

## BEST PRACTICE

## Paediatric tuberculosis

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Children are important in the epidemiology of tuberculosis as a marker of recent disease transmission and a reservoir for the future. Once infected they have a higher risk of progressing to tuberculous disease. Chest radiography and tuberculin testing with or without tissue for culture are still the standard tools for confirming the diagnosis once this is considered. Well researched treatment protocols are available but multidrug resistant tuberculosis and coexistent HIV are a challenge. Ensuring compliance with treatment is a major concern. Controversy still surrounds the place of BCG. Advances in the molecular genetics of tuberculosis hold out the possibility of better vaccines.

Paediatric tuberculosis should be primarily concerned with prevention. By and large in developed countries this is the case and the incidence of tuberculous disease in children (that is, under 16 years of age) is small.<sup>1</sup> A child with tuberculous disease is an opportunity to analyse the failings of the preventive system. The strategies for preventing disease are (in decreasing order of importance):

- (1) Identification and treatment of infectious cases.
- (2) Contact tracing and treatment of non-infectious disease and latent infection.
- (3) Vaccination with BCG.

The natural history of untreated tuberculosis has been well described in the pre-treatment era in the medical literature,<sup>2,3</sup> and it is a feature of our literary past such that anyone who coughs in a period drama can be confidently diagnosed as having terminal tuberculosis.

## NATURAL HISTORY AND EPIDEMIOLOGY

Analysis of childhood tuberculosis is important for epidemiological purposes. The normal natural history of an infectious disease from contact to infection to disease is often arrested in tuberculosis so there are numerous infected individuals who contain the bacteria and are asymptomatic. This containment may fail resulting in disease often many years after the primary infection. The distinction between disease resulting from a primary infection and reactivation of dormant tuberculosis is difficult so a patient presenting with disease may have been infected at any time in their lives. Tuberculosis in the young therefore gives an indication of the extent of recent spread in the population.

The approximate time scale for development of the various manifestations of tuberculosis is given in table 1. Children have a higher risk of progressing from infection to disease than adults (fig 1) and also have a higher risk of developing disseminated disease (miliary and meningeal).<sup>4</sup> The reason for this relates to the qualitative and quantitative immaturity of the immune system.<sup>5</sup> Reduced chemotaxis, activation, and antigen presentation by macrophages and reduced specificity of T-cell maturation and specific response have been documented in young infants—all factors which would predispose to spread of tuberculosis within the body. This increase in risk is the rationale for treatment of latent infection (or chemoprophylaxis) in children but not in adults.

In general, post-primary disease with lung cavities is the infectious form of the disease and is seen in adults and occasionally teenagers. Tuberculosis in children is usually primary and paucibacillary. Transmission of tuberculosis even to close contacts is therefore unlikely. However the recommendation for hospitalised children is to keep them isolated, and particularly to keep their visitors isolated from other patients as an undiagnosed relative may be the source case and an infection risk.<sup>6</sup>

## DIAGNOSIS

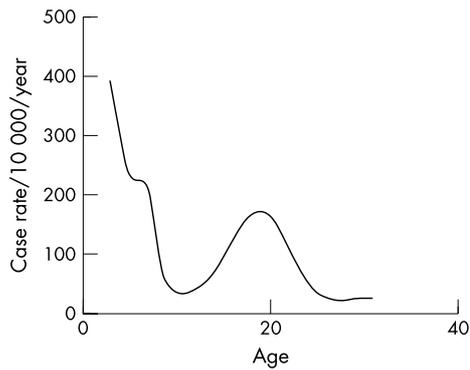
The main problem with the diagnosis of tuberculosis is thinking of it in the first place. This is not too difficult if there is a history of contact and the patient is from a high risk area or ethnic group. In the absence of these factors the diagnosis is often delayed. In one case report, of three patients presenting with disseminated tuberculosis, two were in white children where the source case (a mother and an aunt) had had undiagnosed respiratory symptoms for months before the diagnosis was

**Table 1** Timetable for development of tuberculosis

Form of tuberculosis	Time from infection to onset
Immune conversion	4-8 weeks
Primary complex	1-3 months
Local lung complications	3-9 months
Pleural effusion (usually teenagers)	3-12 months
Miliary/meningeal	3 months onwards
Bone	10-36 months
Skin	5 years onwards
Renal	10 years onwards
Secondary breakdown	5 years onwards

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**Figure 1** The graph shows otherwise normal tuberculin reactors who were followed up to assess their subsequent risk of developing tuberculosis (data redrawn from a study in Puerto Rico<sup>14</sup>).



