Tuberculosis xxx (2015) 1–8

Contents lists available at ScienceDirect

Tuberculosis

journal homepage: http://intl.elsevierhealth.com/journals/tube

DRUG DISCOVERY AND RESISTANCE

Resistance profile and risk factors of drug resistant tuberculosis in the Baltic countries

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ARTICLE INFO

Article history:
Received 25 January 2015
Received in revised form
6 May 2015
Accepted 29 May 2015

Keywords:
Multi/extensive drug resistant tuberculosis
Risk factors
Clinical management
Baltic countries

SUMMARY

The rates of multi- and extensively drug-resistant tuberculosis (X/MDRTB) in the Baltic countries are the highest within the European Union hampering recent achievements of national TB control programmes.

We included all consecutive culture-confirmed X/MDRTB patients registered for treatment in 2009 in Latvia, Lithuania and Estonia into this multicenter case–control study. Cases were compared with randomly selected controls with non-MDRTB registered for treatment in the same year across these sites.

Of 495 MDRTB patients, 243 (49.7%) showed resistance to at least one second-line drug, 206 (42.1%) had pre-XDRTB (i.e. MDRTB with additional resistance to a second-line injectable or fluoroquinolones) and 64 (13.1%) had XDRTB. Younger age, male gender and known contact with an MDRTB case were associated with increased risk of primary infection with X/MDRTB strains. Previous treatment and alcohol abuse were strong predictors for MDRTB acquisition; defaults and failures in the past triggered XDRTB development. All patients received appropriate therapy; less than half of the patients were fully adherent.

An erroneous treatment strategy is unlikely to drive resistance development. Increasing patients' compliance, addressing issues of social support, rapid detection of drug resistance and improving infection control is crucial for prevention of further spread of X/MDRTB and achieving higher cure rates.

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1. Background

Multidrug-resistant tuberculosis (MDRTB) is a growing threat to national tuberculosis control programmes seriously jeopardizing the success of global efforts to fight tuberculosis [1,2]. MDRTB patients are difficult and costly to treat and failure is more common resulting in high death rate especially in HIV co-infected persons [3]. Resistance to two of the most powerful groups of reserve drugs (fluoroquinolones and injectable agents, extensive drug resistance, XDR) decreases chances of survival and success of therapy further [4–6],

Despite well-functioning and dedicated national control programmes that have slowed down the epidemic of TB, reverted the

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http://dx.doi.org/10.1016/j.tube.2015.05.018
1472-9792/© 2015 Published by Elsevier Ltd.

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Please cite this article in press as: Ignatyeva O, et al., Resistance profile and risk factors of drug resistant tuberculosis in the Baltic countries, Tuberculosis (2015), http://dx.doi.org/10.1016/j.tube.2015.05.018

rates of drug resistance and significantly improved cure rates [7–10], the Baltic States still have some of the world's highest rates of drug resistance including MDRTB which reached 8.8% in Latvia, 11% in Lithuania and 17% in Estonia in 2013 among new cases; rates of XDR were also reported to be among the highest in the world [1].

Evaluation of risk factors for primary and acquired X/MDRTB is important to identify patients vulnerable to getting drug-resistant TB and is necessary for scaling up the programmatic management of drug-resistant TB [11]. It becomes even more relevant in case of limited availability of rapid molecular assays or high laboratory workload. Early identification of patients likely to be infected with MDRTB strains aid in defining targeted groups for rapid diagnostics and will help to ensure timely initiation of appropriate treatment thus limiting X/MDRTB transmission in the community.

In this international multi-centre case–control study we aimed to identify the socio-demographic and clinical determinants of primary infection with drug-resistant tuberculosis as well as further acquisition of drug resistance across Latvia, Lithuania and Estonia. We also defined the spectrum of drug resistance to second-line drugs and described some of the main aspects of clinical management of X/MDRTB patients in these Baltic countries.

