Some current concepts on childhood tuberculosis

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As children acquire infection with Mycobacterium tuberculosis from adults in their environment, the epidemiology of childhood tuberculosis (TB) follows that in adults. While global burden of childhood tuberculosis is unclear, in developing countries the annual risk of tuberculosis infection in children is 2-5 per cent. Nearly 8-20 per cent of the deaths caused by tuberculosis occur in children. It has been suggested that BCG vaccination is responsible for decrease in the occurrence of disseminated and severe disease. Localized forms of illness, e.g., intrathoracic lymphadenopathy, and localized CNS disease have been reported to occur with greater frequency in vaccinated children. Human immunodeficiency virus (HIV) infected children are at an increased risk of tuberculosis, particularly disseminated disease. Diagnosis of TB in children presents special problems as the sputum is generally not available for examination. Diagnostic algorithms include scoring system utilizing clinical parameters and results of investigations. Various diagnostic techniques such as improved culture techniques, serodiagnosis, and nucleic acid amplification have been developed and evaluated to improve diagnosis of childhood tuberculosis. Serodiagnosis is an attractive investigation but till date none of the tests showed desirable sensitivity and specificity. Tests based on nucleic acid amplification are a promising development. Relatively less experience in children, need for technical expertise and high cost are the limiting factors for their use in childhood tuberculosis. Short-course chemotherapy for childhood tuberculosis is well established. Treatment with intermittent regimens is comparable to daily regimens. Directly observed treatment strategy (DOTS) has also shown encouraging results. Pattern of drug resistance among children with TB tends to reflect those found among adults in the same population. The rates of drug resistance to any drug vary from 20 to 80 per cent in different geographic regions.

Key words Childhood tuberculosis - DOTS - epidemiology - polymerase chain reaction - serodiagnosis

Tuberculosis still is one of the deadliest diseases in the world killing nearly 2 million people every year. More than ninety per cent of all tuberculosis cases occur in the developing countries, where limited resources are available for optimal treatment. Tuberculosis continues to be an important cause of morbidity and mortality for children worldwide.

Epidemiology

Since most children acquire the organism from adults in their surroundings, the epidemiology of childhood tuberculosis follows that in adults. Because of the difficulty of confirming the diagnosis, the global burden of childhood tuberculosis in the world is unclear. Another important reason is that children do not make a significant contribution to the spread of tuberculosis. Several estimates make use of an arbitrary calculation assigning 10 per cent of the tuberculosis burden to children. Available data linking the incidence of tuberculosis to the proportion of the tuberculosis case load represented by children suggest an exponential rise in the proportion of the tuberculosis case load caused by children as the
Tuberculosis incidence rises so that children may constitute nearly 40 per cent of the case load in certain high incidence communities\(^1\).

Tuberculosis infection and disease among children are much more prevalent in developing countries, where resources for control are scarce\(^2\). It is estimated that in developing countries the annual risk of tuberculosis infection in children is 2-5 per cent. The estimated lifetime risk of developing tuberculosis disease for a young child infected with \textit{Mycobacterium tuberculosis} as indicated by positive tuberculin test is about 10 per cent\(^3\). About 5 per cent of those infected are likely to develop disease in the first year after infection and the remaining 5 per cent during their lifetime. These rates increase about six-fold in HIV infected individuals. Nearly 8-20 per cent of the deaths caused by TB occur in children\(^4\). The age of the child at acquisition of TB infection has a great effect on the occurrence of tuberculosis disease. Approximately 40 per cent of infected children less than 1 yr of age if left untreated develop radiologically significant lymphadenopathy or segmental lesions compared with 24 per cent of children between 1-10 yr and 16 per cent of children 11-15 yr of age\(^5\).

**Clinical manifestations**

Widespread coverage with BCG vaccine has possibly led to modification in the pattern of clinical manifestations. It has been suggested that BCG vaccination is responsible for decrease in the occurrence of disseminated and severe disease. Localized forms of illness, \textit{e.g.}, intrathoracic lymphadenopathy, and localized CNS disease have been reported to occur with greater frequency\(^6\) but these need confirmation from large epidemiological studies.

