

PostScript

LETTERS TO THE EDITOR

Isoniazid resistant TB and non-compliance

We read with interest the report by Ruddy *et al*¹ on the outbreak of isoniazid resistant tuberculosis in North London. We share their concern about the development of multidrug resistant tuberculosis (MDR-TB) in patients infected with a *Mycobacterium tuberculosis* strain with primary isoniazid resistance which may occur especially in cases of non-compliance.

In the Netherlands the incidence of TB is approximately 9 per 100 000, and it occurs more frequently in the high risk groups comprising people with a high risk for non-compliance. We therefore consider directly observed therapy (DOT) absolutely mandatory in all patients in the high risk groups, especially those infected with a primary isoniazid resistant strain.

Over the last 10 years 620 patients with TB have been treated in our hospital, of whom 33 (5%) had a primary isoniazid resistant strain, a percentage close to the 6% reported in England and Wales.¹ To date, all but one of these 33 patients successfully finished the standard treatment (isoniazid, rifampicin, pyrazinamide and ethambutol). The one patient who was non-compliant developed MDR-TB. Restriction fragment length polymorphism (RFLP) typing confirmed that the MDR-TB was caused by the same strain.

However, besides non-compliance, two other factors are also important in the development of MDR-TB. Firstly, it may develop in patients with proven compliance but in whom perfusion is inadequate; and, secondly, it may be the result of poor penetration by the medication such as in cases with abscesses and empyemas.^{2,3} This occurred in two of our patients with gross thickening and extensive calcifications of the pleura who were infected with a susceptible *M tuberculosis* strain at the beginning of their treatment.

We do not agree that prolonged treatment should be applied in non-compliant patients with isoniazid resistance^{1,4} as recommended by the BTS.⁵ Simply extending the duration of unsupervised treatment might even increase the problem of resistance. In the Netherlands it is easier to detain patients who are infectious, and also those who are non-adherent if there is a reasonable risk that the patient may become infectious.

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Authors' reply

van Altena *et al* raise several interesting points regarding factors involved with the development of drug resistance during treatment of tuberculosis. We concur with the need to fully investigate any patients with clinical or laboratory evidence of persisting disease despite full treatment, including assessment of drug tissue penetration and the need to consider individual tailored therapy.

The rationale behind the British Thoracic Society (BTS) guidelines¹ for prolongation of treatment for isoniazid resistant cases is to minimise relapse and the development of further resistance. This may be more likely to occur as a result of the decreased effectiveness of regimens lacking the early bactericidal effect of isoniazid,² particularly if the patient had been commenced on triple rather than quadruple therapy before the availability of drug susceptibility results. It is also important to establish the level of isoniazid resistance to assess any residual efficacy (isolates in this outbreak were all highly resistant to isoniazid by resistance ratio testing on solid media).³ The guidelines do

acknowledge that standard regimens may be effective⁴ due to the sterilising actions of rifampicin and pyrazinamide. The Incident Control Committee (ICC) for the outbreak concurred with the BTS view that, if tolerated, it would be more prudent to prolong treatment,⁵ but would agree that ensuring compliance with chemotherapy (standard or prolonged) is essential to avoid encouraging drug resistance.

The key point raised by van Altena and colleagues concerns the use of directly observed therapy (DOT). We would agree with the suggestion that DOT should be used for all patients in high risk groups including the homeless, alcohol and injecting drug users, those with mental health problems or previously demonstrated poor compliance, especially if isoniazid resistant. Attempts to address these barriers to compliance should also be considered. The ICC has recommended DOT for cases with such risk factors in line with BTS guidelines and, in light of the continuation of the outbreak, the institution of DOT in all isoniazid resistant cases not already on DOT unless the clinician is confident the patient is complying and can demonstrate this, recognising that it can be very difficult to predict compliance in some patients. The importance of objective assessment of compliance (for example, urine analysis) has been stressed.

A major issue is the availability of resources to provide DOT with many of the cases concentrated in areas of London with TB notification rates in excess of 100 per 100 000 population (HPA, London, 2004). This necessitates a prioritisation of cases by clinicians and case managers. The Netherlands TB management model is much admired and it is hoped that, in future, resources will enable TB services in London to achieve more frequent DOT.

Withdrawing treatment from non-compliant patients, especially with strains showing resistance, is contentious but needs to be confronted to prevent selection of multidrug resistance. We note with interest the ability in the Netherlands to detain non-compliant TB patients in cases of non-adherence without the need for proof of infectiousness. A similar approach is reported in other countries.^{6,7} This is a matter being urged for consideration when the long awaited review of public health law in England and Wales takes place. Detention, however, should always be a measure of last resort and should be combined with a multidisciplinary approach to patient support which encourages compliance.

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