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RAPID PUBLICATION

Clinical and operational value of the XDR-TB definition

Giovanni Battista Migliori[*], Giorgio Besozzi[†], Enrico Girardi[‡], Kai Kliiman[¶], Christoph Lange[§], Olga S Toungoussova[#], Giovanni Ferrara[**], Daniela M. Cirillo[††], Andrea Gori[‡‡], Alberto Matteelli[§§], Antonio Spanevello[#], Luigi R Codecasa[¶¶], Mario C. Raviglione[##] and SMIRA/TBNET Study Group***

* WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Tradate, Italy

† E. Morelli Hospital, Reference Hospital for MDR and HIV TB, Sondalo, Italy

‡ National Institute for Infectious Diseases (INMI) L. Spallanzani, Rome, Italy

¶ University of Tartu, Tartu, Estonia

§ Division of Clinical Infectious Diseases, Medical Clinic, Research Centre Borstel, Borstel, Germany

Fondazione S. Maugeri, Care and Research Institute, Cassano delle Murge, Italy

** University of Perugia, Internal Medicine, Section of Respiratory Diseases, Perugia, Italy

†† Supranational Reference Laboratory, S. Raffaele Institute, Milano, Italy

‡‡ San Paolo Hospital, University of Milan, Milano, Italy

§§ University of Brescia, Brescia, Italy

¶¶ TB Reference Centre, Villa Marelli Institute, Niguarda Hospital, Milano, Italy

Stop TB Department, World Health Organization, Geneva, Switzerland

Corresponding Author:

G.B. Migliori, WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute/ TBNET Secretariat (TuBerculosis Network in Europe Trialsgroup)/ Stop TB Italy, via Roncaccio 16, 21049, Tradate, Italy; Fax 39.0331829402; E-mail gbmigliori@fsm.it

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Summary

No information is available on the effect of resistance/susceptibility to first-line drugs different from isoniazid and rifampicin in determining the outcome of extensively drug-resistant tuberculosis (XDR-TB) patients, and if being XDR-TB is a more accurate indicator of poor clinical outcome than being resistant to all first-line anti-TB drugs.

To investigate this issue large series of multidrug-resistant (MDR-) and XDR-TB cases diagnosed in Estonia, Germany, Italy and Russian Federation (Archangels Oblast) in the period 1999- 2006 were analyzed.

Drug susceptibility testing for first- and second-line anti-TB drugs, quality assurance and treatment delivery was performed according to WHO recommendations in all study sites.

Out of 4,583 culture-positive TB cases analyzed, 361 (7.9%) were MDR and 64 (1.4%) XDR . XDR-TB cases had a relative risk of 1.58 to have an unfavourable outcome compared with "MDR-TB cases resistant to all first-line drugs" (isoniazid, rifampicin ethambutol, streptomycin and, when tested, pyrazinamide) and a RR of 2.61 compared with "other" MDR-TB cases (those susceptible to at least one first-line anti-TB drug among ethambutol, pyrazinamide and streptomycin, regardless to resistance to the second-line drugs not defining XDR-TB).

The emergence of XDR-TB confirms that problems in TB management are still present in Europe. While waiting for new tools which will facilitate management of XDR-TB, accessibility to quality diagnostic and treatment services should be urgently ensured and adequate public health policies should be rapidly implemented to prevent further development of drug resistance.

Introduction

XDR-tuberculosis (TB) is defined as resistance to at least rifampin (R) and isoniazid (H) (that is the definition of multidrug-resistant (MDR)-TB) in addition to any fluoroquinolone, and at least one of the three injectable anti-TB drugs (capreomycin, kanamycin, amikacin). The XDR-TB definition was made on the assumption that these classes of drugs are essential to treat successfully a case of TB, although evidence on its clinical relevance was not available at the time [1-4].

In a preliminary analysis of European patients, we recently demonstrated higher probability of death and worse outcomes in XDR-TB when compared to MDR-TB cases [5].

Previous studies demonstrated that among MDR-TB cases the probability to achieve treatment success varies, depending on the number of first-line drugs to whom the patient is susceptible [6]. However, it is not known if being XDR-TB is a more accurate indicator of poor clinical outcome than being resistant to all first-line anti-TB drugs [6]. In fact, there is no information available on the effect of resistance/susceptibility to first-line drugs different from HR in determining the outcome of XDR-TB patients. To investigate this issue we analyzed a larger series of MDR-and XDR-TB cases diagnosed both in Western and Eastern European countries.

Methods

Data from all culture confirmed TB cases diagnosed consecutively by the TB clinical reference centers in Estonia (Tallin, Tartu), Germany (Borstel, Grosshansdorf, Bad-Lippspringe), Italy (Sondalo, Milan, Rome) and Russian Federation (Archangels Oblast) were analyzed.