A recent study from Spain\(^7\) reported an increase in number of children with single hilar adenopathy (32\% for the period 1978-1987 to 43.4\% for the period 1988-1997) in comparison with those with parenchymal involvement or a mixed pattern (62\% vs 45\%). The authors also reported a non-significant trend towards a lower rate of tubercular meningitis in the last decade\(^7\).

Indian experience from a tertiary care referral centre in north India suggests an increase in the proportion of cases of extra-pulmonary TB over the last 3 decades. The increase was predominantly due to increase in lymph node TB. The severe form of tubercular meningitis decreased over the last three decades\(^8\).

**HIV and tuberculosis**

It has been reported that HIV infection is probably one of the most important factors for the resurgence of TB in adults as well as in children. In 1990, 4.2 per cent of tuberculosis cases worldwide occurred in HIV-infected individuals and estimates for the year 2000 were around 14 per cent\(^9\). Adults with HIV infection are more likely to develop tuberculosis from latent infection, and those who encounter \textit{M. tuberculosis} after HIV related immune suppression have a more rapid progression to disease\(^10\).

The impact of the HIV epidemic on paediatric TB has been reported in several studies. A prospective cohort study of children with TB diagnosed in Addis Ababa from December 1995 to January 1997 in which HIV-positive children were compared with HIV-negative children, reported that HIV-positive children were younger, more underweight and had a 6-fold higher mortality than HIV-negative children\(^11\). The tuberculin skin test was less sensitive and chest radiography was less specific in HIV-infected patients. Adherence to treatment was high (96\%), and the cure rate was 58 per cent for HIV-positive and 89 per cent for HIV-negative paediatric TB patients. The study concluded that HIV-positive children are at risk of diagnostic error as well as delayed diagnosis of TB. Clinical manifestations were more severe and progression to death was more rapid in HIV-positive children than in HIV-negative children. Weight for age may be used to identify children at high risk of a fatal outcome\(^11\).

In a retrospective study of 118 culture proven tuberculosis patients in Durban, South Africa; 57 (48\%) children were detected to be HIV-1 infected, 44 (37\%) non-HIV-1-infected, and in 17 (14\%) HIV-1 status was not determined\(^12\). In contrast to previous studies, this study has shown that TB-HIV
Coinfection in children is common (48% of all culture proven cases), the presentation of tuberculosis may be acute (43%), and supportive tests are individually useful in confirming the diagnosis in one-third of cases. All culture for \textit{M. tuberculosis} were positive by 8 wk. Clubbing and age over 2 yr were the most reliable indicators of underlying HIV-1 disease in a child with tuberculosis, while clinical features, radiology and supportive tests were found to be similar between HIV-infected and non-infected TB cases. Hospital-related mortality was higher (17.5%) in HIV-1-infected children compared to that in non-infected group (11.4%). The changing pattern of presentation of childhood tuberculosis and the high prevalence of TB in HIV endemic areas have made it imperative to maintain a high index of suspicion, with culture evaluation being an important part of clinical practice\textsuperscript{12}. There are not many studies from India on proportion of children co-infected with HIV and TB. In a small study from Mumbai\textsuperscript{13}, 18 per cent of children with disseminated tuberculosis (N=50) were HIV seropositive. Reported co-infection of HIV and TB in various Indian studies was 16-68 per cent\textsuperscript{14-16}. Since follow up data of HIV infected children are not available, it is very difficult to estimate annual infection rate of tuberculosis in HIV positive patients.

\section*{Diagnosis}

The diagnosis of tuberculosis in childhood continues to be surrounded by considerable uncertainty. It is very difficult to obtain sputum from children. Gastric aspirate is used as an alternative to sputum for identification of acid-fast bacilli (AFB). The sensitivity of smears for identification of \textit{M. tuberculosis} is low (in the range of 25-30%) but specificity is very high (in the range of 90-99\%)\textsuperscript{17-18}. The yield of mycobacteria is high when the samples are repeated, in extensive pulmonary disease and in infants, where it is up to 70 per cent\textsuperscript{19}. 

Although an elevated erythrocyte sedimentation rate (ESR) may be expected in children with tuberculosis, a recent study found that one-third of children with TB had a normal ESR at the time of diagnosis, suggesting little value in using ESR as a diagnostic test for childhood tuberculosis\textsuperscript{20}.

