hepatocytes and also stimulates other acute-phase proteins.

Both inhaled and oral corticosteroids are effective in reducing serum CRP levels in patients with COPD. Long-term, large multicentre trials are needed to determine whether inhaled corticosteroids can modify cardiovascular outcomes in COPD.

Impact of preventing exacerbations on deterioration of health status in COPD

Spencer S, Calverley PM, Burge PS, Jones PW. *Eur Respir J* 2004; **23**: 698–702

BACKGROUND. Exacerbations of COPD are associated with worse health status. The Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study showed that treatment with fluticasone propionate reduced exacerbation frequency and the rate of deterioration in health status compared with placebo. The present study analysed these data to test whether the effect of fluticasone propionate on health status was attributable to its effect on exacerbations. Rates of deterioration in SGRQ total score were obtained for 613 patients with moderate to severe COPD followed for a maximum of 3 years. Exacerbation rates were skewed and could not be normalized; therefore, patients were stratified into three exacerbation groups: none, infrequent (<1.65 exacerbations per year) and frequent (>1.65 exacerbations per year).

INTERPRETATION. There were 91 patients with no exacerbations (mean ± SD FEV_1 55 ± 15% predicted), 285 with infrequent exacerbations, with a mean of FEV_1 53 ± 15% predicted, and 235 with frequent exacerbations, with a mean of FEV_1 45 ± 13% predicted. Frequent exacerbations were independently associated with a worse baseline SGRQ score (P <0.0001) and a faster rate of deterioration in health status (P = 0.0003) (Fig. 4.6). Exacerbation frequency and rate of decline in FEV_1 were independently related to the rate of deterioration in SGRQ score.

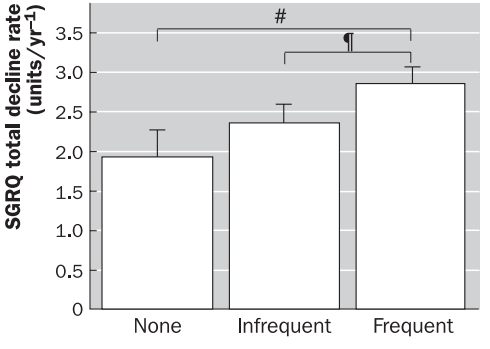

Fig. 4.6 Deterioration in St Georges Respiratory Questionnaire (SGRQ) total score by exacerbation category. Data are presented as mean and 95% CI (bars). Higher scores indicate faster deterioration in health. #P <0.0001; ¶P =0.004. No exacerbations, n = 91; infrequent (<1.65 exacerbations/year), n = 285; frequent (>1.65 exacerbations per year), n = 235. Source: Spencer *et al*. (2004).

Comment

Statistical modelling showed the beneficial effect of fluticasone propionate on the attenuation of deterioration in health status to be largely due to its effect in reducing exacerbation frequency.

Combination of a long-acting β_2-agonist with an inhaled corticosteroid

Although these medications can be provided singly, the use of multiple inhalers can result in poor compliance. Combination inhalers are in vogue and will hopefully improve compliance by simplifying the treatment regimen.

Studies to date have shown that combination therapy with an inhaled corticosteroid and long-acting β_2-agonist for 1 year improves symptoms and FEV_1 and lessens exacerbation rates, and that there is a trend for improvement in health status in patients with moderate to severe COPD |**10,11**|.

The next paper describes a 1-year study that evaluated the effectiveness of the combination of a long-acting β_2-agonist with an inhaled corticosteroid. The primary end-points were time to first exacerbation and change in post-medication FEV_1.

Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease

Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H.
Eur Respir J 2003; **22**: 912–19

BACKGROUND. COPD patients (*n* = 1022; mean ± SD pre-bronchodilator FEV_1 36 ± 10% predicted) initially received formoterol (9 μg twice daily) and oral prednisolone (30 mg once daily) for 2 weeks. After this time, patients were randomized to twice-daily inhaled combination (budesonide/formoterol) 320/9 μg (*n* = 254), twice daily budesonide 400 μg (*n* = 257), twice daily formoterol 9 μg (*n* = 255) or placebo (*n* = 256) for 12 months.

INTERPRETATION. Post-medication FEV_1 improved by 0.21 l and health-related quality of life (using the SGRQ) by 4.5 units after run-in of formoterol (9 μg twice daily) and oral prednisolone (30 mg once daily) for 2 weeks (an improvement of 4 units in the SGRQ is a clinically significant difference). Fewer patients receiving the combination (budesonide/formoterol) withdrew from the study than those receiving budesonide, formoterol or placebo ($P < 0.05$). Patients receiving the combination had a longer time to first exacerbation than patients on all other treatments ($P < 0.05$) (median 254 days for patients receiving the budesonide/formoterol combination versus 96 days for patients on placebo; $P = 0.006$). The mean exacerbation rate per patient per year was 1.38 with the combination, which was significantly lower ($P < 0.05$) than the rates for patients on the formoterol treatment (1.85) and patients receiving placebo (1.8), but not significantly different from the rate for patients receiving budesonide (1.6). Neither budesonide nor

formoterol affected the time to first exacerbation or the mean exacerbation rate compared with placebo. Over 12 months, patients receiving the budesonide/formoterol combination maintained a higher FEV_1 percentage of baseline (Fig. 4.7) and clinically relevant improvements in SGRQ. All active treatments improved the total SGRQ score versus placebo ($P < 0.05$). At 12 months the group receiving the combination showed a greater improvement in the total SGRQ score than the groups receiving the individual components (budesonide, $P = 0.001$; formoterol, $P = 0.01$) or placebo ($P < 0.001$). The differences in SGRQ at 12 months were –7.5, –3.0 and –4.1 versus placebo for patients receiving the combination, budesonide and formoterol respectively (a fall of 4 units represents a clinically significant improvement).

Comment

The combination of budesonide/formoterol was more effective than either individual component with respect to both primary variables (time to first exacerbation and change in post-medication FEV_1). The combination of budesonide/formoterol in a single inhaler (Symbicort) maintains the benefit of treatment optimization by stabilizing lung function and delaying exacerbations more effectively than either component drug alone or placebo.

Overall, the treatment with combination inhalers should be reserved for patients with moderate to severe COPD, and the patients most likely to benefit are probably

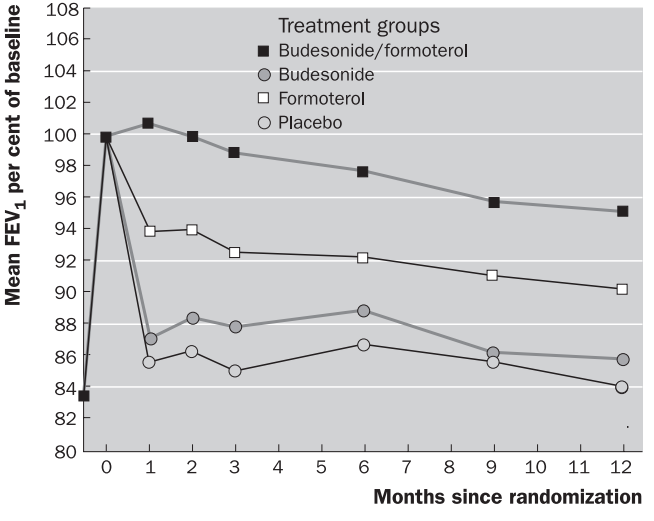

Fig. 4.7 Changes in mean forced expiratory volume in one second (FEV_1) in the four treatment groups from randomization to the average of all available measurements during the 12-month treatment period. Budesonide/formoterol versus budesonide, $P < 0.001$; budesonide/formoterol versus formoterol, $P = 0.002$; budesonide versus placebo, $P = 0.145$; formoterol versus placebo, $P < 0.001$; budesonide/formoterol versus placebo, $P < 0.001$. Source: Calverley *et al*. (2003).

those with moderate to severe COPD with frequent exacerbations. Although these studies indicated a significant group response, individual patients may not show a significant response. A trial of 3–12 months is indicated for determining whether there are any subjective and/or objective improvements or any adverse effects. If there is improvement continuation may be indicated, but if there is no improvement the treatment should be reduced or stopped, but with careful monitoring to check that there is no rebound worsening of symptoms after reduction or withdrawal of treatment.

The GOLD |**1**| and national clinical guideline |**2**| recommends influenza vaccination in all patients with COPD. The next paper explores the role of influenza vaccination in such patients in preventing influenza-related acute respiratory illness and overall acute respiratory illness, including the common cold, influenza-like illness, acute exacerbation of COPD and pneumonia.

Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: a randomized controlled study

Wongsurakiat P, Maranetra KN, Wasi C, Kositanont U, Dejsomritrutai W, Charoenratanakul S. *Chest* 2004; **125**: 2011–20

Background. The aim of this study was to determine the effectiveness of influenza vaccination in preventing influenza-related acute respiratory illness (ARI) and overall ARI, including the common cold, influenza-like illness, acute exacerbation of COPD and pneumonia in patients with COPD, and its relationship to the degree of airflow obstruction. This was a randomized, double-blind, placebo-controlled trial from June 1997 to November 1998 at a single university hospital. One hundred and twenty-five patients with COPD were stratified, on the basis of their FEV_1, as having mild ($FEV_1 \geq 70\%$ predicted), moderate (FEV_1 50–69% predicted) and severe ($FEV_1 < 50\%$ predicted) COPD. Within each group, they were randomized to the vaccine group (62 patients who received purified, trivalent, split-virus vaccine) or the placebo group (63 patients). Measurements were the number of episodes and the severity of total ARI (classified as outpatient treatment, hospitalization, and requirement for mechanical ventilation) and the number of episodes and severity of influenza-related ARI.

Interpretation. The incidence of influenza-related ARI was 28.1 per 100 person-years in the placebo group and 6.8 per 100 person-years in the vaccine group (relative risk [RR] 0.24; $P = 0.005$, vaccine effectiveness, 76%). The incidences were 28.2, 23.8 and 31.2 per 100 person-years respectively in the patients with mild, moderate, and severe COPD in the placebo group and 4.5, 13.2, and 4.6 per 100 person-years in the patients with mild, moderate and severe COPD in the vaccine group. For mild COPD the vaccine effectiveness was 84% (RR 0.16; $P = 0.06$). For moderate COPD the vaccine effectiveness was 45% (RR 0.55; $P = 0.5$). For severe COPD the vaccine effectiveness was 85% (RR 0.15; $P = 0.04$). Bivariate analysis revealed that the effectiveness of influenza

vaccination was not modified by the severity of COPD, comorbid diseases, age, gender or current smoking status. There was no difference in the incidence or severity of total ARI between the placebo group and the vaccine group (RR for common cold was 1.05; 95% CI 0.67–1.60; $P = 0.8$; RR for an acute exacerbation of COPD was 0.92; 95% CI 0.67–1.3; $P = 0.6$; and RR for pneumonia was 0; 95% CI 0–2.5; $P = 0.1$).

Comment

This was a small study that supports the use of influenza vaccination in reducing influenza-related ARI. Influenza vaccination did not, however, reduce the incidence of other acute respiratory illnesses, including the common cold, acute exacerbations of COPD or pneumonia. This study supports the use of influenza vaccination in patients with COPD. Larger studies are needed to determine whether influenza vaccination has an impact on other acute respiratory illnesses.

The next two papers explore the use of an iron lung as opposed to conventional mechanical ventilation and the value of non-invasive intermittent positive pressure ventilation for patients that develop respiratory failure after extubation.

Iron lung versus conventional mechanical ventilation in acute exacerbation of COPD

Corrado A, Ginanni R, Villella G, *et al*. *Eur Respir J* 2004; **23**: 419–24

BACKGROUND. The aim of this randomized study was to compare the effects of iron lung ventilation (ILV) with those of invasive mechanical ventilation (IMV) in patients with acute respiratory failure due to exacerbation of COPD. Patients were eligible if the arterial carbon dioxide tension ($PaCO_2$) was greater than 9.3 kPa and pH was less than 7.25 while breathing room air or during oxygen therapy. Forty-four patients with acute respiratory failure were assigned either to ILV (22 patients) or IMV (22 patients). The primary end-points were the improvement in gas exchange and complications related to mechanical ventilation.

INTERPRETATION. On admission, the ILV and IMV groups did not differ significantly ($P > 0.1$) in age (mean ± SD, 72.2 ± 6.1 and 74.5 ± 7.5 years respectively), simplified acute physiology core II (mean 32 and 35 respectively), arterial oxygen tension (PaO_2)/inspiratory oxygen fraction (FiO_2) (mean 192.0 ± 59.8 and 172.0 ± 61.7 respectively), $PaCO_2$ (mean 12.8 ± 2.1 and 13.3 ± 2.4 kPa respectively) and pH (mean 7.20 ± 0.04 and 7.20 ± 0.04 respectively). Compared with baseline, ILV and IMV induced a similar and significant improvement in PaO_2/FiO_2, $PaCO_2$ and pH after 1 h of treatment and at the end of treatment, when ventilation was discontinued. Major complications tended to be more frequent in patients treated with IMV than in those treated with ILV (27.3 vs 4.5%), although the difference failed to reach conventional statistical significance ($P = 0.09$). This was, however, a small study and larger studies are needed to address this. Mortality rate was, however, similar (27.3% with IMV vs 18.2% with ILV). The ventilator-free days and the length of hospital stay were significantly lower in the ILV than in the IMV group (Table 4.3).

Table 4.3 Clinical outcomes in patients treated with iron lung ventilation (ILV) and invasive mechanical ventilation (IMV)

	ILV	IMV	*P*-value
Patients *n*	22	22	
Deaths in ICU	4/22 (18.2)	5/22 (22.7)	1.0
Deaths in hospital	4/22 (18.2)	6/22 (27.3)	0.719
Duration of MV* days	2 (1–6)	7 (1–26)	0.0001
Rate of endotracheal intubation	4/22 (18.2)		
Rate of tracheostomy	1/22 (4.5)	5/22 (22.7)	0.188
Length of hospital stay* (days)	15 (6–55)	25 (11–65)	0.007

Data are presented as n/total n (%) or median (range) unless otherwise stated. ICU, intensive care unit; MV, mechanical ventilation.
* In survivors.
Source: Corrado *et al*. (2004)

Comment

This study suggests that ILV is as effective as IMV in improving gas exchange in COPD patients with acute respiratory failure, and is associated with a tendency towards a lower rate of major complications. The reduced complications with ILV may be due to the avoidance of endotracheal intubation reducing infectious complications and as ILV can be administered intermittently weaning can be less problematic. This small study offers potential benefits with ILV compared with IMV. A large multi-centre controlled trial would be welcome comparing the outcomes of ILV with IMV.

Non-invasive positive-pressure ventilation for respiratory failure after extubation

Esteban A, Frutos-Vivar F, Ferguson ND, *et al*. *N Engl J Med* 2004; **350**: 2452–60

BACKGROUND. The need for reintubation after extubation and discontinuation of mechanical ventilation is not uncommon and is associated with increased mortality. Non-invasive positive-pressure ventilation (NIPPV) has been suggested as a promising therapy for patients with respiratory failure after extubation, but a single-centre, randomized trial recently found no benefit |12|. The authors conducted a multicentre, randomized trial to evaluate the effect of NIPPV on mortality in this clinical setting. Patients in 37 centres in eight countries who were electively extubated after at least 48 h of mechanical ventilation and who had respiratory failure within the subsequent 48 h were randomly assigned to either NIPPV by face mask or standard medical therapy.

INTERPRETATION. A total of 221 patients with similar baseline characteristics had been randomly assigned to either NIPPV (114 patients) or standard medical therapy (107 patients) when the trial was stopped early, after an interim analysis. There was a mixture of patients, including patients with pneumonia, post-operative respiratory failure, sepsis, trauma, cardiac

failure, adult respiratory distress syndrome, neuromuscular disease, asthma, COPD and others (COPD accounted for 10% of the patients; $n = 23$). There was no difference between the NIPPV group and the standard therapy group in the need for reintubation (rate of reintubation, 48% in both groups; RR in the NIPPV group, 0.99; 95% CI 0.76–1.30) and there was a similar interval between extubation and respiratory failure (median 9 h in both groups). The median time from respiratory failure to reintubation was longer in the NIPPV group (12 h vs 2 h 30 m in the standard therapy group; $P = 0.02$). The rate of death in the intensive care unit was higher in the NIPPV group than in the standard therapy group, with a RR of 1.78 (95% CI 1.03–3.20; $P = 0.048$). In the NIPPV group the mortality rate was 25% (95% CI 17–34%), which was higher ($P < 0.05$) than in the standard therapy group (14%; 95% CI 8–23%).

Comment

Evidence-based guidelines recommend a trial of spontaneous breathing to determine whether mechanical ventilation can be discontinued. Even with this approach reintubation rates vary from 13 to 19%. It is recognized and not unexpected that patients who require reintubation have a significantly higher mortality than those who are successfully extubated on the first attempt.

NIPPV does not prevent the need for reintubation, and increased the mortality in unselected patients who had respiratory failure after extubation. It is possible that the delay in reintubation was the reason for the significant increase in the risk of death.

This is an important study that highlights that NIPPV after extubation can be potentially harmful by prolonging the time to reintubation. The study, however, does not address whether this is applicable to COPD patients as the cohort of COPD patients was too small in this study. Large multicentre studies in COPD patients are needed to address this.

Pulmonary rehabilitation has been proved to be an effective treatment for COPD, independently of its severity. It can reduce symptoms, improve exercise capacity, improve health-related quality of life and provide psychosocial benefits. A pulmonary rehabilitation programme ideally should be multidisciplinary, with components including exercise training, nutrition counselling and education, and should run for at least 2 months. Longer programmes are likely to lead to more effective results. However, the benefits that follow rehabilitation tend to wane over a 2-year period.

The following papers explore the role of oxygen therapy during and after exercise, the benefits of inhaled furosemide and testosterone, the role of inspiratory muscle training, and finally the role of community rehabilitation after hospital admission with an exacerbation of COPD.

Benefits of supplemental oxygen in exercise training in non-hypoxemic chronic obstructive pulmonary disease patients

Emtner M, Porszasz J, Burns M, Somfay A, Casaburi R. *Am J Respir Crit Care Med* 2003; **168**: 1034–42

BACKGROUND. The aim of this study was to determine whether non-hypoxaemic COPD patients undergoing exercise training while breathing supplementary oxygen achieve higher intensity and therefore improve their exercise capacity more than patients breathing air. A double-blind trial was performed that involved 29 non-hypoxaemic patients (mean 67 years, exercise SaO_2 ≥88%) with COPD (FEV_1 <50% predicted with a mean FEV_1 36% predicted). All exercised on cycle ergometers for 45 min three times per week for 7 weeks with high-intensity targets. During exercise, they received oxygen (3 l/min) (*n* = 14) or compressed air (3 l/min) (*n* = 15).

INTERPRETATION. Both groups had greater exercise tolerance after training. However, the oxygen-trained group increased the training work rate more rapidly than the air-trained group (Fig. 4.8). The mean ± SD work rate in the oxygen-trained group during the last week of training was 62 ± 19 W, which was 138% of the pretraining peak work rate, and in the air-trained group it was 52 ± 22 W, which was 96% of the pretraining peak work rate (P <0.01). After training, endurance in constant work rate tests increased more in the

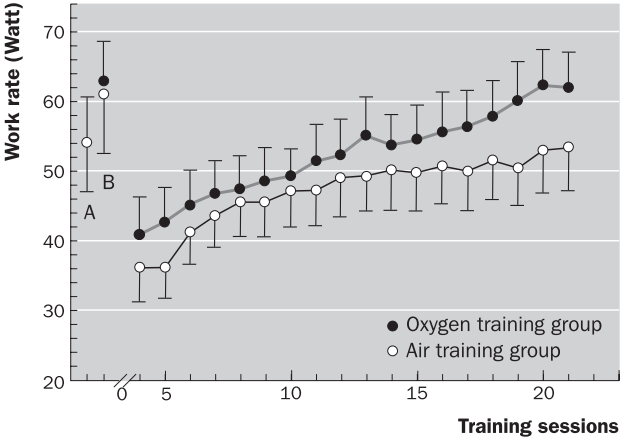

Fig. 4.8 Training work rate (watts) achieved during the last 6 weeks of training. A and B represent the peak work rate in the pretraining incremental exercise test breathing air (A) (the same peak work rate for both groups) and 30% oxygen (B). Values and error bars represent the mean and SEM. Despite nearly identical pre-training exercise tolerance, the oxygen-training group was able to exercise at a higher work rate throughout the training programme, and the work rate increased more rapidly than in the air-training group. Source: Emtner *et al*. (2003).

oxygen-trained group (14.5 ± 6.2 min) than in the air-trained group (10.5 ± 6.0 min) (P <0.05). At isotime (response to identical exercise durations at identical work rates) the breathing rate decreased by four breaths per minute in the oxygen-trained group and by one breath per minute in the air-trained group (P = 0.001).

Comment

This was an interesting small study supporting the use of supplementary oxygen in non-hypoxaemic patients (even with exercise) with severe COPD (FEV_1 <50% predicted) undergoing exercise training. With supplementary oxygen training intensity could be kept at a higher level, with improvements in endurance capacity and breathing pattern.

Effect of oxygen on recovery from maximal exercise in patients with chronic obstructive pulmonary disease

Stevenson NJ, Calverley PM. *Thorax* 2004; **59**: 668–72

BACKGROUND. The aim of this study was to determine whether oxygen given after maximal exercise reduced the degree of dynamic hyperinflation and so reduced the perception of breathlessness. Eighteen patients with moderate to severe COPD (mean ± SD FEV_1 40.2 ± 15.9% predicted) performed maximal symptom-limited exercise on a cycle ergometer. During recovery they received either air or oxygen at identical flow rates in a randomized, single-blind, crossover design. No patient was hypoxaemic at rest and none desaturated during exercise to SaO_2 less than 88%. Inspiratory capacity, breathing pattern data, dyspnoea intensity and leg fatigue scores were collected at regular intervals during recovery. At a subsequent visit patients underwent a similar protocol but with a face mask *in situ* to eliminate the effects of instrumentation.

INTERPRETATION. When oxygen was given, the time taken for resolution of dynamic hyperinflation was significantly shorter (mean ± SD difference between air and oxygen 6.61 ± 1.65 min; 95% CI 3.13–10.09; P = 0.001). Oxygen did not, however, reduce the perception of breathlessness during recovery, nor did it affect the time taken to return to baseline dyspnoea scores in either the instrumented or the non-instrumented state (Fig. 4.9).

Comment

Oxygen reduces the degree of dynamic hyperinflation during recovery from exercise but does not make patients feel less breathless than breathing air. This suggests that factors other than lung mechanics may be important during recovery from exercise, or it may reflect the cooling effect of both air and oxygen.

A study by Nandi *et al.* |**13**| demonstrated that short burst oxygen therapy either before or after exercise in patients with severe COPD with oxygen desaturation on exercise resulted in neither subjective nor objective benefits.

Short burst oxygen therapy should only be prescribed for patients if they have shown subjective or objective evidence of benefit with oxygen on exercise testing.

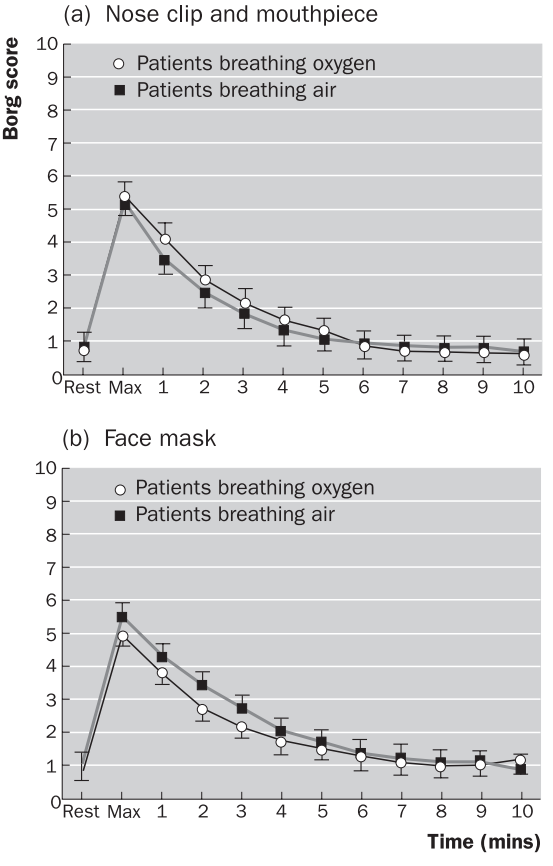

Fig. 4.9 Borg score for breathlessness before and after exercise in (a) patients breathing oxygen or air with nose-clip and mouthpiece and (b) patients breathing from a face mask. Source: Stevenson and Calverley (2004).

Effects of inhaled furosemide on exertional dyspnoea in chronic obstructive pulmonary disease

Ong KC, Kor AC, Chong WF, Earnest A, Wang YT. *Am J Respir Crit Care Med* 2004; **169**: 1028–33

BACKGROUND. The aim of this study was to investigate the effects of inhaled furosemide on the sensation of dyspnoea produced during exercise in patients with stable moderate to severe COPD. In a double-blind, randomized, crossover study the authors compared the effect of inhaled furosemide (40 mg) with that of placebo on dyspnoeic sensation, the primary outcome measure, during exercise testing.

Spirometry and incremental and constant load exercise testing were performed immediately after inhalation of placebo or furosemide on two separate days in 19 patients with moderate to severe COPD (mean FEV_1 ± SD 42.1 ± 16.3% predicted). Subjects were asked to rate their sensation of respiratory discomfort using a 100-mm visual analogue scale.

INTERPRETATION. There was a significant but small improvement in mean FEV_1 and FVC after inhalation of furosemide ($P = 0.038$ and 0.005, respectively) but not after placebo. Before furosemide the mean FEV_1 was 1.05 ± 0.39 l and after furosemide the FEV_1 was 1.10 ± 0.42 l. Before furosemide the mean FVC was 2.14 ± 0.62 l and after furosemide the FVC was 2.34 ± 0.63 l. At a standardized exercise time during constant load exercise testing but not during incremental exercise, the mean dyspnoeic visual analogue scale score was lower after inhalation of furosemide compared with placebo (33.7 ± 25.2 and 42.4 ± 24.0 mm respectively; $P = 0.014$) (Fig. 4.10). There were no significant adverse effects of furosemide during the study.

Comment

This was an interesting small study that revealed that inhalation of furosemide alleviated the sensation of dyspnoea induced by constant load exercise testing in patients with COPD and that there is a small bronchodilator effect compared with placebo.

It had no impact on exercise endurance time. It is not known, however, from this study whether the test was terminated because of limitation in the ventilatory capacity or for non-ventilatory reasons, such as leg fatigue.

Inhaled furosemide is unlikely to be used in current rehabilitation programmes unless further studies reveal that inhaled furosemide can affect the workload or endurance time. It may have a role in palliative care in patients with terminal COPD but further studies are needed.

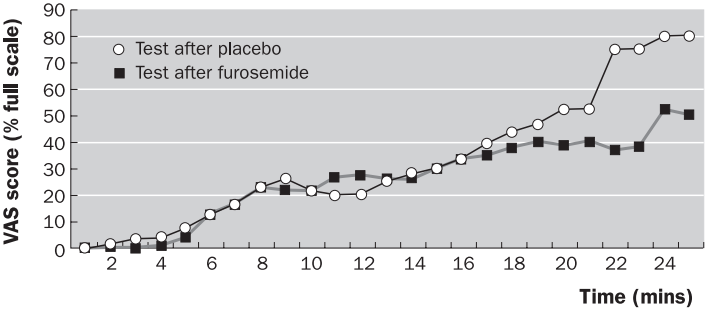

Fig. 4.10 Mean visual analogue scale scores during constant work rate exercise testing Source: Ong *et al*. (2004).

Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease

Casaburi R, Bhasin S, Cosentino L, *et al*. *Am J Respir Crit Care Med* 2004; **170**: 870–8

BACKGROUND. Dysfunction of the muscles of ambulation contributes to exercise intolerance in COPD. Men with COPD have high prevalence of low testosterone levels, which may contribute to muscle weakness. The authors determined the effects of testosterone supplementation (100 mg of testosterone enanthate injected weekly) with or without resistance training on body composition and muscle function in 47 men with COPD (mean FEV_1 40% predicted) and low testosterone levels (≤400 ng/dl; mean 320 ng/dl). Resistance training was for 45 min three times weekly, focusing on muscles of ambulation. Subjects were randomized to 10 weeks of placebo injections with no training (n = 12; mean ± SD FEV_1 38.6 ± 12.1% predicted), testosterone injections with no training (n = 12; mean FEV_1 43.0 ± 15.4% predicted), placebo injections with resistance training (n = 12; mean FEV_1 35.9 ± 9.2% predicted), or testosterone injections with resistance training (n = 11; mean FEV_1 42.4 ± 11.9% predicted).

INTERPRETATION. Testosterone injections yielded a mean increase of 271 ng/dl in the nadir serum testosterone concentration (to the middle of the normal range for young men). The increase in lean body mass (by dual-energy X-ray absorptiometry) averaged 2.3 kg with testosterone alone and 3.3 kg with combined testosterone and resistance training (P <0.001). The increase in one-repetition maximum leg press strength averaged 17.2% with testosterone alone, 17.4% with resistance training alone, and 26.8% with testosterone plus resistance training (P <0.001), but did not significantly increase in the control group with no training. The measure of quadriceps fatigability (leg press repetitions to failure at 80% of the pre-intervention one repetition maximum) increased significantly compared with the control group by 17% with testosterone alone, 45% with resistance training alone, and 81% with testosterone plus resistance training. There was no significant increase in inspiratory muscle strength. In the incremental and constant work rate cardiopulmonary exercise testing, there were no significant benefits with placebo, testosterone and no training, or with placebo and resistance training. With combined testosterone and resistance training there were small increases (all P <0.05) in peak oxygen uptake (6%), peak work rate (6%) and lactic acidosis threshold (4%) in the incremental exercise test, but the increase in the duration of the constant work rate test just failed to reach conventional statistical significance (baseline 6.3 ± 2 min; post-testosterone and training 8.7 ± 5.4 min; P = 0.06). Interventions were well tolerated, with no abnormalities in safety measures, with the exception of a rise of about 7% in haemoglobin level.

Comment

Further studies are required to determine the long-term benefits of adding testosterone supplementation and resistance training to rehabilitative programmes for carefully screened men with COPD and low testosterone levels.

Maintenance of inspiratory muscle training in COPD patients: one-year follow-up

Weiner P, Magadle R, Beckerman M, Weiner M, Berar-Yanay N. *Eur Respir J* 2004; **23**: 61–5

BACKGROUND. In COPD patients dyspnoea and functional exercise capacity may improve as a result of inspiratory muscle training |14|. The present study investigated the short-term and long-term benefits of inspiratory muscle training for inspiratory muscle performance (strength and endurance), exercise capacity and the perception of dyspnoea in patients with COPD. Thirty-eight patients with moderate to severe COPD had 3 months of basic inspiratory muscle training (six times per week, incrementally until 60% maximal inspiratory mouth pressure [Pi_{max}]) and were then randomized into a group that received maintenance inspiratory muscle training for the next year three times weekly at 60% of their Pi_{max} (mean FEV_1 45 ± 2.6% predicted) and a group that got training with very low load three times weekly with a fixed load that required generation of mouth pressure of 7 cmH_2O (mean FEV_1 45 ± 2.6% predicted).

INTERPRETATION. Following the basic 3-month training there was a statistically significant ($P < 0.005$) increase in inspiratory muscle performance and 6-min walk test (6MWT) (Fig. 4.11) and a decrease in dyspnoea. During the second stage of the study, the training group continued to maintain the improvement in all parameters, while there was deterioration in inspiratory muscle performance, exercise capacity (Fig. 4.11) and dyspnoea in the low-intensity group during the 6- to 12-month period.

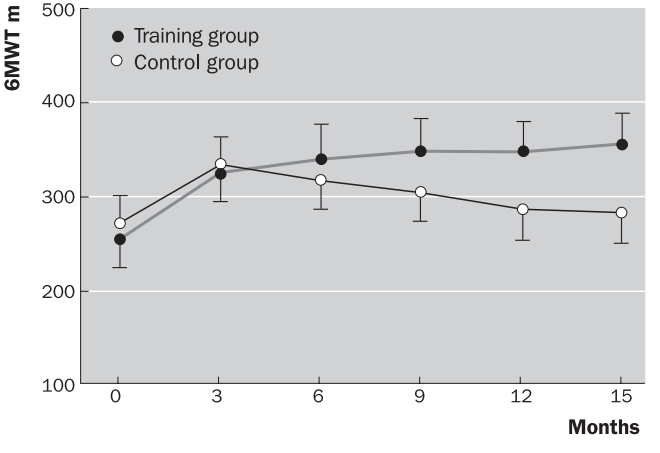

Fig. 4.11 The mean ± SEM distance walked in 6 min (6MWT) before and after the training period (basic training between 0 and 3 months). The difference between the groups became statistically significant at the end of the twelfth month. Source: Weiner *et al*. (2004).

Comment

In patients with moderate to severe COPD, inspiratory muscle training over a 3-month period improved performance, exercise capacity and sensation of dyspnoea. The benefits of the 3 months of inspiratory muscle training declined gradually over 1 year of follow-up if maintenance training was not performed.

Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study

Man WD, Polkey MI, Donaldson N, Gray BJ, Moxham J. *BMJ* 2004; **329**: 1209

Background. The aim of this single-centre randomized controlled trial study was to evaluate the effects of an early community-based pulmonary rehabilitation programme after hospitalization for acute exacerbations of COPD. An 8-week pulmonary rehabilitation programme for outpatients (n = 21; mean FEV_1 36.7 ± 14.9% predicted), started within 10 days of hospital discharge, or usual care (n = 21; mean FEV_1 41.7 ± 18.9% predicted) was carried out in 42 patients admitted with an acute exacerbation of COPD. The rehabilitation programme was twice weekly for 8 weeks and each session was for 2 h (1 h of exercise, including aerobic walking and cycling and strength training for the upper and lower limbs, and 1 h of educational activities). The main outcome measures were incremental shuttle walk distance, disease-specific health status (SGRQ, chronic respiratory questionnaire (CRQ) and generic health status (medical outcomes Short Form-36 questionnaire [SF-36]) 3 months after hospital discharge.

Interpretation. Compared with usual care, early pulmonary rehabilitation after hospitalization for an acute exacerbation of COPD led to significant improvements in median incremental shuttle walk distance, mean SGRQ total score, all four domains of the CRQ and the mental component score of the SF-36. Early pulmonary rehabilitation, compared with usual care, led to significant improvements in median incremental shuttle walk distance (60 m; 95% CI 26.6–93.4 m; P = 0.0002). A lower score in the SGRQ denotes improvement and a change of 4 units is clinically significant. Pulmonary rehabilitation compared with usual care led to an improved mean SGRQ total score (–12.7; 95% CI –5.0 to –20.3; P = 0.002). In the CRQ an increase denotes clinical improvement; the minimally clinical important difference is 2.5 for the dyspnoea domain, 2 for the fatigue domain, 3.5 for the emotion domain and 2 for the mastery domain. Pulmonary rehabilitation, compared with usual care, improved all four domains of the CRQ (dyspnoea 5.5; 95% CI 2.0–9.0; P = 0.003; fatigue 5.3; 95% CI 1.9 to 8.8; P = 0.004; emotion 8.7, 95% CI 2.4–15.0; P = 0.008; and mastery 7.5; 95% CI 4.2–10.7; P <0.001). Pulmonary rehabilitation compared with usual care led to improvements in the mental component score of the SF-36 (20.1; 95% CI 3.3–36.8; P = 0.02). Improvements in the physical component score of the SF-36 did not reach conventional statistical significance (10.6; 95% CI –0.3 to 21.6; P = 0.057). Visit rates to the accident and emergency department

were reduced ($P = 0.01$) in the pulmonary rehabilitation group (10%) compared with the control group (42.9%). There was no significant difference in the hospital re-admission rate or total number of days in hospital. However, this was a small study and an effect may have been shown with a larger study.

Comment

Early pulmonary rehabilitation after admission to hospital for acute exacerbations of COPD is safe and leads to statistically and clinically significant improvements in exercise capacity and health status at 3 months.

Lung volume reduction surgery

Lung volume reduction surgery |**15–18**| by a median sternotomy or video-assisted thoracoscopic surgery resects 20–35% of each lung, targeting the most diseased areas. This is thought to improve the pulmonary mechanics, which may ultimately improve lung function, exercise capacity and prognosis.

Lung volume reduction surgery is not without risk and there has been increased mortality, particularly in patients with an FEV_1 ≤20% predicted and either homogeneous emphysema on CT scanning or a carbon monoxide gas transfer ≤20% predicted (90-day mortality 29%). Increased mortality has also been found in patients who had an exercise capacity >25 W for women and >40 W for men who had emphysema predominantly in the lower lobes or who had diffuse emphysema.

The patients thought to benefit most are patients with heterogeneous predominant upper lobe emphysema with an FEV_1 21–45% predicted, evidence of hyperinflated lungs with an elevated total lung capacity ≥100% predicted and residual volume ≥150% predicted without respiratory failure.

These selected patients can have long-term functional improvements in exercise tolerance, have improved health-related quality of life and less mortality. Along with the potential benefits of surgery, patients should be aware of the potential morbidity and mortality from lung volume reduction surgery (90-day mortality 5–7%). Finally, lung volume reduction surgery is costly, at least over a 3-year period. However, the procedure may be cost-effective if the benefits with lung volume reduction surgery can be maintained over a longer time, such as 5–10 years, but this requires long-term prospective follow-up.

The final two papers in the COPD section explore the influence of lung volume reduction surgery on exercise in patients with COPD and health-related quality of life.

The influence of lung volume reduction surgery on exercise in patients with COPD

Dolmage TE, Waddell TK, Maltais F, *et al*. *Eur Respir J* 2004; **23**: 269–74

BACKGROUND. This randomized controlled trial evaluated the effects of lung volume reduction surgery (treatment group) on exercise with repeated measures over 12 months compared with conventional medical management (control). After 6 weeks of pulmonary rehabilitation, subjects were randomized to lung volume reduction surgery or conventional medical therapy. Incremental exercise tests were carried out at 6 months, as well as endurance tests (constant power of 25 ± 1 W) at 3, 9 and 12 months.

INTERPRETATION. Thirty-nine patients with severe COPD were selected, with mean ± SE FEV_1 32 ± 2% predicted and functional residual capacity 195 ± 6% predicted. The peak oxygen uptake ($V'O_{2pk}$) and power were similar between the treatment group ($n = 19$) and control groups ($n = 20$) at baseline. At 6 months the treatment group had a significantly greater ($P = 0.04$) $V'O_{2pk}$, with a mean difference of 1.28 (95% CI 0.07–2.50) ml/kg per min and power (13 W; 95% CI 6–20; $P = 0.0003$). The treatment group achieved a significantly greater minute ventilation (7.1 l/min; 95% CI 2.9–11.3; $P < 0.002$), with a greater tidal volume (0.16 l; 95% CI 0.04–0.28; $P < 0.01$). Baseline endurance was similar between groups. After surgery, the treatment group had a greater endurance time at 3, 9 and 12 months (7.3 min; 95% CI 3.9–10.8 min at 12 months; $P < 0.05$) (Fig. 4.12).

Comment

Lung volume reduction surgery in patients with severe COPD was associated with an increase in exercise capacity and endurance compared with conventional medical

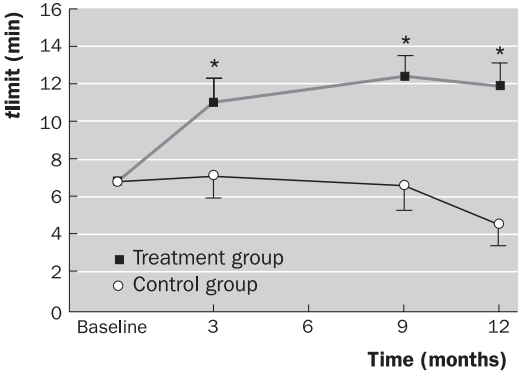

Fig. 4.12 Endurance time of constant power exercise (t_{limit}) for the treatment and control groups at baseline and 3, 9 and 12 months after randomization. Values at follow-up are baseline-adjusted least squares means. *$P < 0.05$, baseline-adjusted difference between groups. Source: Dolmage *et al*. (2004).

treatment up to 12 months after surgery. This is consistent with the trial by Fishman and colleagues, which revealed that lung volume reduction surgery was associated with increased exercise capacity at 2 years. Longer-term follow-up is required to determine the long-term outcomes from lung volume reduction surgery.

Impact of lung volume reduction surgery versus rehabilitation on quality of life

Mineo TC, Ambrogi V, Pompeo E, *et al*. *Eur Respir J* 2004; **23**: 275–80

BACKGROUND. This study evaluated the effects of lung volume reduction versus respiratory rehabilitation on quality of life, assessed by the Nottingham Health Profile, the SF-36 and the SGRQ.

INTERPRETATION. Sixty emphysematous patients were randomized to receive either surgery ($n = 30$; mean FEV_1 30.2 ± 1.9% predicted) or 6 weeks of rehabilitation ($n = 30$; mean FEV_1 31.4 ± 2.7% predicted). Health status was evaluated with the Nottingham Health Profile, the SF-36 questionnaire and the SGRQ. As reported previously, at both 6 and 12 months the dyspnoea index, FEV_1, residual volume, 6MWT and PaO_2 improved after surgery more than after rehabilitation |**19**|. At 12 months health status was significantly improved after surgery compared with the rehabilitation group, as follows: physical mobility in the Nottingham Health Profile ($P = 0.04$); physical ($P = 0.0001$) and social functioning ($P = 0.004$), mental ($P = 0.01$) and general health ($P < 0.0001$) and emotional role ($P = 0.003$) in the SF-36; and activity ($P = 0.0001$) in the SGRQ. Functional and especially symptomatic improvements persisted in the lung volume reduction surgery group: the dyspnoea index, residual volume, SF-36 and SGRQ physical scores were still significant at 4 years.

Comment

Lung volume reduction surgery produces greater and longer effects than rehabilitation on health status by improving both physical and psychosocial domains. Symptomatic improvements persisted during the 4 years studied.

Conclusion

Throughout the world chronic obstructive pulmonary disease remains a major cause of chronic morbidity and mortality. Patients with COPD develop progressive and predominantly fixed airflow obstruction that leads to a history of progressive worsening breathlessness that can affect daily activities and health-related quality of life. Frequent exacerbations can further impair health-related quality of life and have a major impact on health cure utilization.

Out of 1746 articles published on COPD from the beginning of November 2003 until the end of December 2004, 25 articles of clinical relevance have been selected for

this section of the book, and both negative and positive studies have been selected. The principle messages from the papers are as follows:

Paper 1: Bourdin *et al.* (2004). The histopathological features from endobronchial biopsies were not sufficiently discriminatory to distinguish asthma and COPD.

Paper 2: Pinto-Plata *et al.* (2004). The 6-min walk distance predicted mortality better than other traditional markers of disease severity, such as FEV_1 in patients with severe COPD.

Paper 3: Kim *et al.* (2004). Both chronic COPD severity (exacerbation frequency in the last 12 months) and acute COPD exacerbation (self-reported activity limitations and initial respiratory rate) were associated with increased risk of relapse following an exacerbation of COPD treated in the emergency department. Further larger prospective studies are needed to address reasons for relapse in COPD patients from the emergency department.

Paper 4: Monninkhof *et al.* (2003). This study failed to show positive effects of a self-management programme over 1 year among patients with moderate to severe COPD. It would be interesting to repeat the study in patients with more severe COPD, a group that would be more likely to benefit from a self-management programme, and also to look at other outcome measures, such as anxiety and depression or coping strategies.

Paper 5: Wilkinson *et al.* (2004). Patients who receive prompt therapy after the onset of the exacerbation are likely to recover faster than those who delay reporting and thus the initiation of treatment. Patients who fail to seek treatment for their exacerbations had a poorer health-related quality of life and were more likely to be hospitalized for their exacerbation. Patient education will be a key component in implementing change.

Paper 6: Wilson *et al.* (2004) and Paper 7: Lode *et al.* (2004). Moxifloxacin had similar clinical success to standard therapy for infective exacerbations of COPD. However, moxifloxacin improved bacteriological success, clinical cure (return to pre-exacerbation status) and the time to next exacerbation, although the changes were small. Levofloxacin, compared with clarithromycin, was associated with a significantly higher bacteriological eradication rate but had similar clinical success rates and exacerbation-free interval in patients with COPD exacerbation. Overall amoxicillin as first-line therapy in acute exacerbations of COPD is a cheap and effective option. In patients who have not responded, alternative antibiotics will be chosen, and the choice is usually based on sputum microbiology and sensitivity testing. The data from moxifloxacin looks promising in that treatment is once daily for 5 days, it has high bacterial eradication rates, achieves clinical success in the majority of patients and can lengthen the time to the next exacerbation.

Paper 8: Christ-Crain *et al.* (2004). Serum procalcitonin guidance substantially reduced antibiotic use in lower respiratory tract infections and withholding antimicrobial treatment did not compromise the outcome. In view of the current overuse of antimicrobial therapy in acute respiratory tract infections, which are often self-limiting, treatment based on serum procalcitonin measurement could have important clinical and financial implications.

Paper 9: O'Donnell. *et al.* (2004). Tiotropium was associated with sustained reductions in lung hyperinflation at rest and during exercise. The resulting increases in inspiratory capacity permitted greater expansion of tidal volume and contributed to improvements in both exertional dyspnoea and exercise endurance.

Paper 10: Man *et al.* (2004). Despite the non-reversibility of spirometric parameters, long-acting β_2-agonists can cause both symptomatic and physiological improvement during exercise in severe COPD by reducing dynamic hyperinflation and respiratory muscle activity.

Paper 11: McNicholas *et al.* (2004). Sustained anticholinergic blockade with tiotropium improved oxygen saturation during sleep in patients with severe COPD independent on whether tiotropium was taken in the morning or the evening. These effects were accompanied by improvements in pre- and post-sleep spirometry but there was no significant change in subjective or objective sleep quality.

Paper 12: Sin *et al.* (2004). Both inhaled and oral corticosteroids are effective in reducing serum CRP levels in patients with COPD. Long-term and large multicentre trials are needed to determine whether inhaled corticosteroids can modify cardiovascular outcomes in COPD.

Paper 13: Spencer *et al.* (2004). Statistical modelling showed the beneficial effect of fluticasone propionate on the attenuation of deterioration in health status to be largely due to its effect in reducing exacerbation frequency.

Paper 14: Calverley *et al.* (2003). Use of a combination of budesonide with formoterol over a 1-year period was more effective than either individual component on time to first exacerbation and change in post-medication FEV_1. The combination of budesonide/formoterol in a single inhaler (Symbicort) maintained the benefit of treatment optimization by stabilizing lung function and delaying exacerbations more effectively than either component drug alone or placebo.

Paper 15: Wongsurakiat *et al.* (2004). This was a small study that supports the use of influenza vaccination in reducing influenza-related acute respiratory illness. Influenza vaccination did not, however, reduce the incidence of other acute respiratory illnesses, including the common cold, acute exacerbations of COPD and pneumonia. Larger studies are needed to determine whether influenza vaccination affects other acute respiratory illnesses.

Paper 16: Corrado *et al.* (2004). Iron lung ventilation is as effective as invasive mechanical ventilation in improving gas exchange in COPD patients with acute respiratory failure, and is associated with a tendency to a lower rate of major complications. A large multicentre controlled trial would be welcome, comparing the outcomes of iron lung ventilation with invasive mechanical ventilation.

Paper 17: Esteban *et al.* (2004). NIPPV does not prevent the need for reintubation and increased the mortality in unselected patients who have respiratory failure after extubation. This is an important study that highlights that NIPPV after extubation can be potentially harmful by prolonging the time to reintubation. The study, however, does not address whether this is applicable to COPD patients as the cohort of COPD patients was too small in this study. Large multicentre studies in COPD patients are needed to address this.

Paper 18: Emtner *et al.* (2003). This small study supported the use of supplementary oxygen in non-hypoxaemic patients (even with exercise) with severe COPD (FEV_1 <50% predicted) undergoing exercise training. With supplementary oxygen, training intensity could be kept at a higher level, with improvements in endurance capacity and breathing pattern.

Paper 19: Stevenson and Calverley (2004). This study addressed whether oxygen helped in the recovery phase post exercise in patients with moderate to severe COPD without oxygen desaturation on exercise. Oxygen treatment reduced the degree of dynamic hyperinflation during recovery from exercise but did not make patients feel less breathless than when they were breathing air.

Paper 20: Ong *et al.* (2004). This small study revealed that inhalation of furosemide alleviated the sensation of dyspnoea induced by constant load exercise testing in patients with COPD and that there is a small bronchodilator effect compared with placebo. Inhaled furosemide is unlikely to be used in current rehabilitation programmes unless further studies reveal that inhaled furosemide can affect the workload or endurance time.

Paper 21: Casaburi *et al.* (2004). Further studies are required to determine the long-term benefits of adding testosterone supplementation and resistance training to rehabilitative programmes for carefully screened men with COPD and low testosterone levels.

Paper 22: Weiner *et al.* (2004). In patients with moderate to severe COPD, inspiratory muscle training over a 3-month period improved performance, exercise capacity and sensation of dyspnoea. The benefits of the 3 months of inspiratory muscle training declined gradually over 1 year of follow-up if maintenance training was not performed.

Paper 23: Man *et al.* (2004). Early pulmonary rehabilitation after admission to hospital for acute exacerbations of COPD was safe and led to statistically and clinically significant improvements in exercise capacity and health status at 3 months.

Paper 24: Dolmage *et al.* (2004). Lung volume reduction surgery in patients with severe COPD was associated with an increase in exercise capacity and endurance compared with conventional medical treatment up to 12 months after surgery. Longer-term follow-up is required to determine the long-term outcomes from lung volume reduction surgery.

Paper 25: Mineo *et al.* (2004). Lung volume reduction surgery produces greater and longer effects than rehabilitation on health status by improving both physical and psychosocial domains. Symptomatic improvements persisted during the 4 years studied.

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Part III

Pulmonary fibrosis

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5

Interstitial lung diseases

JOHN SIMPSON, NIK HIRANI

Introduction

Interstitial lung diseases were recently reclassified according to pathological characteristics |**1,2**| (Fig. 5.1). This represented a significant advance for two principal reasons. Firstly, the conditions defined by pathological classification generally have characteristic prognoses. Secondly, reclassification provided criteria allowing clinicians from different institutions in different countries to know when they were talking about the same disease entity.

The knock-on effects for both basic and clinical research have been profound, resulting in a proliferation of work carried out in the confidence that clinical samples are taken from patients with the same disease. Significant work has emerged relating to the epidemiology, pathogenesis, imaging and treatment of interstitial lung diseases (ILDs).

The following collection of papers is intended to reflect this background. The first half of the chapter concentrates largely on idiopathic pulmonary fibrosis (IPF), a generally progressive disease with a median survival time of approximately 3 years. The second half considers a miscellany of important conditions, illustrating how the careful evaluation of imaging, histology and epidemiology can enhance understanding of conditions as diverse as systemic sclerosis, hypersensitivity pneumonitis and sarcoidosis.

The articles discussed have been selected from literature published in 2004 in the hope of reflecting a variety of important questions directly relevant to clinicians dealing with ILD. Inevitably, a number of exciting and important papers have been omitted. However, several excellent reviews appeared in 2004 and the interested reader could, for example, begin with the collection of reviews in the September and December editions of *Clinics in Chest Medicine*.

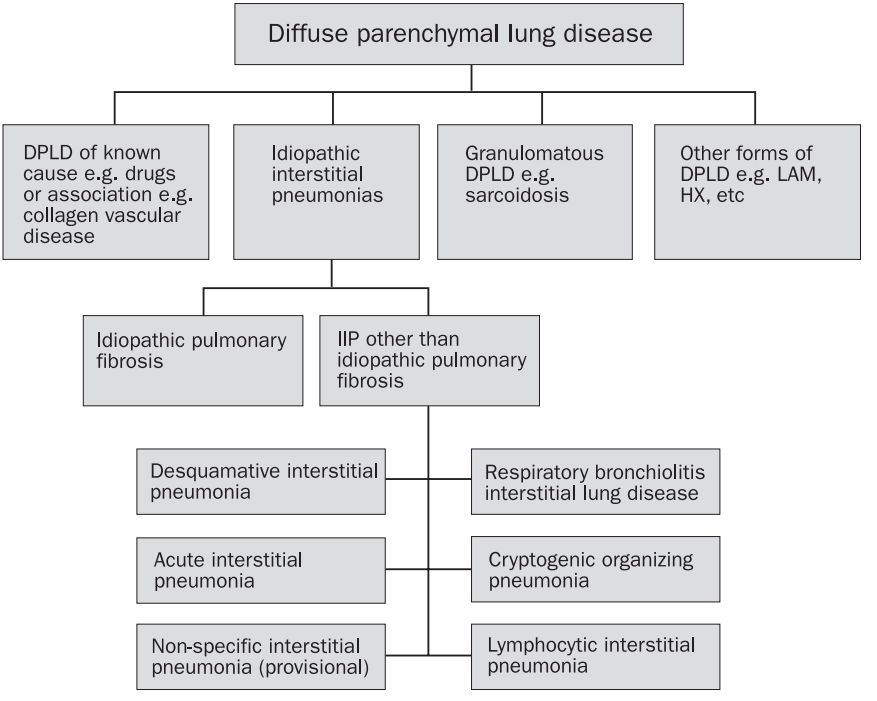


Fig. 5.1 Diffuse parenchymal lung diseases (DPLDs) consist of disorders of known causes (collagen vascular disease, environmental or drug-related) as well as disorders of unknown cause. The latter include idiopathic interstitial pneumonias (IIPs), granulomatous lung disorders (e.g. sarcoidosis), and other forms of ILD, including lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis/histiocytosis X (HX), and eosinophilic pneumonia. The most important distinction among the IIPs is that between idiopathic pulmonary fibrosis (IPF) and the other interstitial pneumonias (IPs), which include non-specific interstitial pneumonia (a provisional term), desquamative interstitial pneumonia, respiratory bronchiolitis-associated ILD, acute interstitial pneumonia, cryptogenic organizing pneumonia, and lymphocytic interstitial pneumonia. Source: Travis and King (2002) |**2**|.

Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis?

Flaherty KR, King Jr TE, Raghu G, *et al*. *Am J Respir Crit Care Med* 2004; **170**: 904–10

Background. It is increasingly apparent that natural history and response to treatment varies from one idiopathic interstitial pneumonia (IIP) to another. In particular, it is important to differentiate IPF from other IIPs, but the clinical

distinction can be difficult. This study set out to determine whether interaction between clinician, radiologist and pathologist could add measurable diagnostic value to the diagnostic process in IIPs.