Clinical outcomes (available on the original clinical records) were measured as part of an “ad hoc” study performed in the countries mentioned above in the period 1999-2006 (Italy and Germany: 2003-2006; Estonia: 2001-2004; Archangels Oblast: 1999-2001) [5,7-8]. Drug susceptibility testing (DST) for first- and second-line anti-TB drugs was performed according to WHO recommendations by quality assured laboratories and retested at WHO’s Supranational Reference Laboratories (Rome/Milan; Borstel, Stockolm, Oslo) [9-10]. In Italy, Germany and Estonia the BACTEC™ MGIT 960™ TB System (Becton Dickinson Diagnostic Systems, Sparks, MD, USA)

was used to test first-line drugs and the proportion methods on Lowenstein-Jensen was used to test second-line drugs in all centers. In Archangels Oblast the proportion method on Lowestein-Jensen medium was used. In Oslo DST for both first- and second-line drugs was done using the BACTEC 460 TB System (Becton Dickinson Diagnostic Systems, Sparks, MD, USA).

In all countries, regimens to treat MDR-/XDR-TB cases were tailored to the DST results according to WHO recommendations, the main categories of second-line drugs being generally available to treat patients during the study period (injectable agents – amikacin , capreomycin and kanamycin; fluoroquinolones; second-line oral agents – ethionamide/prothionamide; para-aminosalycilic acid and cycloserine). Third-line agents (e.g. amoxicillin/clavulanicacid, clarithromycin, clofazimine) were not available in Archangels Oblast.

We defined "MDR-TB cases resistant to all first-line drugs" those resistant to H,R, ethambutol, streptomycin and, when tested, pyrazinamide; and "other" MDR-TB cases those susceptible to at least one first-line anti-TB drug among ethambutol pyrazinamide and streptomycin (regardless to resistance to the second-line drugs not defining XDR-TB).

Outcomes were compared by χ^2 test (categorical variables) on cases achieving a final outcome (different from default, transferred-out and still on treatment), and by Kaplan-Meier curve where appropriate.

Results

Out of 4,583 culture-positive TB cases analyzed (Italy: 2,140; Germany: 748; Estonia: 900; Archangels: 795), 361 (7.9%) were MDR (Italy 83, Germany 43, Estonia: 194, Archangels: 41) and 64 (1.4%) XDR (Italy 8, Germany 3, Estonia 53, Archangels 0). In Italy 1.46% of all the notified culture-positive cases are MDR (4.2% in our study), in Germany they are, respectively, 2.1% and 6.1%; in Estonia they are 27.4% and in Archangels 5.2% as all case are included in the study. 178 (49.3%), out of 361 MDR-TB cases and 48 (75%) out of 64 XDR-TB cases were re-treatment cases ($P<.001$). Seventeen (5%) out of 341 MDR-TB cases tested for HIV were HIV-infected; among XDR-TB cases they were, respectively, 2 (3.2%) out of 61.

Out of 361 MDR-TB cases, 267 (74%) were resistant to all first-line drugs, 51 (14.1%) were resistant to H, R and streptomycin, 19 (5.3%) to H, R and ethambutol, and 24 (6.6%) to HR.

Out of 64 XDR-TB cases none was resistant only to H,R, one fluoroquinolone and one injectable drug: 58 (90.6%) were resistant to all first-line drugs, (plus, eventually other second-line drugs) and 6 (9.4%) were resistant to HR, plus, ethambutol or streptomicin and/or other second-line drugs.

The cases included in the outcome analysis were 240 MDR-TB cases (187 were resistant to all first-line drugs) and 48 XDR-TB cases achieving a final outcome.

XDR-TB cases were more likely to be resistant to all first-line drugs than MDR-TB cases ($P<.005$).

The cases excluded from the analysis were equally distributed among groups (patients still on treatment: XDR-TB 8/64; MDR-TB resistant to all first-line drugs 38/267; "other" MDR 31/94; default/transferred-out: XDR-TB 8/64; MDR-TB resistant to all first-line drugs 42/267; "other" MDR 10/64).

No difference in the profile of drug resistance for second-line drugs was found among the groups analyzed excluding the XDR-defining second-line drugs (XDR-TB: mean 1.3, median 1; MDR-TB resistant to all first-line drugs: mean 1.3, median 1; "other" MDR-TB: mean 0.8; median 1). Details on outcomes by resistance pattern are summarized in the Table.

At the univariate analysis XDR-TB cases had significantly worse outcomes than MDR-TB cases resistant to all first-line drugs and other MDR-TB cases, respectively.

XDR-TB cases had a relative risk (RR) of 1.58 to have an unfavourable outcome compared with MDR-TB cases resistant to all first-line drugs (95% CI 1.14-2.20; 26/48 vs 64/187, $P<.05$) and a RR of 2.61 (95% CI 1.45-4.69; 26/48 vs 11/53, $P<.001$) compared with "other" MDR-TB cases.

MDR-TB cases resistant to all first-line drugs were more likely to have an unfavourable outcome than "other" MDR-TB cases (death or failure: 64/187 vs 11/53, RR= 1.65, 95%CI 0.94-2.89) although the difference was not significant at the conventional p 0.05 level (p= .06). The difference is statistically significant if patients still on treatment are not removed from the analysis (64/225 vs 11/84, $P<.01$). This analysis is done under the assumption that the patients still on regular treatment

will achieve a successful treatment outcome. If we assume the converse (i.e. that all patients still on treatment achieve an unsuccessful treatment outcome) no more statistically significant difference is detected between the two groups.

