

THE PROBLEM OF MULTIDRUG RESISTANT TUBERCULOSIS

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Abstract: After the 1940s it was believed that tuberculosis (TB) will be eradicated. Nowadays there is a recrudescence of the disease since the '80s, recorded difficulties associated with resistance to therapy, the emergence of multidrug-resistant tuberculosis (MDR TB) and since 2006 the extensive chemoresistant form (XDR TB). Severe cases of TB were recorded also in the Pneumology Hospital Sibiu, and in the recent years have been reported the first cases of XDR TB. We proposed conducting a prospective analysis of the degree of resistance to the tuberculostatic therapy, how it was installed in time and characteristics of the patients taken in the study (epidemiological, habitual, clinical, therapeutic etc.). The study found a high risk of primary resistance among MDR TB close contacts in the family (9 patients of the 21 identified with primary resistance MDR), a relatively high prevalence of XDR TB cases (7 patients in the 58 taken in the study, representing 12.06%), increased resistance to Fluoroquinolones and Kanamycin.

Cuvinte cheie: tuberculoza multidrogrezistentă, terapia tuberculostatică, rezistența primară

Rezumat: După ce în anii 1940 se credea că tuberculoza (TB) va fi eradicată, se constată o recrudescență a bolii începând cu anii 80, înregistrându-se ulterior dificultăți asociate instalării rezistenței la terapie, apariția tuberculozei multidrog-rezistente (TB MDR) și începând din anul 2006 definirii formei extensive de chimiorezistență TB XDR. Cazuri deosebit de grave de TB s-au înregistrat și în cadrul Spitalului de Pneumofiziologie Sibiu, iar în ultimii ani au fost semnalate primele cazuri de TB XDR. Ne-am propus efectuarea unui studiu prospectiv de analiză a gradului de rezistență a bacililor la terapia tuberculostatică, felul în care aceasta s-a instalat în timp și anumite caracteristici ale pacienților luați în studiu (epidemiologice, habituale, clinice, terapeutice, etc.). Studiul a relevat un risc crescut al rezistenței primare în rândul contacților TB MDR în mediul familial (9 pacienți din cei 21 identificați cu rezistență primară MDR), o prevalență relativ ridicată a cazurilor de TB XDR (7 pacienți din cei 58 luați în studiu, reprezentând 12,06%), o creștere a rezistenței la Fluoroquinolone și Kanamicină.

INTRODUCTION

Through the measures established by the National Tuberculosis Control Program (that is supervised by the World Health Organisation - WHO) that provides the free diagnosis, treatment, monitoring and prevention of disease for all the population, tuberculosis endemic in Romania is declining. Year 2010 was the 8th consecutive year of the incidence decline of disease. However according to WHO, Romania still remains among countries that have the highest incidence of TB in Europe.(12) In addition, as assessed by WHO in 2006, Romania situated with MDR TB incidence rate in group 6 to 20%. By comparison, in Germany and the USA the incidence of MDR TB is less than 6%, in the former Soviet Union member countries it exceeds 40%. (8)

Due to negative impacts on population, health and social costs, tuberculosis also nowadays is considered a major problem of public health.

In developed countries, TB incidence is higher among the elderly, while in countries with low economic level, the disease is more common among young people.

From a public health perspective, the incomplete or inadequate treatment is responsible for the emergence of multidrugresistant germs (noncompliant patients who do not meet prescribed posology or discontinue prematurely). It is

necessary to detect mutant strains of Mycobacterium tuberculosis resistant to tuberculostatics, the cause of failure in first-line therapy and especially for the expansion of drug resistance among the population.

The terms of chemoresistant defined by WHO: MDR TB means that M. tuberculosis resistance refers to at least Isoniazid (H) and Rifampin (R), only two major tuberculostatics, while XDR TB is a subgroup of MDR TB bacilli, with resistance to all fluoroquinolones and least one of the following chemotherapeutic agents: Kanamycin (K), Amikacin and Capreomycin.(2) (9) Recent studies indicate that in some parts of Europe, the number of XDR-TB cases comprise 15% of MDR-TB.(8)

THE OF THE STUDY

Starting from the fact that TB always raises treatment issues associated with prolonged hospitalization, high infectivity and morbidity, causing social isolation and disdain, we decided to analyze the incidence of MDR-TB and XDR aspects of resistance to therapy in Hospital Pneumology Sibiu, namely primary drugresistance (acquired by prolonged contact with a TB patient MDR / XDR) or as a result of early treatment abandon, inconsistency, lack of patient compliance, inadequate treatment.