**Figure 2** Miliary tuberculosis: the lung fields are studded with small opacities of uniform size.

made in the child.<sup>7</sup> In 2001 there was the biggest school outbreak of tuberculosis recorded in the UK at Crown Hills School in Leicester. The source case was a white child of 13 who had had symptoms for almost a year diagnosed as asthma (personal observation).

Tuberculosis may present in almost any organ with such a variety of symptoms that it is in the differential diagnosis of



**Figure 3** Post-primary tuberculosis: the right upper lobe is very abnormal with areas of collapse/consolidation and multiple radiolucent cavities. This 15 year old patient was smear positive.

most presentations (but near the bottom of the list). The common presentations in symptomatic children are:

- Cough and respiratory symptoms.
- Weight loss and anorexia.
- Fever.

Lymph node enlargement in children is rarely caused by tuberculosis in UK residents but is worth consideration in immigrants from high prevalence countries.

All the above symptoms are common in paediatric practice, but in tuberculosis they are usually gradual in onset over more than three weeks, unremitting in nature, and increasing in severity. A history of tuberculosis contact or a relative with a chronic productive cough is helpful but not always forthcoming.

Once the suspicion is raised, the mainstay of diagnosis remains chest radiography and tuberculin test (see below). Sputum for culture is rarely positive but is an important consideration to predict infectivity, drug resistance, and for epidemiological purposes. Direct testing of sputum using polymerase chain reaction techniques has been disappointing<sup>8</sup> but once an organism has been isolated using conventional culture (2–3 weeks liquid culture or 4–6 weeks solid medium) it is possible to type the strain and to identify very quickly known antibiotic resistance genes.<sup>9</sup> For most clinical situations this is still too long to influence initial management unless the sputum smear is positive.

Clinical practice varies in how aggressively to chase a positive culture. The factors to bear in mind are:

- (1) Culture rates of only 50% even in optimum conditions.<sup>10</sup>
- (2) Better recovery from multiple gastric aspirates compared with bronchoscopy.<sup>10</sup>
- (3) The likelihood of obtaining a positive sample from a presumed source case.
- (4) The clinical condition of the patient.
- (5) The risk of the organism being a non-tuberculous mycobacterium or resistant.
- (6) The need to identify a possible outbreak.

In general, the increasing prevalence of drug resistance over the last few years and the ability to type strains to plot infectious pathways has put more emphasis on collecting samples.

Obviously if the presentation is extrapulmonary, biopsy tissue may be obtained and cultured. However most laboratories are selective in putting up tuberculosis cultures so it is not unusual to be referred a child with a granulomatous lymph node biopsy and no sample sent for culture.

### CHEST RADIOGRAPHY

A number of features may suggest tuberculosis but none is diagnostic with the exception of miliary tuberculosis (fig 2). Typical post-primary cavitating tuberculosis is unusual in children but is occasionally seen in teenagers (fig 3). The most typical feature is hilar (fig 4) or paratracheal (fig 5) lymphadenopathy. This may occur with collapse/consolidation (fig 6), with localised hyperinflation from partial bronchial obstruction (fig 7) or, particularly in infants, with bronchopneumonia (fig 8). In addition, adolescents seem to be particularly prone to pleural tuberculosis (fig 9). In some cases the interpretation of the plain chest radiograph may be difficult and a computed tomogram with contrast may be helpful in deciding whether enlarged nodes are in fact present and may be demonstrable even if the chest radiograph is normal.<sup>11</sup> The differential diagnosis of hilar/paratracheal enlargement in a child is mainly between other infective causes (for example, mycoplasma) and neoplastic change (T-cell lymphoma, neuroblastoma), sarcoidosis being extremely rare in childhood. In most cases there is little confusion because of the clinical context but



