



Drug-resistant tuberculosis in children

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Drug-resistant tuberculosis (TB), and especially multidrug-resistant (MDR) TB (i.e. resistance to isoniazid and rifampicin with or without resistance to other drugs) or extensively drug-resistant (XDR) TB (i.e. MDR resistance plus resistance to the fluoroquinolones and one of the second-line injectables – kanamycin, amikacin or capreomycin),¹ has very important implications for affected children and the TB control programme. These children are difficult to manage because of the increased adverse effects of the second-line anti-TB drugs and the prolonged duration of treatment. Furthermore, they are often diagnosed late because the history of a drug-resistant contact was not obtained or responded to. Children mainly have paucibacillary disease, which means that diagnosis of a child, especially with MDR TB, usually points to recent transmission in the community and therefore a failure of the TB control programme.

Infectiousness of drug-resistant *Mycobacterium tuberculosis* strains

It was initially postulated from experimental (animal) studies that isoniazid-resistant, and therefore also MDR *Mycobacterium tuberculosis* strains are less infectious and less likely to cause disease than drug-susceptible strains. However, even during the 1950s new (no previous anti-TB treatment or treatment for < 1 month) isoniazid-resistant TB in children soon followed the development of isoniazid-resistant TB in adults. The rates of isoniazid-resistant TB for children and adults of similar backgrounds and from the same area were similar and the rapid rise of drug-resistant TB among adults in New York city during 1985 - 1995 also occurred in children.^{2,3} Snider *et al.*⁴ found that the infection rate among children was similar and even higher in child contacts of isoniazid-resistant index cases compared with drug-susceptible index cases. A study from the Western Cape (WC) confirmed similar infection rates in childhood contacts of adults with drug-susceptible (48% infection) and MDR pulmonary TB (64% infection).⁵

Transmission was initially confirmed by the same drug susceptibility test (DST) results found in adult-child contact pairs: 14 of 15 isoniazid-resistant strains (93%) obtained from adult-child pairs had identical DST and 20 of 29 (69%) adult-

child pairs with any drug resistance had identical susceptibility patterns.⁶ A study from the WC showed that 18 of 22 MDR strains (82%) obtained from adult-child pairs had identical susceptibility patterns.⁷ In 5 of 6 cases where *M. tuberculosis* isolates from the child and adult source case were available in a prospective study of child contacts of MDR TB cases, the restriction fragment length polymorphism analyses were identical.⁸

Drug resistance surveillance in children

Children should be a good source for surveillance of true new drug-resistant TB and may accurately reflect the transmission of these organisms in the community. Two surveys have been done in children < 13 years of age at Tygerberg Children's Hospital: the first from August 1994 through April 1998 and the second, in which a community component was included, from March 2003 through February 2005.⁹ The results are summarised in Table I.

There was a significant increase in human immunodeficiency virus (HIV) infection in children with confirmed TB between the surveys. There was no difference in drug resistance among HIV-infected compared with HIV-uninfected children. Children who were previously treated had a significantly higher rate of drug resistance, but in the majority this was still due to transmission of a drug-resistant strain.⁹ An interesting finding in the second survey was that there was no significant difference in drug resistance between the community-based compared with the hospital-based groups (18/130 (14.3%) v. 23/199 (12.3%), respectively).⁹ This implies that hospital-based surveillance of TB drug resistance in children is a reasonably reliable reflection of the drug resistance among children in this community.

Diagnosis of drug-resistant TB

Drug-resistant TB is a microbiological diagnosis. There are no clinical or radiological features that distinguish drug-resistant from drug-susceptible cases. In children a diagnosis of drug-resistant TB is more difficult, as they usually have paucibacillary disease and specimens for culture are more difficult to obtain and less often culture-positive. The diagnosis is only confirmed if a resistant *M. tuberculosis* strain is isolated from the child; therefore it is important to obtain specimens from all possible sources for culture and DSTs if drug-resistant TB is suspected. If a child presenting with TB is a known contact of an adult with MDR pulmonary TB, the child is a probable MDR TB case and should be managed accordingly.

