LESSONS FROM RESPIRATORY MEDICINE 2000*

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RESPIRATORY INFECTIONS

Streptococcus pneumoniae (*S. pneumoniae*) remains the most frequently identified pathogen in patients with community acquired pneumonia in the UK, and is probably the causative organism in most of the 40–50% of patients in whom no pathogen can be found (M. Woodhead, Manchester†). Serological evidence of infection by the recently identified *Chlamydia pneumoniae* (*C. pneumoniae*) is found in up to 20% of patients hospitalised with pneumonia, but several observations suggest that it may not be the causative organism. Other bacterial pathogens (particularly *S. pneumoniae*) are also frequently identified, and patients usually improve following treatment with a ß-lactam drug, to which *C. pneumoniae* is resistant. Moreover, *C. pneumoniae* can frequently be found in respiratory secretions well after the patient has recovered.

Results from three studies that have compared the prevalence of pathogens in different age groups suggest that infection with Mycoplasma and Legionella are rare in elderly patients suffering from pneumonia in the UK. The clear implication for treatment regimens is that a single agent ß-lactam drug (such as amoxycillin) may be quite adequate in the elderly. The new British Thoracic Society guidelines for community acquired pneumonia will emphasise the importance of severity assessment. In addition to the previously validated measurements of respiratory rate, diastolic blood pressure and blood urea, it is proposed that the presence or absence of mental confusion should be added to improve accuracy of the simple algorithm of severity assessment. The new guidelines will continue to recommend the use of an oral ß-lactam drug together with a macrolide for the initial treatment of most patients hospitalised with community acquired pneumonia.

Antibiotic resistant pneumonia has important economic implications for the treatment of community acquired pneumonia (D. Nathwani, Dundee). Drug resistance contributes to increased treatment cost for the index case, and also for secondary cases resulting from spread of bacterial infection. Such economic implications have to be considered in the control of an outbreak. Awareness of drug resistance may influence subsequent empirical antibiotic choice for 'blind' treatment of pneumonia. *Streptococcus pneumoniae* is the commonest identified organism causing community acquired pneumonia, but fortunately only about 5% of pneumococcal isolates in the UK currently express the abnormal penicillin-binding proteins that are responsible for penicillin resistance. Ampicillin and amoxycillin can therefore be still considered as first line agents for the treatment of most cases of community acquired pneumonia. With the passage of time, resistance to penicillin and to macrolides is steadily increasing.

Whether *in vitro* drug resistance necessarily leads to treatment failure is another matter. A recent study showed that treatment failure was only likely with high level resistance, as determined by a minimum inhibitory concentration >2 mcg/ml in the laboratory.[1] A fluoroquinolone (such as ciprofloxacin) would be a reasonable alternative drug for a sick patient when penicillin resistance is suspected. Overuse of quinolones has led to the emergence of resistant strains which are likely to become more common.

Drug resistance of *Mycobacterium tuberculosis* is a major global health problem. For example, of the one million detainees in Russian prisons, about 10% have active tuberculosis, and many of these strains will be resistant to first line anti-tuberculous drugs (R. Coker, London). Overcrowding, homelessness and HIV infection are recognised risk factors. These problems were highlighted in New York City in 1990, which had the dubious reputation of accounting for 60% of all US cases of multiple drug resistant tuberculosis (MDRTB). It is well recognised that MDRTB is a man-made phenomenon, caused by inadequate treatment of the disease with too few drugs. The response to MDRTB in New York was to fund directly observed treatment (DOT) to increase treatment completion rate, which had been as low as 11% in Harlem Hospital. Law changes and the threat of detention for compliance failure have been considered to reduce the incidence of MDRTB in America and Europe.

A thoracic empyema occurs when an exudative pleural effusion following pneumonia becomes invaded by bacteria (C. Davies, Reading). Reduced fibrinolytic activity in the pleural space may contribute to the development of septations, lactic acid lowers pH and release of fibroblast growth factors leads to organisation and scarring, resulting eventually in impairment and restriction of lung function. Some 50,000 people are hospitalised each year in the UK because of pneumonia, and in one study 44% of these cases were complicated by pleural effusions. Although only 10% of these were true pleural infections (the remainder being 'reactive' effusions), this equates to 2,500 cases of empyema per year. In the 1996 British Thoracic Society empyema series of 119 patients, 44% required surgery to try to improve outcome. The overall mortality rate was 18%, principally due to comorbid disease rather than the empyema *per se*. If the patient was deemed unfit for surgery, mortality may be as high as 58%.[2] The pathogenic organisms were often anaerobes, with *S. pneumoniae* isolated in only 10% of cases. Although conservative management of empyema has been advocated,

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† *Names in brackets indicate speakers involved in the Symposium*

many physicians would opt to insert a chest drain in the presence of frank pus, organisms identified on direct microscopy, fluid pH <7·2 or multiple septations on ultrasound scanning. Traditionally, large bore drains have been used, but small drains placed under radiological guidance may be equally effective.[3] Anecdotal evidence suggests that instillation of intrapleural thrombolytic agents (such as streptokinase) may reduce the size of the pleural collection without any detectable effect on blood coagulation.[4] A large randomised controlled trial (the multicentre intrapleural streptokinase trial (MIST)), is still recruiting patients.