**Figure 4** Hilar tuberculosis: there is a prominent node in the left hilum of the lung.



**Figure 5** Paratracheal tuberculosis: there is a right paratracheal swelling the normal distance between the trachea and the right lung being about 1 cm.

occasionally further investigations or a trial of anti-tuberculosis treatment are necessary.

### TUBERCULIN TESTING

The tuberculin test is not ideal and like most clinical tests has to be interpreted in context.

The test measures the skin reaction to intradermal purified protein derivative. The usual methods of administration in this country are the Heaf and the Mantoux tests with a grade 2 Heaf equivalent to 5 mm induration from a 5 tuberculin unit (TU) Mantoux.<sup>12</sup> The nomenclature for Mantoux tests is somewhat confusing. The terms 1 in 1000 and 1 in 10 000 (for 100 and 10 TU/ml respectively) are best avoided. The standard test is 0.1 ml of 100 TU/ml (that is, 10 TU) but in situations where a strong reaction is likely 1 TU is given. In the USA 5 TU is the standard strength. The cut off for a positive test is also variable and US guidance gives 5, 10, or 15 mm as the critical size depending on the degree of risk.<sup>13</sup> When measuring at 48–72 hours it is the diameter of induration that is recorded not the extent of any erythema. This is done by palpation (and if necessary marking the edge with a ballpoint pen) and measuring in two planes at right angles. The larger the Mantoux result the more likely the patient is to already have or go on to develop tuberculous disease.<sup>14</sup> At smaller levels of reaction, distinguishing tuberculosis infection from “normal” is difficult so it is not surprising that there is a variation in



**Figure 6** Collapse/consolidation: there is a large right hilar mass with collapse/consolidation of the lateral segment of the right middle lobe. There is also a small right pleural effusion.



**Figure 7** Partial bronchial obstruction: there is a large right hilar and superior mediastinal mass with shadowing in the right upper zone. The trachea and main bronchi are distorted and there is hyperinflation of the right lower zone.



**Figure 8** Tuberculosis bronchopneumonia: there is widespread blotchy airspace shadowing; the child is intubated.

strengths of tuberculin and cut off points advocated. This is particularly the case where non-tuberculous mycobacterial infection (including BCG vaccination) is common. Although there is a suggestion that small reactions on Mantoux testing



**Figure 9** Pleural tuberculosis: there is a large left pleural effusion with some mediastinal shift.

**Table 2** Interpretation of tuberculin tests

False positive	False negative
Faulty technique: administration/reading	Faulty technique: administration/reading
Previously treated tuberculosis	Overwhelming tuberculosis
Other mycobacterial infection	Infants
BCG	Very recently acquired infection (<8 weeks)
	Immunosuppression: HIV, steroids/cytotoxic agents, leukaemia/lymphoma
	Malnutrition
	Infection: measles/chickenpox, live vaccines

may be protective,<sup>15</sup> it is best to regard a Mantoux test as an indicator of risk of disease rather than evidence of immunity. My own practice is to use 10 TU as standard, but to use 1 TU with a 5 mm cut off after BCG (which in the local population I deal with includes most patients). This has been shown to give a reasonable differentiation in tuberculous disease<sup>16</sup> and an acceptably low rate of false negative responses<sup>17</sup>

A list of causes of false positive and false negative Mantoux responses is given in table 2. Because of the difficulties of interpreting tuberculin tests there is considerable interest in finding a more specific test of tuberculous infection. Tests using lymphocytes from peripheral blood have given encouraging results.<sup>18</sup> The lymphocytes are exposed to tuberculous antigen and, in infected individuals, competent T-cells produce interferon- $\gamma$  which can be measured. The test can distinguish tuberculosis from BCG and may revert to negative after adequate treatment. However, because of the complexity and expense of this and similar tests they are unlikely to replace the tuberculin skin test completely.

