REPORT ON THE THIRTEENTH ABERDEEN SPRING SYMPOSIUM ON RESPIRATORY MEDICINE: WHERE ARE WE NOW AND WHERE WILL WE BE IN TEN YEARS' TIME?*

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LECTURE 1

Professor Roger Finch, Department of Infectious Diseases, City Hospital, Nottingham

ANTIBIOTICS AND RESPIRATORY INFECTION

Professor Finch reminded us that respiratory tract infection places a significant burden on both hospital and community healthcare systems. The demographics of an increasingly elderly population is likely to cause a further rise in the prevalence of respiratory infection in the next ten years. There is increasing pressure to curb overspending on antibiotics both because of the need to target limited resources effectively and due to concern about the development of antibiotic resistance. A more rational and evidence-based approach to antibiotic prescribing is essential, particularly at a time when we are seeking to standardise antibiotic usage with European colleagues. Strengthening links with Europe can also be expected in areas such as research and new drug development. Drug companies, rather than belonging to a single member country, are becoming more pan-European in stance and new drugs are having to pass through European Community Regulatory processes.

Professor Finch saw one of the main challenges for the next decade as combating the rising prevalence of antibiotic resistance. Our diagnostic armamentarium also needs improvement in order to reduce the number of undiagnosed or late-diagnosed infections.

ANTIBIOTIC RESISTANCE

Significant developments in antibacterial chemotherapy have resulted in several effective drugs which we can use as empirical therapy in community-acquired pneumonia (CAP) (Table 1). No significant developments in the antibiotics available are anticipated over the next three years, yet emergence of microorganisms resistant to standard therapy is a serious issue.

The three most common pathogens affecting the respiratory tract can now exhibit significant resistance to our standard first-choice antibiotic therapy. *S. pneumoniae* is responsible for approximately 65-70% of cases of CAP while *H. influenzae* and *Moraxella catarhalis* are the organisms most frequently implicated in infective exacerbations of chronic obstructive pulmonary disease (COPD). A recent North Atlantic European co-operative study revealed significant resistance to penicillin in all three organisms. Penicillin resistance rates of up to 24% were identified for *S. pneumoniae* with amino-penicillin resistance rates of around 18% for *H. influenzae*. Whilst UK penicillin resistance to *S. pneumoniae* (currently around 8-9%) remains less of a problem than in Central Europe, a significant rise in resistance over the last decade has been seen and this trend is set to continue (Table 2). Linked penicillin and macrolide resistance has also been reported. Even more alarming is the emergence of organisms with multiple antibiotic resistance, some of which are becoming resistant to almost all available therapy.

MRSA is increasing in prevalence and in some cases is colonising or infecting the respiratory tract. The emergence of Vancomycin-resistant MRSA (the 'Doomsday bug') was reported in the *New England Journal of Medicine* in February 1999.[1] Other such micro-organisms include *Burkholderia cepacia* (of concern in the management of cystic fibrosis [CF]) and multi-drug resistant tuberculosis (MDRTB). These

TABLE 1

Empirical treatment of non-severe CAP

	Co-morbidity absent	Co-morbidity present
Preferred treatment	Amoxycillin (oral) *or* Ampicillin IV *or* Benzylpenicillin IV	Amoxycillin + Clavulanic acid
Alternative treatment	Erythromycin *or* Clarithromycin *or* Azithromycin	Macrolide *or* second or third generation Cephalosporin *or* Fluroquinolone

Empirical treatment of severe CAP

	Co-morbidity absent	Co-morbidity present
Preferred treatment	Aminopenicillin + Clavulanic acid and Macrolide +/- Rifampicin	Cefotaxime *or* Ceftriaxone and Macrolide
Alternative treatment	Cefotaxime and Macrolide	

Adapted from Finch & Woodhead 1998

TABLE 2
Reported antibiotic resistance rates for *S. pneumoniae* in England and Wales.

	Penicillin resistance	Erythromycin resistance
1989	0.3%	3.3%
1997	7.5%	11.8%

*Held in the Aberdeen Medical School on Wednesday 10 March 1999

and similar multi-resistant organisms will drive changes in our therapeutic practice and in the development of new therapeutic agents.

In vitro resistance to antibiotic therapy does not necessarily imply that an antibiotic is therapeutically redundant. It can be seen in Table 3 (pneumococcal susceptibility data) that *in vitro* resistance reflects predominantly an increased MIC 90. Serum concentrations of penicillin high enough to be therapeutic can still be achieved with increased daily dosages. In common non life-threatening infections due to *S. pneumoniae*, penicillin therefore remains the treatment of choice for *in vitro* resistant organisms, although a greater total daily dosage should be administered. For serious infections (e.g. meningitis or closed space infections) an alternative drug is best used.

TABLE 3
Susceptibility of *S. pneumoniae* to penicillin.

Level of penicillin resistance	MIC_{90}
Fully sensitive	<0.1 mg l^{-1}
Intermediate resistance	<0.1-1 mg l^{-1}
Fully resistant	>1 mg l^{-1}

DIAGNOSIS OF RESPIRATORY TRACT INFECTION

Despite modern microbiological techniques, in many cases of respiratory tract infection and CAP the causal organism is never established. This inevitably means that therapy lacks precision and outcomes are difficult to assess. This is particularly unsatisfactory for respiratory infections due to Legionella or Gram-negative bacilli which continue to have a high mortality rate.

New investigative techniques should be characterised by:

1. Speed of establishing diagnosis
2. Sensitivity and specificity
3. Ability to distinguish pathogens from commensals
4. Therapeutic relevance
5. Ability to meet nationally and internationally set quality standards
6. Syndromically useful

Among such new technologies the use of polymerase chain reaction (PCR) allows rapid diagnosis of specific conditions. Chip technology is likely to be increasingly important in this area and commercially developed silicon-based chips are becoming available. These are infused by injecting a serum specimen and will rely on oligonucleotide probes which are engineered to be precise in targeting specific microbial DNA. After a reaction time of <30 minutes they should, by a process of signal transduction, offer a read-out to the clinician. The chip can match the DNA identified against an internal database to diagnose the presence of a particular organism. Probes can even be made to focus on the presence or absence of specific resistance-markers thus giving rapid information as to the potential sensitivity of the organism identified without the need for prolonged microbiological culture. Chips are being created for infections of the gastro-intestinal tract and chips for infections of the respiratory tract are likely to follow in the near future.

GRAM-POSITIVE QUINOLONES

Early quinolones such as ciprofloxacin and ofloxacin were limited in their effectiveness against Gram-positive organisms such as *S. pneumoniae*. The development of the new Gram-positive quinolones is likely to become a major advance in respiratory therapeutics. Some are already licensed, e.g. Levofloxacin, while others are due to be licensed within the next three to five years. Gatifloxacin is also currently under trial and on present evidence this agent appears highly potent with broad spectrum activity. Gatifloxacin has an MIC 90 versus *S. pneumoniae* of 0.5 mg/l, compared to 2.0 mg/l for Ciprofloxacin.

New drugs are not, however, a therapeutic panacea. These new Gram-positive quinolones do not have increased efficacy against *Pseudomonas* and are not likely to have a major impact in the management of cystic fibrosis. They appear, however, to be extremely effective against organisms such as *Legionella* which 'melts at the mention of some of the names'.

There continue to be some safety concerns regarding this class of drug. Some of the initial quinolones had to be withdrawn due to multi-organ failure and subsequent agents have been found to have serious side-effects. Sparfloxacin is limited by photosensitivity problems and prolongation of QTc interval is, also noted in Grepafloxacin. Clinafloxacin may stimulate insulin release and has been associated with hypoglycaemia. CNS side-effects such as anxiety or seizures appear to correlate with GABA binding activity.

OXOZOLINIDONES AND EVERNINOMYCINS

It seems that these drugs may have a modest part to play in the management of respiratory tract infection due to their reputed improved efficacy against Streptococcus and modest activity against some other important organisms. Without greater diagnostic precision their place in the treatment of respiratory infection remains unclear.

PREDICTING THERAPEUTIC RESPONSE

Randomised double-blind controlled trials have been used for many years as the gold standard in demonstrating therapeutic efficacy. They provide reasonably good data to show that one drug is equivalent to another but are less effective at showing which of two possible agents is superior. The Food and Drug Administration in the United States now uses dose response curves which may be more helpful in this respect (Figure 1). In this format, drug concentration is plotted against time. Target MIC can then be added. The ratio of Cmax to MIC, or the area graphically delineating time spent above MIC, are useful guides to therapeutic response, and have been demonstrated to be valuable predictors of therapeutic outcome in both animal and human studies. The technique offers a way of optimising our choice of the most effective therapy and might be used to compare the efficacy of one drug versus a specific organism against alternative therapies. Dose response curves, however, are not useful in providing safety data. Structure activity analysis will continue to be used in development of new agents and also in predicting how these agents will respond and what side-effects are likely.

