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Use of Xpert® for the Diagnosis of Pulmonary Tuberculosis in Severely Malnourished Hospitalized Malawian Children

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Abstract

Background—Pulmonary tuberculosis contributes to increased morbidity and mortality in severely malnourished children in endemic settings. Despite high clinical suspicion, few tuberculosis prevalence estimates exist in malnourished African children. Diagnostics such as Xpert MTB/RIF may help to determine pulmonary tuberculosis prevalence, however its performance in severely malnourished children is largely unknown.

Methods—We conducted a cross-sectional observational study evaluating Xpert compared to smear microscopy and liquid culture on induced sputums among severely malnourished children (aged 6 to 60 months) at Kamuzu Central Hospital in Lilongwe, Malawi. From February 1 to May 30, 2012, children who met World Health Organization 2006 guidelines for severe acute malnutrition were evaluated using clinical symptoms, tuberculin skin tests, chest radiographs, and induced sputums. National Institute of Health (NIH) consensus case definitions were used to estimate tuberculosis prevalence.

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Conflicts of Interest: All authors report no conflicts of interest.

Preliminary data were presented at the 17th Annual Conference of the Union Against TB and Lung Disease-North America Region, Vancouver, 2013 and included in the WHO 2013 Xpert® guidelines for the diagnosis of pulmonary and extrapulmonary TB in adults and children.

Results—Three hundred severely malnourished children (median age 18.5 months, IQR 12.1-25.6) had one induced sputum performed; 295 (98.3%) received two. Fifty-two (17.6%) were HIV-infected. Over 25% had tuberculosis exposure with 48/297 (16.2%) reporting contact and 40/287 (13.9%) with positive TST. Two (0.7%) patients had confirmed tuberculosis by Xpert and culture, but only one had positive smear microscopy. Twenty (6.7%) patients fulfilled probable and 97 (66%) met possible tuberculosis NIH case definitions. Overall mortality was 9.7%.

Conclusions—Microbiologic confirmation likely underestimates the prevalence of pulmonary tuberculosis in severely malnourished children. In our study, Xpert on induced sputums did not increase case finding. Future studies are needed using Xpert among targeted groups of severely malnourished children and on non-sputum specimens.

Keywords

pediatric tuberculosis; malnutrition; Xpert MTB/RIF

BACKGROUND

Of the nearly nine million annual tuberculosis diagnoses, one quarter occur in Africa, with approximately 530,000 in children.(1) Pediatric tuberculosis diagnosis is challenging due to protean presentation, sample collection difficulties, paucibacilliary disease and limited availability of microbiologic culture.(2) Malnourished children are at increased risk of tuberculosis infection, disease progression and worse outcomes.(3) HIV further increases mortality in this highly vulnerable group.(4,5) Nevertheless, few tuberculosis prevalence estimates exist in malnourished African children.(4,6–8)

The complex triad of HIV, tuberculosis and malnutrition exists in Malawi where approximately 180,000 children are HIV-infected and mortality among HIV-infected malnourished children is high.(5) Children account for 11% of new tuberculosis diagnoses annually (Malawi National Tuberculosis Program, unpublished).

Xpert MTB/RIF® (Xpert, Cepheid, Sunnyvale, CA) is a polymerase chain reaction-based rapid tuberculosis diagnostic test and the World Health Organization (WHO) recommends its use in children suspected of tuberculosis.(9) In 2012, the WHO began reporting global pediatric tuberculosis incidence, however improved estimates are needed.(1) Testing induced sputums of high-risk children with Xpert may help determine pulmonary tuberculosis prevalence in high-HIV burden areas, and better target treatment.(10–14) Xpert's performance in severely malnourished children is largely unknown.

We aimed to determine pulmonary tuberculosis prevalence among hospitalized severely malnourished Malawian children with Xpert compared to smear and culture on induced sputums, and characterize patients by National Institutes of Health (NIH) consensus case definitions (Supplement 1).(15) We hypothesized that severely malnourished children would have a high tuberculosis prevalence and Xpert would be superior to smear and similar to culture on induced sputums.