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CLINICAL ASPECTS

MATERIAL AND METHOD

We studied a total of 58 MDR TB infected patients admitted to Pneumology Hospital Sibiu in 2006-2010, all patients having performed extensive pathogen antibiograms.

We analyzed demographic general data (age, gender, area of origin), risk factors, clinical, laboratory and therapeutic data, and also extended antibiogram.

Inclusion criterion was the presence of MDR or XDR chemoresistant type.

We watched the sensitivity of isolated germs, and we related the results to existing data in the literature.

RESULTS

We took in the study patients with tuberculosis hospitalized in the period 2006-2010 in the Department of Pneumology I, having extensive positive antibiograms, with criteria for including in the notion of MDR-TB. We followed the general data, factors, conditions in that TB infection has occurred, the susceptibility to etiologic therapy, the degree of MDR and XDR, antibiogram evolution.

The germs showed chemoresistant at least to Hydrazide (H) and Rifampicin (R), all falling within the criteria for MDR TB, additional 7 patients were XDR resistant type.

Patients were confirmed with TB during 1990-2010, following successive admissions, because of abandonment, treatment failure, relapse, chronicity, other lung associated diseases, while developing resistance MDR TB or XDR type.

Statistics revealed the following: distribution by gender revealed a total of 36 cases associated with male gender, percentage representing 62.9% of all patients studied. Among female gender were reported 22 cases. By area of origin, most cases came from urban areas, with 32 patients (55.17%) than rural (26 cases). Regarding the age group of MDR TB, we obtained the following distribution: 4 cases in 20 years (ages 16-18), 18 cases belonged to age group 20-30 years, 13 cases were have framed the age of 30-40 years, 13 cases in 40-50 years age group and 5 cases for the group 50-60 years. Over 60 years at the time of initial diagnosis have been no reports. Higher incidence found it in 20-30 years age group, representing 31.03% of the total percentage, followed by 30-40 age groups and 40-50 years, each with 13 patients (22.41%).

Sex ratio (Male/Female) 1,63
 Aria (Urban/Rural) 1,23
 Median age at time of TB diagnosis 34,29 (16; 58)

Symptoms of XDR-TB are not usually different from those associated with sensitive TB germs: cough associated or not with muco-purulent sputum, hemoptysis, more than 2 weeks, fever, shiver and night sweats, asthenia, fatigue, weight loss, dyspnoea, stabbing chest.

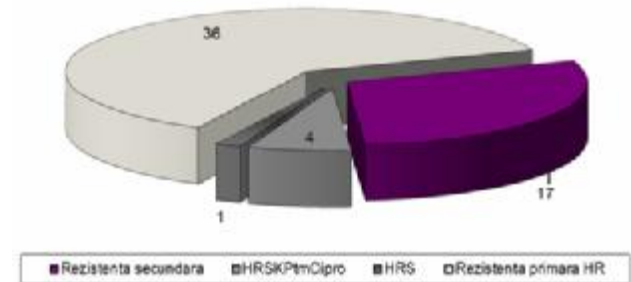
In terms of associated risk factors, 37 patients were chronic consumers of ethanol (63.79%), 32 smokers (55.17%). A total of 25 patients (43.10%) were social cases. A total of 19 patients had associated all 3 hard (32.75%), which advocates for a low compliance to treatment and increased risk of early therapeutic failure. Number of early treatment abandonment amounted to 13 cases (22.41%). Time the cultures became MD or XD resistant varied from one patient to another, in most cases

(30 patients, representing 51.72%) by setting up resistance more than a year after first diagnosis TB. However a significant number of 28 patients found resistance to first tuberculostatic after less than a year (48.27%), and among them 21 were primary MDR resistant (36.2% of all 58 patients, of which 17 cases with HR primary resistance and 4 cases with primary resistance to HR Streptomycin=HRS). In a case was reported XDR primary resistance (HRS Kanamycin Prothionamide Ciprofloxacin= HRSKPtM Cipro)-table no.1, figure no.1.

Table no. 1. Frequency of primary resistance

Primary resistance to chemotherapy	No. of cases	Percentage
H R	17	29,3%
H R S	4	6,9%
H R S K PtM Cipro	1	1,7%
Secondary resistance	36	62,1%
Total patients in study	58	100%

Figure no. 1. Frequency of primary resistance among the 58 MDR TB patients



A significant number of primary MDR TB patients (9 patients out of 21) came from families with MDR TB contacts, but have been reported cases in which resistant bacteria contamination source could not be identified.

