

The spread of drug-resistant tuberculosis in children: an Italian case series

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SUMMARY

Drug-resistant paediatric tuberculosis (TB) is an overlooked global problem. In Italy, the epidemiology of TB has recently changed and data regarding drug-resistant forms in the paediatric setting is scanty. The aim of this case series was to report the cases of drug-resistant TB, diagnosed between June 2006 and July 2010 in four Italian tertiary centres for paediatric infectious diseases, in children and adolescents living in Italy. Twenty-two children were enrolled, of these 17 were resistant to one or more drugs and five had multidrug-resistant TB. All but one child were either foreign born or had at least one foreign parent. Twenty-one patients completed their treatment without clinical or radiological signs of activity at the end of treatment, and one patient was lost to follow up. The outcomes were good, with few adverse effects using second-line anti-TB drugs. Although this series is limited, it might already reflect the worrisome increase of drug-resistant TB, even in childhood.

Key words: Adolescent, children, drug resistance, treatment, tuberculosis.

INTRODUCTION

Tuberculosis (TB) is a major cause of morbidity and mortality worldwide. In 2011 the estimated global incidence and prevalence was 8·7 million and 12 million cases, respectively [1]. In some industrialized countries, the epidemiology of TB has been changing over the last decades, mostly driven by migration

from countries with high prevalence of disease and high rates of *Mycobacterium tuberculosis* strains resistant to one or more first-line anti-TB drugs [2]. In particular, multidrug-resistant TB (MDR-TB; defined as a strain resistant to at least rifampicin and isoniazid [3]) is a growing problem in Europe, where more than 29 000 cases were reported in 2010 [4].

Almost 40 000 paediatric cases of TB were notified in the past decade in the European Union with two different epidemic settings: in high-incidence countries there has been a decline or a stabilization in the rate of notification; conversely, in low-incidence countries this rate has increased, due to migration flow [4].

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Indeed foreign-born children may acquire the infection before entering the country, thus not reflecting the local epidemiological situation [5].

With 4418 cases notified in 2008 (50% in foreign people) Italy is a low-prevalence TB country. However, a slight increase was seen in children and adults aged <65 years [6], with mono- and multi-drug resistance to first-line anti-TB drugs observed in ~14% of the cases, whereas MDR-TB strains occurred in 3.7% of cases [6].

According to the latest Italian National Health Service Report in 2008, in Italy the estimated incidence of TB in children aged 0–14 years was 2.7 cases/100 000 children and the percentage of MDR-TB forms appeared as just above 2% [6].

Treatment of drug-resistant TB requires prolonged therapy, sometimes with second-line drugs, which are often more toxic and expensive.

In children, diagnosis for all forms of TB is limited by the difficulty in obtaining adequate specimens, and microbiological data, including drug susceptibility testing (DST), are not always looked for or obtained [7, 8].

Moreover, there are two main problems in the treatment of paediatric TB: (i) drug formulations, which are often not readily available and (ii) the off-label use of a large proportion of second-line drugs.

We describe the characteristics of drug-resistant TB diagnosed in children and adolescents, living in Italy, focusing especially on the clinical characteristics, treatment regimens adopted, their effectiveness and safety.

METHODS

A retrospective multicentre survey, involving four Italian tertiary centres for paediatric infectious diseases, under the auspices of the Italian Society of Paediatric Infectious Diseases (SITIP), was conducted to identify children and adolescents (0–18 years) with drug-resistant TB, diagnosed from 1 June 2006 to 31 July 2010. Demographic, microbiological, clinical characteristics, type and duration of treatment, possible side-effects and outcome of every patient, were collected through a target unified form, by each centre and analysed using Excel 2007 (Microsoft Corp., USA).

According to WHO definitions, a TB case was considered as drug-resistant when: (a) *M. tuberculosis*, resistant to at least one of the anti-TB drugs, was isolated or (b) a close contact with a known adult source

of infection with drug-resistant TB was recorded, even without *M. tuberculosis* isolation [9].

Furthermore, mono-resistant TB was considered in cases of resistance to one anti-TB drug, MDR-TB in cases of resistance to both isoniazid and rifampicin, while poly-resistant TB if resistance to more than one drug, other than both isoniazid and rifampicin, was present. Finally, we considered extensively drug-resistant (XDR)-TB as MDR-TB strains additionally resistant to either any fluoroquinolone, and to at least one of the three injectable second-line anti-TB agents, i.e. amikacin, kanamycin and capreomycin [7, 10, 11].