\textit{Bronchoalveolar lavage}: It has been documented that gastric aspirate (GA) is superior to bronchoalveolar lavage (BAL) fluid for the yield of AFB in childhood tuberculosis\textsuperscript{21,22}. A recent study\textsuperscript{23} on 58 children comparing GA and BAL showed that in 10 (17.2\%) children \textit{M. tuberculosis} was grown from gastric lavage whereas 12 children had their BAL positive for this bacteria. Overall, mycobacterial isolation was possible in 20 patients (34.4\%) as two children had grown \textit{M. tuberculosis} in GA as well as BAL. Addition of BAL to the diagnostic work up increased the mycobacteriological yield from 17.2 per cent with gastric lavage alone to 34.4 per cent when BAL was also performed. Results of this study suggest that there is no difference in mycobacterial isolation rates from gastric lavage and BAL when studied in isolation. However, when both GA and BAL are used, these procedures complement each other to increase the diagnostic yield\textsuperscript{23}.

Gastric lavage for isolation of \textit{M. tuberculosis} is a well accepted method. Use of BAL in diagnosis of tuberculosis in children needs further evaluation. It is suggested that one should try to obtain gastric aspirate for diagnosis of tuberculosis in children as far as possible. Bronchoscopy may be considered when diagnosis is doubtful or a possibility of resistant tuberculosis is considered.

\textit{Culture of Mycobacterium tuberculosis}: Lowenstein-Jensen (LJ) medium is the most widely used medium for determination of characteristic features of colonial morphology, growth rate and pigment production. Though the culture technique is simple, 7-10 wk of incubation may be necessary for detection of organisms. Microscopic examination of thin layer culture plate may lead to detection of microcolonies of \textit{M. tuberculosis} as early as after 7 days. However, recovery of \textit{M. tuberculosis} from this is less efficient and labour intensive\textsuperscript{24}. The yield of culture of gastric aspirate varies from 30-50 per cent in children with TB\textsuperscript{25,26}. The cultures were positive in 37 per cent of children with pulmonary tuberculosis when gastric aspirates were obtained from ambulatory patients while the same was 48 per cent in patients admitted in the hospital\textsuperscript{25}. The yield was 39 per cent in children with pulmonary TB, it was 0 per cent in children when only hilar adenopathy was observed on X-ray.
Higher yield (up to 70%) has been reported in infants and children with extensive disease\textsuperscript{19}. It has been suggested that poor yield due to contamination with anerobic spore bearers can be reduced by using vancomycin in the culture media\textsuperscript{27}.

Excessively long period required for isolation of \textit{M. tuberculosis} by conventional culture techniques has led to the development of other techniques for culture such as BACTEC radiometric assay, Septi-check AFB system, and mycobacterial growth indicator tube system (MGIT).

The BACTEC system improves the yield of positive cultures from clinical specimen while the time taken to detect \textit{M. tuberculosis} is 9-14 days\textsuperscript{28}. The capability of performing rapid mycobacterial drug sensitivity is an additional advantage of the BACTEC system\textsuperscript{29}. The limitations of BACTEC system include high cost of instruments, inability to observe colony morphology and detect mixed cultures, overgrowth by contaminants, need for disposal of radioactive material and extensive use of needles. Most of the studies used sputum in BACTEC system; the experience with other body fluids including gastric lavage fluid is limited. In a study using gastric aspirate in BACTEC, there was not even a single case positive in primary pulmonary complex (PPC)\textsuperscript{30}.

Septi-check AFB system requires about 3 wk incubation. In a study carried out in adults Septi-check system was found to be more sensitive than conventional culture on LJ media/7H11 broth and BACTEC in percentage of isolates recovered\textsuperscript{31}. Though, paediatric studies are not available, this system may be useful in children as well.

MGIT uses a fluorescent compound embedded in silicone on the bottom of the tube containing modified 7H11 broth with antibiotic mixture and growth supplements for mycobacteria. As this fluorescent compound is sensitive to oxygen, depletion of the latter by growth of mycobacteria, unmasks the fluorescence, which can be detected by observing the tube under long wave ultraviolet light. Available literature suggests that this method is as sensitive as the BACTEC system\textsuperscript{32}. The use of this technique is limited to research laboratories.

