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Drug-resistance of mycobacterium tuberculosis in time

L. MAZZEI, G.F. CROCE*, A. ZARZANA, D. BIAGIOLI, B. SPOSATO, A. PULCINELLI

2nd Department of Pneumology, "La Sapienza" University, C. Forlanini Hospital - Rome (Italy)
*4th Division of Infectious Disease, "L. Spallanzani" IRCCS Hospital - Rome (Italy)

Abstract. – Tuberculosis is heavily worldwide spreading in the last years. More and more signalations seem to indicate that the incidence of drug-resistant Mycobacteria is increasing in almost all industrialized countries.

The authors have carried on a study on the percentage of drug-resistant strains of Mycobacterium Tuberculosis (MT) among isolates from patients affected by active pulmonary tuberculosis hospitalized through the years 1992-94. Out of 59 isolates of MT, 20.3% were drug-resistant: 25% of them to 2 drugs and 16.6% to 3 or more drugs. Resistance to single drug was so distributed: Streptomycin 11.8%, Isoniazid 6.7%, Rifampycin 3.4%, Ethambutol 6.7%, Ansamycin 3.4%, Pyrazinamide 5.0%, Ethionamide 1.7%. These results were confronted with analogous data on MT drug-resistance collected in the same hospital division in the years 1978-82 and 1985-87. The data analysis shows that actual incidence of drug resistant strains of MT is only slightly decreased but quite similar to that observed in 1978-82, except for Ethambutol, while there is a remarkable reduction vs. 1985-87; in that period, in fact, the highest incidence of drug resistance was recorded. The authors' conclusion is that only little differences were observed in the total amount of resistant strains of MT through 20 years; they also outline that resistance to Ansamycine, most recent out of all tested drugs, is quite similar to that observed for Rifampycine, that is chemically analogous.

Key Words:

Tuberculosis, Mycobacterium Tuberculosis, Drug resistance.

Introduction

In 1994 WHO has stated that *"... Tuberculosis represents a world health emergency"*. The increasing number of new cases is going to produce from 1990 to 2000 90 millions of affected persons of which 1/3 (30 millions) will die of Tuberculosis (TBC)[2].

A WHO study indicates a 28.7% global increment of TBC worldwide in the period 1990-91, compared to the period 1984-85, with a 39% increase in Africa and South East Asia[1].

More detailed epidemiological studies carried on in the USA show that the increment of new signalated cases (+14% compared to the expected cases) occurred within the ethnic minorities and most of all in patients who were born outside the USA. Recently published data show an increasing number of immigrants among new cases in Europe, too (51% in Switzerland, 41% in Netherlands and Sweden, 38% in Denmark and 16% in Italy)[3].

A correct epidemiological evaluation concerning TBC in our country, is not easy to perform, and this is also due to a lack of centralized surveillance; some data, though, indicate a tendency to a marked increment of cases in Italy, too. A national trial concerning the incidence of TBC (GISTA) in HIV-infected persons has indeed shown a positive trend in this group of patients in Italy; moreover, all Italian *phthisiologists* do know that an increasing number of immigrants affected by TBC is admitted into Italian hospitals, and this is also happening in Northern Europe and North America[11].

Many single signalations, mainly from the USA, Spain, Great Britain, France and Italy, outline an increasing number of drug-resistant strains of Mycobacterium Tuberculosis (MT-DR); the great majority of the reported cases concern small epidemics among convicted or hospitalized persons, particularly HIV-infected patients[6-10].

Table I. Percentage of mono- and multi-resistant isolates in the compared years.

Resistance	1978-82	1985-87	1992-94
1 drug	55.7%	33.3%	58.3%
2 drugs	21.3%	24.4%	25.0%
3 or more drugs	23.0%	42.3%	16.6%

Our aim was to verify the percentage of drug-resistant Mycobacterium Tuberculosis (MT) strains among isolates in our division, comparing our results with analogous data collected in the same hospital division in the years 1978-82 and 1985-87, in order to reveal possible important differences in the drug-resistance pattern through the years[4-12].