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**Table I. Comparison of two drug resistance surveillance studies at Tygerberg Children's Hospital**

Characteristics	1994 - 1998 survey	2003 - 2005 survey	Odds ratio (95% confidence interval)
All culture-positive cases	338 (%)	323 (%)	
Median age (years)	2.6 (0.06 -13.0)	2.5 (0.04 -12.9)	
Boys	193 (57.1)	173 (53.6)	NS
Previous TB Rx	32 (9.5)	59 (18.3)	0.47 (0.29 - 0.76)
HIV test done	166 (49.1)	243 (75.2)	0.32 (0.23 - 0.45)
HIV-infected*	13 (7.8)	64 (26.3)	0.24 (0.12 - 0.46)
DST available†	306 (90.5)	307 (95.0)	0.50 (0.26 - 0.96)
Drug-susceptible	285 (93.1)	267 (87.0)	2.03 (1.13 - 3.67)
Drug-resistant (all)	21 (6.9)	40 (13.0)	0.49 (0.27 - 0.88)
Isoniazid-resistant and rifampicin-susceptible	14 (4.6)	23 (7.5)	NS
Multidrug-resistant	7 (2.3)	17 (6.5)	0.40 (0.15 - 1.04)

* As percentage of tests done.

† DST results as percentages of DST done.

HIV = human immunodeficiency syndrome; DSTs = drug susceptibility tests.

Table adapted from Schaaf *et al.*⁸

Drug-resistant TB should be suspected if a child deteriorates on appropriate, adherent anti-TB treatment or if an adult source case with unknown susceptibility pattern: (i) is a treatment failure (sputum smear-positive after 5 months' treatment); (ii) is a retreatment case; (iii) is a chronic TB case (TB despite 2 previous treatment courses); or (iv) has poor adherence to treatment.

DSTs could routinely be requested for isoniazid, rifampicin and ethambutol. DST for second-line drugs is less reliable, but should be done for the aminoglycosides and fluoroquinolones to identify XDR TB cases in all newly diagnosed MDR TB cases.

Treatment and chemoprophylaxis for isoniazid-mono-resistant TB in children

A 4-drug intensive phase including ethambutol as the fourth drug and a longer continuation phase of 7 months should be sufficient if isoniazid resistance is recognised from the onset of treatment. Once a treatment regimen fails or the isoniazid resistance is diagnosed long after the onset of regimen 3 treatment (3-drug intensive phase), 2 or more drugs should be added to the treatment regimen, as further resistance could have developed.

Rifampicin as a single drug for 6 months could be used as chemoprophylaxis in child contacts of infectious isoniazid-resistant pulmonary TB cases.

Treatment of MDR TB in children

The management of MDR TB is difficult and should preferably be done by an expert at a specialised unit. No randomised controlled studies are available to guide treatment. There are, however, a number of important principles that should be adhered to in treating MDR TB cases:

1. Never add a single drug to a failing regimen.
2. Give directly observed therapy with daily treatment only.
3. Use the adult index case's isolate DST result if no isolate from the child is available.
4. Give 3 or preferably more drugs to which the patient's or adult source case's isolate is susceptible and/or naïve.
5. Counsel parents at every visit for support, about adverse events (which are more difficult to assess in children), and importance of adherence to treatment.
6. Follow-up is essential: clinical, radiological and cultures.
7. Although the optimal duration of treatment is not known, a minimum of 18 months after the first negative culture is usually recommended. In children with early primary disease (lymph node disease only) this could probably be less.

The drugs that could be used in the treatment of MDR TB are summarised in Table II. Isoniazid at high dose (15 - 20 mg/kg/day) may still add value to the treatment regimen because many new isoniazid-resistant cases have low-level isoniazid resistance.¹⁰ It should, however, not replace any other drug in such a regimen. Some drugs, such as capreomycin, para-aminosalicylic acid (PAS), amoxicillin-clavulanic acid and clarithromycin are reserve drugs for the management of XDR TB cases.