2. Material and methods

2.1. Study population and case definitions

A standardized strategy, data questionnaire and unified database were agreed and planned by the national TB treatment centres (National Tuberculosis and Infectious Diseases University Hospital in Vilnius, Centre of TB and Lung Diseases at Riga East University hospital, and Lung Hospital at Tartu University Clinics). All adult new and re-treatment patients with culture-confirmed pulmonary X/MDRTB and conventional drug susceptibility testing (DST) results registered for treatment in 2009 in each country were included into the multi-centre case–control study. This group included patients who were newly diagnosed in 2009 with primary X/MDRTB as well as re-treatment patients who started a new treatment episode in 2009. Some of these re-treatment cases were initially diagnosed with X/MDRTB ("primary resistance") and some-were initially infected with a non-MDRTB strain and later developed X/MDRTB ("acquired resistance"). The control group was composed of patients infected with non-MDRTB strains registered for treatment in each country in 2009. A random fraction of fully sensitive (at ratio 1:1) and mono/polyresistant patients (at ratio 1:10 of the number of cases that were sampled at each center) was included. The sample size calculations were based on 80% power at the 5% significance level aiming to detect the effect of a risk factor which is present in 50% of controls and has an odds ratio of 1.5, or of a risk factor which is present in only 10% of controls and has an odds ratio of 2.0. The random selection of controls for the study was determined by an independent statistician in London, UK, using a list of all non-MDRTB patients registered at each study site by means of computer-generated random number selection.

Most of the data was collected retrospectively; treatment details were collected prospectively during 2009–2012 for all enrolled patients. For some variables (the history of imprisonment, marital status, education, contact with MDRTB, etc.) the data were available for a limited number of patients only.

All specimens were cultured on solid Lowenstein–Jensen media and liquid media (BACTEC MGIT 960 System, Becton Dickinson, USA) with culture identification using a combination of phenotypic, biochemical and molecular identification methods [12,13]. Drug susceptibility testing (DST) for first and second line drugs (including isoniazid, rifampicin, streptomycin, ethambutol, pyrazinamide, fluoroquinolones (ofloxacin), injectable agents (kanamycin, amikacin, capreomycin), ethionamide, prothionamide, P-aminosalicyclic acid, cycloserin) is performed routinely on all positive cultures prior to or within four weeks of treatment initiation using the proportion method on Lowenstein–Jensen media or in the MGIT 960 system across all study sites [14–18]. XDRTB was defined when an isolate was resistant to isoniazid, rifampicin, ofloxacin and kanamycin or amikacin or capreomycin. Specimens testing was based at National Tuberculosis Reference Laboratories in Vilnius and Riga and Mycobacteriology department of Tartu University Hospital United Laboratories. The methods and the drugs used are the same across the study sites. All the laboratories underwent annual quality assurance through the WHO Global Project on Drug Resistance and/or European Center for Disease Control European Reference Laboratory Network EQA programme [19] with good results. GenoType MTBDRplus assay (Hain Lifescience, Germany) for confirmation of *Mycobacterium tuberculosis* and resistance to isoniazid and rifampicin was used on positive isolates across the study sites as a screening assay.

2.2. Data collection and management

Detailed demographic and clinical characteristics were obtained from National TB Registers and complemented by data from individual medical records at each study site. Structured questionnaires were used for anonymized data collection. Data was double-entered into an identical customized password-protected Access database at each site, and integrated into a single unified database at the study coordinator partner site; it was then re-checked by the coordinating team centrally independently.

2.3. Data analysis

We assessed risk factors for primary infection with X/MDRTB strains and risks for X/MDRTB acquisition after initial infection with a non-MDR *M. tuberculosis* strain. A descriptive analysis was carried out; the strength of the association between selected factors and drug resistance was estimated by calculation of unadjusted odds ratios (ORs) and their 95% confidence intervals (CIs). Multivariable logistic regression models included all variables from univariable analysis with sufficient number of observations. Two-tailed p-values of <0.05 were considered significant. The analysis was carried out with SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

2.4. Ethics review

The project was reviewed and approved by the Ethics Review Committees of the University of Tartu and Riga Stradini University and received a waiver of informed consent as anonymized data was used. The study was exempt from an ethics review in Lithuania by the local Ethics Committee. The study was approved by Queen Mary College Research Ethics Committee.

3. Results

3.1. Study population and prevalence of drug resistance

The majority of the study population were young males with a median age of 46 years. Two-thirds of the patients admitted alcohol abuse; 72% smoked, 17% had history of imprisonment. Drug abuse was relatively uncommon, as well as homelessness. The unemployment rate was very high reaching 40% in Estonia and 50% in Latvia and 80% in Lithuania (Table 1).

Over 23% of all the patients have had contact with an MDRTB patient, with the highest (46%) in Estonia. HIV-infection was detected in 5% of tested cases (n = 26), ranging from 2.1% in

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