NOVEL THERAPEUTIC APPROACHES

The genomic structure of most common respiratory pathogens is now known and there is some understanding of the language of bacterial communication. Clinicians are well aware that a single organism can cause a spectrum of

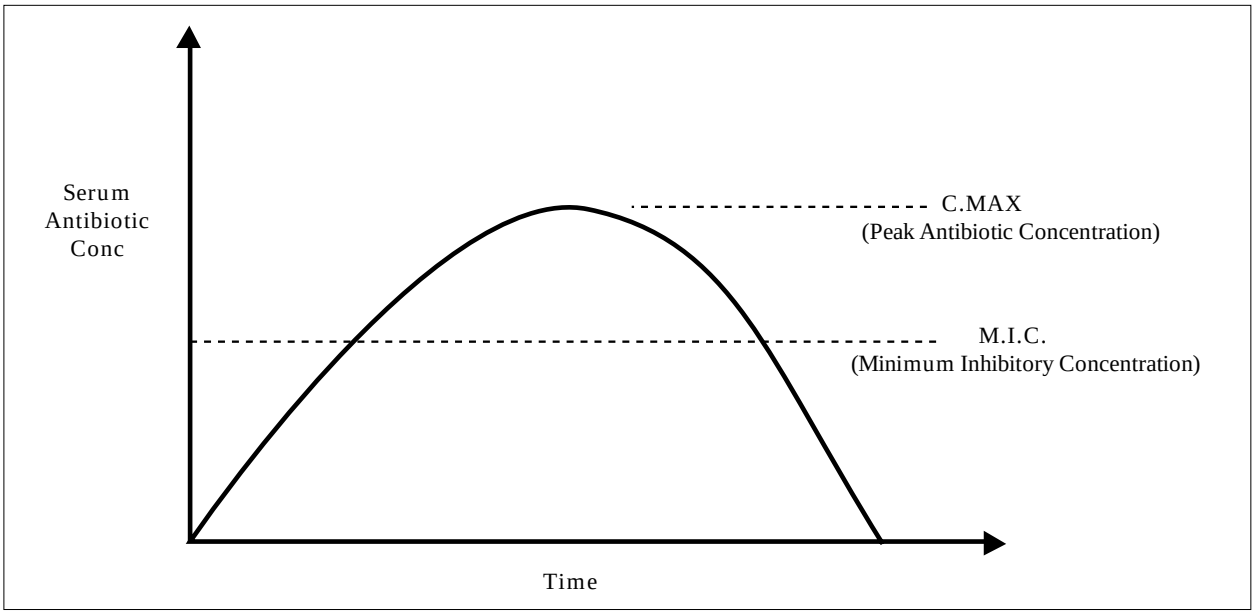

FIGURE 1
US Food and Drug Administration dose response curve.

different diseases according to the environmental circumstances in which it finds itself. *S. aureus* can cause a spectrum of disease including impetigo, boils, septicaemia, abscess or toxic shock. The vagaries of behaviour of organisms can be thought of as an example of environmental adaptation. A microorganism at cellular level is likely to sense the environment and produce signal molecules (e.g. homoserines or lactones in Gram-negative infection, or octapeptides in *S. aureus* infection). These may act in an autocrine or paracrine fashion to affect the subsequent development of local cells and influence production of virulence factors. This eco-system could perhaps be interfered with by artificially producing molecular mimickers which could act specifically to block production of virulence factors. These molecules are likely to be small, at around 250 Daltons, and would not cause cell death with associated release of endotoxin and inflammatory mediators. They could act as a 'magic bullet' to specifically target virulence expression. Because they would target virulence factors rather than microorganisms themselves they should have less impact on normal flora resulting in less superinfection, e.g. *Candida or Clostridium difficile*.

KEY POINTS

- In non life-threatening infection due to *S. Pneumoniae* with demonstrable *in vitro* penicillin resistance, high dose penicillin therapy remains the treatment of choice.
- Rapid specific identification of respiratory pathogens may soon be available using oligonucleotide probes with PCR and microchip technology.
- New fluoroquinolones with increased efficacy versus gram-positive organisms are likely to have a major role in respiratory therapeutics.

LECTURE 2

Dr John Macfarlane, Respiratory Unit, City Hospital, Nottingham

COMMUNITY-ACQUIRED PNEUMONIA

CAP remains a major cause of morbidity across Europe. Of the total European population of 350 million, approximately one million people will be treated annually for CAP, 100,000 of whom will require hospital admission.

THE NEED FOR GUIDELINES

In an attempt to improve and optimise care, several recent guidelines were published by committees in Britain,[2] Europe[3] and North America.[4] However, problems may be encountered in trying to use guidelines outwith the population they were meant to serve. Differences in overall management strategy, systems of healthcare delivery and aetiological agents can affect the development of local guidelines. For instance, the pragmatic approach favoured in the UK of treating non-severe CAP with one antibiotic, and broadening therapy only if treatment is initially unsuccessful, is unlikely to be acceptable in North America. In the US, patients often initially present to assessment units where a full diagnostic work-up is carried out prior to subsequent community management. In contrast, UK guidelines have to keep in mind GPs who manage patients in the community, often with very limited access to investigation. Several studies have pointed out that where chest X-rays are not available the presence of focal chest signs correlates well with the presence of radiographic changes.

Difficulties remain in the criteria used to diagnose CAP. Pneumonia has to be differentiated from non-pneumonic causes of lower respiratory tract infection (LRTI) or non-pneumonic exacerbations of COPD. Clearly there are difficulties in relying on radiological criteria, particularly in primary care where the opportunity to perform chest X-rays may be limited. In over 2,000 patients treated in Nottingham for LRTI with antibiotics, X-ray changes were found in only 5%. Thus extrapolating pneumonia guidelines

TABLE 4
Fine criteria to predict low risk patients with CAP (mortality rate in patients meeting these criteria is 0.1%).

- Age <50
- Absence of co-morbidity
- Normal mental function
- Pulse <125
- RR <30 minute
- Systolic BP >90 mmHg
- Temperature 35-40°C

Adapted from Fine et al. NEJM Jan 1997; 336(4):243-250

to general lower respiratory tract infection and non-pneumonic exacerbations of COPD could lead to inappropriate therapy being instituted. Over-treatment results in escalating drug costs, contributes to the development of antibiotic resistance and increases the possibility of drug-related side-effects. Overuse of cephalosporin antibiotics results in increased drug spending and rising numbers of cases of antibiotic-associated diarrhoea. Overuse of intravenous antibiotics has been shown to cause discharge delays of approximately 24-48 hours and confirms the need for an effective IV to oral switch policy.

Once the diagnosis of CAP is established, the likely microbiological cause should be considered together with some assessment of severity. *S. pneumoniae* remains the commonest pathogen, and it is clearly essential that any therapeutic regimen should cover this organism effectively. The American Thoracic Society approach of identifying 'core pathogens' which must be covered, and 'additional pathogens' which should be considered if specific risk factors apply, is an attractive approach to the problem. For mild CAP, *S. pneumoniae* is the 'core pathogen' and therapy for this with an amino penicillin would be appropriate. Additional pathogens should be considered and therapy broadened if necessary. Thus if the patient presented during a four-yearly Mycoplasma epidemic or had a history of recent foreign travel, antibiotics might be extended to include, for example, a macrolide. For severe CAP, a separate group of core pathogens are identified. *S. pneumoniae* again remains the commonest but *Legionella* and *S. aureus* are much more frequent. As a result, the treatment of these core organisms would be deemed essential. The three sets of guidelines available show a broad measure of agreement as to the management of severe CAP suggesting a beta-lactam-stable cephalosporin or coamoxiclav plus a macrolide (or in the US a Gram-positive fluoroquinolone as a possible alternative).

Guidelines are consistent in emphasising that the assessment of disease severity is pivotal in patient management. This process assists decision-making as to which cases require hospital admission and which can be managed in primary care. For those admitted to hospital, a more thorough severity assessment is required, particularly for those who might require management in specialist or intensive care facilities.

SEVERITY ASSESSMENT

Simple user-friendly protocols should allow severity of pneumonia to be graded. Current European Respiratory Society (ERS) and Infectious Disease Society of America (IDSA) criteria are somewhat over-complicated.[5] In contrast, the 'Fine Criteria'[6] might be useful in identifying patients at low risk who can be managed as an out-patient (Table 4). These identify a subgroup of patients with low mortality who very rarely need subsequent hospital admission and who can be safely managed at home. If the patient does require admission, the BTS severity criteria in identifying those patients at higher risk (Table 5) can be very useful. These have reasonable sensitivity and specificity, and usefully have a high negative predictive value. Thus patients with none of these features are unlikely to die as a result of their illness.