Although cycloserine (or terizidone) is usually reserved for patients resistant to ethambutol, there is evidence for a better response to MDR TB treatment if this drug is added from the start even in patients whose isolates are reported as ethambutol-susceptible. There is discordance between the DST for ethambutol and the gene mutation showing resistance. Therefore it is best to start cycloserine in any child with MDR TB whose (or whose source case's) isolate is resistant to ethambutol, has extensive pulmonary or extrapulmonary



Table II. Drugs for the treatment of multidrug-resistant tuberculosis

Antituberculosis drug	Daily dose (mg/kg)	Maximum dose (mg)
Isoniazid*	15 - 20	400
Ethambutol	20 - 25	2 000
Ethionamide	15 - 20	750
Pyrazinamide†	25 - 35	2 000
Aminoglycosides		
Kanamycin	15 - 30	1 000
Amikacin	15 - 22.5	1 500
Fluoroquinolones		
Ofloxacin	15 - 20	800
Levofloxacin	7.5 - 10	750
Ciprofloxacin	30 - 40	2 000
Moxifloxacin	7.5 - 10	400
Capreomycin	15 - 30	1 000
Cycloserine/terizidone	15 - 20	1 000
Para-aminosalicylic acid (PAS)	150 (2 - 3 divided doses)	12 000

* Additional drug – not to replace any drug in treatment regimen.

† Susceptibility difficult to test – given as additional drug for full duration of treatment.

disease or who has central nervous system involvement (cycloserine penetrates the blood-brain barrier well).

In children, amikacin is preferred to kanamycin as it is less painful to inject intramuscularly and causes fewer adverse effects. An aminoglycoside is part of almost all MDR TB treatment regimens and according to the 2006 World Health Organization (WHO) MDR TB guidelines should continue for a minimum of 6 months.¹

Although the fluoroquinolones are not usually recommended for use in children, they form an important part of MDR TB treatment. In our experience, adverse effects are rare and mainly consist of some nausea and rare cases of insomnia or arthralgia. Ofloxacin is currently the preferred drug in children, but because levofloxacin has more of the active ingredient and can be given at a lower dose with less adverse effects, this could become the drug of choice if available. In very young children, ciprofloxacin can be used as it is available in a suspension.

Gastrointestinal adverse effects are common with ethionamide. This can usually be overcome by initially splitting the dose into 2 - 3 divided doses per day, which should be given as a single dose again as soon as the vomiting or severe nausea stops.

Chemoprophylaxis for child contacts of MDR TB cases

Chemoprophylaxis for contacts of MDR TB cases is controversial. No randomised controlled studies are available.

The WHO 2006 MDR guidelines recommend isoniazid only for the possibility that there could be a drug-susceptible contact, and further recommend close clinical follow-up only. Several failures of isoniazid or isoniazid/rifampicin to prevent MDR TB in contacts have been reported, including 5 recent cases.¹¹ In a prospective study of contacts of MDR TB source cases, 2/41 children (5%) who received 6-month chemoprophylaxis with 2 drugs for which the adult case's strain was susceptible v. 13/64 children (20%) who did not receive appropriate chemoprophylaxis developed TB ($p = 0.05$).¹² This implies that MDR chemoprophylaxis could be effective in preventing MDR TB. We currently manage our young MDR TB contacts with high-dose isoniazid plus two drugs to which the source case is susceptible, given for 6 months. Close follow-up (2-monthly for the first 6 months and then 6-monthly for 12 - 18 months) remains important. In case of known XDR TB, this probably will not do, and high-dose isoniazid together with close follow-up is most likely the only current option available.

Conclusion

MDR TB (and probably XDR TB) is as infectious as drug-susceptible TB. Drug resistance is a laboratory diagnosis and isolates of the child or adult source case are important for diagnosis and management of the child. Previously treated children have a significantly higher rate of MDR TB, but this is most likely transmitted disease that was initially missed, although older children with cavitary disease may develop drug resistance with poor management of their TB. Aggressive treatment is necessary for M(X)DR TB, as there is only one opportunity to cure their TB. Treatment is difficult and best done by experts at specialised units.

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