

What are the most useful clinical indicators of tuberculosis in childhood?

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

This review addresses the question: *What are the most useful clinical indicators of tuberculosis in childhood?*

The WHO Pocketbook of Hospital Care for Children states that; "The risk of tuberculosis is increased when there is an active case (infectious, smear-positive pulmonary tuberculosis) in the same house, or when the child is malnourished, has HIV/AIDS, or has had measles in the past few months. Consider tuberculosis in any child with:

A history of:

- unexplained weight loss or failure to grow normally;
- unexplained fever, especially when it continues for more than 2 weeks;
- chronic cough (i.e. cough for more than 30 days, with or without a wheeze);
- exposure to an adult with probable or definite infectious pulmonary tuberculosis.

On examination:

- fluid on one side of the chest (reduced air entry, stony dullness to percussion);
- enlarged non-tender lymph nodes or a lymph node abscess, especially in the neck;
- signs of meningitis, especially when these develop over several days and the spinal fluid contains mostly lymphocytes and elevated protein;
- abdominal swelling, with or without palpable lumps;
- progressive swelling or deformity in the bone or a joint, including the spine.

(Pocketbook chapter 4, page 101).

INTRODUCTION

It can be difficult to diagnose tuberculosis (TB) in children, especially pulmonary TB for which the clinical presentation is

non-specific. Many children with TB have extra pulmonary disease and there is a wide spectrum of clinical presentation. Malnutrition is a frequently associated, and so increasingly is HIV. TB in children is paucibacillary and microbiological confirmation is rarely achieved. Radiology and tuberculin skin testing (TST) are difficult to interpret. Adding to the complexity of the problem, most children with TB live in resource-limited settings where diagnostic facilities are basic.

It is important to reliably identify which children have TB. Missing the diagnosis delays therapy and is associated with poor outcome. Diagnosing and treating for TB when it is not present commits a child to prolonged therapy with expensive and potentially toxic drugs while their underlying illness is untreated.

This review aims to identify what clinical indicators are most useful in the diagnosis of TB in children. While it focuses mainly on symptoms and signs, investigations such as TST, radiology and microbiology are mentioned as they are commonly included in diagnostic approaches. Specialised investigations such as PCR and immunological testing are not included as they have limited application to resource-limited settings. TB is common in HIV-infected children living in regions endemic for TB/HIV and HIV infection impacts on the clinical presentation of TB as the infections share many clinical features. A summary of studies evaluating clinical indicators of TB in children with HIV is also included.

Methodology

The review was conducted using PubMed, using Haynes filter method. A variety of search strategies were used, including both the diagnosis and clinical prediction filters, with the scope set to both broad and narrow. The most sensitive search strategy was (clinical OR symptom*) AND child* AND (tb or tuberculosis), using the diagnostic filter and a broad scope; 2246 studies were identified, with 233 reviews. Using the narrow filter identified 136 studies and 12 reviews. While the narrower search was more specific, it lacked sensitivity and failed to identify some important studies, especially those related to TB and HIV. The use of the clinical prediction filter did not identify any new studies. All relevant abstracts were read, and if there was any doubt as to the relevance of the study, the complete article was sourced. References from review articles and book chapters were also sourced.

Table 1. Performance of basic clinical indicators in diagnosing TB in children

Study	Design	Setting	Sample size	Gold standard	Indicator	Performance
Marias et al, 2006 [7]	Prospective	Community based. Cape Town, South Africa.	428	Microbiology OR diagnostic radiology OR suggestive radiology AND response to therapy	Cough > 2 weeks, objective weight loss and reported fatigue Cough > 2 weeks, objective weight loss and TST >10mm	In low risk children (> 3years and HIV -ve) sensitivity 82%, specificity 90%, PPV 82%. In high risk, sensitivity 52%, specificity 93%, PPV 90%. In children < 3 years (HIV -ve), sensitivity 67%, specificity 94%, PPV 90%.