Assessing disease severity is a difficult task. Busy doctors in training grades, who are often the first to institute therapy, should not be criticised for over-treating when patients are admitted in the acute situation. The 'ward round' is a time when formal assessment of severity can take place, and antibiotic therapy rationalised and stepped down as appropriate.

North American and European guidelines suggest that the spectrum of antibiotic therapy should be widened in the presence of co-morbidity or advanced age. The evidence for age being identified as an independent risk factor is based on studies done in North America where Gram-negative enteric bacilli were implicated as causing pneumonia in a high proportion of elderly patients. These results have not been replicated in European studies; little UK data is currently available. What data there is on UK populations suggests that *S. pneumoniae* is still the most frequent pathogen in the elderly with *H. influenzae* being more common, and atypical organisms such as Mycoplasma less common, than in the rest of the population.

Co-morbidity may be a more important factor than age. If other disease processes are present, careful consideration is required as to which microorganisms might be implicated and the therapeutic regimen tailored accordingly.

TABLE 5
BTS severity criteria – clinical and laboratory features of CAP associated with an increased risk of death.

Clinical features	Laboratory features
• RR ≥30	• Urea >7
• Diastolic BP <60 mmHg	• Albumin <35gl
• Age ≥60	• PaO_2 <8kPa
• Co-morbidity	• WBC <4,000 x 10^9 *or* >20,000 x 10^9
• Confusion	
• 'Bacteraemia'/positive blood culture	
• Atrial fibrillation	
• Multilobar involvement	

Adapted from BTS guidelines on Management of CAP as published in British Journal of Hospital Medicine 1993; 49(5):346-50

KEY POINTS

- CAP is a common reason for hospital admission and has a significant mortality.
- Diagnosis of pneumonia should be based upon the presence of radiological evidence or focal chest signs.
- Assessment of pneumonia severity is pivotal in management and can be assisted by utilising existing guidelines.
- Core pathogens such as *S. Pneumoniae* must be covered by initial empiric antibiotic therapy. Additional pathogens should be considered and treated if clinically indicated.

LECTURE 3

Dr Peter Ormerod, Consultant Physician, Blackburn Royal Infirmary

TUBERCULOSIS

The World Health Organisation (WHO) declared tuberculosis a global emergency in 1995 due to its increasing incidence worldwide and the developing problem of drug resistance. Of a world population of 5.1 billion, an estimated 1.7 billion individuals are thought to have latent infection on the basis of a positive tuberculin test, and there are 8 billion new cases of active disease per year with a yearly toll globally of 3 million deaths.

INCIDENCE RATES

The incidence of tuberculosis in the Indian Subcontinent, Africa and South America approximates to 2-300 per 100,000 population per year. The incidence is steadily climbing and in some areas has dramatically accelerated. In Tanzania, the incidence increased five-fold in the decade from 1985-1996 with rates increasing from 120 to 600 cases per 100,000 per year. In the UK incidence rates are currently around ten per 100,000 per year. In England and Wales, the historical decline in incidence of tuberculosis stopped in 1987 at which stage there were approximately 5,000 cases per annum. Since then the number of cases notified each year in England and Wales has gradually increased to just over 6,000. In 1993 46% of patients were Caucasian but in 1998 this had fallen to 37%. An increasing proportion of cases come from ethnic minority groups who currently account for two thirds of cases in England and Wales. The greatest rise is in the British Black African population, who now account for 12% of cases as opposed to 1.5% of cases ten years ago. In Scotland, incidence has stayed relatively stable over the past ten years at around 500 cases per year. 85% of cases are Caucasian and 15% arise from other ethnic groups (8% of cases being individuals from the Indian Subcontinent).

Three main approaches have been put forward to control tuberculosis, which in order of importance are:

1. Appropriate and complete antituberculosis chemotherapy
2. Appropriate measures to identify cases (including screening of contacts)
3. Preventative interventions

ANTITUBERCULOSIS CHEMOTHERAPY

Guidelines for the management of tuberculosis have been updated by the Joint Tuberculosis Committee of the BTS and were published in *Thorax* in1998.[7] The many randomised controlled trials of antituberculosis chemotherapy have made treatment of this disease one of the most evidence-based areas of medical practice.

The current recommended regimen is for six months chemotherapy (unless there is CNS involvement). Rifampicin, Isoniazid, Pyrazinamide and Ethambutol are given for two months, followed by a four month continuation phase with Rifampicin and Isoniazid alone. Ethambutol can be omitted from the initial treatment phase if the patient meets the criteria specified in Table 6 to identify an individual at low risk of drug resistance. This standard treatment should only be modified if drug resistance is identified or if a drug reaction occurs requiring permanent withdrawal of an agent. The latter should only occur in approximately 3% of patients. If a modified regimen is to be used, it should be supervised by a physician with an interest in Respiratory Medicine or Infection with an appropriate level of expertise. Compliance is the major determinant of outcome and appropriate supervision of therapy is required. Consistency in our therapeutic approach should be ensured by regular audit.

TABLE 6

Criteria suggesting low risk of drug resistance (Ethambutol can be omitted from the initial phase of therapy if all criteria are fulfilled).

- No previous treatment for tuberculosis
- Caucasian ethnic origin
- Known or thought likely to be HIV antibody negative
- No history of contact with drug resistant tuberculosis

CASE FINDING

Cases should be identified from within high-risk groups which should include routine screening of new immigrants from high prevalence areas. Worldwide, all areas are considered as high prevalence with the exception of Australia, New Zealand, European Union and North America. The prevalence of tuberculosis in those staying in hostels or sleeping homeless approaches 100 times that of the general population, and such individuals should be selected out for specific screening programmes. It remains important to screen household contacts of respiratory cases, which account for approximately 10% of all new cases of this disease brought to medical attention.

In England and Wales there are very low notification rates with 80% of health districts having rates well below the national average, while approximately 50% have virtually no notifications. Clinical suspicion is important as respiratory symptoms can be non-specific. Rates of tuberculosis increase with advancing age, and in the Asian and Black African community. It is important not to miss this treatable condition and in a patient from these ethnic groups evidence of pleural effusion, mediastinal lymphadenopathy, cervical lymphadenopathy (persistent for four weeks or more) or monoarthritis should all be assumed to be due to tuberculosis unless and until further appropriate investigations show otherwise.

PREVENTATIVE MEASURES

Preventative measures include BCG vaccination and chemoprophylaxis. BCG vaccination is offered in a non-selective manner to individuals of secondary school age who do not have evidence of appropriate levels of immunity on Heaf testing. In this group BCG gives 80% protection for at least 15 years. Selective BCG vaccination is also appropriate for individuals at high risk such as healthcare workers, tuberculin-negative contacts of cases, and new immigrants to the UK.

Chemoprophylaxis involves administration of antituberculosis chemotherapy (normally Isoniazid) to tuberculin-positive individuals in certain circumstances to prevent the subsequent development of disease.

EMERGING DRUG RESISTANCE

In the UK, the rate of resistance to any first-line antituberculosis drug is approximately 1–2% in Caucasians and 5-10% in other ethnic groups. Every reasonable effort should therefore be made to obtain a bacteriological diagnosis and ensure sensitivities are checked. Globally, drug resistance in tuberculosis is monitored by the WHO. The rate of primary resistance (i.e. resistance in individuals never previously treated) is most prevalent in the Dominican Republic with rates as high as 46%. High rates are also seen in the Far East (e.g. Thailand 47%, Vietnam 42%) and in Eastern Europe (Estonia and Russia 28%, Latvia 34%).

Whereas primary resistance tends to reflect failure of disease control, acquired secondary resistance (resistance arising in individuals previously given therapy) usually results from ineffective or inappropriate drug therapy. The highest rates of acquired resistance occur in areas such as Latvia, Russia and Estonia, Korea and focally in pockets of Argentina. Portugal has the worst rate of acquired resistance and the highest prevalence of tuberculosis in the European Union.

Particular problems with resistance occur in areas where war or unstable government has fragmented medical services. In the Russian prison system 3% of individuals per annum develop tuberculosis. Along with HIV co-infection, this makes the Russian prison system the best amplifier of tuberculosis in the world.

