Diagnosis and treatment of tuberculosis in children

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There has been a recent global resurgence of tuberculosis in both resource-limited and some resource-rich countries. Several factors have contributed to this resurgence, including HIV infection, overcrowding, and immigration. Childhood tuberculosis represents a sentinel event in the community suggesting recent transmission from an infectious adult. The diagnosis of tuberculosis in children is traditionally based on chest radiography, tuberculin skin testing, and mycobacterial staining/culture although these investigations may not always be positive in children with tuberculosis. Newer diagnostic methods, such as PCR and immune-based methods, are increasingly being used although they are not widely available and have a limited role in routine clinical practice. Diagnostic approaches have been developed for use in resource-limited settings; however, these diagnostic methods have not been standardised and few have been validated. Short–course, multidrug treatment has been adopted as standard therapy for adults and children with tuberculosis, with or without directly observed therapy. Compliance is a major determinant of the success of drug treatment. Although uncommon in children, multidrug-resistant tuberculosis is also increasing and treatment will often involve longer courses of therapy with second-line antituberculosis drugs. Treatment of latent infection and chemoprophylaxis of young household contacts is also recommended for tuberculosis prevention, although this may not always be carried out, particularly in high incidence areas.

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There is clear evidence that the worldwide incidence of tuberculosis is increasing. It is estimated that between 2000 and 2020, nearly 1 billion people will be newly infected with tuberculosis, 200 million people will develop the disease, and 35 million will die from tuberculosis.[1] The most profound influence on the incidence of tuberculosis is HIV infection, particularly in sub-Saharan Africa where HIV and tuberculosis form a lethal combination, each speeding the other's progress. HIV infection has been estimated to account for an excess of 34% of new cases.[2] In countries with high burdens of both tuberculosis and HIV, the continued increase of tuberculosis will depend upon the level and trend of both HIV and tuberculosis infection in the community.[3] However, the advent of HIV has not changed the basic characteristics of tuberculosis and it has been suggested that well-organised tuberculosis control programmes might reduce the impact of HIV considerably.[4] Other important factors contributing to the global resurgence of tuberculosis include poverty, overcrowding, increased travel/immigration, breakdown of tuberculosis control programmes, multidrug resistant tuberculosis (MDR tuberculosis), and incomplete treatment.[5]

Accurate figures for the burden of childhood tuberculosis in the world are not readily available. This is because of the difficulty of accurately diagnosing childhood tuberculosis, inadequate health information systems in developing countries, and the lack of importance attributed to childhood tuberculosis by tuberculosis control authorities. With increasing incidence of tuberculosis in a population, the percentage of the tuberculosis caseload due to the childhood population has been estimated to increase exponentially reaching 40% of total cases.[6] In developed countries with a lower incidence of tuberculosis, childhood tuberculosis represents less than 5% of all cases. However, childhood tuberculosis notifications rates in some developed countries have also been increasing parallel to an overall increase in tuberculosis incidence. A third of London boroughs have reached the WHO high prevalence level of greater than 40 notifications per 100 000 population.[7] These recent changes reflect the global epidemiological patterns of tuberculosis associated with alterations in travel and immigration.

Childhood tuberculosis represents a sentinel event within a community suggesting recent transmission most commonly from an infectious adult with pulmonary or cavitary tuberculosis. The public health dimensions of childhood tuberculosis are thus important both with respect to overall tuberculosis control in a population, and for earlier diagnosis and treatment of children through identification of infectious adult cases.

We review the natural history of tuberculosis in children and outline both established and new diagnostic methods for tuberculosis infection and disease. Furthermore, an overview of treatment of children with tuberculosis disease and infection will be given.

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Natural history of tuberculosis and clinical spectrum of disease

It has been traditionally useful to distinguish between "infection" and "disease" in the natural history of tuberculosis. Following initial exposure to a case of transmissible tuberculosis, the hallmark of tuberculosis infection is conversion of the tuberculin skin test (TST). Subsequent tuberculosis disease is characterised by the development of signs and symptoms and/or radiographical changes. Without chemoprophylaxis, 40–50% of infants and 15% of older children with infection will develop disease in 1–2 years.[8] In adults, the distinction between tuberculosis infection and disease is usually clear and often separated by a period of years before the onset of reactivation-type disease. The major reason for making a distinction between infection and disease is because each is treated differently. Infection is generally treated with a single antituberculosis drug, whereas disease is treated with three or more antituberculosis drugs. The division of infection and disease in some children may, however, not be so obvious since progression from infection to disease may occur more rapidly in children.