METHODS

We conducted a cross-sectional study at Kamuzu Central Hospital, a tertiary referral center serving central Malawi, from February 1-May 30, 2012. Enrollees met WHO severe acute malnutrition criteria for children aged 6–60 months with: weight-for-height z-score ≤-3 standard deviations below the median, mid-upper arm circumference (MUAC) ≤115mm, or bilateral pedal edema.(16) Weight-for-height was not calculated in children with edema since this falsely elevates weight. We excluded patients already receiving tuberculosis treatment, those with conditions (besides malnutrition) causing edema, and if induced sputums were contraindicated.

After informed consent was obtained from a guardian, a tuberculin skin test (TST, Tubersol®, Sanofi Pasteur, Swiftwater, PA) and anterior-posterior and lateral digital chest radiograph were performed. Radiographs were read by two blinded reviewers per a standardized protocol, with discrepant reads adjudicated for final consensus.(15) TST of ≥5mm was considered positive. Children with unknown HIV-status were tested per Malawi protocols. Children were evaluated for the presence of tuberculosis-associated sign/symptoms according to NIH guidelines, including: fever (>1 week), cough (>2 weeks not antibiotic responsive), and lethargy/decreased playfulness (Supplement 1).(15) All children met NIH weight loss criteria.

Induced sputums were performed after a 2–3 hour fast with a second sputum collected ≥4 hours later.(14) Each sample was evaluated by AFB smear/liquid culture (BACTEC MGIT, Becton Dickinson, Franklin Lakes, NJ) and Xpert in an internationally accredited research laboratory (University of North Carolina Project). Anti-tuberculosis treatment initiation was made in conjunction with hospital staff and prescribed per Malawian national guidelines. All children were scheduled for six weeks clinical follow-up. Children were clinically improved if they had symptom resolution and improvement in weight-for-height, edema, or MUAC.

Each subject was assigned a final NIH clinical case diagnosis of confirmed, probable, possible, or unlikely tuberculosis (Supplement 1). These guidelines combine microbiologic confirmation, tuberculosis signs/symptoms, chest radiograph, tuberculosis exposure, TST, and/or treatment response if applicable.(15)

Statistical Analysis

Categorical data were summarized as proportions and non-normally distributed continuous variables were summarized by median and interquartile range. Prevalence ratios (PR) were calculated with two-sided tests and 95% confidence intervals. EpiInfo™ (version 7, Atlanta, GA) was used to calculate weight-for-height z-scores. SPSS (IBM, version 19.0, Chicago, IL) was for all other statistical analysis. For sensitivity analysis, culture was considered the gold standard.

Ethical consideration

This study was approved by the Malawi National Health Sciences Research Committee and the University of North Carolina Institutional Review Board.

RESULTS

We enrolled 300 severely malnourished children with a median age of 18.5 months (Supplement 2). Median weight-for-height z-score was −2.9; 64.3% (193) had a MUAC ≤115mm, while 57.7% (173) had bilateral pedal edema. Fifty-two (52/295, 17.6%) patients were HIV-infected, with 36.5% (19/52) new diagnoses and 28.8% (15/52) on anti-retrovirals. Twelve percent (35/295) were HIV-exposed (Supplement 2). Most patients had received Bacillus Calmette–Guérin vaccine (292/297, 98.3%).

All patients were assessed for tuberculosis signs/symptoms; 12% (36/300) had cough >2 weeks not antibiotic-responsive, while 26% (78/300) had fever >1 week (Supplement 2). Reduced playfulness/lethargy was reported in 90% (269/299). A tuberculosis contact was reported by 16.2% (48/297). TST was positive in 13.9% (40/287) and 3.1% (9/287) had both a reported contact and positive TST. Only one child previously received isoniazid. Sixteen percent (48/299) of radiographs were interpreted as certain tuberculosis. All participants received at least one induced sputum, and 295 (98.3%) received two. Most were performed the next day.

Two (0.7%) patients were categorized as confirmed tuberculosis, both with positive Xpert and culture, but only one with positive smear microscopy (Supplement 1). One patient had a positive Xpert result (including rifampin resistance) but negative smear and culture. Repeat Xpert testing of the same specimen was negative, thus it was considered a false positive. Twenty (6.7%) patients met NIH definitions for probable, 197 (65.7%) possible and 81 (27%) unlikely tuberculosis.