LUNG TRANSPLANTATION

Lung transplantation is performed for a variety of lung diseases, and although operative mortality is small, most deaths occuring in the first year following transplant are due to chronic rejection, manifested as obliterative bronchiolitis (J. Wallwork, Cambridge). This is defined pathologically as obliterative lesions of both the airways and the vasculature. Frequent early rejection and positive cytomegalovirus serology have been identified as risk factors for obliterative bronchiolitis. This is one of the reasons for the research effort into xenotransplantation, using genetically modified pig organs that express altered cell surface proteins to reduce the risk of rejection. Many experts believe that xenotransplantation represents the future of lung transplantation, but this is still a long way off.

CANCER

E. Neville (Portsmouth) and A. Price (Edinburgh) debated how best to manage patients with malignant mesothelioma. Both speakers highlighted the results of Sugarbaker and colleagues[5] who subjected patients to trimodality treatment with radical surgery, radiotherapy and chemotherapy. The patients were selected with stage I disease and good performance status, who in practice make up only one to three per cent of the typical patients seen with this condition. Even for these patients, median survival was only 19 months, and trimodality treatment was associated with four per cent mortality, 25% major morbidity and 41% minor morbidity. Both speakers agreed that such radical treatment was not indicated for the vast majority of patients with mesothelioma. There was consensus on the role of chemical pleurodesis for dyspnoea caused by the pleural effusion, and radiotherapy for chest wall pain. Cordotomy is a little used procedure which may be very effective for controlling chest wall pain.[6] Although much touted by some, local radiotherapy is probably of limited value for needle track invasion (seeding of tumour to the external chest wall following pleural biopsy or tube drainage).[7] Although single agent chemotherapy is of unproven effectiveness in mesothelioma, combined treatment with regimes including newer drugs (such as gemcitabine and vinorelbine) may give both symptomatic benefit and objective response; there are as yet no data from phase III trials. In a depressing conclusion, the audience vote after the debate revealed that 87% were not optimistic about improving the prognosis of mesothelioma in the next decade.

It is a depressing fact that the poor prognosis from lung cancer has changed little over recent decades (F. Moss, Middlesex). The principal prognostic factors in order of importance are: age; stage of disease; histological type; and country of residence. It should be emphasised that much more complete and inclusive cancer registration in the UK, including older and frailer patients, may account for the apparent poor prognosis figures in the UK compared with other European countries. It should be borne in mind, however, that Sweden, for example, has significantly more doctors, nurses, and other health employees per 1,000 population than the UK. It was suggested that involvement in clinical trials will be good for the participating patients regardless of randomised treatment group, on account of the information given, informed choice and access to named help.

Whether palliative chemotherapy is given for common cancers such as non-small cell lung cancer (NSCLC) is decided by weighing up the risks of benefit and toxicity for each patient (M. Cullen, Birmingham). Newer regimens with better chemotherapy drugs combined with modern antiemetics (such as ondansetron and other $5HT_3$ antagonists) are preferable, but demonstrable survival benefit is still small. However, quality of life (e.g. as assessed by the SS14 score) may be better with modern regimens (e.g. single agent gemcitabine), even in the absence of survival benefit.[8]

In contrast to NSCLC, small cell lung cancer (SCLC) is particularly sensitive to anti neoplastic drugs, and chemotherapy is the treatment of choice. Karnofsky reported objective improvement in bronchial carcinoma with nitrogen mustard treatment as early as 1948 (H. Hansen, Copenhagen). Currently, the median survival for SCLC is only six to 12 weeks from diagnosis without treatment, compared with ten to 16 months (depending on the extent of disease) with standard chemotherapy regimens (such as cisplatin plus etoposide). Overall, three to five per cent five year survival rates have been quoted, although many physicians would regard these figures as optimistic. Recent studies have suggested a survival advantage for more intensive chemotherapy regimens, such as doxorubicin, cyclophosphamide and etoposide given every two weeks (rather than every three weeks as is standard). Better response rates are expected with regimens using more agents or newer agents.[9]

Surgical resection offers the best chance of cure for stage I or II NSCLC (small primary tumour with or without local hilar lymph node involvement). Unfortunately, subsequent tumour recurrence is a common problem. Since only about a quarter of recurrences occur at the regional site alone, there were high hopes that adjuvant chemotherapy would lead to improved survival. Initial optimism was tempered when trials with alkylating agents given post-operatively showed that survival was worse rather than better, although the same results may not hold true for more modern drug regimens. Studies are ongoing, but there is currently no convincing evidence to support adjuvant chemotherapy following surgical resection for stage I or II disease. In stage IIIA NSCLC (with ipsilateral mediastinal nodes involved) three small randomised controlled trials have shown a survival advantage for neoadjuvant chemotherapy (given before surgery to shrink or 'downstage' the cancer).[10-12]

Preliminary evidence summarised at this meeting suggesting that new treatment regimens may improve survival and quality of life is heartening, especially since the five year survival rate for lung cancer has not changed

over the last decade. Such optimism should, however, be balanced by an appreciation that lung cancer is largely a preventable disease.

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