### Polymerase chain reaction (PCR):

PCR is the most commonly used technique of nucleic acid amplification, for diagnosis of tuberculosis. The PCR may be used to (i) diagnose tuberculosis rapidly by identifying DNA from \textit{M. tuberculosis} in clinical samples that are negative by microscopic examination; (ii) determine rapidly whether acid-fast organisms identified by microscopic examination in clinical specimens are \textit{M. tuberculosis} or atypical mycobacteria; and (iii) identify the presence of genetic modifications known to be associated with resistance of some antimycobacterial agents.

In children, results of PCR have been compared with clinical diagnosis and not culture. The most commonly used target for detection of \textit{M. tuberculosis} is the insertion sequence IS6110. The sensitivity ranges from 4-80 per cent and the specificity 80-100 per cent\textsuperscript{30, 33-35} (Table I).

A blinded study comparing results obtained on specially prepared standardized samples by 7 different laboratories, demonstrated significant differences in the results obtained\textsuperscript{36}. This demonstrates the variability in the pick-up rates in different laboratories. In addition, the clinical laboratories may not obtain results similar to those in research laboratories. PCR gives rapid results and has a greater sensitivity compared with traditional microbiological methods. This makes PCR a suitable technique in childhood TB, especially when diagnosis is difficult or needed urgently. However, the possibility of false positive results must be considered, especially when the clinical symptoms and history of exposure of the child make the diagnosis improbable. The commercially available PCR test lacks sensitivity and specificity; thus it would be necessary to develop better commercial easy-to-use PCR kits that provide better yield\textsuperscript{37}.

### Serodiagnosis:

In absence of good diagnostic method for childhood TB, a lot of interest has been generated in serodiagnosis. ELISA has been used in children to detect antibodies to various purified or complex antigens of \textit{M. tuberculosis}. Despite a large number of studies\textsuperscript{38-42} published, serology has found little place in the routine diagnosis of tuberculosis in children, even though it is rapid and does not require
specimen from the site of disease. Sensitivity and specificity depend on the antigen used, gold standard for the diagnosis, and the type of tubercular infection. Though most of these tests have high specificity, the sensitivity is poor \(^{38-42}\) (Table II). In addition, these tests may be influenced by factors such as age, prior BCG vaccination and exposure to environmental mycobacteria. At present, serodiagnosis does not have any role in diagnosis of childhood pulmonary tuberculosis.

Srivastava \textit{et al} \(^{43}\) measured antigen and antibody in circulating immune complexes (CIC) in 52 children with pulmonary and extra-pulmonary TB. CIC-antigen was present in 92.3 per cent and CIC antibody in 88.96 per cent of children. Of the CIC antigen and antibody were present in all 20 confirmed cases. Current recommendations of diagnostic methods

To overcome the problem of diagnosis of TB in children, combination of clinical features, history of exposure to adult patient with TB, result of tuberculin test and radiological finding have been evaluated. Various scoring systems have been developed after giving different weightage to these variables \(^{44-45}\). More weightage is given to laboratory test \textit{i.e.}, AFB detection, tubercles in biopsy, suggestive radiology and tuberculin test >10mm induration. These scoring systems need validation in individual countries before being used for screening children for tuberculosis. One of the suggested guidelines for diagnosis of pulmonary TB in children in developing countries is shown in Table III \(^{46}\). This is based on clinical history and contact with adult tuberculosis patients with results of radiographs and tuberculin test.