Initial infection in the lung is characterised by a Ghon focus with regional lymphadenitis, called the primary complex, which may not be obvious radiologically. In most children this resolves spontaneously with residual calcification or scarring. Some children, particularly infants, may develop progressive lymphadenopathy.[9] The primary parenchymal infiltrate may also progress to a caseating lesion, known as progressive primary tuberculosis. This may result in the rupture into pleural or pericardial spaces leading to pleural or pericardial effusions. Erosion of caseating lesions into pulmonary vessels can result in haematogenous dissemination to the lung and distant anatomical sites. The most common manifestation of this is miliary tuberculosis. Miliary tuberculosis usually occurs as an early complication of primary infection and usually affects infants and young children. Older children and adolescents usually develop adult-type reactivation pulmonary disease (post-primary disease). This follows infection acquired after 7 years of age, especially at the time of puberty.[10] Extensive infiltration and cavitation, especially of the upper lobe of the lung, are usually found on a chest radiograph.

Extra-pulmonary tuberculosis disease is more common in children than adults, occurring in approximately 25% of infants and young children less than 4 years of age.[11] Superficial lymphadenitis is the most common form of extra-pulmonary tuberculosis in children, typically involving the supraclavicular, anterior cervical, tonsillar, and submandibular nodes. Without treatment, cold abscess and chronic sinus formation may occur. Central nervous system (CNS) disease, especially tuberculosis meningitis, is the most serious complication of tuberculosis in children and occurs in about 4% of children with tuberculosis.[12] The overall mortality has been reported to be 13%, with approximately half of survivors developing permanent neurological sequelae.[13] Tuberculomas are less common manifestations of CNS infection usually characterised by solitary brain lesions. Bone and joint tuberculosis may involve weight-bearing bones and joints, particularly the vertebrae (Pott's disease).[14] Other extra-pulmonary manifestations of tuberculosis, such as gastrointestinal or renal, are rare in children because of long incubation periods required following haematogenous dissemination to manifest as disease.

Established diagnostic methods

Microscopy and culture

Early and timely diagnosis of tuberculosis relies heavily on microscopic examination of clinical samples for acid-fast bacilli using the Ziehl-Neelsen (ZN) stain. Microscopy can detect 60–70% of culture positive samples with a lower limit of detection of 5×10^3 organisms/mL. Newer fluorochrome stains, such as the auramine and rhodamine, are superior to the ZN stain.[15] These tests are easy to perform and are cheap and rapid. However, younger children with pulmonary tuberculosis rarely produce sputum and early morning gastric aspirate samples are often collected. Less than 20% of children with proven tuberculosis will have a sputum or gastric aspirate sample that is positive on ZN stain, compared with 75% in adults.[16] The rates of positivity of ZN staining from other body fluids and tissues in children, especially those with extra-pulmonary tuberculosis, are even lower.

Mycobacterial culture of gastric aspirates has provided a more useful method of diagnosis in children with suspected pulmonary tuberculosis. Three consecutive morning gastric aspirates yield *Mycobacterium tuberculosis* in 30–50% of cases and may be as high as 70% in infants.[17] The culture yield from other body fluids or tissues from children with extra-pulmonary tuberculosis is usually less than 50% due to the paucibacillary nature of the disease.[18]

The role of bronchoscopy in evaluating children with pulmonary tuberculosis is controversial. The culture yield is usually lower than for three properly obtained gastric aspirates.[19] This procedure may, however, be useful in the diagnosis of endobronchial tuberculosis and excluding other causative agents such as opportunistic infections particularly in immunocompromised children. More recently, sputum induction with nebulised 5% saline has been used safely in young infants with a 4·3% increase in yield compared with two or three consecutive early morning gastric aspirates.[20] However, there are concerns regarding spread of tuberculosis to other patients and staff and it is recommended that sputum induction be performed with appropriate infection control procedures (eg, negative pressured cubicles), and by appropriately trained staff.

Tuberculin skin test

A positive tuberculin skin test (TST) reaction is a hallmark of primary infection with *M tuberculosis*. In most children, tuberculin reactivity becomes apparent in 3–6 weeks, but occasionally can take up to 3 months after initial infection. Tuberculin reactivity due to *M tuberculosis* infection usually remains positive for the lifetime of the individual, even after treatment.[21]

There are two major techniques currently used for TST—the Mantoux test and the multi-puncture technique. The Mantoux test, which uses 5–10 tuberculin units of

purified protein derivative, is the standard method used in many countries for detecting infection by *M tuberculosis*. This test involves the intradermal injection of purified protein derivative solution into the most superficial layer of the skin of the forearm, which raises an immediate wheal. The reaction is measured as millimetres of induration (not erythema) after 48–72 h.

Several multipuncture methods, such as the Heaf and tine tests, are available and used widely (especially in the UK) because of the speed and ease with which they can be administered. These tests involve the inoculation of purified protein derivative solution using a multipuncture device placed on the skin of the forearm. The Heaf test uses a spring-loaded "gun", which drives six needles into the skin that has previously been coated with purified protein derivative solution. The tine test is similar, except that purified protein derivative is dried onto four spikes (tines) on a small, single-use, disposable unit. The skin test is read after 5–7 days (2–3 days for the tine test) and based on the induration pattern surrounding the puncture sites. These tests are most commonly used as screening methods, such as the school's BCG programme in the UK.