INTERPRETATION. The diagnosis of IIPs is not straightforward! Whereas it was once accepted that a pathological diagnosis was the gold standard, it is now apparent that the final diagnosis should be the one that best fits the clinical, radiological and pathological evidence available. Hence, active discussion between clinician, radiologist and pathologist considerably enhanced interobserver agreement in the diagnosis of IIPs. Furthermore, a confident clinicoradiological diagnosis of IPF almost invariably predicts compatible histology, arguing against lung biopsy in this setting. Conversely, histology radically improved interobserver agreement in cases where a clinicoradiological diagnosis of IPF was in doubt.

Comment

This study was based around 58 consecutive cases of IIP for which clinical data, high-resolution computed tomography (HRCT) and surgical lung biopsy were available. Acknowledged experts in IIP (three clinicians, two radiologists, two pathologists) were assembled. Clinical information was then introduced step-wise. At each stage, each individual present recorded their preferred diagnosis and the confidence of that diagnosis. Only physicians and radiologists were involved in steps 1 (interpretation of HRCT alone, without conferring), 2 (interpretation of HRCT and clinical information without conferring) and 3 (interpretation of HRCT and clinical information after discussion). At step 4 pathologists arrived to add their findings to the discussion, and at step 5 an attempt was made to arrive at a consensus diagnosis where possible.

Several important points emerged. Perhaps most importantly, interobserver agreement improved steadily with each step. Furthermore, with each step the preferred diagnosis of each clinician/radiologist tallied more closely with the final, consensus diagnosis. In general terms, the addition of histology was far more likely to alter the diagnosis than was clinical information. Physicians were more likely than radiologists to change their diagnosis at the time clinical information was added, and were more likely at this stage to provide a diagnosis consistent with the final consensus. Prior to the introduction of pathology, if physicians/radiologists made a diagnosis of IPF, their assessment was almost invariably borne out by the pathology.

The key question in assessing these data is how relevant the specifics are to real life. As the authors readily acknowledge, the results may have been radically different had less experienced observers been assembled. Nevertheless, these findings provide objective evidence to support the widely held belief that decisions about when to pursue lung biopsy and the final working diagnosis of an IIP are best made after close communication between physicians, radiologists and pathologists, each with a dedicated interest in IIPs.

Combined corticosteroid and cyclophosphamide therapy does not alter survival in idiopathic pulmonary fibrosis

Collard HR, Ryu JH, Douglas WW, *et al*. *Chest* 2004; **125**: 2169–74

BACKGROUND. Based on the traditional view that inflammation drives the fibrotic process in IPF, many physicians continue to treat patients with immunosuppressants, usually in the form of prednisolone along with azathioprine or cyclophosphamide. No clear advantage for this approach has been demonstrated in clinical trials. With the increasingly emergent view that IPF is driven not by inflammation but by an aberrant fibroproliferative response to local healing, prospective trials of immunosuppressant therapy versus placebo are now unlikely to be performed. Therefore, this study retrospectively compared survival in closely matched patients with IPF who had received either no treatment or the combination of prednisolone and cyclophosphamide.

INTERPRETATION. Prednisolone and cyclophosphamide did not influence survival in patients with IPF.

Comment

Patients were from two American centres with longstanding expertise in IPF. All patients had either a lung biopsy or clinicoradiographic features characteristic of IPF. From 155 untreated patients and 543 patients treated with prednisolone and cyclophosphamide, the authors performed matching by age and forced vital capacity (FVC) as a percentage of the predicted value, resulting in 82 patients in each group. It is worth noting that all 82 treated patients were from Denver and had a lung biopsy, while all 82 untreated patients were from the Mayo Clinic, and only 15% of these had a lung biopsy. Standard prednisolone and cyclophosphamide regimens were prescribed in the treated group. Data were analysed on an intention-to-treat basis.

The average age was 68 years and the mean FVC was 67% of predicted. No survival advantage was observed for prednisolone and cyclophosphamide (Fig. 5.2), and this observation was maintained when considering only matched patients with lung biopsies or matched patients with a starting FVC of 60% predicted or more.

As the authors discuss, the retrospective design inevitably brings limitations. These include the small numbers in each group, making it less likely that the study had statistical power to detect small differences in survival. Also, all-cause mortality was the only outcome variable that could reliably be tested, and no information was available regarding duration of treatment, average doses or adverse events. Furthermore, there could have been undetected histological differences in the untreated group or inherent differences in demographics or healthcare provision, given that the two groups came from distinct geographical regions. However, it is reassuring that the demographics of the study population and survival in both groups (at least to 500 days) were very similar to those in the placebo group described in the multicentre trial by Raghu and colleagues, discussed below.

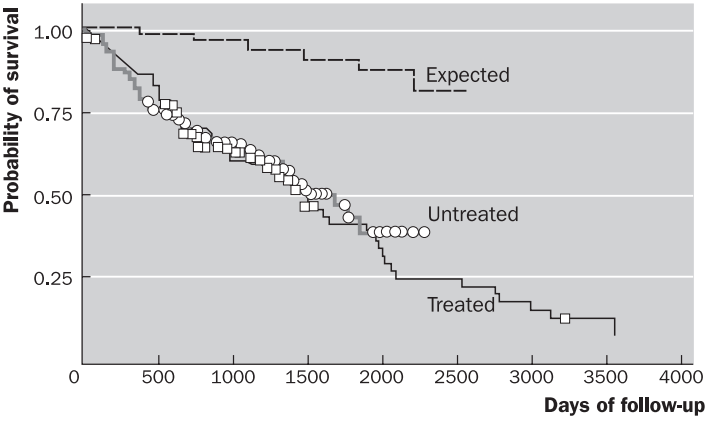


Fig. 5.2 Survival in treated versus untreated patients. Kaplan–Meier survival curves for patients treated with corticosteroid and cyclophosphamide (*thin black line*; $n = 82$) and patients who were not treated (*thick grey line*; $n = 82$), and the expected survival of 68-year-olds in the general US population (*dashed line*). *Circles* and *squares* represent censored observations. Source: Collard *et al*. (2004).

Overall, this study is consistent with the body of literature assessing immunosuppressant treatment for IPF |**3–6**|, and makes a welcome and powerful addition to the field.

A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis

Raghu G, Brown KK, Bradford WZ, *et al*., for the Idiopathic Pulmonary Fibrosis Study Group. *N Engl J Med* 2004; **350**: 125–33

Background. Initial reports of clinical benefit for the antifibrotic agent interferon γ1b (IFN-γ1b) in IPF |7| prompted a larger, multicentre, randomized, double-blind, placebo-controlled trial of IFN-γ1b for this condition.

Interpretation. IFN-γ1b did not have a significant influence on progression-free survival, overall survival, quality of life or the rate of decline in lung function or oxygenation. Respiratory infections, headaches, fevers, rigors and myalgia were commoner in patients receiving IFN-γ1b.

Comment

This is a landmark study in ILD. Its considerable strengths include the recruitment of 330 patients from three continents in a randomized, double-blind, placebo-controlled fashion *after* the international consensus statement on IPF was formulated |**8**|. Patients

satisfied HRCT criteria for IPF and had either surgical lung biopsy compatible with usual interstitial pneumonia (UIP) (the histological hallmark of IPF) or a transbronchial biopsy refuting alternative diagnoses. Recruitment also required progressive lung function abnormality, chest X-ray abnormality or progression of breathlessness. Patients over 79 or with particularly severe disease were excluded.

Both groups were well matched at baseline, with mean FVC of 64% predicted, diffusing capacity for carbon monoxide 37% predicted and PaO_2 (partial pressure of oxygen in arterial blood; on air at rest) 74 mmHg. Patients received IFN-γ1b (100 μg subcutaneously three times weekly, progressing to a maintenance dose of 200 μg three times a week; $n = 162$) or placebo ($n = 168$). The primary end-point was progression-free survival (the time to death or clear evidence of progression, where progression was defined as a fall in FVC of at least 10% predicted or an increase of 5 mmHg in $P(A\text{-}a)O_2$ [difference between partial pressure of oxygen in the alveolar space and partial pressure of oxygen in arterial blood]). Secondary end-points included changes in lung function, oxygenation, the extent of fibrosis on HRCT over 48 weeks, and assessments of breathlessness and quality of life.

Median follow-up was for 58 weeks. No significant difference in progression-free survival (Fig. 5.3) or in secondary end-points was detected. Interestingly, there was no evidence of disease progression in 48% of patients in the placebo group (and in 54% of the IFN-γ1b group), so the chances of observing a biological effect of IFN-γ1b in this trial may have been diminished by the natural history of the disease. With this in mind, interest has focused upon a subgroup analysis demonstrating that patients with mild disease appeared to respond better to IFN-γ1b. However, it must be emphasized that predetermined study end-points did not include subgroup analyses and it remains to be seen whether demonstrable benefit for patients with early disease can be confirmed.

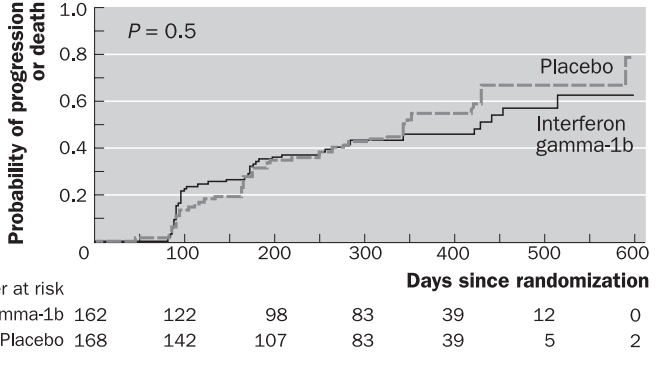


Fig. 5.3 Kaplan–Meier estimates of progression-free survival among patients with idiopathic pulmonary fibrosis. Source: Raghu *et al*. (2004).

Almost all (n = 326) patients described adverse effects. However, the IFN-γ1b group had significantly more headache, upper respiratory tract infection, fever, rigors and myalgia.

This important study demonstrates the enormous benefits of coordinated, multicentre trials in the study of relatively rare diseases such as IPF. The trial also provides unequivocal evidence that the routine use of IFN-γ1b cannot be advocated in IPF at present. The intriguing observation that patients with the earliest disease may respond to IFN-γ1b is the focus of ongoing trials.

Effects of interferon-γ 1b on biomarker expression in patients with idiopathic pulmonary fibrosis

Strieter RM, Starko KM, Enelow RI, Noth I, Valentine VG; Idiopathic Pulmonary Fibrosis Biomarkers Study Group. *Am J Respir Crit Care Med* 2004; **170**: 133–40

BACKGROUND. The huge body of *in vitro* and *in vivo* studies describing mechanisms of fibrogenesis has been instrumental in defining therapeutic strategies for pulmonary fibrosis. These are beginning to find application in multicentre, randomized controlled trials, as exemplified by the study from Raghu and colleagues (see above). As these trials proliferate it remains important that biological as well as clinical end-points are investigated, with the aim of further understanding the pathogenesis of IPF. This randomized controlled trial therefore aimed to establish the influence of IFN-γ1b on biomarkers relating to the regulation of fibrosis, angiogenesis, host defence and inflammation.

INTERPRETATION. IFN-γ1b therapy was associated with trends towards a biomarker phenotype that was less fibrotic, less angiogenic and more antimicrobial.

Comment

This trial is fundamentally important because it comprehensively assessed changes in the regulation of biomarkers linked to fibrogenesis within the framework of a multicentre, randomized, placebo-controlled therapeutic trial of IFN-γ1b for IPF. Fifteen American centres participated. Entry criteria included clinical and HRCT changes consistent with IPF, as well as clinical deterioration despite corticosteroids. Patients were randomized to receive IFN-γ1b 200 μg three times weekly (n = 17) or placebo (n = 15) for 6 months. It is hard to tell precisely whether patients received prednisolone or other potentially important therapeutic agents.

Messenger ribonucleic acid (mRNA) and protein levels for multiple candidate biomarkers were serially measured by sampling three distinct compartments, namely alveolar tissue (by transbronchial biopsy), bronchoalveolar lavage (BAL) fluid and blood.

The primary end-points related to changes in transforming growth factor β (TGFβ) mRNA and connective tissue growth factor (CTGF) mRNA in alveolar tissue at 6 months relative to baseline, based on observations made in a pivotal clinical trial

of IFN-γ1b by Ziesche and colleagues |**7**|. No significant difference was detected for either variable. However, levels of CXCL11/ITAC (an anti-angiogenic peptide with antimicrobial properties; ITAC, interferon-inducible T-cell α chemoattractant) were significantly elevated in BAL fluid and serum from the IFN-γ1b group, while the pro-fibrotic molecule platelet-derived growth factor (PDGF)-A was reduced in BAL fluid. A significantly higher proportion of patients in the placebo group had increased interleukin 4 expression in alveolar tissue. Otherwise, no statistically significant observations arose. Interestingly, however, trends (defined as $P < 0.1$) in biomarkers all went in the direction consistent with the expected antifibrotic action of IFN-γ1b (suppression of type III collagen, elastin and PDGF-B mRNA in alveolar tissue, decreased protein levels for IFN-γ, CXCL5/ENA [epithelial/neutrophil-activating protein]-78, type I procollagen and PDGF-A in BAL fluid). The only exception to this rule was alveolar Smad-7 mRNA, which was upregulated more often in the placebo group.

In retrospect it is a pity that the trial was not larger, to confirm whether the observed trends became significant. Furthermore, absolute or relative changes in biomarker levels do not necessarily imply a change in function. Nevertheless, this is a remarkable study, partly because it lays the ground for other carefully designed and ambitious studies of its kind, but also because it suggests mechanisms of importance to human fibrogenesis *in situ*, thereby proposing molecular targets for the treatment of fibrosis.

Impact of angiotensin-converting enzyme inhibitors and statins on survival in idiopathic pulmonary fibrosis

Nadrous HF, Ryu JH, Douglas WW, Decker AP, Olson EJ. *Chest* 2004; **126**: 438–46

BACKGROUND. ***In vitro*** **experiments using human cells have demonstrated antifibrotic potential for angiotensin-converting enzyme (ACE) inhibitors and statins, and these findings have been extended to the demonstration of efficacy in animal models of pulmonary fibrosis. This retrospective study therefore aimed to determine whether the use of ACE inhibitors and/or statins was associated with improved survival in IPF.**

INTERPRETATION. Survival in patients with IPF appeared to be uninfluenced by ACE inhibitors or statins.

Comment

This retrospective study analysed 478 patients with a clinical diagnosis of IPF, with lung biopsy contributing to the diagnosis in approximately 20%. From this cohort, 52 patients were on an ACE inhibitor at the time of diagnosis. Patients taking an ACE inhibitor were older than those not taking ACE inhibitors, but otherwise the two groups were well matched, particularly with regard to lung function. Median survival times for those taking and not taking ACE inhibitors were 2.2 years and 2.9 years,

respectively (not significant). Regression analysis adjusting for ischaemic heart disease, congestive heart failure, hypertension and diabetes did not suggest that inherent differences in survival had been masked by cardiovascular disease.

Similar findings were described when considering statins, median survival being estimated at 2.9 years whether patients were ($n = 35$) or were not taking statins, with no significant confounding influence of cardiovascular morbidity. The same patterns were described when patients taking ACE inhibitors and/or statins were compared with those taking neither drug.

Clearly, these data provide little to suggest that ACE inhibitors or statins improve survival in IPF. The remaining question is how much further these drugs should be investigated as treatments for pulmonary fibrosis. With this in mind, the authors succinctly demonstrate the dilemma facing assessments of therapy in IPF – the planning of randomized, placebo-controlled trials of these drugs would require significant resources and organization, and would have to compete for patients with trials currently assessing other therapeutic candidates. Also, retrospective studies like this, while easier to compile, are necessarily attended by problems in design. Indeed, the authors are frank in pointing out that relatively small numbers of patients in their study were taking ACE inhibitors or statins, and that a variety of different ACE inhibitors and statins were used for variable durations. They also acknowledge that patients had received heterogeneous treatments for IPF. Furthermore, the authors had no way of checking compliance with ACE inhibitors and statins, and of course the primary indications for these drugs were cardiovascular, not respiratory. All of these limitations would have made it virtually impossible to assess whether ACE inhibitors or statins influenced the rate of progression of IPF as opposed to all-cause mortality.

In summary, prospective, randomized, placebo-controlled trials will be required to address the question of whether ACE inhibitors and statins can meaningfully disrupt the natural history of IPF. In the meantime, this study provides the best evidence currently available and suggests that mortality is not significantly altered by these drugs.

Association between pulmonary fibrosis and coronary artery disease

Kizer JR, Zisman DA, Blumenthal NP, *et al*. *Arch Intern Med* 2004; **164**: 551–6

BACKGROUND. This analysis was stimulated by the knowledge that recruitment of inflammatory cells and exuberant deposition of extracellular matrix are common to coronary atherosclerosis and pulmonary fibrosis.

INTERPRETATION. Among a cohort of patients referred for lung transplantation, after adjustment for potential confounding variables, coronary artery disease (CAD) was significantly more common in patients with fibrotic lung disease than in patients with non-fibrotic lung disease.

Comment

The authors took advantage of the fact that patients referred to a lung transplantation centre in Pennsylvania were likely to undergo coronary arteriography as part of routine evaluation. Over a 9-year period, 694 patients were referred. Of these, seven were excluded because they had had known CAD prior to the detection of lung disease, and 57 did not have arteriography, leaving 630 patients for analysis. Lung fibrosis was diagnosed in 186 patients (113 had 'non-granulomatous fibrosis' [IPF in 76], and 73 had 'granulomatous fibrosis' [sarcoidosis in 58]). The reference group (non-fibrotic lung disease) comprised 444 patients, the commonest single diagnosis being chronic obstructive pulmonary disease.

After adjustment for confounding variables (principally smoking, family history, hypertension and age), fibrotic lung disease was associated with a significantly higher rate of CAD than was non-fibrotic lung disease (Fig. 5.4). The authors postulate that the relationship may be causal, the systemic response generated by pulmonary fibrosis driving the development of atherosclerosis.

These data are intriguing, and if verified they will have important implications for the study of pulmonary fibrosis and CAD alike. It is tempting to speculate that the association may explain part of the increase in all-cause mortality associated with fibrosis across different ILDs, alluded to elsewhere in this chapter.

However, interpretation of these findings should consider certain elements of study design. For example, there was no comparison with the rate of CAD among age- and sex-matched patients with no lung disease. With the exception of corticosteroid use, the potential influences of medications used, particularly for IPF and chronic obstructive pulmonary disease, are not factored in. Also the 'fibrotic' population referred to a tertiary centre for transplant is highly unlikely to reflect lung

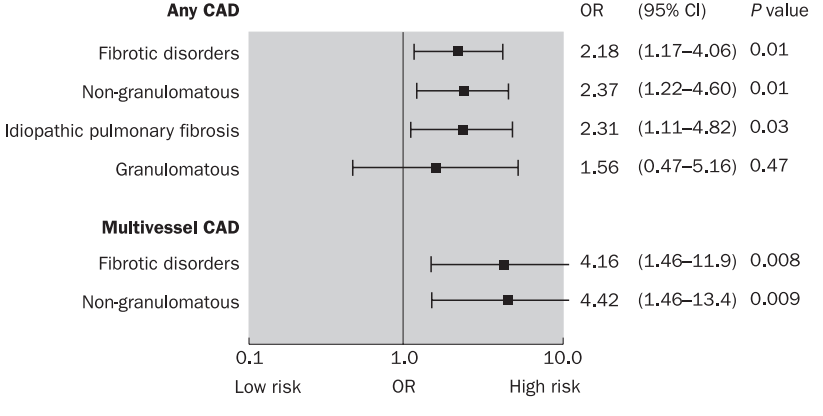


Fig. 5.4 Multivariable-adjusted odds ratios (ORs) (logarithmic scale) and 95% confidence intervals (CIs) for CAD in the various lung disease groups. Source: Kizer *et al*. (2004).

fibrosis generally, and indeed evidence for referral bias is borne out by the low mean age of 55 years for non-granulomatous lung disease. In addition, the 'fibrotic' group clearly includes heterogeneous pathologies, and while the association with CAD appears to remain for IPF, extrapolation to other disorders cannot be made. This problem is compounded by the fact that no detailed discussion of pathological diagnosis derived from explanted lungs is provided.

Nevertheless, this valuable paper introduces an enticing concept for further study. As the authors discuss, confirmation that pulmonary fibrosis drives CAD requires further study, the results of which will be of fundamental importance to patients with pulmonary fibrosis.

The effect of pulmonary fibrosis on survival in patients with hypersensitivity pneumonitis

Vourlekis JS, Schwarz MI, Cherniack RM, *et al*. *Am J Med* 2004; **116**: 662–8

BACKGROUND. Relatively little is known about the determinants of survival in subacute and chronic forms of hypersensitivity pneumonitis (or extrinsic allergic alveolitis). This study aimed to address this issue with particular reference to whether the presence of fibrosis portended an adverse outcome, as has been described for other ILDs.

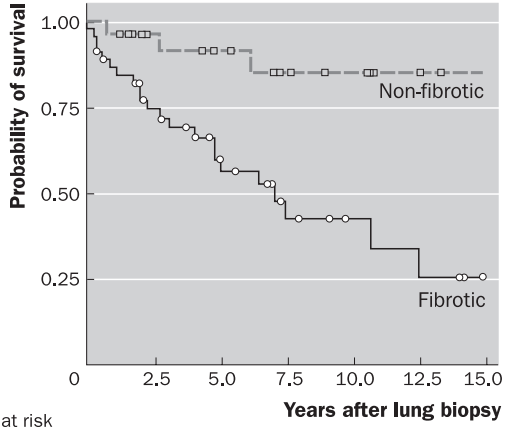
INTERPRETATION. The presence of fibrosis at lung biopsy was a significant independent risk factor for increased mortality in subacute and chronic hypersensitivity pneumonitis.

Comment

This study assessed outcome among patients in whom the clinical picture and lung biopsy were compatible with subacute or chronic hypersensitivity pneumonitis. A total of 72 patients (diagnosed over an 18-year period) were considered to fulfil the study criteria. A variety of clinical variables were collected. In addition, pathologists blinded to the identity of the patients quantified the degree of mature fibrosis on lung biopsy specimens using strict predetermined criteria.

Established fibrosis was present in 64% of patients, and was associated with increasing age, longer duration of symptoms, a restrictive pattern of lung function, and less cellular BAL. Importantly, fibrosis was associated with significantly increased mortality (Fig. 5.5). Indeed, median survival for the entire cohort was 12.8 years, compared with 7.1 years for the subgroup with fibrosis. Conversely, the absence of fibrosis predicted a very favourable outcome.

The authors sought differences between survivors and those who died, and found that survivors were more likely to present at an earlier age, to have finger-clubbing, to have a cellular, relatively lymphocytic lavage, and to have no fibrosis. However, in regression analysis with adjustment for age, only the presence of fibrosis (hazard ratio 6.01; 95% confidence interval [CI] 1.68–21.45) was a significant determinant of mortality.



Number at risk				
Non-fibrotic subjects	26	19	14	10
Fibrotic subjects	46	28	18	5

Fig. 5.5 Kaplan–Meier plot of survival for patients with hypersensitivity pneumonitis, stratified by the presence of fibrosis. The numbers at risk for each sample at selected time-points are presented below the *x*-axis. Source: Vourlekis *et al*. (2004).

These data underline the fundamental importance of pulmonary fibrosis in influencing mortality in specific ILDs, in keeping with data from IPF and non-specific interstitial pneumonia (NSIP) |**9,10**|. The challenge for the future is to learn how to prevent the formation (or progression) of fibrosis in individual patients. The study also provides fresh information on the prognosis of subacute/chronic hypersensitivity pneumonitis. However, some caution should be exercised in extrapolating these results, given that these patients had been referred to a tertiary centre and had undergone biopsy. Also, the authors were unable to determine the influence of routine treatment on outcome or to provide data pertaining to HRCT.

Importantly, the study raises several intriguing questions to be addressed, such as whether florid alveolar lymphocytosis has any inhibitory influence on the deposition of fibrosis in hypersensitivity pneumonitis. Such issues are of central importance to the future understanding of the disease and the design of therapeutic approaches.

CT features of lung disease in patients with systemic sclerosis: comparison with idiopathic pulmonary fibrosis and non-specific interstitial pneumonia

Desai SR, Veeraraghavan S, Hansell DM, *et al*. *Radiology* 2004; **232**: 560–7

Background. A range of ILDs may be manifest in patients with connective tissue disease. These have been the focus of increased research recently, but the prevalence of different patterns of ILD and their contribution to outcome in

connective tissue diseases remains relatively unclear. The best available data relate to systemic sclerosis, but even for this disease debate continues regarding the predominant pattern of associated ILD and the subsequent impact on prognosis. This study therefore compared HRCT features of systemic sclerosis-ILD with those of IPF and idiopathic NSIP.

INTERPRETATION. The pattern and distribution of ILD in systemic sclerosis bears a striking resemblance to that observed in idiopathic NSIP.

Comment

The strength of this study lies with the impressive number (225) of consecutive patients with systemic sclerosis who had HRCT, and the experience of the authors in this field. The scans were compared with those from consecutive patients with biopsy-proven IPF ($n = 40$) or idiopathic NSIP ($n = 27$) using a detailed, standardized radiological template. Two independent observers blinded to clinicopathological data reviewed scans, with impressive interobserver agreement.

Key data are shown in Table 5.1, where the 'coarseness score' equates to the pattern of reticular/fibrotic change (the higher the score the greater the fibrosis, up to a score of 15), while 'overall grade' refers to a global impression of whether ground glass was greater than (grade 1), equal to (grade 2) or less than (grade 3) reticular/fibrotic change. With the exception of disease extent, the most compelling observation is the similarity between systemic sclerosis-ILD and idiopathic NSIP. This pattern permeates all findings in the study, even after adjustment for age, extent of disease, smoking and lung function.

These findings appear extremely robust. The authors do mention that 56 patients with systemic sclerosis who were excluded had no disease on HRCT; thus, the systemic sclerosis group is not representative of 'all systemic sclerosis'. Similarly (of

Table 5.1 Extent and severity of CT patterns in patients with systemic sclerosis, IPF and NSIP

CT pattern	Patients with SSc ($n = 225$)	Patients with IPF ($n = 40$)	Patients with NSIP ($n = 27$)	*P*-value
Disease extent (%)	13.0 (1.0–84.0)	34.0 (10.0–91.5)	29.5 (3.0–82.5)	<0.001*†
Coarseness score	5.5 (0.0–13.3)	8.8 (2.5–15.0)	5.5 (2.0–12.5)	<0.001†
Ground-glass opacification proportion (%)	49.9 (0.0–100.0)	23.5 (0.0–97.2)	59.6 (0.0–96.6)	<0.001†
Overall grade‡				
1	77 (34)	7 (18)	12 (44)	NA
2	66 (29)	7 (18)	6 (22)	NA
3	82 (36)	26 (65)	9 (33)	NA

Unless indicated otherwise, data are medians. Data in parentheses are ranges. NA, not applicable.
* SSc vs NSIP
† SSC vs IPF
‡ Data are number of patients. Data in parentheses are percentages.
Source: Desai *et al*. (2004).

necessity for the purposes of this investigation), all patients with IPF/idiopathic NSIP in this study had had a biopsy, and these groups may be skewed towards patients with atypical presentations referred to a tertiary centre (the patients with IPF were relatively young, for example). Furthermore, the extent to which iatrogenic influences may have contributed to ILD in systemic sclerosis is unclear, and the authors do not describe how many patients with systemic sclerosis had lung biopsy. However, these are relatively minor considerations and the study must be viewed as one of the most important in systemic sclerosis-ILD to date.

In summary, this paper provides clear supportive data for the argument that in systemic sclerosis-ILD global lung architecture (represented better on HRCT than on lung biopsy) is far more akin to idiopathic NSIP than IPF |**11**|. The challenges ahead are to establish whether the natural history of systemic sclerosis-ILD and idiopathic NSIP is as closely linked, and to clarify the determinants of disease progression and therapeutic responsiveness.

A case control etiologic study of sarcoidosis; environmental and occupational risk factors

Newman LS, Rose CS, Bresnitz EA, *et al*., and the ACCESS Research Group. *Am J Respir Crit Care Med* 2004; **170**: 1324–30

BACKGROUND. A variety of occupational and environmental factors have been associated with sarcoidosis. A more comprehensive evaluation of the significance of these is required if they are to prove instructive in dissecting disease pathogenesis. This case–control study therefore aimed to clarify occupations and environmental exposures associated with biopsy-proven sarcoidosis.

INTERPRETATION. A variety of positive and negative associations were defined, no single exposure predominating. Striking risk factors for sarcoidosis included occupations involving musty odours and the use of pesticides. The strongest negative association was between smoking and sarcoidosis.

Comment

This study comes from the ACCESS Research Group, which has done a great deal to further our understanding of sarcoidosis through collaborative links between ten American centres. Thus, 736 adults with biopsy-proven sarcoidosis (95% had lung disease) were enrolled. The authors constructed hypotheses linking various environmental and occupational exposures to sarcoidosis, and collected extensive data using a standardized questionnaire. Univariate and multivariate analyses were performed to identify factors linked to sarcoidosis.

A wide range of factors emerged from the univariate analysis, though several of these (including employment as a physician) were no longer significant in multivariate analysis. Positive associations on multivariate analysis included occupational exposure to musty odours (odds ratio [OR] 1.62; 95% CI 1.24–2.11; $P < 0.001$) and

occupational exposure to pesticides (OR 1.61; 95% CI 1.13–2.28; $P = 0.008$). Significant positive associations (though statistically weaker) were found for teaching, cotton ginning, exposure to birds, car manufacturing, use of air conditioning at home, and exposure to ionizing radiation.

Apparently protective factors included smoking (OR 0.65; 95% CI 0.51–0.82; $P < 0.001$) and work using computer consoles (OR 0.70; 95% CI 0.54–0.91; $P = 0.009$). Significant negative associations were also described for unpaid childcare and exposure to cats, among others.

The authors readily acknowledge potential limitations of this study. For example, only 706 controls were enrolled and the demographic composition of the patients was very different from that of patients in the UK, for example. Furthermore, the size of the study dictates that many occupations were represented by tiny numbers, and the possibility of some associations arising by chance must be considered. Also, the questionnaire design is inevitably open to bias. For example, patients with known sarcoidosis may already have thought extensively about their previous occupational/environmental exposure, thus influencing their responses.

Despite these inevitable concerns, this study is extremely informative. The concept that complex environmental factors influence sarcoidosis is reinforced. However, the findings do lean towards the significance of aerosolized organic exposures in the pathogenesis of disease. Thus, the search for relevant triggers in susceptible individuals can be increasingly refined, while researchers can also begin to investigate mechanisms of protection conferred by factors such as cigarette smoking.

Leflunomide for chronic sarcoidosis

Baughman R, Lower LE. *Sarcoidosis Vasc Diffuse Lung Dis* 2004; **21**: 43–8

BACKGROUND. When patients with sarcoidosis fail to respond to prednisolone, or if they are intolerant of corticosteroids, existing evidence points to methotrexate as second-line treatment |12|. However, what should we do if patients are then unresponsive to, or intolerant of, methotrexate? Less evidence is available with which to answer this question. In rheumatoid arthritis leflunomide, a dihydroorotate dehydrogenase inhibitor, has been successful as an alternative or adjunct to methotrexate. This study, from one of the world's foremost sarcoidosis clinics, describes experience with the use of leflunomide in chronic sarcoidosis.

INTERPRETATION. Leflunomide appeared to be effective in at least 75% of patients, and was well tolerated. Although this series was small and randomized controlled trials are required in order to confirm these observations more rigorously, it seems logical to consider leflunomide if patients require discontinuation of methotrexate.

Comment

This observational study comes from a single American tertiary referral centre, and with the exception of case reports provides the first published experience of lefluno-

mide for sarcoidosis. The authors reviewed case records for all patients attending with confirmed or probable sarcoidosis over a 1-year period ($n = 669$). Thirty-two patients were taking leflunomide (of whom 15 and eleven were concurrently taking methotrexate and corticosteroids respectively). The 17 patients taking leflunomide alone had all previously stopped methotrexate because of nausea ($n = 12$) or pulmonary toxicity ($n = 5$). The commonest organs involved in patients taking leflunomide were the eyes (88%) and lungs (50%).

Among the 17 patients taking leflunomide alone, a complete or partial response was observed in 13 (complete and partial responses defined as 90 and 50% improvements in maximal disease involvement, respectively). In the 15 taking concurrent methotrexate, twelve were considered to have had a complete or partial response. Turning specifically to the lung, 16 patients had pulmonary manifestations, of whom 13 had a complete or partial response to leflunomide (eight of these 16 patients received leflunomide without methotrexate, but it is impossible to say whether the complete response rate was influenced by methotrexate).

Leflunomide was generally well tolerated. Three patients stopped the drug because of nausea (one of whom was taking methotrexate). Of the five patients who stopped methotrexate because of adverse pulmonary effects, all tolerated leflunomide, while ten of twelve who stopped methotrexate because of nausea tolerated leflunomide. No serious haematological or hepatic abnormalities were associated with leflunomide (blood was checked every 2 months).

Obviously, these results, from a small and selected cohort of patients, are purely observational and must be regarded as such. Overall, the results are impressive, especially when it is considered that the treatment was generally reserved for patients who had done badly with corticosteroids and/or methotrexate. One important caveat to bear in mind, however, is that leflunomide has itself recently been linked with the development of ILD, and this association requires careful monitoring |**13**|. These observations propose leflunomide as a good candidate for randomized controlled trials in sarcoidosis. In the meantime it seems reasonable at least to consider this drug in the setting of sarcoidosis for which corticosteroids and/or methotrexate have been unsuccessful.

Conclusion

Significant strides continue to be made in the understanding of IPF. The emergence of large randomized controlled trials for the study of this relatively rare disease should be regarded as a significant organizational triumph. However, while we learn more and more about the role of fibrosis in IPF, our therapeutic options remain bleak, as exemplified by the negative results described for IFN-γ1b, the combination of prednisolone and cyclophosphamide, and the epidemiological analyses for statins and ACE inhibitors. This depressing picture adds further impetus to the search for new mechanisms and treatments for IPF. In this regard, several more randomized controlled trials are currently under way, and final results from these, some of which will be published this year, are awaited with great excitement.

Many of the methods used so successfully in the study of IPF are being rigorously applied to other ILDs with considerable success. In particular, the value of HRCT in making a global assessment of lung architecture continues to help us revise our understanding of ILDs, as exemplified in the study of systemic sclerosis by Desai and colleagues. Similarly, the meticulous application of epidemiological methods has identified novel environmental candidates for the pathogenesis of sarcoidosis, in turn suggesting selected antigens for vigorous scientific study.

Finally, the paper by Flaherty and colleagues emphasizes that the clinical application of the advances in ILD is critically dependent upon close collaboration between physician, radiologist, pathologist and surgeon. This level of cooperation is best provided by specialist clinics for ILD.

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Part IV

Respiratory infections

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6

Tuberculosis

ADAM HILL

Introduction

Tuberculosis (TB) remains a global problem, the World Health Organization (WHO) estimating that one-third of the world's population is latently infected with *Mycobacterium tuberculosis* and that TB accounts for approximately two million deaths throughout the world annually.

In order to reduce the burden of TB, there has been a focus on treating active TB, rigorous contact-tracing and treating latent TB infection, and bacillus Calmette–Guérin (BCG) vaccination in some countries.

There have been 4026 articles published on TB from the beginning of November 2003 until the end of December 2004. Fifteen articles of clinical relevance have been selected for this chapter.

Latent TB

Latent TB infection is defined as evidence of *Mycobacterium tuberculosis* infection (a strongly positive tuberculin skin test) without evidence of active TB. The identification and treatment of latent infection is central to the elimination of TB because the development of active TB in persons with such an infection can effectively be prevented with treatment, thereby stopping further spread of the disease. Latent *M. tuberculosis* infection is predominantly identified by tracing TB contacts, although it can be detected through other routes, for example immigrant screening, pre-employment screening or as part of a BCG vaccination programme. In order to reduce the probability of developing active TB, a variety of regimens are recommended internationally for treating latent *M. tuberculosis* infection. Some of the available regimens include 6–9 months of isoniazid therapy, 4 months of rifampicin therapy, 3 months of treatment with a combination of rifampicin and isoniazid, and 2 months of combination therapy with rifampicin and pyrazinamide. Two papers are reviewed. The first explores the selection of patients clinicians should target for the treatment of latent TB. The next paper compares the 4-month rifampicin regimen with 9 months of isoniazid therapy.

Priorities for the treatment of latent tuberculosis infection in the United States

Horsburgh CR Jr. *N Engl J Med* 2004; **350**: 2060–7

BACKGROUND. The prevention of active TB through the treatment of latent TB infection is a major element of the international strategy for eliminating TB. Targeted treatment for persons who are at the highest risk of TB reactivating will be needed to achieve this goal. Following exposure, the lifetime risk of the development of TB is estimated to be about 5–10%. Currently, the rate of completion of treatment for latent TB is low. A more precise assessment of the lifetime risk of the reactivation of TB could help to identify patients who are at the highest risk and motivate them to complete treatment. In this study, published reports were reviewed to obtain estimates of the risk of TB among persons with a positive tuberculin skin test. The study stratified the lifetime risk based on age, the size of the skin test and presence or absence of specific medical conditions.

INTERPRETATION. The lifetime risk of TB reactivating is shown in Table 6.1. In this study a recent conversion of a tuberculin skin test was defined as a conversion from a negative to a positive test within the previous 2 years or a positive test in a person in close contact with a person with active pulmonary TB. All others with a positive test were recorded as having a non-conversion positive test. The relative risk (RR) of TB reactivating among persons with medical conditions that impair the immune control of *M. tuberculosis* was 1.3–1.4 for persons with gastrectomy, 1.6 for underweight persons (>10% below normal weight), 1.2–1.7 for persons with silicosis, 1.7 for those with diabetes, 2.0 for those receiving infliximab therapy, 2.4 for those with chronic renal failure, 5.2 for those with old healed TB, and 9.4–9.9 for patients with advanced human immunodeficiency virus (HIV) infection.

Comment

This is an important study and helps stratify the lifetime risk of TB based on age, the size of the skin reaction and the presence or absence of specific medical conditions. Clinicians can use this information to target chemoprophylaxis in high-risk groups.

Treatment completion and costs of a randomized trial of rifampin for 4 months versus isoniazid for 9 months

Menzies D, Dion MJ, Rabinovitch B, Mannix S, Brassard P, Schwartzman K. *Am J Respir Crit Care Med* 2004; **170**: 445–9

BACKGROUND. Rifampicin daily for 4 months is an alternative to isoniazid for 6–9 months for the treatment of latent TB. This randomized study assessed treatment completion and the safety and efficacy of rifampicin administered daily for

Table 6.1 Lifetime risk of reactivation tuberculosis*

Size of induration on skin test and age	Non-converstion positive skin test	Recent conversion of skin test	Immunosupressive therapy	Old, healed tuberculosis	Advanced HIV infection
	Percentage (95% confidence interval)				
Induration of ≥15 mm					
0–5 yr	13 (10–16)	17 (12–24)	25 (7–87)	66 (34–100)	100 (88–100)
6–15 yr	7 (6–8)	8 (6–10)	14 (4–46)	37 (21–67)	70 (52–92)
16–25 yr	8 (5–15)	13 (8–21)	17 (3–84)	44 (15–100)	83 (39–100)
26–35 yr	7 (4–13)	12 (8–19)	15 (3–74)	39 (14–100)	73 (35–100)
36–45 yr	4 (2–7)	7 (5–12)	8 (2–39)	21 (8–57)	40 (20–79)
46–55 yr	3 (2–6)	6 (4–10)	6 (1–32)	17 (6–46)	32 (16–44)
56–65 yr	3 (2–4)	3 (1–7)	5 (1–23)	13 (5–33)	25 (14–46)
≥66 yr	2 (1–3)	2 (1–5)	4 (1–17)	9 (4–24)	18 (10–33)
Induration of 10–14 mm					
0–5 yr	10 (6–15)	13 (8–21)	20 (4–82)	53 (22–100)	100 (56–100)
6–15 yr	4 (3–5)	5 (3–7)	8 (2–30)	20 (10–44)	38 (24–61)
16–25 yr	7 (3–13)	10 (6–17)	13 (2–73)	35 (12–100)	66 (30–100)
26–35 yr	6 (3–12)	9 (5–15)	12 (2–64)	31 (10–93)	58 (26–100)
36–45 yr	3 (2–6)	5 (3–9)	7 (1–34)	17 (6–50)	33 (15–68)
46–55 yr	3 (1–5)	5 (3–8)	5 (1–8)	14 (5–40)	26 (12–55)
56–65 yr	2 (1–4)	3 (1–6)	4 (1–20)	11 (4–29)	20 (11–39)
≥66 yr	2 (1–3)	2 (1–5)	3 (1–14)	8 (3–20)	15 (8–28)
Induration of 5–9 mm					
0–5 yr	3 (2–6)	6 (2–12)	6 (1–31)	16 (6–45)	31 (15–63)
6–15 yr	2 (1–3)	3 (2–5)	4 (1–17)	11 (5–25)	21 (13–34)
16–25 yr	6 (2–14)	8 (4–17)	11 (2–79)	29 (7–100)	55 (19–100)
26–35 yr	5 (2–13)	7 (3–15)	10 (1–69)	25 (6–100)	48 (17–100)
36–45 yr	3 (1–6)	4 (2–9)	5 (1–34)	12 (3–50)	24 (8–68)
46–55 yr	2 (1–5)	4 (2–8)	4 (1–28)	10 (3–40)	19 (7–55)
56–65 yr	2 (1–3)	2 (1–6)	3 (0–18)	8 (2–26)	15 (6–36)
≥66 yr	1 (0–2)	2 (0–5)	2 (0–13)	6 (2–19)	11 (4–26)

* Data on the risk associated with recent conversion are from studies of household contacts of patients with active tuberculosis and are applicable to situations in which recent infection is likely, such as among persons with recent skin-test conversion, persons living in prison or a homeless shelter, intravenous-drug users, or persons who immigrated from a country with a high incidence of tuberculosis within the previous five years. Data on the risk associated with immunosuppressive therapy are from a study involving patients who were receiving infliximab and are applicable to patients undergoing long-term therapy with other medications that are known to impair cell-mediated immunity. HIV, human immunodeficiency virus.
Source: Horsburgh (2004).

4 months compared with 9 months of isoniazid for therapy of latent TB infection. In an open-label trial, consenting patients whose treating physician had recommended therapy for latent TB infection were randomized to daily self-administered rifampicin for 4 months ($n = 58$) or daily self-administered isoniazid for 9 months ($n = 58$).

Interpretation. Ninety-one per cent of patients randomized to rifampicin took 80% of doses and 86% took more than 90% of doses within 20 weeks compared with patients randomized to isoniazid (76 and 62% took 80 and 90% respectively of doses of isoniazid within 43 weeks). In summary, patients randomized to rifampicin had higher treatment completion rates than patients randomized to isoniazid; the RR of taking 80% of the doses was 1.2 (95% confidence interval [CI] 1.02–1.4; $P < 0.05$) and the RR of taking 90% of the doses was 1.4 (95% CI 1.1–1.7; $P < 0.05$). Three per cent of patients in the rifampicin group had adverse events that resulted in permanent discontinuation of therapy compared with 14% in patients taking isoniazid. Five per cent developed drug-induced hepatitis that led to discontinuation of therapy, and all were taking isoniazid. Overall, the total costs of therapy were significantly higher for isoniazid (Can$27 014) than rifampicin (Can$17 182), although most costs were related to routine follow-up visits.

Comment

In conclusion, completion of therapy was significantly better, major side effects were somewhat lower and the shorter regimen was less expensive with 4 months of rifampicin than with 9 months of isoniazid. However, this was a small study and larger-scale and longer studies are needed to assess the safety and efficacy of the 4-month rifampicin regimen.

In order to reduce the burden of TB, BCG vaccination is offered. In the UK, neonates at high risk of contracting TB, all teenagers at school, travellers to countries with a high incidence of TB, and TB contacts with a negative tuberculin skin test are all offered BCG vaccination. Two papers are reviewed here. The authors of the next paper studied the long-term efficacy of BCG vaccine and the following paper evaluated the effectiveness of an inactivated mycobacterial vaccine for the prevention of TB in patients with HIV.

Long-term efficacy of BCG vaccine in American Indians and Alaska natives: a 60-year follow-up study

Aronson NE, Santosham M, Comstock GW, *et al*. *JAMA* 2004; **291**: 2086–91

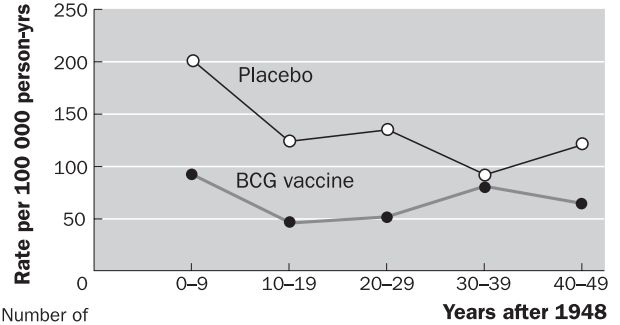
Background. The duration of protection from TB given by BCG vaccines is not known. In 1935 a cohort of Native Americans were enrolled in a placebo-controlled BCG vaccine trial (1935–1938). A retrospective record review was carried out for

the follow-up period from 1948 to 1998 using Indian health service records, TB registries, death certificates and supplementary interviews with trial participants.

INTERPRETATION. Data from 1483 participants in the BCG vaccine group and 1309 in the placebo group were analysed. The main outcome measures were the efficacies of the BCG vaccine calculated for each 10-year interval using a Cox regression model with time-dependent variables based on TB events occurring after 31 December 1947 (the end of the prospective case-finding). Since 1948, the overall incidence of TB was 66 cases per 100 000 person-years in the BCG vaccination group compared with 138 cases per 100 000 person-years in the placebo group, giving an unadjusted BCG vaccine efficacy of 52% (95% CI 27 to 69%). Adjustments for age at vaccination, tribe, subsequent BCG vaccination, chronic medical illness, isoniazid use and BCG strain did not substantially affect vaccine efficacy. Since 1948, the efficacy of BCG vaccination in protection against pulmonary TB was found to be 52% (95% CI 14 to 74%), in extrapulmonary TB 63% (95% CI –11 to 90%), in cases with both pulmonary and extrapulmonary TB 45% (95% CI –20 to 75%) and for preventing death due to TB 44% (95% CI –22% to 70%). There was slight but not statistically significant waning of the efficacy of BCG vaccination over time (Fig. 6.1). There appeared to be a difference in waning by sex, with a decline for males ($P < 0.02$) but not for women.

Comment

This is an important long-term follow-up of a placebo-controlled BCG vaccine trial. The efficacy of the BCG vaccine persisted for 50–60 years, suggesting that a single dose of an effective BCG vaccine can have a long duration of protection. New TB vaccines to improve efficacy are currently being developed.



Number of tuberculosis cases	0–9	10–19	20–29	30–39	40–49
Placebo	25	14	14	8	5
BCG vaccine	13	6	6	8	3
Vaccine efficacy (%)	54	62	62	12	48

Fig. 6.1 Tuberculosis incidence rates and efficacy by treatment group and decade since 1 January 1948. Source: Aronson *et al*. (2004).

Immunogenicity of an inactivated mycobacterial vaccine for the prevention of HIV-associated tuberculosis: a randomized, controlled trial

Vuola JM, Ristola MA, Cole B, *et al*. *AIDS* 2003; **17**: 2351–5

BACKGROUND. Prior to the widespread use of *M. bovis* BCG, inactivated whole-cell mycobacterial vaccines had been shown to be effective in the prevention of TB. In HIV patients this has potential advantages, including a better safety profile than live vaccines, improved immune recognition compared with subunit vaccines containing only one or two antigens, and a greater likelihood of boosting BCG than live vaccines, which have limited replication in subjects with prior mycobacterial immunity. The present randomized controlled study was conducted to determine the safety and immunogenicity of an inactivated whole-cell mycobacterial vaccine in persons with HIV infection. A total of 39 HIV-positive patients with prior BCG immunization and CD4 cell counts of at least 200 $\times$ 10^6 cells/l were randomized to five doses of inactivated *Mycobacterium vaccae* (MV) vaccine or control vaccine (CV) at 0, 2, 4, 6 and 12 months. Lymphocyte proliferation (LPA) and interferon γ (IFN-γ) responses to mycobacterial antigens were assayed at baseline, after three and five doses of vaccine and more than 1 year later. Parallel studies were conducted in ten HIV-negative subjects with prior BCG immunization.

INTERPRETATION. Among HIV-positive patients, 19 MV recipients had higher LPA and IFN-γ responses to MV sonicate (new mycobacterial antigens) than 20 CV recipients after three and five doses of vaccine and more than 1 year later (Fig. 6.2). LPA responses to *M. tuberculosis* whole-cell lysate (recall mycobacterial antigens) increased over time in both groups, consistent with prior BCG immunization and current antiretroviral therapy; after three doses, responses were boosted to higher levels in subjects receiving MV subjects than in those receiving CV. LPA responses to the *M. tuberculosis* whole-cell lysate were also boosted in HIV-negative MV recipients. Immunization was safe and had no adverse effects on HIV viral load or CD4 cell count.

Comment

In BCG-primed, HIV-positive and HIV-negative subjects, *Mycobacterium vaccae* induces durable cellular immune responses to a new mycobacterial antigen and boosts pre-existing responses to whole-cell lysate. *Mycobacterium vaccae* is a candidate for clinical trials for the prevention of HIV-associated TB.

The next three papers explore the role of the quinolone moxifloxacin in the treatment of TB, the addition of dexamethasone in the treatment of TB meningitis, and a comparison of two 8-month regimens for the treatment of pulmonary TB. The following three papers review paradoxical reactions whilst on TB therapy in patients with and without HIV co-infection, treatment outcomes comparing directly observed therapy and self-administered therapy, and the response of pulmonary tuberculomas to anti-TB treatment.

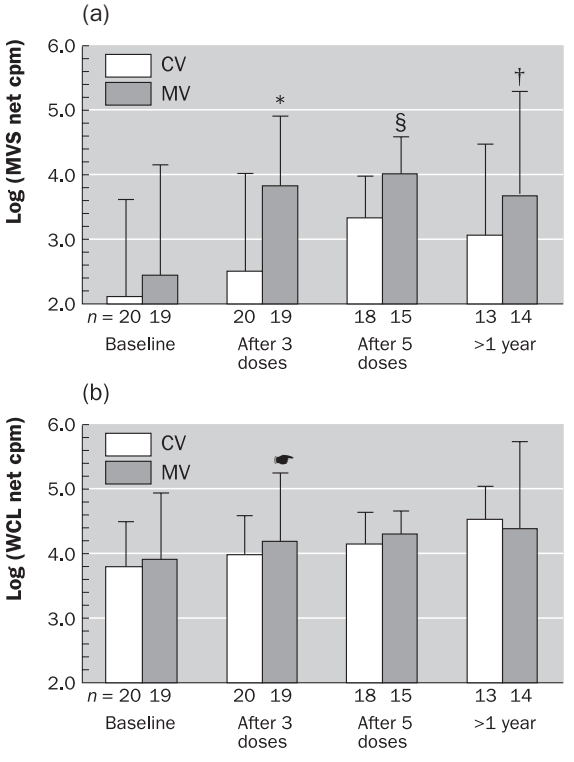


Fig. 6.2 Lymphocyte proliferation responses to (a) *Mycobacterium vaccae* sonicate (MVS) or (b) *Mycobacterium tuberculosis* whole-cell lysate (WCL) among HIV-positive subjects who received *M. vaccae* (MV) or control vaccine (CV). Responses are shown as mean and standard deviation of $\log_{10}$ value of net counts per minute (cpm). *P*-values ≤0.05 are shown: (a) **P* = 0.0004; §*P* = 0.0027; † *P* = 0.0198; (b) **P* = 0.046. Source: Vuola *et al*. (2003).

The bactericidal activity of moxifloxacin in patients with pulmonary tuberculosis

Gosling RD, Uiso LO, Sam NE, *et al*. *Am J Respir Crit Care Med* 2003; **168**: 1342–5

Background. There is growing interest in the development of new drugs active against TB, both in view of the rising rates of multidrug-resistant TB and in patients who are intolerant of first-line drugs, such as rifampicin, ethambutol, isoniazid and pyrazinamide. The 8-methoxyfluoroquinolone moxifloxacin inhibits DNA gyrase and is thought to be bactericidal against *M. tuberculosis*. The authors evaluated the bactericidal activity of moxifloxacin and compared moxifloxacin with the standard

first-line drugs rifampicin and isoniazid. Patients with newly diagnosed smear-positive pulmonary TB were randomized to receive 400 mg moxifloxacin, 300 mg isoniazid or 600 mg rifampicin daily for 5 days. Sixteen-hour overnight sputum collections were made for the 2 days before and for 5 days of monotherapy. Bactericidal activity was estimated by the time taken to kill 50% of viable bacilli, and early bactericidal activity was estimated as the fall in sputum viable count during the first 2 days.

INTERPRETATION. In terms of the time taken to kill 50% of viable bacilli, isoniazid was more active than both rifampicin and moxifloxacin ($P = 0.03$). Using the early bactericidal activity method, isoniazid was significantly more active than rifampicin ($P < 0.01$) but not moxifloxacin (Table 6.2).

Comment

Moxifloxacin has bactericidal activity similar to that of rifampicin in human subjects with pulmonary TB.

In recent experimental studies using the mouse model of TB, treatment with a combination of rifampicin, moxifloxacin and pyrazinamide was able to shorten the time to negative lung cultures by up to 2 months compared with the standard regimen of rifampicin, isoniazid and pyrazinamide. In addition, moxifloxacin-containing regimens of reduced duration produce a stable cure in murine TB with no relapse |**1**,**2**|.

These preliminary data are promising but studies in humans are needed to evaluate the effectiveness of moxifloxacin as part of a short-course regimen for the treatment of drug-susceptible TB.

Table 6.2 The mean (95% CI) time to kill 50% of viable bacilli and the early bactericidal activity

	Time taken to kill 50% of viable bacilli	Early bactericidal activity
Moxifloxacin	0.88 days (0.43–1.33)	0.53 (0.28–0.79)
Isoniazid	0.46 days (0.31–0.61)*	0.77 (0.54–1.00)†
Rifampicin	0.71 days (0.48–0.95)	0.28 (0.15–0.41)

* Isoniazid was significantly different from both rifampicin and moxifloxacin ($P = 0.03$); † isoniazid was significantly more active than rifampicin ($P < 0.01$) but not moxifloxacin.
Source: Gosling *et al*. (2003).

Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults

Thwaites GE, Nguyen DB, Nguyen HD, *et al*. *N Engl J Med* 2004; **351**: 1741–51

BACKGROUND. TB meningitis kills or disables more than half of those affected with the disease. This study was a randomized, double-blind, placebo-controlled trial in Vietnam in patients over 14 years of age who had TB meningitis, with or without HIV infection. The aim of the study was to determine whether adjunctive treatment with

dexamethasone reduced the risk of death or severe disability after 9 months of follow-up.