## TREATMENT

The list of drugs with activity against tuberculosis includes isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z) as first line drugs and ciprofloxacin, clarithromycin, cycloserine, para-amino salicylate (PAS), prothionamide, streptomycin (or amikacin) as second line. Notes on first line drugs are given in table 3.

There have been numerous treatment studies but relatively few in children. However, much of the work in adults is probably applicable to children with appropriate dosing changes and precautions. A six month course of treatment is sufficient

for pulmonary tuberculous disease<sup>19</sup> and probably for localised extrapulmonary disease, assuming good compliance, but all patients on antituberculosis treatment should be under a clinician with experience in tuberculosis care.<sup>20</sup> Three drug treatment H<sub>6</sub>R<sub>6</sub>Z<sub>2</sub> (numbers indicate length of treatment in months) or H<sub>6</sub>R<sub>6</sub>E<sub>2</sub> is standard if the risk of drug resistance is low but four or more drugs are indicated with an individualised regimen if it is high.<sup>21</sup> Treatment of multiple drug resistant tuberculosis is beyond the scope of this article but the principles are the same; treatment with an adequate number of drugs to which the organism is sensitive, ensuring compliance with treatment, monitoring for complications, and prevention of cross infection.

There are a variety of regimens for treatment of latent infections (otherwise described as chemoprophylaxis). In the UK treatment is recommended for asymptomatic children under the age of 16 with a positive tuberculin test.<sup>21</sup> In the US the age cut off is 35 years.<sup>22</sup> Nine months of isoniazid treatment is effective<sup>23</sup> but there is a search for shorter regimens to improve compliance. Six months of isoniazid has a higher relapse rate and two months of pyrazinamide/rifampicin is effective but there have been reports of liver toxicity.<sup>24</sup> In the UK rifampicin and isoniazid for three months is recommended. Although there are no randomised trials of efficacy it seems to be safe,<sup>25</sup> and there is extensive experience of both drugs. Pyridoxine to counteract the peripheral neuropathy of isoniazid is not necessary unless the child is malnourished, preterm, or a breastfed infant. Given the prolonged nature of the treatment and the importance of compliance the fewer medications prescribed the better.

Adverse reactions to medication (liver failure being the most significant) are rare in children. Mild rises in transaminases are not uncommon but significant liver toxicity is more likely in those who are malnourished or severely unwell at diagnosis. The other group of children at risk are those on concurrent medication, most commonly anticonvulsants. Cases reported in the adult literature that have developed liver failure have usually had unrecognised symptoms for some time,<sup>26</sup> and if diagnosed early the features improve on stopping medication. My personal practice is not to check liver function routinely before or during treatment unless the patient is in a high risk group. However patients and parents should be warned of potential side effects and given contact telephone numbers to the tuberculosis service in case they are concerned. Perhaps surprisingly this support is rarely abused. Introduction of drugs one at a time at low dose and increasing with close monitoring may be necessary if the risk of liver toxicity is high.

## COMBINED TUBERCULOSIS/HIV INFECTION

Tuberculosis and HIV are synergistic, replication of each being enhanced by the other. Co-infection is a huge problem in much of the developing world particularly sub-Saharan Africa. In the UK the overlap is small, mainly seen in drug abusers and immigrants from high prevalence areas. The latter provide most cases in the paediatric age group. The management of these cases is highly specialised and well covered elsewhere.<sup>27</sup>

The key points are:

- (1) As with tuberculosis in HIV negative patients, most of the data on treatment are in adults but the results are generally applicable to children.
- (2) The differential diagnosis of tuberculosis with HIV is much wider, encompassing opportunistic infections including non-tuberculous mycobacteria.
- (3) Drug interactions between rifampicin and both protease inhibitors and non-nucleoside reverse transcriptase inhibitors are inevitable and alternative tuberculosis therapy may be necessary if these drugs are to be used.