RESULTS

Basic clinical Indicators

The clinical presentation of TB varies depending on the age and nutritional state of the child. A review of the pre-chemotherapy literature (1920 -1950) identified that young children (<3 years) often have severe asymptomatic disease following infection [1]. In a study of 258 children with TB, 11 had TB meningitis or miliary TB, with 9 of these being younger than two years [2]. A retrospective study of 214 patients admitted with TB meningitis to a Turkish hospital found 77% younger than 5 years of age [3]. Malnutrition is also associated with severe infection but it is difficult to differentiate cause and effect. In an Indian study of 100 patients admitted with tuberculosis in 1974, 55 children had TB meningitis[4]. While this population was not BCG immunised, more than half (55%) had marasmus. In contrast to these 'high risk' children, older children rarely have primary progressive disease, and often have symptoms of a chronic and non-remitting nature[1].

Symptoms commonly associated with TB are not specific or sensitive for TB. A cross-sectional study of children living in a TB endemic area found that 26% of 1397 children without TB had reported cough in the preceding 3 months, 11% fever or night sweats and 5% had reported weight loss [5]. Comparison of symptoms found that only weight loss was significantly more common in children with TB compared to those without (OR 4.5: 91%CI 1.5-12.3) while the combination of cough and weight loss was most significant.

In a community-based pilot study, 151 children (age < 13yrs) referred with cough > 2 weeks, not responsive to oral antibiotics were followed [6]. Confirmed TB was defined by positive microbiology, with probable TB as CXR indicative of TB as read by two experts. Of these children, persistent, non-remitting cough > 4 weeks was uncommon (16/151) and strongly associated with confirmed TB (15/16). Persistent fatigue and weight loss were also associated with TB, while night sweats and fever were not.

Following the pilot study, 428 children (age <13 years) with cough > 2 weeks were followed [7]. Subjects were subdivided into high risk (< 3yrs or HIV positive) and low risk (>3years and HIV negative). The three variables found to be most significantly associated with a diagnosis of TB were chronic unremitting cough > 2 weeks, objective weight loss and reported fatigue. A combination of these three variables had a sensitivity of 82% and specificity of 90% in the low risk group (see table 1). It found that in children less than 3 years of age who were HIV negative, the use of positive TST as the third variable instead of fatigue was slightly more sensitive (67% vs 52%). The study found a symptom based approach to be unreliable in high risk groups. In particular, in the HIV infected group, the combined

symptoms only had a sensitivity of 56% and a specificity of 62% (see table 4).

A prospective study of 135 Peruvian children admitted to hospital with a presumptive diagnosis of TB found chronic cough > 2 weeks significantly associated with TB [8]. Of these, 50 were confirmed TB based on microbiology whilst 55 were classified as probable TB based on clinical suspicion. Contact history was not associated with TB, however this is likely to be explained by the inclusion of contact history in the diagnosis of probable TB. Other studies have found a strong association between contact history and TB, even in an endemic setting [2]. In this prospective study of 258 children (<13 years) there was a significant association between household contact with TB and diagnosis ($p < 0.01$). While not statically significant, there also appeared a trend between prolonged duration of symptoms and diagnosis (47% of those with confirmed TB vs. 33% of not TB). There was no association with weight loss or physical examination findings.

Table 2. Keith Edwards score [13]

Feature	0	1	3	Score
Length of illness	Less than 2 weeks	2 to 4 Weeks	More than 4 weeks	
Nutritional status	More than 80% line	Between 60-80% line	Less than 60% line	
Recent contact history of tuberculosis	No recent contact history	Verbal contact history	Sputum +ve contact history	

Add a score for any other features (if present) as below:

Significant Mantoux (.....mm)	Score 3	
Enlarged, painless rubbery neck glands	Score 3	
Night sweats or unexplained fever	Score 2	
Angle deformity of spine	Score 4	
Malnutrition not improved after 1 month treatment	Score 3	
Firm, non-fluid, non-traumatic swelling of joint	Score 3	
Unexplained abdominal swelling (ascites)	Score 3	
Coma for more than 48 hours (with or without con send to hospital if possible)	Score 3	
	Total	

Scoring systems

In 1969, the Kenneth Jones Criteria were published, perhaps the first scoring system to aid in the diagnosis of TB in children [9]. The authors commented 'our attention was drawn to the similarity between the difficulties encountered in the diagnosis of tuberculosis and rheumatic fever, and the way in which the diagnosis of the latter has been simplified by the application of the Jones criteria'; A variety of scoring systems have been proposed since.

