Totally Drug-Resistant and Extremely Drug-Resistant Tuberculosis: The Same Disease?

To the Editor—The emergence of totally drug-resistant (TDR) tuberculosis in India and Iran has been recently discussed in the literature [1, 2]. The 15 TDR tuberculosis cases previously described in Iran were cited as resistant to “all first-line drugs (FLDs) and second-line drugs (SLDs)” [1, 2]. The 4 Mumbai cases were resistant to all FLDs (isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin) and SLDs tested (ofloxacin, moxifloxacin, kanamycin, amikacin, capreomycin, para-aminosalicylic acid, ethionamide) [1].

In 2007, we proposed for the first time the acronym XXDR for extremely drug-resistant tuberculosis [3, 4] to define Mycobacterium tuberculosis strains that were resistant to all FLDs and SLDs available, and we described [4] the first 2 cases in Italy. Both strains were resistant to all FLDs and SLDs (fluoroquinolones, ethionamide, amikacin, para-aminosalicylic acid, capreomycin, kanamycin, cycloserine) and to additional drugs (rifabutin, clofazimine, dapsone, claritromycin, thiacetazone); linezolid was not yet available.

The first case, in a patient who died after 422 days in the hospital and 94 months of treatment, was initially mismanaged and was already resistant to most of the available drugs on the patient’s admission to a reference center. The second case, in a patient who died 625 days after hospital admission and after 60 months of treatment, was managed suboptimally, with poor adherence to the prescribed regimen, before the patient’s admission to a reference center (Table 1).

After reaching agreement on the definition of multidrug-resistant (MDR) tuberculosis (eg, resistance to at least isoniazid and rifampicin) and extensively drug-resistant (XDR) tuberculosis (eg, MDR tuberculosis with additional resistance to any fluoroquinolone and to ≥1 injectable SLD, eg, capreomycin, kanamycin, or amikacin), the international community needs to agree on a definition for the step that follows XDR tuberculosis in terms of severity: TDR or XXDR tuberculosis. Which drugs should compose the panel defining this condition? Should it include all the drugs considered by the World Health Organization to be of unknown or not adequately proven efficacy? Should it include other antimicrobials?

Table 1. Drug-Resistance Profiles in 4 Individual Totally Drug-Resistant Tuberculosis Cases From India and 2 Extremely Drug-Resistant Tuberculosis Cases From Italy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>First-Line Drugs</th>
<th>Second-Line Drugs</th>
<th>Additional Drugs</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>India [1]</td>
<td>Isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin</td>
<td>Ofloxacin, moxifloxacin, kanamycin, amikacin, capreomycin, para-aminosalicylic acid, ethionamide</td>
<td>...</td>
<td>TDR</td>
</tr>
<tr>
<td>1</td>
<td>Isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin</td>
<td>Ofloxacin, moxifloxacin, kanamycin, amikacin, capreomycin, para-aminosalicylic acid, ethionamide</td>
<td>...</td>
<td>TDR</td>
</tr>
<tr>
<td>2</td>
<td>Isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin</td>
<td>Ofloxacin, moxifloxacin, kanamycin, amikacin, capreomycin, para-aminosalicylic acid, ethionamide</td>
<td>...</td>
<td>TDR</td>
</tr>
<tr>
<td>3</td>
<td>Isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin</td>
<td>Ofloxacin, moxifloxacin, kanamycin, amikacin, capreomycin, para-aminosalicylic acid, ethionamide</td>
<td>...</td>
<td>TDR</td>
</tr>
<tr>
<td>4</td>
<td>Isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin</td>
<td>Ofloxacin, moxifloxacin, kanamycin, amikacin, capreomycin, para-aminosalicylic acid, ethionamide</td>
<td>...</td>
<td>TDR</td>
</tr>
<tr>
<td>Italy [3]</td>
<td>Isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin</td>
<td>Ofloxacin, moxifloxacin, kanamycin, amikacin, capreomycin, para-aminosalicylic acid, ethionamide + cycloserine</td>
<td>Rifabutin, clofazimine, dapsone, claritromycin, thiacetazone</td>
<td>XXDR</td>
</tr>
<tr>
<td>1</td>
<td>Isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin</td>
<td>Ofloxacin, moxifloxacin, kanamycin, amikacin, capreomycin, para-aminosalicylic acid, ethionamide + cycloserine</td>
<td>Rifabutin, clofazimine, dapsone, claritromycin, thiacetazone</td>
<td>XXDR</td>
</tr>
</tbody>
</table>

Abbreviations: TDR, totally drug-resistant; XXDR, extremely drug-resistant.
should these drugs be tested? At present, no agreement/recommendation is available at the international level for in vitro testing of some SLDs. Should this panel be rediscussed when new drugs demonstrate potential activity against \( M. \) \textit{tuberculosis}?

Does this new potentially severe form of tuberculosis (TDR, XXDR, or other definition) really reflect a more severe prognosis than XDR tuberculosis? In 2007, analyzing a large MDR/XDR tuberculosis cohort from 4 European countries [5], we demonstrated that the internationally agreed-upon XDR tuberculosis definition had both clinical value (outcomes of XDR tuberculosis cases were worse than those of MDR tuberculosis cases) and operational value (development of superresistance to SLDs reveals the programmatic difficulties of ensuring patients’ adherence to the prescribed drugs).

The present debate on the new definition has an advocacy taste on top of its scientific interest. Looking at the media messages reported worldwide over the last weeks, we realized that the terms TDR tuberculosis and XXDR tuberculosis were used to generate interest in the average news reader—as well as probably anxiety or panic.

The tuberculosis control community needs clear definitions, which reflect clinical and operational facts and support the laboratory, clinical, and public health efforts to prevent the emergence of drug resistance and to cure the resistant cases we have already produced.

Notes

Financial support. This work was supported by current research funds from participating Institutions and European Community’s Seventh Framework Programme (FP7/2007–2013 under grant agreement FP7-223681). The funding source had no role in any stage of the manuscript development.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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\textbf{Clinical Infectious Diseases} \textbf{2012};\textit{54}(9):1379–80

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DOI: 10.1093/cid/cis128