**Table 3** Antituberculosis drugs

Drug	Dosage (mg/kg/day)	Side effects
Isoniazid	5–10	Resistance not uncommon, hepatitis, peripheral neuropathy in risk groups
Rifampicin	10–20	Microsomal enzyme induction leading to drug interactions, colours urine, hepatitis, flu-like syndrome (vomiting, fever, myalgia), skin rash
Pyrazinamide	20–35	Hepatitis, uricaemia, arthralgia
Ethambutol	15–25	Retrolubar neuritis. Contraindicated in children <5 years who cannot report eye symptoms

**Figure 10** Comparison of urine from two patients, one taking and one not taking rifampicin.

(4) Standard length tuberculosis treatment is usually adequate.

(5) Paradoxical deterioration on treatment is not uncommon as the immune response recovers.

### COMPLIANCE WITH TREATMENT

Most people given a one week course of antibiotics will fail to complete it. Ensuring reasonable compliance with a 3–6 month course of treatment is a major challenge especially when the patient is asymptomatic for much of that time. There are a number of ways of assessing compliance with treatment including a history from the child. Children of 5 years and over can respond to questions like “do you take your medicine every day” and “what colour are the medicines you take”. Younger children can often indicate answers to more directive questions. The answers can be correlated with the parents’ responses to assess consistency. On the whole, children under 10 try to answer directly and truthfully whereas teenagers are more likely to assess the implications of the question before framing a response.

Checking urine at every clinic visit for the red colouration of rifampicin is standard practice (fig 10). However the colour disappears after a few hours, which may be a problem with afternoon clinics. In addition if too much attention is focused on the urine result, non-compliant patients may take their medication only on clinic days.

Home visits, announced or unannounced, by the tuberculosis nurses are valuable in assessing the home situation and making a judgment about the likelihood of defaulting from treatment. Good communication between the hospital team, general practitioner, and tuberculosis nurses is essential. It is also possible to do tablet counts and check prescription records.

The trick of ensuring compliance is to make the family and child believe that taking the medication is the easiest option. For most parents understanding the nature of the treatment, and an awareness of the monitoring is enough. However, for some families their chaotic lifestyle or hostility to authority make directly observed therapy (DOT) essential. There are validated regimens for three times weekly treatment that can be supervised by a combination of school, district, tuberculosis, and paediatric community nursing services.<sup>28</sup> The local practice is only to initiate treatment with DOT if there are obvious concerns or a past history of defaulting and to convert to DOT if poor compliance is discovered at a later stage. This is partly pragmatic as DOT is very labour intensive.

### BCG

There has been ongoing debate about the effectiveness of BCG vaccination for a number of years. Effectiveness in different studies varies between zero and 80%.<sup>29</sup> Partly because of this, BCG policies in different countries vary between no immunisation (US), high risk immunisation at birth with universal immunisation at 13 (UK), universal neonatal immunisation (Indian subcontinent and much of Africa), and multiple immunisation (much of Eastern Europe).

BCG seems more effective in trials in temperate rather than tropical areas. A theory to explain the variability of BCG has been proposed based on the immunity generated by naturally occurring soil mycobacteria, more prevalent in the tropics, which may be enough to nullify any additional effect of BCG.<sup>30</sup>

Proponents of BCG will point to the fact that it is extremely safe<sup>31</sup> and that it has a definite effect in reducing disseminated (and life threatening) forms of tuberculosis<sup>32</sup> even if results overall are inconclusive. Opponents counter that the benefit of BCG is marginal and it increases reactions on tuberculin testing<sup>33</sup> making identification of infected individuals more difficult. Universal neonatal BCG is also potentially dangerous for those rare newborn infants with severe combined immunodeficiency or other congenital T-cell abnormalities. Immunisation at 12–13 years in the UK is a continuation of the protocol from the national BCG trials of 50 years ago and is not logical given the increased susceptibility of young children. If BCG is to be given, it makes sense to give it soon after birth and protect the group who are at greatest risk of disseminated disease. The length of time BCG protects for is not known. In the Medical Research Council study there was diminution of the effectiveness of BCG from 80% to 59% after 10–15 years,<sup>29</sup> but in the longer term there are no good data.