Multi-drug resistant tuberculosis (MDRTB) is the 'new kid on the block' and represents a particular threat. It is identified by its resistance to both Isoniazid and Rifampicin. Treatment is difficult, prolonged, specialised and expensive. Drug treatment has to be continued for 18 to 24 months and the minimum cost per case is £150,000 (as opposed to an estimated £1,000 per case if the organism is fully sensitive). Despite this level of intensive therapy, mortality rates still approach 70%. Worldwide MDRTB is a considerable problem. In Latvia up to 65% of those previously treated have MDRTB, 27% being equivalent figures for Korea and Russia. Barcelona has a particular problem with MDRTB relating to its large HIV population.

Approximately 50 cases of MDRTB each year are identified in England and Wales. Risk factors include being born abroad, HIV positivity and previous antituberculosis chemotherapy. The majority of cases in England and Wales are treatment failures imported from abroad. Three cases of MDRTB have been identified in Scotland in the last two years, none of whom was HIV infected. In one case the infection was acquired during Voluntary Service Overseas in the developing world.

CO-EXISTENCE OF HIV INFECTION

Where an HIV-positive individual is also found to be tuberculin-positive, co-infection with tuberculosis can be said to exist. Such an individual is 170 times a year more likely to develop clinical tuberculosis than a tuberculin-positive individual without HIV. Inpatients with HIV who are tuberculin-positive, it is almost a case of *when*, rather than *if*, active tuberculosis will develop. Co-existing HIV infection is associated with more rapid progression of tuberculosis with more frequent involvement of extrathoracic sites. Tuberculosis also accelerates progression of HIV-associated illness with more rapid development of AIDS. The co-existence of both illnesses causes increased problems therapeutically due to reduced tolerance of essential chemotherapy and increased problems with drug interaction.

Co-existence of infection with HIV and tuberculosis is an established problem in Africa. In sub-Saharan Africa up to 20% of asymptomatic mothers are HIV-positive. In Harari and Mombasa up to 80% of those presenting with tuberculosis have HIV co-infection, and in Mombasa 98% of prostitutes are HIV-positive. In Bombay HIV positivity among prostitutes has increased from 20% to 50% over the past four years while in Thailand 10% of new army recruits are found to be HIV-positive at enlistment. Infection with HIV is also increasing in the Indian Subcontinent with 4 million predicted HIV cases by the end of the year 2000. In South East Asia there is an increasing overlap between HIV and tuberculosis and it is here the next phase of the HIV pandemic is likely to take place.

1993 figures for England and Wales suggest overall HIV positivity rates among tuberculosis cases of 2% (in those from the Indian subcontinent 0.6%, Caucasian 2.2%, Black Africans 6.8%). In Scotland the rate of HIV positivity among cases of tuberculosis is 1.6% (<1% Caucasians and highest in the Black African community).

PREDICTIONS FOR THE NEXT TEN YEARS

The WHO has reported that on demographic criteria alone, increasing world population will result in an estimated rise in tuberculosis cases from 8.5 million per year in 1995, to 10.9 million cases per year in 2005. Mortality is set to rise from 3 to 4 million deaths annually over this ten year period. If measures were taken to address current under-funding and difficulties in the provision of healthcare in problem areas, the WHO estimates that the final annual death toll could be cut to 1.6 million. As a result of these figures, many governments in the developed world are contributing to programmes aimed at tuberculosis control in the Third World. The UK supports a number of countries in this regard via the Overseas Development Agency.

Co-infection with tuberculosis and HIV is also set to rise. The WHO predicts a doubling in the worldwide incidence of tuberculosis/HIV co-infection from 8.4% in 1995 to 19% in 2005, most of this occurring in countries who can ill-afford the drug costs involved in treating the illness.

In terms of specific trouble spots, South East Asia is the region which will have the largest increase in population with an anticipated 40% increase in the prevalence of tuberculosis. The Indian subcontinent is expected to have 4 million HIV cases by the end of the year 2000, with a resulting increase in spread of tuberculosis. In sub-Saharan Africa the prevalence of tuberculosis is rising exponentially.

In Tanzania, which has a population smaller than Scotland, the number of cases is doubling every three years, and there are now 25 times more cases than in Scotland. In South Africa, 1,500 new cases of HIV are identified each day and prevalence rates approach 1,000 per 100,000 per annum. In South African mines, prevalence rates approach double that figure because of the associated exposure to silicon dust.

In Europe, the overall prevalence is likely to remain relatively stable and in Caucasians will probably continue to slowly decline. Economic migration from Eastern Europe and the former 'Eastern bloc' may increase prevalence of tuberculosis in certain areas.

Closer to home, in England and Wales tuberculosis incidence among Caucasians is again likely to continue to fall; however, within other ethnic groups it may continue to cause problems. England and Wales have the highest proportion of non-white tuberculosis in the European Union. HIV co-infection in England and Wales is largely confined to specified minority groups, e.g. Black Africans and intravenous drug abusers.

In Scotland tuberculosis among Caucasians seems likely to decline by around 5% per year. The ethnic minority proportion of tuberculosis cases in Scotland is low in comparison with other European countries. However, in Scotland the expected gradual decline in prevalence may not occur if there is increasing immigration or a rise in HIV prevalence.

KEY POINTS

- The global incidence of tuberculosis is increasing at an alarming rate.
- Co-existence of tuberculosis and HIV infection results in more rapid progression of both illnesses.
- MDRTB is an emerging threat which is expensive, difficult to treat and has a high mortality.
- It is vital that our existing drug therapy and scientific knowledge is applied effectively if pulmonary tuberculosis is to be controlled.

LECTURE 4

Professor Duncan Geddes, Department of Respiratory Medicine, Royal Brompton Hospital, London

CYSTIC FIBROSIS

While CF is uncommon compared with other topics covered in this symposium, it is important particularly as a model for the future investigation and management of genetic disorders. It affects 7-8,000 people in the UK and around 70,000 individuals worldwide. The problem is due to a mutation of the CF gene which codes for a 1,480 aminoacid protein called the cystic fibrosis transmembrane conductance regulator (CFTR), the main function of which is as a chloride channel. In CF, this transmembrane protein is absent or defective.

MOLECULAR PATHOLOGY

The molecular pathology of CF can be classified as shown in Table 7.

TABLE 7

Class 1	No production of CFTR.
Class 2	CFTR is produced by endoplasmic reticulum but is abnormal. It fails 'quality control' assessment at the Golgi apparatus and never gets to the cell membrane.
Class 3	CFTR is produced and reaches its membrane site of action. However, due to failure of phosphorylation the chloride channel is unable to open and is functionally ineffective.
Class 4	CFTR is produced and reaches its membrane site of action. The channel opening occurs as a result of phosphorylation but is defective. CFTR function is, therefore, suboptimal.

In the UK the most common CF mutation is the absence of a single codon (coding for phenylalanine) at position 508. This ΔF508 variation accounts for 70% of mutations in the UK and results in a class 2 fault in CFTR production. The primary abnormality is, therefore, absence of a membrane protein (CFTR) which acts as a calcium channel, and as a result chloride ions are unable to leave the cell in the normal way. Secondary abnormalities also occur and it is not clear whether these relate to absence of the calcium channel or to some other intracellular function of CFTR. Most notably, sodium influx into the cell is increased and since water tends to travel with sodium, this leads to relative dehydration of the cell surface. In addition, surface glycoproteins are altered which may affect antimicrobial defences. The result is that, wherever epithelial cells are arranged as tubular structures transporting water and salt, problems are likely to arise. Thus relative dehydration in the lumen of the vas deferens during development leads to maldevelopment as a result of which virtually all males with CF are infertile (despite satisfactory sperm development). The pancreatic ducts are similarly affected leading to subsequent pancreatic tissue damage and insufficiency. In the same way diminished bile flow, stasis and obstruction in the biliary tree can result in focal biliary fibrosis and subsequent liver disease. In the bowel, poor clearance of hyperconcentrated intestinal contents can lead to distal intestinal obstruction or 'meconium equivalent syndrome'.

THE DEVELOPMENT OF LUNG DISEASE

As a result of the increased life-span of cystic fibrotis patients, the major cause of death in adults is now respiratory failure. The small airways of the lungs are susceptible to chronic infection which produces progressive lung injury.

Two main hypotheses have been put forward as to why chronic infection occurs in CF:

1. Defective mucociliary clearance
2. An abnormality of host/bacterial interaction

It remains unclear which of these is the major influence and whether or not both factors play a contributory role. Defective mucociliary clearance has generally been viewed as the main pathological abnormality. Ciliary structure and function in CF remains normal but there is abnormal mucus viscoelasticity and altered mucus chemistry. Unfortunately,

it is not possible to study this in neonates (at which time it might be possible to ascertain the primary abnormality) and studies of older patients may cause difficulties in separating out to what extent mucus changes are secondary to co-existing chronic infection. In diseases with a primary abnormality of mucociliary function such as primary ciliary dyskinesia, involvement is mainly in the lower pulmonary lobes. It is, therefore, surprising if impaired mucociliary clearance is accepted as the main factor leading to chronic infection and subsequent bronchiectasis, since it is the upper lobes which are predominantly affected in CF.

