Multidrug resistant tuberculosis

We read with interest the report by White and Moore-Gillon1 on the resource implications of multidrug resistant tuberculosis (MDR-TB) in the UK. We studied the outcome of 44 HIV negative patients with MDR-TB admitted to two tertiary care tuberculosis units in the Netherlands between 1985 and 1998.2 Most (38 patients) had pulmonary tuberculosis and 6 patients had extrapulmonary disease.2

In contrast, only 43 cases of MDR-TB were identified from a surveillance study of 1993 and 1997. In that study, 0.6% of the bacilli were MDR.2 Between 1993 and 1997, only 43 cases of MDR-TB were identified, of which 28% (2.8 patients per month) were MDR.2

Infectious patients have been successfully treated in the Netherlands.2 Treatment of patients with the combination of antituberculosis drugs for a mean period of 608 days.2 We estimated the cost of treatment per patient to be £US60 000 which included admission fee, costs for outpatient visits, and the cost of drug provision. Although we did not include cost of toxicology monitoring and additional procedures, our costs compare favourably with those of White et al (mean £US60 000) and Mahmoudi (mean £US180 000).2

In the Netherlands the number of patients with tuberculosis resistant to any antituberculous drug is limited to 11%, and only 0.6% of the bacilli are MDR.2 Between 1993 and 1997 only 43 cases of MDR-TB were identified, of which 28% had received previous treatment for tuberculosis.2

This suggests that transmission of MDR-TB is still rare but inadequate treatment contributes to the problem in the Netherlands.2 In poor resource countries, directly observed short course chemotherapy of tuberculosis is generally recommended to prevent the occurrence of MDR-TB.2 We feel that new rapid molecular methods for detecting resistance should be developed to limit the period of contagiousness (nosocomial and community) transmission of MDR bacilli and thus prevent the emergence of MDR-TB.2 Such tests should then be made available to poor resource countries at an affordable price.

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Cost of physiotherapy in CF

Increasing survival is associated with increasing numbers of adults with cystic fibrosis (CF). It is recognised that management at specialist CF units is associated with improved health outcomes.1 Assessment of the allocation of staff and resources to adults with CF and accurate costs of these services are essential to evaluate the cost effectiveness of the existing CF services and prediction of future requirements. Global costs of care for young people with CF have been estimated, but studies of the cost of providing physiotherapy for a CF service are scarce.2,3

The cost and utilisation of providing a physiotherapy service (with two admissions each) was determined from February to June 1999 (late summer, autumn and early winter). Using staff designation (pay level), time of physiotherapy (5 minute unit allotments), and after hours availability, comparison was made with actual funding for the service.

At the time of the study the Adult CF Unit at the Prince Charles Hospital in Brisbane provided clinical care for 120 adults with CF from Queensland, New South Wales, and patients travelling up to 1800 km. Despite an active home intravenous antibiotic programme, many patients require admission for treatment of pulmonary exacerbations. Physiotherapy management included respiratory therapy, education, and exercise and was available to all inpatients with CF on a 24 hour basis when required. Outpatient and domiciliary physiotherapy service provision was excluded by the study.

During the 5 month study period (150 days) there were 102 inpatient admissions in 58 patients (mean length of stay 12.1 days). Two patients with two admissions each were inpatients for a total of 116 and 129 days, respectively, and two patients died during the study. In 5 months 1498 hours of physiotherapy were provided at a cost of £3 700 ($AUD33 000.00) per patient per day. This involved a mean of 9.9 hours of physiotherapy per day. This cost exceeded funding for the service by 28% ($630/month). The total time of physiotherapy varied from 233 to 401 hours per month. The majority of the service was provided during normal working hours (72.9%). During penalty wage rates for after hours work, only 58.5% of the total cost was provided during normal working hours. The weekend and public holiday physiotherapy used 22.8% and 3.3% of the time but accounted for 33.6% and 6.8% of cost, respectively. Physiotherapy care provided during weekday evenings amounted to 1% of total time and total cost.

This analysis shows that the cost of inpatient physiotherapy in a tertiary referral service is $52 (AUD$253) per day or £12 per patient per day. Provision of a service outside normal working hours accounts for a significant proportion of the cost of this service. Regular analysis of time utilisation is required to determine staffing levels and funding are available to meet the challenge of an increasing population of adults with CF.

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The study by Harrison and colleagues suggests that inhaled fluticasone in a dose of 1500 µg/day can cause pituitary suppression as measured by urinary total cortisol metabolites (TCM) in healthy subjects compared with asthmatics, but that budesonide in a dose of 1600 µg/day does not. For fluticasone, the mean difference between healthy and asthmatic TCM after 7 days treatment with fluticasone was significant but the same comparison for budesonide was not. The confidence interval for the mean difference in TCM between the healthy and asthmatic subjects given budesonide was positive but with a p value of 0.2. Is this explained by the omission of a sign?

