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CONCISE ARTICLE

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Multidrug-resistant tuberculosis in Russia: clinical characteristics, analysis of second-line drug resistance and development of standardized therapy

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Abstract The aim of the study presented here was to identify patients with multidrug resistant tuberculosis (MDRTB) in the Samara region of Russia and to analyze the susceptibility of their isolates to second-line drugs in order to develop an empirical, standard, second-line treatment regimen. Treatment of MDRTB can be individualized based on in vitro laboratory analysis or standardized. In the latter case there is still a need to ascertain local second-line drug-resistance patterns. Described here are the clinical characteristics of 251 MDRTB patients identified in the study and the second-line drug susceptibility of 69 MDRTB isolates obtained from them. Antimicrobial resistance to the following agents was detected in the isolates: rifabutin (88.2%), streptomycin (42.8%), amikacin (7.2%), doxycycline (7.4%), ciprofloxacin (4.3%), clofazimine (2.9%), cycloserine (7.4%), and prothionamide (1.5%). The results of the study indicate it is possible to develop a standard, effective, clinical treatment regimen using ethambutol, pyrazinamide, prothionamide, a fluoroquinolone and amikacin.

Introduction

Global rates of tuberculosis (TB) continue to rise, as do rates of drug-resistant TB. Exact rates of drug resistance are unknown, but the World Health Organization's Global Programme on Drug Resistance has reported over 60 surveys [1] noting high rates of multidrug-resistant TB (MDRTB) (i.e., strains resistant to at least isoniazid and rifampicin) in some areas of the world, such as Eastern Europe. However, these surveys did not examine resistance to second-line drugs. Within Russia, studies have indicated the prevalence of MDRTB is high, with rates varying from approximately 17 to 25% in different regions [2, 3, 4, 5, 6, 7, 8]. Cure rates for patients with MDRTB are low when standard first-line DOTS (directly observed therapy short course) is administered [9], but with second-line drugs, treatment success varies with 48% to more than 80% of patients being reported as cured or probably cured [10].

There is continuing debate regarding the value of treating MDRTB cases and whether or not it diverts resources from key DOTS programs in poorer parts of the world [11]. If one accepts it is appropriate ethically and clinically to treat MDRTB patients in lower income countries, then which strategy should be employed? Second-line treatment is prolonged and can be either individualized based on in vitro drug resistance or standardized. The former model is the gold standard in the industrialized world, but it is more costly than standardized therapy, since it requires an extensive and highly controlled laboratory infrastructure. Both standardized and individualized treatment strategies have been used in studies in Peru [10, 12]. In one study that investigated an individualized approach, few failures were observed and, over a median follow-up period of 40 months, 23% of the patients died [12]. This model relied upon considerable financial support from donors since treatment and drug susceptibility testing was conducted in the USA. In comparison, the standardized approach resulted in significantly higher failure rates (32%) but fewer deaths (11%) over a shorter assessment period [4, 10, 12].

Even with standardized protocols there is a need for accurate resistance data for second-line drugs after the preliminary drug resistance surveys are completed. This is complicated by the associated costs and the lack of standardized sampling and testing methods for most second-line drugs. There is little independent data on which to base a standardized regimen in Russia. Lack of prior use of prescription drugs typically used to treat TB, such as fluoroquinolones, is an insufficient indicator of

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likely efficacy since antibiotics can be (and are) purchased without a prescription to treat other infections.

In the present study our aim was to identify patients with MDRTB, describe the clinical features of these patients, and analyze the susceptibility of their isolates to second-line drugs in order to develop an empirical, standard, second-line treatment regimen.

Materials and methods

Over a period of 1 year from 2001 to 2002 we identified patients with MDRTB in the Samara region of Russia. Patients with pulmonary disease and culture-proven TB were recruited from all 18 civilian TB dispensaries located across the region and from the prison TB hospital-colony that admits all TB cases occurring in the prison sector. Consecutive patients aged over 18 years were invited to take part. After giving informed written consent, they were interviewed by a team of trained Russian doctors and nurses using a structured questionnaire. The questionnaire was developed and approved by the Federal Tuberculosis Institutions (Moscow), Samara TB Service, the Samara Ethics Committee and the Samara Regional Health Department, under whose auspices the study was conducted. The questionnaire was supplemented and verified with information from the patients' medical notes.

An expectorated sputum sample was obtained from each patient and cultured onto Löwenstein–Jensen media. Resistance to first-line drugs was tested for in London and Samara, and 251 patients with MDRTB were identified. Sixty-nine MDRTB isolates were available for second-line drug-resistance testing using the resistance ratio method on Löwenstein–Jensen media [13]; they were collected throughout the entire testing period from patients at all of the TB treatment centers.

Results and discussion

The principal characteristics of the 251 study patients with MDRTB are shown in Table 1. The majority of patients were male and collectively they exhibited typical signs and symptoms of TB. Nevertheless, for each parameter, with the exception of productive cough, shortness of breath and fatigue, a majority of patients failed to show a typical clinical symptom or sign; fever, weight-loss and night sweats were exhibited by only approximately one-third of the patients. The frequency with which productive cough was present in this group reinforces the importance of taking sputum samples for high-quality microbiological examination and culture or molecular analysis. Drug resistance, however, cannot be diagnosed clinically or radiologically and is strictly a laboratory diagnosis.

Death from MDRTB is not inevitable (just as death from TB before the advent of chemotherapy was not a certainty), but survival is poor when standard first-line drug regimens are administered [14, 15]. Treatment of new MDRTB cases in lower income countries is more likely to be successful than treatment of chronic cases, since the strains are usually resistant to fewer antibiotics and treatment is often limited to this group. However, when selecting empirical treatment for cases as they present to the physician, there is also a need to consider the worst-case scenario represented by previously treated and chronic cases; our study addresses this issue as well.