In pulmonary TB, clinical samples for microscopy and mycobacterial cultures were obtained through expectoration or through three consecutive early-morning gastric aspirations, in case of difficulty in producing sputum samples [9].

The diagnosis of drug-resistant TB was based upon phenotypic DST methods using BACTEC MGIT 960 TB system (Becton Dickinson, USA) and/or genotypic DST methods, detecting resistance-associated mutations to isoniazid and rifampicin in target genes of *M. tuberculosis* through GenoType MTBDRplus (Hain Lifesciences, Germany). Treatment outcomes were evaluated according to WHO criteria [12].

The study was conducted using anonymized data. When off-label second-line drugs were given, written informed consent was obtained from the children's parents.

RESULTS

Description of cohort

Twenty-two children (50% males) were included; their median age at diagnosis was 5.2 years (range 0.5–17.9 years). Characteristics of patients, their patterns of TB drug resistance, therapeutic regimens and outcomes are described in Table 1.

Fourteen (63.6%) patients were born in Italy, five (22.6%) in Peru and one (4.6%) each in Sierra Leone, Pakistan, and Ukraine. Of the 14 children born in Italy, 13 (92.9%) had at least one foreign parent [five (38.5%) from Latin America, five from Eastern Europe, two (15.3%) from Asia and one (7.7%) from sub-Saharan Africa]. No patients had a previous history of TB.

Regarding personal history, the source of infection was identified for 12 (54.5%) patients; 11 were relatives, of whom 10 were household contacts.

Table 1. *Patients' demographic and clinical characteristics, Chest X-ray findings at diagnosis, patterns of resistance, treatment and outcome*

Case no.	Sex; age (years)	Country of origin	BCG vaccination	TST result	Site of disease	Symptoms	Chest X-ray findings	Resistance pattern	Drug regimen† (duration of treatment, months)	Adverse effects	Outcome
1	F; 6·3	Romania	No	P	Lung + pleura	Vomiting, diarrhoea	Nodular infiltrates in the medium lobe of right lung and ipsilateral pleural effusion	S*, H	R (6), Z (6), E (6), MFX (4)	No	Cured
2	M; 0·9	Moldova	No	P	Lung	Cough	Infiltrate in the apex of right lung	S, R, H, E, Z, Cs, PAS, ETO	ETO (3), PAS (3), MFX (3), LZD (3), AMK (1)	No	Lost to follow-up
3	M; 13·9	China	No	P	Lung	Fever, cough, haemoptysis	Cavitated infiltrate in the apex of left lung	S, R	H (13), E (13), MFX (12), Z (2·8)	No	Cured
4	F; 1·8	Romania	No	P	Lung	Fever	Left para-hilar nodular infiltrates	S, R, H, E, Z	MFX (13), LZD (13), PAS (5), ETO (2)	No	Cured
5	M; 0·5	Romania	No	N	Lung	Fever, cough	Right hilar nodular infiltrates	H*, Cs, PAS	R (8) MFX (7·5), Z (6), S (1) → E (3·5)	No	Cured
6	F; 1·3	Peru	No	P	Lung	No symptoms	Parenchymal infiltrates in the upper lobe of the left lung	S, H	R (7), Z (7), E (6), MFX (5·5)	No	Cured
7	F; 3·3	Senegal	No	N	Lung	No symptoms	Left para-hilar nodular infiltrates	S*, R	H (9), MFX (9), E (5) Z (2·3)	Hepatitis	Cured
8	M; 14·3	Peru	Yes	P	Lung	Cough	Nodular and cavitated infiltrates in the right lung and in the apex of LLL, with right pleural effusion	H	R (12), E (12), Z (3), LFX (11)	No	Cured
9	M; 13·6	Peru	Yes	P	Lung + mediastinal and mesenteric lymph nodes	Fever, cough	Nodular infiltrates in the ULL of the apex of the LLL	S, H	R (12), E (12), Z (5)	No	Cured
10	M; 1·7	Peru	No	P	Cervical lymph node + pleura	Fever, cough	Right pleural effusion	H*, Z	R (6), E (6)	No	Cured
11	M; 16·8	Peru	Yes	P	Peritoneum	Fever, abdominal pain	–	S	H (7), R (7), Z (2), E (2)	No	Cured
12	F; 16·6	Sierra Leone	Yes	P	Lung + breast	Fever, cough	Multiple parenchymal infiltrates in both upper lobes and a cavitated infiltrate in the LRL. Bilateral hilar adenopathy	S (low doses)	H (7), R (7), Z (2), E (2)	No	Cured
13	F; 15·8	Ukraine	Yes	P	Lung	n.a.	Bilateral apical patchy infiltrates	S, R, H, E, Z, Cs, PAS, ETO, KM	MFX, LZD (8), AMX/CLV (4), CFZ (2)	Vomiting, leg pain	Cured

Table 1 (cont.)