Methods to diagnose latent tuberculosis infection

Till date, tuberculin skin test was the only method to diagnose latent tuberculosis infection. Recently, a new test QuantiFERON®-TB test (QFT) was approved by the Food and Drug Administration (FDA) as an aid for detecting latent \textit{M. tuberculosis} infection \(^{47}\). This is an \textit{in vitro} diagnostic aid that measures a component of cell-mediated immune reactivity to \textit{M. tuberculosis}, and is based on the quantification of interferon-gamma (IFN-\(\gamma\)) released from sensitized lymphocytes in whole blood incubated overnight with purified protein derivative (PPD) from \textit{M. tuberculosis} and control antigens \(^{47}\).
Primary tuberculosis is the commonest form encountered in children. Chest radiography remains the initial imaging technique and the radiographic features are hilar or mediastinal lymphadenopathy, with or without opacities in the unilateral lung. Occasionally, the chest radiograph may be normal and lymphadenopathy may be detected on computed tomography (CT), which is not evident radiographically. In addition, CT features such as low attenuation lymph nodes with peripheral enhancement, lymph node calcification, branching centrilobular nodules and miliary nodules are helpful in suggesting the diagnosis in cases where the radiograph is normal or equivocal. Other features such as segmental or lobar consolidation and atelectasis are non-specific. In a study by Kim et al, CT

### Table II. Serodiagnosis in childhood TB

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Antigen used</th>
<th>Antibody</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 culture positive TB, 17 probable TB, 16 infected, but healthy, 198 Healthy controls</td>
<td>A 60</td>
<td>IgG</td>
<td>Culture positive TB - 71</td>
<td>98</td>
</tr>
<tr>
<td>58 definite pulmonary TB, 161 controls</td>
<td>A 60</td>
<td>IgG, IgA, IgM</td>
<td>IgM</td>
<td>55.2</td>
</tr>
<tr>
<td>122 children with clinical diagnosis of TB, 187 controls</td>
<td>Polymerised old tuberculin (OT), PPD, 30 kD antigen</td>
<td>IgG</td>
<td>OT 40.3</td>
<td>96.3</td>
</tr>
<tr>
<td>35 asymptomatic primary TB (ATB), 29 symptomatic TB (STB), 23 past TB, 81 controls</td>
<td>A 60</td>
<td>IgG, IgM</td>
<td>ATB 6</td>
<td>95</td>
</tr>
<tr>
<td>74 active TB, 49 healthy contact children, and 149 suffering from non-mycobacterial diseases</td>
<td>16 kDa antigen</td>
<td>IgG, IgM and IgA by enzyme-immunoassay</td>
<td>Active IgG</td>
<td>95</td>
</tr>
</tbody>
</table>

ATB, asymptomatic tuberculosis; STB, symptomatic TB; OT, old tuberculin; PPD, progressive primary disease

### Table III. Suggested guidelines for the diagnosis of pulmonary tuberculosis in children

**Suspected tuberculosis:**
- Any child with history of contact with a confirmed case of pulmonary TB, who is not gaining normal health after measles, pertussis
- Has loss of weight, cough and wheeze not responding to antibiotic therapy for respiratory disease
- Has painless swelling in superficial group of lymph nodes

**Probable tuberculosis:**
- A suspected case and any of the following
  - Positive Mantoux test (induration > 10mm)
  - Suggestive radiological finding
  - Suggestive histological appearance in biopsy
  - Favorable response to antituberculosis therapy

**Confirmed tuberculosis:**
- Detection of tubercle bacilli by microscopy or culture
- Identification of tubercle bacilli as *Mycobacterium* by culture characteristics

*Source:* Ref. 46
[including high-resolution (HR) CT] revealed lymphadenopathy, which was not demonstrated in 21 per cent of radiographs, and parenchymal abnormalities, not seen on 35 per cent of radiographs. HRCT is more sensitive than chest radiography for the detection of military TB. The HRCT findings are wide-spread multiple small (< 2 mm diameter) nodules\textsuperscript{50}. The nodules may be so numerous that they coalesce to form larger nodules greater than 2 mm in diameter or even consolidation with air bronchograms. Thickening of the interlobular septa may also be a feature. Mediastinal and hilar lymphadenopathy may also be present. Cavitation is reported to be rare on chest radiography in children with TB. However, children with both HIV and TB may have atypical radiographic features and cavitation has been reported\textsuperscript{51-52}. CT may show areas of cavitation that are not apparent on chest radiography, which may raise the possibility of a previously unsuspected underlying immune disorder.