Table 3. Performance of previously described scoring systems in diagnosing TB in children

<i>Study</i>	<i>Design</i>	<i>Setting</i>	<i>Sample size</i>	<i>Gold standard</i>	<i>Indicator</i>	<i>Performance</i>
Mathur et al, 1974 [4]	Prospective	Hospital, Jaipur India.	100	Admitted with diagnosis of TB	Kenneth Jones [9] score > 7.	73/ 100 score >7. If marasmus included, 95/100.
Van Beekhuizen, 1998 [14]	Retrospective	Hospital, Aitape PNG	301	Response to treatment	Keith Edwards [13] score > 7	Sensitivity 62%, specificity 95%
Narayan, 2003 [15]	Prospective	Hospital, Pondicherry India	101	Microbiology OR histology OR diagnostic radiology	Keith Edwards [13] score >7	Sensitivity 91%, Specificity 88%
Migliori et al, 1992 [17] ¹	Prospective	Regional TB clinic, Uganda	210	Ghidey and Habte criteria [16] AFB in gastic washings	AFB in gastric washing Ghidey and Habte score [16]	Sensitivity 96%, Specificity 92%, PPV 68% Sensitivity 68%, Specificity 99%.
Schaff et al, 1995 [2]	Prospective	Hospital, Tygerberg South Africa	258	Microbiologically confirmed	WHO EPI [18]	Sensitivity and specificity not calculated as tiered classification.
Houwert et al, 1998 [21]	Prospective	Hospital, Tygerberg South Africa	627	Microbiologically confirmed	WHO EPI. [18]	Weight loss, cough and household contact PPV 63%.
Sant'Anna et al, 2004 [23]	Retrospective	Outpatient clinic, Bahia, Brazil	164	Response to treatment	Sant'Anna et al [23] Score > 40	Sensitivity 82%
Seth & Sharma, 2002 [27]	Prospective	Hospital, Jaipur India	42	Response to therapy	Ajuja criteria for TBM [26] Modified Ahuja criteria including family history and Mantoux	Sensitivity 65%, Specificity 75%. Sensitivity 83%, Specificity 63%

1 In the original study, the Ghidey & Habte approach is used as the gold standard to assess the value of AFB in gastric washings. A calculated sensitivity and specificity is presented, redefining AFB in gastric washings as the gold standard.

Table 4. Performance of clinical indicators in diagnosing TB in children with HIV

<i>Study</i>	<i>Design</i>	<i>Setting</i>	<i>Sample size</i>	<i>Gold standard</i>	<i>Indicator</i>	<i>Performance</i>
Marias et al, 2006 [7]	Prospective	Community based. Cape Town, South Africa.	Subset of 428, 297 tested (37 HIV positive)	Microbiology OR diagnostic radiology OR suggestive radiology AND response to therapy	Persistent non-remitting coughing > 2 weeks, objective weight loss and reported fatigue	Sensitivity 56%, Specificity 62%, PPV 62%.
Van Rheenon, 2002 [38]	Prospective	Hospital, Copperbelt Zambia	147	Microbiology OR diagnostic radiology OR (Mantoux OR suggestive radiology) AND response to therapy	Keith Edwards score > 7	Sensitivity 88%, Specificity 25%.