INTERPRETATION. A total of 545 patients were randomly assigned to groups that received either dexamethasone (274 patients) or placebo (271 patients). Only ten patients (1.8%) had been lost to follow-up at 9 months of treatment. Treatment with dexamethasone was associated with a reduced risk of death (RR 0.69; 95% CI 0.52–0.92; $P = 0.01$). It was not associated with a significant reduction in the proportion of severely disabled patients among survivors (18.2% in the dexamethasone group and 13.8% in the placebo group; $P = 0.27$). It was also not associated with a significant reduction in the proportion of patients who had either died or were severely disabled after 9 months (odds ratio [OR] 0.81; 95% CI 0.58–1.13; $P = 0.22$). There were significantly fewer serious adverse events in the dexamethasone group than in the placebo group (9.5% patients in the dexamethasone group and 16.6% patients in the placebo group; $P = 0.02$). The treatment effects with dexamethasone were not influenced by disease severity or HIV infection.

Comment

Early treatment with dexamethasone along with anti-TB treatment in patients with TB meningitis over 14 years of age, independently of disease severity or HIV status, improves survival but does not prevent severe disability.

Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomized trial

Jindani A, Nunn AJ, Enarson DA. *Lancet* 2004; **364**: 1244–51

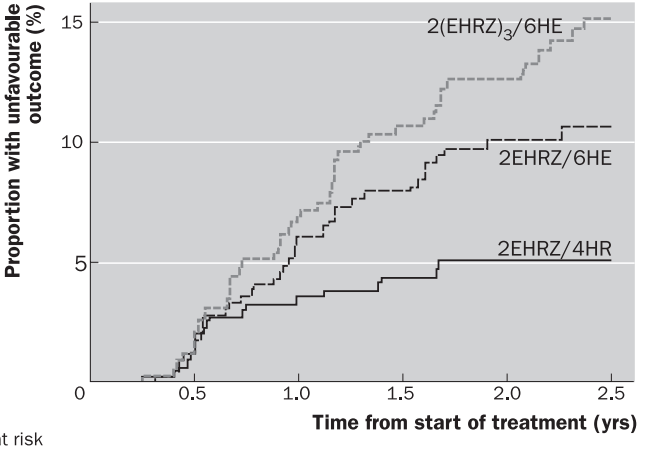
BACKGROUND. An 8-month regimen recommended by the WHO, based on ethambutol and isoniazid, was evaluated in a randomized clinical trial against a 6-month standard regimen. A total of 1355 patients with newly diagnosed smear-positive pulmonary TB were randomly assigned to one of three regimens. In regimen 1, patients received daily ethambutol (E), isoniazid (H), rifampicin (R) and pyrazinamide (Z) for 2 months, followed by isoniazid and ethambutol for 6 months (2EHRZ/6HE). In regimen 2, patients received the same drugs but they were given three times weekly in the initial intensive phase, followed by isoniazid and ethambutol for 6 months (2[EHRZ]3/6HE). In regimen 3, patients received the same initial intensive phase as the first regimen, followed by 4 months of daily isoniazid and rifampicin (2EHRZ/4HR). The follow-up was to 30 months after the start of anti-TB treatment. Sputum was examined regularly by microscopy and culture for TB. An unfavourable outcome was defined as failure during treatment or relapse following treatment.

INTERPRETATION. At 2 months, a significantly higher proportion of patients assigned the daily intensive phase (regimens 1 and 3) than of those assigned the three-times-weekly regimen (regimen 2) were culture-negative (85 versus 77%; $P = 0.001$). Twelve months after the end of anti-TB treatment, the proportions of unfavourable outcomes were 10% with

regimen 1 (2EHRZ/6HE), 14% with regimen 2 (2[EHRZ]3/6HE) and 5% with regimen 3 (2EHRZ/4HR) (Fig. 6.3). Overall, both 8-month regimens (1 and 2) were significantly inferior to the standard 6-month regimen (3) (Fig. 6.3).

Comment

Overall, the regimen with the greatest success was daily treatment for 2 months with the combination of ethambutol, isoniazid, rifampicin and pyrazinamide followed by rifampicin and isoniazid for 4 months. This is the standard first-line regimen used in the UK and many international centres.



Number at risk			
2EHRZ/6HE	456	348	227
$2(EHRZ)_3$/6HE	466	366	231
2EHRZ/4HR	433	350	248

Fig. 6.3 Time to unfavourable outcome by regimen. Source: Jindani *et al*. (2004).

Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection

Breen RA, Smith CJ, Bettinson H, *et al*. *Thorax* 2004; **59**: 704–7

Background. It has been suggested that deterioration of TB during appropriate treatment, termed a paradoxical reaction, is more common and severe in HIV-positive individuals on highly active antiretroviral therapy (HAART). This retrospective study was undertaken to determine the frequency of paradoxical reaction and its associated features in a population of TB patients with (*n* = 50) and without co-infection with HIV (*n* = 50). A paradoxical reaction was defined as worsening of clinical or radiological findings following the initiation of appropriate

anti-TB treatment in the absence of evidence of disease relapse or the presence of another diagnosis. Dissemination was defined as clinical or radiological apparent disease at more than one site.

INTERPRETATION. Paradoxical reaction occurred in 28% of HIV-positive patients and 10% of HIV-negative patients. Disseminated TB was present in at least 65% of patients with paradoxical reaction. In 28 HIV-positive patients starting HAART, paradoxical reaction was significantly associated with commencing HAART within 6 weeks of starting anti-TB treatment ($P = 0.03$) and was more common in those with disseminated TB, although in the latter group the association just failed to reach conventional statistical significance ($P = 0.09$). No association was found between the development of paradoxical reaction and baseline CD4 count or CD4 response to HAART. Nine out of 24 patients received corticosteroids because of severe systemic manifestations or prolonged duration of the paradoxical reaction. This led to an improvement in all cases after a median of 3 days (range 1–7 days).

Comment

Paradoxical reaction is common in HIV-infected and -uninfected individuals with TB. Early introduction of HAART and the presence of disseminated TB appear to be important in co-infected patients. This may influence when HAART should be initiated but further prospective studies are needed.

Tuberculosis treatment outcomes: directly observed therapy compared with self-administered therapy

Jasmer RM, Seaman CB, Gonzalez LC, Kawamura LM, Osmond DH, Daley CL. *Am J Respir Crit Care Med* 2004; **170**: 561–6

BACKGROUND. Effective treatment of TB requires adherence to a minimum of 6 months of treatment with multiple drugs. To improve adherence and cure rates, directly observed therapy (DOT) has been recommended internationally in groups at high risk of non-adherence for the treatment of pulmonary TB. This retrospective study compared treatment outcomes, DOT compared with self-administered therapy, among all culture-positive patients treated for active pulmonary TB ($n = 372$) in San Francisco County, California from 1998 to 2000. Patients treated by DOT received treatment daily for the first 2 months (the weekends were not supervised); during the continuation phase they received either daily or twice weekly supervised therapy or self-administered therapy.

INTERPRETATION. In this retrospective study, 149 patients who received DOT at the start of treatment were compared with the 223 patients who received self-administered therapy at the start of treatment. Seventy-one per cent of patients who started on DOT were treated by DOT throughout. Of those who received self-administered therapy, 44% were considered by the authors to have risk factors for non-adherence and should have been assigned to DOT. The patients on self-administered therapy were split into those with and without risk factors for non-adherence and were then compared with the DOT group. The results are shown in

Table 6.3; only significant changes are highlighted. Treatment cure rates were higher and death due to TB was lower in the DOT group but the explanation for the differences is that 44% in the self-administered therapy group should have received DOT as they were at risk of non-adherence to therapy. After exclusion of this group there were no significant differences between DOT and self-administered therapy.

Comment

This is a useful retrospective study and highlights the importance of DOT in high-risk groups of non-adherence to TB therapy. As in previous reports, DOT has not been proven to be superior to self-administered therapy in those not at risk of non-adherence.|**3,4**| This allows resources to be targeted for the patients who need DOT.

Table 6.3 Outcomes comparing directly observed therapy with self-administered therapy

	No. of patients	Treatment cure rate	Death due to TB	Relapse	Acquired drug resistance
DOT	149	97.8%	0%	0%	0%
SAT	223	88.6%*	5.5%*	2%	0.9%
SAT, at risk of non-adherence	97	80.3%†	10.6%†	1.8%	1%
SAT, not at risk of non-adherence	126	94%	1.6%	2.1%	0.8%

DOT, directly observed therapy; SAT, self-administered therapy. *$P \leq 0.002$ in comparison with patients receiving DOT at the start of treatment; †$P < 0.0001$ in comparison with patients receiving DOT at the start of treatment.
Source: Jasmer *et al*. (2004).

Response of pulmonary tuberculomas to anti-tuberculous treatment

Lee HS, Oh JY, Lee JH, *et al*. *Eur Respir J* 2004; **23**: 452–5

BACKGROUND. Pulmonary tuberculomas are well-circumscribed masses caused by *M. tuberculosis*. The aim of this retrospective study was to assess the response of tuberculomas to anti-TB treatment. The natural history of tuberculomas without treatment is variable (about one-third decrease in size, 30–50% have a stationary course and 21.7% enlarge) |5,6|.

INTERPRETATION. Forty-five patients diagnosed with pulmonary tuberculomas between January 1997 and December 2001 were studied. Tuberculomas were diagnosed in 93.4% by the presence of acid-fast bacilli or chronic granulomatous inflammation with caseating necrosis on percutaneous needle aspiration or biopsy. Of these 93.4%, 6.6% had chronic

granulomatous inflammation without caseating necrosis on percutaneous needle aspiration or biopsy, but had positive TB cultures from sputum or bronchoalveolar lavage; 68.9% of nodules were located within the upper lobes; 77.8% patients had one nodule; and 22.2% had two or more nodules. The areas of pulmonary tuberculoma were estimated by calculating the product of the longest diameter and the perpendicular short diameter on chest radiographs. The response to anti-TB treatment was categorized as 'decreased' (>25% reduction in area versus its initial area), 'increased' (>25% increase) and 'no change' (the remainder). The mean ±SD treatment duration was 11.5 ± 3.6 months, which is much longer than the conventional 6 months of treatment used for pulmonary TB. Three months after treatment, 40.0% were categorized as having a decreased response, 55.6% as showing no change and 4.4% as having an increased response. Twelve months after treatment, out of 42 patients available for chest radiographs, 76.2% were categorized as having a decreased response, 21.4% as showing no change and 2.4% as having an increased response. At the last follow-up (mean follow-up 27.0 ± 10.2 months), 82.2% were categorized as having a decreased response.

Comment

The majority of pulmonary tuberculomas were decreased during anti-TB treatment and this tendency continued after cessation of anti-TB treatment, although a transient enlargement during the early period of treatment was observed infrequently. The duration of treatment needed is not known and merits further study.

The final papers explore the use of IFN-γ gamma assays for the diagnosis of TB, the use of polymerase chain reaction (PCR) assays in diagnosing pulmonary TB in a low-incidence area, the risk of TB relapse, the transmission of TB and the value of a screening programme of chest radiography.

Specific detection of tuberculosis infection: an interferon-gamma-based assay using new antigens

Mori T, Sakatani M, Yamagishi F, *et al*. *Am J Respir Crit Care Med* 2004; **170**: 59–64

BACKGROUND. The tuberculin skin test for immunological diagnosis of *M. tuberculosis* infection has many limitations, including being confounded by BCG vaccination or exposure to non-tuberculous mycobacteria. *M. tuberculosis*-specific antigens have been identified that are absent from BCG and most non-tuberculous mycobacteria. The authors examined the use of two of these antigens, CFP-10 and ESAT-6, in a whole-blood IFN-γ assay as a diagnostic test for TB in BCG-vaccinated individuals. Because of the lack of an accurate standard with which to compare new tests for *M. tuberculosis* infection, the specificity of the whole-blood IFN-γ assay was estimated on the basis of data from people with no identified risk of *M. tuberculosis* exposure (216 BCG-vaccinated Japanese adults) and sensitivity was estimated on the basis of data from 118 patients with culture-confirmed *M. tuberculosis* infection who had received less than 1 week of treatment.

Interpretation. There were 216 people with no identified risk of *M. tuberculosis* exposure (mean age 20 years, range 18–33). None reported any TB contact or of working in a healthcare setting, and all had prior BCG vaccination. The other group consisted of 118 persons with culture-confirmed TB (mean age 54 years, range 13–86). No patients were known to be HIV-positive. The individual results are shown in Fig. 6.4. The cut-off used for CFP-10 and ESAT-6 was 0.35 IU/ml. The specificity for CFP-10 was 98.6% (95% CI 96–99.7) and that for ESAT-6 was 99.5% (95% CI 97.5–100). The sensitivities were 65.3% (95% CI 55.9–73.8) for CFP-10 and 81.4% (95% CI 73.1–87.9) for ESAT-6. Using a combination of CFP-10 and ESAT-6 responses, the test was regarded as positive if at least one of the two antigens was judged as test-positive. Using the combination of CFP-10 and ESAT-6 responses, the specificity of the test for the low-risk group was 98.1% (95% CI 95.3–99.5) and the sensitivity for patients with *M. tuberculosis* infection was 89.0% (81.9–94.0).

Comment

The results demonstrate that the whole blood IFN-γ assay using CFP-10 and ESAT-6 was highly specific and sensitive for *M. tuberculosis* infection and was unaffected by BCG vaccination status. Combining the two antigens improved the sensitivity of the test without compromising the specificity.

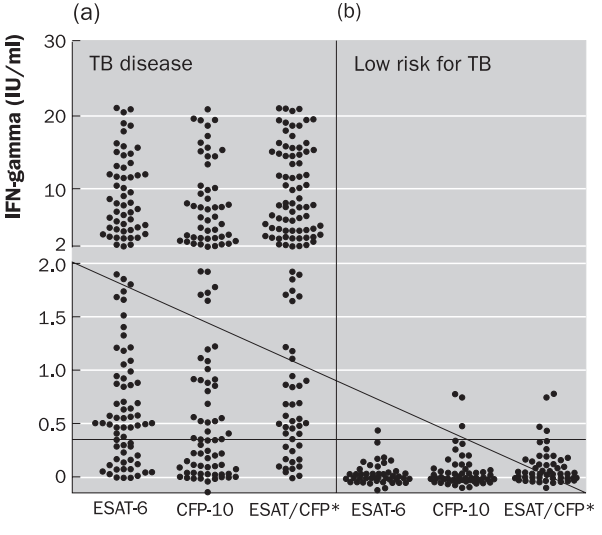


Fig. 6.4 Dot plot of individual responses to CFP-10 and ESAT-6 for 118 culture-positive patients with tuberculosis (TB) (a), and 216 subjects with a low risk for TB exposure (b). *For 'ESAT/CFP' the data for the antigen (ESAT-6 or CFP-10) giving the highest response is shown. The *dashed line* represents the cut-off of 0.35 IU/ml for IFN-γ. Source: Mori *et al*. (2004).

Economic evaluation of the use of PCR assay in diagnosing pulmonary TB in a low-incidence area

Rajalahti I, Ruokonen EL, Kotomaki T, Sintonen H, Nieminen MM. *Eur Respir J* 2004; **23**: 446–51

BACKGROUND. The aim of this study was to determine whether PCR testing in the initial diagnosis of pulmonary TB is cost-effective in a low-prevalence population. An economic evaluation was carried out between the smear and culture (without PCR) and smear, culture and PCR strategies. A decision tree model based on retrospective laboratory data was developed to assess the strategies of testing patients with suspicion of TB. Direct healthcare costs prior to confirmation of TB or non-tuberculous mycobacteria by PCR or culture were included. Effectiveness was measured by the probability of correct treatment and isolation decisions.

INTERPRETATION. In the baseline situation, smear and culture (without PCR) cost 29.50 euros less than the smear, culture and PCR strategy per patient tested. According to sensitivity analyses, reducing the PCR test price, shortening test performance time or increasing the proportion of smear-positive patients in the tested population would contribute to cost savings with the smear, culture and PCR strategy. Routine PCR testing of all specimens from suspected TB patients in a low-prevalence population was not cost-saving.

Comment

In low-prevalence countries, delays in both diagnosis and the initiation of treatment contribute to the spread of disease. The acid-fast smear test rapidly identifies patients with infectious TB but it is neither sensitive nor specific for *M. tuberculosis*. This can lead to inappropriate treatment if mycobacteria other than TB are subsequently cultured and can also lead to inappropriate contact-tracing.

PCR has the advantage of differentiating *M. tuberculosis* from mycobacteria other than TB and therefore treatment and contact-tracing could be commenced early and limit the spread of disease if PCR indicates *M tuberculosis* (PCR could also identify *M. tuberculosis* from some smear-negative cases). It would also prevent inappropriate treatment and contact-tracing if PCR were to indicate mycobacteria other than TB.

Applying the PCR assay to all samples (smear-negative and -positive cases) was not cost-effective. When the PCR assay was applied only to smear-positive sputum specimens, the smear and culture strategy was clearly dominated by it; that is, the PCR applied to smear-positive cases was less costly and more effective in producing correct treatment decisions and isolations.

The role of PCR is very variable. In many centres in the UK, the PCR is currently reserved for smear-positive cases that pose a large public health problem, such as healthcare workers. This allows contact-screening to be done in the appropriate cases or contact-tracing to be prevented if PCR indicates a mycobacterium other than TB.

A nested case–control study on treatment-related risk factors for early relapse of tuberculosis

Chang KC, Leung CC, Yew WW, Ho SC, Tam CM. *Am J Respir Crit Care Med* 2004; **170**: 1124–30

BACKGROUND. This nested case–control study evaluated treatment-related risk factors for the relapse of TB under a service programme of directly observed treatment.

INTERPRETATION. Out of 12 183 patients with pulmonary TB who completed treatment within 1 year, 113 relapsed within 30 months after commencement of therapy. The overall 30-month relapse rate was 0.9% (95% CI 0.8–1.1). On matching 113 cases with 226 control subjects in a univariate conditional logistic regression analysis, the following conditions were associated with relapse: history of opiate abuse (OR 6.0; 95% CI 1.2–29.7; $P \leq 0.1$); co-existing extrapulmonary TB (OR 3.2; 95% CI 1.6–6.6; $P \leq 0.1$); initial radiographic extent more than right upper lobe (OR 1.9; 95% CI 1.1–3.4; $P \leq 0.1$); cavitation on the initial chest radiograph (OR 1.8; 95% CI 1.1–2.9; $P \leq 0.1$); initial body weight <50 kg (OR 1.7; 95% CI 1.0–2.8; $P \leq 0.1$); three times weekly treatment throughout (OR 2.0; 95% CI 1.2–3.3; $P \leq 0.1$); and persistence of a positive TB culture after 2–3 months of treatment (OR 2.5; 95% CI 0.8–7.2, $P \leq 0.1$). In a conditional logistic model, three times weekly treatment increased the risk of relapse in comparison with daily treatment (OR 3.92; 95% CI 1.78–8.63), whereas prolonging both intensive phase and overall treatment by 50% or more protected against relapse (OR 0.24; 95% CI 0.08–0.70). When pretreatment culture was positive and cavitation was absent, the 30-month relapse rate for the standard three times weekly regimen was 1.1% (95% CI 0.6–2.0). The corresponding rates in the presence of cavitation were 7.8% (95% CI 4.0–14.6) for the standard three times weekly regimen, 3.3% (95% CI 1.9–5.5) for the standard daily regimen, 0.5% (95% CI 0.1–2.6) for the extended three times weekly regimen, and 0.4% (95% CI 0.1–0.9) for the extended daily regimen.

Comment

This study has important implications as internationally directly observed therapies are promoted to improve adherence and treatment outcomes. For patients with extensive TB or in patients who are still culture-positive after 2 months of TB therapy the three times weekly regimens are likely to lead to higher relapse rates, and in these cases daily therapy would be advised. Alternatively, prolongation of three times weekly therapy in both the initiation and the continuation phase in this study would be an alternative. Further studies are required to reduce the risk of relapse in programme settings.

Transmission of tuberculosis from smear negative patients: a molecular epidemiology study

Hernandez-Garduno E, Cook V, Kunimoto D, Elwood RK, Black WA, FitzGerald JM. *Thorax* 2004; **59**: 286–90

Background. Traditionally, patients who are smear-positive with TB are considered highly infectious whereas patients who are smear-negative are considered to be of low infectivity. This was a molecular epidemiology study of 791 patients in the Greater Vancouver regional district that estimated the number of episodes of TB transmission from two groups of smear-negative clustered patients assumed to be involved in recent transmission by the use of restriction fragment length polymorphism (RFLP). Group 1 ($n = 79$) included patients with pulmonary TB or pulmonary plus extrapulmonary disease; Group 2 ($n = 129$) included all patients in Group 1 plus extrapulmonary cases alone. A cluster was defined as all patients having isolates with the same DNA fingerprint and was likely to be involved in recent transmission.

Interpretation. In the total sample the mean ± SD age was 51 ± 21 years, 54.3% were male, and 17.0% of patients were clustered. Compared with smear-negative patients, smear-positive patients were more likely to be in a cluster (OR 2.0; 95% CI 1.1–3.6) and to have had a history of ethanol abuse (OR 2.7; 95% CI 1.0–6.7), diabetes mellitus (OR 2.8; 95% CI 1.1–7.0), injection drug use (OR 3.1; 95% CI 1.1–8.3) and to have had a previous hospital admission (OR 8.5; 95% CI 5.1–14.0). The proportion of episodes of transmission from smear-negative clustered patients ranged from 17.3 to 22.2% in Group 1 and from 25 to 41% in Group 2.

Comment

These data suggest that smear-negative cases are the cause of transmission for at least one in six patients with pulmonary involvement. When patients with extrapulmonary TB are included there is a further increased risk of spread but it is unclear whether this is from the site of extrapulmonary disease or unrecognized pulmonary involvement (in patients with extrapulmonary TB and a normal chest radiograph sputum samples are sometimes not sent for TB smear and culture).

The transmissibility from smear-negative cases has important public health implications. In particular, in the UK no contact screening is carried out in patients with extrapulmonary TB alone. Further studies are needed.

Value of chest radiography in a tuberculosis prevention programme for HIV-infected people, Botswana

Mosimaneotsile B, Talbot EA, Moeti TL, *et al*. *Lancet* 2003; **362**: 1551–2

Background. To exclude TB, WHO/UNAIDS recommends considering the medical history, symptom screen and chest radiograph before starting TB prevention in

people infected with HIV. The value of a chest radiograph for this purpose is unknown. The authors prospectively assessed 935 HIV-infected outpatients seeking preventive therapy with isoniazid.

INTERPRETATION. Of 935 patients, 692 (74%) had no signs or symptoms of TB. Six hundred and eighty-six of these 692 agreed to have a chest radiograph but 123 (18%) were lost during the chest radiograph process. A total of 560 patients finally completed the chest radiograph process. One (0.2%) of the remaining 560 was diagnosed with TB on the basis of the chest radiograph (pleural effusion), 23 (4%) had non-specific pneumonitis on the chest radiograph and 536 (96%) had normal chest radiographs.

Comment

A screening chest radiograph should not be required routinely for asymptomatic people taking isoniazid as preventive treatment in settings where it is possible to screen for signs and symptoms of TB.

Conclusion

TB remains a global problem. WHO estimates that one-third of the world's population is latently infected with *M. tuberculosis* and that TB accounts for approximately 2 million deaths throughout the world annually.

In order to reduce the burden of TB there has been a focus on treating active TB, rigorous contact-tracing and treating latent TB infection, and BCG vaccination in some countries.

There have been 4026 articles published on TB from the beginning of November 2003 until the end of December 2004. Fifteen articles of clinical relevance have been selected for this chapter. The principal messages from the papers are summarized below.

Paper 1: Horsburgh *et al.* (2004). This paper stratified the lifetime risk of TB based on age, the size of the tuberculin skin test and the presence or absence of specific medical conditions. Clinicians can use this to target chemoprophylaxis in high-risk groups.

Paper 2: Menzies *et al.* (2004). For the treatment of latent infection, completion of therapy was significantly better with 4 months of rifampicin than 9 months of isoniazid treatment. Major side effects were somewhat lower with the shorter regimen, which was also less expensive. This was, however, a small study and larger-scale and longer studies are needed to assess the safety and efficacy of the 4-month rifampicin regimen.

Paper 3: Aronson *et al.* (2004). This is an important long-term follow-up of a placebo-controlled BCG vaccine trial. The BCG vaccine efficacy persisted for 50–60 years, suggesting that a single dose of an effective BCG vaccine can have a long duration of protection. New TB vaccines to improve efficacy are currently being developed.

Paper 4: Vuola *et al.* (2003). In BCG-primed, HIV-positive and HIV-negative subjects, *Mycobacterium vaccae* induces durable cellular immune responses to a new mycobacterial antigen and boosts pre-existing responses to whole-cell lysate. *M. vaccae* is a candidate for clinical trials for the prevention of HIV-associated TB.

Paper 5: Gosling *et al.* (2003). Moxifloxacin has bactericidal activity similar to rifampicin in human subjects with pulmonary TB. These preliminary data are promising but studies in humans are needed to evaluate the effectiveness of moxifloxacin as part of a short-course regimen for the treatment of drug-susceptible TB.

Paper 6: Thwaites *et al.* (2004). Early treatment with dexamethasone along with anti-TB treatment in patients with TB meningitis over 14 years of age, independently of disease severity or HIV status, improves survival but does not prevent severe disability.

Paper 7: Jindani *et al.* (2004). The regimen with greatest success for the treatment of pulmonary TB was daily treatment with 2 months combination of ethambutol, isoniazid, rifampicin and pyrazinamide followed by rifampicin and isoniazid for 4 months. This is the standard first-line regimen used in the UK and many international centres.

Paper 8: Breen *et al.* (2004). Paradoxical reaction is common in HIV-infected and -uninfected individuals with TB therapy. Early introduction of HAART and the presence of disseminated TB appear to be important risk factors for paradoxical reactions in co-infected patients. This may influence when HAART should be initiated, but further prospective studies are needed.

Paper 9: Jasmer *et al.* (2004). This is a useful retrospective study and highlights the importance of DOT in groups at high risk of non-adherence to TB. As in previous reports, DOT was not proved to be superior to self-administered therapy in those not at risk of non-adherence. This allows resources to be targeted for the group that need DOT to improve compliance with treatment and improve outcomes.

Paper 10: Lee *et al.* (2004). The majority of pulmonary tuberculomas were decreased during anti-TB treatment and this tendency continued after cessation of anti-TB treatment, although a transient enlargement during the early period of treatment was observed infrequently. The duration of treatment needed is not known and merits further study.

Paper 11: Mori *et al.* (2004). The whole-blood IFN-γ assay using the antigens CFP-10 and ESAT-6 was highly specific and sensitive for *M. tuberculosis* infection and was unaffected by BCG vaccination status. Combining the two antigens improved the sensitivity of the test without compromising the specificity.

Paper 12: Rajalahti *et al.* (2004). Applying the PCR assay to all samples (smear-negative and -positive cases) was not cost-effective. When the PCR assay was applied only to smear-positive sputum specimens, the smear and culture strategy was clearly dominated by it; that is, the PCR applied to smear-positive cases was less costly and more effective in producing correct treatment decisions and isolations.

Paper 13: Chang *et al.* (2004). In patients with extensive TB and patients who are still culture-positive after 2 months of TB therapy, the three times weekly regimens

are likely to lead to higher relapse rates. In these cases daily therapy would be advised. Alternatively, prolongation of three times weekly therapy in both the initiation and the continuation phase would be an alternative. Further studies are required to reduce the risk of relapse in programme settings.

Paper 14: Hernandez-Garduno *et al.* (2004). TB cases that are smear-negative are the cause of transmission for at least one in six patients with pulmonary involvement. The transmissibility from smear-negative cases has important public health implications. In particular, in the UK no contact-screening is carried out in patients with extrapulmonary TB alone. Further studies are needed.

Paper 15: Mosimaneotsile *et al.* (2004). A screening chest radiograph should not be required routinely for asymptomatic people taking isoniazid as preventive treatment in settings where it is possible to screen for signs and symptoms of TB.

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7

Pneumonia

JOHN SIMPSON

Introduction

Community-acquired pneumonia (CAP) remains a common cause of mortality, with particular impact in elderly and very young patients |**1,2**|. In some ways these observations have polarized research into CAP towards the identification of risk factors for severe disease and an understanding of the natural history, diagnosis and management of patients hospitalized with severe CAP. This chapter aims to provide a flavour of how these issues are being addressed. The chapter begins by considering childhood pneumonia, concentrating on randomized controlled trials that explore interventions for the prevention or treatment of CAP. Attention then turns to the epidemiology of CAP, including risk factors for the disease and the critical interaction between viral infection and predisposition to bacterial pneumonia, before quantifying the devastating impact of CAP upon the elderly. The focus then switches to the treatment of CAP, with discussion of the impact of guidelines on management, the thorny question of how to identify patients at risk of treatment failure, the microbiological aetiology of severe CAP, and trials of therapy for severe CAP.

While CAP generally involves the interaction between host inflammation and a relatively predictable spectrum of microbes, a quite different picture emerges in hospital. Hospital-acquired pneumonia is the commonest fatal nosocomial infection. It is associated with a variety of unpredictable pathogens, high rates of microbial resistance to antibiotics, and mortality rates of up to 70% for selected series of ventilator-associated pneumonia (VAP). The final section of the chapter focuses on nosocomial pneumonia, progressing from biomarkers aiding diagnosis, through preventive measures, to trials of management.

All of the articles discussed were published in 2004 with one exception, which was e-published in 2004. Given the vast literature on pneumonia, it is not possible to give much more than a broad overview of recent developments in clinical research, but good starting points for further reading can be found in a number of excellent reviews published in the past few years |**3–6**|.

Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial

Chintu C, Bhat GJ, Walker AS, *et al*., on behalf of the CHAP trial team. *Lancet* 2004; **364**: 1865–71

Background. Co-trimoxazole (combination of trimethoprim and sulphamethoxazole) is a widely used and effective antibiotic. Co-trimoxazole has been shown to be effective chemoprophylaxis in human immunodeficiency virus (HIV)-infected adults in the Ivory Coast, significantly reducing mortality |7|. The present study assessed the effectiveness and safety of co-trimoxazole in HIV-positive children, concentrating specifically on a geographical region where *in vitro* resistance to co-trimoxazole is reportedly high.

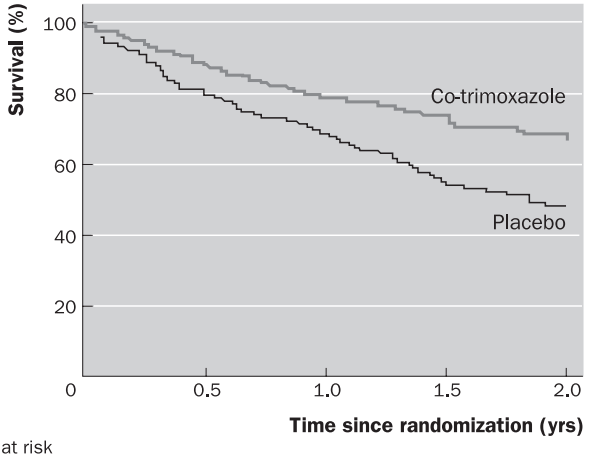
Interpretation. The trial was discontinued early because of a significant reduction in mortality in the co-trimoxazole group. Importantly, the benefits of co-trimoxazole appeared to persist irrespective of age or baseline CD4 lymphocyte count. These findings suggest that co-trimoxazole prophylaxis benefits HIV-positive children even in regions where *in vitro* bacterial resistance to co-trimoxazole is prevalent. The observations have huge significance for the planning of public health strategy.

Comment

This randomized, double-blind, placebo-controlled study was performed in Lusaka, Zambia. The initial design targeted children aged 6 months to 5 years, but was amended early in the trial to include children from 1 to 14 years on the basis that co-trimoxazole became universally recommended for infants and because of the increasing incidence of HIV-positivity in children aged over 5. HIV-positive children were randomized to co-trimoxazole suspension (240 mg daily for those under 5 years, 480 mg otherwise) or placebo. The primary end-points incorporated mortality and objectively defined adverse reactions.

The trial was designed to recruit 700 patients but was stopped at 541 (268 co-trimoxazole), when interim analysis demonstrated an unequivocal benefit for co-trimoxazole (Fig. 7.1). Importantly, benefit was demonstrated irrespective of age or CD4 count. Co-trimoxazole was also associated with significantly reduced hospital occupancy. No significant differences were observed for adverse events. Co-trimoxazole was associated with a statistically significant fall in mean neutrophil count, but neutrophils below 0.5×10^9/litre occurred in only 6% of patients receiving co-trimoxazole compared with 3% of the placebo group ($P = 0.06$).

Intriguingly, *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*) was conspicuous by its absence in microbiological samples. Indeed, the mechanism of protection conferred by co-trimoxazole is unclear and further studies addressing this question are ongoing. Crucially, as witnessed by the divergence shown in Fig. 7.1, co-trimoxazole's beneficial effects were statistically significant not only in the first



Number at risk					
Co-trimoxazole	265	232	177	106	47
Placebo	269	211	143	72	29

Fig. 7.1 Survival in children on co-trimoxazole or placebo. Source: Chintu *et al*. (2004).

6 months but also from 6 to 12 months and in the period beyond 12 months (median follow-up was around 18 months). There is nothing to hint at resistance to co-trimoxazole emerging over this time-frame, but this is the subject of further study. Other remarkable features of the study include the apparently high levels of drug compliance and tolerability.

This trial has far-reaching implications. The strong message is that co-trimoxazole prophylaxis is safe and reduces childhood mortality associated with HIV even in countries where co-trimoxazole resistance is common.

Oral amoxicillin versus injectable penicillin for severe pneumonia in children aged 3 to 59 months: a randomised multicentre equivalence study

Addo-Yobo E, Chisaka N, Hassan M, *et al*., for the Amoxicillin Penicillin Pneumonia International Study (APPIS). *Lancet* 2004; **364**: 1141–8

BACKGROUND. Parenteral antibiotics are widely advocated for treating severe childhood pneumonia but recent evidence has suggested similar efficacy for oral antibiotics. This randomized, controlled trial therefore examined whether oral amoxicillin was as effective as intravenous penicillin in severe childhood pneumonia.

INTERPRETATION. Oral amoxicillin and parenteral penicillin were equally effective. These findings have important implications for reducing costs and complications associated with parenteral antibiotic administration in children with pneumonia.

Comment

This study encompassed eight geographically diverse developing countries. Patients aged 3–59 months with severe pneumonia (cough and/or dyspnoea, chest wall indrawing and a respiratory rate of over 50 breaths/min for infants; over 40 breaths/min for those over 1 year) were eligible. Exclusion criteria included a history of asthma; wheeze and chest indrawing responding rapidly to bronchodilators; 'very severe' pneumonia; or prior antibiotics for more than 48 h. In total, 1702 children were randomized to oral amoxicillin (45 mg/kg per day, $n = 847$) or parenteral penicillin G (200 000 IU/kg per day, $n = 845$). The trial was not blinded as the authors did not feel placebo injections were justifiable.

The primary end-point was treatment failure at 48 h. Secondary outcomes included relapse at days 5 and 14. Treatments were considered equivalent if 95% confidence intervals (CIs) for risk differences related to treatment failure were between –5 and 5%.

Most patients were male infants. Failure rates for both treatments at 48 h and 5 days were 19 and 22% respectively, while at 14 days rates were 27% for amoxicillin and 26% for penicillin (the high failure rates reflect strict study definitions, and there were only twelve deaths). Specifically, the risk of treatment failure for penicillin relative to amoxicillin at 48 h was –0.4% (95% CI –4.2 to 3.3%), i.e. well within the definition of treatment equivalence. Both treatments appeared safe.

Interestingly, half of the randomized children had wheeze. Furthermore, radiography was not required for enrolment and there is nothing to state that inspiratory crepitations were required. This raises concerns that non-bacterial causes of dyspnoea would, by being unresponsive to antibiotics, bias the trial in favour of equivalence. Analysis confined to non-wheezing children showed similar rates of treatment failure (relative treatment failure rate 0.52%; 95% CI –4.7 to 5.6%). While this falls just outside the definition of equivalence, the authors stress that CIs are expected to spread with smaller sample sizes. In practical terms, wheezing therefore appeared to influence the study minimally. Finally, subgroup analysis of the small proportion of HIV-positive patients showed that amoxicillin or penicillin alone is insufficient treatment for severe pneumonia in this specific population.

This important study demonstrates that oral antibiotics for severe pneumonia in young children in developing countries could save valuable health resources, reduce requirements for needles, and open the way for trials of community-based treatment.

Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial

Brooks WA, Yunus M, Santosham M, *et al*. *Lancet* 2004; **363**: 1683–8

Background. Zinc deficiency is associated with reduced immunity. A therapeutic role for zinc supplementation has been described in the setting of childhood

diarrhoea |8|. This randomized, double-blind, placebo-controlled trial aimed to determine whether zinc supplementation could influence the rate of resolution in severe childhood pneumonia.

INTERPRETATION. Oral zinc supplementation (20 mg per day) significantly reduced the duration of severe pneumonia and associated length of hospital stay in Bangladeshi children aged between 2 and 23 months. The mean reduction in hospitalization was 1 day. Zinc appeared to be well tolerated and inexpensive. The study strongly supports use of zinc supplementation for severe pneumonia in young children from areas where relative zinc deficiency is endemic.

Comment

This was a single-centre study performed in rural Bangladesh. Cough, tachypnoea (respiratory rate >50 breaths/min) and crepitations were required to make the diagnosis of pneumonia (compatible radiology was not necessary), while *severe* pneumonia demanded additional chest indrawing, cyanosis, lethargy or inability to feed. Children aged between 2 and 23 months were eligible. Importantly, concomitant diarrhoea or severe malnutrition led to exclusion.

In accordance with power calculations, 270 children were enrolled (135 in each group). Study outcomes were defined as the duration of chest indrawing, respiratory rate >50 breaths/min, hypoxia, severe pneumonia, and hospitalization. Predetermined criteria were used to define antibiotic regimens, progress to 'non-severe' pneumonia and suitability for discharge. Each outcome variable (except length of hospital stay) was measured serially at 8-hour intervals. Analysis was performed 'per protocol', but there were only seven withdrawals (three in the zinc group). The two groups were well matched at baseline. No children died, and after initial clinical improvement none relapsed to severe pneumonia.

Mean durations of severe pneumonia were 4 and 5 days in the zinc group and placebo groups respectively (relative hazard ratio [HR] 0.70; 95% CI 0.51–0.98). Similarly, lengths of stay were 5 and 6 days respectively (HR 0.75; 95% CI 0.57–0.99). Reductions in the duration of tachypnoea, chest indrawing and hypoxia were also observed in the zinc group (tachypnoea, HR 0.74; 95% CI 0.7 0.57–0.98; chest indrawing, HR 0.80; 95% CI 0.61–1.05; hypoxia, HR 0.79; 95% CI 0.61–1.04). Interestingly, the benefit of zinc appeared to be clinically manifest relatively late in the admission, after day 4. Beneficial effects were preserved when children with coexistent wheeze were excluded from analysis. Zinc appeared to be well tolerated, though little specific information was provided.

The authors emphasize that zinc deficiency is common in Bangladeshi children, and it cannot necessarily be inferred that zinc should hasten recovery from severe pneumonia in countries where the population has normal zinc levels. In addition, no attempt was made to determine the mechanisms by which zinc enhanced the response to treatment. Nevertheless, this carefully designed study is a most welcome addition to the literature on severe childhood pneumonia and has the potential to have a significant impact on a commonly fatal disease in developing countries.

A role for *Streptococcus pneumoniae* in virus-associated pneumonia

Madhi SA, Klugman KP, the Vaccine Trialist Group. *Nat Med* 2004; **10**: 811–13

BACKGROUND. It is widely believed that viruses and bacteria interact in the pathogenesis of pneumonia, yet there is a lack of clear evidence for specific interactions of direct relevance to humans. An opportunity to address this problem came with the design of a randomized, double-blind, placebo-controlled trial which set out to determine whether pneumococcal conjugate vaccination (PnV) could affect rates of invasive pneumococcal disease or radiographic pneumonia among Sowetan infants. Systematic virological analysis allowed determination of the impact of PnV on the rate of virus-associated pneumonia.

INTERPRETATION. PnV was associated with a 22% reduction in virus-associated pneumonia, providing strong evidence that co-infection with respiratory viruses and pneumococcus contributes to the pathogenesis of pneumonia in infants. The study suggests a powerful role for PnV in the prevention of virus-associated pneumonia.

Comment

This study follows on from previous work describing a beneficial impact of PnV on invasive pneumococcal invasive disease and radiographic pneumonia in infants |**9**|. Almost 40 000 infants were randomized to receive three doses of placebo or vaccine (the vaccine comprised nine *Streptococcus pneumoniae* capsular sugar moieties conjugated to a diphtheria toxin mutant). The infants also received *Haemophilus influenzae* type b vaccination, but not influenza vaccination. In the analysis considered here, nasopharyngeal aspirates were collected from all children with suspected pneumonia, and were assessed for the presence of influenza A and B, parainfluenza viruses 1–3, adenovirus and respiratory syncytial virus (RSV).

Results of the intention-to-treat analysis are shown in Table 7.1. The data describe a 22% reduction in virus-associated pneumonia, manifest principally as reductions in pneumonia associated with isolation of influenza A and parainfluenza virus. The reduction in virus-associated pneumonia of approximately 22% extended to HIV-negative and HIV-positive infants, though statistical significance was lost in the latter cohort. Predictably, protection was still more striking in a per-protocol analysis confined to infants receiving all three protocol vaccinations. Because the 9-valent vaccine does not immunize against all serotypes of pneumococcus associated with pneumonia, still greater protection could probably be achieved with coverage of further serotypes. One implication of the study is that antibiotics may be efficacious in 'viral' pneumonia, though the authors stress that their data only support this approach for infants hospitalized with pneumonia.

This paper is extremely important in describing a clear association between pneumococcus and respiratory viruses in the generation of human pneumonia. The observed importance of the effect may have been still greater had more respiratory

Table 7.1 Percentage efficacy of pneumococcal conjugate vaccine by intent-to-treat analysis

All children

Clinical diagnosis	Vaccine (n = 19 922)	Placebo (n = 19 914)	Efficacy (95% CI)	P-value
Total number of pneumonia cases	975	1162	16 (9 to 23)	0.00003
Pneumonia with alveolar consolidation	356	428	17 (4 to 28)	0.01
Pneumonia without identified virus	726	845	14 (5 to 22)	0.002
Any identified virus-associated pneumonia	274	353	22 (9 to 34)	0.001
Influenza A	42	71	41 (13 to 60)	0.006
RSV	184	208	12 (–8 to 27)	0.2
PIV types 1–3	31	55	44 (3 to 64)	0.01
Adenovirus	16	16	0.0 (–100 to 50)	1

RSV, respiratory syncytial virus; PIV, parainfluenza virus.
Source: Madhi *et al*. (2004).

viruses been tested. The question remains as to whether the isolated viruses *caused* pneumonia, and it must be emphasized that viral samples were obtained from upper respiratory tract secretions, not from the alveolar space. The conclusion at present appears to be that upper respiratory tract viral infection and pneumococcus commonly interact in the pathogenesis of pneumonia. The challenges ahead include the characterization of the interaction between specific viruses and pneumococcus in man, and the promotion of PnV among infants susceptible to pneumococcal disease.

Influenza-associated hospitalizations in the United States

Thompson WW, Shay DK, Weintraub E, *et al*. *JAMA* 2004; **292**: 1333–40

BACKGROUND. Influenza generates considerable respiratory and cardiovascular morbidity every year |10|. The longitudinal impact of influenza on hospitalization rates deserves attention in order to plan the organization of health services, including vaccination strategies. The authors performed a comprehensive analysis of influenza-associated hospitalization in the US during the period from 1979 to 2001.

INTERPRETATION. A trend emerged describing a progressive increase in influenza-associated hospitalizations with time. This is partly related to the increasing numbers of elderly persons in the population. Although the specific effects of vaccination could not be assessed, the study appears to encompass the introduction of widespread vaccination. Therefore, the enormous impact of influenza on health resources appears likely to increase.

Comment

This epidemiological study used data from US virology laboratories involved in annual influenza surveillance, as well as statistics generated by the US National Hospital Discharge Survey. This strategy allowed the authors to extrapolate the effect of influenza upon hospitalizations across the US for such a prolonged period. The authors estimated the effect of influenza on both 'pneumonia and influenza hospitalizations' and 'respiratory and circulatory hospitalizations'.

The authors estimate that among hospitalizations given a diagnostic code under 'pneumonia and influenza', an average of 94 735 per annum were directly associated with influenza (equating to 37 admissions per 100 000 person-years). The annual figure rose sharply in years characterized by infections with influenza A of type H3N2 (as opposed to H1N1), but even allowing for this the general trend was for a year-on-year increase in influenza-associated admissions. Broadly similar trends were observed in admissions primarily for 'respiratory and circulatory' illness. Influenza-associated 'pneumonia and influenza' admissions showed a J-shaped curve with a peak under the age of 5, then a trough before a precipitous increase from the age of 50 onwards. A similar slope was described for age-related length of hospital stay, but without the peak in childhood. In other words, influenza in the elderly has an enormous impact on healthcare resources, which seems likely to increase as the elderly population increases.

By necessity, epidemiological surveys like this rely on statistical models to derive estimates of admissions linked to influenza. Obvious potential limitations include the accuracy of diagnostic coding and the likelihood that technologies to detect influenza would have improved over the course of the study period. Nevertheless, this comprehensive assessment tallies broadly with previous, smaller estimates and is among the most useful tools we have to calculate and predict the impact of influenza. Unfortunately, assessment of the efficacy of influenza vaccination could not be incorporated into this study.

The challenge ahead is to optimize vaccination and other prevention strategies for vulnerable individuals, to determine the impact of this upon mortality and morbidity, then to use data like these to inform decisions regarding the expansion of vaccination (for example, to incorporate groups of children at particular risk of influenza-associated mortality and morbidity).

The burden of community-acquired pneumonia in seniors: results of a population-based study

Jackson ML, Neuzil KM, Thompson WW, *et al*. *Clin Infect Dis* 2004; **39**: 1642–50

BACKGROUND. The elderly population is rising steadily, and pneumonia has a particular impact among older patients. Therefore it seems logical to describe pneumonia quantitatively among a large population of elderly persons, with a view to planning prevention and health service provision. This study observed the

development of inpatient and outpatient CAP among a population of 46 237 persons in the US aged 65 or over.

INTERPRETATION. The estimated rate of all CAP was 28.4 cases per 1000 person-years, 60% of this being managed on an outpatient basis. These are staggering statistics, suggesting that each year one in 35 persons over 64 will develop pneumonia. Potentially preventable associations with pneumonia included smoking and influenza.

Comment

This was a retrospective, population-based cohort study from Washington State. All persons studied were over 64, living independently in the community and affiliated to a health maintenance organization. The authors retrospectively checked discharge and outpatient International Classification of Diseases (ICD) codes for pneumonia over the 3 years from March 1998. For each case arising, records were scrutinized to confirm that the responsible clinician had considered pneumonia the most likely diagnosis.

The rate of CAP increased steadily with age, but was more frequent in men at all ages. There was also a striking correlation between seasonal rises in CAP and nationally recorded rates of 'influenza and pneumonia' (Fig. 7.2). As discussed earlier, this emphasizes the critical link between pneumonia and influenza.

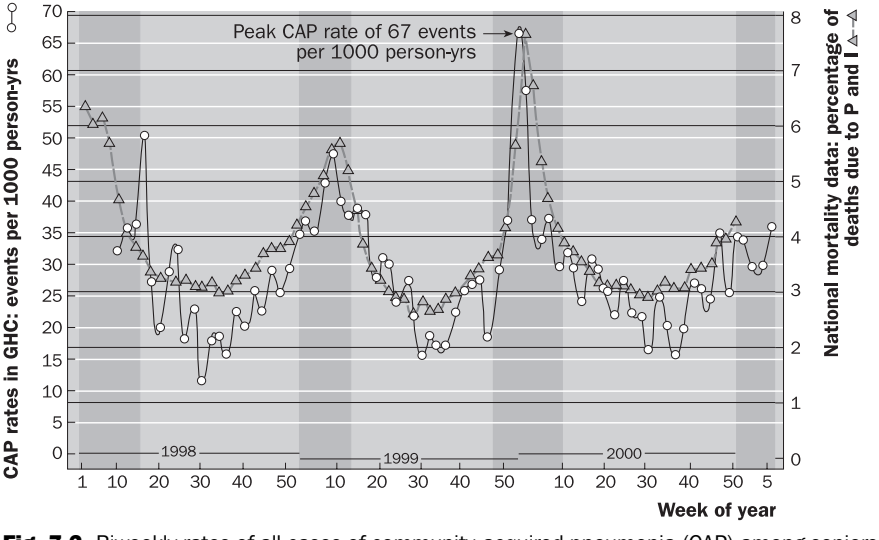


Fig. 7.2 Biweekly rates of all cases of community-acquired pneumonia (CAP) among seniors in the Group Health Cooperative (GHC), including hospitalizations and outpatient visits for CAP, during the study period. Periods of influenza virus circulation, as defined by Centers for Disease Control and Prevention surveillance data, are shaded dark grey. For comparison, the biweekly proportion of all deaths in the US attributed to pneumonia and influenza (P&I), as reported by national vital statistics data, is also presented. Source: Jackson *et al*. (2004).

Predictably, high rates of comorbidity were described. However, in multivariate analysis the factors independently associated with the development of pneumonia were chronic obstructive pulmonary disease (COPD), increasing age, male sex, current smoking, diabetes, congestive heart failure (but not ischaemic heart disease), lung cancer, various other cancers, dementia, stroke, asthma without COPD, prednisolone therapy, home healthcare, home oxygen, frequent outpatient attendance, and hospitalization for pneumonia in the year prior to the study starting. It is immediately apparent that, at present, few of these factors can be readily removed for a given individual.

A few questions should be borne in mind when evaluating these data. For example, the study relies on accurate diagnoses made by attending physicians. It is conceivable that the close links between pneumonia and COPD or influenza could have been influenced by misclassification (for example, pneumonia may be overdiagnosed in the influenza season). Similarly, it is conceivable that the population signing up for a health maintenance organization is not representative of the general population. Finally, care should be taken in extrapolating more than the core principles when comparing data from different healthcare systems. Nonetheless, this is a powerful, insightful and important work. The description of outpatient CAP is especially welcome, as few data exist to inform the planning of outpatient services for pneumonia in the elderly. This paper illuminates the enormous organizational challenge required to meet the needs of an increasingly elderly population.

Medium-term survival after hospitalization with community-acquired pneumonia

Waterer GW, Kessler LA, Wunderink RG. *Am J Respir Crit Care Med* 2004; **169**: 910–14

BACKGROUND. Patients hospitalized with CAP usually survive the illness. However controversy surrounds the issue of whether subsequent survival in this group is influenced by the episode of pneumonia *per se*. The authors addressed this question by studying a prospective cohort of patients admitted with CAP and following them over 2–4 years.

INTERPRETATION. Variables measured at the time of admission which independently influenced subsequent survival included age, altered mental state, cerebrovascular disease, cardiovascular disease, haematocrit less than 35%, and elevated blood glucose. The presence of comorbid illness profoundly influenced survival. When survival among patients with CAP but no comorbid illness was compared with expected national averages no statistically significant differences were found, though a trend towards excess mortality in the group who had CAP was observed. Therefore, the debate as to whether pneumonia itself adversely affects medium-term survival continues.

Comment

This prospective cohort study observed 404 patients admitted to hospital with CAP in a single American city. A total of 378 patients were discharged from hospital and

366 were followed prospectively. From this population, 125 patients (34%) died during the follow-up period, which averaged just under 3 years. Multivariate analysis identified the variables listed above (in particular age and altered mental state) as independent predictors of subsequent mortality.

The authors did not prospectively follow a control group of hospitalized patients with comparable comorbidity (matching would by definition have been difficult). Instead they compared survival with expected age-, sex- and race-matched mortality derived from published American data. The principal findings are illustrated in Table 7.2. The left side of the table demonstrates the excess mortality associated with CAP. However, the difference is attributable to the prevalence of comorbidities in this group. Therefore, the authors compared mortality among patients with CAP but *no* comorbidity with age-, sex-, and race-matched subjects with no comorbidity (right side of Table 7.2). Observed mortality exceeded expected mortality, particularly in the age range 41–60, but the difference did not reach statistical significance. The overall trend observed suggests that larger studies may detect a significant impact of pneumonia on subsequent survival, but no clear conclusion can be drawn yet. The mechanisms by which pneumonia might affect future health remain to be elucidated. Serial biological measurements were not made after discharge, the cause of death was not established, and the frequency with which underlying lung cancer was detected was unclear, so no significant clues arise from this study.

This interesting study generates several additional questions, such as why a low haematocrit predicts an adverse outcome after CAP, and whether active intervention for hyperglycaemia, anaemia or confusion can influence subsequent mortality. In the meantime it is reassuring that patients under the age of 40 appear to do relatively well after an episode of CAP. However, the vexed question of whether pneumonia confers a late survival disadvantage on patients over 40 deserves further attention.

Table 7.2 Observed and expected* mortality

	All subjects			Subjects with no comorbid illnesses		
Age group (years)	**Observed**	**Expected**	***P*-value**	**Observed**	**Expected**	***P*-value**
18–40	7 (9.6)	0.4 (0.6)	0.01	1 (1.7)	0.4 (0.6)	1.0
41–60	29 (24.2)	2.2 (1.8)	<0.001	7 (11.3)	1.1 (1.7)	0.06
61–80	56 (44.1)	10.3 (8.1)	<0.001	7 (16.3)	3.6 (8.3)	0.5
≥ 81	33 (71.7)	12.0 (26.1)	<0.001	5 (29.4)	4.3 (25.4)	1.0

* Expected mortality calculated from age-, sex-, and race-matched US population data.
Data in parentheses indicate percentage of mortality.
Source: Waterer *et al*. (2004).

Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs

Laheij RJF, Sturkenboom MCJM, Hassing RJ, Dieleman J, Stricker BHC, Jansen JBM. *JAMA* 2004; **292**: 1955–60

BACKGROUND. Evidence has linked therapeutic suppression of gastric acid in the intensive care unit (ICU) with increased risk of nosocomial pneumonia |11|. Whether the association between hypochlorhydria and pneumonia is maintained outwith hospital has not been examined comprehensively. The present study addressed this issue.

INTERPRETATION. Patients actively taking acid-suppressive drugs have a significantly increased risk of CAP.