Host bacterial interactions in CF may also be important, particularly defensins and bacterial attachment. Defensins are polypeptide proteins produced by most mammalian epithelial cells which appear to exert an antibiotic effect. If a culture of airway epithelial cells is sprinkled with a bacterial agent such as Pseudomonas, airway surface liquid from this culture will act to inhibit growth of the bacterial species tested and this effect is thought to be due to defensins. If the same experiment is carried out with a CF explant, the antibacterial effect of airway surface liquid is lost. If the CFTR protein is returned artificially to the CF explant, then normal function is restored. It therefore appears that the CFTR protein is important in some way in ensuring production or normal function of defensins.

Bacterial attachment is also an important component. Interestingly, pseudomonal attachment seems to be increased in CF airway epithelial cells, which can be corrected by replacing the normal version of the gene.

These two different host/bacterial interactions in CF are potential therapeutic targets. In the USA the Cystic Fibrosis Foundation is investing many millions in learning more about defensins in the hope of developing new topical antibiotics.

How can the recurring respiratory infections in CF be managed best? In children *S. aureus* and *H. influenzae* are the main pathogens, and chronic colonisation with *Pseudomonas aeruginosa* occurs in over 80% of adult patients. An unwell CF patient requires treatment during an acute exacerbation but there are gaps in our knowledge as to when and with what to treat. How many antibiotics should be given? One drug alone can encourage resistance in Pseudomonas infections and at least two are normally recommended. The optimal duration of therapy and the relative benefits of different drug regimens, dosage schedules and home versus hospital treatments are all issues which require clarification.

Should antibiotics be given early in life to try to prevent infections due to *S. aureus* and perhaps *H. influenzae*? Similarly, later in life, once chronic Pseudomonas colonisation has developed, should regular intravenous or nebulised anti-Pseudomonas therapy be given to prevent the patient becoming ill, or should treatment only be instituted when the patient is symptomatic? There is little evidence to guide us although the publication by Beardsman *et al.* in 1994[8] seemed to indicate a possible role for regular Flucloxacillin from CF diagnosis in childhood. Thirty-eight patients with CF were randomised to either regular daily Flucloxacillin, or to Flucloxacillin given if required for symptomatic infection. In those given regular Flucloxacillin, there was less cough, reduction in overall antibiotic requirements, reduction in isolation of *S. aureus* from sputum and an approximate 50% reduction in hospital admission rates. No trend towards earlier colonisation with Pseudomonas was noted.

It is still unclear whether regular three-monthly intravenous chemotherapy should be given for chronic Pseudomonas colonisation (as practised at the Danish Cystic Fibrosis Centre) or whether antibiotics should be reserved for when the patient becomes unwell. The Danes feel they have reasonably good evidence that chronic suppressive therapy is superior to 'on demand treatment'. Ninety per cent of their patients survive for at least ten years after the onset of chronic infection and this contrasts with earlier periods where on demand treatment was associated with only 50% survival at five years. Despite good results, however, this therapy is expensive and antibiotic side-effects can occur. Other improvements in management may also have contributed to this improved survival. Emphasising its anecdotal nature, Professor Geddes related the case of a 40-year-old lady who developed Pseudomonas colonisation at age 15. If she had received regular intravenous therapy (as used in Denmark), she would have had an additional 1,320 days of therapy and would have received 0.5 kg of Gentamicin and 5.3 kg of Ceftazidime at an additional cost of £50,000. Without this therapy, she had maintained reasonably satisfactory lung function at the age of 40! It therefore seems difficult to believe that in her particular case she would have benefited from regular treatment.

In an attempt to clarify this issue, the BTS performed a study involving 60 CF patients over eight years comparing the use of elective three-monthly antibiotic therapy versus therapy given only when the patient was symptomatic. The trial was complicated by protocol breaks. It was found that the elective group received more antibiotics but that there was no consistently significant difference in patients' symptoms, chest X-ray score or antibiotic resistance. Slightly more deaths were noted in the elective group. While this could be a statistical quirk, a larger trial involving numbers in excess of 600 patients would be required to prove that there was no effect on mortality. This BTS study is normally used to suggest a lack of sufficient evidence of advantage for 'chronic suppressive' chemotherapy. Three-monthly IV therapy, therefore, does not tend to be given in the UK.

Nebulised antibiotic prophylaxis does appear to be beneficial. A meta-analysis published in *Thorax* in 1996[9] suggested that regular nebulised antibiotic therapy reduced the number of exacerbations requiring treatment, improved final FEV^1 and reduced load without evidence of increased Pseudomonas resistance. Drugs used were nebulised Tobramycin and Colomycin. Professor Geddes commented that he is not aware of any cases where *Pseudomonas aeruginosa* resistance occurred due to nebulised Colomycin therapy. UK practice is to administer regular nebulised Colomycin to patients with chronic Pseudomonas colonisation when there is a need to reduce the number of infective exacerbations.

PREVENTION OF LUNG DAMAGE

It has been shown that non-steroidal anti-inflammatory agents can reduce lung injury in *Pseudomonas aeruginosa* pneumonia in experimental animal models. A four year study assessed the effect of Ibuprofen administration in children and adults with mild lung disease (FEV^1 60% of predicted) and suggested slowing of decline in lung function, better maintenance of body weight and reduced number of hospital admissions in patients given Ibuprofen regularly as compared with placebo. Systemic corticosteroids may also preserve lung function although at the cost of

unacceptable steroid-related side-effects. The possible role of inhaled corticosteroid in slowing disease progression remains unproven.

LATE COMPLICATIONS

Pneumothorax, a late complication of CF, can sometimes be difficult to diagnose, and CT of thorax has a useful role in diagnosing and ensuring optimal management.

Antibiotic resistance is also an important problem. At the Royal Brompton Hospital around 40% of patients with chronic Pseudomonas colonisation have fully sensitive organisms with 30% being resistant to one, two or three antipseudomonal drugs. Some Pseudomonas organisms are now resistant to every available drug except Colomycin.

The organism, *Burkholderia cepacia*, has a prevalence of around 3-5% in adult patients. It is even more resistant to antibiotics than Pseudomonas making it 'almost untreatable' and, unfortunately, its prevalence seems to be increasing in the CF population.

LUNG TRANSPLANTATION

Heart and lung transplant or double lung transplant offers hope for patients with endstage pulmonary disease. However there is a lack of donor organs and while there is a 70-75% one year survival after transplantation, subsequent attrition related primarily to obliterative bronchiolitis results in a five year survival of only around 50%.

NON-PULMONARY ASPECTS

Nutrition

A persisting problem is malnutrition in CF patients. In 1990 30% were found to be undernourished according to North American Cystic Fibrosis Foundation data and rates had improved little by 1994 with 26% of patients remaining undernourished.

Male infertility

Although male infertility has been overcome by epididymal sperm aspiration and *in vitro* fertilisation, the NHS does not provide a uniform service nationwide and some patients can find this service difficult to access without going to the private sector. This service appears to be more easily obtained in Scotland.

CYSTIC FIBROSIS AND GENE THERAPY

Gene therapy for CF *may* be achievable within a further five years but the chance of success over this time scale remains in considerable doubt. Worldwide, six groups in the USA, three in the UK and one group in France are working in this area. The Americans and French are predominantly using viral vectors which appear to be more efficient than non-viral methods but problems are being encountered with adverse effects due to the host's immune response. US researchers are trying to develop vaccines which are not affected by the host's immune system. In the UK work has concentrated on non-viral methods. The way ahead probably lies somewhere between these two approaches, perhaps a lipid-base synthetic compound with viral add-ons. Unpublished data from the Cystic Fibrosis Lung Study show improvements from gene therapy in chloride channel function but evidence of significant clinical benefit is still lacking.

KEY POINTS

- CF is an autosomal recessive disorder which is an important model for the investigation and management of other genetic conditions.
- 70% of cases in the UK are due to the delta F508 mutation with resultant absence of the CFTR calcium channel.
- New insights into the pathogenesis of lung damage may allow novel therapeutic approaches.
- Successful gene therapy is predicted over the next decade.

LECTURE 5

Dr Martin Partridge, Consultant Physician, Whipps Cross Hospital, London

ASTHMA

Doctors are currently doing well in the battle against asthma but we have not yet won the fight. Worldwide, at least 150 million people suffer from asthma and prevalence appears to be increasing. GP consultation rates in the UK have risen in the last 20 years across all age groups. Despite an increasing burden of disease, some success has been achieved in reducing severe exacerbations. The rate of hospitalisation due to asthma in the UK has now peaked and is starting to decline. Death rates are also falling.