Materials and Methods

A retrospective study was performed on 97 patients (47 males and 50 females), admitted in our pneumophtisiologic division between 1992 and 1994; 38 patients (39%) were affected by extra-pulmonary clinical forms of TBC. Sputum culture for MT and common bacteria on the remaining 59 patients showed 12 drug-resistant isolates (20.3%); 14 patients (23.7%) had a mixed bacterial flora and/or mycetes. Percentage of drug-resistance was compared with the results of two analogous studies that we performed in 1978-82 and 1985-87[4,12]. Percentage of drug-resistant strains settled around 20%, with minimal changes compared to previous data. Single drug resistance evidenced a slight decrement for Streptomycin (SM = 11.8%) and Isoniazid (INH = 6.7%), while was stable for Rifampycin (RFP = 3.4%) and slightly increased for Kanamycin (KANA = 1.7%); it is interesting notice that drug-resistance for Rifabutin (RFB), most recent out of all tested drugs, is already 3.4% which is a percentage quite similar to that observed for the chemically analogous Rifampycine, and this may be due to cross resistance. SM is still the drug with the highest percentage of resistant strains, followed by INH, Ethambutol (ETB), Pyrazinamide, RFP and RFB (Table II).

Five out of 12 (41,6%) isolated drug-resistant mycobacteria were multi-resistant: 3 of them (25%) to 2 drugs and 2 (16.6%) to 3 or more drugs. Four of the multi-resistant MT were isolated by patients with inveterate or chronic pulmonary TBC forms (Table I). The percentage of isolates resistant to 3 or more drugs is greatly reduced compared to the past. None of our patients was HIV-infected.

Among common bacteria associated to MT Gram-negative ones were highly prevalent, and mainly Haemophilus, Pseudomonas spp. and Klebsiella, while Gram-positive (Streptococci) and Mycetes (Candida), similarly to our previous observations were rare[13].

Table II. Percentage of single drug resistance in the considered periods.

Drug	1978-82	1985-87	1992-94
Streptomycin	12.9%	19.8%	11.8%
Isoniazid	8.4%	13.8%	6.7%
Rifampycin	3.9%	11.3%	3.4%
Ethambutol	3.9%	10.2%	6.7%
Kanamycin	0.8%	6.0%	1.7%
Cicloserin	0.3%	1.8%	–
PAS	0%	2.5%	1.7%
Pyrazinamide	–	–	5.0%
Ethionamide	–	–	1.7%
Rifabutin	–	–	3.4%

Discussion

Our analysis shows that MT drug-resistance is a well defined and stabilized reality. The greater amount of resistant isolates found in the years 1985-87 may be due to the larger numeric consistence of isolates (282 vs. 59) and to the higher quantity of chronic and/or relapsed forms of TBC in that study, with more incidence of multi-resistant isolates (Table I).

Those data, however, very well reflect the incidence of drug resistance to the single drugs; it is very interesting to note the MT drug-resistance trend toward the years: there was an increase of drug resitant strains for all the considered drugs in the years 1985-87, with a reduction to levels very similar to 1978-82 in the present study (Figure 1). This trend is not easy to explain; more immigrant patients, mainly affected by recent forms of TBC, were enrolled in the present study compared to the previous ones, and this might explain the lower incidence of drug-resistant isolates. The apparent reduction of drug-resistance in the last 10 years is not actually true, and it is more correct to affirm that there has been a substantial stabilization of MT drug-resistance since the 70s.

Although no relevant change was evidenced for any considered drug, it seems that a slight decrement in drug resistance may be noted for SM (-1.1%) and INH (-1.7%), while a slight increment is present for ETB (+2.8%). More *"recent"* drugs, such as Pyrazinamide and Rifabutin, show drug resistance percentages overlapping the ones of the drugs from which they are derived, Isoniazid and Rifampycin; cross resistance probably plays an important role in this phenomenon (Table II).

Drug-resistance is still, therefore, an important phenomenon, which has to be carefully investigated and prevented with drug alternation as far as possible; if there is an ascertain drug-resistance to 1 or more major anti-TBC drugs, it may be advisable to associate other modestly active drugs against MT (such as Quinolones or Claritromycin).

