REVIEW ARTICLES

DRUG RESISTANT TUBERCULOSIS IN CHILDREN IN INDIA

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Abstract

Children acquire tuberculosis (TB) from an infectious adult in the community. Since the introduction of Anti-tuberculous therapy (ATT) in 1952, M.tuberculosis strains have acquired resistance to all first line anti-tuberculosis drugs (ATD) and some second line anti-tubercular agents. Strains resistant to streptomycin were first reported in 1940s and by mid 1990s, most countries reported resistance to isoniazid and rifampicin (multidrug resistant TB - MDR TB). In 2006, extensively drug resistant TB (XDR-TB) emerged with resistance to first and second line drugs which is a serious emerging threat to global health. (1) Extensively drug resistant (XDR) TB (MDR TB with additional resistance to at least a fluoroquinolone and one of the injectables i.e. kanamycin, amikacin or capreomycin) has been reported in 77 countries across the globe by October 2011. (2) Thus, the occurrence of M.TB strains resistant to multiple anti-tuberculosis drugs is increasing. (3) China and India carry approximately 50% of global DR-TB with the Russian Federation a further 7%. It is estimated that 489139 cases of drug resistant TB have emerged in 2006 globally (4) and nearly half a million cases emerge every year. The management of patients with MDR-TB is tedious as response to treatment may be poor, these patients need to be treated with expensive and toxic second line drugs, and may require hospitalization to manage their toxic reactions and other complications and they require a sizeable proportion of health care resources.

Introduction

Though drug resistance (DR) in TB has been reported from children in India most of the available information is limited to a small number of patients. This in form of case series or observational studies. (5,6). Among adults, recent estimates on the prevalence of MDR-TB in new smear positive pulmonary TB (PTB) cases in adults in India is <3% and 12 to 17% amongst smear positive previously treated PTB cases. (7) Schaaf, et al in South Africa reported a prevalence of 6.5% of MDR TB in 2003-2005 in children <13 years of age at Tygerberg Children's Hospital. (8) Similarly, we have reported a prevalence of drug resistant TB in children at our tertiary referral pediatric hospital to be 6.8%. (6) In India, data from studies conducted by Tuberculosis Research Centre (TRC) and National Tuberculosis Institute (NTI) have found MDR-TB levels of less than 1% to 3% in new cases and around 12% in re-treatment cases. (1) Initial resistance to INH (H) is below 20% followed by streptomycin (S) (below 10%) and to rifampicin (R) (around 1%) while acquired resistance to INH varies between 40 and 70%, streptomycin 15-30% and rifampicin 20-30%. (9) Further, an alarming increase in infection due to the human immunodeficiency virus (HIV) has accelerated the problem of drug resistance TB.

Types of Drug resistance (9)

A patient is determined to have drug-resistant TB only through laboratory confirmation of in vitro resistance to one or more first-line anti-tuberculosis drugs. A child is considered to be mono-resistant when there is resistance to one antituberculosis drug, poly-resistant when resistance is to more than one antituberculosis drug, other than both isoniazid and rifampicin and MDR when there is resistance to at least isoniazid and rifampicin. XDR TB is when a patient has MDR TB with additional resistance to at least a fluoroquinolone and one of the injectables i.e. kanamycin, amikacin or Capreomycin.

Causes of drug resistance in children with tuberculosis

Children may be infected with drug resistant TB if they are non compliant with medications with poor monitoring of treatment, if the drugs are used of poor quality or they are prescribed in wrong doses. Transmission of drug resistant bacilli from a close contact is also one of the key reasons of drug resistant (DR) TB in children in India. (6) Also past treatment with anti-tuberculous therapy (ATT) is an important risk factor in development of DR-TB in children as seen in our previous report. (6) Thus drug resistance should be suspected in a child when the child is in contact with a known case of drug-resistant TB or is not responding to the anti-TB treatment regimen or has been treated improperly for TB in the past.

Mutations associated with DR-TB

Drug resistance in M. tuberculosis occurs by random, single step, spontaneous mutation at a low but predictable frequency, in large bacterial populations. The probability of incidence of drug resistant mutants is 108 for rifampicin, while for isoniazid and some of the other commonly used drugs it is 106. Therefore, the probability for resistance to both isoniazid and rifampicin to develop is 1014, which is much larger than the number of organisms present in a medium sized cavity in a patient with open pulmonary TB. (10)

Mutation in the rpoB gene are responsible for 97% of rifampicin resistant strains. Mutations in katG and inhA genes account for the majority of the INH resistant strains: Resistance to INH due to inhA mutation is associated with resistance to ethionamide. Mutations in rpsi and rrs genes are responsible for streptomycin resistance; mutation in embB gene is responsible for ethambutol resistance and pncA gene for pyrazinamide resistance. (11)

Diagnosis of DR- TB

Identification of drug resistant M. tuberculosis is done by culture on solid media (Lowenstein Jensen media) which may take 3-6 weeks for the organism to grow and 1-2 weeks on broth media (Mycobacterial Growth Inhibitor Tube [MGIT] 960 system (Becton-

Dickinson, Sparks, MD) followed by drug susceptibility testing (DST) of an M. tuberculosis isolate which may take an additional 2 weeks. DST of pyrazinamide is difficult to perform and phenotypic DST to ethambutol is unreliable. (11) When doing a DST it is important to look at MIC of various anti TB drugs (Table 1).