Comment

This meticulous study took advantage of a large and detailed primary care database operating throughout the Netherlands. The database records all prescriptions and all working diagnoses, allowing the authors to gather data on cases of confirmed (or probable) pneumonia, as well as prescriptions of proton pump inhibitors (PPIs) and/or H_2-receptor antagonists among 364 683 persons over an 8-year period.

The relative risk of CAP was significantly higher among patients taking acid-suppressive drugs compared with those not taking such medication (odds ratio [OR] 4.47; 95% CI 3.82–5.12). However, the authors stress that this is a crude estimate, and go on to demonstrate significantly more risk factors for pneumonia among the cohort prescribed acid-suppressive drugs. Using a nested case–control design, models were therefore constructed to adjust for many potential confounding variables. After such adjustment, the active, present use of acid-suppressive drugs was still significantly associated with the development of CAP (OR 1.27; 95% CI 1.06–1.54). Importantly, similar statistically significant observations were made when comparing the current use of PPIs with discontinued PPIs (OR 1.89; 95% CI 1.36–2.62) and when comparing current H_2-receptor antagonists with discontinued H_2-receptor antagonists (OR 1.63; 95% CI 1.07–2.48). Interestingly, the risk of pneumonia appeared to be dose-dependent, at least for PPIs (which were generally associated with slightly higher risk of CAP than H_2-receptor antagonists), while discontinuation of acid-suppressants rapidly reduced the overall risk.

These findings provide an important addition to the list of risk factors for the acquisition of pneumonia. While all large epidemiological studies of this nature are open to criticisms regarding confounding variables and problems with case ascertainment, the sheer size of the study and the careful design appear to have minimized these concerns. Furthermore, the observations made are based upon clear biological plausibility, as acid suppression significantly reduces the innate immunity of the upper gastrointestinal tract. Inevitably, the question asked in clinical practice will be

how great the risk is—after all, these are important and effective drugs for dyspeptic syndromes. The authors address this issue as best they can with the available evidence, estimating that one case of CAP will be caused among 226 patients prescribed a course of PPI (or one for each 508 patients in the case of H_2-receptor antagonists). Thus, the overall risk appears small. As the authors discuss, however, the risk and importance of CAP are altogether different in elderly individuals with pre-existing cardiorespiratory disease (who appear to be prescribed acid-suppressants more frequently), and we should be particularly mindful of these data when prescribing acid-suppressants for such patients.

Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial

Christ-Crain M, Jaccard-Stolz D, Bingisser R, *et al*. *Lancet* 2004; **363**: 600–7

BACKGROUND. Serum procalcitonin levels are increased during sepsis. More recently, it has been suggested that procalcitonin is far more commonly elevated in bacterial infection than in viral infection. This has implications for the accurate determination of patients with respiratory illness, who are likely to benefit from antibiotics. With the validation of a new, more sensitive procalcitonin assay, this study assessed the potential impact of procalcitonin-guided management on antibiotic prescription in lower respiratory tract infections (LRTIs).

INTERPRETATION. Procalcitonin-guided management resulted in a reduction of approximately 50% in antibiotic use without discernibly influencing outcome.

Comment

This prospective, cluster-randomized, single-blind study ran for 119 days in a single Swiss emergency department. Patients with cough and dyspnoea attributed to LRTI were assigned to standard therapy alone or to treatment directed by physicians in response to guidance based on procalcitonin levels. Serum levels greater than 0.25 and 0.5 μg/litre were considered to indicate possible and likely bacterial infection respectively, and results were available within an hour. Power calculations dictated the group sizes of 119 (standard treatment) and 124 (procalcitonin-guided treatment).

For the procalcitonin group, physicians indicated *prior to* receiving procalcitonin levels whether they would ordinarily have prescribed antibiotics for the patient in question. In 80% of cases the answer was affirmative, but with the procalcitonin result available only 44% prescribed antibiotics. This significant reduction in prescription was not attended by adverse outcome as, comparing standard with procalcitonin-guided treatments, death rates were 3% in each group, ICU admission rates were 5 and 4%, and length of hospital stay 11.2 and 10.7 days respectively. Procalcitonin-guided treatment reduced antibiotic costs by US$106 per patient.

The greatest reductions in antibiotic prescribing occurred in patients with exacerbations of COPD or acute bronchitis. However, in the context of this chapter, while procalcitonin may be better placed to discriminate acute pneumonia from other important causes of radiographic alveolar shadowing, knowledge of serum levels allowed antibiotics to be withheld in 10% of patients with clinical pneumonia, all of whom improved.

A few points are worth considering. Firstly, the authors stress that procalcitonin assays complement, but do not substitute for, clinical assessment. Secondly, physicians prescribed antibiotics despite low procalcitonin in at least 22 cases, and it remains possible that antibiotic savings could be improved still further. Thirdly, this study detected serological evidence for viral illness in 81% of the tested patients, emphasizing the role of viruses in LRTIs. Fourthly, this was a single-blind study, and a degree of bias cannot therefore be excluded. Finally, a cautionary note should be sounded regarding diagnostic accuracy in studies like these. Indeed, 10% of patients were later found to have an alternative diagnosis to LRTI.

Overall, however, these findings offer considerable promise for future reliable discrimination of bacterial from viral LRTI in clinical practice. Associated reductions in antibiotic prescribing would have far-reaching implications for cost and the spread of antibiotic resistance.

Effects of guideline-concordant antimicrobial therapy on mortality among patients with community-acquired pneumonia

Mortensen EM, Restrepo M, Anzueto A, Pugh J. *Am J Med* 2004: **117**: 726–31

BACKGROUND. A number of authoritative national bodies have published guidelines for the diagnosis and management of CAP in recent years |12–14|. These guidelines were based on large bodies of published evidence and compiled by experts. Clinical studies are required to test the effectiveness of such guideline recommendations. This retrospective analysis therefore examined whether compliance with guidelines for antibiotic prescription influenced mortality associated with CAP in two Texan hospitals.

INTERPRETATION. Guideline-concordant antibiotic prescription, based on US national guidelines, was associated with significantly lower mortality than non-concordant therapy. These findings support the continued widespread application of published guidelines for the management of CAP.

Comment

The study was based upon retrospective review of case records. Randomly selected records from 420 patients with a clinical diagnosis of pneumonia and a compatible chest X-ray were included. Antibiotic prescription was considered concordant if it aligned with guidelines from the American Thoracic Society (ATS) or the Infectious

Diseases Society of America |**13,14**|, and if at least one dose had been administered within 48 h of admission.

The mean age for the cohort was 63 years and 20% were admitted to the ICU within a day. Overall 30-day mortality was 9.8%. Guideline-concordant antibiotic prescription was observed for 323 cases (77%).

Thirty-day mortality was 6.2% in the guideline-compliant group compared with 21.7% in the remaining 97 patients ($P < 0.001$). Statistically lower mortality associated with concordance was maintained across all levels of the pneumonia severity index (PSI) |**15**|, and when considering patients admitted to ward areas. A trend towards lower mortality for compliance with guidelines was also observed for ICU admissions but did not reach statistical significance. Interestingly, patients who did not receive guideline-concordant treatment were significantly more likely to be admitted to the ICU and to have had a delay in receiving the first dose of antibiotics. Indeed, 56 patients (13%) did not receive antibiotics within 8 h of presentation, despite delay being associated with increased mortality in CAP |**16**|.

The commonest deviation from guidelines appeared to involve the use of a β-lactam alone. The authors constructed models to reduce the effect of confounding variables on antibiotic prescription, after which a significant survival advantage for guideline-compliant prescribing was maintained (Fig. 7.3).

As with all studies of CAP, one must be cautious when extrapolating data from one healthcare system to another, and there is no substitute for verifying the efficacy of local guidelines directly. In addition, some methodological considerations are worth noting. For example, the study carries the problems inherent in any retrospective analysis, it is not clear how sample size number was derived, and it seems

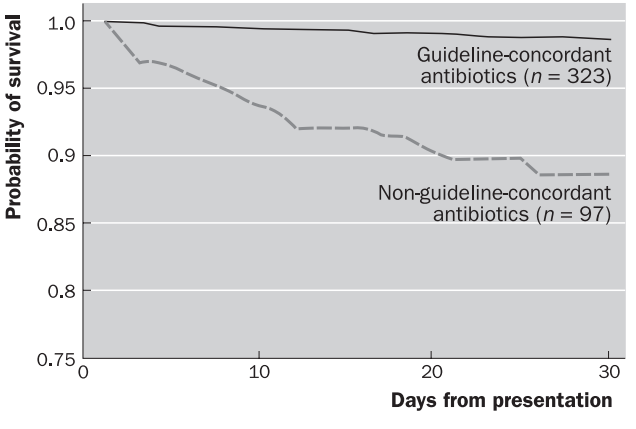


Fig. 7.3 Survival curves demonstrating that 30-day survival was greater for patients treated with guideline-concordant antimicrobial therapy ($P < 0.001$) than for those treated with non-concordant antimicrobial therapy after adjusting for potential confounders.
Source: Mortensen *et al*. (2004).

unusual that the study spanned admissions in 2000–2001 when the earlier of the two guidelines used was published after January 2000. Furthermore, the study describes all-cause mortality, not mortality due to pneumonia. However, while keeping such considerations in mind, these findings are clearly important in providing reassuring evidence to support the continued application of guideline recommendations.

Risk factors of treatment failure in community acquired pneumonia: implications for disease outcome

Menéndez R, Torres A, Zalacain R, *et al*.; Neumofail Group. *Thorax* 2004; **59**: 960–5

BACKGROUND. Patients with CAP who fail to respond to initial empirical therapy clearly have a poor prognosis. However, the clinical variables predicting an inadequate response to treatment remain poorly characterized. The authors therefore prospectively evaluated 1424 adults admitted to hospital with CAP in Spain in order to determine factors associated with treatment failure.

INTERPRETATION. Treatment failure was observed in 15% of patients and was associated with a mortality rate of 25%. Liver disease, leucopenia, multilobar pneumonia, cavitation, pleural effusion and a higher PSI were independently associated with treatment failure. The presence of these variables at the time of admission should alert physicians to the greater possibility of treatment failure. Conversely, vaccination against influenza, empirical treatment with fluoroquinolones and the presence of COPD were associated with reduced rates of treatment failure.

Comment

This prospective, observational cohort study ran from October 2000 to April 2001 in 15 Spanish hospitals. The authors collected a wide range of demographic and clinical data at the time patients were admitted with CAP, and provided clear definitions for the subsequent diagnosis of treatment failure. They further classified treatment failure according to whether it arose within or after 3 days of admission.

In total, 215 patients (15%) were considered to have treatment failure, with 134 cases identified within the first 72 h. Treatment failure was associated with an overall mortality of 25% compared with 2% among patients without evidence for treatment failure. However, treatment failure within 72 h was associated with a particularly high mortality (30%) and rate of admission to the ICU (31%).

The importance of this study lies in the detailed confirmation that treatment failure is common and clinically important. The identification of independent risk factors for treatment failure provides the clinician with valuable information. In particular, the risk factors identified (PSI, liver disease, leucopenia, multilobar pneumonia, cavitation and pleural effusion) are readily determined upon admission, and therefore they are not only useful but also practical. Equally interesting is the observation that influenza vaccination protects patients even in the face of established

pneumonia. In contrast, the suggestion that COPD protects against treatment failure remains unexplained, though it is tempting to infer a role for treatments confined to COPD but not CAP.

Inevitably, a few cautions are necessary in interpreting the results. In particular, a number of false-positive diagnoses of CAP may have been included, and it remains possible that these were over-represented among treatment failures. Also, one must consider how far to generalize seasonal results from Spanish hospitals. However, this study provides some of the best data we have on which to base the identification of patients with treatment failure, and paves the way for important randomized controlled trials in the future.

Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia

Rosón B, Carratalà J, Fernández-Sabé N, Tubau F, Manresa F, Gudiol F.
Arch Intern Med 2004; **164**: 502–8

BACKGROUND. This study follows on from, and is complementary to, the previous study by Menéndez and colleagues. The objective was to determine factors specifically influencing early treatment failure in CAP.

INTERPRETATION. In this longitudinal, single-centre study, early failure was associated with significantly increased mortality. Predictors of early failure included severe pneumonia (by PSI class), multilobar pneumonia, antibiotic therapy at odds with sensitivity patterns, and pneumonia caused by Gram-negative pathogens or *Legionella pneumophila*.

Comment

This study was similar to that of Menéndez and colleagues in size and objectives. However, Rosón and colleagues prospectively observed patients in a single Catalan hospital over almost 6 years and concentrated exclusively on early failure. Definitions of early failure and CAP were broadly similar in the two studies, but subtle differences did exist.

Rosón and colleagues described 81 early treatment failures among 1335 patients with CAP (6.1%), as determined by review at 48–72 h. Progressive pneumonia accounted for two-thirds of these, empyema and uncontrolled sepsis accounting for 20 and 11% respectively. Isolated pathogens were evenly distributed among patients with or without early failure, with the exception that *L. pneumophila* and Gram-negative bacilli were significantly over-represented in the early failure group. Early failure was associated with higher mortality (22 vs 4%), length of hospital stay (22 vs 10 days), complications (58 vs 24%) and initial use of antibiotics incompatible with subsequent sensitivities (31 vs 9%; $P < 0.001$ for each observation). In the early failure group, the use of β-lactam monotherapy with subsequent isolation of *L. pneumophila* was the commonest reason for non-concordant therapy. In a multivariate

analysis, only the factors listed in the Interpretation above were positively and significantly predictive of early failure.

Remarkable similarities emerge in the results described by Menéndez and colleagues and Rosón and colleagues, adding considerable weight to the findings. Overall mortality rates (excluding deaths in the first 48 h in each study) were 5.6 and 5.4% respectively, early failure rates were 9.4 and 6.1% respectively, and both studies found multilobar pneumonia and high PSI to predict early failure on multivariate analysis. An unexpected but intriguing similarity was the apparent protective effect of COPD against 'all failure' in the Menéndez study and a significantly reduced prevalence of COPD among patients with treatment failure in the Rosón study.

In general, there is a trend in these papers towards host factors being greater determinants of treatment failure than microbial or iatrogenic factors. This trend needs to be confirmed in other studies and the mechanisms dissected. One implication is that neither study identified predictors of early treatment failure that are readily amenable to intervention. In the meantime we must aim to prevent early failure where possible and to recognize features of early treatment failure promptly in order to provide good supportive care. Further research is required to identify therapeutic means with which to regulate the ineffective host response during severe CAP.

Severe community-acquired pneumonia: assessment of microbial aetiology as mortality factor

Paganin F, Lilienthal F, Bourdin A, *et al*. *Eur Respir J* 2004; **24**: 779–85

BACKGROUND. CAP requiring ICU admission is associated with high mortality. The influence of specific pathogens on the determination of outcome in CAP is relatively poorly understood. This study therefore aimed to establish risk factors for mortality in severe CAP, paying particular attention to the influence of specific microbes.

INTERPRETATION. In the setting of an ICU on an Indian Ocean island, aggressive use of microbiology led to the identification of *Klebsiella pneumoniae* in 22% of patients. Overall mortality was 43%. *K. pneumoniae*, septic shock, positive blood culture and Simplified Acute Physiology Score II score >40 were identified as independent predictors of mortality.

Comment

The study was based in an ICU on the island of Réunion, a French territory in the Indian Ocean. Consecutive immunocompetent patients with good evidence for severe CAP were studied (the total number was 112). Recognized risk factors for poor outcome were recorded (e.g. comorbidities and physiological recordings at admission) and considerable efforts were made to obtain a microbiological diagnosis. All patients had blood cultures, 76% had bronchoalveolar lavage (BAL) and serological assessment for atypical pathogens was performed in an unspecified number. The group had severe CAP, as evidenced by a mean PaO_2 of 53 mmHg on air, shock in 48%, a requirement for mechanical ventilation of 82%, and an overall mortality of 43%. The

study population was relatively young (mean age was 55 years) with a high rate of alcohol excess (62%).

The aggressive microbiological policy yielded impressive detection rates: 33% for blood culture and 65% for BAL. Two predominant organisms were isolated, namely *Streptococcus pneumoniae* (43% of patients) and *K. pneumoniae* (22%); only 21% of patients had no organism identified. In multivariate analysis, however, the only independent predictors of mortality were those mentioned in the Interpretation above.

This valuable study highlights several important points. The microbiological pattern emphasizes yet again the central importance of *S. pneumoniae* in the aetiology of CAP, though interestingly *Streptococcus* was not an independent predictor of mortality. The importance of *K. pneumoniae* in this study reiterates the requirement for good local microbiological epidemiology (the high rate of *Klebsiella* may partly reflect high alcohol consumption). Also, even if *S. pneumoniae* did cause the 21% of unexplained CAP, one-third of severe cases in this study were caused by organisms other than *Streptococcus*; this is broadly in keeping with other studies and emphasizes both the requirement for vigilance and the importance of good microbiology.

Interestingly, the isolation rate of pathogens was extremely high if antibiotics had not been given prior to arrival in ICU (97%), but the yield remained relatively high even when antibiotics had been received previously (47%). The incorporation of BAL in microbiological protocols was extremely safe and had a huge impact upon microbial identification, allowing more targeted use of antibiotics. Indeed, sensitivities revealed that all patients received appropriate antibiotics. Depressingly, however, mortality was still 43%, emphasizing the complexity of factors contributing to death in severe CAP.

Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia

Baddour LM, Yu VL, Klugman KP, *et al*. and the International Pneumococcal Study Group. *Am J Respir Crit Care Med* 2004; **170**: 440–4.

BACKGROUND. The significant mortality associated with pneumococcal bacteraemia demands the characterization of the best effective treatment. Retrospective studies have suggested that combination antibiotic therapy is more effective than monotherapy in reducing mortality associated with pneumococcal bacteraemia, and the present study aimed to resolve this issue prospectively.

INTERPRETATION. Overall mortality was similar irrespective of whether combination or single antibiotic therapy was used. However, in a subgroup of patients with severe pneumococcal bacteraemia combination therapy was associated with a striking reduction in mortality. No single combination regimen demonstrated a clear therapeutic advantage.

Comment

A distinct strength of this prospective study was the enrolment of 844 patients with proven pneumococcal bacteraemia from six continents. It must be stressed that this

was not a randomized, double-blinded comparison of combination versus single antibiotic therapy. Indeed, analysis was confined to those 592 patients who received consistent single or combination antibiotic therapy in the 48-hour period after a positive blood culture was obtained. Among these 592 patients, 14-day mortality was 11.5% in those receiving monotherapy (n = 390) and 10.4% in those receiving combination therapy (n = 202) (no significant difference; Fig. 7.4a). Interestingly, 14-day mortality in the cohort of 844 was 16.5%, and the implication is that mortality reached 29% in the 252 patients who received no antibiotics, delayed antibiotic treatment or an inconsistent regimen in the 2 days after identification of pneumococcal bacteraemia.

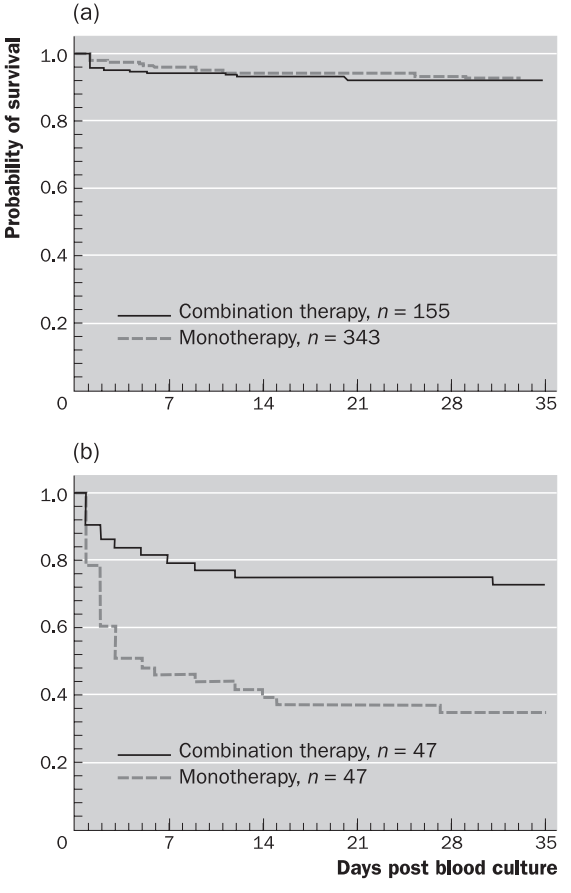


Fig. 7.4 Survival graphs stratified by severity of illness. (a) Kaplan–Meier survival plot for patients who were not critically ill, as defined by the Pitt bacteraemia score. (b) Kaplan–Meier survival plot for 94 patients who were critically ill, as defined by the Pitt bacteraemia score. Combination therapy was superior to monotherapy in critically ill patients (P <0.008, Mantel–Cox). Source: Baddour *et al*. (2004).

A subgroup analysis was performed among patients with severe pneumococcal bacteraemia, as defined by a Pitt bacteraemia score greater than 4 (the score is derived from temperature, blood pressure, mental status, requirement for mechanical ventilation, and whether cardiac arrest occurs; a score of 5 could be achieved, for example, in a disoriented patient with a temperature of 40.1°C and blood pressure of 86/50). In this group, combination therapy was associated with significantly reduced mortality (Fig. 7.4b). A variety of antibiotic combinations was used in these patients (the commonest was a β-lactam plus a macrolide or vancomycin), with no clear advantage for any individual pairing. Interestingly, *in vitro* antibiotic resistance did not obviously influence mortality among severely ill patients.

Together, these data show that combination therapy is required for critically ill patients with pneumococcal bacteraemia and that less severe illness can be managed with monotherapy. One difficulty remaining for the clinician is where exactly to draw the line between severe and non-severe bacteraemia. The authors do not state whether a Pitt bacteraemia score greater than 3 led to the same conclusions, for example. Furthermore, this study does not identify the optimal duration of antibiotic therapy. Nevertheless, in the absence of a double-blind, randomized controlled trial, this study provides convincing evidence for the use of combination antibiotic therapy in critically ill patients with pneumococcal bacteraemia.

Hydrocortisone infusion for severe community-acquired pneumonia; a preliminary randomized study

Confalonieri M, Urbino R, Potena A, *et al*. *Am J Respir Crit Care Med* 2005; **171**: 242–8

BACKGROUND. Severe CAP is associated with high mortality and good, appropriate antibiotics appear to have relatively little impact on this problem. The inference is that inappropriately aggressive pulmonary and/or systemic inflammation contributes to mortality in these patients. This study targeted systemic inflammation in a preliminary multicentre, randomized, placebo-controlled, double-blind trial of continuous low-dose hydrocortisone infusion in severe CAP.

INTERPRETATION. The study was stopped after randomization of 48 patients because of significant benefits associated with hydrocortisone in terms of oxygenation and in-hospital mortality.

Comment

This study was performed in six Italian hospitals. Patients were randomized if they fulfilled standard criteria for severe pneumonia, and clear exclusion criteria were established. Forty-eight patients were randomized to intravenous hydrocortisone (a 200-mg bolus then 10 mg/h for 7 days) or placebo. One patient in each group subsequently left the study, leaving 46 for analysis. Primary end-points included improve-

ment in PaO_2:FiO_2 (FiO_2 is the fraction of inspired oxygen) ratio of at least 100 by day 8, improvement in multiple organ dysfunction score (MODS) score and the rate of delayed septic shock. Secondary end-points included mortality (in hospital and at 60 days) and length of stay in a unit capable of providing ventilatory support.

Critically, statistical analysis was performed periodically after blocks of patients had completed data collection. This resulted in discontinuation of the trial after completion of data collection for 46 patients (23 in each group) because of a clear benefit favouring hydrocortisone. Figure 7.5 demonstrates the significant rise in PaO_2:FiO_2 associated with hydrocortisone and the concomitant fall in C-reactive protein, suggesting a profound effect on systemic inflammation. At day 8 the MODS score was significantly reduced in the treatment group ($P = 0.003$), while nine patients in the placebo group but none in the hydrocortisone group had delayed septic shock ($P = 0.001$). No patients receiving hydrocortisone died and the median length of ICU stay was 10 days, compared with seven in-hospital deaths ($P = 0.009$), eight deaths at 60 days ($P = 0.001$) and a median ICU stay of 18 days ($P = 0.01$) in the placebo group.

The potential limitations of the study relate principally to the sample size; for example, randomization was uneven across participating centres. It may be important that at baseline more patients in the placebo group appear to have been intubated. The placebo group also had more frequent comorbidities and more frequent isolation of *Legionella* species. These considerations all arose by chance as a consequence of randomization, and a larger trial would smooth out these issues. It is also worth noting that 73 patients screened for eligibility were not suitable for randomization; thus, these results cannot necessarily be generalized to all patients with CAP entering the ICU.

In summary, although this study was small, it is of immense importance to the understanding of severe CAP and has significant implications for treatment if the dramatic effects on mortality can be confirmed in larger, multinational randomized controlled trials. These are awaited with great interest.

Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia

Gibot S, Cravoisy A, Levy B, Bene MC, Faure G, Bollaert PE. *N Engl J Med* 2004; **350**: 451–8

Background. In critically ill, mechanically ventilated patients it can be extremely difficult to make a confident diagnosis of pneumonia. The difficulty arises principally because many other conditions can stimulate new chest X-ray changes, leucocytosis and fever, and most mechanically ventilated patients have mucopurulent tracheal secretions at some stage. Microbiological diagnosis is technically demanding, and culture takes time. Any rapid laboratory test specific for infection would be enormously valuable in this regard. Triggering receptor expressed on myeloid cells-1 (TREM-1)

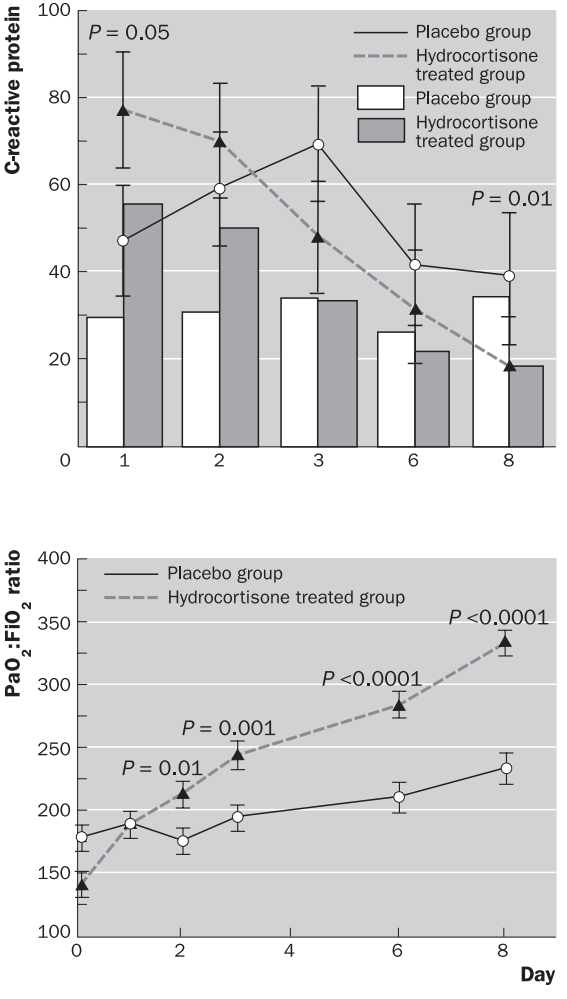


Fig. 7.5 Values over time for serum C-reactive protein (CRP) and PaO_2:FiO_2 in patients randomized to hydrocortisone and placebo. The graph for CRP contains two censored outliers for day 8, as shown in the line graph. Two placebo patients were censored because their day-8 CRP value was beyond 3 SD of the mean day-8 value. If the outliers are included, the difference between groups on day 8 is more significant ($P = 0.008$). The bar graph represents median values. The *P*-values shown are median comparisons between groups. The PaO_2:FiO_2 graph contains censoring for day-6 and day-8 values of the placebo patient who exited to receive hydrocortisone therapy for septic shock. Source: Confalonieri *et al*. (2005).

is expressed on phagocytes in response to infection |17|, and this study therefore sought to find out whether levels of soluble TREM-1 in BAL fluid were specific for pneumonia.

INTERPRETATION. Among mechanically ventilated patients a concentration of soluble TREM-1 in BAL fluid greater than 5 pg/ml was highly sensitive and specific for the diagnosis of pneumonia.

Comment

This study was based in a single French ICU. The authors performed 'mini-BAL' in consecutive mechanically ventilated patients in whom a diagnosis of pneumonia was suspected. Pneumonia was confirmed if a pathogen was cultured at greater than 10^3 colony forming units (CFU)/ml, and independent observers judged whether pneumonia was community-acquired or ventilator-associated. Soluble TREM-1 was assayed by immunoblot.

In total, 148 patients were assessed: 46 with VAP, 38 with CAP and 64 with no microbiological evidence for pneumonia. The soluble TREM-1 concentration was significantly higher in cases of pneumonia (Fig. 7.6). Using a cut-off of 5 pg/ml soluble TREM-1 gave a sensitivity of 93% and a specificity of 90% for the diagnosis of pneumonia. In a multivariate analysis, soluble TREM-1 was found to be superior to all other variables in predicting pneumonia (OR 41.5; 95% CI 20.9–77.6). Placing this in context, the other variables independently associated with pneumonia had far

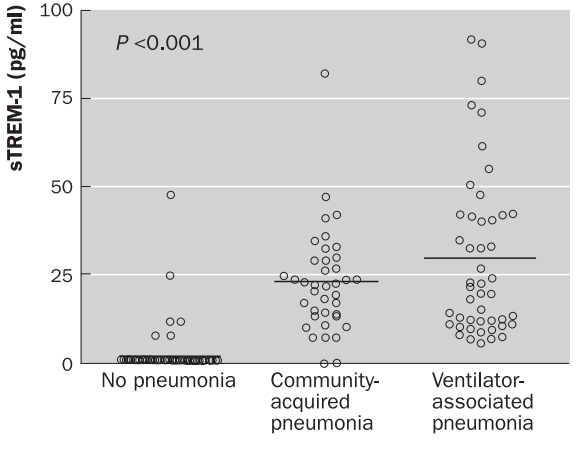


Fig. 7.6 Levels of soluble triggering receptor expressed on myeloid cells (sTREM-1) in bronchoalveolar lavage fluid from 64 patients without pneumonia, 38 patients with community-acquired pneumonia and 46 patients with ventilator-associated pneumonia. Individual values are plotted, and the *bars* represent the means of the values. $P < 0.001$ for the comparison between the group of patients without pneumonia and each group of patients with pneumonia. Source: Gibot *et al*. (2004).

lower ORs (clinical pulmonary infection score [CPIS] >6, tumour necrosis factor α >150 pg/ml in BAL fluid, interleukin-1β >75 pg/ml in BAL fluid).

Three comments should be made in connection with this elegant paper. Firstly, the microbiological threshold for pneumonia is more often set at 10^4 CFU/ml when using BAL fluid |**18**| and it is conceivable that pneumonia was overdiagnosed. Secondly, it is a pity that the authors group CAP and VAP together in analysis. The diagnosis of CAP requiring mechanical ventilation is usually straightforward, whereas the diagnosis of VAP is much harder. The data suggest, but do not explicitly confirm, that soluble TREM-1 is predictive specifically of VAP. Finally, it must be remembered that measurement of soluble TREM-1 is a snapshot of a dynamic process, and the kinetics of its release remain to be elucidated.

In summary, soluble TREM-1 rapidly and effectively distinguishes pneumonia from pulmonary conditions other than pneumonia in mechanically ventilated patients. Soluble TREM-1 should prove a particularly valuable tool if these results are confirmed in large studies specifically addressing the diagnosis of VAP.

Prevention of MRSA pneumonia by oral vancomycin decontamination: a randomised trial

Silvestri L, van Saene HKF, Milanese M, *et al*. *Eur Respir J* 2004; **23**: 921–6

BACKGROUND. Prolonged hospital stay is associated with contamination of the oropharynx with nosocomial organisms which are implicated in the subsequent development of hospital-acquired pneumonia. The increasing emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) as a nosocomial pathogen has raised the contentious issue of whether/how to keep the oropharynx free of this pathogen. This study assessed whether oral vancomycin gel could influence rates of LRTI caused by MRSA.

INTERPRETATION. Vancomycin gel appeared to be associated with a small but statistically significant reduction in nosocomial LRTI associated with MRSA. However, this effect was not associated with a reduction in overall mortality, length of hospital stay or incidence of pneumonia.

Comment

This study was performed in a single Italian ICU and randomized 84 mechanically ventilated adults to routine ICU care with or without oral vancomycin gel (42 patients received 0.5 g of 4% gel four times daily). Regular microbiological surveillance of the oropharynx was performed, allowing the authors to determine whether MRSA was acquired before or during the ICU stay. The group then monitored the development of nosocomial infection.

Fifteen patients in the control group acquired oropharyngeal MRSA in the ICU; six of these developed MRSA LRTI compared with none in the vancomycin group (P <0.01), among whom ICU-acquired MRSA was not detected. Control

patients with MRSA LRTI had a particularly long average length of stay. Importantly, no vancomycin-resistant pathogens were isolated throughout the duration of the study.

Although these findings hint at an important role for vancomycin gel, several points should be considered in interpreting these data. For example, this trial was neither blinded nor placebo-controlled. The results do not appear to have been analysed on an intention-to-treat basis (patients who did not complete 3 days of mechanical ventilation were excluded), the predetermined primary outcome variable for the study is difficult to find, and no data on the safety of vancomycin gel is provided. Furthermore, 'pneumonia' was not confirmed using bronchoscopic sampling.

In addition, it is important to note that the total number of episodes of MRSA LRTI in each group (including those in patients who had oropharyngeal MRSA on arrival in the ICU) showed no significant difference. Similarly, the overall number of 'pneumonias' (irrespective of pathogen isolated) was 22 in the vancomycin group and 19 in the control group. No significant difference in overall mortality was observed when comparing the groups. Thus, while vancomycin may potentially affect nosocomially acquired MRSA LRTI, any putative global effect on outcome is lost in this small study. Finally, it is always difficult to extrapolate data from one ICU to another in view of inevitable differences in the case mix and local microbiological epidemiology.

In summary, this paper suggests a potentially important protective role for a simple intervention in ICU, but inevitably large randomized, multinational, double-blind, placebo-controlled trials will be required to address this issue more comprehensively.

Meropenem monotherapy for the treatment of hospital-acquired pneumonia: results of a multicenter trial

Berman SJ, Fogarty CM, Fabian T, Melnick D, Lesky W, on behalf of the Merrem Hospital-Acquired Pneumonia Study Group. *J Chemother* 2004; **16**: 362–71

BACKGROUND. Hospital-acquired pneumonia (HAP) is associated with high mortality, and better treatment is required. However, in practical terms the selection of empirical antibiotics is difficult because of the wide variety of potential pathogens, the increasing emergence of antibiotic resistance associated with the injudicious use of antibiotics, and the toxicity associated with broad-spectrum antibiotics. Meropenem, a broad-spectrum carbapenem, has *in vitro* activity against many pathogens associated with HAP. This study assessed its efficacy as a single agent in patients with HAP, many of whom were mechanically ventilated.

INTERPRETATION. This non-randomized, open-label trial showed a satisfactory clinical outcome after meropenem monotherapy in 64% of evaluated patients at follow-up. However, it should be noted that efficacy was assessed in a highly selected group of patients with HAP.

Comment

This study was carried out in 28 American centres and was commercially sponsored. In total, 255 patients with suspected HAP were enrolled, each having microbiological samples sent. Importantly, patients were excluded from efficacy analysis if they had no microbiological evidence of infection before treatment, if a meropenem-resistant organism was isolated before treatment, if a second antibiotic was clinically indicated, and if the patient did not complete 3 days of meropenem. For these, and a variety of other reasons, 144 patients were excluded from efficacy analysis. The primary endpoint for efficacy was based on clinical assessment at follow-up.

Considering the 111 patients in the efficacy analysis, 64% had a satisfactory response at follow-up, with 74% deemed to have a satisfactory response upon discontinuation of meropenem. The response was similar considering patients with (n = 60) and without VAP. Safety was assessed in 254 patients. Although 86% of patients had adverse events, the authors considered these to be drug-related in 12%, the commonest single event being an abnormal liver function test.

These results are encouraging, but extreme caution must be attached to their interpretation. The non-randomized, open-label design has the potential for selection bias. Perhaps more importantly, the 111 patients with meropenem-sensitive organisms clearly had a higher chance of responding than did the total cohort of 254, who much more closely represent 'real-life' HAP. The exact diagnosis in the remaining 144 patients with 'suspected HAP' remains unclear—some of these patients may not have had HAP, some had meropenem-resistant HAP, and several probably had HAP for which the aetiological agent was not detected. Of course, in real life we do not have the luxury of microbiological sensitivities when we start therapy.

Thus, it seems reasonable to conclude that meropenem monotherapy appears safe and efficacious in HAP when a meropenem-sensitive organism is isolated. This is undoubtedly valuable information but one could argue that it was to be expected. The next, more pressing question is whether meropenem (perhaps with additional cover for MRSA) outperforms other logical therapies for HAP among unselected cases of HAP in large, randomized, double-blind trials.

Value of the clinical pulmonary infection score for the identification and management of ventilator-associated pneumonia

Luyt CE, Chastre J, Fagon JY, and the VAP Trial Group. *Intensive Care Med* 2004; **30**: 844–52

Background. Significant debate surrounds the optimal strategy for diagnosis and management of VAP. Over 50% of clinically suspected VAP can be explained by an alternative (often non-infective) aetiology |19|. An empirical approach using carefully selected antibiotics may reduce mortality, but is likely to overprescribe antibiotics significantly, with a variety of adverse consequences. In contrast,

bronchoscopic sampling to obtain quantitative microbiology is associated with greater diagnostic accuracy, but requires meticulous bronchoscopic and microbiological methods. Recently, an alternative strategy has been developed based on a modified CPIS |20,21|. This grades five clinical criteria at baseline (temperature, white cell count, appearance of tracheal secretions, PaO_2:FiO_2 ratio and radiographic score), while the score at day 3 uses the same criteria plus the change in chest X-ray and culture results of tracheal aspirates. Thus, in clinically suspected VAP a score greater than 6 on day 1 triggers 10–21 days of antibiotics while a score of 6 or less prompts 3 days of intravenous ciprofloxacin then a re-evaluation of CPIS, a score of 6 or less allowing discontinuation and a score greater than 6 triggering a full course of antibiotics. This retrospective study aimed to evaluate how the modified CPIS algorithm would have performed if applied to a cohort of patients in whom clinically suspected VAP was confirmed/refuted using bronchoscopically derived quantitative microbiology.

INTERPRETATION. The CPIS algorithm would have resulted in unnecessary antibiotics for 53% of patients with no evidence for VAP, and would have underprescribed antibiotics for 11% of patients with proven VAP.

Comment

This study drew upon data from a landmark randomized trial comparing outcomes associated with invasive (bronchoscopic) and non-invasive approaches to suspected VAP |**22**|. Data from the invasive arm were used to assess retrospectively how the modified CPIS would have influenced management. Fortuitously, the study by Fagon and colleagues |**22**| had recorded all criteria required to calculate the modified CPIS (the only exception being that bronchoscopic culture results, and not aspirate cultures, were used by Fagon and colleagues).

Key results are shown in Fig. 7.7. Modified CPIS had a sensitivity of 89% but a specificity of only 47% for detecting VAP. The emerging impression is that modified CPIS is relatively good at excluding VAP (negative predictive value 84%) but poor at defining the presence of VAP (positive predictive value 57%).

The authors acknowledge limitations of this analysis, including its retrospective nature, lack of aspirate cultures and potential problems in using bronchoscopic microbiological analysis as the gold standard for diagnosing VAP. Importantly, this was never intended to be a direct comparison of diagnosis by CPIS or the bronchoscopic microbiological approach, for which a prospective randomized trial would be required. Furthermore, this study cannot quantify the consequences of false positives and false negatives resulting from the use of CPIS (e.g. length of stay, mortality, cost, emerging antibiotic resistance). Nevertheless, because these data are derived from such a robust trial, they add further support to an invasive strategy for the diagnosis of VAP.

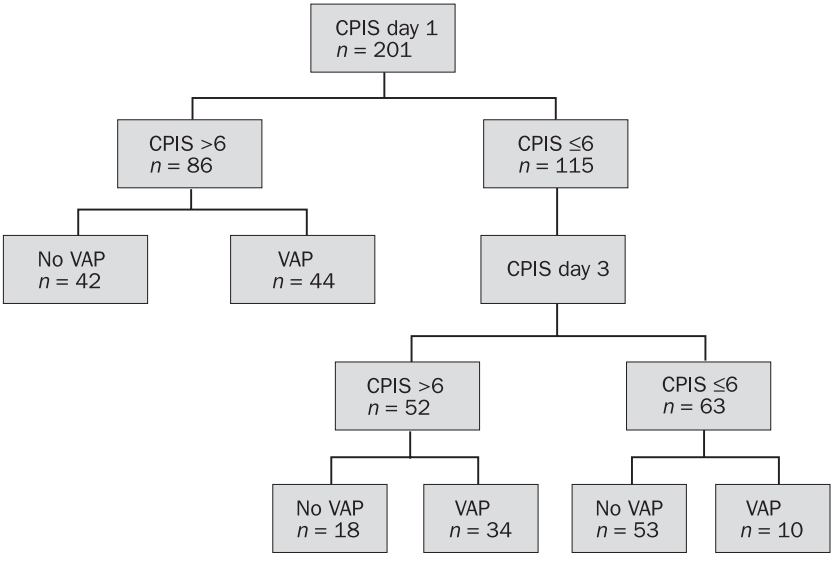


Fig. 7.7 Number of patients assessed and enrolled in the trial. Actual number of patients falling into each category are reported. Source: Luyt *et al*. (2004).

A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia

Micek ST, Ward S, Fraser VJ, Kollef MH. *Chest* 2004; **125**: 1791–9

Background. The optimal duration of antibiotics for an episode of pneumonia remains poorly defined. This issue takes on particular importance in the ICU, where adequate antibiotic cover for life-threatening infections is clearly required, yet protracted courses of antibiotics are likely to be associated with increased toxicity, cost and propagation of antibiotic resistance. This trial therefore formally assessed the effectiveness of an antibiotic discontinuation policy based on careful monitoring of clinical and laboratory indices and/or the identification of an alternative cause for radiographic infiltrates in a cohort of patients with suspected VAP.

Interpretation. A formal antibiotic discontinuation policy was associated with significantly shorter antibiotic use without significant alteration in clinical outcomes.

Comment

This single-centre American study was based in a medical ICU. Patients were included if the attending physician considered VAP to be likely. In accordance with unitary

guidelines it was recommended that patients be treated with triple intravenous therapy (vancomycin or linezolid plus gentamicin or ciprofloxacin plus cefepime). Patients were randomized to standard care directed by the attending physicians, or to standard care in which specific recommendations to discontinue antibiotics were issued if the investigators detected an alternative cause for radiographic infiltrates or if they found that a battery of clinical and laboratory tests were no longer consistent with active infection. Initial antibiotics complied with unitary guidelines in around 82% of cases, and in the antibiotic discontinuation group the recommendation to stop antibiotics was adhered to within 48 h in 89% of cases.

The mean duration of antibiotics in the discontinuation group was 6 days compared with 8 days in the control group ($P < 0.001$). In contrast, hospital mortality, length of stay (hospital or ICU), duration of mechanical ventilation and subsequent infection rate were similar in the two groups.

The authors discuss potential limitations of the study thoroughly. In particular, the trial was not blinded and one of the investigators was involved in clinical care in the ICU. Also, the randomization process is not explained (however, the groups appear well matched) and analysis was not on an intention-to-treat basis (however, there were few exclusions after randomization). It is important to note that these patients had *probable* VAP, i.e. the majority did not have a confirmatory quantitative culture from the alveolar space. This was a deliberate part of the trial design, in order to make the study more representative of real life in most ICUs, but it must be recalled that clinical suspicion of VAP is more often wrong than right |**19**|. Ironically, it could therefore be argued that unnecessary antibiotics may have been prescribed in some patients in this trial.

Despite the issues described, these are valuable data and they support the emerging picture that relatively short courses of antibiotics are safe in VAP |**23**|, particularly when close attention is paid to the patient's clinical response.

Conclusion

Important messages are emerging from clinical research into pneumonia. From an epidemiological perspective, the increasing life expectancy of the population dictates that pneumonia will exert greater and greater pressures on health services unless more effective preventive measures, such as improved vaccination strategies, are implemented. At the other extreme of life, the demonstration that short-course oral amoxicillin is efficacious and safe in childhood pneumonia in developing countries has enormous implications for the provision of affordable, easily organized treatment. Equally, trials in adults demonstrating that compliance with published guidelines predicts a good prognosis in CAP is as important as it is reassuring.

Evidence is also emerging to help guide the management of patients with severe CAP and nosocomial pneumonia. It is increasingly apparent that the microbial aetiology of these conditions varies from location to location, and that local microbiological epidemiology is invaluable in guiding treatment. In the specific context of nosocomial

pneumonia, the diagnosis can be extremely difficult to distinguish from non-infective respiratory conditions, and the gradual emergence of biomarkers capable of discriminating infection is most welcome. Conversely, it is also increasingly apparent that patients with severe pneumonia often die despite the administration of apparently effective antibiotics. This points to the role of the host inflammatory response in determining prognosis, and in this regard the preliminary trial by Confalonieri and colleagues showing benefit for hydrocortisone in severe CAP is fascinating.

Perhaps the most important message to emerge is that pneumonia is changing all the time and we fail to keep up at our peril. Thus, the organisms implicated vary temporally and geographically, antibiotic resistance emerges here and there, new microbial aetiologies (e.g. severe acute respiratory syndrome [SARS]) rear up periodically, the interaction between host immunity and microbe is constantly changing, and now we have evidence suggesting that pneumonia may have long-term sequelae even after apparent resolution. These challenges are being met by advances in epidemiology, basic science and clinical trials. The importance of good research in this area cannot be overemphasized. Approximately 200 children under the age of 5 died of pneumonia around the world while you were reading this chapter |**1**|.

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Part V

Thoracic malignancy

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Thoracic malignancy

RON FERGUSSON

Introduction

Lung cancer remains the most common malignancy in the world, with an estimated 1.2 million new cases and 1.1 million deaths worldwide annually. Most patients have non-small-cell histology and present with a fairly advanced disease stage. Prognosis is closely related to a number of factors, including the histological type, the stage of disease, performance status and the treatment received. Most patients have inoperable disease at presentation, although patients undergoing surgery have the best survival. Other important treatment modalities include combination chemotherapy and radiotherapy, which is given with both palliative and curative intent.

This section looks at important advances in lung cancer management that have appeared in the literature in 2004. Chapter 8 deals with advances in diagnosis and staging techniques, and Chapter 9 looks at new data concerning lung cancer treatment.

Accurate diagnosis and staging are central to the selection of the most appropriate treatment for an individual patient. Two recent important advances in diagnosis and staging have been the development of positron emission tomography (PET) scanning and the use of ultrasound to improve the sampling of disease within the mediastinum. The precise place of these different techniques in the assessment of lung cancer patients is becoming clearer. Chapter 8 also deals with the usefulness of screening asymptomatic patients for distant metastases and also covers an interesting paper that looks at the effects of delays in the time taken for diagnosis and treatment on the outcome of therapy.

Perhaps the most important advance in lung cancer treatment in the last decade has been the development of chemotherapy for non-small-cell lesions. Chapter 9 covers the place of chemotherapy in relation to other treatment modalities, such as surgery and radiotherapy, and the usefulness of chemotherapy in elderly patients with advanced disease. Radiotherapy techniques continue to advance and important information is appearing about the most appropriate timing and schedule of radiation therapy in both curative and palliative settings.

The use of specifically targeted drug treatments is being pursued because current cytotoxic agents show little activity and may have significant toxicity. In the last year important information has appeared which may explain the genetic basis for the success of a specific targeted therapy (gefitinib) in a small subgroup of patients with non-small-cell lung cancer.

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8

Diagnosis and staging techniques in lung cancer

RON FERGUSSON

Introduction

The importance of accurate diagnosis and staging in lung cancer cannot be overstressed. The stage of disease is the most powerful predictor of survival in these patients. The vast majority of patients with lung cancer have an abnormal chest X-ray after presenting with respiratory symptoms. This leads to further investigations to establish the diagnosis and stage the disease. In general, histological confirmation is obtained by sputum cytology, bronchial biopsy at bronchoscopy or percutaneous fine needle aspiration (FNA), or from the sampling of metastases either within the mediastinum or at distant sites.

The extent or stage of disease is assessed traditionally by computed tomography (CT) scanning. This allows the precise location of abnormalities to be pinpointed, with the detection of distant metastases as well as enlarged mediastinal lymph nodes. It is possible for CT scanning to either over- or underestimate the stage of disease, as it is possible for normal-sized lymph glands to contain tumour tissue and for enlarged glands to be merely reacting to the presence of a local tumour. Newer techniques are appearing which improve the diagnostic accuracy of existing tests and allow more precise staging of the disease. This should lead to more appropriate management strategies for patients and may prevent futile treatments that may have significant toxicity.

Endoscopic ultrasound

It is possible to biopsy enlarged mediastinal nodes through the wall of the trachea or bronchi at bronchoscopy or through the oesophagus on upper gastrointestinal endoscopy. More data are appearing in the literature outlining the usefulness of these techniques. It may also be possible to sample normal-sized lymph nodes in the mediastinum using endoscopic ultrasonography (EUS). Early data suggest that the routine use of EUS may be cost-effective.

Real-time endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal and hilar lymph nodes

Yasufuku K, Chiyo M, Sekine Y, *et al*. *Chest* 2004; **126**: 122–8

BACKGROUND. A number of techniques are available for sampling mediastinal lymph nodes, including mediastinoscopy, CT-guided percutaneous needle aspiration, transoesophageal EUS-guided aspiration and conventional transbronchial needle aspiration. Endobronchial ultrasonography (EBUS), using a flexible bronchoscope, can identify mediastinal and hilar lymph nodes. It is possible to use this technique to obtain specimens through a transbronchial needle. This technique has not been widely reported in the literature.

INTERPRETATION. Patients were entered into the study if they had significant (>1 cm) mediastinal and/or hilar lymphadenopathy with known or suspected malignancy. Real-time endobronchial ultrasonography using a new convex probe (CP-EBUS) was performed on 70 patients over an 18-month period. The convex probe allows scanning parallel to the insertion direction of the bronchoscope, images being obtained by direct contact of the probe on the bronchial wall or by inflating a balloon at the tip of the scope with saline. Transbronchial needle aspiration (TBNA) was performed using a 22-gauge needle, which could be visualized by direct vision and via the ultrasound image. All lymph nodes detected on CT scans prior to the procedure could be visualized using CP-EBUS. Samples were obtained from 58 mediastinal nodes and 12 hilar nodes. There were no complications. Adequate specimens were obtained in 68 patients (96%), malignancy being detected in 45 and benign disease in 25. The sensitivity, specificity and accuracy of CP-EBUS-guided TBNA in distinguishing benign from malignant nodes was 95.7, 100 and 97.1% respectively. Of the 25 benign results, 21 were confirmed by histology obtained by other routes (surgery or thoracoscopy). Three patients had sarcoidosis and one had a cystic lesion on ultrasonography. The two patients with inadequate specimens turned out to have malignancy (false negative)

Comment

This study suggests that direct real-time CP-EBUS-guided TBNA is a safe and accurate method of evaluating mediastinal and hilar lymph nodes. The use of transbronchial ultrasound allows much more accurate localization of lymph nodes. It is possible to obtain results from most lymph node stations. This is in comparison with both mediastinoscopy and transoesophageal ultrasound biopsies. The newer convex probe would appear to improve the diagnostic yield of EBUS-guided TBNA. The authors admit that there is a fairly steep learning curve for the procedure and that adequate training is needed. They also comment that the yield would be increased by the use of a large-gauge needle.

Impact of EUS-guided FNA of enlarged mediastinal lymph nodes on subsequent thoracic surgery rates

Savides TJ, Perricone A. *Gastrointest Endosc* 2004; **60**: 340–6

BACKGROUND. The confirmation of involvement of mediastinal lymph glands from lung cancer usually spares the patient surgical treatment. A number of techniques are evolving by which the mediastinum can be sampled using EUS from either the oesophagus or through the bronchial wall. EUS-guided FNA has yet to be established as a routine technique and its effect on the thoracotomy rate is still not clear.

INTERPRETATION. This was a prospective observational study in patients with enlarged posterior mediastinal lymph nodes who were candidates for mediastinoscopy. Patients were followed for a year after EUS to determine the subsequent rate of mediastinoscopy and thoracotomy, and thus to give the diagnostic accuracy of EUS-guided FNA. Fifty-nine patients were included in the study. Twenty-three (39%) had malignancy confirmed in the mediastinum by EUS FNA. Thirteen patients in the series went on to surgery, including one patient with a positive EUS FNA. A resection rate of 42% (11 out of 26) was possible in patients with a CT finding of a peripheral lung lesion plus mediastinal lymphadenopathy and a negative EUS. Among patients with mediastinal lymphadenopathy alone (33 of the 59), only two (6%) were operable. The overall sensitivity, specificity and accuracy for EUS-guided FNA was 96, 100 and 95%, respectively.

Comment

This study provides further evidence that EUS FNA can spare patients unnecessary mediastinoscopy and thoracotomy. The weakness of the trial was that these patients were selected with lymph nodes that were more likely to be seen at EUS. Further work is needed to determine the clinical usefulness of EUS-guided FNA in all potentially operable patients, since EUS is useful only for sampling lymph nodes near the oesophagus.

Endoscopic ultrasound in lung cancer patients with a normal mediastinum on computed tomography

Wallace MB, Ravenel J, Block MI, *et al*. *Ann Thorac Surg* 2004; **77**: 1763–8

BACKGROUND. EUS FNA has been shown to be useful in staging the mediastinum in patients with non-small-cell lung cancer who have enlarged mediastinal lymph nodes on CT scanning. This study looked at the accuracy and yield of EUS FNA in patients without enlarged mediastinal nodes on CT.

INTERPRETATION. Eighty-seven consecutive patients with pathologically proven non-small-cell lung cancer and no evidence of enlarged mediastinal lymph nodes on CT were included in the study. All were thought to be fit for surgical staging. Patients underwent a conventional CT scan. Positron emission tomography (PET) scanning was not routinely performed. Standard EUS FNA staging was carried out in all patients. This included routine

inspection of the left adrenal gland through the stomach. Lymph nodes with features of malignancy (size >1 cm; a round, sharp margin; diffusely hypoechoic) were sampled. Patients without distant metastases or lymph node involvement proceeded to surgical exploration. Sixty-nine patients were suitable for evaluation (18 dropped out because they were given other treatment or were unfit for surgery). EUS FNA identified mediastinal or adrenal disease in 15 patients, direct invasion of the mediastinum (T4) being found in two patients. Of the 52 patients without evidence of advanced disease by EUS, 11 were found to have advanced disease on further invasive staging (thoracotomy in 45). Figure 8.1 shows the outcomes for all patients in the study. The sensitivity of EUS for advanced mediastinal disease was 61% and the specificity was 98%.