Hesseling et al (2002) reviewed the various scoring systems and diagnostic approaches used in the diagnosis of TB [10]. This comprehensive review of all literature from 1950 onwards identified 16 diagnostic approaches, with 11 of these being related in some way to another system. The diagnostic approaches identified were either point scoring systems, diagnostic classifications (e.g. suspect, probable or confirmed), diagnostic algorithm/ flowcharts or a combination of these. Interestingly, all 16 approaches included contact history, chest radiography and TST score but only 8 included duration of symptoms. The review identified that definitions used across the different approaches were inconsistent, particularly in regards to the interpretation of TST and of the chest radiograph. The scoring systems were based heavily on clinical experience, poorly validated and lacked a gold standard. In their review, 14 studies were identified that were designed to assess the validity of the diagnostic approaches, with only 7 of these having independent study populations. Of these 7, 5 were prospective and none had a control population. Only one of these studies was clinic based. Due to these limitations, no one scoring system was identified as the most useful tool in diagnosing TB in children.

The Kenneth Jones criteria is a point scoring system based heavily on diagnostic tests [9]; features such as AFB in sputum or a Mantoux greater than 10mm score 3 points, while suggestive radiology or smaller Mantoux reaction (5 - 9mm) score 2 points; 1 point is deducted for recent BCG. While most clinicians would regard the demonstration of AFB as diagnostic, the Kenneth Jones criteria places less weighting due to the possibility of AFB being 'pseudo tuberculosis bacillus'. It is argued that tuberculosis should also have other symptoms and signs which will give a diagnostic score. Aside from contact history, symptoms are not included in the score. Despite its wide application, there is no validation of this scoring system. Based on their own application of the scoring system in a Chilean hospital over 6 months, 'tuberculosis seems unquestionable' if the score is >7, with lower scores suggesting a graded lower probability of TB. In an Indian study of 100 children admitted to hospital with TB, 73 had a score > 7 [4] (see table 3). In this study, 53% of children with TB were marasmic, and if marasmus was scored +1, 95 / 100 children would score >7. This scoring system has subsequently been revised [11, 12], placing more weighting on microbiology; neither of these studies validated the scoring system with an appropriate gold standard.

The Keith Edwards score was developed in PNG and is based almost entirely on clinical findings [13]; microbiology and radiology are not included in the main score as it is argued that these investigations are not widely available. As shown in table 2, the three main criteria are duration of illness, nutritional status and contact history of tuberculosis, with additional points scored for Mantoux, and clinical findings such as ascites, spine deformity or adenopathy. Diagnostic algorithms are also proposed for TB presenting as malnutrition, pneumonia and coma. The original study proposes a score >7 being suggestive of TB based on clinical experience, however this is not validated. Heleen van Beekhuizen evaluated the Keith Edwards score in a retrospective study of 301 children (HIV negative) admitted with likely TB in Aitape, PNG [14]. The study is limited with the use of response to treatment as the gold standard of diagnosis. Excluding those who died (and no definitive diagnosis made), the score had a sensitivity of 62% and specificity of 95% (see table 3). A recent prospective study of 101 children (<12 years) found the scoring system to perform very well [15]. In this study the gold standard was TB diagnosed on microbiology or imaging. Of the 65 children were diagnosed with TB, 59 of these having a score >7, with the score having a sensitivity of 91% and specificity 88%.

Ghidey and Habte (1983) proposed a diagnostic classification, diagnosing TB if a child had two or more of five main criteria; history of contact, suggestive symptoms, positive Mantoux, suggestive radiology or microbiology [16]. Miglori et al (1992) applied this score to 210 children aged <5 referred with likely pulmonary TB in Uganda (low HIV prevalence) [17]. In the original study, Miglori et al use the score as the gold standard to assess the reliability of gastric washings and response to therapy. Redefining positive gastric washing as the gold standard, the score has a sensitivity of 68% and a specificity of 99%.

