What are the indicators of multi-drug resistant tuberculosis in children?

Primary Reviewer: **Amy Gray**[1] Secondary Reviewer: **Ben Marais**[2]

First Published online: 9th September 2008

1 University of Melbourne, Australia
2 Stellenbosch University, Cape Town, South Africa

The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at:
http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What are the indicators of Multi-drug resistant TB in children?*

The WHO Pocketbook of Hospital care for children outlines the diagnosis, investigation and treatment of tuberculosis (TB) with advice to follow the national tuberculosis programme recommendations where available, or WHO guidelines where they are not. There is no specific reference to the diagnosis and management of multi-drug resistant TB but a comment that if improvement is not seen after one month of treatment, the patient should be reviewed, adherence to treatment checked and the diagnosis reconsidered. (Pocketbook chapter 4.8)

The WHO guidelines [1] state the following : that MDR-TB is a laboratory diagnosis but should be considered in any child with any of the following features:

1. Contact with a source case with features suggestive of drug resistant TB
    a. Contact with a known case of drug resistant TB
    b. Remains sputum smear-positive after 3 months of treatment
    c. History of previously treated TB
    d. History of treatment interruption

2. Features of a child suspected of having drug resistant TB
    a. Contact with a known case of drug resistant TB
    b. Not responding to the anti-TB treatment regimen
    c. Recurrence of TB after adherence to treatment

INTRODUCTION

Multi-drug resistant tuberculosis (MDR-TB) is an increasing health problem, particularly in areas with high incidence of both TB and HIV. Drug-resistant (DR) tuberculosis refers to resistance to any of the first line anti-tuberculosis drugs. Multi-drug resistance is resistance to both isoniazid and rifampicin, with or without resistance to other first-line drugs. Extensively drug-resistant TB (XDR) has also emerged which, in addition to rifampicin and isoniazid, is resistant to fluoroquinolones and injectable second line agents.

Childhood TB is usually pauci-bacillary, making the acquisition of drug resistance in previously treated patients less likely, since the chance of resistance arising is proportional to the mycobacterial load. [2],[3] Instead the presence of drug resistant TB in children most likely reflects transmission of a resistant strain from an adult source case with whom the child had contact. The incidence of TB in children can be used as a marker of successful functioning of the TB control programme, as child TB cases represent ongoing transmission within the community. Studies have confirmed transmission of MDR-TB from adult source cases to child contacts using both drug-susceptibility profiles and restriction fragment length polymorphism (RFLP) strain typing. [4-7] Furthermore, rates of infection in household contacts of MDR-TB cases may be high compared to drug sensitive cases due to poor treatment response that prolongs duration of infectivity.

The pauci-bacillary nature of the disease and difficulties in getting sputum from young children mean that childhood pulmonary TB is frequently smear or culture-negative, and bacteriological confirmation of MDR-TB is often not possible. Outcomes of MDR-TB are generally good if diagnosed early, but with delayed diagnosis, particularly if there is disseminated disease, outcome is often poor. [5],[6]

This review addresses the question - What are the indicators of MDR TB in children? A previous review in the International Child Health Review Collaboration addressed the question – what are the most useful clinical indicators of tuberculosis in childhood?[7] The review identified persistent, non-remitting symptoms that were useful in the diagnosis of TB including, cough for more than 2 weeks despite first line therapy, documented weight loss despite adequate nutrition and de-worming, fatigue and a contact history. In combination these symptoms were powerful indicators of disease in a high-burden setting, while clinical follow-up provided additional diagnostic value in those with an uncertain diagnosis. The current review does not re-visit this question, but specifically addresses indicators that may or may not distinguish MDR TB from drug-sensitive TB in children.

METHODOLOGY

A search of the Pub Med database was conducted using the search strategy: Multi-drug resistant [MeSH] AND child* AND diagnosis, and was limited to articles in English on Humans. This yielded 84 results. In addition, book chapters, guidelines and references from reviews were sourced for additional relevant peer reviewed publications. After review of all abstracts (full texts in cases where there was doubt regarding the article's relevance), six articles were included in the review. All six articles were case series, representing level 4 evidence according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001).

