



EDITORIAL

Multidrug- and extensively drug-resistant tuberculosis: an emerging threat

M. Berry^{*,#} and O.M. Kon^{*,¶}

Despite dramatic improvements in public health and medical care, *Mycobacterium tuberculosis* remains as much of a threat in the 21st century as it was when first identified as a pathogen by KOCH [1] in 1882. Tuberculosis was reported to be the seventh leading cause of death worldwide by the World Health Organization (WHO) in 2004 [2]. Recent figures show an increase in the total number of cases, with an estimated 9.2 million new cases and 1.7 million deaths attributed to tuberculosis in 2006 [3]. Drug-resistant strains of *Mycobacterium tuberculosis* represent an emerging problem in the struggle to contain tuberculosis. In this issue of the *European Respiratory Review*, SASSE and TEICHMANN [4] describe their experience of managing a patient infected with a strain of *Mycobacterium tuberculosis* with a wide spectrum of drug resistance.

The latest estimates based on survey data report that 11.1% of new tuberculosis cases showed resistance to any drug, which rises to 25.1% in previously treated cases. 1.6% of new cases and 11.7% of previously treated cases met the definition of multidrug-resistant tuberculosis (MDR-TB), this being resistance to rifampicin and isoniazid, the two most potent first-line antituberculosis drugs. Much of this burden is carried by eastern Europe, where 45.5% of previously treated tuberculosis cases meet the definition for MDR-TB. The patient described by SASSE and TEICHMANN [4] was originally from Burma, where MDR-TB accounts for 4% of new tuberculosis cases [5]. Outcomes in MDR-TB are worse than for non-MDR-TB, with one retrospective study in Estonia finding a cure rate of 83.4% in non-MDR-TB, compared with only 57.4% in MDR-TB [6]. More recently, attention has been drawn to the emergence of a form of MDR-TB that has a more extensive pattern of resistance, including resistance to the second-line agents conventionally used in MDR-TB cases. This extensively drug-resistant tuberculosis (XDR-TB) was originally defined by the US Centers for Disease Control and Prevention and WHO in 2006 as isolates with resistance to isoniazid and rifampicin, and at least three of the six main classes of second-line agents. This

definition was subsequently revised later in the same year to take account of the differing reproducibility and reliability of drug susceptibility testing for certain antimycobacterial drugs, along with emerging data highlighting particular classes of drug that may exert a greater impact on the outcome of treatment than others. Consequently, XDR-TB is currently defined as resistance to rifampicin and isoniazid plus resistance to any fluoroquinolone and at least one second-line injectable drug (these being amikacin, kanamycin and capreomycin) [7]. Attention was drawn to the potential implications of the emergence of XDR-TB by an outbreak in KwaZulu-Natal, South Africa, in which 52 out of 53 patients with XDR-TB died, with a median survival of only 16 days from the time of sputum collection in those for whom this data was available [8]. Subsequent studies have confirmed that XDR-TB has been isolated from all geographic regions and is thus a global problem [9]. Further studies confirmed that XDR-TB has a worse outcome than other MDR-TB but, somewhat reassuringly, no study to date has identified an equivalently high rate of mortality to that seen in KwaZulu-Natal. These other studies have also challenged the misconception that XDR-TB is predominantly a disease of HIV-infected patients; in fact, the majority of these studies have a typical HIV prevalence in the studied population of <5% [10].

The emergence of XDR-TB has focused attention on the question of whether or not MDR-TB that is resistant to additional classes of treatment, or that is resistant to all first-line treatments, leads to a worse outcome, in a similar manner to that seen in XDR-TB. The patient described by SASSE and TEICHMANN [4] is just such a patient, being initially resistant to all first-line agents, plus an injectable agent and a fluoroquinolone. A European study by MIGLIORI *et al.* [11] found that XDR-TB patients had higher mortality and lower treatment success than MDR-TB patients, even when compared with those MDR-TB patients with resistance to all first-line drugs, but that outcomes for the latter group did not significantly differ from other MDR-TB patients. However, the isolate from the patient described by SASSE and TEICHMANN [4] also demonstrated resistance to a fluoroquinolone and an injectable agent. Several studies in different populations have identified that isolates with resistance to fluoroquinolones or second-line injectable agents are associated with worse outcomes [6, 11–15]. It should be noted, however, that each of these studies is limited by the inevitably relatively small numbers of patients available for analysis. This limitation of the available data was also encountered in a systematic review of the management of XDR-TB [10]. Thus, current practice is being shaped by the findings of compelling individual studies.

*Dept of Respiratory Medicine, St Mary's Hospital, Imperial College Healthcare NHS Trust.

#Division of Immunoregulation, National Institute for Medical Research. ¶Centre for Respiratory Infection, St Mary's Hospital Campus, Imperial College, London, UK.