An extension of the diagnostic classification is the hierarchal approach, such as the WHO EPI [18]. In this approach, TB is suspected if there is contact history, suspicious CXR or suggestive symptoms, probable if there is a positive Mantoux or suggestive x-ray, and confirmed if microbiology is positive. This approach has been modified with the addition of response to therapy as an indicator of probable TB [19], and inclusion of suspicious CXR in the classification of probable TB in an endemic area [20]. In these approaches, inclusion of microbiologically confirmed TB as a separate classification makes validation difficult. Schaff et al (1995) screened all children (<13 years) presenting to a hospital in South Africa over a 16 month period [2]. Those that were suspicious for TB had a focused assessment including radiology and Mantoux, identifying 258 with probable TB; of these 109 (42%) had confirmed TB on microbiology. In a similar study based in a South African hospital, Houwert et al (1998) prospectively screened 627 children aged <13 [21]. They identified 206 who had contact history, weight loss or prolonged cough; 11 had all three features. Of these 11, 7 were identified to have confirmed (3) or probable TB, suggesting a PPV of 63%.

In 1998, the International Union against Tuberculous Lung Disease (IUATLD) published a scoring system based on retrospective case reports from 10 different countries [22]. 879 children < 15 years were TB were definitive or highly probable were included. For each subject, clinicians ranked the relevance of clinical criteria used in making the diagnosis for that patient. The five most 'relevant' criteria were included; Contact history, Mantoux, persistent cough, low weight/ weight loss and unexplained/ prolonged fever. The Gold standard was TB diagnosed by radiology or microbiology, and the criteria were weighted to maximise the performance of the model. The score was optimised for different epidemiological settings. As only subjects with TB were included and there were no controls, a true sensitivity and specificity of the model can not be determined. Unfortunately, the performance of this model has not been further assessed.

In 2004 a novel scoring system was proposed for use in Brazil [23]. The score is derived from clinical features, radiology, contact history and Mantoux, with additional points scored for severe malnutrition. In this scoring system symptoms are poorly defined, with 'Fever or cough, lost energy, sputum, weight loss, night sweats > 2 weeks' scoring +15 points; a score > 40 suggests TB, with a score <25 suggesting TB is unlikely. Retrospectively applying this score to 164 who demonstrated a response to therapy identified 134 patients (82%) who were identified as having TB with the scoring system. This scoring system was evaluated retrospectively in a case control study, with 45 microbiologically confirmed cases and 96 unmatched controls [24]. If a cut-off for diagnosis of TB was 30 points, the scoring system had a sensitivity of 89% and specificity of 87%. While these results seem promising, the vague definitions used in the scoring system and the retrospective nature of the study are likely to introduce bias. Another study in Brazil assessed the

performance of three main scoring systems (Kenneth Jones, Keith Edwards and WHO criteria) in 94 children exposed to TB [25]. This study, printed in Portuguese, appears to use a radiological diagnosis of TB as a gold standard. Whilst this study can not be evaluated completely, the Keith Edwards score had the best sensitivity and specificity.

The Ahuja criteria were proposed in 1994 to aid in the diagnosis of TB meningitis [26]. TB meningitis is 'highly probable' if the child has all of four main criteria; persistent fever and headache >2 weeks, pleocytosis on CSF, suggestive CT radiology and evidence of extra-neural TB. In a small prospective study, 31 children with clinically suspected TB meningitis were followed to assess the validity of the Ahuja criteria [27]. Using response to therapy as the gold standard, the sensitivity of the criteria was 65%, with a specificity of 75%. In this study, modified criteria was proposed which included family history and Mantoux result. This modified approach had a sensitivity of 83% and specificity of 63%. In an interesting retrospective study of 843 children and adults with meningitis found history of illness > 5 days to be significantly associated with microbiologically confirmed TBM compared to bacterial meningitis (OR 9.0, $p < 0.001$) [28]. In this study, seizures were less likely in those with TBM compared with bacterial meningitis (OR 0.3, $p < 0.001$). A prospective study of 232 children admitted with meningitis in Lucknow, India also found that prodrome (> 7 days) was associated with a diagnosis of TBM ($p < 0.005$) [29]. In this study, 110 of the 232 children were diagnosed with TBM based on culture and five features were identified that were independently predictive of TBM; prodromal stage > 7 days, optic atrophy on fundal examination, focal deficit, abnormal movements, and CSF leucocytes < 50% polymorphs. Convulsions did not differentiate those patients with TBM from those with bacterial meningitis. In this study, 1 or more of the 5 features had a sensitivity of 98% and specificity of 44% for TBM, while 3 or more had a sensitivity 56% and specificity of 98%.