Up to 10% of otherwise normal children with culture-proven tuberculosis do not react to tuberculin initially.[18] Most of these children will become reactive during treatment, suggesting that tuberculosis disease may itself contribute to immunosuppression. False-negative TST may also occur in children with severe tuberculosis disease soon after infection, those with debilitating or immunosuppressive illnesses, malnutrition, or other severe infections. The rate of false-negative TST in children with tuberculosis who are infected with HIV, is unknown, but it is certainly higher than 10% and is dependent on the degree of immunosuppression (ie, CD4 counts).

There has been much uncertainty regarding the effect of BCG vaccination on TST results. BCG vaccination may cause a transiently reactive TST, but most children who received BCG as infants have a non-reactive TST at 5 years of age.[22] A recent meta-analysis suggests that the effect of BCG on TST measurements was less after 15 years, and induration greater than 15 mm was more likely to be due to tuberculosis infection than BCG.[23] Among older children or adolescents who receive BCG, most develop a reactive TST initially; however, by 10–15 years post-vaccination, the majority will have lost tuberculin reactivity.[24] Recent studies have shown that BCG vaccination had little impact on the interpretation of TST in children being tested as part of a contact investigation.[25]

False-positive TST are often attributed to asymptomatic infection by environmental non-tuberculous mycobacteria.[26] Skin reactivity can also be boosted, probably through antigenic stimulation, by serial testing with TST in many children and adults who received BCG.[27]

Table 1 summarises interpretation of TST as recommended by the British Thoracic Society (BTS), American Academy of Paediatrics, and the WHO.[28–30] The American Academy of Paediatrics' guidelines are significantly different from the BTS and WHO guidelines in that they exclude the effect of BCG in interpretation of TST responses. Furthermore, the American Academy of Paediatrics' guidelines interpret TST based on risk in different populations. Based on the sensitivity and specificity of TST and the prevalence of tuberculosis in different groups, three cut-points have been recommended for defining a positive tuberculin reaction: greater than 5 mm, greater than 10 mm, and greater than 15 mm.[31]

Table 1. Summary of interpretation of positive TST results for Mantoux and Heaf test in children[28–30]

British Thoracic Society	WHO	American Academy of Paediatrics
Mantoux Test (10TU)	**Mantoux test**	**Mantoux test**
Positive: 5–14 mm (no BCG) >15 mm (BCG) **Heaf test*** Positive: grade 2–4 (no BCG) grade 3–4 (BCG)	Positive: >10 mm (no BCG) >15 mm (BCG)	Positive: >5 mm, and one or more of the following Children in close contact with known or suspected contagious case of tuberculosis disease—ie, households with active or previously active cases if treatment cannot be verified as adequate before exposure, treatment was initiated after the child's contact, or reactivation of latent tuberculosis infection is suspected Or Children suspected to have tuberculosis disease—ie, chest radiograph consistent with active or previously active tuberculosis; or clinical evidence of tuberculosis disease Or Children receiving immunosuppressive therapy or with immunosuppressive conditions including HIV infection Positive >10 mm, and one or more of the following Children at increased risk of disseminated disease—ie, younger than 4 years of age; or other medical condition, including Hodgkin's disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition Or Children with increased exposure to tuberculosis disease—ie, born or whose parents were born in high-prevalence regions of the world; or frequently exposed to adults who are HIV-infected, homeless, users of illicit drugs, residents of nursing homes, incarcerated or institutionalised, and migrant farm worker Positive >15mm, and children 4 years of age or older without any risk factors

TU=tuberculin units; *Heaf grading: grade 0, no induration; grade 1, discrete induration at three or more puncture sites; grade 2, induration at each puncture site merging with the next to form ring; grade 3, confluent area of induration; grade 4, more intensive induration with necrosis.

Radiology

Radiological evidence of pulmonary tuberculosis usually includes lymphadenopathy (hilar or mediastinal) (figure 1), and lung parenchymal changes. The most common parenchymal changes are segmental hyperinflation, atelectasis, alveolar consolidation, pleural effusion/empyema (figure 2) and, rarely, a focal mass. Cavitation is rare in young children but is more common in adolescents (figure 3), who may develop adult-type post-primary disease.[8] Miliary tuberculosis is characterised by fine bilateral reticular shadowing, sometimes called a "snowstorm" appearance (figure 4).

Computed tomography (CT) imaging may be helpful in demonstrating pulmonary disease such as endobronchial disease, early cavitation, and bronchiectasis following pulmonary tuberculosis where chest radiographs are normal or unhelpful. CT imaging is also useful in investigating CNS disease, such as tuberculosis meningitis or tuberculoma (figure 5). More recently, CT imaging has been used to identify enlarged or prominent mediastinal or hilar lymph nodes.[32] It remains unclear what the significance of these findings are in asymptomatic children. It may well imply a lower bacterial load and hence indication of infection rather than disease. Thus further evaluations of CT imaging in this population is warranted.