RISING PREVALENCE

Is this apparent rise in asthma prevalence genuine? Clearly other factors, such as increased awareness of the condition or diagnostic transfer, could be operating. To determine a true increase in prevalence, studies are required which are methodologically identical and carried out in the same geographical area in a comparable study population but at different points in time. Some such work exists. In a study by Burr *et al.*[10] the prevalence of asthma among children in South Wales had increased from 9.8 % in 1973 to 15.2% in 1988. A similar Australian study by Woolcock[11] reported that the incidence of wheeze had increased from 12% in 1982 to 24% in 1992. An accompanying doubling in airway hyper-responsiveness suggested that this was not simply due to a change in diagnostic trends. Therefore, prevalence appears indeed to be rising.

What then is the reason for the increase in asthma prevalence? A correlation exists with Westernisation which might relate to environmental or life-style factors. Two studies from Africa suggest an increased prevalence of the condition with a more Westernised lifestyle, a reduced frequency in poorer urban areas, and a rarity of incidence in rural Africa.

Host factors may be important in the aetiology of the condition and modern living may result in inherited predisposition to atopy. Maternal nutrition or other dietary factors could be affecting susceptibility at population level. Smoking is increasing among women in the UK, and maternal smoking correlates with a higher incidence of child wheeziness. First borns have a higher likelihood of

developing asthma than later siblings. Traditionally the explanation for this was that as they are less likely to be exposed to common childhood illnesses, this might predispose them to becoming atopic. Demographic factors may be at play with smaller families resulting in a trend towards increased asthma prevalence.

Environmental factors associated with modern living could be relevant. Much of our time is spent indoors where factors such as ventilation, central heating, indoor pollutants or allergen load may be playing a role. Other dietary or lifestyle factors might be important, as might more general environmental influences such as pollution. The teasing out and establishing of causal relationships from among this tangled web of associations is going to be difficult. Interventional studies are required but these are likely to be difficult to plan and expensive to run.

PREVENTION AND MANAGEMENT

The primary prevention of asthma is a major challenge for the future. It may prove possible to identify the 'at risk' infant and to determine whether there is a critical window during which intervention might prevent the development of subsequent sensitisation.

Our present main challenge is secondary prevention, i.e. optimising control of existing disease. The BTS asthma guidelines[12] were published in 1995 and set out management protocols; these guidelines require to be reviewed and rewritten in due course.

One area of change in practice is at Step 3 of the asthma guidelines. Currently it is suggested that a patient poorly controlled on low-dose inhaled steroid be changed to high-dose inhaled steroid. It may, however, be more beneficial to continue the low-dose inhaled steroid and add additional therapy such as long-acting ßeta2 agonist or Theophylline. In 1994 Greening *et al.*[13] found that the addition of Salmeterol to low-dose inhaled steroid resulted in better peak flows and symptom control than increasing to high-dose inhaled steroid. Equally good evidence exists for the addition of inhaled Formoterol or oral Bambuterol. A similar but slightly less marked effect is shown with low-dose inhaled steroids plus Theophylline.

The biggest transformation in the lives of asthmatics in the last ten to twenty years has been the advent of inhaled steroid. However there is a trend to use rather higher doses than are always required. It is essential that low-dose inhaled steroids are still used, but there is a need for an increased awareness of alternative drugs and for regular review of inhaled medication with stepping down of treatment where appropriate.

In general terms inhaled steroid therapy is safe with little systemic absorption, but it is not entirely without risk. High-dose inhaled steroids can affect bone growth in children, and there is the possibility of inhaled steroids being an independent risk factor for the development of posterior subcapular cataract.

One therapeutic advance which can be looked forward to is the increased use of multiple drug regimens. The WHO guidelines suggest that optimal blood pressure control requires 'two drugs in combination, possibly three' and that 'clinicians need to use available drugs intelligently rather than sticking to one individual category'. A similar scenario is arising in asthma management. However, disadvantages exist in the use of multiple drugs. It makes the task of educating patients about their therapy harder, and asking patients to use several drugs will reduce compliance. If patients were to selectively stop using inhaled steroid, this would clearly be detrimental to their control.

In ensuring patient compliance, combination therapy may have a role. A combined inhaled steroid and long-acting ßeta2 agonist preparation is already available, and future innovations such as oral therapy with combined leukotriene modifier and long-acting ßeta2 agonist can be foreseen. Such therapy is likely to be preferred by patients and may benefit compliance but with some loss of flexibility. For example it is not easily possible to increase inhaled steroid therapy during a period of worsening control unless an additional back-up steroid inhaler is also available. There may be an increasing role for dry powder devices as their cost continues to decline. Hand-held nebulisers or similar devices may also become more accessible as technology improves.

If asthma guidelines were to be rewritten today, we would be hampered by a lack of information from comparative trials of multiple drug regimens. More research is needed. The long-term effects of therapeutic intervention in maintaining health and lung function should be studied rather than just focussing purely on short-term abolition of symptoms. Dr Partridge foresaw a possible role for pharmacogenetics in identifying patient sub-groups amenable to particular forms of therapy which might allow targeting of specific drugs to specific individuals.

IMPROVING THE DOCTOR/PATIENT RELATIONSHIP

In asthma management the doctor/patient relationship is of fundamental importance. Doctor/patient communication must be maintained no matter how much the workload is shared with nursing or paramedical staff. The advantages are better diagnoses, better management decisions and a more professionally rewarding work experience. The patient also benefits from better understanding, better recall, reduction of uncertainty and anxiety, improved overall satisfaction and improved compliance. Hopefully, this will all result in improved traditional health outcomes.

Our communication with patients leaves much to be desired. Only one in five asthmatics diagnosed in the UK feel they have had a good discussion with their doctor; just under 10% felt they had been given sufficient information regarding their condition. Approximately one third of UK patients are given inhalers without advice as to how to use them and only 27% are given any specific written advice regarding their treatment despite three to four good controlled trials which show that the simple expedient of writing out details of medication improves outcome. In one series of taped doctor/patient communications, doctors did not specify how much treatment to take in 38% of cases, and did not specify how long the treatment should last in 50% of cases. In this study, as in so many others, it is clear that within ten minutes of the end of a consultation the patient has forgotten 50% of what was said. Many patients may not fully believe that they have asthma, or may feel angered or stigmatised by the diagnosis. Communication may be done jointly by doctors, nurses and other paramedical staff with a role for written or audiovisual information. The nature of the doctor/patient interface has changed and the doctor is now only one source of information among many others. The patient is no longer a passive recipient but wishes to take more active

responsibility for his/her own health.

National Asthma Campaign surveys have established that patients with asthma dislike the symptoms of the condition, and the unpredictable nature of attacks and the resultant sense of 'loss of control'. Patients value being able to enter a genuine partnership with their doctor which allows the opportunity to discuss their condition and to become more actively involved in management decisions, helping them regain a sense of control over their illness. Our aim should be guided self-management, and our performance should be compared with that of our competitors. National Asthma Campaign surveys show that nearly half of those surveyed had used complementary therapies. Few patients report great benefits but more than two thirds state they would consider using complementary therapies in the future. Studies in this area have found that the patients feel they have a more equal relationship with complementary practitioners than with their own doctor. They feel it is easier to talk to a complementary practitioner. As a profession we have to continue to make efforts to improve this area of our practice.

Self-management is not only what patients desire, but a recent Cochrane Airways Group meta-analysis of 22 good studies in this area shows a consistent improvement in outcome measures with self-management and education when compared with routine care, particularly where a written self-management plan had been issued.

KEY POINTS

- Asthma prevalence in the developed world is increasing.
- Patients inadequately controlled on low dose inhaled steroid should receive additional long acting β_2 agonist therapy.
- Many patients require multiple drug therapy to optimise asthma control.
- Patients deserve effective doctor/patient communication. There is a clear role for guided patient self-management.
- Primary prevention of asthma is a goal for further research.

LECTURE 6

Professor Peter Calverley, University Department of Respiratory Medicine, Aintree Trust, University of Liverpool

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is a diagnosis which can be established using objective spirometry-based criteria. COPD is defined as a chronic slowly progressive disorder with FEV^1 <80% predicted and FEV^1/FVC ratio <70%. These values should not change markedly over several months of observation. Establishing a positive diagnosis is essential; some outreach spirometry studies of patients labelled as having COPD reveal that in many cases the diagnosis is incorrect. An early diagnosis enables an appropriate therapeutic plan to be established and ensures alternative diagnoses are not missed. While much of the impairment in lung function in COPD is fixed, therapeutic nihilism should be avoided.