HIV and TB

Few studies have specifically studied TB in children with HIV. Kiwanuka et al (2001) followed all children (aged 4 - 14 months) admitted to a hospital in Malawi with suspected TB (persistent fever, cough or weight loss) [30]. Of the 120 children enrolled, 102 had HIV testing with 72 being positive. There was a significantly higher prevalence of HIV in children younger than 6 in this study ($p = 0.03$). TB was diagnosed in 45 and included confirmed (microbiological, $n = 8$) or probable (Mantoux > 10mm regardless of BCG/ HIV status or diagnostic radiology). TB was diagnosed in 26 of 72 HIV infected children compared with 19 of 30 uninfected children ($p = 0.02$). Importantly, 40 children (39%) had no clear diagnosis (30 of these were HIV positive). This is likely to be explained in part by the use of Mantoux and radiology to define TB in this study, both of which are known to be unreliable in a setting of HIV. In this study, 8 children had microbiologically confirmed TB, with 7 of these having a Mantoux > 15mm (the other child had a Mantoux of 8mm and was HIV positive). Smear positive contact history was common (61%) and significantly associated with HIV infection ($p < 0.05$), making it a poor indicator of TB in this study. Interestingly, digital clubbing was significantly associated with HIV infection ($p < 0.01$) in those with TB, also found in a retrospective study in Durban, South Africa [31]. This is likely to be explained by the clinical overlap or co-infection with other forms of HIV-related lung disease such as lymphocytic interstitial pneumonitis and bronchiectasis in HIV-infected children with suspected TB.[30]

A retrospective study of 238 South African children admitted with TB found amongst those with known HIV status (138), 43

were HIV positive and significantly more likely to have severe malnutrition and previous TB treatment [32]. A prospective study in Addis Ababa found similarly that amongst children admitted with TB, those that had HIV were significantly more underweight [33]. In this study, they also found that HIV positive children were younger and more likely to have a non-reactive tuberculin skin test (TST). In the large community based survey of 428 described earlier in the basic clinical indicators section, 297 children were tested for HIV, with 37 found to be positive [7]. In the children with HIV, the combined symptoms of cough > 2 weeks, objective weight loss and reported fatigue performed poorly with a sensitivity of 56% and specificity of 62% (see table 4).

A prospective study in South Africa enrolled 161 children with tuberculosis (based on the Ghiddey/ Miglori approach) and compared those with HIV infection (68/ 161) to those not infected.[34] Children with TB and HIV were more likely to have chronic weight loss, malnutrition and absence of BCG scar compared to children with TB who were immunocompetent. Children with HIV were also significantly less likely to have a reactive TST. HIV infected children were more likely to have pulmonary cavitation or disseminated (miliary) disease on CXR and prognosis was poorer. The mortality rate was 13.4% in those HIV infected compared to 1.5% in immunocompetent children.

A Peruvian study of 47 children with HIV admitted with a suspected infectious process identified 8 children with culture or PCR positive for TB [35]. Of all the clinical features, weight loss was found to be significantly associated with a diagnosis of TB.

A prospective study of children with HIV admitted with lymphadenitis found the clinical finding of firm, matted lymph nodes to correlate well to microbiological diagnosis of tuberculosis, with an odds ratio of 12 [36]. In this study, pleural opacity on chest x-ray, positive tuberculin test and raised ESR were also associated with TB adenopathy.

In a recent retrospective case control study, 34 children with TB meningitis were compared with 56 HIV uninfected patients, matched for age and stage of TB meningitis [37]. Children with HIV were similar to uninfected children in terms of clinical presentation, suggesting that a diagnostic approach like the Ahuja criteria may be of some benefit, even in the child with HIV. Importantly, children with HIV were significantly more malnourished (OR 0.7, 95% CI 0.4 - 0.97) and also more likely to have previously been treated for TB (OR 4.3, 95% CI 1.3 - 13.9).

