

Drug resistant tuberculosis: problems on the horizon

One aspect of the AIDS pandemic which has provoked considerable media interest and concern is the development and spread of multiple drug resistant tuberculosis particularly, but not exclusively, in the USA. Individuals infected with HIV have increased susceptibility to tuberculosis acquired both de novo¹² and by reactivation of latent infection.³ The emergence of drug resistant organisms seems to have arisen because of poor compliance with antituberculosis therapy, particularly in some subgroups such as intravenous drug users and alcoholics,^{4,6} and by reactivation of disease in immigrants from countries with high rates of both tuberculosis⁵ and drug resistance.^{5,7} Because of the increased susceptibility of HIV infected individuals, nosocomial transmission of tuberculosis can occur in HIV units and has been reported with drug sensitive¹ and multiple drug resistant⁸⁻¹¹ tuberculosis. Such nosocomial transmission has involved not only infection of HIV positive patients but other patients and health care workers who are immunocompetent.¹¹ The organisms in outbreaks of multiple drug resistant tuberculosis⁸⁻¹¹ have been resistant to isoniazid and rifampicin, and sometimes to streptomycin, ethambutol, and other drugs as well. Deaths from such organisms have occurred in HIV positive patients, other patients, doctors, other health care workers, and prison staff.

These deaths have led the Centres for Disease Control (CDC) in Atlanta to make recommendations to try to prevent such nosocomial transmission,¹² a problem which has recently been reviewed.¹³ These measures¹² include early identification of such cases by maintaining high clinical awareness and initiating effective treatment based on clinical and local drug resistance data; measures to prevent spread of infection within the health care setting; and regular surveillance of health care workers and the prompt contact tracing for staff, patients and visitors if untreated or inadequately treated cases are found. The suggested measures for prevention of spread in the health care setting are: isolation in a single room with negative pressure relative to the outside with six air exchanges per hour; the room to be exhausted to the outside; consideration of ultraviolet lamps or particulate filters to supplement ventilation; use of disposable particulate respirators for persons entering the room and during cough inducing procedures. It is recommended that these precautions should continue until there is evidence of reduced infectivity by negative smears in those with suspected or proven drug resistant tuberculosis.

The situation in New York city is now so serious that 33% of new isolates are resistant to at least one drug, 26% are resistant to isoniazid, and 19% to both isoniazid and rifampicin.¹⁴ Drug resistance in infections with *Mycobacterium tuberculosis* in the UK has been recognised since the 1950s. Drug resistance to one or more of streptomycin, isoniazid, or PAS was reported in 4.5% of cases in 1955-6,¹⁵ and in 11% of newly diagnosed cases used as a control group in an acquired resistance survey in 1960-1,¹⁶ these surveys having no ethnic breakdown of cases. The 1963 primary resistance survey¹⁷ showed primary resistance rates of 3% in white patients compared with 7% and 11% respectively in Indian and Pakistani patients. More recent cross sectional data are available

from the Medical Research Council tuberculosis surveys of 1978-9, 1983, and 1988. In 1978-9¹⁸ 1.6% of previously untreated white patients and 7.5% of patients from the Indian subcontinent had primary drug resistance. In 1983¹⁹ these figures were 1.7% and 13.1% respectively, and in 1988²⁰ the rate in white patients was 2.3% but in patients from the Indian subcontinent it had fallen to 4.7% in previously untreated cases. Longitudinal data from a high incidence area of the UK^{21,22} from 1960-89 show a progressive decline in primary and acquired drug resistance in white patients, no progressive increase in primary or acquired drug resistance in the cases from the Indian subcontinent, and no evidence of cross infection between the two ethnic groups.