PREVALENCE, COSTS AND SMOKING

In 1990 approximately 2.4 million deaths were attributed to COPD worldwide, currently the sixth most common cause of death. A steady increase in prevalence is likely with COPD becoming the third commonest cause of death globally by the year 2020, largely attributable to the impact of cigarette smoking on Asian Pacific countries.

In the UK, prevalence is relatively stable, but its impact in terms of human suffering and cost is vast, with an estimated total loss to the UK economy of £1,500 million per year, £600 million per year being spent on Social Security Benefits. Average length of hospital stay is ten days (compared to 3.6 days for asthma) with NHS costs per patient per year estimated at £781 (compared to £233 for asthma). Drug prescribing costs are estimated at £124 per patient. This results in an overall bill to the NHS of £174 million per year for managing acute exacerbations of COPD.

Normally FEV^1 declines in non-smokers at an average rate of 30 mls per year. Approximately 20% of cigarette smokers are particularly susceptible to COPD and in them FEV^1 declines at around 70 mls per year. Individuals who are malnourished at an early age or who have an additional background respiratory pathology start at a lower level of FEV^1 and are particularly susceptible to the development of disabling COPD early in life. If an individual stops smoking the rate of decline of their lung function returns to normal. The benefits of identifying individuals with mild COPD and encouraging them to abstain from cigarettes is, therefore, huge. Even ex-smokers may still develop symptomatic disease in later life and, with an increasingly elderly population, the incidence of COPD is likely to rise.

PATHOGENESIS

In approximately 96% of cases COPD results from previous cigarette smoking. Cigarette smoke is a complex mixture of toxic particulates and hydrocarbons which penetrates the periphery of the lung and damages small airways and alveoli. As a consequence neutrophil polymorphs migrate into the area releasing elastases and other enzymes which destroy elastic fibres and collagen in the alveolar wall, resulting in structural damage. Normally the lungs are defended by endogenous antiproteases the most important of which is alpha1 antitrypsin. Oxidants are biologically important molecules which cause inactivation of endogenous antiproteases and act to disable the protective screen defending the lung, in addition to having other more direct damaging effects on the airways.

Recent animal research carried out by Dr Shapiro in Washington used a mouse model. Exposing normal mice for six months on a smoking machine resulted in marked centrilobular emphysema. Interestingly, other mice deficient in mouse macrophage elastase when subjected to similar environmental conditions did not develop these changes. Macrophage elastase appears to be important in the aetiology of this condition in this particular animal model.

COPD is an inflammatory illness and the worse the objective COPD present, the greater the associated pulmonary inflammation. The inflammation is ongoing and active, and the more inflammation that is present, the greater the structural alveolar damage. Even in burnt out endstage disease, many intrapulmonary inflammatory cells and an intense inflammatory bronchiolitis are typical findings. The more severe the objective disease, the greater the number

of neutrophil polymorphs present. The whole process may not be entirely neutrophil-driven and other inflammatory cells are likely to be involved. Macrophages are also abundant in lung tissue, and the interplay between these cells and neutrophils may be important. An association was also shown between the number of CD8 suppressor cells in the sub-epithelium and the degree of impairment of FEV^1. Interesting work is also emerging on the possible role for eosinophils in COPD. The presence of increased numbers of eosinophils in induced sputum may be a predictor of steroid reversability.

THE USE OF INHALED STEROID

Prevention of further decline in lung function in established COPD can be achieved by stopping smoking. Approximately one in five patients shows evidence of significant response to oral steroids and these tend to be given inhaled steroid to maximise lung function. The possible role of inhaled steroid in non-steroid responders is being studied in the hope that the anti-inflammatory effect of these drugs may slow decline in lung function.

The Euroscop[14] and Copenhagen Lung Studies both looked at mild COPD and showed that inhaled Budesonide taken over three years did not affect the rate of decline in FEV^1. Similarly, the recently published Isolde study[15] where patients had moderate to severe COPD (mean FEV^1 1.4) again revealed no change in the rate of decline of FEV^1. While the two earlier studies suggested no beneficial role from inhaled steroid in non-steroid responders, the later Isolde study suggested a reduction in the rate of exacerbations requiring oral steroids in more severe disease with an associated slowing of the rate of decline in patients' self-perceived health status. There may therefore be a role for inhaled steroid therapy in the treatment of patients with moderate to severe COPD even if there is no steroid reversibility demonstrated on formal testing.

POTENTIAL NEW THERAPEUTIC AGENTS

Tiotropium is a long-acting anticholinergic bronchodilator effective for 36 hours following inhalation, which may give a new spin to the bronchodilator story. Combination therapies such as Budesonide/Formoterol and Fluticasone/Salmeterol are currently undergoing trials in COPD: their role remains to be established. Very little progress has been made on the use of alpha1 antitrypsin in the treatment of COPD. The new Phosphodiesterase (PDE4) inhibitors were described by Professor Calverley as 'up-market Theophyllines for the New Millennium'! Leukotriene B4 antagonists may have a role in reducing severity of COPD exacerbations, but neutrophil elastase inhibitors will be 'the next big thing' as far as modulating inflammation in the airways is concerned.

OTHER THERAPEUTIC OPTIONS

The role of domiciliary oxygen is clearly established for those patients in whom pO2 on air falls to <7.3 kPa, particularly those with associated clinically diagnosed cor pulmonale. It could be argued that identifying milder degrees of hypoxia may also benefit from earlier oxygen therapy. However Gorecka,[16] reporting in 1997, showed no such benefit, and suggested that we should continue to adhere to current guidelines.

Respiratory impairment due to COPD naturally leads on to poorer overall fitness and exercise tolerance with resultant social isolation and depression. Respiratory rehabilitation programmes appear to interrupt this cycle, and recent meta-analysis has revealed an overall improvement in both exercise capacity and subjective sensation of breathlessness. Improvements in six minute walk, in exercise tolerance and in quality of life have been reported in patients with severe COPD (FEV^1 30-35% predicted) after respiratory rehabilitation. The amount of benefit is three times the order of magnitude achieved by bronchodilator therapy. There is concern as to whether these benefits from respiratory rehabilitation are short-term or sustained. It has been found however that both walking distance and patient-perceived health status were improved after respiratory rehabilitation with persistent benefit in patient wellbeing at the end of one year.

Traditionally peripheral muscle weakness in COPD is thought to be due to reduced exercise capacity and subsequent disuse atrophy. In addition, oral steroids have a detrimental side-effect on skeletal muscles. However, global muscle wasting is now shown to be associated with COPD and changes in muscle fibre type occur. Severe forms of COPD seem to have some systemic effect on skeletal muscle. In 1997 Decramer[17] reported that quadriceps muscle strength is likely to be much lower in high consumers of healthcare than in low consumers and, surprisingly, this seems to be a better indicator of patients' reliance on healthcare support than simple spirometry. Body fat-free mass is reduced in 25% of patients with advanced COPD, the reason for which is also unclear. Further research is clearly required to review the effect of nutrition on prognosis in COPD.

The future management of COPD over the next ten years lies in the saying 'first know your enemy, know the problem, grade it and then take action'.

KEY POINTS

- COPD should be objectively diagnosed on spirometry by demonstrating a persistent obstructive ventilatory defect with FEV^1 <80% and FEV/FVC <70%.
- COPD is usually the result of cigarette smoking. Further decline in FEV^1 can be reduced by stopping smoking.
- Inhaled steroid does not slow the rate of decline in FEV^1. Inhaled steroid may however have a role in moderate to severe COPD even in the absence of steroid reversibility.
- Pulmonary rehabilitation is well established as a useful form of therapy.

LECTURE 7

Dr Martin Muers, The General Infirmary, Leeds

LUNG CANCER

Lung cancer is the commonest form of malignant disease in the Western world. It should not be thought of as solely a problem of developed countries. Epidemiologically, the single most important factor which determines the future incidence of lung cancer 30 years hence is the smoking habit of the population.

PREVALENCE

While tobacco consumption in the UK has fallen, it has risen in Asia and the Third World, and an increasing lung cancer burden is predicted in these regions, particularly in China.

In the UK the overall impact of the disease is likely to remain approximately stable, but recently a particularly sharp rise in lung cancer incidence rates in the elderly population has been seen. Rates appear to have peaked in males but continues to rise exponentially in females over 70. It is predicted that there will be a rise in the age of presentation from its current mean of 67 to approximately 70 years of age over the next decade. This was reinforced by Yorkshire data suggesting that in 1979 20% of lung cancer patients were aged over 75 at presentation, this proportion having risen to 40% by 1999. At present the male:female sex ratio approximates to 2:1 but this balance is likely to shift significantly with increasing prevalence of the disease among women.