A prospective study was conducted to evaluate the Keith Edwards score in a population with high HIV prevalence [38]. 147 children aged <12 years admitted with cough > 3/52 or weight <80th centile were included; 44 had HIV (30%). 22 children had confirmed TB (culture positive), while 53 had either probable or possible TB based on symptoms, contact history or investigations. 120 children had a Keith Edwards score >7, not surprising given the inclusion criteria. While the study claims the sensitivity of the score to be 88% and specificity 25%, the gold standard was poor, including children with confirmed, probable or possible TB in the definition.

Few studies have directly compared clinical scoring systems with each other. In a hospital based study in the Democratic Republic of Congo, 91 children who scored > 7 on the Keith Edwards score were retrospectively re-scored with other clinical scoring systems [39]. Of the 91, 42 were HIV positive, and they were significantly more likely to have been previously treated for TB ($p = 0.002$). Seven scoring systems were

compared with the Keith Edwards score. There was poor correlation between the various scoring systems, independent of the HIV status of the child. In 14% of children in this study, at least one alternative score suggested they should not be treated. As a gold standard was not used, sensitivity and specificity of the various scoring systems can not be assessed.

DISCUSSION

The most useful clinical indicators of tuberculosis vary greatly, depending on the characteristics of the child who is being investigated. Positive microbiology or the 'diagnostic triad' of contact history, positive tuberculin test and abnormal chest x-ray can only be satisfied in the minority of children with TB [40-44]. Young children (<3 years) or those with HIV are at 'high risk' of progressive, disseminated disease and often have atypical symptoms. In older, HIV negative children, the low risk of progressive disease and the presence of symptoms provides an opportunity to make a clinical diagnosis. The two main factors determining the risk of progressive disease in the child are age and immune status [45].

In immune-competent children, well-defined symptoms are very useful in diagnosing TB. In particular, persistent, unremitting symptoms > 2 weeks, objective weight loss and fatigue (although more subjective) are all useful indicators; A combination of these three is particularly sensitive and specific for pulmonary tuberculosis[7]. Close contact history with TB also appears a useful indicator, even in endemic areas [2]. The Keith Edwards score is based on similar symptoms, with the basic score derived from presence of chronic symptoms > 2 weeks, objective weight loss and contact history [13].

Developed for resource limited settings, the Keith Edwards score is easy to use, does not depend on investigations apart from TST, and also applies to the diagnosis of extra-pulmonary tuberculosis. This score forms the basis for the TB guidelines in the predecessor to the 'WHO pocket book of Hospital care for children' [46]. While studies validating the score are limited, it seems to perform well in low HIV settings [14, 15, 25, 38, 47]. In particular, the prospective study conducted by Narayan et al (2003) which included an appropriate gold standard showed a sensitivity of 91% and a specificity of 88% [15]. A study evaluating a combination of indicators similar to the Keith Edwards score (contact history, weight loss and prolonged cough) found a PPV of 63% for microbiologically confirmed TB [21]. Symptom based approaches work best when risk is stratified; they are of limited use in high risk children such as those with HIV. A limited evaluation of the Keith Edwards score in a HIV setting found a sensitivity of 88% and specificity of 25% [38]. Symptoms such as fever, haemoptysis and sweats and physical findings seem to be poor indicators.

Longitudinal follow-up of children is an important component of diagnosis; in most diagnostic approaches, only the minority of children can be clearly diagnosed as having TB at first encounter. The WHO hierarchal classification appears to work well in an endemic setting. All children are screened, with those where TB is suspected having a more focused assessment identifying those where TB is probable, with microbiological testing confirming TB. Longitudinal follow-up complements the evaluation of chronic symptoms and measurement of objective weight loss.