Case no.	Sex; age (years)	Country of origin	BCG vaccination	TST result	Site of disease	Symptoms	Chest X-ray findings	Resistance pattern	Drug regimen† (duration of treatment, months)	Adverse effects	Outcome
14	M; 17·9	Peru	Yes	P	Lung	Cough	Right hilar adenopathy with para-hilar nodular infiltrate	Z	H (6), R (6), E (6)	No	Cured
15	F; 3·2	Peru	No	P	Lung + pleura	Fever, cough	Right hilar adenopathy	H	R (9), E (9), Z (2)	No	Cured
16	F; 4·2	Peru	No	P	Lung	Fever, cough	Parenchymal infiltrate of the LLL	H*	R (8), Z (8), E (2)	No	Cured
17	F; 16·3	Peru	Yes	P	Miliary TB	Fever, vomiting, chest pain	Parenchymal infiltrate of the LRL. Mediastinal adenopathy with calcifications	S, R, H, KM	R (12), E (12), Z (11), MFX (5)	Myelotoxicity	Cured
18	M; 0·6	Italy	Yes	n.e.	Lung	Cough	Parenchymal infiltrate of the LRL. Right hilar enlargement	R, H	R (8), Z (8), E (3)	No	Cured
19	F; 15·9	China	No	P	Lung	Cough	Multiple inflammatory infiltrates in the right lung	R	H (13), E (13), Z (1), LFX (11)	No	Cured
20	M; 2·4	Moldova	No	P	Lung + joint	Joint pain	Overall reduction of pulmonary transparency	H	H (13), R (13), Z (3), E (2)	No	Cured
21	F; 15·2	Pakistan	n.a.	P	Bones	Fever, pain	–	H	R (12), Z (12), E (12), CFX (11)	Hepatitis	Cured
22	M; 2·6	Peru	No	P	Lung + pleura	Cough	Roundish parenchymal infiltrate of the medium lobe of the right lung, with ipsilateral hilar enlargement and pleural effusion	H	R (14), H (14), Z (7), E (2)	No	Cured

BCG, Bacille Calmette-Guérin; MDR-TB, multidrug-resistant tuberculosis; M, male; F, female; H, isoniazid; R, rifampicin; Z, pyrazinamide; S, streptomycin; E, ethambutol; AMK, amikacin; KM, kanamycin; MFX, moxifloxacin; LFX, levofloxacin; CFX, ciprofloxacin; CS, D-cycloserine; PAS, *para*-aminosalicylic acid; ETO, ethionamide; LZD, linezolid; AMX/CLV, amoxicillin/clavulanic acid; CFZ, clofazimine; LLL, left lower lobe; ULL, upper left lobe; LRL, lower right lobe; TST, tuberculin skin test; P, positive; N, negative; n.e., not executed; n.a., not available.

Drug 1 (*x*) → drug 2 (*y*): drug 1 administered for *x* months and then substituted with drug 2, used for *y* months.

* Index case's pattern of resistance.

† Drug regimen adopted after identification of resistance

The identification of the index case was not possible for nine patients; in one subject (no. 13) TB was diagnosed in a foreign country and the personal history was missing.

The information on clinical symptoms was available from 21/22 (95.5%) patients' records (this information was missing for child no. 13): 19/21 (90.5%) were symptomatic at diagnosis; cough was the most frequent symptom (13/19, 68.4%), followed by fever (11/19, 57.9%). No patient had weight loss. Two patients were asymptomatic and they were diagnosed during investigations for close contacts.

A QuantiFERON[®] TB Gold In-Tube assay (Cellestis Ltd, Australia) was performed in nine (40.9%) subjects, of which eight were positive. No patient was HIV positive.

Sixteen (72.8%) children had a pulmonary disease (including one with miliary TB), two (9%) an extra-pulmonary disease, and four (18.2%) had both pulmonary and extra-pulmonary TB.

Microbiology

Specimens were collected for microscopy and mycobacterial culture for all patients. In those with lung involvement, clinical samples were obtained through expectoration in five cases and through three consecutive early-morning gastric aspirations in 12 cases. For patients with extra-pulmonary involvement, specimens were collected from the site of infection, e.g. synovial and peritoneal fluid, bone, breast and lymph node.