RESULTS AND DISCUSSION

A prospective case series of 338 children 0-13 years presenting to Tygerberg Children's Hospital in the Western Cape of South Africa aimed to determine the incidence of DR-TB and compare the clinical and radiological feature of DR and susceptible TB.[8] Over the study period, 538 isolates were obtained from 338 children. Drug susceptibility testing was available for 90.5% (306/338 patients) of cases - 6.9% were isoniazid resistant and 2.3% MDR. All children with MDR-TB were under 5 years of age. Clinical and radiological features, including age, weight, previous treatment, Mantoux result, X-ray findings and rates of pulmonary TB, were not significantly different between children with DR-TB and children with a susceptible strain. Data for children with MDR-TB were not analyzed separately to other forms of DR-TB. There were 11 deaths in children with drug susceptible TB (4%), 3 in children whose drug sensitivity testing was not done (9%) and none in children with DR-TB, though the differences between group did not reach statistical significance.

These results were consistent with a longitudinal study conducted between 1961 and 1980 of children treated for tuberculosis at the Kings County Hospital Medical Center.[9] Of 355 strains isolated, 56 (15.8%) were resistant to at least one anti-tuberculosis drug. The majority of these were resistant to isoniazid (9.9%) and/or streptomycin (9.2%). Rifampicin resistance, and therefore MDR-TB, incidence was low (1%). Tuberculosis manifestations and severity were no different between children infected with a resistant or susceptible strain.

Of the studies included in this review, the largest was a prospective case series of 596 children less than 13 years of age diagnosed with cultured-confirmed TB at two hospitals (Tygerberg Children's Hospital and Red Cross Children's Hospital) in Cape Town, South Africa. [10] The study aimed to describe the clinical, radiological and microbiological features of TB in children and compared HIV-infected and non-infected children. The same comparison was not made between drug-sensitive and drug-resistant cases but the study did show there was no difference in drug susceptibility between HIV-infected and non-HIV infected individuals. HIV-testing was performed at the discretion of the attending doctor on 69.4% of patients; 22.3% infected and 47.1% un-infected. 592 patients (99.3%) had drug-sensitivity testing done on their isolates and, of these, 7.3% were isoniazid-resistant, 0.3% rifampicin-resistant and 3.7% MDR. Patients previously treated for TB were more likely to have drug-resistance compared to patients without previous treatment (OR 0.31, 95%CI 0.17-0.59) yet in the majority of cases initial treatment was probably inappropriate and resistance was most likely transmitted from an adult source. [4] Nine of 67 patients (13.4%) with DR-TB died, including 3 patients with MDR, and five were HIV infected. This was compared to 32/525 (6.1%) of patients with susceptible TB (OR 2.39, CI 1.00-5.99).

In adults treatment failure on adherent directly observed TB therapy (DOT) has been shown to be strongly predictive of MDR-TB. [11],[12] In a case-control study of adults in Peru treatment success was indicated by greater weight gain and smear conversion by the second month of treatment. Information on this in children is limited. Three case series in children were identified that described the outcome of treatment for MDR- and the clinical features of cases, including the treatment history.

A small case series of the first 16 children with MDR-TB enrolled in the DOT-plus programme in Peru [13] described all cases as having clinical and/or radiological progression of disease while adherent to directly observed therapy and a known contact with MDR-TB. The mean duration of previous TB treatment was 10 months. 15/16 (94%) of these patients were smear or culture positive and 7/16 (44%) had cavitary disease on X-ray.

A later study from Peru reported on the outcomes of 38 children enrolled in individual treatment regimens for MDR-TB [14] . Two thirds of these patients had documented treatment failure on at least one regimen before commencing individualized treatment for MDR-TB, including 20 out of 27 (74%) patients with a known MDR-TB contact. Thirty out of 38 (79%) patients were culture positive and 29% had cavitary or severe bilateral disease on X-ray. Median time from diagnosis of TB to commencement of an individual treatment regimen was 6.5 months (range 0-46 months).

