Diagnosis of Tuberculosis Following World Health Organization–Recommended Criteria in Severely Malnourished Children Presenting With Pneumonia

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Abstract

Evidences on diagnosis of tuberculosis (TB) following the World Health Organization (WHO) criteria in children with severe acute malnutrition (SAM) are lacking. We sought to evaluate the WHO criteria for the diagnosis of TB in such children. In this prospective study, we enrolled SAM children aged <5 with radiological pneumonia. We collected induced sputum and gastric lavage for smear microscopy, mycobacterial culture, and Xpert MTB/RIF. Using the last 2 methods as the gold standard, we determined sensitivity, specificity, and positive and negative predictive values of WHO criteria (n = 388). However, Xpert MTB/RIF was performed on the last 214 children. Compared to mycobacterial culture–confirmed TB, sensitivity and specificity (95% confidence interval) of WHO criteria were 40 (14% to 73%) and 84 (80% to 87%), respectively. Compared to culture- and/or Xpert MTB/RIF-confirmed TB, the values were 22 (9% to 43%) and 83 (79% to 87%), respectively. Thus, the good specificity of the WHO criteria may help minimize overtreatment with anti-TB therapy in SAM children, especially in resource-limited settings.

Introduction

Recent data suggest that in endemic countries tuberculosis (TB) may contribute to 10% to 20% of total deaths in children[1,2] under the age of 15 years. The 2015 global TB report of the World Health Organization (WHO), based on vital registration data, indicated that there were 140 000 deaths in children due to TB.[3] TB represented 2% of total deaths in children in year 2012.[4] However, among the notified new TB cases in Southeast Asia and Sub-Saharan Africa, less than 4% are among children[4]; the low rate is likely due to poor case detection. Due to difficulties in diagnosis, the actual burden of childhood TB is likely to be higher than the aforementioned estimates. The diagnosis of adult TB is based mainly on the

routine use of sputum microscopy; however, children below the age of 7 years cannot produce sputum. This makes the detection of *Mycobacterium tuberculosis* and thereby the diagnosis of TB difficult. Additionally, microscopy of induced sputum or gastric lavage, even when possible, often yields negative results due to the

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paucibacillary nature of childhood TB. The conventional culture method for isolating *Mycobacterium tuberculosis* takes as long as 8 to 12 weeks. In contrast, the Xpert MTB/RIF assay, a highly sensitive real-time polymerase chain reaction (RT-PCR) test, is specific for TB[5]; however, it requires high-quality samples, is expensive, and is not readily available in resource-poor and TB-endemic countries. This is why clinicians in such places rely mostly on a combination of epidemiology, history of exposure, clinical features, chest X-rays, and tuberculin skin test (TST) following WHO criteria in making a diagnosis and treating childhood TB.[3] However, clinical signs of TB in children, especially those with severe acute malnutrition (SAM), are often subtle,[5] and the diagnosis of TB is even more difficult when such children present with acute pneumonia.[5,6] The WHO criteria, which is also endorsed by the Bangladesh National Guideline for the Management of Tuberculosis in Children,[7] relies mainly on clinical data rather than laboratory tests.[3] This makes it potentially very useful where TB is endemic, childhood malnutrition is common, microscopy is often negative, and Xpert MTB/RIF is unavailable. Dhaka Hospital, part of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), treats a large number of children suffering from malnutrition and diarrhea[8] each year. Some of the children with SAM also present with pneumonia and may have pulmonary tuberculosis.[5] Within this context, the present study aimed to validate the use of WHO criteria for diagnosing TB in pneumonic SAM children by comparing it with culture and Xpert MTB/RIF methods.

Materials and Methods

Ethics Statement

The study (Protocol Number: PR-10067) was approved by the Research Review Committee and the Ethical Review Committee of the icddr,b. Written informed consent was obtained from parents or guardians of each of the participating children; children whose caregivers did not give consent were not enrolled.

Study Setting

The study was conducted at Dhaka Hospital, part of icddr,b. The description of the study site is available in a recently published article based on the same prospective study.[5]

Study Design

We enrolled all SAM children of either sex, aged 0 to 59 months, who were admitted to the intensive care unit,

high dependency unit, or acute respiratory infection ward between April 2011 and June 2012, with symptoms of cough and/or respiratory difficulty, and radiological pneumonia. We collected induced sputum and gastric lavage fluid for acid-fast bacilli (AFB) microscopy, mycobacterial culture, and performed RT-PCR by Xpert MTB/RIF whenever the Xpert MTB/RIF facility at icddr,b became available. Using positive diagnosis by mycobacterial culture and/or Xpert MTB/RIF as the gold standard, we determined sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of the WHO criteria (Table 1).[3,7] Identification of SAM children, diagnosis of radiological pneumonia, collection of induced sputum, and Xpert MTB/RIF protocols have been described previously by the authors.[5]

Patient Management

A description of the management of study participants has been described in a recently published article based on the same study.[5]

Measurements

A description of the measurements has also been described in a recently published article based on the same study.[5]

Analysis

All data were entered into a personal computer using SPSS for Windows (version 17.0; SPSS Inc, Chicago, IL) and Epi-Info (version 6.0, USD, Stone Mountain, GA). We had evaluated the number of sputum samples that were sent, number of available reports, children with culture- and/or Xpert MTB/RIF-confirmed TB, and children with positive and negative WHO criteria. Using positive diagnosis by mycobacterial culture and/or Xpert MTB/RIF as the gold standard, we had also evaluated the sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and their 95% confidence intervals of the WHO criteria (Table 1)[3,7] for the diagnosis of TB in severely malnourished children.