However, when change from baseline is examined in healthy subjects, both drugs suppress TCM and the difference between them was not significant. If equipotent dosages of fluticasone 1500 µg/day and 1600 µg budesonide/day had been given, would the urinary TCM be significantly different for healthy subjects? This is of practical importance if inhaled corticosteroids are considered for treating patients who do not have asthma. Children with isolated persistent cough, which is not asthma, are often prescribed inhaled corticosteroids. Adrenal crises in patients believed to have asthma who have been prescribed inhaled steroids must be examined carefully.

This paper and others which have reported systemic effects of inhaled steroids in healthy subjects should caution against indiscriminate use of these drugs in patients who do not have asthma.

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AUTHORS’ REPLY

We appreciate the valuable comments by Drs Murray and O’Brien regarding our study on immunocompromised patients. In our study the diagnostic yield of non-invasive methods was 41%.

The good results obtained with these techniques, as well as their availability and relatively low cost, make them very useful in the clinical management of immunocompromised patients. In this sense, HRCT scanning, as Drs Murray and O’Brien point out, has a demonstrated role in the diagnosis of some pulmonary complications, particularly Aspergillus pneumonia, and can be included in the diagnostic strategies of non-invasive diagnostic techniques. Whether or not an HRCT scan might facilitate the early start of antifungal treatment and improve the mortality from Aspergillus pneumonia will need to be evaluated in properly designed studies.

Although non-invasive techniques must be considered as a first step in the clinical management of immunocompromised patients, their use cannot justify any delay in performing a bronchoscopic exploration. In this sense, contrary to the experience reported by Drs Murray and O’Brien, the systematic use of endoscopic techniques allowed a bronchoscopic exploration. In this context, the low diagnostic yield of the 25 bronchoscopies performed in the series by Murray et al and the lack of impact on survival, also reported by other groups, may well be due to the fact that the endoscopic techniques are performed too late in the evolution of the disease when the possibilities of influencing the outcome are very few.

Replacing bronchoscopic techniques by HRCT scanning carries the risk of misdiagnosing polymicrobial lung infectious and non-infectious pulmonary complications in which bronchoalveolar lavage and bronchial aspirates have a known diagnostic role. Remarkably, in 11 of the 15 polymicrobial infections reported in our series, both Aspergillus and/or cytomegalovirus (CMV) were involved. In these cases the use of HRCT scanning instead of bronchoscopy would probably have missed one of the other co-existent pathogens. We therefore do not believe that HRCT scanning of the chest can replace bronchoscopy in the clinical management of immunocompromised patients with pulmonary infiltrates.

Severe bullous emphysema associated with cocaine smoking

Pulmonary emphysema is characterised by permanent enlargement of airspaces distal to the terminal bronchiole accompanied by destruction of alveolar walls. The loss of elastic tissue contained in the interalveolar septa is caused by an imbalance between proteinase and antiproteinase activity, most commonly caused by cigarette smoking. Congenital deficiency of α1-antitrypsin, the most well known antiproteinase, is an important risk factor for the development of premature emphysema. In addition, various other causes have been reported including intravenous drug abuse, particularly Ritalin. More recently, Johnson et al reported four cases of bullous emphysema associated with marijuana smoking. We want to report an additional case of severe premature bullous emphysema in a man with a longstanding history of cocaine smoking. To the best of our knowledge, this relationship has only once been reported in the Spanish medical literature.

A 40 year old man was admitted with progressive dyspnoea, cough, and fever. According to his relatives he had been smoking cocaine (so called “free basing”) for the past 17 years. A reliable history of tobacco smoking could not be obtained because of his respiratory distress and poor level of consciousness. His medical history consisted of recurrent respiratory tract infections. Chest
radiographs and computed tomographic scans showed impressive bilateral bullous emphysema with a large air-fluid collection in the right lung, suggesting pulmonary abscess formation (figs 1, 2, 3). Because of progressive respiratory failure he was intubated and mechanically ventilated. Further treatment consisted of intravenous broad spectrum antibiotics (clindamycin and ceftazidime followed by amoxicillin-clavulanic acid) and chest tube drainage because of ventilator associated pneumothorax. The patient eventually died of treatment resistant respiratory failure as a result of pneumonia in the scarce residual pulmonary tissue. Sputum cultures yielded Enterobacter cloacae and Streptococcus species. HIV infection was excluded serologically. The definitive diagnosis of cocaine induced pulmonary emphysema was established after the concentration of α1-antitrypsin was found to be within the normal range.