Alternatives to BCG have been sought, so far without effect, but the sequencing of the genome of tuberculosis raises the possibility of DNA and subunit vaccines.<sup>34</sup> The difficulties of devising and testing antigens or bacteria that will provide immunity against a facultative intracellular organism with the ability to remain dormant for years are not to be underestimated.

### CONCLUSION

Tuberculosis is much less common in the UK than in past generations and rates in children are low. However there is no

**Further reading**

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**Websites**

- <http://www.cdc.gov/nchstp/tb>  
This is the US government division of tuberculosis elimination which has a variety of guidelines and updates. Also the related <http://www.cdc.gov/mmwr/> which gives access to the Morbidity and Mortality Weekly Report.
- <http://www.who.int/gtb/>  
World Health Organisation website about tuberculosis.

room for complacency as there are threats in the form of high rates in much of the developing world with high rates of HIV co-infection. Drug resistance, mainly as a result of inadequate treatment, is also on the increase. In addition, the diagnosis of clinical tuberculosis is more difficult if the incidence is low. The HIV epidemic has led to a vast body of research into the human immune response to disease, which has the potential to create new avenues for prevention and treatment of tuberculosis. Sequencing the tuberculosis genome may ultimately lead to a better understanding of how and why the organism causes disease and raises the possibility of developing a more efficacious vaccine than BCG. The control of tuberculosis still relies on a high index of suspicion to make the diagnosis and motivated individuals working in a team to ensure compliance with treatment.

**REVISION QUESTIONS AND ANSWERS**

Q1. In what ways does the spectrum of paediatric tuberculous disease differ from that of adults?

- Higher risk of disseminated disease
- Higher risk of pleural effusion in teenagers
- Lower risk of cavitary (infectious) disease

Q2. Why is treatment of a latent tuberculosis infection appropriate for a child but not for an adult?

- The risk of progression to disease in the near future is higher
- Their life expectancy is higher so the lifetime risk of disease is higher
- The risk of disseminated disease (and therefore morbidity/mortality) is higher

Q3. What are the causes of a false negative tuberculin test?

- Faulty preparation of the tuberculin
- Faulty administration (extravasation, subcutaneous injection)
- Faulty reading (wrong time, use of erythema not induration)

- Immunodepression
- Immunosuppression

Q4. You see a child in clinic with a positive Mantoux test and an abnormal chest radiograph. What factors would make you admit the child to attempt a bacteriological diagnosis rather than starting treatment there and then?

- Lack of a known source case
- Parenchymal lung disease or cavitation
- Recent immigrant from high risk area for drug resistance
- Known HIV positive
- Part of a cluster of tuberculosis cases

Q5. What methods can be used for assessing compliance with treatment?

- History from child and carer
- Urine colouration
- Pill/prescription counts
- Home visits

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## IMAGES IN MEDICINE.....

### Iatrogenic harlequin syndrome

**T**horacoscopic sympathectomy is a safe, effective, minimally invasive treatment for primary hyperhidrosis.<sup>1</sup>

A 29 year old man with severe facial hyperhidrosis underwent an uncomplicated right thoracoscopic sympathectomy. Before operating on his left side, a starch-iodine preparation was applied to his face in order to demarcate residual sudomotor function. The preparation becomes blue on exposure to moisture, thereby representing residual sweat gland activity.

Figure 1 demonstrates that sympathetic innervation to the face is strictly unilateral, and nerve fibres do not appear to cross the midline. This is essentially an iatrogenic variation of the harlequin syndrome,<sup>2</sup> which usually results from interruption of post-ganglionic sympathetic fibres secondary to malignant invasion.

His facial hyperhidrosis was completely treated once the contralateral sympathectomy was performed.

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**Figure 1** Starch-iodine preparation applied to patient's face (published with patient's permission).