TB diagnosis was confirmed microbiologically in 17 (77.3%) subjects, including six (35.3%) who had positive smears for acid-fast bacilli. In 12/17 (70.6%) patients with positive cultures, phenotypic DST methods were performed. Of these, three were also tested by molecular methods to detect mutations associated with isoniazid or rifampicin resistance and the results were in accordance with phenotypic methods. Five patients were diagnosed through genotypic assay.

In the five subjects where *M. tuberculosis* had not been isolated, the index case's pattern of resistance was used for planning treatment regimens. All the index cases had been tested by phenotypic DST assays, together with genotypic detection in two cases; the results were similar in one case, while in the other, rifampicin was undetermined by genotypic assay, while no resistance to the drug emerged from the phenotypic test (case no. 1).

Treatment regimens

Before the identification of the *M. tuberculosis*-resistant strain all patients received a recommended first-line drug regimen [9, 12], using three or four drugs, pending their own or the index case's DST results. After identification of resistance, different drug regimens were chosen by each centre, even if the resistance patterns were similar.

Second-line anti-TB drugs were used for 12 patients: eight with mono- or poly-resistant TB and four with MDR-TB. In all cases a fluoroquinolone was administered for a mean duration of 7 months; moxifloxacin or levofloxacin were added to first-line anti-TB drugs to treat extensive pulmonary mono- or poly-resistant TB, while ciprofloxacin was used for one child with severe extra-pulmonary isoniazid-resistant TB involving the spine and one rib (no. 21).

The other 10 cases of mono- or poly-resistant TB were treated with first-line drugs, as shown in Table 1.

Patients with MDR-TB received different combinations of first- and second-line anti-TB drugs, with individually tailored regimens.

The treatment was successfully completed by 21 patients, with no signs of clinical or radiological activity at the end of treatment. Of these, 16 patients with pulmonary involvement and positive culture at the beginning of therapy had sputum conversion during treatment. In one patient (no. 11) with extrapulmonary TB and positive culture of peritoneal fluid at diagnosis, culture was not repeated since the ascites resolved with anti-TB therapy. One child with MDR-TB (no. 2) had sputum conversion after 1 month of treatment, the chest X-ray performed after 2 months of treatment showed an improvement of lung lesions; this child was progressing well at 3 months of therapy but was lost to follow-up.

Drug-associated adverse effects were monitored regularly during therapy through clinical observation, complete blood count and liver functional tests (LFTs). Children treated with fluoroquinolones did not show any important adverse effects, only one child showed an increase of LFTs after 9 months of combined therapy with isoniazid and moxifloxacin, which disappeared after the drugs were discontinued.

The two bacteriostatic second-line agents, ethionamide and *para*-aminosalicylic acid (PAS), suggested for MDR-TB treatment [13–15] in this study were administered to two infants with MDR-TB for a few months. One patient (no. 13) developed vomiting and leg pain with ethionamide (used before the

identification of the *M. tuberculosis* strain resistant to this second-line drug); these symptoms disappeared at discontinuation of the drug.

In our series, linezolid was given to three patients with MDR-TB with no adverse reactions.

DISCUSSION

Drug-resistant *M. tuberculosis* infection is becoming a serious and growing problem in some developed countries [2, 5, 16–18]. For patients infected or suspected of being infected with strains resistant to one or more anti-TB drugs, several medications must be given simultaneously for prolonged periods, sometimes using second-line drugs which may cause toxicities and side-effects [13].

Data on the occurrence of drug-resistant TB in children in Italy are limited to case reports or small case series [16, 19–21]. Two of these published studies described seven patients who were included in the present survey [16, 20].

The phenomenon of drug-resistant TB is presumably underestimated, bearing in mind the paucibacillary nature of pulmonary disease and the difficulty in obtaining adequate culture specimens during infancy and childhood [7]. Despite Italy being a low-incidence country for TB, the number of cases due to strains resistant to at least one of the first-line anti-TB agents has been increasing; according to the latest Italian National Health Service Report in 2008, in adults these forms represent 14% of the reported TB cases in Italy [6].

In Italy, the incidence of paediatric cases of drug-resistant TB is expected to increase over the next years, with increased immigration from high-prevalence countries [6] contributing to this. In fact, about half of our cases occurred in foreign-born people and all but one patient had one or both parents from a country with a high-prevalence of TB [e.g. Peru (45.4%) or Eastern Europe (27.3%)].

The current study confirms the prevalence (3/5 patients) of MDR-TB in patients aged <5 years, already noted by recent surveillance reports on TB epidemiology in Western European countries [4]. As reported in previous studies, the prevalence of MDR-TB in younger children could suggest household transmission, probably revealing higher or prolonged infectivity [22].