An example of primary resistance of MDR type is the intra-familial case of two male patients, 15 and 16, showing primary resistance HR (father being known MDR TB), one of the two brothers subsequently developing type resistant XDR. That also plays an important role the socio-economic conditions, abandonment, noncompliant patients. Total of 7 patients developed resistance XDR type (reported in Isoniazid (H), Rifampicin (R) and Kanamycin (K) in all 7 cases, Ethambutol (EMB) and Streptomycin (S) in 4 cases, in 3 cases Ofloxacin, Ciprofloxacin 2 cases, 1 case Ethionamide und Prothionamide), including one patient having primary resistance of XDR type (HRSKPtM Cipro), the patient died during the evaluation study.

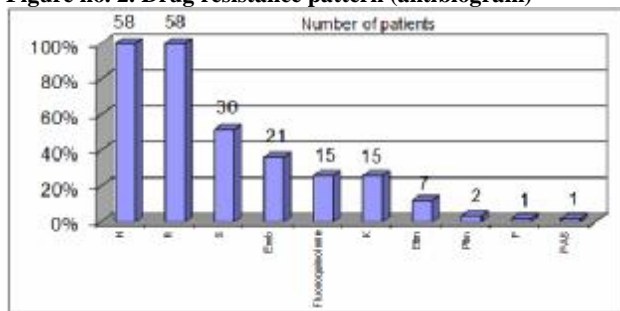
In time the resistance extended to other tuberculostatics as follows: 58 cases followed HR resistance, followed by S frequency rate of 30 cases, Ethambutol (Emb) 21 cases, 15 cases Kanamycin(K), Ofloxacin(Oflx) with 12 cases, 7 cases Ethionamid(Etm), resistance to Ciprofloxacin (Cipro) occurred in 3 cases and one case each Pyrazinamid (P), PAS, Prothionamide(Ptm). Alltogether Fluoroquinolone resistance amounted in 15 cases, representing a significant percentage of 25.86%-table no.2, figure no.2.

Table no. 2. Drug resistance pattern (antibiogram)

Name	H	R	S	Emb	K	Oflx	Cipro	Etm	P	PAS	Ptm
Number	58	58	30	21	15	12	3	7	1	1	1
Percentage	100%	100%	52%	36%	25,86%	20,68%	5,18%	12%	2%	2%	2%

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Figure no. 2. Drug resistance pattern (antibiogram)



We remark a tendency towards a more broad spectrum resistance to tuberculostatic therapy.

CONCLUSIONS

In our study TB was diagnosed among young people, in this view fits us statistically among developing countries.

A percentage of 32.75% of patients with MDR TB / XDR were associated with chronic ethanol consumption, smoking or were social cases, giving rise to low compliance to treatment and increased risk of early therapeutic abandonment (13 cases namely 22.41%).

Besides the HR resistant strains, which is the main criterion for inclusion in the definition of MDR TB, there was recorded a high resistance to Streptomycin and Ethambutol (52% respectively 36%).

Along with resistance to first-line chemotherapy, we found increased frequency of resistance to Kanamycin and Fluoroquinolones (Ciprofloxacin and Ofloxacin), both drugs were included in the class of risk for the development of XDR TB.

The main reason for the development of MDR-type resistance was the primary contact with family occurred MDR TB patient (9 patients out of 23). However there were cases in which the source could not be specified.

In our study of XDR TB cases were 7 of 58 (12.06%), confirming the alarming increase of cases of XDR-resistant type, emphasizing especially fluoroquinolone resistance, partly due to intempestive administration of these drugs in hospitals and family doctors offices for other affections (nonspecific pneumonia or urinary infections), significantly increasing the selection of resistant germs. We also found a high rate of abandonment of therapy (22.41%), impact-resistant additional development.

Very important are the early recognition of cases of MDR TB / XDR, first use of molecular methods for detection of resistance, that reduces the time of ineffective conventional therapy in these cases. According to guidelines developed by WHO in 2011 will be given appropriate therapy according to individual resistance, that will be extended for 20 months. Fluoroquinolone use should be prescribed with caution.

The WHO has set itself with the initiative "Stop TB 2006-2015" a strict deadline: Until 2015, the number of tuberculosis cases worldwide should be reduced by 50 percent compared to 1990 - a goal that could be difficult to achieve, mainly due to increasing resistance to tuberculostatic therapy.(10)

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