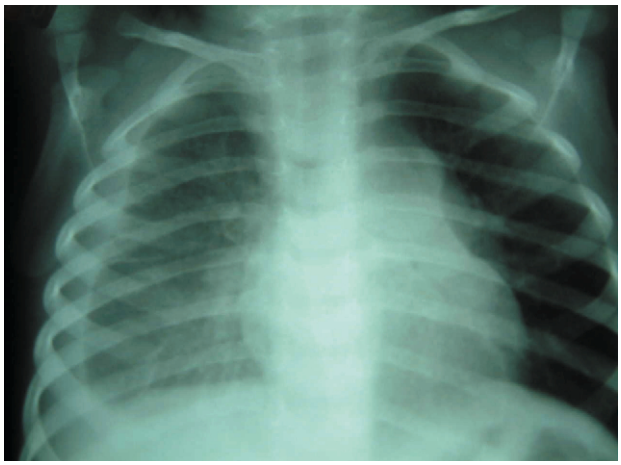

Figure 2. Chest radiograph showing right-sided tuberculous empyema.

Diagnostic approaches used in the diagnosis of childhood tuberculosis

The diagnosis of tuberculosis in children is based mainly on a combination of history of contact with an adult infectious case, clinical signs and symptoms, and investigations mentioned above, particularly chest radiograph and tuberculin skin testing. However, symptoms may often be non-specific with over half of children being asymptomatic with early disease.[8] A positive history of contact with a case of tuberculosis, especially if the source case was a parent or other member of the household who was also bacteriologically positive, has been strongly associated with disease in a child.[33] These epidemiological, clinical, and diagnostic parameters have been used to devise simple, cheap, and reliable tests to enable accurate diagnosis of tuberculosis in children especially in low-income countries. Several diagnostic approaches exist and most are grouped broadly into four families based on point scoring systems, diagnostic classifications, diagnostic algorithms, or combinations of these.[34] An example of a diagnostic approach is that recommended by the WHO which relies on stratified categories of suspected, probable, and confirmed tuberculosis (see panel).[35] Most of these diagnostic approaches have not been standardised, making comparison difficult, and few have been properly validated.[34] Some diagnostic approaches have been modified for populations where HIV is prevalent; however, only one diagnostic approach has been specifically designed to diagnose tuberculosis in such a population.[36] In a high HIV prevalent population, clinical scoring systems have been found to have low specificity (25%) resulting in over-diagnosis of tuberculosis.[37] Further studies are needed to develop standardised diagnostic approaches that are relevant to developing countries with limited resources with a high burden of tuberculosis, malnutrition, and HIV/AIDS.

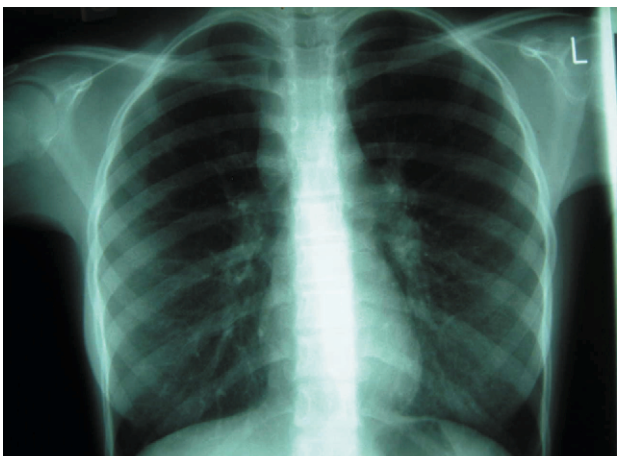

Figure 1. Chest radiograph showing intrathoracic (paratracheal) tuberculous lymphadenopathy.

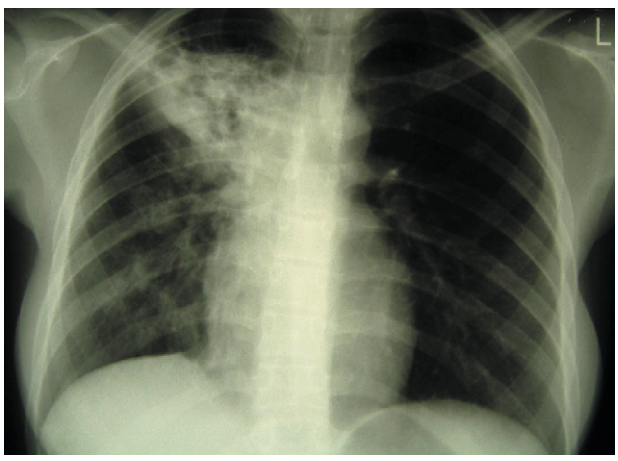

Figure 3. Chest radiograph showing post-primary adult-type right upper lobe consolidation and cavitation.