A case series of 39 children with MDR-TB diagnosed over a 4 year period in the Western Cape region of South Africa [8] also reported high rates of positive smears (44%) and cavitary disease (36%). In these children the median time to appropriate treatment if the possibility of drug-resistance was not recognized at the outset was 246 days, compared to 2 days if an MDR-TB contact was known and the patient treated accordingly. Two of the four deaths in this study occurred in children with advanced disease and significant treatment delay. Children were first diagnosed with TB at a median age of 4.6 years, yet MDR-TB was confirmed by culture at a median age of 6.2 years.

Evidence regarding MDR-TB in children is derived from reported case-series. While a number of these series include several hundred TB cases, the absolute number of drug-resistant and in particular MDR cases, is relatively small. Due to the low numbers, MDR-TB cases were rarely separated from other forms of drug-resistant TB in the analysis. These studies identified no clinical or radiological indicators that may distinguish drug-resistant from drug-sensitive TB in children.

In the three case series of children with MDR-TB from Peru and South Africa a very high proportion were smear or culture positive (44-94%) and around one third to one half had cavitary disease on chest X-ray. This partially results from selection bias identifying children with culture confirmed drug resistant TB, but it may also reflect progression of disease while appropriate treatment is delayed. The latter possibility is supported by studies of childhood pulmonary TB that demonstrated increased bacteriological yield with advanced disease. One study of 307 children in an endemic area, with a relatively high proportion of children with advanced lung disease, achieved bacteriological confirmation of TB in 62% of cases.[15] The yield was lowest (35%) in those with uncomplicated hilar adenoapthy, higher if consolidation was demonstrated on X-ray (82%) and highest in adult-type disease with cavities (100%).

While it has previously been stated in this review that acquisition of drug resistance is rare in children with TB, those with cavitary disease (most commonly adolescents over 10yrs of age and usually sputum smear-positive) are as likely as adults to acquire drug resistance. It is this risk that motivates for the routine use of ethambutol as a fourth drug in these children. [16],[17] Furthermore, the presence of cavities and smear positive sputum render these children potential transmission sources of tuberculosis in the community, whether drug-sensitive or resistant.

Because clinical and radiological features are non-specific and bacteriological confirmation is rarely achieved in children, the

patient's contact and TB treatment history are extremely important markers of potential MDR-TB. This is reflected in the WHO guidelines outlined at the beginning of this review, which are comparable to others suggested in the literature. [2],[5],[18] While they are largely intuitive, the principles are rarely practiced as evidenced by the paucity of MDR data in children and the prolonged treatment delays that have been described. This can be avoided in the vast majority of cases if the relevant history is sought and the diagnosis considered at the outset. In cases where MDR contact history is not known or suspected and drug susceptibility testing is not routinely done, diagnosis will follow after first-line treatment failure with associated treatment delay. Literature from adults suggests that an inadequate response to adherent treatment can be recognised after two to three months.

Finally, the WHO guidelines identify recurrence of TB symptoms after adherence to treatment as a feature in a child that should raise suspicion of drug resistant TB. There is no qualification regarding the time of recurrence, in view of the possibility of a recurrence being a relapse of TB or re-infection with a different strain. Trials in adults demonstrate relapses are most likely to occur in the first 6 months post-treatment.[19] There is no specific evidence for this related to MDR-TB in children, but literature regarding childhood TB supports the view that recurrences occurring more 6-12 months after treatment completion generally represent re-infection and not relapse.[3]

SUMMARY

Multi-drug resistant tuberculosis remains a microbiological diagnosis, although rapid genotypic testing is becoming available. The available evidence demonstrates that clinical and/or radiological features cannot distinguish drug-resistant from susceptible cases. Due to difficulties with bacteriological MDR-TB diagnosis, resulting from difficult specimen collection and pauci-bacillary disease in children, early diagnosis relies on recognition of potential drug resistance, based on contact history and/or response to treatment. A high index of suspicion is paramount to avoid prolonged delays in treatment.