The difference in treatment outcomes among the three groups remains significant also after adjusting for age and country of diagnosis.

At the Kaplan Meier analysis the time to treatment success is significantly different among the three groups, with the lowest rate of treatment success in the XDR-TB group ($P<.005$; Figure).

Discussion

This is the first report showing in a large sample from four European countries at low HIV prevalence that XDR-TB cases have a clinical outcome worse than that of MDR-TB cases who are resistant to all first-line anti-TB drugs and that susceptibility to one or more first-line drugs increases the probability to treat successfully MDR-TB cases.

The results also demonstrate the possible existence of a "continuum" of severity in terms of clinical outcome among XDR-TB, MDR-TB resistant to all first-line drugs, and other MDR-TB cases.

The results of our study, which are consistent with those of a recently performed laboratory-based survey [8], show that: 1) XDR-TB cases with a resistance pattern strictly corresponding to the definition (e.g. H, R, one fluoroquinolone and one injectable drug) are not frequently identified in the clinical practice, as second line drugs are introduced when drug resistance to all first-line drugs is likely to have occurred; 2) the occurrence of XDR-TB, as currently defined, has both a clinical value (predicting poor outcome) and an operational significance (confirming the loss of first-line drugs coupled with key second-line ones).

Limitations of the study include, first, the observation that data are representative in only two of the settings surveyed (Estonia and Archangels Oblast, a North-Eastern region in the Russian Federation). In Italy and Germany the prevalence of MDR-TB in TB clinical reference centers is higher than the prevalence detected at national level.

Second, since 16.4% of patients were lost to follow-up, their outcome is not well characterized. Third, the difference in outcomes between MDR-TB resistant to all first-line drugs vs. "other" MDR-TB cases reached only borderline significance under the assumption. that patients still on regular treatment will reach a successful outcome. In our opinion this assumption is more likely to represent the truth than the converse one, i.e. all patients still on treatment will have an unsuccessful outcome. Due to the difficulty in raising large numbers on a relatively uncommon form of disease like MDR-/XDR-TB, global studies will be necessary to give a final answer to this question. Last but not least, although DST for second-line drugs in our study were quality controlled by WHO Supranational Reference Laboratories, some caution is always needed when interpreting results in relation to XDR-TB. Although protocols to standardize DST for second-line drugs are presently under development, a universally accepted proficiency testing does not exist.

The fact that the results from Italy and Germany [5] remain consistent after including data from Eastern European countries suggests that the study results are robust. The negative impact of TB treatment mismanagement (and sub-optimal infection control in congregate settings) [5,11]) in selecting resistant mutants in Europe is further confirmed by the observation that 75% of XDR- and 49.3% of MDR-TB cases were previously treated for TB.

Further information on XDR-TB will be hopefully available in the next few years when surveillance systems will be equipped to identify all the existing XDR-TB cases and to monitor their risk factors and outcomes [11]. At the same time, the emergence of XDR-TB confirms that problems in TB management are still present in Europe. While waiting for new tools which will facilitate management of XDR-TB, accessibility to quality diagnostic and treatment services should be urgently ensured and adequate public health policies should be rapidly implemented to prevent further development of drug resistance.

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Table: Outcomes of XDR-TB cases, "MDR-TB cases resistant to all first-line drugs and "other" MDR-TB cases in Estonia, Germany, Italy, and Russian Federation (Archangels Oblast)

	Treatment success		Died		Default		Failure		Transferred		Total patients completing treatment
	n	%	n	%	n	%	n	%	n	%	n
XDR-TB	**22**	**39,3**	**14**	**25,0**	**8**	**14,3**	**12**	**21,4**	**0**	**0,0**	**56**
MDR-TB resistant to all first-line drugs	123	53,7	35	15,3	39	17,0	29	12,7	3	1,3	229
"Other" MDR-TB	42	66,7	8	12,7	10	15,9	3	4,8	0	0,0	63
TOTAL	**187**	**53,7**	**57**	**16,4**	**57**	**16,4**	**44**	**12,6**	**3**	**0,9**	**348**

XDR-TB cases: resistance to at least rifampin and isoniazid (that is the definition of multidrug-resistant (MDR-TB) in addition to any fluoroquinolone, and at least one of the three injectable anti-TB drugs (capreomycin, kanamycin, amikacin);

MDR-TB cases resistant to all first-line drugs: MDR-TB cases resistant to isoniazid, rifampicin ethambutol, streptomycin and, when tested, pyrazinamide;

"other" MDR-TB cases: MDR-TB cases susceptible to at least one first-line anti-TB drug.

Default and transferred included in this table were removed from the analysis presented in the text.

Figure: Kaplan-Maier plot showing estimated proportion of Treatment Success (cure + treatment completion) according to the drug resistance profile (XDR-TB cases, MDR-TB cases resistant to all first-line drugs and "other" MDR-TB cases) in Estonia, Germany, Italy, and Russian Federation (Archangels Oblast)