CORRESPONDENCE: O.M. Kon, Dept of Respiratory Medicine, St Mary's Hospital, Imperial College Healthcare NHS Trust, Praed Street, London, W2 1NY, UK. E-mail: Onn.Kon@imperial.nhs.uk

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A Russian study confirmed that treatment failure was more common in XDR-TB than MDR-TB, but still achieved cure in 45% of XDR-TB patients [16]. A similar study in Peru, utilising a coordinated outpatient service, found no difference in key outcomes between XDR-TB and MDR-TB patients, with impressive cure rates of 60.4% and 65.6%, respectively, and mortality of 22.9% and 20.4%, respectively [17]. Interestingly, there were many similar features between these two successful programmes. Both used prolonged individualised treatment regimes (median duration 23 months in the Peruvian study and 18 months in the Russian study) based upon drug sensitivity testing results. Consistent with the inferred importance of fluoroquinolones and injectable agents, based on the outcome studies discussed above, these agents were cornerstones of these treatment regimes, which included a prolonged parenteral phase of therapy (median 10.9 months for the Russian study and 15.4 months in the Peruvian study). In both programmes, patients were supported by nutritional and financial support with close microbiological monitoring and directly observed therapy (DOT). This combined approach was partially validated by a recent meta-analysis of outcome in MDR-TB, which found that combining a treatment duration >18 months and DOT achieved a significantly greater proportion of treatment success (69% *versus* 58%; $p < 0.001$) [18].

Key to the construction of an appropriate regime is knowledge of the sensitivity pattern of the isolate. Standard methods of drug sensitivity testing are limited by the turnaround time of 1–2 months, depending on whether solid or liquid media systems are used [19]. These methods are further complicated by potentially poor correlation between the tested minimum inhibitory concentration *in vitro* and the levels of drug available *in vivo* at the site of disease [20]. In response to these problems, particularly the turnaround time, a variety of novel diagnostic approaches have been employed. All of these offer high sensitivity and specificity, but with improved speed compared with conventional approaches [19]. Indeed, one UK study found that using nucleic acid amplification testing directly impacted on clinical care, predominantly through earlier identification or exclusion of MDR-TB [21].

The treatment used by SASSE and TEICHMANN [4] illustrates these principles; given that their patient's isolate was resistant to ofloxacin and streptomycin, an effective regime was achieved by the use of moxifloxacin and amikacin. In order to use a reasonable number of agents to prevent the development of further resistance, agents which are not conventional antimycobacterial drugs are often used, such as linezolid in this case. A recent study retrospectively comparing 85 linezolid-treated with 110 non-linezolid-treated MDR-TB or XDR-TB patients found no significant difference in treatment outcomes, but 41.2% of those treated with linezolid experienced side-effects, necessitating permanent withdrawal in 22.3% [22]. The side-effects observed were predominantly anaemia/thrombocytopenia, although polyneuropathy was observed in three cases. Interestingly, those prescribed linezolid at 600 mg daily were at lower risk of side-effects than those receiving 1,200 mg daily. The authors concluded that linezolid should be reserved for only the most complicated MDR-TB and XDR-TB cases. Other agents, such as amoxicillin-clavulanate, have also been used [17]. New agents are also being developed, such as the diarylquinoline TMC207. In a randomised, placebo-controlled

trial, the TMC207-treated group had a reduced time to sputum conversion to culture negativity, while nausea was the only significantly increased side-effect [23]. The relative shortage of new drug candidates has focused attention on nonpharmacological therapies, such as vitamin D, and interferon- γ or other immunotherapies, but thus far these have been trialled in only very small numbers of patients, often without appropriate control groups, or are speculative therapies extrapolated from animal models [24–26].

Since there is a lack of new drug treatments, the role of surgery, a mainstay of therapy in the pre-antibiotic era, has been revisited for the treatment of MDR-TB and XDR-TB. Seven XDR-TB patients in the Peruvian study and three in the Russian study underwent adjunctive surgery [16, 17]. The numbers involved in these two studies are too small to draw extensive conclusions, except to say that surgery may play a role in the management of difficult cases. In order to address this knowledge gap, KIM *et al.* [27] conducted a retrospective analysis of 79 patients to identify prognostic factors in MDR-TB patients undergoing surgery for their disease. They identified poor outcome as being associated with low body mass index, primary resistance (*i.e.* MDR-TB in those without history of previous antituberculosis therapy) and the presence of a cavitary lesion beyond the margin of resection.

Our understanding of the different factors that influence outcome and determine optimal management in MDR-TB and XDR-TB is currently limited by the significant gaps in the evidence base. Nonetheless, a reasonable consensus has emerged that the treatment of these difficult patients should be: individualised; guided by available drug sensitivity testing; aimed at incorporating injectable agents, fluoroquinolones and whichever first-, second- and third-line agents are available to make up a five-drug regime; and continued for ≥ 18 months after culture conversion, as per existing recommendations. This management should be supported by drug sensitivity testing and close monitoring of patients. At the present time, novel therapies should be reserved for difficult cases, possibly in the context of a clinical trial.

STATEMENT OF INTEREST

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