REFERENCES

1. Guidance for the national tuberculosis programmes on the management of tuberculosis in children. 2006. WHO/HTM/TB/2006.371

2. Schaaf HS. Drug-resistant tuberculosis in children. S Afr Med J. 2007;97(10):995-7

3. Marais BJ, Gie RP, Schaaf HS, Beyers N, Donald PR, Starke JR. Childhood pulmonary tuberculosis: old wisdom new challenges. Am J Respir Crit Care Med. 2006;173:1078-90

4. Schaaf HS, Marais BJ, Hesseling AC, Gie RP, Beyers N, Donald PR. Childhood drug-resistant tuberculosis in the Western Cape Province of South Africa. Acta Paediatr. 2006:523-28

5. Schaaf HS, Shean K, Donald PR. Culture-confirmed multidrug-resistant tuberculosis: diagnostic delay, clinical features, and outcome. Arch Dis Child. 2003;88:1106-1111

6. Padayatchi N, Bamber S, Halima D, Razia B. Multi-drug resistant tuberculosis in children in Durban, South Africa. Pediatr Infect Dis J. 2006;25:147-50

7. Azzopardi P, Graham S. What are the most useful clinical indicators of tuberculosis in childhood? www.ichrc.org

8. Schaaf HS, Gie RP, Beyers N, Sirgel FA, de Klerk PJ, Donald PR. Primary drug-resistant tuberculosis in children. Int J Tuberc Lung Dis. 2000;4(12):1149-55

9. Steiner P, Rao M, Victoria MS, Hunt J, Steiner M. A continuing study of primary drug-resistant tuberculosis among children observed at the Kings County Hospital Medical Center between the years 1961 and 1980. Am Rev Respir Dis. 1983;128(3):425-8

10. Schaaf HS, Marais BJ, Whitelaw A, Hesseling AC, Eley B, Hussey G, et al. Culture-confirmed childhood tuberculosis cases in Cape Town, South Africa: a review of 596 cases. BMC Infect Dis. 2007;7:140-7

11. Becerra MC, Freeman J, Bayona J, Shin SS, Kim JY, Furin JJ, et al. Using treatment failure under effective directly observed short-course chemotherapy programs to identify patients with multidrug resistant tuberculosis. Int J Tuberc Lung Dis. 2000;4(2):108-14

12. Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, et al. Standard short-course chemotherapy for drug-resistant tuberculosis. JAMA 2000;283(19):2537-45

13. Mukherjee JS, Joseph JK, Rich ML, Shin SS, Furin JJ, Seung KJ et al. Clinical and programmatic considerations in the treatment of MDR-TB in children: a series of 16 patients from Lima, Peru. Int J Tuberc Lung Dis. 2003;7(7):637-44

14. Drobac PC, Mukherjee JS, Joseph JK, Mitnick C, Furin JJ, del Castillo H et al. Community-based therapy for children with multi-drug resistant tuberculosis. Pediatr. 2006;117(6):2022-9

15. Marais BJ, Hesseling AC, Gie RP, Schaaf HS, Enarson DA, Beyers N. The bacteriologic yield in children with intrathoracic tuberculosis. Clin Infect Dis 2006;42:e69-71

16. Marais BJ, Gie RP, Hesseling AH, Beyers N. Adult-type pulmonary tuberculosis in children 10-14 years of age. Pediatr Infect Dis J 2005;24(8):743-4

17. Marais BJ, Gie, RP, Schaaf HS, Hesseling AC, Obihara CC, Starke JJ. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis 2004;8(4):392-402

18. Newton SM, Brent AJ, Anderson S, Wttaker E, Kampmann B. Paediatric tuberculosis. Lancet Infect Dis. 2008;8:498-510

19. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946-1986, with relevant subsequent publications. Int J Tuberc Lung Dis 1999;3:s239-71.