Comment

This study shows that EUS-guided FNA can detect advanced mediastinal disease in patients who have an apparently normal mediastinum on CT scanning. In this study, this means that 25% of patients were spared unnecessary surgical exploration. The results would suggest that all potentially operable patients with non-metastatic non-small-cell lung cancer on CT may benefit from EUS staging.

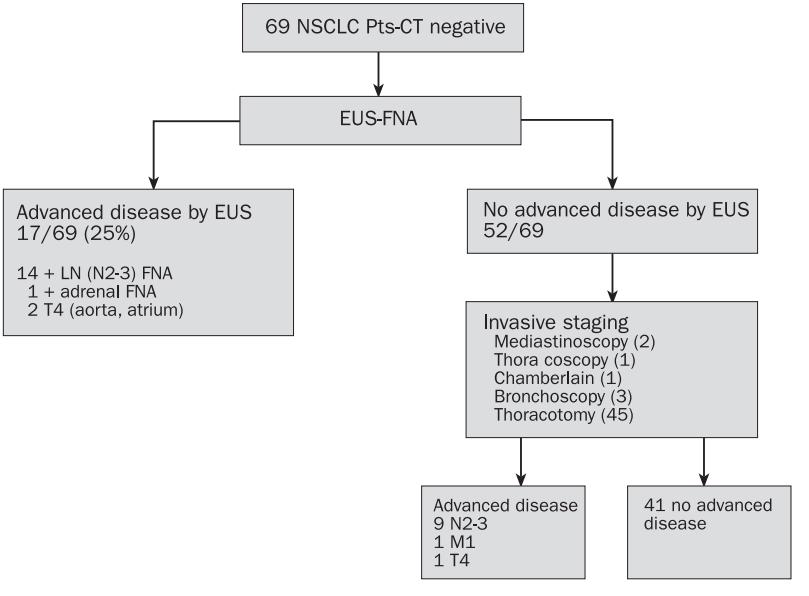

Fig. 8.1 Staging outcomes of patients with NSCLC and no enlarged mediastinal lymph nodes on CT. After CT scan, patients underwent EUS. If no advanced disease (AJCC Stage III/IV) was confirmed, invasive staging was performed. If no advanced disease was confirmed on mediastinoscopy, thoracoscopy, bronchoscopy, a thoractomy and complete mediastinal lymph node resection was performed. AJCC, American Joint Committee on Cancer; CT, computed tomography; EUS-FNA, endoscopic ultrasound guided fine-needle aspiration; LN, lymph node; NSCLC, non-small-cell lung cancer; Pts, patients. Source: Wallace *et al*. (2004).

Oesophageal endoscopic ultrasound with fine needle aspiration improves and simplifies the staging of lung cancer

Kramer H, van Putten JWG, Post WJ, *et al*. *Thorax* 2004; **59**: 596–601

BACKGROUND. EUS FNA would appear to be a useful technique for tissue verification of mediastinal abnormalities picked up in lung cancer staging investigations. Is its routine use after PET scanning cost-effective?

INTERPRETATION. This is a prospective study reported from The Netherlands, where PET scanning is part of the routine staging investigations of lung cancer patients. Of 488 consecutive patients with suspected lung cancer, 81 were found to have mediastinal or upper retroperitoneal abnormalities on PET scanning. These patients went on to have EUS FNA. This was positive for malignancy in 50 patients, who were therefore spared mediastinoscopy. EUS FNA was negative in six (7%) and inconclusive in 25 (31%). Twenty-six of these 31 patients underwent a surgical staging procedure to obtain a tissue diagnosis. Of the six patients with negative EUS FNAs, two had positive nodes at surgery. Three others were negative and one patient had rapidly progressive disease. Of the 25 patients with inconclusive EUS FNAs, twelve were positive and nine were negative at surgery. Four refused further staging and all had progressive disease on imaging. The accuracy of EUS FNA in terms of deciding whether the patient should proceed to surgery was 77% (95% confidence interval [CI] 68–86). An economic analysis was also performed. It showed that the addition of EUS FNA to conventional lung cancer staging (mediastinoscopy) reduced costs by 40% per patient. This was due to a decrease in the number of mediastinoscopies performed (cost of mediastinoscopy US$1758 vs $798 for EUS FNA).

Comment

This is another study showing the value of EUS FNA when added to other staging investigations. Once again the weakness of the technique is that not all areas of the mediastinum can be sampled. Its advantage is that it can confirm or refute a positive PET scan, with virtually no morbidity or mortality as a downside. As yet, EUS FNA is not available to all clinicians managing lung cancer patients. The equipment is expensive and training is required to gain high enough levels of expertise to give meaningful results. It is to be expected, however, that EUS FNA will be used increasingly in the staging of lung cancer patients.

Ultrasound-guided transbronchial needle aspiration—an experience in 242 patients

Herth FJ, Becker HD, Ernst A. *Chest* 2003; **123**: 604–7

BACKGROUND. TBNA allows tissue sampling from mediastinal lymph nodes situated beside proximal airways. The technique, however, relies on blind aspiration, which reduces its sensitivity. EBUS may improve the yield of TBNA.

Interpretation. This report from Germany and Boston describes the use of EBUS in patients with enlarged mediastinal glands. The flexible ultrasound probe was introduced through the bronchoscope with an inflatable balloon at the tip to improve resolution of images through the adjacent airway. Two hundred and forty-two patients were included in the analysis in a 1-year period. In 207 patients (86%) lymph nodes were successfully sampled using the EBUS technique. The authors took the presence of a specific diagnosis or lymphocytes in the specimen as being a successful TBNA. The diagnostic yield was 71%. Of the 35 patients with lymphocyte-negative TBNA, 27 were proved to have malignancy by other techniques; one had sarcoidosis and seven had non-specific findings. There were no complications associated with EBUS and TBNA.

Comment

This is a large series of patients and shows a high diagnostic yield for this technique. Interestingly, the lymph node location did not influence the success of obtaining a successful specimen from the intended node. This is in contrast to conventional TBNA without EBUS, in which diagnostic success depends on the location of the node. This technique, however, does not constitute real-time imaging as the probe had to be removed before TBNA was performed. The authors conclude that the use of dedicated EBUS scopes similar to those used in gastroenterology would increase the yield of the technique even further.

PET scanning

PET scanning is emerging as an important technique in the assessment of patients with lung cancer. The technique depends upon increased uptake by tumour tissue of radiolabelled glucose. Unfortunately, there is a significant false-positive rate (around 16%). Another problem with PET scanning is its inability to locate disease accurately in the mediastinum when compared with conventional CT scanning. It is useful, however, for picking up distant metastases and for deciding whether solitary pulmonary nodules are likely to be malignant. In the last year two papers concerning PET scanning, produced by the same group, are worthy of note. The first looks at the accuracy of combining PET with CT as a staging technique and the second assesses the ability of PET scanning to predict the pathological response in patients undergoing new adjuvant chemotherapy prior to surgery.

The accuracy of integrated PET-CT compared with dedicated PET alone in the staging of patients with non-small-cell lung cancer

Cerfolio RJ, Ojha B, Bryant AS, Raghuveer V, Mountz JM, Bartolucci AA. *Ann Thorac Surg* 2004; **78**: 1017–23

Background. PET scanning is becoming increasingly used as a staging tool for patients with non-small-cell lung cancer. Accuracy in terms of predicting mediastinal

involvement is not particularly impressive. To improve accuracy, some workers have integrated PET scanning with CT scanning. This study compares the accuracy of integrated PET–CT with dedicated PET scanning alone.

INTERPRETATION. This study looked at patients presenting to a single thoracic surgeon with potentially resectable non-small-cell lung cancer. One hundred and twenty-nine patients underwent integrated PET–CT imaging and the TNM (tumour, nodes, metastases) status was assigned by a single radiologist. Within 2 weeks the same radiologist, blinded to the surgical outcome, restudied the PET portion of the integrated images alone and assigned a TNM status. The radiologist, however, had the most recent CT scan of the chest available. Suspicious mediastinal nodes were biopsied either by mediastinoscopy or transoesophageal ultrasound. Suitable patients with negative N2 nodes underwent thoracotomy and complete thoracic lymphadenectomy. Patients with N2-positive disease then underwent neoadjuvant therapy. All suspicious M1 lesions were biopsied or confirmed as malignant by magnetic resonance imaging (MRI) scanning. Perhaps not surprisingly, integrated PET–CT was more accurate than dedicated PET as a diagnostic and staging tool at all stages of disease. This reached statistical significance for Stages I and II (52 vs 33%, 70 vs 36%). Integrated PET–CT was also a better predictor of T status (70 vs 47%; $P = 0.01$) and N status (78 vs 56%; $P = 0.008$). Overall accuracy for N2 and N1 nodes was 96% and 90% respectively for the integrated imaging.

Comment

The results of this small study support previous published results showing that an integrated PET–CT scan where a computer produces one image from two separate scans is more accurate than PET scanning or CT scanning alone. One of the main remaining issues with PET scanning is the continuing high false-positive rate. This means that histological confirmation of a positive scan is still required.

Repeat FDG-PET after neoadjuvant therapy is a predictor of pathologic response in patients with non-small-cell lung cancer

Cerfolio RJ, Bryant AS, Inokur TS, Ohja B. *Ann Thorac Surg* 2004; **78**: 1903–9

BACKGROUND. There has been much interest in neoadjuvant chemoradiotherapy prior to surgery in patients with non-small-cell lung cancer. Can repeat 2-deoxy-2-[^{18}F]fluoro-d-glucose-PET (FDG-PET) and CT scanning effectively predict the response of the primary tumour to this treatment?

INTERPRETATION. This was a retrospective cohort study of 56 patients with non-small-cell lung cancer who underwent neoadjuvant therapy followed by complete resection. All patients had FDG-PET and chest CT scans before and after their neoadjuvant treatment. This comprised chemoradiotherapy in 41% of patients and chemotherapy alone in 59%. Fifty per cent of the tumours were adenocarcinomas and there was a spread of all pre-operative cancer stages apart from IIIb. Forty-one per cent had IIIa disease. There was one patient who had Stage IV disease with an isolated brain metastasis. Seventy-seven per cent of patients subsequently underwent lobectomy. The standardized uptake value (SUV) on PET scanning was determined in the standard fashion by drawing regions of interest on the

images around the primary tumour. The primary outcome of the analysis was the degree of correlation between the percentage change in maximum SUV and the percentage of non-viable tumour in the resected specimen. Tumour volume was calculated in a standard way. Secondary outcomes were the ability of scanning to predict complete pathological response, to assess the correlation based on the type of neoadjuvant therapy, and to compare the degree of correlation based on the two main tissue types of cancer. A nearly linear relationship was seen (Fig. 8.2) between the percentage change in maximum SUV plotted against the percentage of non-viable tumour in the resected specimen ($r = 0.75$; $P < 0.001$). No such correlation was evident between the change in tumour size on repeat CT scanning and the percentage of non-viable tumour ($r = 0.03$; $P > 0.05$).

When the maximum SUV decreased by 80% or more, a complete pathological response could be predicted (sensitivity 90%, specificity 100%, accuracy 96%). FDG-PET was superior to CT scanning as a predictor of the pathological response. There was no difference in the accuracy of the percentage change in maximum SUV for patients with N2 disease compared with those without mediastinal node enlargement.

Comment

This carefully designed study shows the usefulness of repeat PET in the evaluation of the response to treatment. The use of a metabolic marker (FDG-PET) as an indicator of response is interesting. This means that the decision to operate on localized disease may in the future hinge less on the continued presence of a density on a scan than on an abnormality that demonstrates metabolic activity.

Metabolic imaging is likely to be an increasingly useful technique in deciding which patients would benefit from surgical resection in borderline cases.

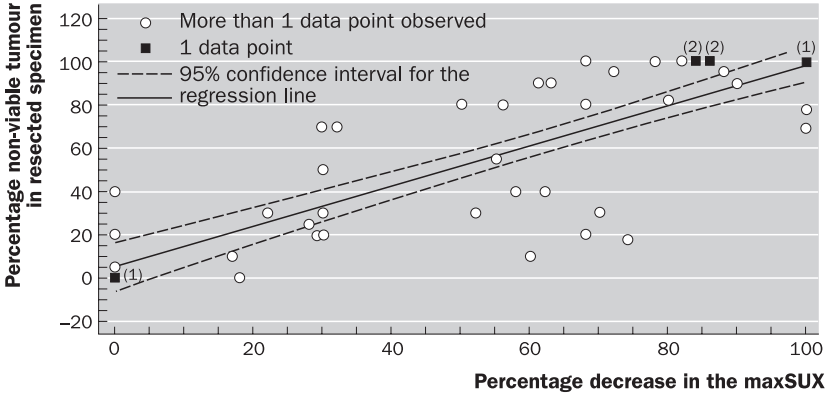

Fig. 8.2 Correlation between the decrease in maximum standardized uptake value (max-SUV) and the percentage of non-viable tumour in the resected specimens. The regression line equation: $y = 0.9501 \times +5.230$; $r^2 = 0.75$; $P < 0.001$. Values where more than one data point was observed have been indicated by *circles* and the number of observations are indicated in *parenthesis*. The *squares* represent one data point. *Dashed lines* indicate the 95% confidence interval for the regression line (*solid line*). Source: Cerfolio *et al*. (2004).

Screening for metastases

The presence of distant metastases (Stage IV disease) in non-small-cell lung cancer carries a grave prognosis. Occult metastases can lie in a number of situations, the adrenal gland, bone and brain being the commonest metastatic sites. At present, routine scanning for metastases has not been advocated as it has been thought that the majority of patients with distant metastases would present with localizing symptoms. The first of three papers presented in this section assesses the ability of isotope bone scanning to detect metastases in symptomatic and asymptomatic patients. The second is a comparison of PET scanning with isotope bone scanning for the detection of osseous metastases. The third is an interesting study looking at the usefulness of routine CT brain scanning for occult metastases in patients thought suitable for resection.

Reliability of symptoms to determine use of bone scans to identify bone metastases in lung cancer: prospective study

Hetzel M, Hetzel J, Arslandemir C, Nussle K, Schirrmeister H. *BMJ* 2004; **328**: 1051–2

BACKGROUND. It has been accepted practice for many years to perform bone scans on lung cancer patients only if they have symptoms suggestive of skeletal metastases. This belief comes from the hypothesis that most skeletal deposits are clinically symptomatic. This dogma has been adopted by many lung cancer guidelines. There is little evidence in the literature of the significance of skeletal symptoms in determining which patients should have skeletal imaging.

INTERPRETATION. This study from Germany recruited 153 consecutive patients over a 2-year period. All had a recent histologically proven diagnosis of lung cancer. One hundred and twenty-one patients were enrolled in the study; 84 of them had non-small-cell and 37 had small-cell histology. Patients were questioned about skeletal complaints and were examined carefully. Calcium and alkaline phosphatase concentrations were measured. New skeletal symptoms (within the previous 6 months) were judged as suspicious. All patients had bone scanning. The gold standard for bone metastases was MRI and the patient's subsequent clinical course. Forty patients (33%) had skeletal metastases. The incidence was identical in non-small-cell and small-cell groups. All these patients had normal biochemistry. Ninety-one patients (75%) of the whole cohort had symptoms. In only 19% the symptoms corresponded to the correct location of metastases. Routine bone scans correctly identified metastases in 29 patients and were truly negative in 80 of 81. This gives a sensitivity of 73% (95% CI 56–85%) and a specificity of 99% (CI 93–10%). The sensitivity fell to 53% if scans had been done only in patients reporting skeletal complaints and to as low as 20% if scans were done in patients with recent bony symptoms suggesting metastases.

Comment

This small study suggests that the pick-up of bone metastases is extremely poor if it is dependent on clinical symptoms or abnormal bone biochemistry. Arthritic complaints are common in lung cancer patients, and this has often allowed the coincidental discovery of bone metastases on bone scanning. If bone scans are reserved for patients whose symptoms suggest metastatic disease (where the test has a sensitivity of 20%), a large number of patients would undergo futile surgery or neoadjuvant chemotherapy.

Comparison of whole-body FDG-PET to bone scan for detection of bone metastases in patients with a new diagnosis of lung cancer

Cheran SK, Herndon JE, Patz EF. *Lung Cancer* 2004; **44**: 317–25

BACKGROUND. The detection of bony metastases confirms Stage IV disease in non-small-cell lung cancer. Historically, isotope bone scanning has been the gold standard for detecting skeletal metastases. Whole-body FDG-PET scans are being used increasingly to detect metastatic disease. How do these two techniques compare?

INTERPRETATION. This study was a retrospective review over a 4-year period in a large North American centre. Patients who were newly diagnosed as having lung cancer and who had received both an isotope bone scan and a whole-body FDG-PET scan prior to therapy were assessed. The sensitivity, specificity and accuracy of this imaging study were calculated. Two hundred and fifty-seven patients were included; 40% had Stage IV disease. Bone metastases were seen in 57 (22%) of patients. The sensitivity, specificity, and positive and negative predictive values of PET were 91, 96, 85 and 97% respectively. The figures for bone scanning were more complicated in that equivocal bone scans could be classified as either positive or negative. Corresponding accuracy figures for bone scanning (equivocal scans taken as positive) were 75, 92, 72 and 93%. There were nine false-positive PET scans, in which bone scanning accurately determined seven to be negative. There were five false-negative PET scans. For three of them, the lesions were outside the region scanned by PET and all were detected on bone scanning. Of the ten patients with false-positive bone scans, nine were correctly determined by PET to be negative for bony metastases and one was a false positive. Fourteen patients had a false-negative bone scan and PET was positive in all these patients. The agreement between PET and bone scanning was reasonable ($r = 0.510$). However, the accuracy of PET scanning was significantly greater (95 vs 90%; $P < 0.05$), although this was only when equivocal bone scan results were excluded.

Comment

This study suggests that PET is more accurate than bone scanning and the authors conclude that it should replace bone scanning in newly diagnosed lung cancer patients. They also admit that the study was subject to a variety of biases. The greatest source of bias was the fact that the presence or absence of bone metastases was not

always verified. It should be stressed, however, that it is difficult to prove the absence of metastatic disease conclusively. Another problem with the study was that the radiologists were never blinded and the results of the second study may have been interpreted with knowledge of the first. These are major shortcomings and a prospective study comparing the two modalities is required before isotope bone scanning is abandoned in favour of FDG-PET scanning.

The value of performing head CT in screening for cerebral metastases in patients with potentially resectable non-small-cell lung cancer: experience from a UK cardiothoracic centre.

Win T, Laroche CM, Groves AM, Nathan J, Clements L, Screaton NJ. *Clin Radiol* 2004; **59**: 935–8

BACKGROUND. Accurate pre-operative staging of non-small-cell lung cancer patients considered for resection is vital. The value of screening for occult intracranial metastases using CT scanning in this group of patients is debatable.

INTERPRETATION. One hundred and five consecutive patients with potentially resectable non-small-cell (Stages I, II and IIIa) underwent routine CT head scanning prior to surgery. None had neurological symptoms or signs. Sixty-three patients also underwent coincidental PET scanning. Patients were followed up for 6 months to detect false-negative scans. Five patients were identified with occult cerebral metastases in a cohort of 105 (4.8%). Eighty-five per cent of the remaining 100 patients underwent resection. In four of the five patients there was squamous cell histology, the lesion was solitary, and it was located in the frontal lobes. Three had a T1 primary. There was one false-negative CT (a cerebellar metastasis picked up 6 months post-operatively).

Comment

The precise prevalence of occult cerebral metastases in potentially resectable lung cancer patients is unknown. This study found a rate of approximately 5%. This figure equates well with an older study |**1**|.

The authors argue that routine CT scanning was cost-effective (savings in avoiding five thoracotomies would be £45000, versus the cost of 105 CT examinations of the head of £16000).

They also argue that the quality of life in the five patients was preserved and they avoided having a thoracotomy in the last few months of their lives. The role of PET scanning in this situation is complex as this form of scanning is not useful in detecting cerebral metastases because of the high level of cerebral glucose metabolism. It would also appear unlikely that MRI would be as cost-effective or as accurate as CT scanning. This study suggests that screening potentially operable patients with non-small-cell lung cancer for cerebral metastases may be cost-effective and may save a small proportion of needless thoracotomies.

Delays and lung cancer management

Patients with lung cancer often present with common respiratory symptoms. Delays in making a diagnosis are not uncommon because of the high prevalence of these symptoms in the smoking population. Patients and clinicians worry that delays in making a diagnosis and starting treatment might adversely affect the efficacy of treatment. In the last year, there appeared an interesting paper looking retrospectively at the influence of delays in both making a diagnosis and starting treatment on outcomes in patients with non-small-cell lung cancer.

Effect of delays on prognosis in patients with non-small cell lung cancer

Myrdal G, Lambe M, Hillerdal G, Lamberg K, Agustsson T, Ståhle E. *Thorax* 2004; **59**: 45–9

BACKGROUND. It may take a significant length of time for a lung cancer patient to have a diagnosis made and treatment given. It is not known, however, whether any delay in the time to make a diagnosis of non-small-cell lung cancer and commence treatment has any impact on overall survival.

INTERPRETATION. This study from central Sweden looked at a cohort of patients with non-small-cell lung cancer diagnosed over a 5-year period. All patients had histologically confirmed disease. Of the 750 patients diagnosed with histologically confirmed non-small-cell lung cancer, 190 received no cancer treatment and 94 were diagnosed at autopsy. This left 466 patients to be included in the study. Information about the patient journey was collected retrospectively from medical records. Two types of delay were studied. The length of time from the onset of symptoms until the start of treatment (symptom-to-treatment delay) and the time taken from the first hospital visit to the start of treatment (hospital delay). The median symptom-to-treatment delay was 4.6 months. Patients with advanced tumour stage (Stage IV) had a shorter median delay (3.4 months). The only other clinical characteristic that had an influence on symptom-to-treatment delay was in surgically treated patients, who had to wait longer than those receiving other types of treatment. Nine per cent of patients with early stage disease (I–II) were treated within 3 months of the onset of symptoms compared with 27% of patients with Stage IIIb disease. The median hospital delay was 1.6 months. This was longer in those who underwent surgery and those with early-stage disease. Three-year survival in the cohort was 31%. Rather surprisingly, patients with the shortest duration of symptoms had poor survival and those who had the shortest hospital delay also had a worse prognosis (3-year survival was 19% compared with 43% in those with a hospital delay of more than 3 months). The relationship between delays and survival is shown in Figs. 8.3 and 8.4.

Comment

At first glance, the results of this study would appear surprising, i.e. shorter delays were associated with a poor prognosis. This is almost certainly due to the fact that patients with advanced, aggressive tumours had more severe signs and symptoms

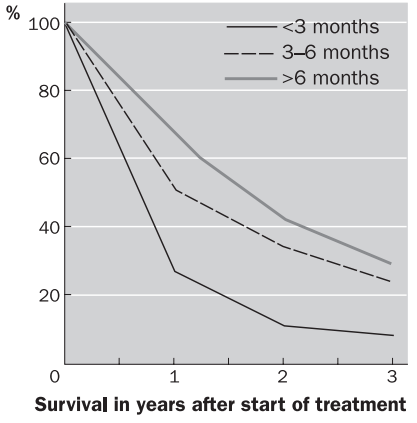

Fig. 8.3 Overall survival in patients treated for primary lung cancer during the study period (1995–1999) in relation to symptom-to-treatment delay. Source: Myrdal *et al*. (2004).

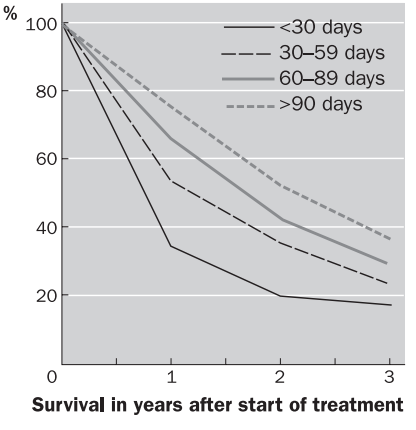

Fig. 8.4 Overall survival in patients treated for primary lung cancer during the study period (1995–1999) in relation to hospital delay. Source: Myrdal *et al*. (2004).

and therefore received prompt treatment. The results of this study would suggest that the biology of the disease and the stage at presentation are far more important than any delay in the patient presenting with symptoms or in making a diagnosis and starting treatment. The study cast doubts on the current trend of investing great resources in pushing patients quickly through the system, as delays seem to have no negative influence on survival. The paper highlights the need to identify patients with potentially radically treatable tumours who should be fast-tracked through the system. This paper would seem to add weight to the call for trials looking at the screening of asymptomatic patients for lung cancer.

Reference

1. Butler AR, Leo JS, Lin JP, Boyd AD, Kricheff II. The value of routine cranial computed tomography in neurologically intact patients with primary carcinoma of the lung. *Radiology* 1979; **131**: 399–401.

9

Treatment of lung cancer

RON FERGUSSON

Introduction

Surgery remains the most effective treatment for non-small-cell lung cancer, although it is only available to a small proportion of patients. This is a result of either an advanced stage of disease at presentation or the presence of comorbidity that precludes surgical intervention. Radiotherapy is an effective treatment when used in high doses in patients who have localized disease and are otherwise unsuitable for resection. Palliative radiotherapy remains a commonly used treatment and is effective in reducing lung cancer symptoms. In the last decade, there has been a huge expansion in the use of chemotherapy, especially in patients with non-small-cell lesions. Small-cell lung cancer remains tantalizingly difficult to manage in that the vast majority of patients will respond initially to chemotherapy and then will subsequently relapse. Median survival is usually around 18 months. A very small proportion of patients will have long-term survival. More effective chemotherapeutic agents are required as the vast majority of patients have systemic disease at presentation. There has been much interest in the last few years in developing targeted therapy as opposed to conventional cytotoxic agents. More is now understood about how these newer treatments may work and which patients may benefit most from them.

Surgery

Surgery is an effective treatment for lung cancer if the disease is localized to a single lobe. Cure following surgery, however, is usually only seen in patients with stage I disease and attempts to improve survival by adding post-operative adjuvant chemotherapy are attracting much attention. A number of important studies looking at this use of chemotherapy in completely resected non-small-cell lung cancer appeared in 2004. Two randomized trials comparing platinum-based regimens provided contrasting results. A third study from Japan looking at the effect of uracil–tegafur was convincingly positive. A systematic review and meta-analysis provides further evidence that post-operative chemotherapy is associated with improved survival compared with surgical treatment alone in non-small-cell lung cancer.

Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer

Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J; International Adjuvant Lung Cancer Trial Collaborative Group (IALT). *N Engl J Med* 2004; **350**: 351–60

BACKGROUND. The 1995 meta-analysis suggested that cisplatin-based adjuvant chemotherapy could improve overall survival by approximately 5% at 5 years. Could this result be replicated in a multicentre clinical trial?

INTERPRETATION. This was a large trial based in Europe which enrolled a total of 1867 patients over a 4-year period from 148 centres in 33 countries. Each participating centre was able to select a number of different options prior to starting the study. These included the dose of cisplatin administered, the drug used in combination with cisplatin (one of three vinca alkaloids or etoposide) and whether post-operative radiotherapy was given depending upon pathological stage. The trial was powered to show an absolute improvement in survival of 5% (from 50 to 55%) at 5 years. The groups were well matched in terms of age, gender, pathological TNM (tumour, nodes, metastases) stage, type of surgery performed, histology and performance status. In the chemotherapy group, 73.8% of patients received adequate platinum therapy and 7.8% did not receive adequate treatment. Five hundred and seventy-two patients (divided almost exactly between the two groups) were assigned to receive adjuvant radiotherapy. Significant toxicity was seen in the chemotherapy arm. At least one episode of Grade 4 toxic effect (mainly neutropenia) occurred in 22.6% of patients, and seven patients died from the toxic effects of chemotherapy. This was predominantly related to the dose of cisplatin administered. Treatment with post-operative chemotherapy was associated with better survival (see Fig. 9.1). The hazard ratio for death was 0.86 (95% confidence interval [CI] 0.76–0.98). Two-year survival was 70.3 vs 66.7% and 5-year survival 44.5 vs 40.4% in favour of chemotherapy.

Comment

This was a large trial and showed that cisplatin-based chemotherapy improved survival in apparently completely resected non-small-cell lung cancer patients. The authors estimate that the absolute benefit derived from adjuvant treatment would be meaningful as approximately 180 000 cases could possibly be treated annually. This was based on a resection rate of non-small-cell cancer of approximately one-third, which is certainly higher than current resection rates in the UK. Extrapolating the results of the trial, a total of 7000 deaths from non-small-cell lung cancer could be averted each year with the use of adjuvant cisplatin-based chemotherapy. This study did not identify predictive factors that could identify groups deriving most and least benefit from post-operative treatment. This treatment is associated with significant toxicity, although the vast majority of deaths in the chemotherapy group were due to disease progression.

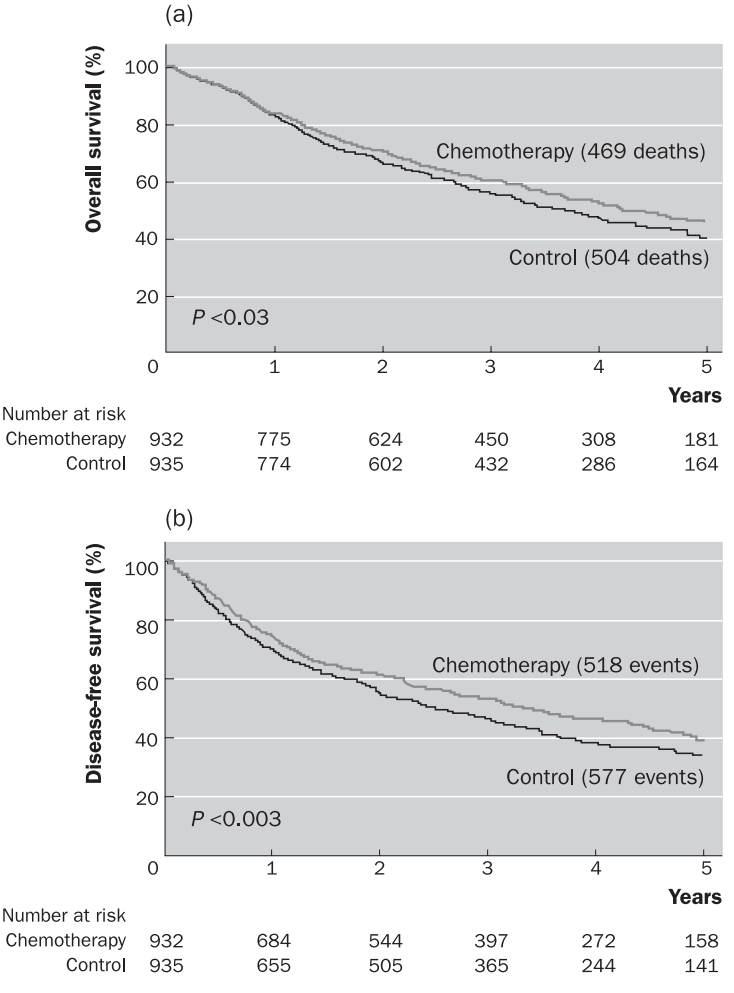

Fig. 9.1 Overall survival (a) and disease-free survival (b). The hazard ratio for death in the chemotherapy group as compared with the control group was 0.86 (95% CI 0.76–0.98), and the hazard ratio for disease progression or death was 0.83 (95% CI 0.7–0.94). Source: Arriagada *et al*. (2004).

Randomized study of adjuvant chemotherapy for completely resected Stage I, II or IIIA non-small-cell lung cancer

Scagliotti GV, Fossati R, Torri V, *et al*.; Adjuvant Lung Project Italy/European Organisation for Research Treatment of Cancer—Lung Cancer Cooperative Group Investigators. *J Natl Cancer Inst* 2003; **95**: 1453–61

BACKGROUND. Most patients treated surgically for non-small-cell lung cancer die of the disease. The role of adjuvant chemotherapy in patient survival has not been established.

INTERPRETATION. This was an Italian trial (Adjuvant Lung Project, Italy [ALPI]) that enrolled 1209 patients with apparently operable non-small-cell lung cancer. Subjects were randomly allocated to receive chemotherapy (mitomycin C, vindesine and cisplatin [MVP]) every 3 weeks for three cycles or to no treatment after complete resection. The primary end-point was overall survival, and toxicity was an important secondary end-point. Median follow-up at the time of publication was 64.5 months. Sixty-nine per cent of MVP-treated patients completed their chemotherapy, though half of these had some dose adjustment. There was a significant dropout rate in the chemotherapy-treated group. Grade 3 and 4 neutropenia occurred in 28% of treated patients. The incidence of nausea and vomiting, however, was low. There was an excess of early deaths among patients in the MVP arm (90 vs 69), although this was predominantly due to cancer progression. There were, however, ten treatment-related deaths during the study. However, only three of these were in the MVP arm. No statistically significant difference between the two patient groups in overall survival was seen. The hazard ratio of death in the treatment arm was 0.96 (95% CI 0.81–1.13; $P = 0.589$).

Comment

This prospective randomized trial failed to show any benefit for adjuvant chemotherapy in completely resected non-small-cell lung cancer. An important confounder was the poor compliance with MVP treatment and the authors felt that future studies should include a chemotherapy arm that would be more easily tolerated. Another possible problem was the high incidence of radiotherapy in the control group (82 vs 65%). However, radiotherapy treatment *per se* was not found to be associated with improved survival compared with disease stage and gender. One interesting part of the study examined tumour markers (p53 expression and K-ras expression). No statistically significant association was seen between the presence of tumour markers and overall survival.

A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung

Kato H, Ichinose Y, Ohta M, *et al*.; Japan Lung Cancer Research Group on Post-surgical Adjuvant Chemotherapy. *N Engl J Med* 2004; **350**: 1713–21

BACKGROUND. Most patients undergoing surgical treatment for lung cancer eventually relapse with recurrence of the disease. The place of adjuvant chemotherapy following resection in non-small-cell lung cancer has not been established despite a meta-analysis suggesting benefit for this form of treatment. There is a need for good randomized trials of adjuvant therapy following resection of early-stage disease.

INTERPRETATION. This is a large Japanese study in which almost 1000 patients were randomized over a 3-year period to receive adjuvant chemotherapy following resection. All patients had completely resected pathological stage I adenocarcinoma. The chemotherapy chosen was oral uracil–tegafur (UFT) and treatment was administered for 2 years after surgery. Patients were followed up at 6-monthly intervals after cessation of therapy. The two groups were well matched for all the important prognostic indicators. Median follow-up was approximately 6 years. Five-year survival was 88% (95% CI 85–91%) in the UFT group and 85% (95% CI 82–89%) in the control group (see Fig. 9.2). This just reached statistical

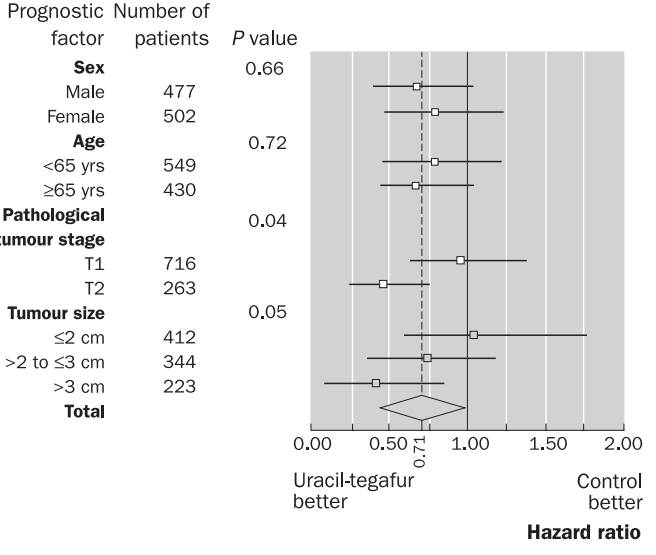

Fig. 9.2 Hazard ratios for death in patients in the uracil–tegafur group as compared with the control group, according to four prognostic factors. Each *square* represents the estimated treatment effect, the *horizontal lines* represent the 95% CI, and the *diamond* corresponds to the 95% CI for the entire group of patients. The *P*-value for the tumour size is for the comparison of patients who had tumours that were 2 cm or less in diameter with patients who had tumours that were more than 3 cm. Source: Kato *et al*. (2004).

significance ($P = 0.047$). The most obvious advantage for treatment was seen in patients with disease at a more advanced stage (T2 tumours larger than 3 cm). UFT was well tolerated, with very few adverse events (2% had a Grade 3 adverse reaction).

Comment

This trial showed that UFT improved the survival rate of patients undergoing resection of stage Ib adenocarcinoma of the lung. Patients with small tumours (stage Ia) showed no benefit. One advantage of this treatment was that it was given orally and was well tolerated. There was a significant drop-off in compliance in the treatment group which was not fully explained, as most adverse reactions were infrequent and mild. In general they were due to patient decisions. There have now been six trials of adjuvant chemotherapy with UFT following surgery. A meta-analysis has been published in abstract form. It shows that this treatment is associated with an overall survival advantage (hazard ratio of death, 0.77; 95% CI 0.63–0.94; $P = 0.01$). Outstanding issues include whether this treatment would help patients with more advanced stage disease after resection (stage 2 or 3a) and the optimum duration of therapy with UFT.

Post-operative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis

Sedrakyan A, van der Meulen J, O'Byrne K, Prendiville J, Hill J, Treasure T.
J Thorac Cardiovasc Surg 2004; **128**: 414–19

BACKGROUND. Post-operative adjuvant chemotherapy is not currently recommended for resected non-small-cell lung cancer. In the last few years trials have looked at the possible benefits of this kind of treatment. Can meta-analysis clarify the position?

INTERPRETATION. The 1995 lung cancer meta-analysis suggested a trend towards benefit for adjuvant chemotherapy after surgical treatment. This paper was a systematic review of new evidence in this area since the 1995 publication. The authors have tried to determine whether post-operative chemotherapy is associated with improved survival compared with surgical treatment alone. Only trials with node-negative patients and chemotherapy regimens containing cisplatinum and UFT were included. Seven new trials were added to the previous 12 trials from the 1995 review, giving a total of 7200 patients in the meta-analysis. The relative reduction in mortality from chemotherapy was 13% (hazard ratio 0.87; 95% CI 0.81–0.93; $P < 0.0001$). When the trials were categorized by drug regimen, the effect of post-operative cisplatin was 11% and that of UFT was 17% ($P = 0.004$ and $P = 0.006$ respectively).

The cisplastin-based trials contain patients with stage I to 3a disease with survival in the control group at 5 years of 45%. The 11% relative reduction in mortality therefore translates into a 4% absolute improvement. This means that approximately 25 patients would need to be treated to prevent one additional death at 5 years. In contrast, the UFT regimens were used mostly in stage I disease in Japan. Survival in the control group was approximately

80% at 5 years and a 17% relative reduction in mortality transforms into an absolute improvement in 5-year survival of approximately 3.5%, requiring 30 patients to be treated to prevent one additional death at 5 years.

Comment

This study adds further weight to the argument that post-operative chemotherapy may be of survival benefit in resected patients.

All the UFT trials were conducted in Japan but the authors found no difference in survival between Japanese and European/North American patients in the platinum trials. The authors therefore felt it was reasonable to extrapolate the results of the UFT findings to non-Japanese patients. One criticism of the meta-analysis was that formal quality evaluation of each study was not included.

The authors conclude that for selected patients post-operative chemotherapy should be offered after complete resection. This obviously will have a major impact on management in resected disease. What is not clear is which of the regimens would be considered the standard treatment. Even more trials are required.

Superior vena caval resection

Involvement of the superior vena cava by lung cancer has traditionally rendered patients inoperable. An interesting paper was published in 2004 suggesting that it may be possible to resect the superior vena cava when it is involved in lung cancer in selected patients.

Results of superior vena cava resection for lung cancer: analysis of prognostic factors

Spaggiari L, Magdeleinat P, Kondo H, *et al*. *Lung Cancer* 2004; **44**: 339–46

BACKGROUND. Superior vena cava invasion by non-small-cell lung cancer has up to now been considered a definitive contraindication to surgical resection. In the last decade small series of patients who have had superior vena cava resection have appeared in the literature. Little is known about the prognostic factors that are important for patient selection for this procedure and there is a need to establish a benchmark for future studies.

INTERPRETATION. This is a retrospective review of series reported in the literature of superior vena cava resection for lung cancer. One hundred and nine patients from four centres (Milan, Paris, Tokyo and Marseille) were included over a 37-year period. All but two patients, however, were operated on after 1991. The median age was 64 years. Twenty-one per cent of patients received pre-operative medical treatment—chemotherapy, radiotherapy or both. A number of different surgical approaches were described. Just over half the patients underwent pneumonectomy, 54 having lobar resection. Eleven patients required an associated resection of the chest wall. Twenty-six per cent of patients underwent complete

resection of the vessel with prosthetic replacement. The other patients required partial superior vena cava resection with reconstruction. Unfortunately, data concerning post-operative anticoagulant therapy were incomplete.

Major post-operative complications occurred in 30% of patients, with a post-operative mortality rate of 12%. Pulmonary complications were responsible for twelve of these 13 deaths. Early superior vena cava thrombosis was seen in 4.5%. Overall intensive therapy unit (ITU) and hospital stay were 3 and 16 days respectively. Median survival after surgery was 11 months, with estimated 1-, 3- and 5-year survival rates of 49, 25 and 21%, respectively (see Fig. 9.3). In a multivariate survival analysis, factors associated with an increased risk of death were pneumonectomy and complete resection of the superior vena cava with prosthetic replacement. Induction treatment was associated with an increased risk of major complications.

Comment

This is an interesting paper describing the radical resection of lung cancer involving the superior vena cava over a long period of time in selected centres. The authors conclude that this type of surgery may result in a permanent cure in carefully selected patients. Cervical mediastinoscopy is recommended in all patients to exclude those with station R2 mediastinal nodes. R4 nodes are an absolute contraindication even after induction treatment. The authors also recommend excluding from surgery patients who still require pneumonectomy after induction therapy. This represented 50% of patients in the series described. This is fairly heroic surgery and this study helps to identify the small subgroup of patients who might benefit from the procedure.

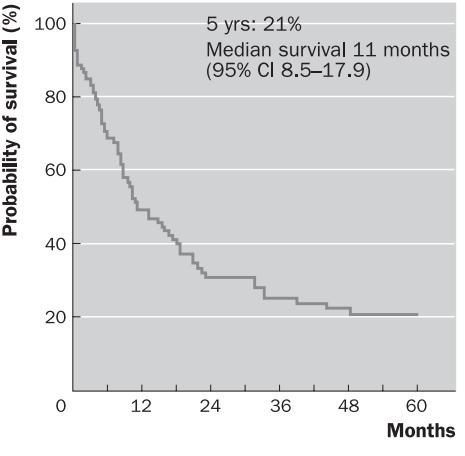

Fig. 9.3 Survival curve (Kaplan–Meier method) of patients who underwent resection of the superior vena cava for NSCLC. The probability of survival at 1, 3 and 5 years were 49, 25 and 21%, respectively. Patients at risk at 12, 24, 36, 48 and 60 months were 44, 23, 18, 14 and 9, respectively. Median survival was 11 months (range: 0.13–127 months; 95% CI 8.5–17.9 months). Source: Spaggiari *et al*. (2004).

Radiotherapy

Radiotherapy remains the commonest treatment for lung cancer worldwide. Most patients are treated with palliative intent as most with localized disease undergo resection. In those with this form of disease who are medically unfit for surgery, radical radiotherapy is a useful alternative. It is clear that there is an obvious dose–response relationship for radiotherapy cytotoxicity. The following papers suggest that high doses of radiotherapy in large tumours give better control, that it is feasible to give high doses of radiotherapy along with chemotherapy, and that the interval between treatments in a hyperfractionated regimen is crucial in determining the effectiveness of this form of treatment.

Improved local control with higher doses of radiation in large-volume Stage III non-small-cell lung cancer

Rengan R, Rosenzweig KE, Venkatraman E, *et al*. *Int J Radiat Oncol Biol Phys* 2004; **60**: 741–7

BACKGROUND. Radiotherapy is the most widely used treatment for inoperable non-small-cell lung cancer. There is some evidence to suggest a direct relationship between dose and local tumour control. Patients with large-volume disease appear to have poor survival. This study investigated whether there is a dose–response relationship for radiotherapy in large-volume tumours in terms of improved local control and longer survival.

INTERPRETATION. This study from the Memorial Sloan-Kettering Cancer Center looked at the influence of total radiotherapy dose on both local control and survival in 72 patients with biopsy-proven stage III non-small-cell lung cancer with gross tumour volumes of more than 100 cc. Standard three-dimensional conformal radiotherapy was used with conventional fractionation. Patients were treated with dose levels ranging from 50 to 84 Gy. In this study the patients were divided into two groups: those treated with less than 64 Gy (37 patients) and those treated with 64 Gy or a higher dose (35 patients). This dose level was chosen as it was the median dose that all stage III patients received.

The two groups were well matched in terms of prognostic indicators. The majority of patients (89%) were also treated with two to four cycles of cisplatin-based chemotherapy before undergoing definitive radiotherapy. The tumour volume was calculated after chemotherapy. The results are shown in Fig. 9.4. The 1- and 2-year local failure rates were 27 and 47% respectively in the group receiving more than 64 Gy and 61 and 76% in those receiving lower doses of radiotherapy ($P = 0.024$). There was a trend towards improved survival with increasing dose (median survival in the higher dose group was 20 months versus 15 months in the group receiving lower treatment doses; $P = 0.068$). Although treatment-related morbidity was higher in the group receiving more than 64 Gy compared to the lower dose group (Grade 2 and 3 oesophageal toxicity, 14 vs 8%), the difference did not reach statistical significance. Similar figures were seen between the two groups for pulmonary toxicity (29 vs 22%). There was one death from radiation pneumonitis in the high-dose group.

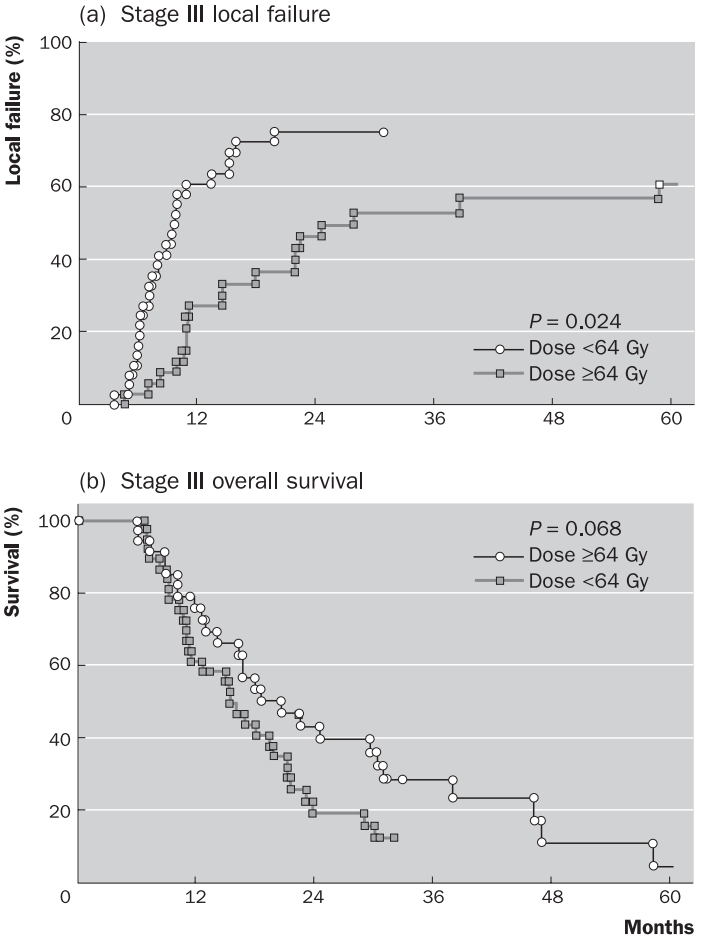

Fig. 9.4 (a) The percentage of patients with local failure in those Stage III non-small-cell lung cancer (NSCLC) patients treated to less than 64 Gy (*diamond*) and 64 Gy or higher (*square*); $P = 0.024$. (b) Overall survival for patients with Stage III NSCLC patients treated to less than 64 Gy (*square*) and 64 Gy or higher (*diamond*); $P = 0.068$. Source: Rengan *et al*. (2004).

Comment

This was a retrospective analysis and supports the concept that an increased radiation dose is associated with better local control and perhaps improved survival. There are a number of flaws in this study, however, including the fact that different staging modalities, such as PET scanning, would have resulted in improved staging for some of the patients. Also, the patients recruited to the study in the last 2 years were treated with the deep inspiration breath-hold technique, which reduces excessive pulmonary toxicity.

The optimum radiation dose for the treatment of non-small-cell lung cancer has yet to be defined, but even in patients with incurable disease higher doses of radiotherapy appear to improve local control.

70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: analysis of Cancer and Leukemia Group B study 39808

Bogart JA, Herndon II JE, Lyss AP, *et al*.; Cancer and Leukemia Group B study 39808. *Int J Radiat Oncol Biol Phys* 2004; **59**: 460–8

BACKGROUND. Combined-modality treatment with radiotherapy and chemotherapy is accepted as standard treatment for limited-stage small-cell lung cancer. The addition of radiotherapy has been shown to reduce the incidence of local relapse. Increasing the dose of radiotherapy administered may improve survival but at the expense of increased toxicity. Can high-dose once-daily thoracic radiotherapy be given to patients undergoing concurrent chemotherapy in small-cell lung cancer?

INTERPRETATION. Seventy-five patients with limited-disease small-cell lung cancer were enrolled in the study. They received two cycles of induction chemotherapy (topotecan and paclitaxel) and were then restaged with appropriate scans. Patients without disease progression received three further cycles of consolidation therapy (etoposide and carboplatin) along with thoracic radiotherapy. After a second restaging, patients with a complete or good partial response were offered prophylactic cranial irradiation.

Thoracic radiotherapy was based on tumour volumes from restaging chest CT scanning. The initial ten patients were given 60 Gy of radiotherapy to assess tolerability and were not included in the analysis. The next 65 consecutive patients were given 70 Gy of radiotherapy; two patients were withdrawn, leaving 63 completed for analysis. Fifty-seven (90%) were available for evaluation of toxicity. There was one treatment death (haemorrhage). Haematological toxicity was common, 41 patients (72%) having Grade 3 or 4 neutropenia. Grade 3/4 dysphagia was seen in 21%. Only three patients had any pulmonary toxicity (Grade 3). The overall response rate was 92%. The complete response rate was 3% after initial chemotherapy and rose to 44% (28 out of 63) after radiotherapy and combined chemotherapy. The median survival at the time of reporting was 22.4 months; 2-year survival was 48%, ten patients relapsing locally within the high-dose radiotherapy volume.

Comment

This was a prospective Phase II trial showing that 70 Gy of radiotherapy can be given as a daily regimen concurrently with chemotherapy in limited-disease small-cell lung cancer. The toxic effects of treatment were comparable with those in other recently reported trials of a more modest dose of radiotherapy, and indeed the incidence of oesophagitis looks less than in reports of accelerated regimens. This trial employed radiotherapy techniques that were not universally available, and the fact that patients were radiated after an initial response to chemotherapy meant that volumes were perhaps smaller than if they had been treated with chemotherapy and radiotherapy

together at the time of diagnosis. A 2-year survival rate of 48% is encouraging. More work is required to clarify the precise timing of radiotherapy in a Phase III trial, in order to establish a basis for efficacy and toxicity in this disease.

Interfraction interval in patients with Stage III non-small-cell lung cancer treated with hyperfractionated radiation therapy with or without concurrent chemotherapy

Jeremic B, Milicic B, Dagovic A, Aleksandrovic J, Milisavljevic S. *Am J Clin Oncol* 2004; **27**: 616–25

BACKGROUND. There have been great changes in the fractionation of radiotherapy regimens for non-small-cell lung cancer over the past two decades. How important is the interfraction interval, i.e. the time between radiotherapy fractions, in patients with non-small-cell lung cancer treated with or without concurrent chemotherapy?

INTERPRETATION. This report is based on results of four prospective studies performed in a teaching hospital in Yugoslavia over a 6-year period (January 1988 to June 1993). These trials, which have been reported separately in the literature, have compared various radiotherapy and chemotherapy regimens in non-small-cell cancer patients (stage IIIa or IIIb). Treatment techniques did not change over this period. The only variable in terms of radiotherapy was the difference in fractionation regimen. The data were pooled and analysed by dividing 536 patients according to the interfraction interval. Two hundred and eighty-five patients had an interfraction interval of between 4.5 and 5 h, and 251 had a longer interfraction interval (5.5–6 h). Treatment with a shorter interfraction interval led to better overall survival and disease-free survival (Figs 9.5 and 9.6).

A number of factors were predictors of survival, including gender, performance status, weight loss, stage and total radiotherapy dose. Multivariate analysis showed that the interfraction interval was an independent prognostic factor for survival ($P < 0.0001$). Patients treated with a shorter interfraction interval had a higher incidence of haematological toxicity (16.3 vs 7.7%; $P = 0.002$), but no other acute high-grade toxicity (World Health Organization [WHO] Grade 3 or 4) was seen with shorter interfraction intervals.

Comment

This study suggests that a shorter interfraction interval would appear to be advantageous in non-small-cell lung cancer patients in terms of improved survival and better local control of disease but not at the cost of increased toxicity. Unfortunately, the retrospective nature of this study and the fact that a number of potential variables, such as comorbidity, were not recorded, may have influenced the result. Also, patients with other good prognostic factors, such as no weight loss, good performance status and an early stage, were more likely to be treated with shorter interfraction intervals. It has to be concluded, therefore, that although this study suggests that shorter treatment intervals are advantageous, a large prospective randomized trial looking at this variable is required.

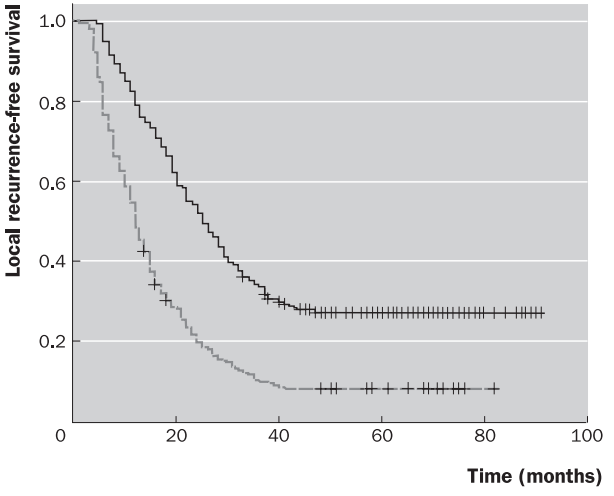

Fig. 9.5 Overall survival according to interfraction interval. Source: Jeremic *et al*. (2004).