While the low rates of primary resistance in the UK are encouraging, there are no grounds for complacency. Drug resistance rates, both primary and in patients with a history of previous treatment, remain very high in patients from the Indian subcontinent. Recent studies have shown primary resistance rates to isoniazid of 14%, and acquired resistance rates of 37% to rifampicin and 55% to isoniazid in India,²³ and 17.7% resistance to isoniazid in Pakistan.²⁴ Patients from the Indian subcontinent now account for 39% of tuberculosis cases in England and Wales.²⁰ Whether the falling proportion of drug resistance in this ethnic group²⁰ continues will depend partly on the level of continuing immigration, and on the resistance characteristics of any clinical tuberculosis developing in those immigrants. It will also partly depend on the extent to which tuberculosis develops in persons born or settled in the UK following visits to the Indian subcontinent. This has been shown to be a risk factor in up to 20% of cases of tuberculosis.²⁵

The treatment of drug resistant tuberculosis should follow the general principle of using at least three drugs not previously used in the patient and to which the organism is sensitive until cultures become negative,²⁶ followed by a minimum of two drugs for a further period, preferably with fully supervised medication to ensure compliance. This can be difficult initially because of the time delays in the isolation and drug sensitivity testing of mycobacteria which can take several weeks, and because of the reduced availability of effective drugs with which to treat the infection. As a result of these difficulties considerable effort is now being applied on two fronts. Firstly, new drug regimens and combinations are being tested which may include rifabutin,²⁷ the newer macrolide antibiotics azithromycin and clarithromycin, and/or fluoroquinolones. Treatment, however, remains difficult and may only give response rates of the order of 50%, with a high death rate often with persistently positive cultures.²⁸ Because of this an alternative form of treatment using immunotherapy with heat killed *Mycobacterium vaccae* has been proposed with some limited success.²⁹ Secondly, the delays in isolation and sensitivity testing of bacteria, during which time drug treatment could be inadequate allowing further resistance to emerge, has given an urgent impetus to rapid methods of diagnosis. These are mainly through identifying specific genetic material by such techniques as the polymerase chain reaction³⁰⁻³² and restriction fragment length poly-

morphism³³⁻³⁵ which, if able to be developed for use directly onto clinical samples, could theoretically reduce the time for diagnosis and sensitivity testing to days if not hours.

The tuberculosis control system in the UK is different from that in the USA and is a major reason why the problems of multiple drug resistant tuberculosis have not so far arisen. Clinical care, particularly for pulmonary disease, is largely but not exclusively provided by thoracic physicians who have training in the management of tuberculosis. As the number of cases in the UK has fallen clinical expertise has reduced and is now most concentrated in areas with urban deprivation, or significant ethnic minority populations, or both. The Joint Tuberculosis Committee of the British Thoracic Society, made up of practising thoracic physicians and doctors from the Departments of Health, with epidemiological and bacteriological input have provided detailed recommendations on tuberculosis control and prevention measures,³⁶ on chemotherapy and clinical management,³⁷ and on the management of interactions between tuberculosis and HIV infections.³⁸ The picture of tuberculosis in Britain in 1993 is being analysed by further national tuberculosis notification surveys which are, for the first time, being accompanied by unlinked anonymised HIV testing. The survey in England and Wales is being carried out jointly by the Communicable Disease Surveillance Centre, the British Thoracic Society, and the Department of Health; that in Scotland is funded by the Scottish Office.

Over the last decade there have been about 10 new cases per year in Britain of tuberculosis with rifampicin and isoniazid resistance (PA Jenkins, personal communication), so there is currently no evidence of widespread or increasing multiple drug resistant tuberculosis in Britain, although two cases in Kurdish refugees have recently been described.³⁹ The Mycobacterium Reference Unit (PHLS), the Joint Tuberculosis Committee, the Communicable Disease Surveillance Centre, and the Department of Health are all aware of the problem which is being actively monitored. To maintain the current situation with a very low level of multiple drug resistance will require considerable vigilance and effort, with adequate screening of new immigrants and refugees, but particularly the comprehensive and uniform application of the principles of prevention,³⁶ clinical management,³⁷ and the management of interactions between tuberculosis and HIV infection.³⁸

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