Besides congenital α1-antitrypsin deficieny, cocaine smoking should be considered as a possible cause of severe premature bullous emphysema. Abscess formation and rapidly progressive respiratory failure may complicate this condition.

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Side effects of antituberculous treatment

Combined antimycobacterial chemotherapy has been shown to be very effective in the treatment of Mycobacterium tuberculosis hominis (MTH) pulmonary infections with a cure rate of > 95% for short term (6 month) courses. Recently, the WHO initiatives have been launched and are aimed at eradicating pulmonary tuberculosis by intensive adoption of directly observed treatment (DOT) strategies in countries in which the incidence is high.

A new drug formulation has recently been produced which provides the three main first line drugs in the same tablet in a fixed ratio (rifampin (RIF) 120 mg, isoniazid (INH) 50 mg, and pyrazinamide (PZM) 300 mg). This formulation is likely to be extremely useful, particularly in developing countries where it can provide reliable simultaneous administration of all the drugs needed on bi-weekly or tri-weekly DOT programmes. However, it is not intended to substitute any (or all) of the single components in countries where they are already available and marketed.

In a recent WHO report, of all the industrialised European countries, Italy reported the highest prevalence of multidrug resistance among previously treated cases of tuberculosis (33.9%, 95% CI 25.7 to 42.7), with any drug resistance accounting for up to 60.6% of the strains. In addition, there was a high prevalence of resistance in new cases of tuberculosis with 12.3% resistance to any drug. In Italy the distribution and marketing of PZM ceased as a single drug formulation between 15 June 2000 and early 2001. This abrupt policy change temporally introduced a new and interesting challenge to the treatment of MTH, and possibly increased risks of toxicity and decreased treatment efficacy for some patients.

Over the last 2 years we have treated 26 patients with pulmonary tuberculosis using the standard four drug regimens administered as single drugs and have recorded a relatively high rate of hepatotoxicity (35%) compared with what is reported in North American and European analyses (11%). In eight of the nine patients with hepatotoxicity the substitution of INH led to normalisation of liver function. This incidence of side effects approaches the incidence of side effects (26%) reported in a European study of similar design on 519 patients of similar mean age.

In our 26 patients we estimated that, if a fixed dose formulation had been used to maintain the dose of RIF at 10 mg/kg/day, a significantly increased dose of PZM (not correlated to the one that was actually given) would have been administered. Thus, it is reasonable to suggest that the already high rate of toxicity could increase in incidence and severity when PZM is administered daily as a fixed dose formulation. When considered in the context of the unavailability of PZM single drug formulations, two additional considerations are warranted.

Firstly, there is a limited choice of first line regimens which exclude INH for patients with INH-related hepatotoxicity (for example, RIF+STM+EMB but not RIF+PZM+STM). Side effects in hospital treated patients usually lead to withdrawal of one of the basic drugs and replacement by other drugs such as ethambutol or streptomycin. This may lead to more prolonged treatment and to decreased adherence. However, these negative consequences would be considerably enhanced if single drug formulations of PZM are not available since withdrawal of at least two first line drugs would be needed (PZM+INH).

Secondly, the treatment of patients with chronic tuberculosis who are infected with the most frequent INH or RIF resistant MTH (43.3% and 44.9%, respectively) or with multidrug resistant MTH could lead to the drug being acquired from abroad at a high cost, and sometimes to interruptions in the supply with dangerous consequences for the patient’s health. In fact, most tuberculosis units in our area acquired PZM as a single drug formulation from neighbouring countries during the time when it was not available.

Thus, available data do not support the use of fixed dose formulations as the only treatment choice in developed countries. This could be particularly dangerous where there is a high prevalence of multiple drug resistant MTH, including developing countries.


Basic and Clinical Allergy 2002

“Basic and Clinical Allergy 2002” will be held at the National Heart & Lung Institute, Faculty of Medicine, Imperial College, London on 18–22 March 2002. Main topics include: Basic cellular mechanisms and their application in allergic disease; Allergic rhinitis; Indoor allergens; Allergen specific immunotherapy and T cell tolerance; Asthma (aetiology and pathogenesis); Treatment of asthma. CPD/CME approval pending (2001 course maximum 23.5 credits). Further details from the Short Courses Office, Education Centre, Faculty of Medicine, Imperial College, National Heart & Lung Institute, Dovehouse Street, London SW3 6LY, UK. Telephone +44 (0)20 7351 8172. Fax +44 (0)20 7351 8246. Email: shortcourses.nhli@ic.ac.uk; website: www.med.ic.ac.uk/divisions/47a/nts.htm.
Pulmonary infiltrates in non-HIV patients

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