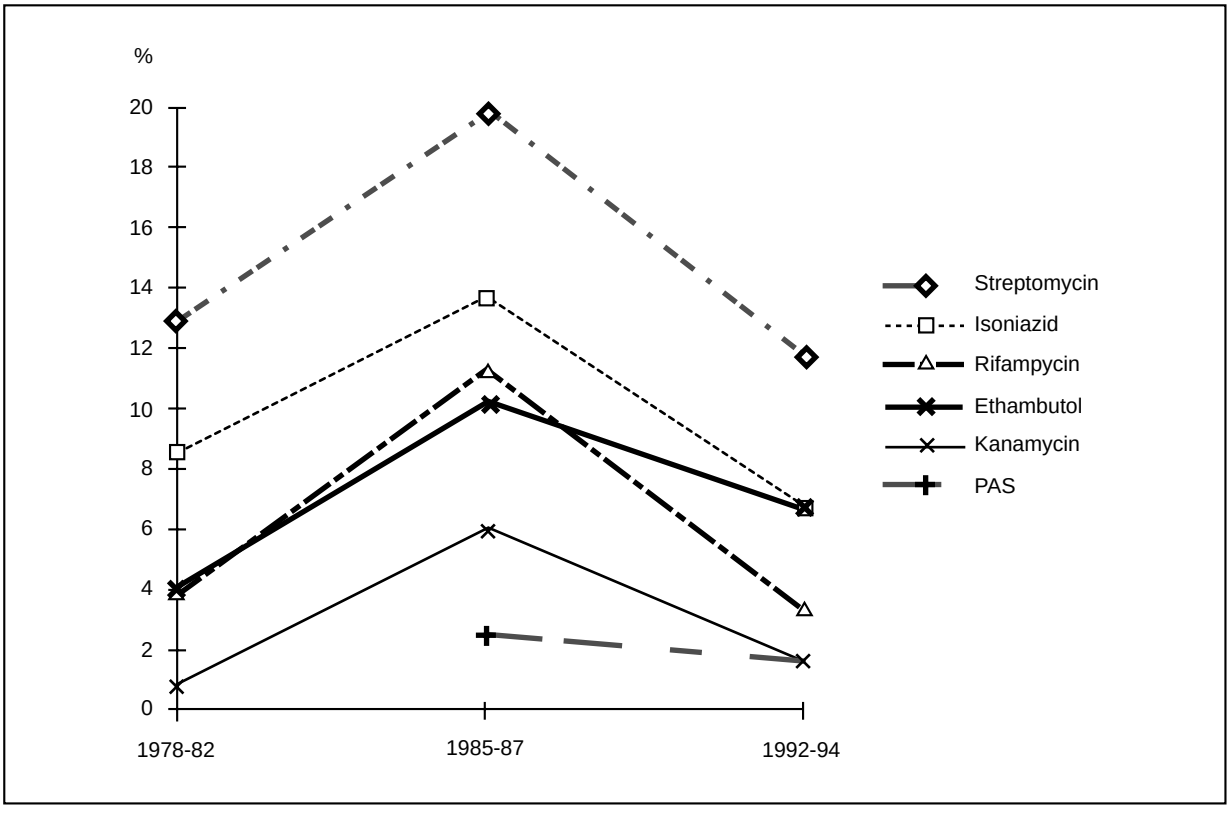

Figure 1. Trend of resistance to single anti-mycobacterial drug from 1978 to 1994.

Finally the association of MT with common bacteria, especially greatly virulent Gram-negatives such as Haemophilus and Pseudomonas, is not to be underestimated; in fact, they confuse the clinical and radiographic aspect of the disease, threatening the life of weakened TBC patients, contributing to massive destructions of pulmonary tissue, with serious outcomes at the time of the eventual recovery. If anti-TBC therapy does not give results we have to wonder if there is one of the above conditions, establishing MT susceptibility test and arranging therapy on its results.

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