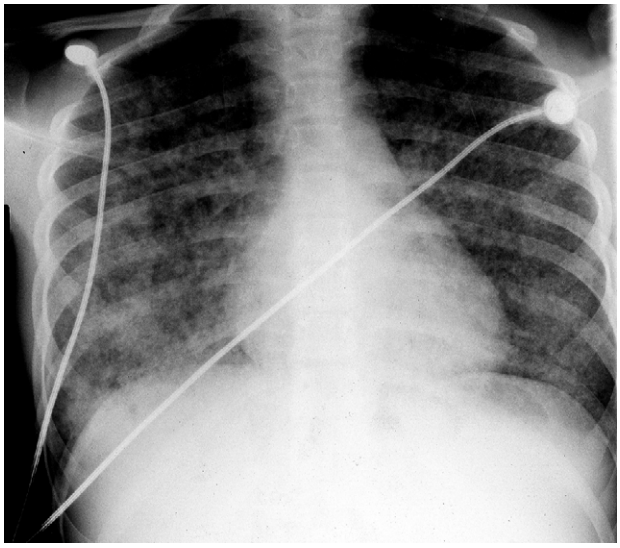

Figure 4. Chest radiograph showing bilateral reticular shadowing or "snowstorm" appearance of miliary tuberculosis.

Newer diagnostic methods

PCR

Due to the slow growth of most pathogenic bacteria, tests have been developed for the detection of mycobacteria directly from clinical specimens. Most have involved amplification of small amounts of bacterial nucleic acid using techniques such as PCR. PCR has been used successfully in identifying many infectious agents, allowing early diagnosis and institution of therapy. Although the specificity of a well-developed PCR can be high, the sensitivity is significantly less than that of the use of culture. The sensitivity of a good quality PCR would be expected to be 90–100% and 60–70% on smear-positive and smear-negative culture-positive respiratory samples, respectively.[38–40] However, there are several problems with applying this technique to routine clinical care, including variations in methodology, high cost, and high risk of contamination resulting in false positives (see page 633).

WHO provisional guidelines for the diagnosis of pulmonary tuberculosis in children[35]

Suspected tuberculosis

- An ill child with a history of contact with a confirmed case of pulmonary tuberculosis
- Any child
  - Not regaining normal health after measles or whooping cough
  - With weight loss, cough, and wheeze not responding to antibiotic therapy for respiratory disease
  - With painless swelling in a group of superficial nodes

Probable tuberculosis

A suspect case and any of the following:

- Positive (>10 mm) induration on tuberculin testing
- Suggestive appearance on chest radiograph
- Suggestive histological appearance on biopsy material
- Favourable response to specific anti-tuberculosis therapy

Confirmed tuberculosis

- Detection by microscopy or culture of tubercle bacilli from secretions or tissues
- Identification of tubercle bacilli as *Mycobacterium tuberculosis* by culture characteristics

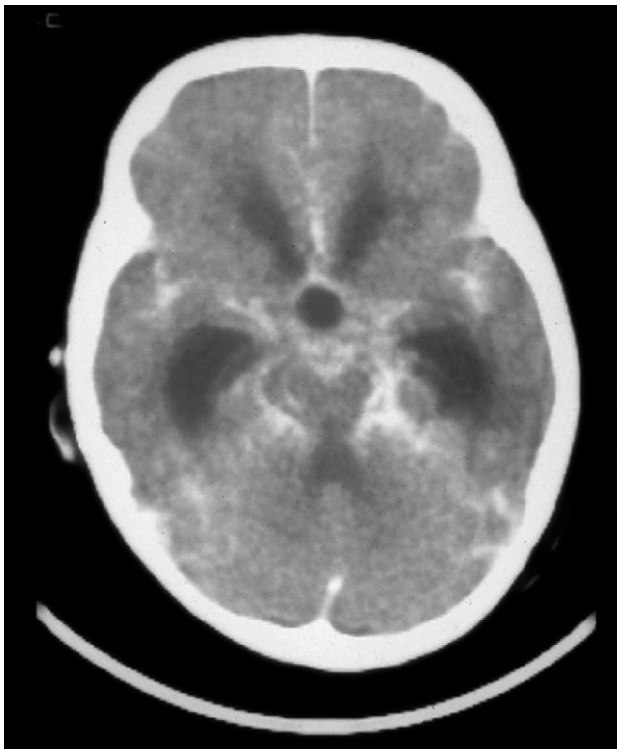

Figure 5. Head CT scan showing hydrocephalus and basal enhancement consistent with tuberculous meningitis.