Drug-resistant TB is essentially a man-made disease, since it derives from an inadequate use of

anti-TB drugs; the first step for its prevention is a well-administered first-line therapy for susceptible cases. An inadequate or poorly administered treatment regimen allows a drug-resistant strain to become the dominant strain. XDR-TB may emerge when second-line anti-TB drugs are misused or mismanaged [23, 24]. Drug-resistant TB is mainly a microbiological diagnosis, although a history of contact with adult drug-resistant TB cases or of previous TB treatment are both extremely important [7, 14, 23, 25]. The availability of the DST and information on the likely adult index case may help in planning appropriate treatment [3, 7, 8, 25, 26]. Drug-resistant TB should always be taken into consideration in a child with signs and symptoms compatible with the disease, if the child or his family come from a high-burden TB country, or in the case of previous TB, or contact with an active TB patient [7, 8]. If resistant strains might be involved, a four-drug first-line initiation phase of therapy should be started while waiting for DST results, then the empirical regimen can be adjusted on the basis of the DST results [12, 13]. Of our patients, none had a previous history of TB; the adult source was identified in 50% of the patients and these were often household contacts. Furthermore, the adult source's DST was used to plan the treatment in five children with negative cultures.

In our study, the treatment regimens were not identical, which was also the case for subjects with similar patterns of resistance. This may be due to the lack of standardized protocols and specific regimens in childhood.

The number of anti-TB drugs needed for the successful treatment of drug-resistant TB and the duration of therapy are dependent on the extent of the disease and the degree of drug resistance [7, 8, 14].

There is general agreement for fluoroquinolone use in paediatric patients with mono-resistance to rifampicin and to consider the addition of a fluoroquinolone to first-line anti-TB drugs in extensive disease with resistance to isoniazid [9, 12, 15]. In two recent series the safety and tolerability of fluoroquinolones, in particular moxifloxacin, have been reported in children presenting first-line drug-resistant TB or extensive forms [20, 27]. Therefore, the benefits of fluoroquinolone administration in children affected by MDR-TB presumably outweigh the risks [12, 13]. In our study, only one child, treated with a combination of isoniazid and moxifloxacin showed an increase of LFTs, which gradually disappeared after drug discontinuation.

The other second-line drugs, such as ethionamide, PAS and linezolid, suggested for use in MDR-TB/XDR-TB cases [13–15, 28–33], have been successfully administered in this study. Only one patient exhibited vomiting and leg pain with ethionamide, which completely disappeared after discontinuing the drug.

The outcome of drug-resistant TB is related to the pattern of drug resistance and to the regimen used [23]. Considering the great variability of regimens used, the outcomes in our patients were good. Regarding MDR-TB, four patients experienced sputum conversion within 3 months from the beginning of treatment; one patient was then lost to follow-up.

The cases reported here come from four Italian tertiary centres, which are referral centres for paediatric infectious diseases in Northern and Central Italy. Therefore the primary limit of this study is that it can not reflect the true national epidemiology of drug-resistant TB in Italian children; however, it highlights the worrisome spread of these forms, even in low-burden TB countries such as Italy. Another limitation of our study is its retrospective nature. In the collection of information some data might not have been included; moreover, we did not collect data about the follow-up after treatment interruption, thus we cannot rule out possible recurrences. A further limit concerns statistical analysis on the possible risk factors for developing drug-resistant TB; this analysis could not be performed due to the small sample size and because all patients were cured, except one who was lost to follow-up. Finally, we could not calculate the incidence of this disease in Italian children, because the information concerning how many children, in every centre, had a drug-susceptible TB form was not available.

In conclusion, even if drug-resistant TB is uncommon in high-income countries like Italy, drug-resistant strains continue to circulate in children and adolescents. Clinicians must keep in mind drug-resistant TB when starting any anti-TB treatment or when making decisions to change the therapeutic regimen in affected children, particularly when they or their parents come from high-risk areas. Drug-resistant TB in children has been poorly investigated, mainly because of the difficulty in obtaining a microbiological diagnosis in this population. Moreover, as reported by recent findings of Zignol *et al.*, children are as likely as adults to have MDR-TB [34]. Outcome in our patients was good and adverse effects were relatively rare. Further studies, particularly those with surveillance purposes, are needed to better understand the burden

of drug-resistant TB in paediatric settings, especially in Europe, and to clarify its management and clinical follow-up.

DECLARATION OF INTEREST

None.

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