Role of high-resolution and colour Doppler ultrasonography (US) in diagnosis of cervical lymphadenopathy has been reported\textsuperscript{53}. Central irregular hyperechogenic areas, blurred margins and central necrosis were most frequent in bacterial, tuberculous and cat scratch disease. Though individual sonographic signs were not specific, the categorization and combination of findings might be highly suggestive of diagnosis of the underlying disease presenting with cervical lymphadenopathy\textsuperscript{53}.

TB of the spine is the most common site of osseous involvement and has a higher prevalence in developing nations with an increasing incidence in developed nations. There are few reports of TB spondylitis in paediatric population that include magnetic resonance imaging (MRI) findings\textsuperscript{54,55}. In a retrospective review of patients’ records and MRI scans, by three readers using a consensus method, of 53 patients below 13 yr of age, MRI showed contiguous involvement of two or more vertebral bodies in 85 per cent\textsuperscript{54}. An intraspinal or paraspinal soft tissue mass or abscess was present in 98 per cent. Subligamentous extension was noted in 64 per cent patients. Ring enhancement of the soft tissue mass was shown in 65 per cent patient after gadolinium\textsuperscript{54}.

Contrast enhanced MRI is emerging as a very useful technique for diagnosing CNS tuberculosis, as it demonstrates the localized lesions, meningeal enhancement and the brain stem lesions\textsuperscript{55}.

**Drug resistant tuberculosis**

Pattern of drug resistance among children with TB tends to reflect that found among adults in the same population. A 4-yr prospective study in the Western Cape province of South Africa evaluated 149 child contacts of 80 adult multi drug resistant (MDR) pulmonary TB cases\textsuperscript{55}. Culture for \textit{M. tuberculosis} was obtained from both the adult source cases as well as the child contacts. Isolates were compared by drug susceptibility pattern and restriction fragment length polymorphism (RFLP) analysis. Six adult-child pairs with cultures positive for \textit{M. tuberculosis} were identified. Drug susceptibility pattern and RFLP analysis were identical for five adult-child pairs. One child, with no other known source case, had a strain different from that of the identified source case, but the MDR \textit{M. tuberculosis} strain with which he was infected was prevalent in the community he resided. This study confirms that most of the childhood contacts of adults with MDR TB are likely to be infected by these MDR source cases despite their exposure to other drug-susceptible adults with TB in some instances. Child contacts of adults with MDR TB should be treated according to the drug susceptibility patterns \textit{M. tuberculosis} strains of the likely source cases unless their own strain’s susceptibility testing indicates otherwise. Contact tracing remains of fundamental importance in identifying children at risk\textsuperscript{56}.

In Western Cape province of South Africa, initial isoniazid (INH) resistance and MDR among adults was 3.9 and 1.1 per cent, respectively, during 1992-1993. In a report of 306 of 338 children with cultures positive of \textit{M. tuberculosis} the incidence of INH resistance was 5.6 per cent and MDR 1 per cent in children aged <5 yr. Clinical features were similar in children with drug-susceptible and drug-resistantTB\textsuperscript{57}. In India (Delhi region), the prevalence of resistance to any drug was 32.4 per cent, while that of multidrug resistance was 13.3 per cent during 1994-1997\textsuperscript{58}.
Treatment

During the last few years dramatic changes have occurred in the therapeutic approaches to childhood TB as a result of large number of treatment trials for children and increased concern about the development of resistance to antituberculosis drugs. Short-course chemotherapy, with the treatment duration as short as 6 months, has become the standard practice. Intermittent regimens have been documented to be as effective as daily regimen in the paediatric population\textsuperscript{59-62}.

Directly observed therapy short-course (DOTS) has been successfully used in adults but there are no studies in children. An observational trial evaluated directly observed therapy 6-month regimen for pulmonary, pleural and lymph node tuberculosis in children with the use of 2 wk of daily isoniazid, rifampicin and pyrazinamide therapy; followed by 6 wk of twice weekly isoniazid, rifampicin and pyrazinamide therapy; and 16 wk of twice weekly isoniazid and rifampicin\textsuperscript{63}. Of the 175 children evaluated (159 pulmonary/thoracic node, 4 pleural, 12 cervical lymph node), 81 per cent completed treatment in 6 months. Of the 33 patients who received extended treatment, 3 did so because of physician’s choice, 17 had an inadequate response to initial therapy, 2 had significant adverse reactions to drugs, and 16 had poor adherence to the DOT. Only 37 per cent of patients had complete resolution of disease at the end of treatment, but all continued to improve after therapy was stopped. There was only one patient who relapsed after 4 yr. This regimen showed results comparable with those of 6-month regimens with longer durations of daily therapy. Determining treatment response in paediatric TB is difficult because of slow resolution of chest radiographic abnormalities. DOT is an important aspect of treatment but does not solve all problems with treatment adherence\textsuperscript{63}.

