Stool Xpert MTB/RIF and urine LAM for diagnosing TB in HIV-infected Kenyan children

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Background
- Pulmonary tuberculosis (TB) is a leading cause of mortality in HIV-infected children.
- Challenges in obtaining respiratory samples from children and rapid TB/HIV disease progression prior to obtaining culture results can lead to treatment delays.
- Rapid diagnostic tools from easily obtained and less invasive specimens are urgently needed.

Objective
To determine diagnostic test performance of stool Xpert MTB/RIF nucleic acid amplification test and urinary lipoarabinomannan (LAM) assays to detect microbiologically confirmed tuberculosis from respiratory samples.

Methods
- Between May 2013 and March 2015, HIV-infected, antiretroviral therapy (ART) naïve children hospitalized for acute illness were enrolled in a randomized controlled trial (NCT020633880) comparing urgent to post-stabilization ART initiation in Nairobi and Kisumu, Kenya.
- At enrollment, children provided sputum or gastric aspirate (GA), stool, and urine specimens for TB diagnosis with liquid Mycobacterium tuberculosis (MTB) culture, Xpert (sputum/GA and stool), and LAM testing, respectively.
- A second sputum/GA sample for culture was obtained during the hospitalization.
- The diagnostic performance of stool Xpert and urine LAM (grade ≥1 considered positive) was determined by comparing results to respiratory sample culture and Xpert results as follows:
  - Scenario 1) Among children with at least one respiratory sample result (culture #1, culture #2, Xpert) and a positive result on any considered a true positive
  - Scenario 2) Among children with all three respiratory sample results (culture #1, culture #2, Xpert) and a positive result on any considered a true positive
  - 95% confidence intervals (CI) were estimated assuming a binomial distribution.

Results

Table 1. Included participant characteristics

<table>
<thead>
<tr>
<th>Participant Characteristics</th>
<th>N=166</th>
<th>N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SocioDemographic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24</td>
<td>86</td>
<td>(52)</td>
</tr>
<tr>
<td>24-59</td>
<td>40</td>
<td>(24)</td>
</tr>
<tr>
<td>≥60</td>
<td>40</td>
<td>(24)</td>
</tr>
<tr>
<td>Male</td>
<td>90</td>
<td>(54)</td>
</tr>
</tbody>
</table>

Clinical Presentation
- CD4 % (Median [interquartile range])
  - 14 (8.9-22)
- Immunosuppressed a
  - 114 (69)
- Any sign/symptom suggestive of TB
  - 128 (77)
  - Persistent cough (≥ 14 days) 42 (25)
  - Persistent fever (> 7days) 63 (38)
  - Failure to thrive b 103 (64)
  - Persistent Lethargy(≥ 14 days) 30 (18)
- Wasted (weight-for-height z-score < -2) f
  - 57 (46)
- Stunted (height-for-age z-score < -2)
  - 98 (61)
- Underweight (weight-for-age z-score < -2)
  - 99 (63)

TB Results
- Any respiratory sample positive 13 (8)
- Culture #1 9 (4)
- Culture #2 7 (5)
- Xpert (sample #1) 9 (5)
- Stool Xpert positive 7 (5)
- Urinary LAM positive a 14 (11)

Table 2. Diagnostic performance of stool Xpert MTB/RIF and urine lipoarabinomannan (LAM) for microbiologically-confirmed pulmonary tuberculosis in HIV-infected Kenyan children

<table>
<thead>
<tr>
<th>Respiratory Sample Culture and Xpert</th>
<th>Scenario #1</th>
<th>Scenario #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive/Total</td>
<td>% 95%CI</td>
<td>Positive/Total</td>
</tr>
<tr>
<td><strong>Stool Xpert MTB/RIF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>7/11</td>
<td>64 (31-89)</td>
</tr>
<tr>
<td>Specificity</td>
<td>137/137</td>
<td>100 (97-100)</td>
</tr>
<tr>
<td>PPV</td>
<td>7/7</td>
<td>100 (59-100)</td>
</tr>
<tr>
<td>NPV</td>
<td>137/141</td>
<td>97 (93-99)</td>
</tr>
<tr>
<td><strong>Urine LAM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>5/5</td>
<td>56 (21-86)</td>
</tr>
<tr>
<td>Specificity</td>
<td>111/120</td>
<td>93 (86-97)</td>
</tr>
<tr>
<td>PPV</td>
<td>5/5</td>
<td>100 (36-100)</td>
</tr>
<tr>
<td>NPV</td>
<td>111/115</td>
<td>97 (91-99)</td>
</tr>
</tbody>
</table>

Conclusions
- Stool Xpert had moderate sensitivity (identified over half of confirmed cases) and had very high specificity and PPV (identified no false positives) compared to sputum/GA culture and Xpert.
- The agreement between urinary LAM and respiratory culture and Xpert was poor, but assessed in fewer children.
- Stool Xpert may be useful for accelerating a TB diagnosis in HIV-infected children, particularly in those who cannot produce sputum.

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