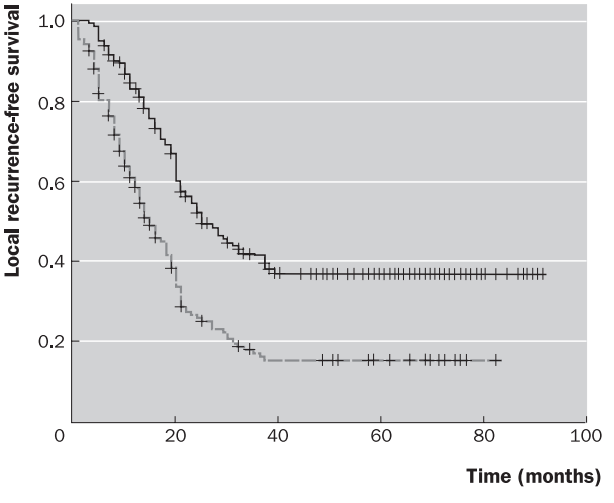

Fig. 9.6 Local recurrence-free survival according to interfraction interval. Source: Jeremic *et al*. (2004).

Chemotherapy

In 1995 a meta-analysis of randomized trials investigating the value of adding chemotherapy to other primary treatments for non-small-cell lung cancer suggested a small survival benefit if platinum was included in the regimen |**1**|.

In 2004, a large randomized trial of chemotherapy versus best supportive care was reported from the UK (Big Lung Trial). The results from this study would appear to validate the meta-analysis, showing improved survival with cisplatin-based chemotherapy compared with best supportive care. Other important publications in this area have shown that it is possible – and indeed beneficial – to give selected elderly patients with non-small-cell lung cancer chemotherapeutic regimens. A further paper suggests that comorbidity may not be an important predictor of outcome in elderly patients receiving treatment for non-small-cell lung cancer.

Chemotherapy versus supportive care in advanced non-small lung cancer: improved survival without detriment to quality of life

Spiro SG, Rudd RM, Souhami RL, *et al.*; Big Lung Trial participants. *Thorax* 2004; **59**: 828–36

BACKGROUND. The 1995 meta-analysis which compared the benefit of chemotherapy in non-small-cell lung cancer versus best supportive care showed a small survival advantage for treatment. This analysis involved many small trials with different chemotherapy regimens. The authors investigated whether the benefits of chemotherapy suggested by the meta-analysis could be confirmed in a large randomized trial of cisplatin-based chemotherapy and supportive care versus supportive care alone.

INTERPRETATION. This was a large multicentre randomized trial performed in the UK over a 6-year period (1995–2001). Seven hundred and twenty-five patients were randomized to either supportive care alone ($n = 361$) or supportive care plus cisplatin-based chemotherapy ($n = 364$). Patients in the arm given supportive care alone could receive any treatment, including palliative radiotherapy but not chemotherapy. Patients in the chemotherapy arm were prescribed three cycles of cisplatin-based chemotherapy using four different regimens. Patients were staged according to local practice. The primary end-point was overall survival. Quality of life and the cost of management were investigated as optional substudies.

It was planned to recruit 800 patients to this study but recruitment was stopped early because of funding problems and poor accrual. The median age was 65 and 95% of patients had stage III or IV disease. Sixty-five per cent of patients in the chemotherapy arm received their prescribed three cycles. Not surprisingly, patients with better performance status were more likely to receive the full therapy regimen. More patients in the supportive care arm received thoracic radiotherapy (74 vs 47%).

The administration of chemotherapy was associated with improved survival (hazard ratio 0.77; 95% CI 0.66–0.89; $P = 0.0006$). Median survival was 8 months for chemotherapy patients and 5.7 months for those receiving best supportive care. One and two-year survival figures were 29 and 10% respectively in the chemotherapy arm and 20 and 5% in the supportive care arm (see Fig. 9.7). Not surprisingly, survival was related to stage, performance status and squamous histology. Survival was not related to age or the chosen chemotherapy regimen. Toxicity was as expected for these chemotherapy regimens (31% experienced Grade 3–4 toxicity). There were 19 (5%) treatment-related deaths in the chemotherapy group. Quality of life data were difficult to interpret. Only 134 patients had complete data at baseline and 12 weeks. Global quality of life scores were slightly higher for patients given chemotherapy. A cost analysis showed that the cost of chemotherapy was offset by longer survival.

Comment

This is the largest and probably the last trial that compares supportive care and chemotherapy in the treatment of advanced-stage non-small-cell lung cancer. The median survival benefit of 2 months reported in the previous meta-analysis was confirmed, with a 9% increase in survival at 1 year. This survival did not come at the cost of increased toxicity and decreased quality of life.

An important question remains—that of whether the findings of the study will persuade nihilistic chest physicians to consider treating more of these patients. One important factor in this area is the patient's opinion about chemotherapy and its benefits.

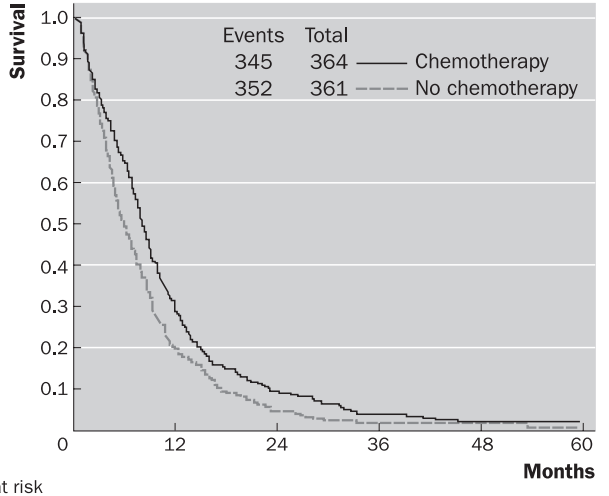

Fig. 9.7 Overall survival. Source: Spiro *et al*. (2004).

Studies in the literature have shown surprising results: patients often choose to receive essentially toxic treatment for what seems a small benefit. It would seem important, therefore, to arm patients with the results of randomized clinical trials in this area and allow them to decide whether the benefits of chemotherapy outweigh any drawbacks.

Cisplatin versus carboplatin in combination with mitomycin and vinblastine in advanced non-small-cell lung cancer: a multicenter, randomized phase III trial

Paccagnella A, Favaretto A, Oniga F, *et al.*; GSTVP (Gruppo di Studio Tumori Polmonari del Veneto). *Lung Cancer* 2004; **43**: 83–91

BACKGROUND. Chemotherapy using platinum-containing regimens has become standard treatment for fit patients with advanced (stage IIIb and IV) non-small-cell lung cancer. Carboplatin would seem to have efficacy similar to that of cisplatin but with a better toxicity profile. The authors investigated whether carboplatin is an effective substitute for cisplatin in improving quality of life in these patients.

INTERPRETATION. This was a multicentre Italian study in which 153 patients with advanced (stage IIIb or similar IV) non-small-cell lung cancer were randomized to either MVP (mitomycin C, vinblastine and cisplatin, $n = 75$) or MCV (mitomycin C, vinblastine and carboplatin, $n = 78$). The primary objective of the trial was the assessment of quality of life. This was evaluated with Spitzer's questionnaire and the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ – C30 + QLC – LC 13). These questionnaires were administered before chemotherapy, after one and three cycles, and then every 6 weeks for the first 6 months and every 3 months thereafter. Secondary objectives were to compare the activity, toxicity and overall survival of the two combinations.

The results obtained with the Spitzer questionnaire suggested an advantage for MVC in terms of global quality of life ($P = 0.05$). Using the EORTC questionnaire, there was significantly less nausea and vomiting ($P = 0.001$), anorexia ($P = 0.01$), insomnia ($P = 0.03$), constipation ($P = 0.01$) and peripheral neuropathy ($P = 0.01$) in favour of MVC. No differences were observed in global quality of life between the two regimens. The study was underpowered to assess other outcomes adequately. However, the response rates were similar for MVP and MVC (43.1 and 38.6% respectively), median survival being 10.2 and 7.2 months respectively. These differences were not significant.

Comment

The carboplatin regimen had a significantly better toxicity profile in this randomized trial than the cisplatin-containing combination. There were no differences in terms of response rate, time to progression and overall survival between the two groups. The regimens showed similar effectiveness in symptom palliation, although global quality of life favoured neither regimen. This study would certainly support the substitution of carboplatin as it produces less toxicity but has a similar potential for symptom control in comparison to a similar cisplatin-containing combination. However, the drug is significantly more expensive than cisplatin.

Effect of comorbidity on the treatment and prognosis of elderly patients with non-small-cell lung cancer

Janssen-Heijnen MLG, Smulders S, Lemmens VEPP, Smeenk FWJM, van Geffen HJ, Coebergh JW. *Thorax* 2004; **59**: 602–7

BACKGROUND. Lung cancer is a disease of the elderly. Many patients suffering from the condition have other smoking-related comorbidity. Available treatments for lung cancer, such as surgery, high-dose radiotherapy and newer chemotherapeutic agents, can have significant toxicity and may not be suitable for elderly or unfit patients. This study evaluated the effects of age and comorbidity on treatment and prognosis in patients with non-small-cell lung cancer.

INTERPRETATION. This report from the Eindhoven Cancer Registry included over 4000 patients with non-small-cell lung cancer diagnosed in a 4-year period. This area of the southern Netherlands has a population of around 2 million. Details of significant comorbidity were extracted from patients' records. Details of treatment given and survival up to a minimum of 3 years following registration were recorded. The prevalence of comorbidity increased with age and this comorbidity was predominantly due to cardiovascular disease and chronic obstructive pulmonary disease. Age had a significant influence on treatment received for localized (stages I and II) non-small-cell lung cancer, surgery and chemotherapy being given to 92 and 24% respectively in those under the age of 60 but only 9 and 2% in those aged over 80. Treatment rates also decreased with comorbidity (see Fig. 9.8).

The number of comorbid conditions present had no influence on treatment choices for patients with more advanced disease. Multivariate survival analysis showed that age, tumour size and the treatment given were prognostic factors for patients with localized disease. However, age had no impact as a prognostic factor for those with advanced disease. Comorbidity had no independent prognostic effect. The authors concluded that patients should not be denied aggressive treatment on the basis of age alone and that comorbidity had a negligible influence on survival.

Comment

The finding that comorbidity was not that important is at variance with other studies, predominantly in surgically treated patients. The strength of this study is that the data relate to a population-based cohort rather than a selected group of patients. It is perhaps not surprising that comorbidity has little effect on lung cancer survival as the vast majority of patients die due to the disease in a fairly short time and have little chance of dying from their comorbid conditions. One weakness of this study was that the comorbid conditions were not accurately defined in terms of severity; that is, a patient with medically treated hypertension was given the same weighting as one with severe chronic obstructive pulmonary disease, significant cardiac decompensation or another malignancy.

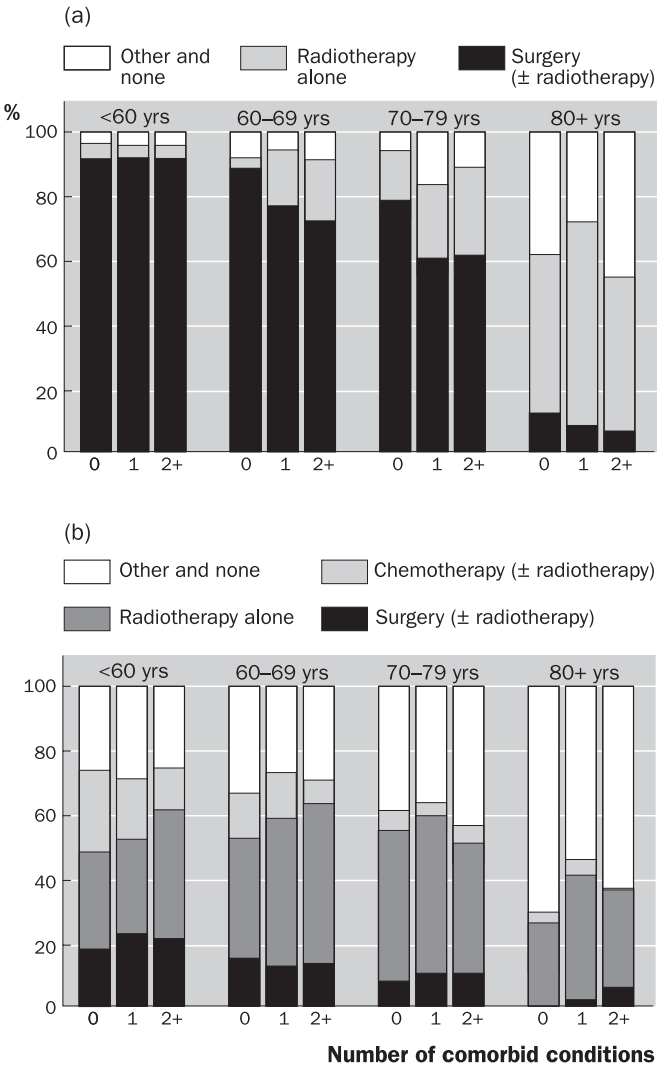

Fig. 9.8 Treatment of (a) localized non-small-cell lung cancer (NSCLC) and (b) non-localized NSCLC according to age, comorbidity, and stage. Source: Janssen-Heijnen *et al*. (2004).

Second-line chemotherapy

Chemotherapy is best viewed as palliative treatment for patients with non-small-cell lung cancer. The disease, therefore, will almost certainly relapse. Many clinicians are sceptical about the benefit of second-line chemotherapy but papers appearing in the

literature this year would suggest that in selected patients this may be a useful strategy. Docetaxel has shown promising activity in this setting, with quality of life usually used as the primary end-point.

Quality of life assessment of second-line docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy: results of a prospective, randomized phase III trial

Dancey J, Shepherd FA, Gralla RJ, Kim YS. *Lung Cancer* 2004; **43**: 183–94

BACKGROUND. Docetaxel has been shown to confer a survival advantage as second-line chemotherapy in non-small-cell lung cancer. The authors investigated whether this was associated with an improved quality of life.

INTERPRETATION. This study reports the quality of life data from the TAX 317 trial. This was a prospective, multicentre Phase III comparison of second-line docetaxel versus best supportive care in 204 previously treated patients with advanced non-small-cell lung cancer. The trial reported a significant improvement in median survival (7 vs 4.6 months) and time to progression (10.6 vs 6.7 weeks) in those receiving docetaxel. Two validated quality of life assessments (the EORTC QLQ-C30 and the LC13 lung cancer module) were carried out at baseline, during treatment and every 2 months during follow-up. Patients treated with docetaxel had more favourable patient-related pain scores. There were trends in favour of docetaxel for observer-related scales of pain and fatigue. Deteriorating quality of life appeared to be slowed by docetaxel treatment and global quality of life deteriorated less in the treatment arm using both assessment tools.

Comment

This is an important study as second-line chemotherapy is always given with palliative intent and little is known about the changes in quality of life in this group of patients. It could be argued that the success of any treatment in this setting would be far better assessed in terms of quality of life rather than survival. One of the problems with this kind of study is that patient survival is poor and the numbers included in the analysis rapidly fall away. One problem with this study was that some patients were given a high initial dose of docetaxel (100 mg/m^2), which was associated with significant toxicity. Quality of life, however, was better in patients who could tolerate this treatment; these patients had a significant improvement in pain scores and reduction in opioid analgesic use. The results of this study support the concept of second-line chemotherapy on a palliative basis for patients with non-small-cell lung cancer who have relapsed with standard first-line chemotherapy. One may question the argument that best supportive care in these patients now represents best practice.

Randomized Phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy

Hanna N, Shepherd FA, Fossella FV, *et al*. *J Clin Oncol* 2004; **22**: 1589–97

BACKGROUND. Most patients with advanced stage non-small-cell lung cancer derive a small survival advantage from chemotherapy. Docetaxel has shown some advantage as a second-line treatment in patients whose disease has progressed following first-line chemotherapy. The authors investigated whether pemetrexed, a new antifolate agent, has a place as second-line chemotherapy in advanced non-small lung cancer.

INTERPRETATION. Patients with stage III or IV non-small-cell lung cancer who had relapsed following prior chemotherapy were included in the study. Patients were randomized to receive either pemetrexed or docetaxel. Those in the pemetrexed arm were pre-treated with oral folic acid and intramuscular vitamin B12 to reduce haematological toxicity. Standard toxicity evaluations and outcome measurements in terms of response and survival were made. Five hundred and seventy-one patients were randomized, and in both treatment arms the patients received more than 95% of the planned dose intensity. There was no significant difference in the overall response rate (9.1 vs 8.8%). The median survival time for pemetrexed was 8.3 months versus 7.9 months for docetaxel. More than 40% of patients received other anticancer drugs after completing the study, almost a third of the pemetrexed arm eventually receiving docetaxel off protocol. One-year survival rates for each arm were identical, at 29.7%. Treatment with docetaxel was associated with a higher incidence of significant neutropenia (40.2 vs 5.3%), resulting in an increase in hospitalization for neutropenic fever (13.4 vs 1.5%). These patients required greater use of granulocyte colony stimulating factor (GCSF; 19.2 vs 2.6%) and had a much higher incidence of alopecia (37.7 vs 6.4%).

Comment

This was a very large Phase III study of second-line treatment for advanced non-small-cell lung cancer. All end-points of efficacy in terms of survival were comparable between the treatment arms. There was a dramatically different toxicity profile between the two drug regimens. It would appear from this study that treatment with pemetrexed gives clinically equivalent efficacy with a significantly improved toxicity profile compared with docetaxel as a second-line treatment for advanced non-small-cell lung cancer.

Other multimodality regimens

A feature of recent research in non-small-cell lung cancer treatment has been the combining of different treatment modalities. This is especially important in patients who are considered to have only borderline suitability for resection (stage IIIa dis-

ease). An interesting trial has been reported comparing treatment in this group of patients with either concurrent chemoradiotherapy or with induction chemotherapy followed by surgical resection.

Equivalent outcome of patients with clinical Stage IIIa non-small-cell lung cancer treated with concurrent chemoradiation compared with induction chemotherapy followed by surgical resection

Taylor NA, Liao ZX, Cox JD, *et al*. *Int J Radiat Oncol Biol Phys* 2004; **58**: 204–12

BACKGROUND. The optimal treatment of stage IIIa (N2) non-small-cell lung cancer is controversial. In Europe the presence of N2 disease usually precludes surgery and radiotherapy is the treatment of choice. Across the Atlantic, minimal N2 disease is still often managed surgically with or without radiotherapy. Chemotherapy can be used here in both a neoadjuvant and an adjuvant setting. There are, as yet, few data comparing these differing management strategies.

INTERPRETATION. This is a report from a single large cancer centre in Texas. Over a 10-year period, 107 patients with clinical stage IIIa non-small-cell lung cancer were treated with either induction chemotherapy followed by surgery ($n = 55$) or concurrent chemoradiotherapy ($n = 52$). This was not a randomized trial, although the two treatment groups were well matched in respect of important prognostic indicators. In the surgical group, induction chemotherapy included two to four cycles of cisplatin-based regimens followed by lobectomy. Post-operative radiotherapy was given to more than half the patients. The concurrent chemoradiation group received three cycles of cisplatin-based chemotherapy concurrent with radiotherapy to a total dose of 60–70 Gy, given in 30–35 fractions in 27 patients and in 58 fractions (twice daily) in 25.

No statistically significant differences were found between the two treatment groups in terms of efficacy. The median survival was 31 and 27 months and the 5-year survival rate 33 and 30% in the surgical and concurrent chemoradiotherapy groups respectively. Five-year local control (58 vs 61%) and disease-free survival rates in the two groups (24 vs 23%) were not significantly different. Post-operative radiotherapy significantly improved the 5-year local control rate from 33.8% to 81.5% ($P = 0.007$) but did not significantly improve overall survival.

Comment

These data would suggest that similar outcomes result from treating stage IIIa non-small-cell lung cancer with either induction chemotherapy and surgery or concurrent chemoradiation. Patients undergoing induction chemotherapy and surgery, however, often needed post-operative radiotherapy to achieve local control. This study was not a prospective randomized trial and is therefore subject to significant bias. Many different chemotherapy and radiotherapy regimens were used. Despite the results of the study, the authors conclude that until better data are available surgery should be the treatment of choice for highly selected patients. They suggest that patients who are fit but

have a slightly greater disease burden should not be put through surgery because concurrent chemoradiotherapy is a good alternative. This study highlights the great need for newer systemic agents that reduce and control distant metastases.

EGFR mutations and gefitinib sensitivity

Gefitinib is a drug which targets the epidermal growth factor receptor (EGFR). Only a small proportion of patients, however, respond to this drug. Two important reports appeared simultaneously in 2004 suggesting that sensitivity to the drug may depend upon genetic mutations within the EGFR receptor.

Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib

Lynch TJ, Bell DW, Sordella R, *et al*. *N Engl J Med* 2004; **350**: 2129–39

BACKGROUND. Gefitinib (Iressa) is a new EGFR inhibitor which has activity in non-small-cell lung cancer. Only approximately 10% of patients have a clinical response to the treatment, but this may be rapid and dramatic. The authors investigated why this small percentage of patients are sensitive to this drug.

INTERPRETATION. This important study from Boston examined tissue from nine patients who had a good response to gefitinib in clinical trials. A control group of seven patients who had no response was included. Mutations in the EGFR gene were searched for. Eight of the nine patients who had responded to treatment with gefitinib had somatic mutations in the tyrosine kinase domain of the EGFR gene. Mutations were not found in matched normal tissue from these patients or in the seven patients who had had no response to the drug ($P < 0.001$). The mutations found were either small dilutions or amino acid substitutions around the ATP-binding pocket of the tyrosine kinase domain. The authors also looked at 25 patients with primary non-small-cell lung cancer who had not been exposed to Iressa, and found two patients (both with alveolar cell cancer) who had identical mutations and gefitinib sensitivity.

In an attempt to confirm the clinical relevance of these mutations, the authors then transfected the most common mutation into a non-small-cell lung cancer cell line (Cos-7). Enhanced tyrosine kinase signalling was seen in response to EGFR compared with the wild-type gene and there was increased sensitivity to gefitinib *in vitro*. These effects were seen at drug concentrations which could be achieved *in vivo*. Complete inhibition was seen with the mutant protein at 0.2 μmol, compared with 2.0 μmol for the wild-type EGFR.

Comment

This fascinating study attempts to understand the molecular basis of responsiveness to gefitinib and raises hope that patients whose tumours will respond to the drug can be identified prospectively. Unfortunately, the vast majority of non-small-cell lung cancer patients have tumours which are not sensitive to gefitinib.

EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy

Paez JG, Jänne PA, Lee JC, *et al*. *Science* 2004; **304**: 1497–500.

BACKGROUND. Targeted therapies are emerging in lung cancer which specifically inhibit certain growth factors. Response rates have been disappointing in clinical trials, though some patients do appear to be sensitive to these treatments. This work sought to find out if an understanding of the molecular biopsy of the specific target will allow the prediction of drug sensitivity.

INTERPRETATION. This study involved a search for somatic genetic alterations in a group of 119 primary non-small lung cancer tumours (58 samples from Japan and 61 from Boston). Seventy tumours were of the adenocarcinoma type. None of the patients had been treated with gefitinib. The exons encoding the activation groups of the majority of human receptor tyrosine kinase genes were amplified and sequenced. Three of the tumours (all adenocarcinoma) showed heterozygous missense mutations in EGFR that were not present in the DNA from normal lung tissue from the same patients. Further heterozygous mutations were seen in 16 of the full complement of 119 non-small-cell tumours. These mutations were somatic in origin. Mutations were more frequent in adenocarcinoma compared with other non-small-cell lung cancers, more frequent in women and more frequent in Japanese patients. The highest incidence of EGFR mutations was, therefore, observed in Japanese patients with adenocarcinoma (eight out of 14 or 57%). To investigate whether these

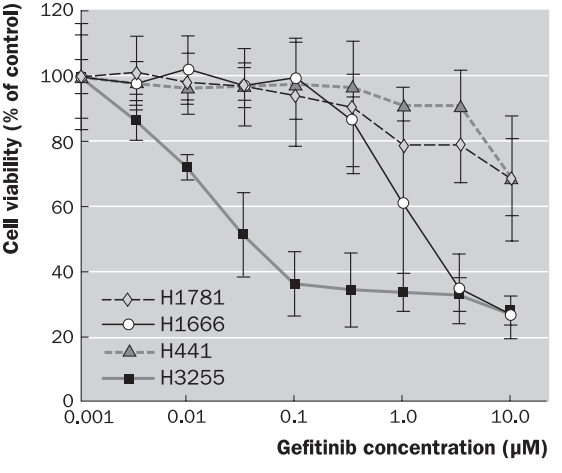

Fig. 9.9 A lung adenocarcinoma cell line with EGFR receptor mutation is sensitive to growth and signalling inhibition by gefitinib. Cells were treated with gefitinib at the indicated concentrations, and viable cells were measured after 72 hours of treatment. Percentage of cell growth is shown relative to untreated controls. H3255 cells have the EGFR L858R mutation, whereas the three remaining cell lines have wild-type (WT) EGFR. Source: Paez *et al*. (2004).

mutations might determine gefitinib sensitivity prior to treatment, non-small-cell lung cancer samples were obtained from five patients who responded and four patients who progressed during treatment with gefitinib. All five tumours from responsive patients harboured EGFR kinase domain mutations. The authors then went on to show that EGFR mutations confer gefitinib sensitivity *in vitro* in four lung adenocarcinoma cell lines (see Fig. 9.9). One cell line (H3255) showed the L858R mutation whereas the other three cell lines did not. This cell line with mutant EGFR is particularly sensitive to gefitinib.

Comment

This trial produced data which are very similar to those from the paper from Lynch and colleagues, and indeed the two papers were published almost simultaneously. It shows that gefitinib sensitivity depends not on EGFR kinase expression but on the EGFR mutation. The fact that the EGFR mutation is much commoner in Japanese patients might explain why this drug has been shown to be much more clinically active in Japanese trials than in American studies. This obviously has fairly major implications for the interpretation of treatment trials in cancer performed throughout the world, and the extrapolation of results from one centre may not be applicable to another.

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Part VI

Obstructive sleep apnoea/hypopnoea syndrome

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10

Overview of diagnosis of obstructive sleep apnoea/hypopnoea syndrome

TOM MACKAY

Introduction

The obstructive sleep apnoea/hypopnoea syndrome (OSAHS) is possibly the most prevalent disease to be discovered in the 20th century. The definition of this syndrome has evolved over the last four decades and it will continue to evolve in the future. The most widely accepted current working definition of this syndrome is the coexistence of unexplained excessive daytime sleepiness or at least two other symptoms (Table 10.1) in association with at least five obstructed breathing episodes per hour of sleep (apnoeas or hypopnoeas).

Apnoea is defined in adults as a 10-s breathing pause |**1**| and hypopnoea |**2**| as a 10-s event in which there is continued breathing but ventilation is reduced by at least 50% from previous baselines during sleep |**3**|.

Table 10.1 List of symptoms of OSAHS

Patient symptoms
Excessive daytime sleepiness and daytime fatigue
Unrefreshing sleep
Nocturnal choking episodes
Nocturia
Depression
Difficulty concentrating
Poor memory
Decreased libido
Partner-reported symptoms
Snoring
Witnessed apnoeic episodes
Restless sleep
Irritability
Change in personality

Patients commonly present to a sleep clinic because of excessive daytime sleepiness or because their partner complains about the intensity of their snoring or expresses concerns about witnessed apnoeic episodes |**4**|. OSAHS has been described as a public health problem comparable to smoking and its effects upon society |**5**|. It is, however, largely under-recognized and undiagnosed |**6**|. Young and colleagues have estimated that 93% of women and 82% of men with moderate severe OSAHS are not diagnosed |**7**|. These patients may seek medical treatment from their general practitioners more than twice as often as patients without OSAHS |**6**|. Among the reasons for the failure to recognize and diagnose OSAHS are the lack of adequate training of medical students in sleep medicine, the general lack of awareness among both the medical profession and the public in general about this common condition, and the lack of specificity of the symptoms with respect to other possible aetiologies |**8**|. Failure to recognize and treat OSAHS is, however, costly to both the individual who has the condition and to society in general, in terms of increased morbidity and mortality |**9,10**|.

The main symptoms of OSAHS at presentation are excessive daytime sleepiness, snoring and witnessed apnoeic or nocturnal choking episodes. Each of these will be discussed briefly in turn.

Symptoms of OSAHS

Excessive daytime sleepiness

Excessive daytime sleepiness is caused by poor-quality fragmented sleep, which in turn is related to repetitive arousals from deep to light sleep in an attempt to keep the upper pharyngeal airway patent during sleep. However, this symptom is extremely common and a poor discriminator of OSAHS as it has been estimated that 30–50% of the general population without OSAHS have moderate to severe daytime sleepiness |**11,12**|. It is very important to try to distinguish between true excessive daytime sleepiness, which can be defined as the subjective urge to sleep, from tiredness or exhaustion, which may be linked to inadequate sleeping time, shift work, the side effects of prescribed or illicit medication, or to some other sleep disorder, such as narcolepsy or restless leg syndrome. Several subjective sleepiness scales have been developed to try to quantify excessive daytime sleepiness and the most widely used scale is the Epworth Sleepiness Scale (ESS), drawn up by Johns and named after the Melbourne district of its origin |**13**|. This is a subjective scale in which patients (and their partners) are asked to rate the likelihood of falling asleep in eight different situations. The original report by Johns suggested that an ESS score above 10/24 was abnormal |**13**| but a larger study using a British normal population of middle-aged men suggested that the 95th centile for ESS was 11/24 |**14**|.

This test is simple, quick, and inexpensive and has a high test–retest reliability |**15**|. The ESS is outlined in Table 10.2.

Objective tests of excessive daytime sleepiness have been devised but they often rely upon the availability of full polysomnographic testing. They include the multiple

Table 10.2 Management of obstructive sleep apnoea/hypopnoea syndrome in adults

The Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations in contrast to just feeling tired? This refers to your usual way of life in recent times. Even if you have not done some of these things, try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation.

0 = would **never** doze
1 = **slight** chance of dozing
2 = **moderate** chance of dozing
3 = **high** chance of dozing

Situation	**Chance of dozing**
Sitting and reading	_____
Watching TV	_____
Sitting inactive in a public place (e.g. a theatre or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in traffic	_____
TOTAL (max. 24)	_____
Are you experiencing difficulty with driving due to sleepiness	YES/NO Delete as appropriate

Source: Johns (1991) |**13**| (modified by Sleep Centre Royal Infirmary Edinburgh (driving question added).

sleep latency test (MSLT) |**16**| and the maintenance of wakefulness test (MWT) |**17**| as well as the Osler test |**18**|, which is a behavioural test based upon reaction time and does not involve full polysomnographic analysis. None of these tests, however, represents an undisputed gold standard analysis of excessive daytime sleepiness and they cannot be relied upon to make a diagnosis of excessive daytime sleepiness in isolation.

Snoring

Snoring is an extremely common symptom in the general population, and it has been estimated that approximately 40% of men and 30% of women habitually snore |**6,11**|. Snoring is caused by vibration of the upper airway and may originate primarily from the nasal passages or from vibration located in the upper pharyngeal area. This symptom may become so troublesome that it can result in significant disharmony in relationships and is often the symptom that precipitates referral to the sleep service. The patients themselves may not recognize that they snore but it is often extremely irritating to their partner. Snoring is a poor predictor of OSAHS as it is so common in the general population |**19**|. However, its absence makes OSAHS unlikely as more than 90% of patients with OSAHS snore |**20**|.

Witnessed apnoeic and nocturnal choking episodes

The bed partner is often extremely alarmed by these symptoms but they may not give a reliable account of apnoeic episodes |**21**|. These episodes can waken the patient with acute panic, and although they only last for a few seconds they do cause considerable distress both to the patient and to the partner. It is important to consider alternative possible causes of nocturnal breathlessness, such as paroxysmal nocturnal dyspnoea, asthma, stridor and Cheyne–Stokes respiration in patients with significant cardiac failure, when a diagnosis of apnoea is being considered.

Diagnosis of OSAHS

The diagnosis of OSAHS is based on the above classical clinical features in association with objective evidence of sleep-disordered breathing. The American Sleep Disorders Association (ASDA) has proposed guidelines on the classification of the severity of OSAHS (Table 10.3) |**15**|.

This guideline emphasizes that there is a need for both symptoms and sleep-disordered breathing to be present before a diagnosis of OSAHS can be made.

It is vital to perform a diagnostic test to support the clinical suspicion of OSAHS based on symptoms to allow an accurate diagnosis to be made. It has been shown that a diagnosis of OSAHS is wrong in up to 50% of cases when it is based entirely upon history and examination without any supportive diagnostic test |**20,22,23**|.

Up to the present time there is no good prediction model for OSAHS based upon either demographic or anthropometric data. These tests tend to have a high sensitivity but a low specificity when tested prospectively |**24**| and they have not been validated in all patient population groups. Further validation of such prediction models needs

Table 10.3 Classification of the severity of OSAHS

Sleepiness	
Mild:	unwanted sleepiness or involuntary sleep episodes which occur during activities that require little attention
Moderate:	unwanted sleepiness or involuntary sleep episodes which occur during activities that require some attention
Severe:	unwanted sleepiness or involuntary sleep episodes which occur during activities that require active attention
Sleep-related obstructive breathing events (apnoea, hypopnoea and respiratory effort-related arousals)	
Mild:	5–15 events/hour of sleep
Moderate:	15–30 events/hour of sleep
Severe:	>30 events/hour of sleep

Source: American Sleep Disorders Association (1999) |**15**|.

to take place in future before their cost-effectiveness can be elucidated in terms of making the diagnosis of OSAHS. There may, however, be a role for prediction models in accurately identifying a subset of patients who are referred to a sleep centre but who do not have OSAHS. Tsai and colleagues |**25**| studied 50 patients referred to a sleep centre with possible sleep apnoea and devised a simple algorithm based upon a cricomental space of more than 1.5 cm, a pharyngeal grade of more than II and the presence of an overbite. In patients with all three predictors there was a positive predictive value of 95% (95% confidence interval [CI] 76–100%) and a negative predictive value of 49% (95% CI 35–63%). A cricomental space of more than 1.5 cm excluded OSAHS (negative predicted value 100%, 95% CI 75–100%). This algorithm needs further validation but may be an important simple clinical test that can be performed routinely in the outpatient department.

Obesity is an important risk factor for OSAHS but 50% of patients with this syndrome are not clinically obese (body mass index <30 kg per m^2) |**26**|.

The location of the excess fat deposition, especially around the upper pharyngeal area, is more important than the distribution of fat elsewhere within the body |**26**|. Neck circumference is an important predictor of OSAHS |**23,26**|, values of below 37 cm and above 48 cm being associated with a low and high risk respectively of OSAHS. Tonsillar hypertrophy, retrognathia and micrognathia are of little predictive value |**27**|.

Diagnostic tests for sleep-disordered breathing

Full polysomnography is traditionally regarded as the gold standard diagnostic test of OSAHS but it usually requires admission to hospital overnight, with trained technical personnel present throughout the night. It is time-consuming and expensive, and it is difficult to compare data from different sleep centres as the interpretation of results can vary from centre to centre |**28**|. The apnoea/hypopnoea index, (AHI) which is the primary result extracted from polysomnographic data, is poorly correlated with excessive daytime sleepiness. It increases in normal people with age |**29**| and has not been shown to predict morbidity or mortality in OSAHS |**30,31**|. Full polysomnography measures both respiratory variables and cortical brain activity, which allows some correlation to be made between the breathing pattern and the stage or depth of sleep at which any breathing abnormality occurs. There are various diagnostic tests available, ranging from a complicated analysis of brain-wave activity during sleep to much simpler measurement of nocturnal oximetry and/or respiration to try to determine whether sleep apnoea is present.

Monitoring brain activity during sleep

Sleep quality and duration are measured by electroencephalography (EEG), electrooculography and chin electromyography and analysed in a standard fashion agreed more than 40 years ago |**32**|. Electrophysiological monitoring allows confirmation that sleep has actually occurred and gives some information about sleep quality and the change in sleep level that occurs overnight (arousals), but unfortunately a number of studies have failed to show any relationship between the arousal index over-

night with daytime symptoms |**31,33,34**|. It has also been shown that EEG analysis of sleep does not alter the diagnosis of sleep apnoea, which can be diagnosed as accurately by measuring the number of apnoeic and hypopnoeic episodes per time in bed using respiratory variables alone compared with measuring these events per hour asleep (i.e. the AHI) |**35**| by EEG analysis. Thus, the available evidence does not support the need for routine polysomnography for the diagnosis of OSAHS.

Respiration monitoring

Sleep-disordered breathing can be detected by changes in either respiratory effort or by oronasal airflow. Both of these events usually produce loud snoring in patients with moderate to severe OSAHS. The reproducibility of measures of respiratory parameters from night to night is good |**36**|, but for mild cases of OSAHS a single negative study may not exclude OSAHS and a repeat study may need to be considered |**37,38**|. Factors such as sleep position and acclimatization to a strange hospital room rather than the home environment may change sleeping quality and lead to underestimation of the severity of the OSAHS. Airflow sensors usually detect apnoeas reliably but the ability to detect hypopnoeas can be more limited |**28**|. Oronasal airflow can be measured using thermistors, which detect changes in temperature with respiration, but they are not sufficiently reliable to detect all apnoeic episodes and cannot be relied upon to make the diagnosis. However, they are relatively cheap and are consequently used in many commercially available sleep diagnostic kits. Nasal airflow detection using pressure sensors are more accurate than thermistors but may give falsely high readings if nasal obstruction is present.

Respiratory effort can be detected using strain-gauge impedance leads placed around the chest and abdomen. The information that they give allows obstructive sleep apnoeic events to be distinguished from central apnoeic events and they too can be found in many commercially available diagnostic kits.

Pulse oximetry

Transcutaneous pulse oximetry is simple and inexpensive and can be easily interpreted, but the oxygen desaturations seen in obstructive sleep apnoea may be absent in mild cases or if there is no coexisting cardiorespiratory disease present. These sensors may also be prone to artefact, they may be inaccurate in obese or anaemic patients, and they may give a falsely reassuring negative reading if the patient does not sleep overnight. Commercially available machines give large ranges (between 30 and 100%) of sensitivity and specificity, and a negative result should not be relied upon to exclude a diagnosis of OSAHS if there is a clinical suspicion of this condition |**39**|.

Conclusion

Characteristic histories and examination are important simple markers of OSAHS and they should be taken into account when a diagnostic test to confirm the clinical suspicion is undertaken. A negative diagnostic test should be repeated or a more elab-

orate test performed (moving in complexity from simple pulse oximetry to a limited sleep study [incorporating oronasal airflow, chest wall, abdominal movement, ECG and oxygen saturation] to full polysomnographic analysis) if the clinical suspicion of sleep apnoea remains. The type of diagnostic test which is chosen to confirm the clinical suspicion of OSAHS is, however, probably less important than the expertise available to interpret the test result.

There is increasing evidence linking untreated OSAHS with vascular endothelial dysfunction, which may well lead to an increased risk of cardiovascular and cerebrovascular morbidity and mortality. The next two chapters in Part VI will discuss recent developments in this field and whether OSAHS treatment improves these comorbidities.

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11

Emerging concepts linking OSAHS with vascular endothelial dysfunction

TOM MACKAY

Introduction

There is now a robust epidemiological evidence base that obstructive sleep apnoea/hypopnoea syndrome (OSAHS) is associated with hypertension and this appears to be independent of confounding variables such as central obesity, age, smoking and gender in normal |**1–3**| sleep-apnoeic |**4,5**| and hypertensive |**6**| populations.

The association of OSAHS with hypertension and cardiovascular disease is thought to be explained by increased sympathetic activity and hypoxia, which are associated with recurrent apnoeic episodes |**7**|. These factors may well induce endothelial dysfunction, leading to an abnormal vasodilatory response within the circulation |**8–10**|. Endothelial dysfunction has been found to occur in response to cardiovascular risk factors that could precede or accelerate the development of atherosclerosis |**11,12**|. Many of the previous studies undertaken in this area |**7–10**| have been small case–control studies subject to confounding biases. During the past year further supportive evidence for the hypothesis of OSAHS-induced vascular endothelial dysfunction has been published. These studies may well provide an important insight into the pathophysiological responses underlying the cardiovascular consequences of sleep apnoea and may give important clues as to the underlying aetiology of this association.

OSAHS and vascular endothelial function

Sleep apnoea and markers of vascular endothelial function: a large community sample of older adults

Nieto FJ, Herrington DM, Redline S, Benjamin EJ, Robbins JA. *J Respir Crit Care Med* 2004; **169**: 354–60.

BACKGROUND. This paper explores the concept that obstructive sleep apnoea is associated with impaired vascular tone. Brachial artery flow-mediated dilatation (FMD) was used as a surrogate marker of endothelial dysfunction.

Interpretation. The authors examined the role of endothelial dysfunction amongst older participants in the Sleep, Heart, Health/Cardiovascular Health Study cohort ($n = 1037$, age 68 years or older, 56% female). The indices of sleep apnoea which were used were derived from a twelve-channel home polysomnographic study in which the apnoea/hypopnoea index (AHI; average number of apnoeas/hypopnoeas per hour slept) and hypoxia index (percentage of time below 90% oxygen saturation) were recorded. Baseline arterial diameter and percentage of FMD were measured by ultrasound. Sleep apnoea measures were associated with baseline diameter and the percentage of flow-mediated arterial dilatation, although these associations were weakened after adjustment for other cardiovascular risk factors, particularly body mass index (BMI). However, a statistically significant linear association between the hypoxia index and baseline diameter was observed even after adjustment of BMI and other confounders ($P < 0.001$). The associations were stronger among participants who were younger than 80 years and those with hypertension.

Comment

This important study is the first to be published linking measures of sleep apnoea with indicators of vascular dysfunction (brachial artery baseline diameter and FMD) in a large community-based sample of generally healthy older subjects. The authors have shown that, apart from a partial confounding effect by BMI, the results of the study appear to be largely independent of other risk factors, particularly among younger individuals and subjects with hypertension and especially for baseline arterial diameters. This study adds to the growing body of evidence linking sleep apnoea with vascular dysfunction in older subjects and is consistent with previous descriptions suggesting that sleep apnoea and associated hypoxaemia may be associated with endothelial dysfunction |**4**|.

Endothelial function in obstructive sleep apnoea in response to treatment

Ip MSM, Tse HF, Lam B, Tsang KW, Lam WK. *J Respir Crit Care Med* 2004; **169**: 348–53

Background. Impaired endothelial-dependent vascular relaxation is a prognostic marker of atherosclerosis in cardiovascular disease. Various pathophysiological mechanisms in sleep apnoea have been proposed as factors that contribute to the pathogenesis of vascular morbidity |13,14|. Repetitive episodes of hypoxaemia, hypercapnia, sympathetic activation and intrathoracic pressure swings in OSAHS |15–17| may trigger cellular and biochemical processes which predispose to atherosclerosis |11,12,18,19|.

Interpretation. The authors evaluated endothelium-dependent FMD and endothelium-independent nitroglycerine-induced dilatation of the brachial artery with Doppler ultrasound in 28 men with obstructive sleep apnoea and 12 men without obstructive sleep apnoea. Subjects with OSAHS (AHI ± SD 46 ± 14.5) had lower FMD compared with subjects without OSAHS (5.3 ± 1.7 vs 8.3 ± 1.0%; $P < 0.001$), and major determinants of FMD were

the AHI and age. There was no significant difference in nitroglycerine-induced dilatation. Subjects with OSAHS were randomized to nasal continuous positive airway pressure (CPAP) or observation for 4 weeks. Subjects on CPAP had a significant increase in FMD, whereas those on observation alone had no change (4.4 vs –8.8%, difference of 5.2%; $P < 0.001$) (Fig. 11.1). Neither group showed significant changes in nitroglycerine-induced nasal dilatation. Eight subjects who used CPAP for more than 3 months were reassessed after withdrawing treatment for 1 week. On CPAP withdrawal, FMD became lower than during treatment ($P = 0.02$) and was similar to baseline values (Fig. 11.2). These findings demonstrated that men with moderate/severe OSAHS have endothelial dysfunction and treatment with CPAP could reverse this dysfunction. The effect was, however, dependent on ongoing CPAP usage.

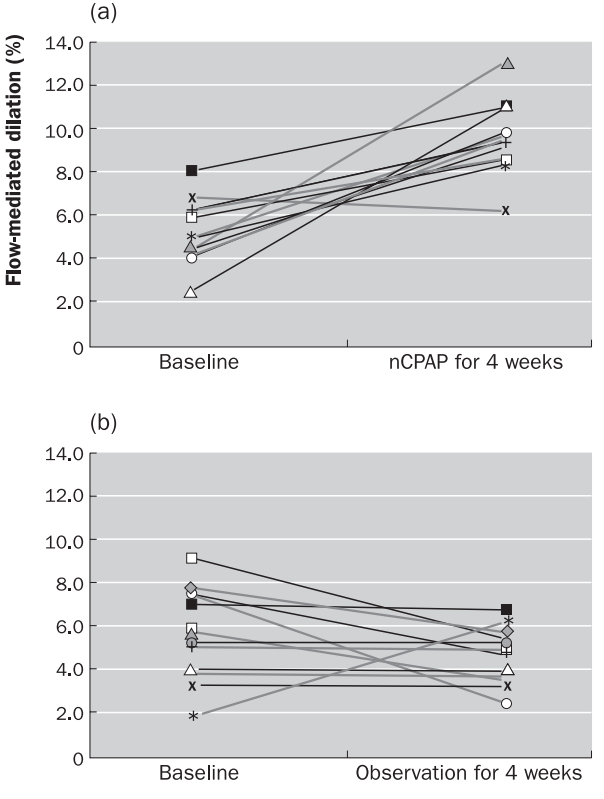

Fig. 11.1 (a) Flow-mediated dilatation (FMD) of brachial artery in 14 subjects with obstructive sleep apnoea at baseline and after 4 weeks of nasal continuous positive airway pressure (nCPAP) showing significant increase in FMD ($P = 0.001$). (b) FMD of brachial artery in 13 subjects with OSA at baseline and after 4 weeks of observation, showing no change in FMD ($P = 0.12$). Source: Ip *et al*. (2004).

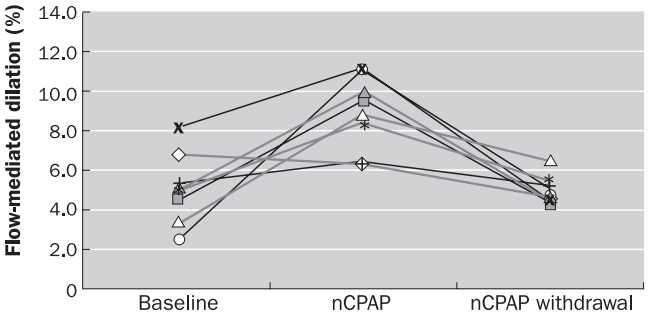

Fig. 11.2 Serial changes in FMD of brachial artery at baseline, after 4 weeks of nCPAP and 1 week after withdrawal of nCPAP in eight subjects with obstructive sleep apnoea. After withdrawal of nCPAP, FMD was lower than during treatment ($P = 0.02$). Source: Ip *et al*. (2004).

Comment

The authors have shown that otherwise healthy subjects with OSAHS have impaired endothelial-dependent FMD in the brachial artery compared with subjects without OSAHS. The endothelial dysfunction was reversible with CPAP use for 4 weeks. OSAHS is a common clinical problem and may well constitute a risk for the development of cardiovascular disease. The vascular endothelium participates in the control of various vascular functions through the regulation of vasoactive mediators in response to physical and biochemical stimuli. Endothelial injury is an important initial event in atherogenesis |**11,12**|. Endothelial dysfunction also has a predictive value for cardiovascular events in patients with coronary artery disease |**20,21**|.

Various circulating markers of endothelial dysfunction |**22**|, including soluble cell adhesion molecules, nitric oxide, fibrinogen and plasminogen activator inhibitor, have all been shown to be altered in patients with untreated OSAHS |**23–26**|.

This paper produces evidence of an independent contribution of OSAHS to the genesis of atherosclerosis. The subjects studied in this case were men with moderate to severe obstructive sleep apnoea and it may well be that the findings cannot be extended to those with mild sleep apnoea or to women, but it is an important study nonetheless.

Obstructive sleep apnoea and thoracic aortic dissection

Sampol G, Romero O, Salas A, *et al*. *Am J Respir Crit Care Med* 2003; **168**: 1528–31

Background. OSAHS is a condition that is associated with the development of arterial hypertension |3,27–29|. This hypertension is the main risk factor for aortic

dissection, and during repeated obstructive episodes, which is a hallmark of OSAHS, there is a marked increase in the transmural pressure of the aortic wall. Aortic dissection is a life-threatening medical emergency that is associated with high morbidity and mortality. It is therefore extremely important to define factors that may influence its onset and/or evolution to try to modify these risk factors at an early stage. The repeated episodes of pharyngeal obstruction which occur in untreated OSAHS lead to sympathetic activation |17|. This can in turn lead to a progressive increase in transmural pressure across the aortic wall (this is the difference between arterial pressure and intrathoracic extravascular pressure). The aim of this study was to evaluate the presence of OSAHS in a group of patients with known thoracic aortic dissection and to compare this group with a control group of hypertensive subjects who did not have OSAHS.

INTERPRETATION. Nineteen consecutive patients with thoracic aortic dissection and 19 hypertensive patients of similar age, sex and BMI were studied by the use of a clinical questionnaire and polysomnography. Snoring and unrefreshing sleep were common in both groups. Thirteen patients (68%) from each group showed an AHI of more than 5 events per hour. However, patients with aortic dissection presented with a higher AHI (mean ± SD 28 ± 30.3 vs 11.1 ± 10.4; $P = 0.032$). Seven patients with dissection presented with an AHI of >30 versus 1 patient in the control group ($P = 0.042$). Patients with thoracic aortic dissection presented a high prevalence of previously undiagnosed and frequently severe OSAHS. Further studies to confirm this possible association are required but the authors recommend that patients with aortic dissection and symptoms consistent with OSAHS should undergo a sleep study.

Comment

The results of this study show an association between thoracic aortic dissection and OSAHS. In particular, a higher AHI was found in patients with aortic dissection compared with the control group of hypertensive subjects. Thoracic aortic dissection frequently requires surgical treatment. OSAHS is known to be associated with an increased risk of perioperative morbidity and mortality |**30,31**| because of a rise in frequency and duration of upper airway obstructive episodes caused by the use of analgesia, sedatives and anaesthetic agents |**32**|. This may be particularly important in patients with aortic dissection and co-existing OSAHS undergoing surgery in whom, in addition to complications secondary to OSAHS *per se*, increases in transmural pressure during upper airway obstructive episodes may have a particularly adverse effect on the recently surgically repaired thoracic aorta.

Obstructive sleep apnoea and carotid artery intima–media thickness

Suzuki T, Nakano H, Maekawa J, *et al*. *Sleep* 2004; **27**: 129–33

BACKGROUND. Patients with OSAHS frequently have multiple risk factors for cardiovascular disease, such as obesity, insulin resistance, hypertension and hyperlipidaemia. In addition to these factors, recurrent episodes of hypoxia, negative

intrathoracic pressure swings and repeated arousals induced by upper airway obstruction during sleep – as well as repeated activation of the sympathetic nervous system – may have a deleterious effect on blood pressure and coagulation factors that may lead to an increased risk of the development of cardiovascular morbidity |33–35|. It has been shown that the levels of soluble adhesion molecules, vascular endothelial growth factor and coagulation factors are increased in untreated OSAHS compared with control subjects but are significantly decreased by the use of CPAP |24,36–39|. These studies have suggested that OSAHS may be associated with the progression of atherosclerosis, but none of these studies assessed showed the degree of atherosclerosis present. The authors have used ultrasonography to assess the carotid artery intima–media thickness (IMT) as a marker of atherosclerosis. It has been reported previously that an increase in IMT is associated with an increased risk of stroke and cardiovascular disease |40–44|. The authors hypothesize that the carotid artery IMT may well be increased in patients with OSAHS. To test this hypothesis the carotid artery IMT was measured by ultrasonography in simple snorers and in patients with OSAHS.

Interpretation. This cross-sectional study, carried out in a sleep laboratory in a general hospital in Japan, included 167 patients referred for screening or treatment of OSAHS. There was no history of chronic obstructive pulmonary disease, cerebral vascular disease or cardiovascular disease. OSAHS was diagnosed by polysomnography. Carotid artery IMT was measured by ultrasonography (Fig. 11.3) and known risk factors for atherosclerosis (obesity, hyperlipidaemia, age, hypertension, diabetes mellitus and insulin resistance) were investigated. Multiple regression analysis was performed to assess the association between IMT and the severity of OSAHS after adjustment for confounding variables. This analysis revealed that the AHI, the duration of oxygen saturation below 90%, and the mean nadir oxygen saturation were significantly associated with the IMT after adjustment for confounding factors that could promote atherosclerosis. In addition, OSAHS-related hypoxaemia was associated with the IMT independently of the AHI. The authors concluded that the severity of OSAHS was independently related to atherosclerosis and that the severity of OSAHS-related hypoxaemia is more important than the frequency of obstructive events.

Comment

This study demonstrates that carotid artery IMT, which is an index of systemic atherosclerosis, was significantly correlated with the severity of OSAHS. This suggests that OSAHS-related hypoxaemia is an independent contributor to the severity of carotid artery atherosclerosis. There is also a relationship between OSAHS and hypertension and this has now been established by cross-sectional population-based studies and prospective studies |**2,3,5**|. Hypertension by itself is a strong promoter of atherosclerosis and the current study shows that systolic blood pressure is correlated with the IMT. However, there was a relationship between OSAHS and the carotid artery IMT even after adjustment of blood pressure, raising the possibility that OSAHS can promote atherosclerosis through mechanisms independent of an increase in blood pressure. These mechanisms may be via vascular endothelial growth factors, as these factors may be stimulated by hypoxia |**45–47**|.