Table 1 Clinical characteristics of 251 patients with multidrug-resistant tuberculosis (MDRTB)

Characteristic	No. of MDRTB-positive patients/total or no. with characteristic	Percentage
Gender		
Male	241/251	96
Female	10/251	4.0
Productive cough	211/251	84.1
Haemoptysis	18/218	8.3
Weight loss	91/251	36.3
Night sweats	94/249	37.8
Fever	76/249	30.5
Shortness of breath	142/251	56.6
Chest pain	102/248	41.1
Fatigue	174/249	69.9
Underlying disease		
COPD	14/225	6.2
Jaundice	29/248	11.7

COPD, chronic obstructive pulmonary disease

When second-line drugs are used to treat MDRTB patients, the success rate (defined as patients cured or probably cured) has varied from 48% to more than 80% [10, 16, 17]. Mortality rates varied from 0 to 37% in studies of HIV-seronegative individuals, and rates of up to 89% were found in HIV-seropositive populations [16, 17]. Even in high-income countries like the UK, where individualized therapy is available, survival was relatively low [18], with a median overall survival time of 3.78 (3.66–6.89) years. Among patients treated with three drugs to which the bacterium was susceptible on in vitro testing (n=62), median survival was 5.7 years, whereas in those not so treated (n=13) survival was only 1.6 years. Side effects are also more common with second-line drugs.

In general, studies using standardized treatment approaches for MDRTB have shown worse outcomes than most studies using individualized treatment regimens in expert hands; however, the results were better for these individuals than for those who received either no treatment or treatment with first-line drugs alone [12]. Although individualized treatment is probably the best, the need for reliable but costly laboratory facilities for drug sensitivity testing means that standardized second-line drug treatment has been advocated for use in middle- and low-income countries. The latter strategy requires detailed knowledge of likely drug-resistance patterns, particularly for MDRTB strains, which requires recent regional surveys or surveillance of resistance.

Table 2 Resistance to second-line drugs in 69 multidrug-resistant tuberculosis (MDRTB) isolates in Samara, Russia

Antibiotic	No. of resistant isolates/no. tested	Percentage
Amikacin	5/69	7.2
Ciprofloxacin	3/69	4.3
Clofazimine	2/68	2.9
Cycloserine	1/69	1.5
Doxycycline	5/68	7.4
Prothionamide	1/69	1.5
Rifabutin	60/68	88.2

Nevertheless, since higher death rates were recorded in the studies with longer follow-up periods it is possible that the effect of MDRTB disease in individuals may not be seen for years. In many of these studies the follow-up duration was relatively short and survival analyses were conducted using a variety of methodologies with outcomes (i.e., cure, success, failure) that were defined in different ways; this makes comparisons between studies difficult.

The results of susceptibility testing for second-line drugs in Samara are given in Table 2. Overall, the results were encouraging in that resistance to ciprofloxacin (and fluoroquinolones in general), clofazimine, cycloserine and prothionamide, although not insignificant, were also not particularly high. Amikacin and doxycycline resistance were the most common at 7.2 and 7.4%, respectively. Nearly half (42.8%) of all isolates were resistant to streptomycin. The former result is not unsurprising, since high rates of streptomycin resistance have been reported widely. One would expect, as is the case here, that many streptomycin-resistant isolates would remain sensitive to amikacin since there are mechanisms of antibiotic action present in the latter that are absent in the former. We did not test for kanamycin resistance in our study, but based on other published data we would expect high rates of resistance.

Resistance to rifabutin was present in 88.2% of the MDRTB isolates we found, reflecting the expected proportion of cross-resistance. Use of rifabutin would be unwise in cases of known MDRTB (or highly suspected MDRTB) in the absence of highly controlled in vitro testing, and the use of rifabutin is likely to be confined to patients coinfected with HIV who are receiving protease inhibitors. Unfortunately, few HIV-positive individuals in Russia have access to antiretroviral treatment.

In the last 2 years there have been reports of patients in lower income countries, notably Peru, being treated successfully with second-line drugs [10, 12]. Standardized treatment regimens that include second-line drugs are usually offered for a period of 1.5–2 years. The National TB Control Programme of Peru adopted this approach using a regimen consisting of kanamycin, ciprofloxacin, ethionamide, pyrazinamide, and ethambutol [12].

It is also possible to develop a standard effective clinical treatment regimen in Russia, and standardized and individualized treatments are being implemented in some areas such as Tomsk. Previously, we showed that resistance to ethambutol and pyrazinamide was seen in between 11.5 and 29.9% of new cases and 6.1 and 14.6% of previously treated cases [19]. It is possible that more recent treatment strategies that include a quinolone may offer advantages in achieving cure [10, 20]. Initial therapy, therefore, for newly diagnosed MDRTB patients would include ethambutol, pyrazinamide, prothionamide, a fluoroquinolone and amikacin. Clearly, it is important that problems of treatment delivery and continuity are overcome to ensure that further resistance does not emerge. In cases in which a patient has had previous treatment, resistance to ethambutol is more likely to be high, but it is probably still worth including this agent in the treatment regimen. A new Russian Federal Law has suggested a similar standardized regimen, and the data presented here provides further evidence in support of this [21]. In order to determine the value of rapid diagnosis of MDRTB and the relative merits of standardized regimens compared to individualized treatment regimens for treating MDRTB in middle-income countries, such as Russia and the Baltic states, further prospective clinical trials are needed. This is particularly important in the context of increasing HIV coinfection.

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