Table 1: Minimum Inhibitory Concentration (MIC) levels of antituberculous drugs

Drug	MIC (mcg/ml)
Isoniazid	0.1
Rifampicin	1
Pyrazinamide	100
Streptomycin	1
Ethambutol	5
Kanamycin	2.5
Ethionamide	5
PAS	4
Ofloxacin	2
Moxifloxacin	1
Clofazimine	0.5
Amikacin	1
Capreomycin	2.5

Since many of the genes encoding resistance have been identified, nucleic acid amplification tests (NAATs) are being increasing used for diagnosis of resistance to isoniazid (H) and rifampicin (R) and results are obtained in 24-48 hours directly from clinical specimens. (11) However, they are usually done on tissue samples that have atleast 2+ acid fast bacilli (AFB) on smear and are not very useful in paucibacillary disease as may be seen in children.

Treatment of drug resistance tuberculosis

Treatment of DR-TB should be tailored as per the DST results. The recommended regimen is the combination of at least four drugs to which MTB is likely to be susceptible. Drugs are chosen with a stepwise selection process through five groups (table 2). Of these PAS, cycloserine are bacteriostatic. All others are weakly bactericidal. The anti-TB drugs have traditionally been divided into first- and second-line drugs with isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin being the primary first- line drugs. (1) Among the aminoglycosides, amikacin is preferred in children as compared to kanamycin due to low minimum inhibitory concentration (MIC). (12) Capreomycin is usually reserved for treatment of XDR-TB. Among the fluoroquinolones, levofloxacin and Moxifloxacin are superior to ofloxacin. Ciprofloxacin is not used for treatment of tuberculosis any longer. Among the group 4 drugs, thionamide and aminosalicylic acid should not be given together due to increased incidence of hypothyroidism. Fluoroquinolones and thionamide also have cross-resistance. (13)

Whenever possible, pyrazinamide, ethambutol and fluoroquinolones should be given once per day because the high serum levels attained in once-a-day dosing may be more efficacious. Once-a-day dosing is permitted for other second-line drugs, depending on patient tolerance. However, ethionamide/protionamide, cycloserine and PAS have traditionally been given in split doses during the day.

The optimal duration of MDR-TB treatment in children is not known. The treatment is given in two phases, the Intensive phase (IP) and the Continuation phase (CP). IP which includes an injectable should be given for at least six months. Treatment is for a minimum duration of 18 months beyond conversion from AFB positive to negative. The recommended treatment of TB is the same for HIV-infected and non-HIV-infected patients, except for the use of thioacetazone, which should not be used in HIV-infected patients. (1)

With increasing MDR-TB in children and adults, DOTS-plus strategy has been devised for treating MDR-TB in context of RNTCP. This consists of giving second line drugs under direct observation in specialized in-patient units during intensification phase and then as out-patients at the DOTS center in the continuation phase under continuous supervision till completion of therapy. (13)

Table 2: Groups of antituberculous drugs (2)

Groups	Drugs
Group 1	First-line oral anti-TB agents Isoniazid (H); Rifampicin (R); Ethambutol (E); Pyrazinamide (Z), Streptomycin (S)
Group 2	Injectable anti-TB agents Kanamycin (Km); Amikacin (Am); Capreomycin (Cm)
Group 3	Fluoroquinolones: Ofloxacin (Ofx); Levofloxacin (Lvx); Moxifloxacin (Mfx); Gatifloxacin (Gfx)
Group 4	Oral second-line anti-TB agents Ethionamide (Eto); Prothionamide (Pto); Cycloserine (Cs); Terizadone (Trd); para-aminosalicylic acid (PAS)
Group 5	Agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients) Clofazimine (Cfz); Linezolid (Lzd); Amoxicillin/Clavulanate (Amx/Clv); thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high-dose isoniazid (high-dose H); Clarithromycin (Clr)

Adverse effects of antituberculous drugs

Table 3 depicts common adverse effects seen with various anti TB drugs. Adverse effects of the drugs (especially ototoxicity, nephrotoxicity with the aminoglycosides and hypothyroidism with thionamides and aminosalicylic acid) are high in these children.

Table3: Adverse effects of various Anti TB drugs

Drugs	Adverse Effects
Aminoglycoside	ototoxicity, nephrotoxicity, electrolyte imbalance
Quinolones	Gastro-intestinal (GI) disturbance, insomnia, arthralgia
Ethambutol	Visual disturbance
Pyrazinamide	Arthralgia, hyperuricemia, hepatitis, pruritis with or without rash
Ethionamide	Gastro-intestinal disturbance (nausea, vomiting, abdominal pain and anorexia), hepatotoxicity, Hypothyroidism
Cycloserine	Psychosis, convulsions, parasthesia, depression
PAS	Gastro-intestinal disturbance (mainly diarrhea), Hypothyroidism
Clofazimine	Photosensitivity
Linezolid	Myelosuppression, Lactic acidosis, peripheral neuropathy, pancreatitis
Clarithromycin	Gastro-intestinal intolerance, rash, hepatitis, prolonged QT syndrome, ventricular arrhythmias

Conclusion

DR-TB is on the rise in children in India. DR-TB in children requires early suspicion, prompt diagnosis and aggressive treatment with combination second line anti-tuberculosis drugs which may be life-saving. A child should be considered at risk for DR-TB if there is clinical and/or radiological progression of TB inspite of chemotherapy or there is contact with a patient having DR-TB. Monitoring of a patient on second line drugs is essential to assess response to treatment and prevent adverse effects.

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E-published: 1st May 2012. **Art**#27

DOI No. 10.7199/ped.oncall.2012.27

Quick Response Code