Several studies in children have found the PCR test on clinical samples to have a sensitivity of 40–60% compared with clinical diagnosis.[41–44] This compares favourably to standard cultures, which have a sensitivity of 30–40%. The specificity of PCR ranges from 80–96% but is dependent on the type of assay used. Furthermore, up to 39% of children with no radiographical or clinical evidence of tuberculous disease also had positive PCR results.[45] With the limitations that exist, the results of PCR alone are insufficient to diagnose tuberculosis in children. PCR detection in other body fluids or tissues, such as cerebrospinal fluid, appears to have been even less successful.

In view of the problems highlighted above, PCR methods have a limited role in the diagnosis of tuberculosis in children; however, they may be useful where the diagnosis is not easily established using standard clinical, microbiological, and epidemiological methods. PCR may also have a future role in the diagnosis of tuberculosis in immunocompromised children, or those with extrapulmonary tuberculosis.

Serological detection

Serology has so far found little place in the routine diagnosis of children with tuberculosis, despite several assays that have been developed. ELISA has been used to detect antibodies to a host of *M tuberculosis* antigens including protein-purified

Table 2. Recommended dosages of first-line standard antituberculosis drugs for children[28,30,50]

Drug	BTS		ATS		WHO	
	Daily	Intermittent	Daily	Intermittent*	Daily	Intermittent
Isoniazid	5–10 mg/kg	15 mg/kg 3 times weekly	10–15 mg/kg	20–30 mg/kg twice weekly	5 mg/kg	10 mg/kg 3 times weekly
Rifampicin	10 mg/kg	15 mg/kg 3 times weekly	10–20 mg/kg	10–20 mg/kg twice weekly	10 mg/kg	10 mg/kg 3 times weekly
Pyrazinamide	35 mg/kg	50 mg/kg 3 times weekly	50 mg/kg	50 mg/kg twice weekly	25 mg/kg	35 mg/kg 3 times weekly
Ethambutol	15 mg/kg	30 mg/kg 3 times weekly 45 mg/kg twice weekly	50 mg/kg	50 mg/kg twice weekly	15 mg/kg	30 mg/kg 3 times weekly

BTS= British Thoracic Society; *three times weekly dosing not recommended in the American Thoracic Society (ATS)/CDC guidelines

derivative, killed *M tuberculosis*, and antigen A60.[46–48] However, none of these methods has adequate sensitivity, specificity, or reproducibility for use in diagnosis of children with tuberculosis.

Immunodiagnosis

The TST suffers from poor specificity due to variable host responses and broad antigenic cross-reactivity that make *M tuberculosis* infection difficult to differentiate from the effects of BCG immunisation and environmental mycobacteria. One approach to developing better diagnostic tests has been to identify specific immune responses, especially cell-mediated ones, to antigens that are specific to *M tuberculosis* and different from other mycobacteria. The early secretory antigenic target or ESAT-6 antigen is present in *M tuberculosis* complex but absent from all strains of *Mycobacterium bovis* BCG, and almost all environmental mycobacteria. Lalvani and colleagues have recently developed an ex-vivo ELISPOT assay of ESAT-6-specific interferon-γ secreting lymphocytes that can reliably differentiate *M tuberculosis* infection from BCG immunisation.[49] However, these tests are not commercially available, and therefore have a limited role in routine clinical practice at present.

Treatment

Treatment of children can be divided broadly into treatment of tuberculosis infection and treatment of tuberculosis disease. As mentioned above, the distinction between these different categories may be unclear in some patients.

Treatment schedules, policies, and drug doses as advocated by a number of national and international bodies often differ. Table 2 and table 3 compare drug regimens and dosages recommended by the BTS, American Thoracic Society (ATS), and WHO.[28–30,50] Traditionally, antituberculous regimens have included bactericidal and bacteriostatic drugs that have required treatment for long periods, between 18 and 24 months. More recently, multidrug regimens have been used with more rapid microbiological cure rates that allow shorter durations of therapy (short-course chemotherapy). Isoniazid, rifampicin, and pyrazinamide are mainstays of anti-tuberculous therapy. Other agents often used in children, include streptomycin and ethambutol (table 3).

Adverse reactions to antituberculosis therapy may also be seen in children who start with this therapy. Isoniazid and rifampicin may both be hepatotoxic causing elevation of serum aminotransferase levels. These hepatotoxic abnormalities are rarely severe in children. Isoniazid has also been associated with symptomatic pyridoxine deficiency, particularly in severely malnourished children. Supplemental pyridoxine is indicated in these malnourished children as well as in breast-feeding infants (dose 5 mg in infants from birth to 1 month, 5–10 mg in infants and children less than 12 years, and 10 mg in children 12–18 years). Pyrazinamide is generally well tolerated in children and rarely causes hepatic dysfunction. Ethambutol has been associated with retrobulbar neuritis, which presents with blurred vision, central scotoma, and colour-blindness.