Results

We performed tests with regard to the WHO criteria for 388 children, all of whom were also tested by AFB microscopy and mycobacterial culture using induced sputum and gastric lavage fluid. RT-PCR by Xpert MTB/RIF was performed only for the last 214 children. The median (interquartile) age of the children in the

Table 1. World Health Organization Criteria for the Diagnosis of Childhood Tuberculosis (TB).

The presence of 3 or more of the following should strongly suggest a diagnosis of TB	
Parameters	Definition
History	A history of recent close contact (within the past 12 months)
Symptom criteria suggestive of TB	Persistent, nonremitting cough for >2 weeks not responding to conventional antibiotics and/or bronchodilators *and/or* Persistent documented fever (>38°C/100°F) >2 weeks *and/or* Documented weight loss or not gaining weight during the past 3 months OR severe malnutrition, *and/or* Fatigue and reduced playfulness
Physical signs highly of suggestive of TB	Gibbus, cervical lymphadenopathy, nonpainful pleural/pericardial effusion, meningitis not responding to antibiotics, ascites, nonpainful enlarged joints, phlyctenular conjunctivitis, erythema nodosum
A positive tuberculin skin test	For children with severe malnutrition or HIV, 5 mm or more; for others, 10 mm or more
Chest X-ray suggestive of TB	End point consolidation, other infiltrate, hilar or para-tracheal lymphadenopathy

Table 2. Summary of WHO Criteria for Diagnosis of TB in Children Under the Age of 5 Years With Pneumonia and Severe Acute Malnutrition[a].

Parameters	Number of Sputum Samples (1 Sample per Patient)	Number of Reports Available	Culture-Confirmed TB	Culture- and/or Xpert MTB/RIF-Confirmed TB	Positive WHO Criteria (≥3) (%)	Negative WHO Criteria (<3) (%)
WHO	388	388	10	27	65 (17)	323 (83)

Abbreviations: WHO, World Health Organization; TB, tuberculosis.
[a]Figures represent percentages, unless specified.

Table 3. Validity of WHO Criteria[a].

Parameter	Compared to Culture Positive TB					Compared to Culture and/or Xpert MTB/RIF Positive TB				
	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	PPV (95% CI) (%)	NPV (95% CI) (%)	Accuracy (%)	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	PPV (95% CI) (%)	NPV (95% CI) (%)	Accuracy (%)
WHO criteria	40 (14-73)	84 (80-87)	6 (2-16)	98 (96-99)	83%	22 (9-43)	83 (79-87)	9 (4-20)	93 (90-96)	79%

Abbreviations: WHO, World Health Organization; TB, tuberculosis; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.
[a]Figures represent n (%), unless specified.

study was 10 (5, 16) months. TB was confirmed in 27 children (6.8%): 10 by culture, 21 by Xpert MTB/RIF, and 4 by both methods. According to WHO criteria, TB was diagnosed in 65 children (17%; Table 2). Only in 5 children was TB diagnosed by both WHO criteria and the reference methods. Table 3 shows sensitivity, specificity, PPV, NPV, and diagnostic accuracy of the WHO criteria compared with TB cases confirmed by either mycobacterial culture or Xpert MTB/RIF.

Discussion

To our knowledge, this is the first reported study that has evaluated the role of WHO criteria in diagnosing TB specifically in severely malnourished children. Diagnosis of childhood TB is difficult due largely to issues with the collection of sputum, the paucibacillary nature of childhood TB, and the subtlety of TB symptoms in SAM children.[5,6] To overcome the problem of diagnosis of TB in the large number of SAM children,[5] like in other resource-poor settings in Bangladesh, Dhaka Hospital routinely uses WHO criteria (Table 1).[3,7] WHO criteria employs simple clinical features and chest X-ray (Table 1).[3,7]

These include prolonged duration of cough and/or fever, failure to thrive or severe malnutrition, result of TST, suggestive physical findings, and a positive chest X-ray (Table 1).

The most important outcome of this study is the reasonable performance of WHO criteria in the diagnosis of TB in pneumonic SAM children. The sensitivity of WHO criteria was only 40%, meaning that 60% of TB cases in a population would be missed if these criteria alone were used. However, a specificity of 84% suggests that only around 16% of non-TB children would be inappropriately treated using WHO criteria. TST is the cornerstone of WHO criteria. The high rate of TST false negatives[9,10] is offset by a positive response in this population, supporting the reliability of WHO criteria. Therefore, clinicians depend heavily on a combination of clinical observations, TST, and chest radiography when applying WHO criteria to diagnose TB. Our findings suggest that clinicians in resource-limited settings may apply WHO criteria for diagnosis and initiation of TB treatment in SAM children presenting with pneumonia. Dhaka Hospital has been using WHO criteria for diagnosing childhood TB since the introduction of criteria in diagnosing childhood TB by WHO in 2006, and the results of this study justify its use in SAM children.

The main limitation of our study was the availability of Xpert MTB/RIF only in the later part of the investigation.

In conclusion, our results suggest that, in spite of low sensitivity of WHO criteria based on simple clinical features and radiologic abnormality for the diagnosis of TB in children with severe pneumonia and severe malnutrition, its high specificity and accuracy help minimize and prevent complications arising from inappropriate treatments, thereby saving money. Whenever possible, diagnosis of childhood TB should be confirmed by Xpert MTB/RIF or mycobacterial culture to increase TB case detection in children as well as minimize potential overtreatment by using the WHO criteria alone.

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Author Contributions

All the authors contributed in designing the study, carrying it out, analyzing the data, and writing the article. Additionally, MJC led the write-up and finally approved the article.

Declaration of Conflicting Interests

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