The major problem in inclusion of children in DOTS is difficulty in demonstration of AFB and classification of different clinical manifestations according to categories described for adults. There have been efforts to develop classification of different types of childhood TB in to 3 categories similar to those for adults. A classification was developed and evaluated in the tuberculosis clinic of a tertiary care hospital\textsuperscript{64}. In this study on 459 children with TB, 365 (80\%) children completed the treatment. Of these, 302 (82.7\%) were cured with the primary regimen assigned to them in the beginning, 54 (14.8\%) required extension of treatment for 3 months and 9 (2.5\%) patients required change in the treatment regimen. The authors concluded that it is feasible to classify and manage various types of tuberculosis in children in different categories similar to WHO guidelines for adult tuberculosis\textsuperscript{64}. Recently a consensus statement jointly prepared by Indian Academy of Pediatrics and Revised National Tuberculosis Control Program (RNTCP) has also proposed a classification of different types of tuberculosis in children into three categories\textsuperscript{65}.

Pharmacological studies of various antituberculosis drugs in children have led to determination of optimal doses of these drugs. The dose of isoniazid has decreased from 20 mg/kg/day in 1970s to 5 mg/kg/day today\textsuperscript{66}. Safety of ethambutol has been objectively documented in young children\textsuperscript{67}. Search for newer, safe and effective drugs continues in the fight against TB.

Tuberculosis control

Tuberculosis is among the top ten causes of global mortality and affects low-income countries in particular. In a recently published review\textsuperscript{68} it is concluded that treatment of smear-positive TB using the WHO, DOTS strategy has by far the highest impact. While BCG immunization reduces childhood tuberculosis mortality, its impact on tuberculosis transmission is probably minimal. Under specific conditions, an additional impact on mortality and transmission can be expected through treatment of smear-negative cases, intensification of case finding for smear-positive tuberculosis, and preventive therapy among individuals with dual (TB-HIV) infection. Of these interventions, DOTS is the most cost-effective at around US$ 5-40 per disability-adjusted life year (DALY) gained\textsuperscript{68}. The cost for BCG immunization is likely to be under US$ 50 per DALY gained. Treatment of smear-negative patients has a cost per DALY gained of up to US$ 100 in low income countries, and up to US$ 400 in middle-income settings. Other interventions, such as
preventive therapy for HIV-positive individuals, appear to be less cost-effective.\(^68\)

**Chemoprophylaxis**: Treatment of infected children with isoniazid alone or a combination of isoniazid and rifampicin can reduce the risk of developing disease.\(^69\) The same is true for chemoprophylaxis administration to paediatric contacts of adult tuberculosis patients.

**Chemoprophylaxis for MDR TB**: In a report from South Africa,\(^70\) all children <5 yr old in contact with adults with MDR TB were evaluated. The child was treated by prescribing at least two drugs to which the contact adult’s strain was susceptible. The remaining children were classified as infected or noninfected and received chemoprophylaxis according to the index cases’ strain susceptibility or were followed up and treated when indicated. All children were followed up for 30 months. Of the total 125 children with median age 27.5 months, 119 were followed up. Fourteen had disease, 61 were infected only, and 44 were not infected. By 30-month follow up, 29 developed disease and 64 were infected only. This study confirms the transmission of MDR TB to childhood contacts. Appropriate chemoprophylaxis, based on the sensitivity results from the adult patients, may prevent disease in these children.

To conclude tuberculosis in children is an important cause of morbidity and mortality. The clinical symptoms and signs are non-specific and lab diagnosis is limited because of paucibacillary nature of illness. There are some suggestions that the clinical manifestations are changing. Short course chemotherapy is the mainstay of treatment.

### References


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