Anti-tuberculosis therapy was prescribed to 44% (132/300) (Supplement 2). Of the treated patients who followed up, the majority (44/58, 75.9%) had symptom resolution and improvement in anthropometric measurements.

Inpatient mortality was 9.3% (28/300), with one additional child dying before follow-up (Supplement 2). A significantly higher proportion of deaths occurred among HIV-infected (11/52, 21.1%) compared to HIV-unexposed children (14/208, 6.7%) (PR 3.1 95% CI 1.5–6.5, p=0.0016). The prevalence of death among HIV-exposed (2/35, 5.7%) and HIV-unexposed children was similar (PR 0.8 95% CI 0.2–3.6, p=0.82).

Xpert’s sensitivity compared to liquid culture was 100% with 2 of 2 cases identified (95% CI 15.8–100.0), with 99.7% specificity (297/298, 95% CI 98.1–100.0). Smear microscopy sensitivity was 50% (1/2 cases, 95% CI 1.3–98.7) with 100% specificity (298/298, 95% CI 98.8–100.0).

DISCUSSION

Malnutrition is a major cause of morbidity and mortality among African children. Although tuberculosis is thought to be a major contributor, there are few prevalence estimates in malnourished children. We consecutively screened 300 severely malnourished hospitalized Malawian children for pulmonary tuberculosis using Xpert and NIH guidelines. We found

only two culture-confirmed tuberculosis cases (both detected by Xpert) but a relatively high proportion of tuberculosis exposure (26.3%) and probable tuberculosis cases (6.7%).

Sputum culture is positive in only 30–62% of clinically diagnosed pediatric pulmonary tuberculosis cases.(17) Among previous pediatric Xpert studies, culture positivity ranged from 8–23% among tuberculosis suspects, with Xpert sensitivity of 57–79% versus culture.(10–14) Children in these studies were less malnourished with median weight-for-height or weight-for-age z-score of −1.9–0.2. Our lower culture positivity rate likely underestimates the true prevalence of pulmonary tuberculosis in this group of severely malnourished children, given the high frequencies of tuberculosis-associated signs/symptoms, positive TSTs, tuberculosis contacts, tuberculosis consistent radiographs and clinical improvement with treatment. Over 25% of our patients had tuberculosis exposure (contact and/or positive TST), which is associated with high risk of developing tuberculosis disease in children.(2,18) Anti-tuberculosis therapy was prescribed to 44% of our patients, similar to previous pediatric Xpert studies, illustrating a high clinical concern for pulmonary tuberculosis disease even among those children without microbiologic confirmation.(10–14)

The prevalence of NIH-defined probable and confirmed tuberculosis was 7.3%, which likely more accurately reflects the burden of tuberculosis than culture-confirmation alone. Potential reasons for our lower rates of culture confirmation may be due to more prevalent paucibacillary pulmonary disease, extrapulmonary or disseminated disease not detected on induced sputum samples. Our estimates were lower compared to the 19–22% prevalence of clinically diagnosed tuberculosis (not culture-confirmed), among severely malnourished hospitalized children in South Africa, Malawi and India, likely due to our use of more stringent NIH definitions.(4,6,15,19)

This study’s limitations include high lost to follow-up that may have biased treatment response and mortality results, although it did not influence inpatient measures. Our research occurred at a single site which may limit generalizability, although malnourished children receive similar care in nutritional rehabilitation units throughout Malawi. Low microbiologic confirmation may have been due to sample collection or lab processing error, however this is unlikely as protocols provided from previous pediatric Xpert trials were followed closely and testing occurred in our internationally accredited lab.

In summary, our study demonstrated high tuberculosis prevalence in severely malnourished children per NIH definitions, but low rates of Xpert or culture-confirmed on induced sputums. Given Xpert and culture did not contribute to additional case finding, our data does not support routine screening of hospitalized severely malnourished children in Malawi using Xpert or culture on induced sputum. Xpert may have increased utility among targeted malnourished children, or on different specimens such as stool, urine or blood. Therefore, we recommend continued clinical tuberculosis screening with a low treatment threshold in severely malnourished hospitalized children suspected of tuberculosis. Additional findings of high HIV prevalence, high proportion of new HIV diagnosis, and low isoniazid preventive therapy suggest important operational gaps.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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