Lung cancer prevalence correlates with areas of urban poverty and social deprivation and, since the middle classes find it significantly easier to give up smoking than lower classes, it is suggested this social gradient is likely to accentuate further. Some change in the histological balance of tumours is expected with increased prevalence of adenocarcinoma and possibly small cell carcinoma. The reasons for this are unclear but may relate to alterations in smoking habit since the 1960s with increased use of filters and low tar cigarettes.

DISEASE PREVENTION

Lung cancer has to be tackled at source by reducing the prevalence of cigarette smoking. The BTS guidelines on smoking cessation are clearly formulated and no one should be in any doubt about the effectiveness of this 'form of therapy'. Smoking cessation clinics which use nicotine replacement therapy have been shown to have achieved quit rates of around 12%.[18] Additionally, two recent good quality studies have suggested a possible further doubling of success rates with the use of the antidepressant drug, Bupropion.[19,20] If these results can be replicated, smoking cessation rates approaching 25-30% might be conceivable.[21] The cost effectiveness of such programmes are no longer in doubt, and the increasing public and political pressure for change should lead to further expansion of this service. It is expected that in ten years' time smoking cessation clinics would be standard in all respiratory centres and most larger GP surgeries.

EARLY DIAGNOSIS OF LUNG CANCER

Lung cancer often comes to clinical attention at a relatively late stage at which time the presence of locally advanced disease or metastases make curative treatment difficult or impossible. Clearly it is important to consider ways of establishing the diagnosis earlier but there is now ample worldwide evidence that screening by sputum cytology or conventional radiology seem to have little impact on mortality. A study from Japan published in 1998 reported on 4,000 patients screened by CT and MMR (miniradiograph). Spiral CT scanning identified 18 out of 19 cancers and a total of 217 other abnormalities were identified which required further investigative procedures such as bronchoscopy or high resolution CT scanning. The low positive predictive value of this test thus raised concerns about increases in workload and unnecessary patient anxiety, and in this particular study there was a suspiciously high rate of lung cancer found in non-smokers. In view of these factors, there is a clear need for a randomised controlled trial to see whether this form of screening could be valuable.

Another potential way of screening for lung cancer might be to identify underlying genetic predisposition. Can it be established why only 15% of cigarette smokers go on to develop lung cancer while the other 85% do not? Studies so far have not been encouraging. A US twin study reporting on the prevalence of lung cancer in 15,924 pairs of twins compared prevalence between monozygotic and dizygotic twins. The hypothesis was that if the proband monozygotic twin developed lung cancer, then the sibling must be at increased risk if a significant genetic predisposition exists. This study revealed no evidence to support this hypothesis - suggesting that, for the time being at least, smoking-associated lung cancer should be attributed to the cigarette smoking and not to a genetic predisposition.

Another way of screening for early lung cancer would be to try and identify pre or early malignant change in the bronchial epithelium. For instance, would it be possible to look for early malignant change in exfoliated cells on sputum examination? Development of malignancy probably involves a sequence of between ten and twenty genetic mutations before a cell becomes neoplastic. Some of these steps result in the change becoming unidirectional and it would be useful if any of these genetic changes could be picked up and used to predict subsequent development of lung cancer. This is not possible at present since we are not sure which of the many identifiable genetic abnormalities lead on to the development of lung cancer and which might be able to be repaired. In addition, ex-smokers often do not produce sputum and could not be screened by this method. Furthermore, this form of screening seems suited to identifying large central tumours (which are less amenable to curative therapy) rather than the small peripheral and potentially curable tumours. There are also grave doubts as to the cost-effectiveness of this mode of screening. Such an approach will not be feasible within the next ten years.

ORGANISATION OF CANCER SERVICES

The majority of lung cancers should be picked up by alert GPs who arrange chest X-ray and subsequently refer to hospital respiratory specialists. Data from 1998 concerning 400 carefully stratified cases from Dr Muer's own practice suggest that only around 50% of patients were referred from general practice while the other 50% presented to hospital through other routes, many thus not being referred to a respiratory physician in the first instance. Dr Muer's local data suggested that the proportion of these patients receiving treatment was low. Of his sample of 400 cases, 7.8% received surgery, 1.1% radical radiotherapy, 12.3% chemotherapy, 29.9% palliative radiotherapy and only 50% overall received any cancer therapy whatever. An age-related gradient of care with older patients getting far less active management is now evident. In a study of 8,000 patients in Yorkshire, in those over 75 only 3% received surgery, as compared with 22% of those aged under 50. Similarly, in those aged over 75, only 20% received radiotherapy as opposed to 55% of those aged less than 50. Data from Southend suggests that this may not necessarily be due to co-morbidity in the older population.

Another factor causing significant district variations in the management of lung cancer is the practice of individual

clinics. Data from the Yorkshire Regional Cancer Registry gathered over an eight year period covering 20,000 patients has suggested an overall regional rate of surgery for non-small cell lung cancer of 11% but with significant district variation of between 8-27%. Similarly, radiotherapy for non-small cell lung cancer has a regional average of 36% with district variation from 30-53%. Chemotherapy for small cell lung cancer has a regional average of 41% with district rates of 39-73%. This variation in treatment from district to district does not seem to relate to socioeconomic grouping. In addition, 15% of patients are not referred to a respiratory physician, while even cancer specialists may not always manage patients optimally. Patients may not always have CT scanning prior to surgery, and the operation rate for lung cancer is low in the UK compared to Europe and the USA. Radical radiotherapy has a five year survival approaching 30%, yet very few patients seem to receive this. Chemotherapy is also not being used universally.

HOW CAN CANCER SERVICES BE IMPROVED?

It is thus vital to provide a more efficient and equitable level of cancer care to our patients, with an already increasing pressure for this both from government and from a better informed public. How then are individual clinicians to improve their services? The days of the single-handed respiratory physician in a district general hospital are over and a minimum of two respiratory physicians per district general hospital should be the norm, with at least one individual having a named responsibility for the provision of dedicated lung cancer services. Back-up staff such as lung cancer specialist nurses are also becoming essential. The delivery of focussed care will increase as treatment protocols become standardised.

NEW TECHNOLOGY

Pre-bronchoscopy CT scanning is likely to become more standard with resultant reduction in the number of bronchoscopies required. Fluorescent bronchoscopy probably has a less certain future. It may have a role as a supraregional service in the assessment of carcinoma *in situ*, or in the investigation of patients with recurrent haemoptysis not diagnosed by other means. It is not likely to play a major role in early diagnosis for the majority of patients. Positron emission tomography (PET) scanning can identify cancer cells due to their active glucose metabolism and can be useful in picking up mediastinal and distant metastases pre-operatively, thus selecting out patients inappropriate for surgical resection. While this may tend to reduce the number of operations carried out, there is also likely to be increasing pressure to operate on patients with borderline lung function using less invasive techniques, such as video-assisted thorascopic surgery.

Chart radiotherapy is a regimen whereby radical treatment is completed in two weeks rather than the conventional method of once daily treatment over six weeks. This clearly has benefits for widely scattered populations, such as in remote parts of Scotland, and appears to have an excellent outcome in comparison to conventional treatment with a probable 50% increase in five year survival. This may become the established policy in all oncology centres. Benefits have also been shown for computer-assisted techniques which improve localisation of the radiotherapy administered.

Photodynamic treatment is a technique being assessed in Japan where patients are fed a dye which can be cytotoxic when a light is shone upon it and thus allows a form of endobronchial therapy. This is unlikely to become established for early lesions as it seems best that these are still resected where possible. Bronchoscopy is likely to have an increasing role in surveillance following other forms of therapy and is likely to become more sophisticated with endobronchial treatment modalities such as stenting, laser or bracheotherapy.

Chemotherapy is being assessed in several studies, the most important of which is the UK Big Lung Trial. It seems likely that chemotherapy will have a role to play in non-small cell lung cancer for the majority of patients although difficult questions regarding cost-effectiveness have to be answered.

MESOTHELIOMA

The incidence of mesothelioma is expected to increase dramatically over the next 20 years. Currently there are approximately 1,000 cases of mesothelioma per annum in the UK which will rise to approximately 15,000 cases per annum by 2010 to 2020. This equates to one case of mesothelioma for every ten cases of lung cancer. Clearly there is a need for further research aimed at improving the management of this condition.

KEY POINTS

- Smoking cessation clinics are cost effective and are likely to have an increasing role in primary prevention of lung cancer.
- Further research into methods of screening for early lung cancer is required.
- Chart radiotherapy should be established in all oncology centres.
- There is likely to be a role for chemotherapy in the majority of patients with non small cell lung carcinoma.
- A pressing need exists to redress geographical and age-related inequities in lung cancer care.

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