Table 3. Recommended treatment schedules for tuberculosis disease in children[28–30]

BTS	American Academy of Paediatrics	WHO
Pulmonary and extrapulmonary tuberculosis	**Hilar adenopathy**	**Pulmonary tuberculosis, severe extra-pulmonary tuberculosis (disseminated acute tuberculosis, abdominal, spinal and pericardial tuberculosis)**
2 months RHZ(E*) then 4 months RH	6 months RH	2 months RHZE then 4 months RH daily, or
Tuberculosis meningitis	**Pulmonary and extrapulmonary tuberculosis**	3 times weekly
2 months RHZ(E/S*) then 10 months RH	2 months RHZ(E/S*) then 4 months RH	**Tuberculosis meningitis**
	Tuberculosis meningitis/bone and joint tuberculosis	2 months RHZS then 4 months RH
	2 months RHZS then 7–10 months RH	**Smear negative pulmonary tuberculosis, less severe extra-pulmonary tuberculosis (tuberculosis adenitis, mediastinal lymphadenopathy)**
		2 months RHZ then 4 months RH daily, or
		3 times daily

R=rifampicin; E=ethambutol; H=isoniazid; S=streptomycin; Z=pyrazinamide; *if resistance suspected

Trebucq reviewed the literature regarding recommendations for ethambutol use in children and concluded that ethambutol was safe in children greater than 5 years of age at a dose of 15 mg/kg/day and also in younger children without undue fear of side-effects.[51] It is often appropriate to obtain a baseline ophthalmological assessment in younger children before starting ethambutol therapy. This should be repeated after 1–2 months.

Compliance is a major determinant of the success of drug treatment—compliance of the physician in prescribing the optimum appropriate regimen and monitoring it, and compliance of the patient in taking the medication as prescribed. Compliance in children is further compounded by the fact that children may have mechanical difficulties in taking medications, many of which are not specifically packaged or produced in paediatric formulations. Difficulties with taste, consistency of formulations, and gastrointestinal toxicity may be important factors in children that may dramatically affect treatment compliance.

DOTS (directly observed therapy, short-course) has become a cornerstone for tuberculosis control across the globe. Direct observation of therapy (DOT) is only one of five key elements. These include government commitment to sustained tuberculosis control activities, case detection by sputum smear microscopy, standardised treatment regimens of 6–8 months for all confirmed smear-positive cases with DOT for at least 2 months, a regular uninterrupted supply of essential antituberculosis drugs, and a standardised recording and reporting system. DOTS has been adopted by 148 of 210 countries worldwide and almost 55% of the world's population lives in countries providing DOTS. The WHO recommends that the DOTS strategy is applicable to all patients with tuberculosis, including children in whom high success rates (over 95%) can be achieved.[30] Many countries have adopted a universal DOT policy, whereas others such as the UK use a selective policy for those who may be unreliable in taking their therapy.[28]

Respiratory tuberculosis including hilar adenopathy

In most cases there is usually a history of contact with a smear-positive patient, commonly a family member. Treatment should consist of rifampicin and isoniazid for 6 months, supplemented by pyrazinamide for the first 2 months. Ethambutol should also be included in the first two months in children who are at high risk of isoniazid resistance. This includes those who are known or suspected to be HIV positive, and for the UK and other developed countries those who are from other ethnic groups, or are recent arrivals such as immigrants and refugees. For children aged 5 years or more, ethambutol is recommended for routine treatment without taking any more precautions than for adults. A routine ophthalmology review is recommended in young infants.

CNS tuberculosis (meningitis and tuberculoma)

Quadruple therapy with rifampicin and isoniazid, with an initial 2 months of pyrazinamide and ethambutol or streptomycin is recommended for CNS tuberculosis. Both ethambutol and streptomycin cross the blood-brain barrier rather poorly, and only when the meninges are inflamed. Nevertheless, streptomycin is recommended by the WHO and ATS for tuberculosis meningitis. An alternative drug that achieves good cerebrospinal concentrations in children with tuberculosis meningitis is ethionamide, particularly when a dose of 20 mg/kg/day is used.[52] A total duration of 12 months is generally recommended, although the WHO recommends a minimum of 6 months of therapy.

Other extra-pulmonary tuberculosis

There are no clinical efficacy trials for the treatment of extra-pulmonary tuberculosis in children. Present recommendations are based on trials in adults, which show favourable responses to 6 months of three to four drug combinations for non-life-threatening extra-pulmonary disease. Treatment of tuberculosis adenitis, bowel disease, pericarditis, bone and joint disease, and other end-organ disease should be with the standard 6-month regimen. However, some authorities recommend longer courses of between 9 and 12 months for bone and joint disease.[29]

Multidrug-resistant tuberculosis

Single, multiple, and multidrug resistance has been on the increase. Isoniazid-resistance has been found in 6·8–7·2% of isolates in children less than 15 years old in England and Wales from 1995–1999. Multidrug resistance (defined as resistance to both isoniazid and rifampicin) over the same period was 0·5–0·7%. Higher levels of resistance occur in ethnic minority groups, especially those from the Indian subcontinent and sub-Saharan Africa. As children have lower rates of tuberculosis isolation, MDR tuberculosis is often initially only identified in the adult index case or in other contacts.

