Multidrug-resistant tuberculosis: diagnosis, checklists, adverse events, advice and outcomes

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In this issue of *ERJ Open Research*, KORHONEN *et al.* [1] describe their experience of multidrug-resistant tuberculosis (MDR-TB) in Finland from 2007 to 2016. 47 clinical cases were included and act as historical background to the major changes in treatment regimens proposed by the World Health Organization (WHO) [2].

One of the key elements in successful management of MDR-TB is to perform a nucleic acid amplification test (NAAT) on a primary specimen (sputum, tissue aspirate or biopsy) so that ineffective drugs are not given. The Finnish study notes that just over half had such a test performed on primary samples. Looking at the WHO data reported for the European Region [3], only seven (16%) countries reported the use of a NAAT in >90% at the time of a tuberculosis diagnosis. This low use of a rapid diagnostic test, which has been recommended by WHO since December 2010 [4], represents a lost opportunity to diagnose MDR-TB early, reduce adverse effects and prevent additional drug resistance. Even if these tests were performed only on those with pulmonary tuberculosis, 21 (47%) out of 45 WHO European countries fell below the average regional rate of 68%: the likely contribution of pulmonary tuberculosis to the diagnoses of active tuberculosis disease.

Whole-genome sequencing was performed retrospectively in this Finnish series. In countries with small numbers of tuberculosis cases, this can be especially helpful in revealing unexpected epidemiological connections. Mutations in genes associated with isoniazid and rifampicin resistance correlated well with phenotypic drug susceptibility testing (pDST) and mostly with pyrazinamide resistance (*pncA* mutations) but less clearly with ethambutol susceptibility [5]. Fortunately, ethambutol is not commonly part of a treatment regimen for MDR-TB. However, apart from fluoroquinolones, the most common elements of an MDR-TB regimen (bedaquiline, linezolid, clofazimine and cycloserine) are not yet well supported by genotypic drug susceptibility testing or pDST and bedaquiline requires testing at a supraregional centre (e.g. San Raffaele Scientific Institute, Milan, Italy) [6]. Disturbingly, the use of pretomanid in the bedaquiline/pretomanid/linezolid regimens for MDR-TB and extensively drug-resistant tuberculosis has been recommended by WHO [2] in the absence of adequate mechanisms for drug susceptibility testing. Higher mean inhibitory concentrations for pretomanid are especially common in Lineage 1 (Indo-Oceanic) strains as well as *Mycobacterium canetti*, which occurs in East Africa [6].

Treatment for MDR-TB involves more than drug treatment. Checklists are widely used in medicine to improve care. They can indicate the nature and frequency of sputum tests, blood tests, radiology and ECGs, ensuring a safe discharge from hospital to community care and recording of treatment outcome [7]. Directly observed therapy should be discussed with each individual and include mental health reviews, and support through social problems by peer groups, housing officers and addiction services as needed.
Initial treatment regimens have been well defined [2]. However, changes in treatment can be required in as many as 40–50% [8]. Multidisciplinary national advisory groups, used in this case series from Finland, can offer immediate advice, note problems with national drug supplies and hold regular cohort reviews to monitor the changes in regimen. Such consilia began in France in 2005 [9], followed by the UK in 2008 [10] and Belgium in 2011 [11], before spreading through much of Europe (figure 1) [12].

Adverse events occurred, especially with linezolid (38 treated, 26 experienced an adverse effect, 24 stopped the drug and at least one pause occurred in 11 individuals during treatment). Peripheral neuropathy (60%) and visual loss (20%) are the most common problems and while they are usually reversible, persistent symptoms are not rare [13]. Bone marrow suppression (anaemia and thrombocytopenia) occurs in perhaps 3–17% of individuals taking linezolid [13, 14] and appears highly dependent on pre-dose (trough) concentrations [15]. Dose reduction from 600 to 300 mg once daily is used but linezolid resistance has developed with this approach [13]. Lactic acidosis occurred in two to five (3–7%) out of 72 treated with linezolid and with non-tuberculosis comorbidities [16]. More rarely, serotonin syndrome (confusion, autonomic dysfunction, myoclonus, rigidity or cramps) has been reported in ~1% [17, 18]. The recent randomised controlled trials (TB-PRACTECAL [2], ZeNix [19] and NExT [20]), with between 44 and 66 subjects in each arm, suggest that 600 mg linezolid for perhaps just 9 weeks may be sufficient. Even so, adverse events were still noted in 20–33% of participants. The search continues for an oxazolidinone that has the same or better efficacy than linezolid with fewer adverse effects [21, 22].

The treatment outcome was successful in 74% in the Finnish case series. This compares well with the overall success (cured and treatment completion as assessed at the end of treatment) rate of 58% for MDR-TB reported in the 2021 Global Tuberculosis Report for the European Region [3]. It would rank Finland as ninth out of 39 European countries reporting treatment outcomes for MDR-TB starting treatment in 2018, and above Switzerland, Israel, Portugal, Germany, Spain and France (using the more recently published data from three centres during 2006–2019 [23] in addition to the WHO reported data) as countries with a similar high income. More importantly, the Finnish series also reports the absence of any relapse in the 12 months after completion of treatment, an essential index to estimate cure.

Attention to the management of MDR-TB will improve successful outcomes and benefit everyone, including health systems and the general public.

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