The authors describe in detail the limitations of the study and point out that patients with OSAHS have more risk factors for atherosclerosis than asymptomatic

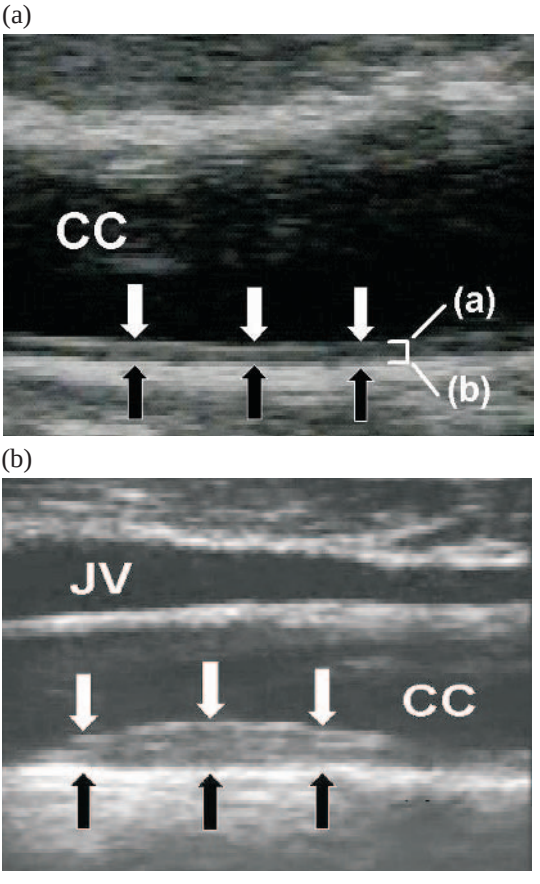

Fig. 11.3 Measurement of the carotid artery intima–media thickness (IMT). Image (a) is from a 48-year-old simple snorer who had IMT of 0.7 mm. Image (b) is from a 59-year-old patient with severe obstructive sleep apnoea, hypertension and diabetes mellitus, who had plaque in the common carotid artery. *White arrows* and (a) indicate the lumen–intima interface, while the *black arrows* and (b) indicate the media–adventitia transition. The IMT was measured as the distance from (a) to (b). JV, jugular vein; CC, common carotid. Source: Suzuki *et al*. (2004).

subjects. Thus, the population sample may be inherently biased. The study was also cross-sectional and thus could not assess any causal relationship between IMT and OSAHS. A prospective study involving clinical intervention with CPAP will be needed to clarify this point.

Nonetheless, this study demonstrates an independent association between hypoxaemia related to OSAHS and the severity of atherosclerosis, suggesting that OSAHS is independently related to the genesis of atherosclerosis and that the severity of OSAHS-related hypoxaemia is more important than is the frequency of obstructive events.

Sleep disordered breathing and cognitive impairment in elderly Japanese-American men

Foley DJ, Massaka K, White L, Larkin EK, Monjan A, Redline S. *Sleep* 2003; **26**: 596–9

BACKGROUND. Epidemiological studies, primarily carried out in middle-aged adults, have shown associations between sleep-disordered breathing and deficits in neuropsychological function, particularly in attention and concentration spans |48,49|. Repeated episodes of oxygen desaturations and poor sleep efficiency in OSAHS may both contribute to causing cognitive impairment and possibly encephalopathy |50,51|. In the Wisconsin Cohort study of 841 men and women aged between 30 and 60 years, an elevated AHI was associated with deficits in psychomotor efficiency and the authors estimated that an AHI of 15 was equivalent to a decrement in psychomotor efficiency associated with 5 additional years of age |48|. In a matched case–control study of extensive neuropsychological testing among 32 adults with mild OSAHS (AHI between 10 and 30) compared with 20 controls, cases performed worse on a visual vigilance test than a test of working memory but did not differ on other memory-related and executive function tasks. This suggests only a very modest decline in neuropsychological function amongst those with mild OSAHS |49|. The prevalences of both OSAHS and mild cognitive impairment increase with age |52,53|, but there have been very few epidemiological studies to assess the relationship between these disorders in large community-based populations. This study describes results from participants of the Honolulu Heart Programme (HHP). This programme began in 1965 as an epidemiological cohort study of cardiovascular disease among 8006 middle-aged Japanese–American men |54|.

INTERPRETATION. This paper reports a cross-sectional study undertaken in Oahu, Hawaii, involving 718 men aged between 79 and 97 years of age who were examined in 1999 and then in 2000. The AHI from in-home overnight polysomnography was correlated with performance in cognitive tests, BMI, neck circumference, Epworth Sleepiness Scale, snoring, depression scales and the presence or absence of physical disability, history of heart disease, stroke, hypertension, diabetes and dementia. Almost 30% of the men had no evidence of any degree of sleep-disordered breathing (AHI <5 per hour) and nearly one-fifth (19%) had severe OSAHS (AHI >30 events per hour). Severe OSAHS was associated with a higher BMI, habitual snoring and daytime sleepiness. No association was found between sleep-disordered breathing and cognitive functioning, including measures of memory function, concentration and attention.

The authors conclude that sleep-disordered breathing was associated with more drowsiness but not with poor performance on standardized cognitive testing used to screen for Alzheimer's disease and other dementias commonly found in older people. They do point out, however, that a healthy participant may have biased the results towards a negative finding, and more extensive cognitive function testing may have revealed a more subtle deficit in cognitive function secondary to disordered breathing.

Comment

Although OSAHS was common among this group of elderly Japanese–American men (19%), this may be related to their advanced age (80 years and over) and to their ethnicity as both factors have been linked to an increased risk of OSAHS |**53,55**|. The lack of an association between OSAHS and performance on a brief screening instrument for cognitive impairment in this study suggests that screening for dementia in healthy older adults will not reveal cognitive defects secondary to sleep-disordered breathing.

Plasma cytokine levels in patients with obstructive sleep apnoea syndrome: a preliminary study

Alberti A, Sarchielli P, Gallinella E, *et al*. *J Sleep Res* 2003; **12**: 305–11

BACKGROUND. The levels of pro- and anti-inflammatory cytokines (interleukin [IL]-1β, tumour necrosis factor α (TNF-α), IL-6, IL-10 and transforming growth factor β (TGF-β) may be different in patients with untreated OSAHS compared with control subjects. Whether these changes play a positive role in the inflammatory mechanisms underlying the genesis of atherosclerosis in such patients or are merely a consequence of underlying pathogenic mechanisms themselves remains unclear. It has been shown that patients with OSAHS have increased levels of TNF-α and IL-6 compared with control subjects |56|. Their levels appear to be significantly correlated with the AHI as well as with the percentage of time spent at an oxygen saturation below 90% during sleep. It has also been found that TNF-α and IL-6 levels are increased in conditions such as narcolepsy and idiopathic hypersomnolence, two conditions in which excessive daytime sleepiness is also prevalent |57,58|.

Short-term variations in cytokine levels in OSAHS patients have never been investigated previously. The present study looked at the plasma levels of the proinflammatory cytokines IL-1, TNF-α and IL-6 and of the anti-inflammatory cytokines IL-10 and TGF-β in patients with a diagnosis of obstructive sleep apnoea immediately on going to bed and after the first documented obstructive apnoeic episode overnight producing an oxygen saturation of less than 85%.

INTERPRETATION. The levels of proinflammatory cytokines (IL-1, TNF-α, IL-6) and anti-inflammatory cytokines (IL-10, TGF-β were measured by enzyme-linked immunosorbent assay) in the plasma of patients with OSAHS at 22.00 h before full polysomnographic recording and immediately after the first measured obstructive apnoea causing an oxygen saturation of less than 85%. Significantly higher levels of TNF-α were found in OSAHS patients assessed before polysomnography compared with the control group ($P < 0.01$) (Table 11.1 and Fig. 11.4). A significant increase in the plasma level of IL-6 was also present ($P < 0.05$). Conversely, a significant decrease in the plasma level of IL-10 was evident at baseline in OSAHS patients ($P < 0.04$). No significant difference was present between the mean values of IL-1, TNF-α and TGF-β between OSAHS patients and controls. Eighteen patients with OSAHS were studied who had a mean AHI of 18.2 ± (15.1 mean ± SD). Twenty control subjects matched for age, sex and BMI, were studied; their mean AHI was <5.

Table 11.1 Cytokine plasma levels (mean ± 2 SD) of patients with obstructive sleep apnoea syndrome at the beginning of polysomnographic recording and after the first obstructive apnoea causing an oxygen saturation below 85%, and of control subjects

	OSAS patients				Control subjects	
Cytokine levels (pg/m^{-l})	**Before obstructive apnoea (22.00 h)**	***P*-value**	**After obstructive apnoea**	***P*-value**	**22.00 h**	**Between midnight and 02.00 h**
IL-1β	2.5 ± 0.6		2.7 ± 0.8	*P* <0.05‡	2.5 ± 0.9	2.3 ± 0.8
TNF-α	9.7 ± 8.5	*P* <0.005* *P* <0.001†	26.9 ± 6.9	*P* <0.002‡	6.3 ± 3.0	6.5 ± 3.1
IL-6	6.4 ± 3.7	*P* <0.05*	6.9 ± 3.3	*P* <0.04‡	4.9 ± 2.9	4.9 ± 2.8
IL-10	3.9 ± 2.6	*P* <0.04*	3.5 ± 2.7	*P* <0.02‡	5.2 ± 1.7	5.4 ± 1.8
TGF-β	3.9 ± 1.8		3.5 ± 1.9		3.5 ± 1.9	3.9 ± 1.7

OSAS, obstructive sleep apnoea syndrome; TNF, tumour necrosis factor; TGF, transforming growth factor; IL, interleukin.
* OSAS patients at baseline versus control subjects.
† OSAS patients at baseline versus OSAS patients after obstructive apnoea.
‡ OSAS patients after obstructive apnoea versus controls assessed between midnight and 02.00 h.
Source: Alberti *et al*. (2003).

Comment

This study shows an increase in the plasma levels of the proinflammatory cytokines TNF-α and IL-6 in a small group of patients with moderately severe OSAHS and a significant decrease in the peripheral plasma level of the anti-inflammatory cytokine IL-10 in patients with OSAHS compared with a control group. Following an obstructive apnoeic episode, the patients with OSAHS showed a further increase in levels of TNF-α. These findings support the hypothesis of activation of the inflammatory response in OSAHS patients, but this response does not appear to be associated with the severity or the duration of the sleep apnoea or with the sleep efficiency or Epworth Sleepiness Scale score of these patients. The authors hypothesize that recurrent hypoxic episodes in patients with OSAHS could lead to the production of proinflammatory cytokines by mononuclear cells, and these may in turn be responsible for the observed increased risk in atherosclerosis and subsequent cardiovascular and cerebrovascular morbidity in these patients. This observation, however, requires further studies to investigate this hypothesis in more detail.

Antioxidant capacity in sleep apnea patients

Christou K, Moulas AN, Pastaka C, Gourgoulianis KI. *Sleep Med* 2003; **4**: 225–8

Background. OSAHS is a condition characterized by repetitive obstruction of the upper airway, resulting in oxygen desaturations and arousal from sleep |59|. OSAHS

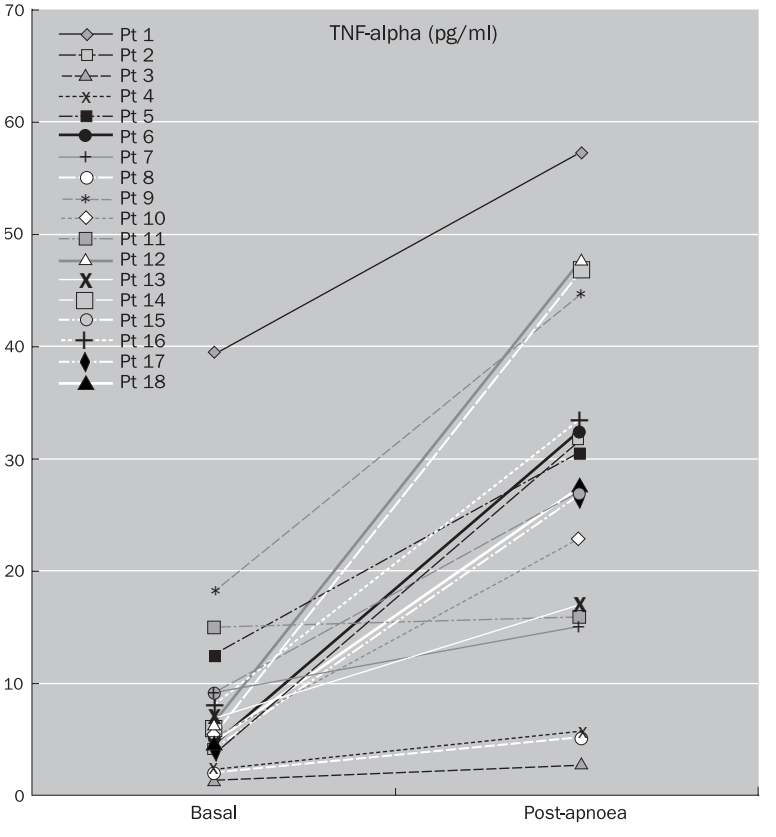

Fig. 11.4 Changes in TNF-α levels (pg/ml) for each obstructive sleep apnoea syndrome patient from the beginning of polysomnography until after the first obstructive sleep apnoea with oxygen saturation <85%. Source: Alberti *et al*. (2003).

is linked to oxidative stress in the respiratory system because of a phenomenon known as hypoxia–reoxygenation: cyclical alterations of arterial oxygen saturation are observed, with oxygen desaturations developing in response to apnoeas followed by resumption of oxygen saturation during hyperventilation |14|. Repeated apnoeas and hypopnoeas are followed by reoxygenation in patients with sleep apnoea and this repeated cycle leads to the production of reactive oxygen species (free radicals). During hypoxia there may also be depletion of cellular reductants, which constitute a main line of antioxidant defence within the body. The combination of the reduction in these cellular reductants and the production of highly reactive oxygen radicals may lead to the development of cardiovascular disease |60,61| through endothelial damage. The authors of this paper evaluated the antioxidant capacity in serum drawn from patients with OSAHS and from healthy controls to confirm the hypothesis that there is a relationship between oxidative stress and OSAHS.

INTERPRETATION. Twenty-five subjects were studied: 17 had OSAHS (mean ± SEM AHI 44.1 ± 23.1) and eight were healthy controls matched for age, sex and BMI. Full polysomnographic studies were performed to confirm the diagnosis of sleep apnoea in these patients. Peripheral venous blood samples were drawn at 8 a.m. after the polysomnographic study. The serum was stored to allow measurement of antioxidant capacity by Trolox equivalent antioxidant capacity (TEAC). This assay is based on the inhibition of antioxidants by radical cation absorbance. The degree of inhibition is proportional to the concentration of antioxidants in the subjects' samples.

Comment

Seventeen out of the 25 subjects had an AHI of greater than 10. The measurement of antioxidant capacity did not differ between the OSAHS patients and the healthy control samples. Furthermore, patients with severe OSAHS (AHI >20, $n = 14$) had a linearly negative correlation between antioxidant capacity in the blood samples and AHI ($r = –0.551$; $P = 0.041$) (Fig. 11.5). The authors conclude that a reduced antioxidant capacity in serum is an index of excessive oxidative stress. Patients with severe OSAHS have reduced values of antioxidant capacity. An imbalance between oxidative stress and antioxidant status may play an important role in the pathophysiological relationship in OSAHS patients between hypoxia and the development of cardiovascular disease.

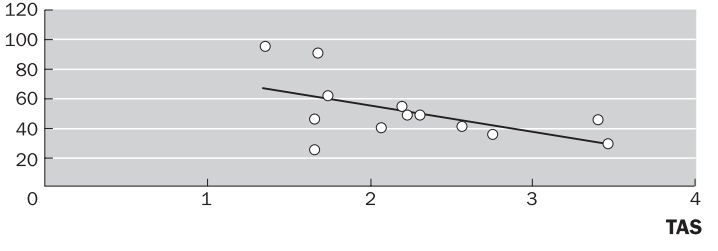

Fig. 11.5 Negative relationship between severe obstructive sleep apnoea and antioxidant capacity. Source: Christou *et al*. (2003).

Phenotypic and functional characterisation of blood γδ T cells in sleep apnoea

Dyugovskaya L, Lavie P, Lavie L. *Am J Respir Crit Care Med* 2003; **168**: 242–9

BACKGROUND. A recent study from Dyugovskaya and colleagues |23| has shown a hypoxia-related increase in monocyte activation in patients with OSAHS. This was manifested as increased expression of adhesion molecules and increased production of reactive oxygen species by OSAHS monocytes. Furthermore, adhesion of OSAHS monocytes to endothelial cells in culture was significantly enhanced. All these

features implicate altered monocyte function in the pathogenesis of OSAHS |23|. The authors postulate that recurrent episodes of hypoxia and possibly hypercapnia experienced nightly by patients with sleep apnoea may induce activation of other circulating inflammatory cells, such as lymphocytes. It is known that cytokine-activated T lymphocytes mediate endothelial activation and release proinflammatory cytokines, such as IL-6, IL-8 and monocyte chemotactic protein-1. This can lead to endothelial cell damage via leucocyte infiltration |62|. There are two main distinct lineages of T cells: those expressing αβ T-cell receptors and those expressing γδ. Fewer than 5% of circulating lymphocytes consist of γδ T cells but their unique migration, cytotoxic features and accumulation in atherosclerotic plaques implicates them in the genesis of cardiovascular disorders. To assess the potential involvement of circulatory γδ T lymphocytes in endothelial cell damage in obstructive sleep apnoea, the authors characterized the phenotype, cytokine profile, adhesion properties and cytotoxicity of γδ T cells in 34 patients with OSAHS and 19 control subjects.

Interpretation. Expression of the inhibitory natural killer B1 receptors was greater in patients than in control subjects. The intracellular content of the proinflammatory cytokines TNF-α and IL-8 was greater in the patients with sleep apnoea than in the control subjects and that of the anti-inflammatory cytokine IL-10 was less. The γδ T cells of patients adhered more avidly to non-activated endothelial cells in culture than did those of control subjects. Expression of L-selectin in γδ T cells was higher in sleep-apnoeic subjects. The adhesion index of γδ T lymphocytes/endothelial cells was decreased by antibodies directed against E/P-selectin and TNF-α in the patients but not in the control subjects. The cytotoxicity of γδ T lymphocytes against endothelial cells was greater in the patients than in the control subjects and could be prevented by pretreatment with antibody against TNF-α. This cytotoxicity was 2.5-fold higher in the sleep-apnoeic subjects.

Collectively, these data implicate γδ T-lymphocyte function in the genesis of atherogenic sequelae in patients with untreated sleep apnoea. This effect may be produced by an increased number of inhibitory natural killer B1 receptors, increased proinflammatory cytokines and decreased anti-inflammatory cytokines, which collectively predispose to endothelial injury and adverse cardiovascular function.

Comment

This paper assesses the potential involvement of circulating γδ T lymphocytes in endothelial cell damage in patients with untreated sleep apnoea. The γδ T-cell phenotype, cytokine profile and interaction with endothelial cells in culture were studied. Important results were demonstrated which implicate the involvement of γδ T cells in the initiation and accentuation of endothelial cell damage in obstructive sleep apnoea, and this may help to explain the increased prevalence of this condition in patients with untreated sleep apnoea.

Conclusion

OSAHS has been repeatedly shown to be associated with increased cardiovascular and cerebrovascular morbidity and mortality |**63**|. Repetitive episodes of hypoxia–

reoxygenation, an increased surge in arterial blood pressure, increased sympathetic nerve activity, swings in intrathoracic pressure, oxidative stress and hypercapnia characteristic of OSAHS have all been implicated in the pathogenesis of cardiovascular morbidity and mortality in this syndrome |**19,64**|. Atherosclerosis is a progressive disease arising from the subclinical condition of endothelial dysfunction |**65**|. Under normal physiological conditions, the endothelium regulates vascular tone and interactions between the vessel wall and circulating substances in blood cells. It thus maintains homeostasis by keeping the balance between vasoconstrictors and vasodilators in check. If this balance is disrupted the endothelium is activated and can acquire a proatherogenic and proinflammatory phenotype |**66**|. This is characterized by overexpression of adhesion in the molecules that mediate leucocyte adhesion to endothelial cells, triggering a cascade of inflammatory responses leading to worsening endothelial dysfunction in a vicious spiral.

There is increasing evidence that impaired endothelial-dependent vasodilatation is present in men with OSAHS who are free of any overt cardiovascular morbidity |**7**|. It is important to develop non-invasive, easily performed, accurate methods to allow evaluation of endothelial function |**67**| and also to test whether the response to CPAP treatment is capable of reversing endothelial dysfunction in patients with previously untreated OSAHS in an attempt to ameliorate future cardiovascular events.

The above papers give an interesting insight into the association between sleep apnoea and endothelial dysfunction and should encourage future studies to look at the role of antioxidants, antihypertensive agents and targeted treatments, such as CPAP therapy, in patients with untreated sleep apnoea to see if endothelial dysfunction could be improved or indeed reversed.

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12

Does sleep apnoea therapy improve sleep apnoea comorbidities?

TOM MACKAY

Introduction

The association between the obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and cardiovascular morbidity was first described more than 30 years ago. Coccagna |**1**| described the disappearance of atrial flutter in a patient with sleep apnoea treated with a tracheostomy. Guilleminault |**2**| reported that blood pressure in two hypertensive children with severe sleep apnoea normalized within 24 h after a tracheostomy. In more recent years cross-sectional and case–control studies have revealed a high rate of OSAHS in unselected cardiovascular patients |**3**|, although it is well known that such studies are open to misinterpretation because of a variety of confounding variables, such as male gender, obesity and middle age. However, over the last 5 years larger, well-controlled studies have been published that provide supporting evidence of an independent association between OSAHS and cardiovascular morbidity |**4–6**|. These studies have taken place both in sleep centre cohorts and in general population cohorts, and have shown that treatment of OSAHS with continuous positive airway pressure (CPAP) can reduce daytime and night-time blood pressure |**5**|.

Several mechanisms have been postulated to account for the effect of sleep apnoea on the cardiovascular system, including sympathetic activation |**7**|, swings in intrathoracic pressure |**8**| and, more recently, oxidative stress |**9**| and consequently vascular inflammation resulting from nocturnal hypoxia–reoxygenation cycles. Increased production of reactive oxygen species has been described in granulocytes and monocytes obtained from patients with OSAHS |**10,11**|. This in turn has been associated with increased expression of adhesion molecules and proinflammatory cytokines, which in turn can lead to endothelial dysfunction and subsequent atherosclerosis.

There is increasing evidence that OSAHS contributes to the development of both congestive cardiac failure and systemic hypertension as well as contributing to a poorer outcome following a stroke. Treatment of OSAHS with CPAP causes a reduction in blood pressure |**12,13**|. There is also increasing evidence that untreated OSAHS is associated with left ventricular diastolic and systolic dysfunction and that treatment

with CPAP improves left ventricular systolic function. Thus, it is important to consider the possibility of underlying OSAHS when assessing patients with congestive cardiac failure or systemic hypertension. The importance of making a diagnosis of underlying OSAHS was highlighted in a recent study by Otake *et al.* |**14**|, which showed 25–50% greater healthcare usage (physician visits and hospitalization mainly for systemic hypertension and cardiovascular disease) in the 5 years before OSAHS diagnosis, compared with control subjects. This patient group also had 3.3 times more prescriptions for a variety of cardiovascular medications over a 12-month period than an aged-matched control group.

The management of congestive cardiac failure has been transformed over recent decades, with the introduction of a variety of new medications, including angiotensin-converting enzyme inhibitors, the cautious use of β-blockers, vasodilators, pacing, and the introduction of artificial mechanical hearts and cardiac transplantation.

Despite all these measures, the mortality of congestive cardiac failure remains approximately 50% at 5 years, with only a very small improvement in survival seen over the past 50 years (Fig. 12.1).

As OSAHS, cardiovascular and cerebrovascular disease are extremely prevalent in Western society any treatment options which can be employed to improve morbidity and mortality from these conditions merits further investigation.

Recent published works linking these conditions will be discussed in this chapter.

OSAHS and cardiovascular disease

Sleep disorders in patients with congestive cardiac failure

Naughton MT. *Curr Opin Pulm Med* 2003; **9**: 453–8

BACKGROUND. OSAHS subjects the failing heart to adverse haemodynamic and adrenergic loads that may well contribute to the progression of the underlying cardiac failure. Large epidemiological studies published recently involved 450 and 81 patients with chronic heart failure |15,16| and found prevalence rates of obstructive sleep apnoea of 37 and 11% respectively in this population. Normally sleeping is accompanied by reductions in central and sympathetic outflow, heart rate, blood pressure and cardiac output |17|. However, recurrent obstructive apnoeic episodes disrupt sleep architecture and subjects the heart to recurring episodes of hypoxia, exaggerated negative intrathoracic swings and bursts of sympathetic activity, provoking surges in blood pressure and heart rate |18,19|. This recurrent nocturnal stress can be improved by CPAP therapy |20,21|.

INTERPRETATION. This excellent review summarizes the association between OSAHS and systemic hypertension and cardiac failure. It highlights the publication of the first randomized controlled trial of CPAP therapy in 24 subjects with OSAHS with coexisting ischaemic or idiopathic congestive cardiac failure by Kaneko *et al*. (reviewed below) (Fig. 12.2). This study

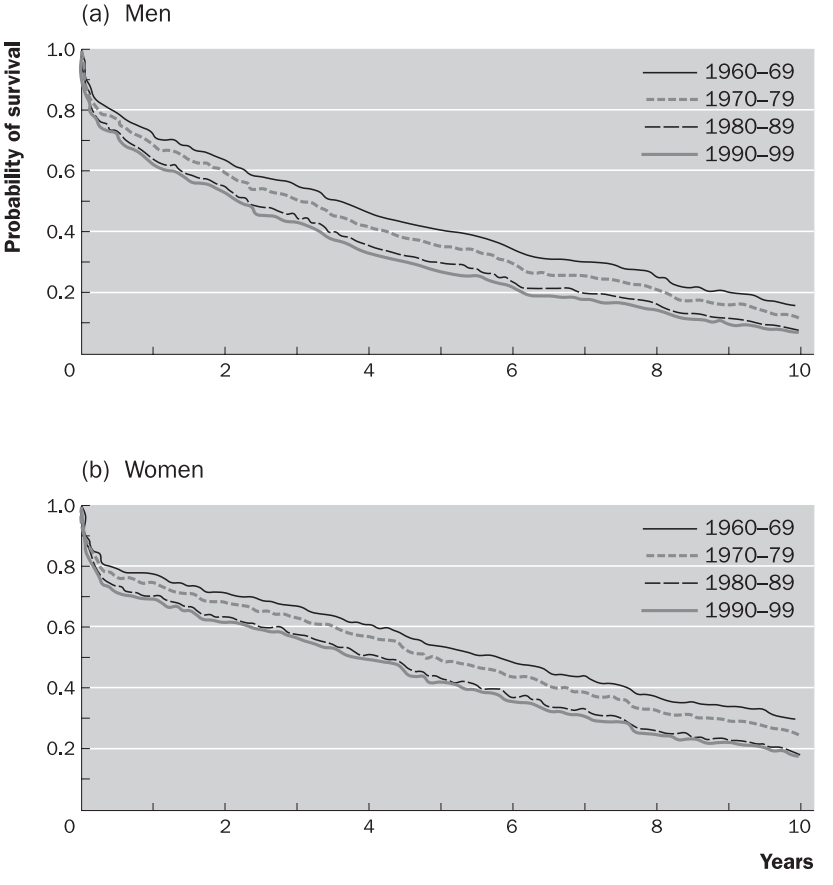

Fig. 12.1 Survival curves for congestive heart failure patients in males and females from 1950 to 1999. Source: Naughton (2003).

showed that the CPAP-treated group had a significant improvement in left ventricular ejection fraction (LVEF) (25–34%) associated with a fall in systolic blood pressure (126–116 mmHg) and a reduction in left ventricular chamber size over a 1-month period compared with untreated control subjects.

The review also discusses the role of central sleep apnoea in patients with cardiac failure as up to 30% of patients with congestive cardiac failure may exhibit non-hypercapnic central sleep apnoea with Cheyne–Stokes respiration. These patients have alternating episodes of central apnoeas followed by crescendo then decrescendo ventilation with repeated arousals, leading to hyperventilation and hypocapnia. Typically there are elevated pulmonary capillary wedge pressures, low left ventricular ejection fractions and elevated overnight urinary and awake plasma norepinephrine levels |**22**|. There is increasing evidence that autonomic

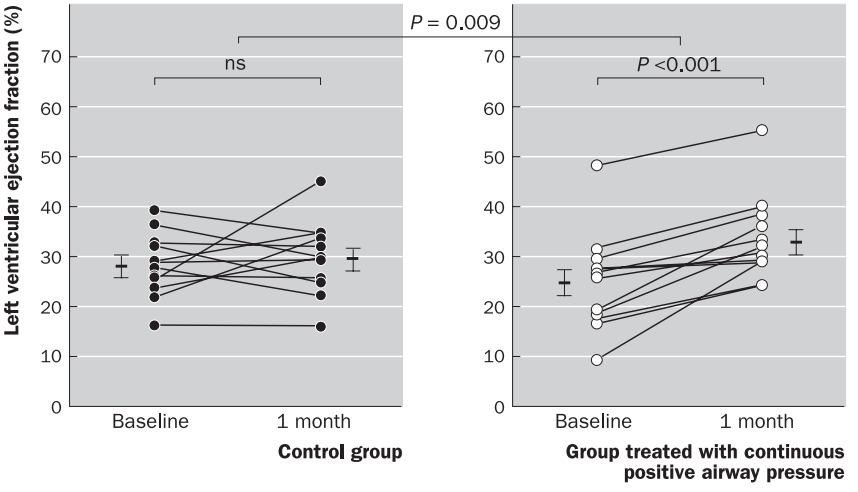

Fig. 12.2 Individual values for the left ventricular ejection fraction (LVEF) in all patients. In the control group there was no significant change in the LVEF from baseline to 1 month (from a mean [± SE] of 28.5 ± 1.8 to 30.0 ± 2.1%). In contrast, the LVEF increased in all 12 subjects treated with continuous positive airway pressure (CPAP), and the mean increase was significant (from 25.0 ± 2.8 to 33.8 ± 2.4%; $P < 0.001$). The change in the LVEF from baseline to 1 month was significantly greater in the group treated with CPAP than in the control group (8.8 ± 1.6 vs 1.5 ± 2.3%; $P = 0.009$). The one patient in the group that received CPAP who had a baseline LVEF of 48% met the pre-trial screening eligibility criterion (the left ventricular ejection was 39%). ns, not significant. *Short horizontal lines* and *I bars* are means ± SE. Source: Kaneko *et al*. (2003).

control is deranged in patients with central sleep apnoea |**23**|, with sympathetic activity up to four times greater than in age-matched controls |**24**| and a diminished vagal tone. We still do not know what mechanisms are responsible for the development of increased ventilatory responses, hyperventilation and hypocapnia in congestive cardiac failure that are sufficient to cause central sleep apnoea, and further work is needed in this important area.

Data from prospective controlled trials are currently lacking for medical therapy in patients suffering from a combination of congestive cardiac failure and central sleep apnoea, but data are becoming available regarding CPAP therapy in this patient population. Kohlein *et al*. |**24**| undertook a randomized control trial of 2 weeks' CPAP (8.5 cm of water) or bilevel treatment Inspiratory Positive Airway Pressure (IPAP) 8.5 cm of water, Expiratory Positive Airway Pressure (EPAP) 3 cm of water, with a backup respiratory rate of 15 breaths per minute) in 16 patients suffering from congestive cardiac failure and central sleep apnoea (mean age 62 years, body mass index 27.3, LVEF 23.6% and apnoea/hypopnoea index [AHI] 27 events per hour). A number of improvements were achieved with both CPAP and bilevel pressure treatments, evident as reductions in the percentage of sleep time spent in central sleep apnoea (from 37 to 14%), AHI (from 27 to 7 events per hour) and circulation time (from 36 to 30 s), but there was no untreated control group and there was a lack of objective data on cardiac function. The group postulated that CPAP and bilevel treatment works in this

patient population by reducing transmural pressure gradients, reducing cardiac work and sympathetic activity. This leads to a reduction in left ventricular dimension and an improvement in inspiratory muscle strength, and hence to a reduction in the overall work of breathing.

Comment

This review highlights an emerging area in respiratory medicine linking two common conditions, namely congestive cardiac failure and OSAHS. It highlights the evidence that OSAHS contributes to systemic hypertension and left ventricular diastolic and systolic dysfunction and documents the evidence that these factors can be improved by treating the underlying OSAHS effectively.

Controlled trial of continuous positive airway pressure in obstructive sleep apnoea and heart failure

Mansfield DR, Gollogly NC, Kaye DM, Richardson M, Bergin P, Naughton MT. *Am J Respir Crit Care Med* 2004; **169**: 361–6

BACKGROUND. OSAHS is a highly prevalent condition among patients with congestive cardiac failure and may contribute to progression of cardiac dysfunction via hypoxia, elevated sympathetic nervous system activity and systemic hypertension. The prevalence of OSAHS in a population with congestive heart failure (CHF) has been shown to have been as high as 40% |15,16,25|. Recurrent hypoxia, hypercapnia |26| and baroreflex inhibition resulting from repetitive surges in nocturnal blood pressure |27| may contribute to elevated sympathetic nerve activity, which in turn is known to be cardiotoxic in CHF |28|. Hypoxia may also independently lead to oxidative vascular wall injury |29,30|. Until recently, little was known of the clinical response to OSAHS treatment in patients with CHF. Small case studies and uncontrolled trials suggest that treatment of OSAHS with CPAP in patients with idiopathic cardiomyopathy leads to significant improvements in heart function |31–33|. A recently published randomized controlled trial by Kaneko *et al*. (reviewed below) demonstrated a significant improvement in cardiac function associated with a fall in systemic blood pressure after 1 month of CPAP treatment in patients with idiopathic and ischaemic cardiomyopathy. The aim of this study was to measure the medium-term effect of treating OSAHS with CPAP on left ventricular systolic function, sympathetic nervous activity and systemic blood pressure, as well as functional outcomes including quality of life and exercise performance.

INTERPRETATION. Fifty-five patients with CHF and OSAHS were randomized to 3 months of CPAP treatment or to a control group. End-points of the study were changes in LVEF, overnight urinary norepinephrine excretion, blood pressure and quality of life data. Nineteen patients in the CPAP group and 21 control subjects completed this study. Compared with the control group, CPAP treatment was associated with a significant improvement in LVEF (mean ± SE; Δ1.5 ± 1.4 and 5.0 ± 1.0%, respectively; $P = 0.04$) (Fig. 12.3), reductions in overnight urinary norepinephrine excretion (Δ1.6 ± 3.7 and –9.9 ± 3.6 nmol/mmol

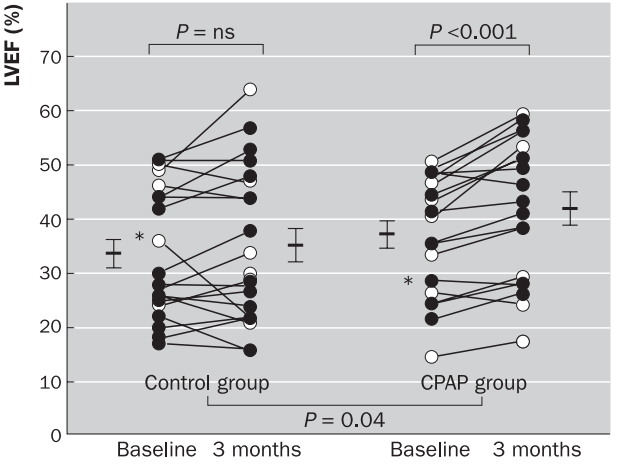

Fig. 12.3 Display of LVEF baseline and follow-up in control and CPAP-treated groups. *Open circles* represent idiopathic and *closed circles* the ischaemic cardiomyopathies. There was a significant improvement in LVEF in the CPAP group compared with the control group. Patients marked with an *asterisk* were in sinus rhythm at study commencement and found to be in atrial fibrillation at the end of the study.
Source: Mansfield *et al*. (2004).

creatinine; $P = 3.036$), and improvements in quality of life. There were no significant changes in systemic blood pressure. The authors suggest that treatment of OSAHS in patients with CHF leads to improvements in cardiac function, sympathetic activity and quality of life.

Comment

This study demonstrates a significant improvement in cardiac function and attenuation of sympathetic nerve activity associated with reduced hypoxaemia following 3 months of nasal CPAP treatment in a group of patients with OSAHS and coexisting CHF using a randomized control trial design. These physiological improvements were associated with significant improvements in general indices and disease-specific symptoms of quality of life. The magnitude of the change in LVEF in this study is similar to |**34,35**| or greater than |**36**| in other large CHF pharmacological intervention trials that have shown important mortality improvements. Given that the patients recruited into this trial were already on optimal medical treatment, the findings indicate an advance in the treatment of patients with CHF.

Oral appliance therapy reduces blood pressure in obstructive sleep apnea: a randomized control trial

Gotsopoulos H, Kelly JJ, Cistulli PA. *Sleep* 2004; **27**: 934–41

BACKGROUND. The recurrent apnoeic episodes characteristic of OSAHS and consequent transient elevations in nocturnal blood pressure have been implicated in the development of sustained systemic hypertension |8,9,36–38|. A number of recent randomized control trials evaluating the effect of CPAP treatment for OSAHS and its subsequent effect on diurnal blood pressure have demonstrated a significant improvement |12,13,39|. Oral appliances are an alternative form of treatment for mild cases of OSAHS |40–42| and they work typically by holding the mandible forward during sleep, thus improving the degree of pharyngeal collapse. In view of the demonstrated beneficial effect of CPAP on blood pressure in OSAHS, it is important to determine whether oral appliances are similarly associated with beneficial responses in blood pressure. This study was designed to test this hypothesis.

INTERPRETATION. This is a randomized, controlled, crossover trial performed in sleep clinics at a university teaching hospital site. The authors studied 61 patients diagnosed with obstructive sleep apnoea on polysomnography (AHI ≥10 events per hour), complaining of at least two of the classical symptoms of OSAHS (excessive daytime sleepiness, snoring, witnessed apnoeic episodes, fragmented sleep, age more than 20 years) and minimum mandibular protrusion of 3 mm. A mandibular advancement splint (MAS) and a control oral appliance were used for 4 weeks. Polysomnography and 24-h ambulatory blood pressure monitoring were carried out at baseline and after each 4-week interventional period. Compared with the control group, patients using the MAS showed a 50% reduction in mean AHI and a significant improvement in both minimum oxygen saturation and arousal index. With the MAS there was a significant reduction in mean (± SEM) 24-h diastolic blood pressure (1.8 ± 0.5 mmHg) compared with the control group ($P = 0.001$), but not in 24-h systolic blood pressure (Fig. 12.4). Awake blood pressure variables were reduced with the MAS by an estimated mean (± SEM) of 3.3 ± 1.1 mmHg for systolic blood pressure ($P = 0.003$) and 3.4 ± 0.9 mmHg for diastolic blood pressure ($P < 0.001$). There was no significant difference in blood pressure measured during sleep. Oral appliance therapy for obstructive sleep apnoea over a 4-week period resulted in a reduction in blood pressure similar to that reported with CPAP therapy.

Comment

This paper adds significantly to the randomized control study previously carried out by the same group showing improved sleep quality and breathing during sleep with oral devices |**43**|. Two unexpected results in this study were, however, the failure to show any drop in blood pressure during sleep (a consistent finding in previous CPAP studies) and the lack of a relationship between oxygenation and blood pressure change across the patients. Both may reflect sample size but they are intriguing. Direct comparative studies with CPAP in some patients with similar degrees of OSAHS severity are needed.

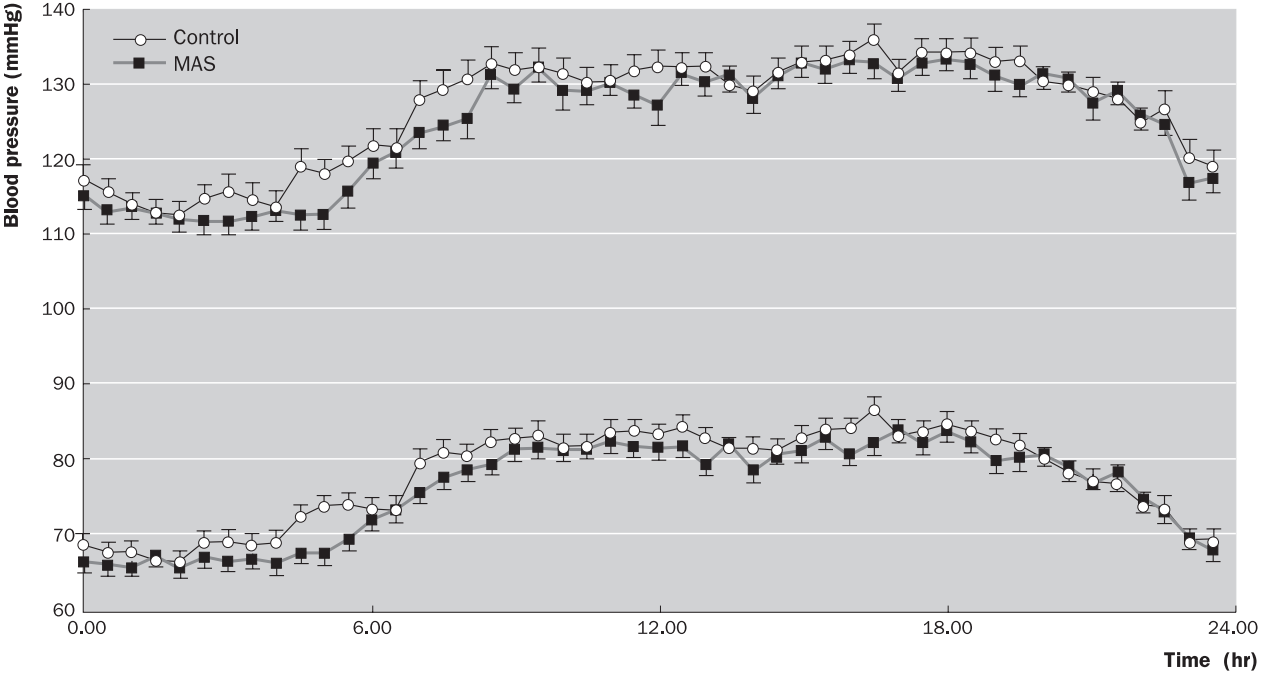

Fig. 12.4 Graph comparing 24-h systolic and diastolic blood pressure (BP) profiles between patients treated with the mandibular advancement splint (MAS) and the control appliance. Error bars represent SEM for every 30 min blood pressure reading, with all recordings synchronized from midnight (00.00 h) to midnight (24.00 h) (n = 61). Note that the greatest differences in systolic and diastolic blood pressure are evident during the morning period. Source: Gotsopoulos *et al*. (2004).

Incidence of Cheyne–Stokes respiration on cardiovascular oscillations in heart failure

Leung RST, Floras JS, Lorenzi-Filho G, Rankin F, Picton P, Bradley TD. *Am J Respir Crit Care Med* 2003; **167**: 1534–9

BACKGROUND. In patients with CHF, Cheyne–Stokes respiration is accompanied by oscillations in blood pressure and heart rate at a very low frequency. To investigate whether the cardiac oscillations are primarily related to oscillations in ventilation or oxygen saturation, Leung and colleagues studied ten patients with heart failure and Cheyne–Stokes respiration during sleep. They highlighted that there is growing evidence indicating that a combination of Cheyne–Stokes respiration and central sleep apnoea is part of a vicious pathophysiological cycle involving the cardiovascular, pulmonary and autonomic nervous systems, and that it ultimately contributes to increased mortality among patients with heart failure |44–47|. One possible mechanism linking Cheyne–Stokes respiration and central sleep apnoea with poor prognosis is through intermittent surges in blood pressure and heart rate occurring in association with oscillations in ventilation. Such surges can be precipitated by cyclical increases in sympathetic nervous activity targeting the heart and peripheral vasculature |48,49|. Several mechanisms have been postulated to account for such cyclical oscillations, including chemostimulation by apnoea-related hypoxia and arousals from sleep. It has also been postulated that periodic breathing can generate such fluctuations in blood pressure and heart rate |49,50|. The authors hypothesize that the abolition of the ventilatory oscillations of Cheyne–Stokes respiration by inhalation of carbon dioxide would eliminate accompanying oscillations in blood pressure and heart rate, but that elimination of hypoxic dips by supplementary oxygen would not.

INTERPRETATION. Ten subjects with heart failure and Cheyne–Stokes respiration were studied during sleep using frequency spectral analysis. During Cheyne–Stokes respiration, heart rate and blood pressure oscillated in association with respiratory oscillations at very low frequency. Inhalation of carbon dioxide abolished Cheyne–Stokes respiration and associated oscillations in both blood pressure and heart rate. In contrast, inhalation of oxygen sufficient to eliminate hypoxic dips had no significant effect on Cheyne–Stokes respiration, blood pressure ($n = 6$) or heart rate ($n = 5$) (Fig. 12.5). The authors concluded that ventilatory oscillations during Cheyne–Stokes respiration rather than oscillations in oxygenation *per se* powerfully induced oscillations in heart rate and blood pressure. Cheyne–Stokes respiration is therefore one of the mechanisms that contribute to the very low frequency oscillations in heart rate and blood pressure that are observed in patients with heart failure.

Comment

This paper demonstrates that the oscillations in heart rate and blood pressure associated with Cheyne–Stokes respiration and central sleep apnoea are more closely linked to oscillation in ventilation than to fluctuations in oxygenation. These cardiovascular oscillations are very common in patients with cardiac failure and are associated with poor prognosis |**51–53**|.

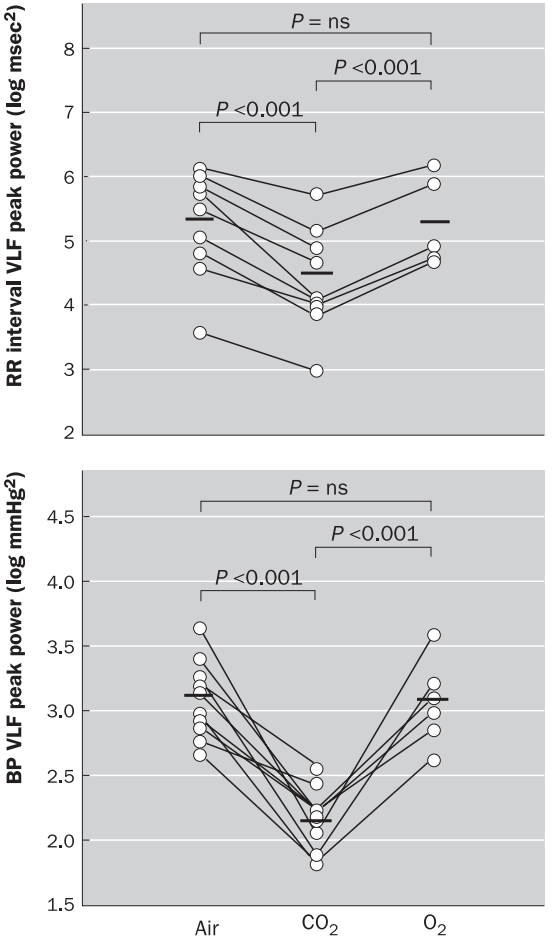

Fig. 12.5 Comparison of effects of air, carbon dioxide and oxygen inhalation on heart rate (*upper panel*) and blood pressure (*lower panel*) peak spectral power at very low frequency (VLF). Elimination of Cheyne-Stokes Respiration–Central Sleep Apnoea (CSR-CSA) by carbon dioxide inhalation causes a highly significant, almost complete abolition of VLF peak spectral power of heart rate (from 5.23 ± 0.83 to 4.37 ± 0.81 log msec^2; P <0.001) and blood pressure (from 3.09 ± 0.30 to 2.13 ± 0.25 log mmHg^2; P <0.001). In contrast, inhalation of oxygen had no effect on peak VLF power of any of the variables (heart rate 5.20 ± 0.71 log msec^2; blood pressure 3.06 ± 0.33 log mmHg^2), indicating that respiration-associated oscillations in heart rate and blood pressure persist. Source: Leung *et al*. (2003).

Model based assessment of autonomic control in obstructive sleep apnoea syndrome during sleep

Jo JA, Blasi A, Valladares E, Juarez R, Baydur A, Khoo MCK. *Am J Respir Crit Care Med* 2003; **167**: 128–36

BACKGROUND. OSAHS is characterized by repeated episodes of upper airway occlusion during sleep, resulting in changes in autonomic tone. This change in autonomic tone may well be linked to increased cardiovascular morbidity and mortality |54–56|. These changes in autonomic tone may be made simply by looking at heart rate variability or by studying a variety of cardiovascular reflex tests |57|. However because the subject's cooperation may be required for such tests, this approach for assessing autonomic activity is limited to wakefulness. Spectral analysis of heart rate durability has been used to quantify autonomic function in OSAHS under spontaneous resting conditions, thus allowing measurements to be made during sleep, but analysis can be difficult and the breathing pattern varies |58|. The authors describe an alternative method of autonomic function assessment in OSAHS that allows the dynamic effects of respiration and heart rate and the baroreflex-mediated feedback relations between blood pressure and the heart rate to be estimated using a computational model |15|. A previous study by the same authors showed that the model-based approach is sensitive in detecting changes in autonomic control resulting from CPAP therapy |53|. The present report describes a modification of their original approach that leads to more accurate results.

INTERPRETATION. During the application of CPAP pressure, nine patients with OSAHS and eight healthy subjects, random modulation of inspiratory pressure was used to increase the variability in respiratory and cardiovascular signals. Compared with the healthy subjects, the patients had a lower respiratory–cardiac coupling gain (36.9 vs 66.1 ms/l) and a lower baroreflex gain (2.3 vs 4.9 ms/mmHg). On falling asleep, the healthy subjects experienced a 2- to 3-fold increase in baroreflex gain, whereas the patients showed little change.

Comment

These findings confirm previous reports from the same group |**15,59**| that obstructive sleep apnoea syndrome is associated with reduced parasympathetic and elevated sympathetic activity. The model-based approach provided a more precise characterization of heart rate variability that can be employed in conjunction with spectral analysis for the non-invasive detection and assessment of autonomic cardiovascular abnormality in OSAHS patients during both sleep and wakefulness.

Left ventricular hypertrophy is a common echocardiographic abnormality in severe obstructive sleep apnoea and reverses with nasal continuous positive airway pressure

Cloward TV, Walker JM, Farney RJ, Anderson JL. *Chest* 2003; **124**: 594–601

BACKGROUND. Left ventricular hypertrophy (LVH) is a leading cause of morbidity and mortality in the Western world. An increase in left ventricular mass predicts a higher incidence of adverse clinical events, including death attributable to cardiac disease |60–63|. The Framingham Heart Study |62| found that the presence of LVH resulted in a 2-fold greater risk of sudden death compared with subjects without LVH. The adverse cardiac consequences of LVH are probably related ultimately to coronary artery ischaemia with an increased mass of muscle that is inadequately perfused, and may lead to endocardiocapillary compression |64,65|. LVH may also cause arrhythmias with sudden death |66,67|. OSAHS is now recognized as an independent risk factor for hypertension |9,68–70|. During obstructive apnoeic events, large negative intrathoracic pressures are generated during inspiration; this increases transmural pressures across the myocardium, increasing the afterload. Increases in preload and pulmonary congestion may also occur as a result of increased venous return. Recurrent hypoxic episodes decrease oxygen delivery to the myocardium, which may promote both angina and arrhythmias. Frequent arousal from sleep, which is characteristic of OSAHS, may lead to an increase in sympathetic nervous activity, which may also adversely affect myocardial function.

Nasal CPAP therapy has been shown to reduce blood pressure in subjects with OSAHS |12,44,71,72|. Treatment of hypertension reduces LVH and can also reduce CHF |73|. It is therefore important to achieve a better understanding of the relationship between LVH and obstructive sleep apnoea, and of the possible effects of CPAP therapy on such a relationship. The purpose of this present study was to determine (i) the incidence of LVH and other cardiac structural abnormalities in patients with severe OSAHS; and (ii) whether changes in LVH occurred after 6 months of CPAP therapy. Polysomnography was conducted on oximetry-screened patients who showed an oxygen desaturation index of more than 40 events per hour and whose cumulative time spent beneath an oxygen saturation of 90% was greater than or equal to 20%. Twenty-five patients with severe OSAHS were selected who did not have daytime hypoxia. They underwent echocardiography before and 1 month and 6 months after CPAP treatment in an outpatient sleep centre in Utah.

INTERPRETATION. Of the 25 patients with severe OSAHS, 13 (52%) had hypertension by history on physical examination. The baseline echocardiogram showed that severe OSAHS was associated with numerous cardiovascular abnormalities, including LVH (88%), left atrial enlargement (64%), right atrial enlargement (48%) and right ventricular hypertrophy (16%). In all patients (intention-to-treat basis) as well as those patients complying with CPAP therapy (84% used CPAP for more than 3 h each night), there was a significant reduction in LVH after

6 months of CPAP therapy, as measured by interventricular septal distance (baseline diastolic): the mean value was 13.0 mm and the 6-month mean after CPAP was 12.3 mm ($P < 0.02$). Right and left atrial enlargements were unchanged after CPAP therapy (Table 12.1).

Comment

This study confirms that multiple cardiac structural abnormalities are present in patients with severe OSAHS. Eighty-eight per cent of these patients had LVH, and hypertension was present in 52% of the subjects. Thus, daytime hypertension *per se* does not account for the high prevalence of LVH observed in this study. In addition to this, ten of the twelve normotensive subjects also had LVH. This suggests that the nocturnal consequences of OSAHS, including increasing transmural pressure due to respiratory effort during apnoeic episodes, recurrent hypoxic events and increased sympathetic neural activity, may account for the development of LVH in patients with severe OSAHS.

LVH also regressed after initiation of CPAP treatment. It is not known whether this was to the improvement in the underlying sleep apnoea itself or whether the CPAP may improve LVH irrespective of any improvement in the underlying OSAHS. The authors point out that a control group of non-OSAHS patients with LVH treated with CPAP therapy would have to be studied in future to clarify the mechanism by which CPAP may exert its beneficial effects. The authors conclude that it may well be beneficial to administer nasal CPAP to patients with coexisting sleep apnoea and LVH in order to try to improve the underlying cardiac failure that the LVH can produce.

Table 12.1 Measures of LVH at baseline, and after nasal CPAP therapy*

Variables	Baseline	1 month	6 months	*P*-value†
Overall (n = 25)				
IVSD	13.0 (1.6)	12.7 (2.5)	12.3 (1.6)	0.011
LVPWT	12.8 (2.0)	12.2 (2.0)	12.2 (1.6)	0.084
Compliant (n = 20)				
IVSD	13.1 (1.8)	12.9 (2.6)	12.3 (1.7)	0.018
LVPWT	13.0 (2.1)	12.3 (2.1)	12.3 (1.6)	0.039
Non-compliant (n = 5)				
IVSD	12.8 (0.4)	12.0 (1.7)	12.4 (1.5)	0.476
LVPWT	12.2 (1.1)	11.8 (1.7)	12.4 (2.6)	0.875

* Data are mean (SD). IVSD, diastolic interventricular septal distance; LVPWT, left ventricular posterior wall thickness.
† Difference between baseline and 6-month values.
Source: Cloward *et al.* (2003).

Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea

Kaneko Y, Floras JS, Usui K, *et al*. *N Engl J Med* 2003; **348**: 1233–41

BACKGROUND. Obstructive sleep apnoea subjects the failing heart to adverse haemodynamic and adrenergic loads and may therefore contribute to the progression of cardiac failure. Sleep-related breathing disorders (including obstructive and central sleep apnoea) often coexist with heart failure. The largest epidemiological studies, which involved 450 and 81 patients with chronic heart failure, found rates of prevalence of obstructive sleep apnoea of 37 and 11% respectively |15,16|. In addition, obstructive sleep apnoea is associated with significantly increased odds of having cardiac failure |74|.

INTERPRETATION. Twenty-four patients with a depressed left ventricular ejection fraction (45% or less) and obstructive sleep apnoea who were receiving optimal medical treatment for heart failure underwent polysomnography. On the following morning their blood pressure and heart rate were measured by digital photoplethysmography, and left ventricular dimensions and LVEF were assessed by echocardiography. The subjects were then randomly assigned to receive medical therapy either alone (twelve patients) or with the addition of CPAP (twelve patients) for 1 month. The assessment protocol was then repeated.

In the control group of patients who received only medical therapy, there were no significant changes in the severity of obstructive sleep apnoea, daytime blood pressure, heart rate, left ventricular end-systolic dimension or LVEF during the study. In contrast, CPAP markedly reduced obstructive sleep apnoea, reduced the daytime systolic blood pressure from a mean (± SE) of 126 ± 6 mmHg to 116 ± 5 mmHg ($P = 0.02$), reduced the heart rate from 68 ± 3 to 64 ± 3 beats per minute ($P = 0.007$), reduced the left ventricular end-systolic dimension from 54.5 ± 1.8 to 51.7 ± 1.2 mm ($P = 0.009$), and improved the LVEF from 25.0 ± 2.8 to 33.8 ± 2.4% ($P < 0.001$).

In medically treated patients with heart failure, the treatment of coexisting obstructive sleep apnoea by CPAP reduces systolic blood pressure and improves left ventricular systolic function. Obstructive sleep apnoea may thus have an adverse effect on the heart failure that can be addressed by targeted therapy.

Comment

One month of therapy with CPAP in a group of patients with coexisting left ventricular heart failure and obstructive sleep apnoea resulted in a 9% absolute increase and a 35% relative increase in LVEF in combination with significant reductions in left ventricular end-systolic dimension, daytime systolic blood pressure and heart rate. These effects were attributed to the alleviation of obstructive sleep apnoea, and the CPAP treatment led to a reduction in obstructive events and arousals overnight, with improvement in arterial oxygenation during sleep. CPAP treatment may well lead to an improvement in the above haemodynamic parameters by attenuating apnoea-related surges in sympathetic vasoconstrictor tone |**61**|, dampening negative

intrathoracic pressure swings and lowering systemic blood pressure, causing a reduction in left ventricular afterload |**19**|. By also abolishing hypoxic dips, CPAP augments the myocardial oxygen supply whilst reducing oxygen demand.

There needs to be a greater awareness amongst physicians treating patients with cardiac failure that coexisting obstructive sleep apnoea may have an adverse pathophysiological role, and that this can be addressed by targeted treatment using CPAP.

OSAHS and cerebrovascular disease

Sleep disordered breathing and stroke

Hermann DM, Bassatti CL. *Curr Opin Neurol* 2003; **16**: 87–90

BACKGROUND. This review summarizes recent studies that show that 20–24% of all ischaemic strokes occur at night or shortly after wakening in the morning. A meta-analysis of 31 publications (11 816 patients) found a 40% increase in all types of stroke (ischaemic, haemorrhagic, transient ischaemic attacks [TIA]) during that time compared with the rest of the day |75|. But most of the evidence on the risk of stroke associated with OSAHS is circumstantial and is based on case–control studies in which patients with a history of snoring with or without other features suggestive of OSAHS are compared with patients with stroke and matched controls |76–81|. Such studies lack objective confirmation of pre-stroke OSAHS, are critically dependent upon the validity of the control population and are subject to recall bias. In studies in which account has been taken of potential confounding factors, such as obesity, smoking and hypertension, the estimated risk of stroke is reduced. However, even when statistical adjustment for hypertension is undertaken, several studies still support an association between OSAHS and stroke |82–86|. These studies cite factors such as abnormal cerebral haemodynamics, increased platelet aggregation, increased fibrinogen concentration and increased blood viscosity as potential contributors to abnormal vascular endothelial function, and hence an increased risk of stroke. However, confirmation of an independent link between OSAHS and stroke requires the publication of large prospective studies. One such study has been published in abstract form |87|; it supports the conclusion that OSAHS is a risk factor for the development of stroke or TIA independently of sex, body mass index, diabetes and hypertension.

INTERPRETATION. Hermann and Bassatti postulate a number of potential mechanisms which may contribute to a link between sleep-disordered breathing and stroke, including blood pressure swings and altered cerebral blood flow, endothelial wall dysfunction, a prothrombotic shift in blood coagulation (including increased factor VII clotting activity and elevated fibrinogen levels, increased platelet activation and aggregation), and increased carotid artery intima–media thickness as a marker of generalized atherosclerosis. These factors may act independently to increase the risk of the development of a stroke in patients with untreated sleep apnoea.

Comment

There is increasing evidence that sleep-disordered breathing may play an important role in the pathophysiology of stroke and its evolution, but several important questions remain to be clarified. It is unclear whether patients with proven sleep-disordered breathing have an elevated cerebral vascular morbidity that is independent of the associated vascular risk profile, but this may well be answered by large-scale prospective studies in the future. Further work is also necessary to confirm the negative impact on long-term stroke outcome in patients with coexisting OSAHS. Thirdly, further studies are needed to determine whether CPAP treatment can both reduce the recurrence of stroke and improve the clinical outcome in patients with sleep-disordered breathing in the medium and long term.

The effect of upper airway obstruction in acute stroke and functional outcome at six months

Turkington PM, Allger V, Bamford J, Wanklyn P, Elliott MW. *Thorax* 2004; **59**: 367–71

BACKGROUND. Stroke diseases are the third leading cause of death in the UK after heart disease and cancer: an estimated 12% of all deaths are due to stroke. There has been recent interest in the recurrence of sleep-disordered breathing and in particular OSAHS following stroke. Two recently published studies have estimated that 62% of stroke patients exhibit sleep-disordered breathing, predominantly upper airway obstruction in the first 24 h after the onset of neurological symptoms |88,89|. Results have previously shown that up to 43% of stroke patients will have a progression of neurological deficits |90,91| which may be linked to blood pressure variability following the stroke |92|. Haemodynamic oscillations, blood pressure, cardiac output and heart rate are well known to be associated with upper airway obstruction, which typically occurs in OSAHS |93–96|. The main aim of this study was therefore to determine whether upper airway obstruction occurring in the first 24 h after a stroke has any detrimental effect on functional outcome and prognosis.

INTERPRETATION. One hundred and twenty patients with acute stroke underwent sleep studies within 24 h of onset to determine the severity of upper airway obstruction (respiratory distress index [RDI]/stroke severity [Scandinavian Stroke Scale, SSS]), and the disability level (Barthel score) was also recorded. Each patient was subsequently followed up at 6 months to determine morbidity and mortality (Fig. 12.6). Death was independently associated with SSS (odds ratio [OR] 0.92; 95% confidence interval [CI] 0.88–0.95; $P < 0.0001$) and RDI (OR 1.07; 95% CI 1.03–1.12; $P < 0.01$). The Barthel score was independently predicted by SSS ($r = 0.259$; 95% CI 0.191–0.327; $P = 0.001$) and minimum oxygen saturation during the night ($r = 0.16$; 95% CI 0.006–0.184; $P = 0.037$). The mean length of the respiratory event most significantly associated with death at 6 months was 15 s (sensitivity 0.625, specificity 0.525) using receiver operating characteristic curve analysis.

The occurrence of upper airway obstruction appears to be associated with a poorer functional outcome following stroke, increasing the likelihood of death and dependency at

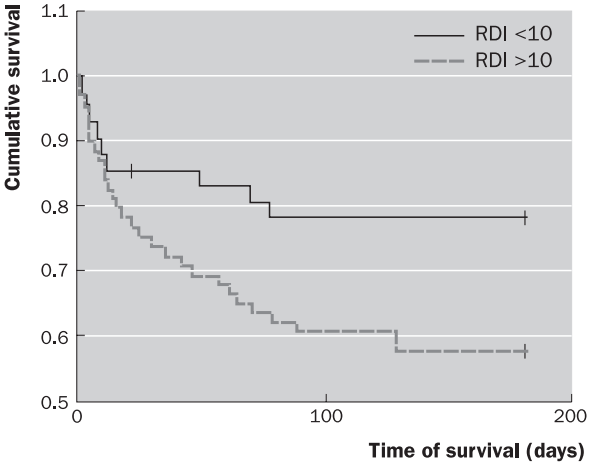

Fig. 12.6 Kaplan–Meier survival plot. Stroke patients with a respiratory disturbance index (RDI) of <10 had significantly longer survival times than those with an RDI of >10 (P <0.04). Source: Turkington *et al*. (2004).

6 months. Longer respiratory events appear to have a greater effect. These data suggest that long-term outcome might be improved by reducing upper airway obstruction in acute stroke at any early stage.

Comment

This study shows that upper airway obstruction occurring within the first 24 h after stroke is associated with a worse functional outcome, increasing the likelihood of death and dependency at 6 months. Furthermore, stroke patients with frequent upper airway obstruction appeared to die sooner than those without upper airway obstruction, and surviving patients spent longer in hospital if they experienced upper airway obstruction. It has been shown previously that there is no correlation between stroke severity and the severity of upper airway obstruction [**92**], which would suggest that upper airway obstruction is not just a marker of severe stroke. This study suggests that it is the longer apnoeas and hypopnoeas that appear to have the most deleterious effect in terms of functional outcome. Upper airway obstruction occurring persistently throughout the night was a better predictor of poor outcome than short bursts of severe airway obstruction. Several key issues remain and need further investigation. Treatment of upper airway obstruction in the acute stroke setting should be considered, with the aim of determining whether it can improve functional outcome. CPAP is the current gold standard treatment for significant OSAHS, but consideration should be given to how it is best delivered (either via a fixed pressure setting or by autotitration) and at what pressure setting. It may be that elderly, confused patients who have suffered a recent acute stroke will find CPAP difficult to tolerate,

but this study suggests that, even if it is not possible to eliminate all upper airway obstructive events, at least an attempt should be made to try to prevent the longer apnoeic and hypopnoeic events, thus stabilizing gross haemodynamic oscillations and oxygen desaturations. This may well be lead to an improvement in outcome.

Conclusion

There is increasingly strong evidence linking sleep-disordered breathing disorders and hypertension, cardiovascular and cerebrovascular disease. There is now no doubt that OSAHS contributes adversely to systemic hypertension and left ventricular diastolic and systolic dysfunction, and that CPAP treatment can lead to an improvement in outcome.

There is also increasing evidence suggesting that patients with pre-existing OSAHS have an increased risk not only of developing stroke but also of an adverse outcome, in terms of both morbidity and mortality from the stroke, if the underlying OSAHS is not identified at an early stage and treated effectively with therapy such as CPAP. If CPAP is to influence the outcome of stroke by limiting the ischaemic damage to the vulnerable areas of the brain, it would seem likely that treatment has to be started very quickly after the event. The practicalities of introducing CPAP at such a stage in patients who are often elderly, disabled and confused is extremely challenging, but future studies looking at selected patients who may be able to tolerate this treatment are urgently required.

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Part VII

Pulmonary embolism

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13

Advances in the understanding of pulmonary embolism

JOHN SIMPSON

Introduction

Pulmonary embolism (PE) is common and is responsible for significant morbidity and mortality. The condition is notoriously difficult to diagnose on clinical grounds alone.

No unequivocal evidence exists linking any single therapy for acute, severe PE with a significant reduction in mortality. After patients recover from acute PE we must decide how long anticoagulation should be provided, based on the relative risks of recurrent PE or iatrogenic haemorrhage. We use surprisingly few anticoagulation regimens despite evidence suggesting that some patients with first-time PE have quite different risk of recurrence than others.

This seemingly chaotic and depressing background has provided fertile ground for innovative and important research addressing some of these key issues.

From the huge number of valuable papers published in 2004, the articles discussed below were selected to reflect the breadth of clinical investigation being undertaken.

The chapter explores significant advances in the understanding of the natural history of PE, including the risk of recurrence and the likelihood of developing complications such as chronic pulmonary hypertension (CPH). Thereafter, consideration is given to the impact of specific risk factors, such as immobility in the sick medical patient and the use of the oral contraceptive pill. Attention then turns to the vexed question of how to detect patients most at risk of death after acute PE, before discussion of papers addressing the merits of specific medical and surgical therapies for acute PE. In the space available, these discussions can give only a flavour of the advances in the understanding of PE. However, further details can be readily obtained from a selection of the excellent reviews published in recent years |**1–3**|.

Symptomatic pulmonary embolism and the risk of recurrent venous thromboembolism

Eichinger S, Weltermann A, Minar E, *et al*. *Arch Intern Med* 2004; **164**: 92–6

BACKGROUND. One of the most important debates surrounding venous thromboembolism (VTE) relates to the risk of second deep venous thrombosis (DVT)/PE after an initial presentation. Decisions regarding optimal duration of anticoagulation depend critically on the ongoing risk of VTE, balanced against risks of anticoagulant-induced haemorrhage. A number of studies have addressed key components of this issue |selected examples include references 4–6|, contributing significantly to current prescribing practice for oral anticoagulants. A related fundamental question is whether PE is a random, incidental consequence of DVT (which might predict an equal rate of recurrent VTE regardless of whether initial presentation was with DVT or PE) or whether the natural history of PE is somehow different from that of DVT. The present study set out to address this specific issue.

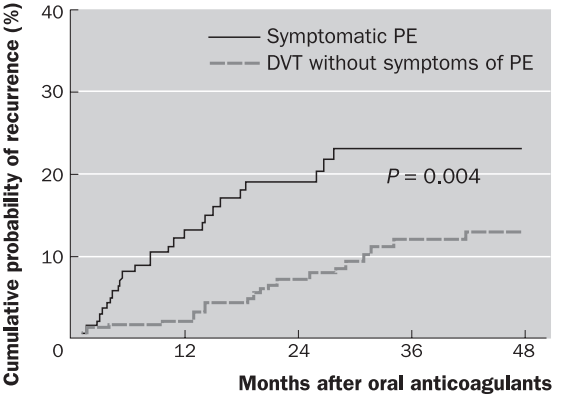
INTERPRETATION. The relative risk of recurrent VTE was greater after a first presentation with symptomatic PE than it was after initial presentation with DVT. Furthermore first presentation with symptomatic PE predicted a significantly higher likelihood that recurrence would be with PE rather than DVT.

Comment

This Viennese study prospectively identified adult patients presenting with VTE over a 10-year period. Each patient was instructed to report symptoms of new VTE, prompting further investigation. Patients were followed prospectively after discontinuation of oral anticoagulants for the initial presentation, with end-points represented by proven recurrent DVT or PE.

Importantly, the authors excluded patients with recent transient risk factors for VTE (recent surgery, trauma, pregnancy) or ongoing risk factors (hereditary deficiency of coagulation inhibitors, cancer) as well as patients taking antithrombotic medication. In total, over 50% of the starting population was excluded from analysis. However, where the study loses on patient numbers it gains by describing a population in which the diagnosis of idiopathic recurrent VTE can be made with greater confidence. The average age of the patients was 47. Patients who first presented with DVT ($n = 274$) had been receiving anticoagulation treatment for an average of 8 months, those with PE ($n = 162$) for 11.2 months.

Overall, the probability of recurrence was significantly higher in patients whose first presentation was with PE (Fig. 13.1). Twenty-eight patients (17.3%) with initial PE had recurrent VTE compared with 26 patients (9.5%) presenting initially with DVT. After adjustment for a variety of potential confounding variables (including age, sex and procoagulant factors), a significantly increased risk of recurrence associ-



Number of patients at risk					
Symptomatic PE	162	98	69	43	29
DVT without symptoms of PE	274	201	140	101	73

Fig. 13.1 Kaplan–Meier estimates of the risk of recurrent venous thromboembolism in patients with symptomatic pulmonary embolism (PE) or deep vein thrombosis (DVT) without symptoms of PE. Source: Eichinger *et al*. (2004).

ated with initial PE remained (relative risk of recurrence 2.2; 95% confidence interval [CI] 1.3–3.7). Although numbers were small, the relative risk that the second presentation would be with PE (as opposed to DVT) was significantly higher if the *first* event was PE (relative risk 4.0; 95% CI 1.3–12.3).

Certain points are worth noting in interpreting these data. Importantly, thanks to the careful study design, these results are largely applicable in the context of *idiopathic* recurrence. One potential limitation of the study is that the diagnosis of PE was largely dependent on ventilation and perfusion (V/Q) scintigraphy, and it is not entirely clear how confidently diagnosis of PE was made after a V/Q scan of intermediate probability |**7**|. Finally, the numbers of patients in the study are relatively small.

However, despite these considerations, this study is of immense importance to the understanding of VTE. That patients with PE have a 19% likelihood of further VTE at 2 years (compared with 7% after isolated DVT) is of huge significance in planning the duration of anticoagulation. These findings demand further prospective, randomized, placebo-controlled trials examining the benefits and risks of courses of anticoagulation longer than those currently used. The findings also provide further tantalizing evidence to support a different natural history for PE compared with isolated DVT. Further study should focus on factors determining progression to PE and the biological consequences of these.

The risk of recurrent venous thromboembolism in men and women

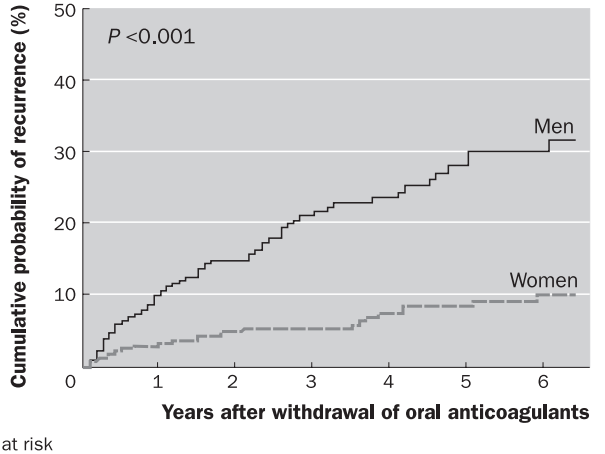
Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. *N Engl J Med* 2004; **350**: 2258–63

BACKGROUND. While the influence of gender on first presentation with VTE is well described |8|, less is known about its influence on recurrence. This study set out to address this specific issue.

INTERPRETATION. Recurrence of VTE is significantly more likely in men.

Comment

This study followed patients who had discontinued anticoagulants for a first VTE, to establish whether recurrence was influenced by gender. The study is from the same group that produced the previous paper, and is broadly similar in design and methods of analysis, with the exceptions that the study period was 11 years, additional Viennese centres were used, and V/Q scans appear to have been used for the diagnosis of PE without contributions from computed tomography pulmonary angiography (CTPA). Therefore, key methodological considerations have been described above and are not



Number at risk

Men	373	263	183	133	95	65	42
Women	453	342	248	193	142	103	72

Fig. 13.2 Kaplan–Meier estimates of the likelihood of recurrent venous thromboembolism according to sex. The cumulative probability of recurrent venous thromboembolism was greater among men than women ($P < 0.001$ by the log-rank test). Source: Kyrle *et al*. (2004).

considered further here. In the present study, 826 patients (373 men) were followed for an average of 3 years, the initial diagnosis being PE in 42%.

VTE recurred in 20% of men and 6% of women ($P < 0.001$). Figure 13.2 illustrates cumulative probability of recurrence. The estimated 5-year probability of recurrence was 30.7% for men and 8.5% for women. As in the paper by Eichinger and colleagues, multivariate analysis adjusting for potential confounding variables was performed, the relative risk of recurrence for men being 3.6 (95% CI 2.3–5.8). It is unclear exactly how many women used oral contraceptives or hormone replacement therapy during the study. However, in subgroup analysis, any influence of oral contraceptives or hormone replacement therapy on first VTE did not appear to influence the rate of recurrence in women.

This study builds on the important findings discussed in relation to the paper by Eichinger and colleagues. Together, these studies strongly suggest that anticoagulation should be continued longer for men with PE than for women with DVT, for example, but the optimal durations remain unknown. The inevitable conclusion is that further study is essential, including large, randomized, placebo-controlled trials assessing the best duration of therapy.

Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism

Pengo V, Lensing AWA, Prins MH, *et al*., for the Thromboembolic Pulmonary Hypertension Study Group. *N Engl J Med* 2004; **350**: 2257–64

BACKGROUND. Although CPH is known to be associated with thromboembolic disease, the rate at which it evolves and risk factors for its development have been poorly characterized. This study aimed to address these issues.

INTERPRETATION. Among patients presenting with a first symptomatic PE, the cumulative incidence of CPH over 2 years was almost 4%. When patients with PE and previous VTE were included, variables associated with the development of CPH included younger age, previous PE, idiopathic PE and size of PE.

Comment

This single-centre Italian study identified 314 consecutive patients with acute PE. From this group, the authors followed 223 patients who had no evidence of previous VTE and no evidence for conditions predisposing to CPH (e.g. advanced emphysema). If these patients had 'otherwise unexplained persistent dyspnoea' they were investigated with echocardiography, and if this proved to be consistent with CPH they progressed to V/Q scan, pulmonary arteriography and estimation of pulmonary artery pressure. Pulmonary hypertension was confirmed if pulmonary arteriography was compatible and if mean pulmonary artery pressure or systolic pulmonary artery pressure was greater than 25 or 40 mmHg respectively.

The 223 patients with no previous VTE were followed for a median of almost 8 years, during which seven were found to have CPH, all arising within the first 2 years. The cumulative incidence of CPH was 3.8% at 2 years. Because the rate of CPH was so low among the initial cohort, the authors included patients with previous VTE ($n = 82$, of whom eleven had evidence of CPH) when assessing risk factors for CPH. On multivariate analysis, CPH was associated with younger age, previous PE, idiopathic PE at presentation and larger PE at presentation (as evidenced by residual perfusion on scintigraphy). Importantly, inadequate anticoagulation was not more common in those patients who developed CPH.

These interesting findings probably approximate to the true incidence of CPH after a first PE. No control group was included, so the rate of incipient pulmonary hypertension in the same population is not known, though this is likely to be extremely low. Conversely, asymptomatic CPH may have been missed among the study group, given that not all patients were assessed objectively. With regard to the multivariate analysis, it is hard to determine from the paper whether chronic obstructive pulmonary disease (for example) could have influenced the higher rate of CPH among the patients with recurrent VTE.

Despite these considerations, this study has a significant impact upon our understanding of the natural history of PE. The implications are that patients with PE and risk factors for CPH should be followed up carefully. What we should do if we detect CPH remains to be answered in further studies, but the authors do mention that pulmonary thromboendarterectomy was performed in eight of the 18 patients with CPH, and all appeared to do well to a median of 22 months.

The outcome after treatment of venous thromboembolism is different in surgical and acutely ill medical patients; findings from the RIETE registry

Monreal M, Kakkar AK, Caprini JA, *et al*., and the RIETE investigators. *J Thromb Haemost* 2004; **2**: 1892–8

BACKGROUND. Many post-operative and immobile patients in hospital develop VTE. Remarkably little is known about the comparative outcome in these patients, especially with regard to fatal PE and treatment-related haemorrhage. The present study aimed to redress this shortfall.

INTERPRETATION. Immobile medical patients who develop VTE in hospital have a significantly higher risk of death from all causes, PE and haemorrhage at 3 months compared with surgical patients developing VTE in hospital. Immobile medical patients were also significantly less likely to have received thromboprophylaxis for their primary VTE.

Comment

The RIETE (Registro Informatizado de la Enfermedad Trombo-Embólica) is based in Spain and prospectively collects data on consecutive patients presenting to partici-

Table 13.1 Clinical outcomes of immobile acutely ill medical patients and surgical patients 3 months after presentation with symptomatic venous thromboembolism (VTE)

	Acutely ill medical patients *n* (%) (*n* = 756)	Surgical patients *n* (%) (*n* = 884)	Odds ratio (95% CI)	*P*-value
Recurrent VTE	25 (3.3)	25 (2.8)	1.2 (0.7–2.1)	ns
Major bleeding	44 (5.8)	18 (2.0)	3.0 (1.7–5.2)	<0.001
Minor bleeding	36 (4.8)	35 (4.0)	1.2 (0.8–1.9)	ns
Overall mortality	182 (24.1)	70 (7.9)	3.7 (2.7–4.9)	<0.001
Fatal PE	27 (3.6)	8 (0.9)	4.1 (1.8–9.0)	<0.001
Fatal bleeding	15 (2.0)	2 (0.2)	8.9 (2.0–39)	<0.001

CI, confidence interval; ns, not significant; PE, pulmonary embolism.
Source: Monreal *et al*. (2004).

pating centres with objectively confirmed VTE. The authors used the registry (to December 2003) to identify all patients with VTE who had undergone surgery, or who had prolonged immobility in hospital. For this analysis, VTE within 2 months of surgery defined the surgical group ($n = 756$), while the 'medical immobility' group ($n = 884$) comprised patients who were bed-bound for at least 4 days in the 2 months prior to VTE. The authors followed these patients for 3 months from the time of the index VTE, specifically aiming to determine rates of death attributable to haemorrhage or PE (defined as death within 2 days of objectively confirmed PE in the absence of an alternative cause).

Alarmingly, thromboprophylaxis in hospital had been received by only 28% of immobile medical patients compared with 67% of surgical patients ($P < 0.001$). Not surprisingly, baseline comorbidities were significantly greater in the medical group, who were also older. Interestingly, the medical patients had a significantly greater incidence of proximal DVT at baseline, while those with PE were more hypoxaemic than their surgical counterparts.

Outcome measurements are shown in Table 13.1. Regression analysis was used to identify factors associated with death from PE/bleeding after a first VTE. While many factors were identified on univariate analysis, only PE, cancer and prolonged immobility ($\geq$4 days) were independently associated with these outcomes.

This study demonstrates the usefulness of the RIETE and makes several important points. It amply emphasizes the depressing shortfall in thromboprophylaxis on medical wards. It also provides clear evidence that, despite anticoagulation, patients with VTE who are immobile do badly (Table 13.1). Why these patients are particularly susceptible to bleeding deserves further study, as does the question of what critical duration of immobility predicts an increased risk of VTE and its consequences. Furthermore, the independent association of PE with poor outcome again hints at a different natural history for PE compared with isolated DVT. The emerging clinical picture is that we fail to prevent primary VTE in sick, immobile patients, and we also currently fail to prevent significant downstream consequences of the disease.

Pulmonary embolism associated with combined oral contraceptives: reporting incidences and potential risk factors for a fatal outcome

Hedenmalm K, Samuelsson E, Spigset O. *Acta Obstet Gynecol Scand* 2004; **83**: 576–85

BACKGROUND. Combined oral contraceptive pills have long been recognized as risk factors for VTE. However, little is known about which host- or treatment-related factors may predispose specifically to a fatal outcome in PE associated with combined oral contraceptive pills. This retrospective study addressed this issue.

INTERPRETATION. In general, fatal PE tended to be associated with atypical symptoms at presentation, increased age, relative delay in investigation of symptoms, and lack of previous exposure to oral contraceptive pills. No clear association emerged between fatal PE and the composition of oral contraceptive pills.

Comment

This retrospective Swedish study was based upon reports of adverse drug reactions submitted to a national registry between 1965 and 2001. Case records and post mortem examination results were analysed for all 248 cases in which suspected PE was reported.

Confirmation of PE (autopsy or imaging) was found for 40 of 41 fatal cases (the remaining case had confirmed DVT). Among 207 survivors PE was confirmed by imaging in 155, with DVT in another 17. The final study group therefore comprised all fatal cases and all survivors in whom VTE was confirmed by imaging ($n = 172$).

Fatal cases were significantly more likely to have an above-knee clot, but this may reflect bias related to autopsy. Importantly, presenting symptoms in the two groups were similar but fatal cases were significantly more likely to have nausea, abdominal pain or no symptoms, and significantly less likely to have chest pain. These findings may partly explain the observation that imaging for VTE was in general more delayed among fatal cases (i.e. they had symptoms for a longer period prior to investigation). The observation that fatal cases were less likely to have received previous treatment with oral contraceptive pills is also interesting, especially given that the pills had been taken for less than 1 year in around two-thirds of fatal cases. The implication appears to be that the risk of fatal PE is greatest shortly after exposure in oral contraceptive pill-naive patients.

No obvious link between the composition of oral contraceptive pills and mortality emerged. The reporting incidence for fatal PE linked to combined oral contraceptive pills was 0.25 per 100 000 treatment years, but this figure must be treated with extreme caution and seems likely to underestimate the true incidence considerably.

This study is inevitably open to all the criticisms that can be levelled at retrospective studies. In addition there are clearly significant limitations inherent in using incidence

reporting to national registries as a means of case recognition. Also, improvements and refinements in medical care, note-keeping and investigations over 36 years make interpretation more difficult. Nevertheless, this type of study is very useful in picking out potential trends that should be verified in prospective studies. The study reminds us to be vigilant for PE in patients taking the combined oral contraceptive pill (particularly when this is prescribed for the first time), to have a low threshold for investigating such patients, and to keep an open mind regarding atypical symptoms.

Increased cardiac troponin I on admission predicts in-hospital mortality in acute pulmonary embolism

La Vecchia L, Ottani F, Favero L, *et al*. *Heart* 2004; **90**: 633–7

BACKGROUND. Significant PE rapidly increases pulmonary vascular resistance and is associated with increased myocardial oxygen requirements, especially for the right heart. As the increased oxygen requirement comes at a time when the partial pressure of oxygen in arterial blood (PaO_2) and cardiac output are reduced, subendocardial right ventricular ischaemia may ensue [9]. This has prompted interest in markers of cardiac injury as indicators of acute PE. This study assessed the prognostic significance of elevated serum cardiac troponin I (cTnI) in patients with acute PE without evidence for coexistent ischaemic heart disease.

INTERPRETATION. In this selected group of patients, elevated serum cTnI levels were generally associated with greater severity of PE. In multivariate analysis cTnI was independently associated with increased mortality.

Comment

This single-centre Italian study recruited consecutive patients admitted to the local coronary care unit with features suggestive of PE over a 2-year period. Blood was drawn on admission to the coronary care unit and at 8, 16 and 24 h. The authors concentrated principally on a cut-off value for cTnI of 0.6 ng/ml. Importantly, patients were excluded if they had a history of angina, previous myocardial infarction, coronary angioplasty or coronary artery bypass grafting, or if they had ECG or echocardiographic evidence of coronary artery disease on admission. Thus, it is probable that elevated cTnI reflected injury associated with PE. Forty-eight patients were studied, with PE confirmed objectively in 46. The severity of PE was high in this selected group, 79% of whom had right ventricular dilatation or hypokinesia at echocardiography.

Patients with cTnI above 0.6 ng/ml had significantly greater mortality (36 vs 3%; $P = 0.008$) and significantly lower PaO_2. They also had a significantly greater thrombus load, with more common involvement of the main pulmonary arteries ($P = 0.004$), though this did not equate to significantly increased right ventricular dilatation at echocardiography. In a multivariate analysis, cTnI emerged as the only

variable independently associated with in-hospital mortality, whether it was entered as a continuous variable (odds ratio [OR] 9.27; 95% CI 1.82–47.1) or as a dichotomous variable using a cut-off of 0.6ng/ml (OR 17.9; 95% CI 1.06–303.8). However, interpretation of these data should be tempered by the fact that only 6 patients died in hospital in this small study.

These results are consistent with the emerging body of evidence regarding troponin evaluation in acute PE |**10,11**|. However, it must be emphasized that this was a small study, and that patients had severe PE with no clear evidence of coexistent ischaemic heart disease. Much larger studies will be required to verify the prognostic significance of cTnI either alone or in combination with other biomarkers, in patients with and without ischaemic heart disease. Further studies should also establish the usefulness of cTnI in guiding and evaluating therapy. In the meantime, the authors point out that in the appropriate clinical context acute PE should enter the differential diagnosis for elevated serum cTnI, especially where there is lack of evidence for ischaemic heart disease.

Right ventricular enlargement on chest computed tomography. A predictor of early death in acute pulmonary embolism

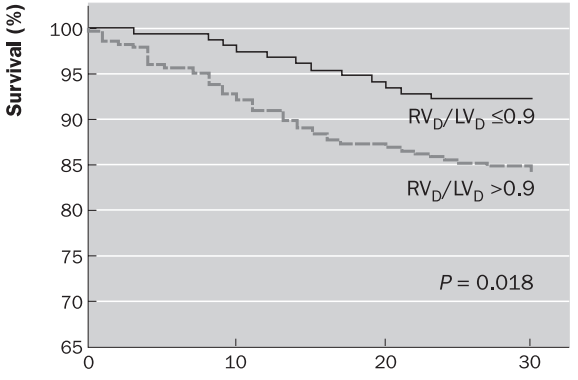
Schoepf UJ, Kucher N, Kipfmueller F, Quiroz R, Costello P, Goldhaber SZ. *Circulation* 2004; **110**: 3276–80

BACKGROUND. In recent years enormous interest has focused on the significance of right ventricular dilatation in acute PE |12–15|. With the increasing emergence of helical CT to detect acute PE, the capacity now exists to assess right ventricular dilatation at the same time that PE is diagnosed. This retrospective study aimed to determine the prognostic utility of right ventricular dilatation, with particular reference to 30-day mortality.

INTERPRETATION. Right ventricular dilatation was significantly and independently associated with increased 30-day mortality. The absence of right ventricular dilatation had a negative predictive value for death within 30 days of acute PE of 92.3%.

Comment

This was a retrospective single-centre American study in which the authors collected data for 454 consecutive patients presenting with acute PE over 27 months. Twenty-three patients were excluded, mainly for technical reasons. Radiological data for the remaining 431 patients were obtained using PE protocols on four- or 16-slice multidetector row CT scanners with reformatting and reconstruction of four-chamber heart views to allow measurement of the maximal distance across the right and left ventricular cavities in the plane perpendicular to the long axis of the heart. The authors defined right ventricular dilatation as a right ventricle:left ventricle ratio of greater than 0.9. Clinical data were collected retrospectively. The primary end-point



Number at risk

RV_D/LV_D				
≤0.9	155	152	146	144
>0.9	276	256	241	234

Fig. 13.3 Survival in 431 patients with acute PE according to the presence or absence of right ventricular enlargement on reconstructed CT 4-CH view. Probability values are from the log-rank test. Source: Schoepf *et al*. (2004).

was 30-day all-cause mortality, with a secondary composite end-point of 30-day mortality and in-hospital complications.

In total, right ventricular dilatation was detected in 64% of patients. Overall 30-day mortality was 12.8%, but was significantly higher among patients with right ventricular dilatation (15.6%). Figure 13.3 demonstrates survival in those with and without right ventricular dilatation. In univariate analysis, patients who died were found to be significantly older and to have greater frequencies of chronic lung disease, pneumonia, cancer and major haemorrhage. Multivariate analysis adjusting for these confounders (except haemorrhage) demonstrated that right ventricular dilatation was an independent predictor of 30-day mortality (hazard ratio 5.17; 95% CI 1.63–16.35). Very similar patterns emerged for the secondary composite end-point.

The study was performed in a tertiary referral hospital, and had high proportions of patients with cancer and pneumonia. Extrapolation therefore requires caution, though results are in keeping with others in the literature. Also, right ventricular dilatation is a dynamic process, and the study design inevitably means that right ventricular size was a snap-shot measurement. Furthermore, there is no way of determining how many patients had pre-existing right ventricular dilatation. However, these relatively minor concerns do not distract from the clear message supporting the role of right ventricular dilatation as a prognostic indicator in acute PE and emphasizing the utility of CTPA in acquiring prognostic as well as diagnostic information. Prospective studies are required to assess the usefulness of right ventricular dilatation in guiding therapy. In the meantime it should be noted that the absence of right

ventricular dilatation appears to suggest a particularly good prognosis for patients presenting with acute PE.

Thrombolysis compared with heparin for the initial treatment of pulmonary embolism

Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. *Circulation* 2004; **110**: 744–9

BACKGROUND. When to use thrombolysis for acute PE remains an extremely contentious issue. Although important, well-designed trials have emerged in recent years |16,17|, these remain too small to address comprehensively the specific issue of whether thrombolysis reduces mortality. This study therefore used meta-analysis of randomized controlled trials comparing thrombolysis with heparin to assess differences in death or recurrent PE.

INTERPRETATION. When considering all patients, no statistically significant difference in the combined end-point of 'death or recurrent PE' was observed. However, 'minor bleeding' was significantly more common among patients treated with thrombolysis. In a small subgroup analysis of massive PE, thrombolysis conferred a significant benefit for the combination of 'death or recurrent PE'. However, no significant differences were observed when death or recurrent PE were considered separately.

Comment

The authors searched extensively for papers/abstracts comparing heparin and thrombolysis as treatment for objectively confirmed, symptomatic acute PE, ending up with eleven randomized controlled trials incorporating 748 patients in which recurrent PE, death and bleeding were defined end-points. Primary efficacy outcome for the present study was the combination of 'recurrent PE or death'.

Results for 'recurrent PE or death' are shown in Fig. 13.4. A trend towards benefit for thrombolysis was observed, but was not statistically significant. Figures regarding 'major bleeding' were 34 for thrombolysis, 23 for heparin (not statistically significant), while 'minor bleeding' was significantly more likely in association with thrombolysis (OR 2.63; 95% CI 1.53–4.54). Only three episodes of intracranial haemorrhage were described (two for thrombolysis). Unfortunately no criteria defining major or minor bleeding were described.

In subgroup analysis of 'massive PE' ($n = 256$) a significant reduction in 'recurrent PE or death' was found for thrombolysis (OR 0.45; 95% CI 0.22–0.92), but this was attended by increased major bleeding (OR 1.98; 95% CI 1.00–3.92). When death and PE were considered separately, no significant differences were detected.

This study is subject to the problems that all meta-analyses have, in that unpublished data could potentially have been missed. Also, trials spanning many years sit together awkwardly, given that there have been improvements in healthcare, and that differences between individual thrombolytics or heparins cannot be factored in. The authors acknowledge these problems and went to significant lengths to address tech-

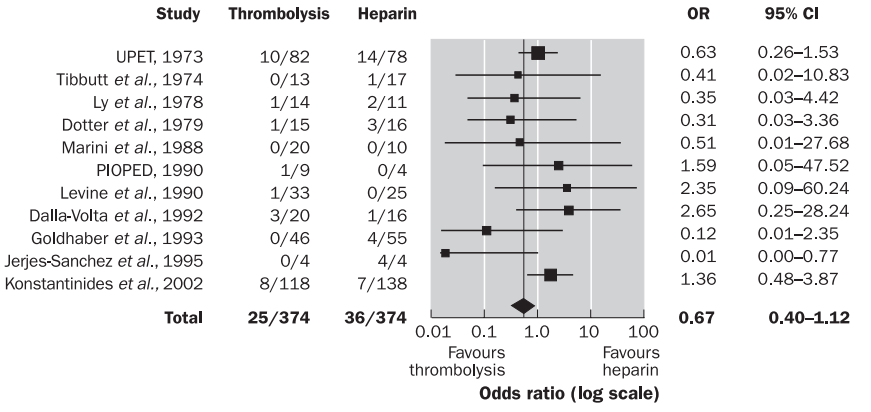


Fig. 13.4 Recurrent pulmonary embolism or death in trials comparing thrombolysis with heparin for initial treatment of acute pulmonary embolism. UPET, Urokinase Pulmonary Embolism Trial; PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis. Source: Wan *et al*. (2004).

nical issues. Importantly, they specifically assessed 'study quality' using predefined criteria, and none of the eleven studies satisfied all four of these.

In general, this study supports the emerging view that thrombolysis is justified for haemodynamically unstable patients with right ventricular dilatation, but not for stable patients with PE. It does not add to the debate regarding the haemodynamically stable patient with right ventricular dilatation. One caveat relates to intracranial haemorrhage associated with thrombolysis in PE. Trials studying thrombolysis are obliged to exclude patients who have the highest risk of bleeding, which possibly explains the low rate of intracranial haemorrhage described here. In real life we must remain mindful of the ICOPER (International Co-operative Pulmonary Embolism Registry) study, which described 3% intracranial haemorrhage after thrombolysis |**18**|.

Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism; a meta-analysis of randomized, controlled trials

Quinlan DJ, McQuillan A, Eikelboom JW. *Ann Intern Med* 2004; **140**: 175–83

Background. While low molecular weight heparin (LMWH) is widely preferred over unfractionated heparin (UFH) for the treatment of DVT, practice varies widely in the choice of heparin for acute PE. This meta-analysis included randomized controlled

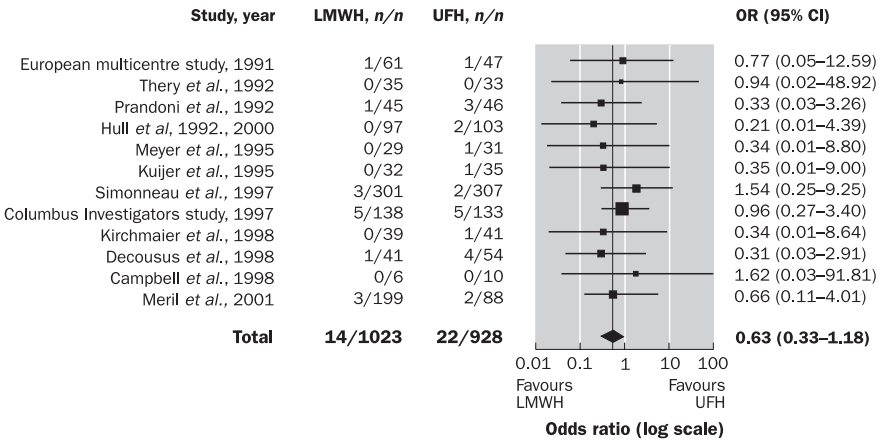


Fig. 13.5 Symptomatic venous thromboembolism at the end of treatment in trials comparing low molecular weight heparin (LMWH) with unfractionated heparin (UFH) for the treatment of acute pulmonary embolism. OR, odds ratio. Source: Quinlan *et al*. (2004).

trials in which fixed-dose subcutaneous LMWH and intravenous UFH were compared in the immediate treatment of acute non-massive PE. The primary outcome variable was recurrent VTE at the end of treatment, while secondary outcomes included recurrent VTE at 3 months, bleeding rates and mortality.

Interpretation. No significant differences were observed when comparing LMWH and UFH for any of the outcome variables. In general, outcome measures tended towards a statistically non-significant effect in favour of LMWH.

Comment

This study is from the same group as the meta-analysis comparing thrombolysis and heparin (Wan *et al*., 2004; see above), and used similar methods. The study described here incorporated not only symptomatic PE but also asymptomatic PE discovered in conjunction with symptomatic DVT. In all, twelve randomized controlled trials ($n = 1951$) fulfilled the inclusion criteria and contained data from which patients with PE could be clearly delineated from those with DVT alone. Importantly, patients with massive PE did not feature in these studies.

The results for symptomatic VTE at the end of treatment are shown in Fig. 13.5. Note that the odds ratio is less than unity (i.e. favouring an effect of LMWH) for ten of the twelve studies. However, note also the wide confidence intervals (in part reflecting the low number of incident events) and the fact that one of the two studies favouring UFH was by far the largest study. Odds ratios specifically for recurrent PE at the end of treatment also marginally favoured LMWH. Very similar trends were observed at 3 months. In terms of overall mortality, rates for LMWH and UFH were

1.4 and 1.2% respectively at the end of treatment and 4.7 and 6.1% respectively at 3 months (no significant difference). No significant differences in bleeding complications were noted, though major bleeding tended to be less common for LMWH.

The limitations of the study are broadly consistent with those discussed for the paper by Wan and colleagues. They also include the small number of incident events (making interpretation more difficult), the variety of LMWHs used (these vary in pharmacokinetics and specific actions), the inability to tell the frequency with which UFH was considered to be in the therapeutic range (i.e. a pharmacological bias for LMWH cannot be strictly excluded), and the fact that only one of twelve studies was double-blinded.

Despite these limitations, this is a valuable addition to the debate surrounding the choice of heparin for acute PE. The data strongly suggest that LMWH is at least as effective and safe as UFH for immediate treatment. However, it must be recalled that these studies did not incorporate massive PE, and these data should not be extrapolated directly to that scenario.

Open pulmonary embolectomy for treatment of major pulmonary embolism

Yalamanchili K, Fleisher AG, Lehrman SG, *et al*. *Ann Thorac Surg* 2004; **77**: 819–23

BACKGROUND. How best to treat massive PE remains unclear. Opinion varies about the effectiveness and safety of medical thrombolysis. Improvements in surgery and anaesthesia inevitably suggest acute surgical intervention as an alternative. This paper describes a single American centre's experience of open pulmonary embolectomy.

INTERPRETATION. In a highly selected series of 13 patients, 92% survival was described after open pulmonary embolectomy for massive or submassive PE. However, no follow-up data are provided. These findings suggest that open pulmonary embolectomy may be a useful addition to emergency measures for massive PE in centres where sufficient expertise exists, but direct comparisons with other forms of therapy are lacking.

Comment

The study covered 19 months from September 2000. Of the 13 cases included, four presented with 'massive' PE (with shock) and nine with 'submassive PE' (right ventricular dysfunction but haemodynamically stable). Two diagnoses of PE were made intra-operatively in the context of acute haemodynamic compromise during unrelated surgery.

The average age of the patients was 54 years. The surgical procedure incorporated median sternotomy and pericardiotomy, cardiopulmonary bypass (with or without cross-clamping of the aorta), excision along the main pulmonary artery (with or without excision along the right pulmonary artery), direct extraction of clot with forceps

and post-operative placement of a caval filter. The authors stress that hypothermia was not required. The only death occurred in a patient who had a cardiac arrest immediately before intra-operative detection of acute PE. In five of seven patients who had post-operative echocardiography there was no evidence of pulmonary hypertension.

These are remarkable findings, but must be placed in context. This technique requires rapid access to experienced surgeons and anaesthetists, limiting its availability. It is frustrating that the authors provide very few details about risk factors or comorbidities at the time of presentation, and no information is provided about treatment prior to surgery. Also, there is no explanation of why haemodynamically stable patients proceeded to surgery (rather than thrombolysis, for example). More importantly, no follow-up data are provided. Not only were these sick patients, but surgery and trauma to the pulmonary arteries are of themselves thrombogenic, and intuitively one would expect a high probability of acute and chronic post-operative venous thrombosis (or bleeding, assuming there was aggressive post-operative anticoagulation). The paper implies that the patients survived to discharge but provides no further information.

In summary, these highly selective results are impressive but much more information is required. Ideally, a randomized comparison with alternative strategies for massive PE, such as thrombolysis and catheter embolectomy, should be performed. As the authors state, however, these trials would be extremely hard to design. Meanwhile it seems unlikely that this technique will displace medical therapy for submassive PE, but in centres with the appropriate facilities open pulmonary embolectomy should be contemplated for cases of massive PE, particularly where there is a contraindication to medical thrombolysis.

Conclusion

The last year has seen improvements in our understanding of the natural history of PE. Good evidence supports differences in rates of recurrence depending on gender and whether the initial presentation is with DVT or PE. Equally, conventional teaching regarding rates of chronic pulmonary hypertension after PE has been convincingly challenged. These findings have considerable implications for the management of PE, and should drive the organization of trials assessing the optimal duration of therapy and the prevention of complications in subgroups of patients with PE.

Data from the last year can also be expected to influence diagnostic strategies for PE and the stratification of risk. In particular, early indications suggest that single (or composite) biomarkers may be able to predict the risk of mortality after PE. Also, the prognostic significance of right ventricular dilatation has been characterized extensively.

The focus on prognostic indicators has inevitably fuelled debate concerning the best management of acute PE. Increasing support appears to be emerging for LMWH as opposed to UFH. However, the question of how best to manage larger PEs remains controversial. The papers described in this chapter clearly do not resolve this issue

definitively. Instead they remind us that for larger, life-threatening PEs thrombolytic and surgical options can be considered for selected patients. However, clearer evidence for the use of these interventions is awaited from clinical trials.

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List of abbreviations

ACE	angiotensin-converting enzyme
AHI	apnoea/hypopnoea index
AHR	airway hyper-reactivity
AIR	Asthma Insights and Reality
AJCC	American Joint Committee on Cancer
ALPI	Adjuvant Lung Project, Italy
ARI	acute respiratory illness
ASDA	American Sleep Disorders Association
ATS	American Thoracic Society
BAL	bronchoalveolar lavage
BCG	bacillus Calmette–Guérin
BDP	beclomethasone dipropionate
BMI	body mass index
CAD	coronary artery disease
CAMP	Childhood Asthma Management Program
CAP	community-acquired pneumonia
CC	common carotid
CFU	colony forming unit
CHF	congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CP-EBUS	convex probe endobronchial ultrasonography
CPH	chronic pulmonary hypertension
CPIS	clinical pulmonary infection score
CRP	C-reactive protein
CRQ	Chronic Respiratory Questionnaire
CSR-CSA	Cheyne-Stokes Respiration–Central Sleep Apnoea
CT	computed tomography
CTGF	connective tissue growth factor
cTnI	cardiac troponin I
CTPA	computed tomography pulmonary angiography
CV	control vaccine
DHGLA	dihomo-γ-linolenic acid
DOT	directly observed therapy
DPLD	diffuse parenchymal lung diseases
DVT	deep venous thrombosis
EBUS	endobronchial ultrasonography
ECRHS	European Community Respiratory Health Survey
EEG	electroencephalography
EFI	exacerbation-free intervention
EGFR	epidermal growth factor receptor
ENA	epithelial/neutrophil-activating protein
EORTC	European Organization for Research and Treatment of Cancer
EPAP	Expiratory Positive Airway Pressure
ESS	Epworth Sleepiness Scale
ETS	environmental tobacco smoke
EUS	endoscopic ultrasonography
FDG-PET	fluoro-glucose-positron emission tomography
FE_{NO}	exhaled nitric oxide
FEV_1	forced expiratory volume in 1 s
FiO_2	fraction of inspired oxygen
FiO_2	inspiratory oxygen fraction
FMD	flow mediated dilatation
FNA	fine-needle aspiration

FVC	forced vital capacity
GCSF	granulocyte colony stimulating factor
GHC	Group Health Cooperative
GINA	Global Initiative for Asthma
GOAL	Gaining optimal Asthma Control (study)
GOLD	Global Obstructive Lung Disease
HAART	highly activated antiretroviral therapy
HAART	highly active antiretroviral therapy
HAP	hospital-acquired pneumonia
HHP	Honolulu Heart Programme
HIV	human immunodeficiency virus
HR	hazard ratio
HRCT	high-resolution computed tomography
HX	histiocytosis X
IC	inspiratory capacity
ICD	International Classification of Diseases
ICOPER	International Co-operative Pulmonary Embolism Registry
ICU	intensive care unit
IFN-γ	interferon-γ
IFN-γ1b	interferon-γ1b
IgE	immunoglobulin E
IIP	idiopathic interstitial pneumonia
IL	interleukin
ILD	interstitial lung disease
ILV	iron lung ventilation
IMT	intima–media thickness
IMV	invasive mechanical ventilation
IP	interstitial pneumonia
IPAP	Inhibitory Positive Airway Pressure
IPF	idiopathic pulmonary fibrosis
ISAAC	International Study of Asthma and Allergies in Childhood
ISOLDE	Inhaled Steroids in Obstructive Lung Disease in Europe (study)
ITU	intensive therapy unit
JV	jugular vein
LAM	lymphoangioleiomyatosis
LMWH	low molecular weight heparin
LN	lymph node
LPA	lymphocyte proliferation
LR	likelihood ratio
LRTI	lower respiratory tract infection
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MAS	mandibular advancement splint
max-SUV	maximum standardized uptake value
MCP-1	monocyte chemoattractant protein
MCV	mitocycin C, vinblastine and carboplatin
MODS	multiple organ dysfunction score
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRSA	methicillin-resistant *Staphylococcus aureus*
MSLT	multiple sleep latency test
MV	*Mycobacterium vaccae*
MVP	mitocycin C, vinblastine and cisplatin
MVS	*Mycobacterium vaccae* sonicate
6MWD	6-minute walk distance
MWT	maintenance of wakefulness test
6MWT	6-minute walk test
NIPPV	non-invasive positive-pressure ventilation
NSCLC	non-small-cell lung cancer
NSIP	non-specific interstitial pneumonia
OR	odds ratio
OSAHS	obstructive sleep apnoea/hypopnoea syndrome

$P(A\text{-}a)O_2$	difference between partial pressure of oxygen in the alveolar space and partial pressure oxygen in arterial blood
$PaCo_2$	arterial carbon dioxide tension
PaO_2	arterial oxygen tension
Pao_2	partial pressure of oxygen in arterial blood
PC_{10}	provocation concentration$_{10}$
PCR	polymerase chain reaction
PE	pulmonary embolism
PEF	peak expiratory flow
PET	positron emission tomography
PIAMA	Prevention and incidence of Asthma and Mite Allergy
Pi_{max}	maximal inspiratory mouth pressure
PIOPED	Prospective Investigation of Pulmonary Embolism Diagnosis
PIV	parainfluenza virus
PnV	pneumococcal conjugate vaccination
PPI	proton pump inhibitor
PSI	pneumonia severity index
RDI	respiratory distress index
REM	rapid eye movement
RFLP	restriction fragment length polymorphism
RR	relative risk
RSV	respiratory syncytial virus
RV/TLC	reduced residual volume/total lung capacity
SaO_2	arterial oxygen saturation
SARS	severe acute respiratory syndrome
SAT	self-administered therapy
SF-36	Short Form-36 (questionnaire)
SGRQ	St George's Respiratory Questionnaire
SRP	significant reduction in post-bronchodilator FEV_1 predicted
SSS	Scandinavian Stroke Scale
START	Steroid Treatment as Regular Therapy in Early Asthma (study)
SUV	standardized uptake value
TB	tuberculosis
TBNA	transbronchial needle aspiration
TEAC	Trolox equivalent antiosidant capacity
TGF-β	transforming growth factor β
Th cell	T helper
TIA	transient ischaemic attack
TNF-α	tumour necrosis factor α
TNM	tumour, nodes, metastases
TREM-1	triggering receptor expressed on myeloid cells-1
UFH	unfractionated heparin
UFT	uracil–tegafur
UIP	usual interstitial pneumonia
UPET	Urokinase Pulmonary Embolism Trial
VAP	ventilator-associated pneumonia
VC	vital capacity
VLF	very low frequency
$V'O_{2pk}$	peak oxygen uptake
V/Q scan	ventilation and perfusion scan
VTE	venous thromboembolism
WCL	whole-cell lysate
WHO	World Health Organization

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