Treatment of patients with drug-resistant tuberculosis should only be carried out by specialists with appropriate experience in the management of such cases. The commonest isolated drug resistance is to isoniazid. It is particularly important to add ethambutol as a fourth agent where isoniazid resistance is suspected, or in those patients at higher risk of resistance. Treatment should be continued for 9–12 months, initially with rifampicin, pyrazinamide, and ethambutol for 2 months followed by rifampicin and ethambutol for the complete duration of therapy. Isolated drug resistance to other first-line drugs is unusual and appropriate therapy must begin based on recommended guidelines.[28] Rifampicin resistance most commonly occurs in conjunction with isoniazid resistance (called MDR-tuberculosis). Treatment should be carried out by a specialist with substantial experience in managing complex resistant cases, and only in hospitals with appropriate isolation facilities. Such treatment should also be monitored closely not only for drug toxicity, but more importantly to ensure compliance. Treatment will in most cases involve five or more drugs and for durations of at least 2 years. Several alternative antituberculosis drugs may need to be used, although the efficacy of these drugs has not been evaluated in children. The drugs that have been used previously include aminoglycosides (streptomycin, amikacin, capreomycin, kanamycin), ethionamide/prothionamide,

cycloserine, quinolones (ciprofloxacin, ofloxacin), rifabutin, macrolides (azithromycin, clarithromycin), and para-amino salicylic acid.

Corticosteroids

Corticosteroids have been found to be beneficial in situations where the host response to *M tuberculosis* contributes to significant tissue damage. Corticosteroids have been shown to significantly decrease mortality and long-term neurological sequelae in patients with tuberculosis meningitis.[53,54] Children with bronchial obstruction due to enlarged lymph nodes may also benefit from corticosteroid therapy.[55] Corticosteroids may also be of benefit in extensive pulmonary tuberculosis, pericardial effusion, and pleural effusion. A dose of 1–2 mg/kg (maximum of 60 mg) for 4–6 weeks is recommended, followed by a period of weaning doses.

Treatment of tuberculosis Infection

Treatment of tuberculosis infection, rather than the disease, involves the use of one or two antituberculosis agents to prevent the future development of tuberculosis disease. Many studies have shown that isoniazid for 12 months is highly effective, as well as shorter courses of between 6 and 9 months' duration. A 6-month regimen of isoniazid is generally recommended in the UK[28] although ATS/CDC recommends a 9-month course.[31] Regimens of rifampicin and isoniazid lasting for 3 months have been used in the UK with good effect and no increased adverse reactions.[56] 2 months of short-course rifampicin and pyrazinamide has been shown to be as efficacious as 12 months of isoniazid in HIV-infected individuals[57]. However, reports of fatal and severe liver injuries with this combination means that it should be used with caution.[58]

Management of young children who are close contacts of smear-positive adults

Young children who are exposed to a household contact with smear-positive pulmonary tuberculosis are at high-risk of developing both infection and disease. Young children (less than 2 years for BTS, less than 4 years for ATS/CDC and less than 5 years for WHO) who are thus exposed should begin isoniazid chemoprophylaxis irrespective of the TST at baseline. TST is repeated at 6 weeks (12 weeks for ATS/CDC). If the TST is positive at baseline or becomes positive on re-testing, then the duration of therapy should be that for tuberculosis infection. Although the WHO has made the recommendation of providing chemoprophylaxis to children younger than 5 years old, it is unclear to what extent this recommendation is being followed in areas of high tuberculosis incidence.

Search strategy and selection criteria

Data for this review were identified by searches of PubMed and references from relevant articles. Search terms were "tuberculosis", "children/child", "diagnosis", and "treatment" used in various combinations. The search was limited to articles in the English language. Additionally, websites from various organisations including those of the WHO, the International Union Against Tuberculosis and Lung Disease, the US Centres for Disease Control and Prevention, the American Thoracic Society, and the British Thoracic Society were searched for recommendations on diagnosis and treatment.

Conclusions

Tuberculosis continues to cause considerable mortality and morbidity in adults and children worldwide. The global resurgence of tuberculosis has been fuelled by several factors including HIV infection, breakdown of tuberculosis control programmes, overcrowding and MDR tuberculosis. Childhood tuberculosis represents a sentinel event within a community suggesting recent transmission from an infectious adult. The early diagnosis and adequate treatment of adults and children with tuberculosis remains a key tuberculosis control strategy. Better diagnostic tests and vaccines are awaited.

Conflicts of interest

None declared.

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