Investigations such as radiology and TST are useful but of limited value. In areas where TB is common, chest radiographs are difficult to interpret, are often of poor quality, and interpreted by health care workers with limited radiological

experience [48]. Mantoux testing is not entirely specific in children where BCG is performed. In a meta-analysis of 26 studies on the effect of BCG on Mantoux in healthy volunteers [49], BCG vaccination was associated with a Mantoux > 10mm (RR 2.1, 95% CI 1.5 - 3.0). Importantly, a Mantoux result greater than 15mm was unlikely to be due to BCG (although such a cut-off is unlikely to be sensitive). Mantoux testing is poorly sensitive in 'high risk' children with severe, disseminated disease [3, 7, 8]. In a recent retrospective study of 605 children diagnosed with TB, Mantoux had an overall sensitivity of 35%, being poorly sensitive (21%) in children with CNS TB [50]. Mantoux is also poorly sensitive in children with HIV [51] or severe protein-energy malnutrition.[52]. Because of its poor sensitivity, some argue that any reaction to tuberculin should be regarded as suggestive of TB in the context of other suggestive indicators. [41]. While microbiological diagnosis is often considered the gold standard, this is rarely achieved due to the difficulty in collecting suitable samples and low yield [53]. Despite the limitations of these indicators, they clearly still play an important role in the diagnosis of TB in children.

There remains the problem of the child where TB is suspected, and longitudinal follow-up with broad investigation does not aid the diagnosis of TB. Most clinicians would trial TB therapy in this setting, prompting some authors to advocate the use of response to therapy as a diagnostic tool for some children with suspected TB. This is problematic as a trial of TB therapy should not be used as a diagnostic test. Clinical improvement on TB therapy still does not necessarily mean that the clinical problem was due to TB especially in the child with predominantly respiratory symptoms. Perhaps the largest challenge is the diagnosis of TB in the child with HIV. In a study in Zambia, 69% of patients admitted with TB in where HIV positive, compared with 9% of those presenting to the emergency department being sero-positive [54]. Children with HIV are likely to behave similar to young children (<3 years) who are immunologically immature. The study outlined by Kiwanuka et al (2001) outlines the problem [30]. In their study with high HIV prevalence (71%), a final diagnosis could not be made in 39% of their population of children with suspected TB, with the majority of these being HIV positive.

There seems no clear indicator for the child at highest risk of severe TB. Young children, those with HIV or children who are severely malnourished require a broader approach to diagnosis. A detailed and focused history of symptoms preceding the illness and screening of family members for TB appear beneficial. Comprehensive and repeated investigation may be indicated. Interestingly, many children diagnosed with TB who were HIV positive had previously been treated for TB [32, 38, 39]. Children with HIV diagnosed with TB, or children with TB found to be HIV positive, were also significantly more likely to be malnourished [32, 33, 35]. In this high risk and diagnostically challenging group, response to therapy may also be considered a reasonable diagnostic maneuver, both in terms of failure to respond to conventional therapy (prolonged coma despite antibiotics and anti-malarial drugs) or improvement with anti-tuberculous drugs.

There needs to be a uniform approach to future studies. Most studies evaluating the validity of diagnostic approaches are limited by the lack of an appropriate gold standard. While some studies use microbiologically confirmed TB as the gold standard, this is unlikely to adequately identify children with TB, especially those who are very young or have HIV. The use of response to therapy as a gold standard is equally a limited measure of disease. Emerging diagnostic techniques, while out of reach of mass implementation, might make an ideal gold

standard for validation studies. There also needs to be a greater focus on TB in children with HIV.

CONCLUSION

With appropriate risk stratification, symptoms are useful in the diagnosis of TB. In particular, chronic symptoms > 2/52, objective weight loss, fatigue, and contact history are useful in the diagnosis of TB in children. A combination of indicators is particularly powerful. The Keith Edwards score seems to be a very useful diagnostic approach; it is simple to apply, does not depend on investigations and appears to perform reasonably well in validation studies. All children with suspected TB in HIV endemic settings should be tested for HIV infection as it has an important effect on clinical diagnosis.

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