Diagnosis of extrapulmonary and paediatric tuberculosis

Introduction

- Part of the global efforts to control tuberculosis (TB) include improving case detection, especially in smear negative (HIV + children) as well as enhancing the diagnosis of multi-drug resistant TB (MDR-TB).
- Molecular diagnostics paves the way for rapid sensitive testing compared to conventional culture.
- Xpert MTB/Rif (Cepheid) assay has revolutionized testing for TB and has been endorsed by the WHO to be used as screening for TB suspects.

Extrapulmonary tuberculosis

- Worldwide: 25% of all TB (even higher in HIV and paediatrics).
- Limited diagnostics tests
  - No gold standard
  - Culture based methods not adequate
  - No standardized processing e.g. concentration
- Composite reference standard is often used (radiological and histological evidence).
- Sample collection: invasive procedures.


- Low numbers especially for CSF
- Low culture sensitivity (many patients on anti-TB therapy, decontamination methods)
- Pooled sensitivity smear neg 64%, smear pos 96% and specificity 99.6%.
Always look at the numbers!

• Systematic review and meta-analysis
• Assess the accuracy of Xpert for the detection of extrapulmonary TB
• Searched multiple databases to October 2013
• Culture and a composite reference standard (CRS)
• Grouped data by sample type

Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Site</th>
<th>Pooled Sensitivity (vs. Culture)</th>
<th>Pooled Specificity (vs. CRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node (tissue or aspirate)</td>
<td>83.1%</td>
<td>81.2%</td>
</tr>
<tr>
<td>CSF</td>
<td>80.5</td>
<td>62.8</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>46.4</td>
<td>21.4</td>
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</tbody>
</table>

• 18 studies (4461 samples)
• Sample processing varied greatly among the studies
• Xpert sensitivity differed substantially between sample types
• Pooled specificity was 98.7%
WHO Policy update in 2013

Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance:

**Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children**

- 22 studies (7 unpublished), 5922 samples
- 59% in high burden settings

<table>
<thead>
<tr>
<th>Specimen type</th>
<th>Comparison</th>
<th>No. of studies, No. of samples</th>
<th>Median (% predicted sensitivity [predicted 95% CI])</th>
<th>Median (% predicted specificity [predicted 95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural fluid</td>
<td>Xpert MTB/RIF compared against culture (17 studies, 1385 samples)</td>
<td>43.7 (25-65)</td>
<td>98.1 (95-99)</td>
<td></td>
</tr>
<tr>
<td>Gastric juice and aspirate</td>
<td>Xpert MTB/RIF compared against a culture reference standard (17 studies, 649 samples)</td>
<td>17 (8-34)</td>
<td>99.9 (94-100)</td>
<td></td>
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<tr>
<td>Other tissue samples</td>
<td>Xpert MTB/RIF compared against culture (12 studies, 609 samples)</td>
<td>81.2 (58-90)</td>
<td>98.1 (87-100)</td>
<td></td>
</tr>
</tbody>
</table>

箱 2. Using Xpert MTB/RIF to diagnose extrapulmonary TB and rifampicin resistance in adults and children.

These recommendations should be read in conjunction with the remarks in section 5.2:

- Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test for CSF specimens from patients suspected of having TB meningitis (strong recommendation given the urgency for rapid diagnosis, very low-quality evidence).
- Xpert MTB/RIF may be used as a replacement test for usual practice including conventional microscopy, culture or histopathology by testing specific non-respiratory specimens (lymph nodes and other tissues) from patients suspected of having extrapulmonary TB (conditional recommendation, very low-quality evidence).

- EPTB specimens (n=7916) from hospitalized patients
- Large volume specimens were centrifuged, tissue biopsies homogenised
- Contaminated samples received NALC-NaOH decontamination prior to liquid culture
- Residual specimens (volumes >1ml) after inoculation of culture(n=1175) were tested using the XpertMTB/RIF sputum protocol
- Overall sensitivity was 59% and specificity 92%
- Pus 91%, Lymphnodes 80%, Lymphnode aspirate 51%, fluids (ascitic 59% and pleural 47%)
- Additional 124 specimen results that were contaminated by MGIT
- Proposed routine testing, setting up SOPs for SA
TB Meningitis

• Vietnam study, 379 suspected TB meningitis
• Sensitivities: Xpert (59.3%), ZN smear (78.6%) and MGIT culture (66.5%)
• Recommended meticulous examination via smear, although not always practical
• Xpert can be an advance

Paediatric tuberculosis

Overview

• 500 000 – 1 000 000 new childhood cases (yet true burden unknown)
• Majority: Smear and culture negative
• Dx: Clinical
• Overdiagnosis → inappropriate treatment
• Underdiagnosis → poor outcome
• HIV (co-infection 5 – 50%)
• Limitations of the tuberculin skin test and IGRA’s
• Investigation: usually hospital admission for gastric lavages or induced sputum

Vs. Adults?

• Children are at much higher risk of progression to active disease
• This risk is greatest for infants and children under 2
• Majority of children develop radiological abnormalities however they control the disease by the host immune response (difficult to diagnose active disease)
• Risk of disease is highest among infants and in late teens (lowest risk between 5 and 10), in the first year following infection
• Disease in young children reflects recent infection (vs. secondary reactivation) → the paediatric disease burden potentially provides a useful measure of current transmission within a community

Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates
Estimates unknown

Systematic review

Setting-specific risk of multidrug-resistant tuberculosis was nearly identical in children and treatment-naive adults

Identified similar risk for transmission of MDR-TB

999,792 children developed tuberculosis disease in 2010

31,948 MDR

Highlighted the need for detection

Jenkins et al. Lancet 2014 published 24 March

WHO Policy update in 2013

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Xpert MTB/Rif and children

Prior to 2011, one study

16 studies (4 unpublished)

Pooled sensitivity was similar on expectorated sputum and gastric lavage/aspiration (66%), specificity (98%)

Poor performance on smear negative (4-15%)

Rif resistance (86%)

Jenkins et al. Lancet 2014 published 24 March
Using Xpert MTB/Rif to diagnose pulmonary TB and rifampicin resistance in children

- **Initial diagnostic test** (rather than smear, culture or DST) for suspected MDR and HIV associated TB (Strong recommendation, very low quality evidence)
- All **suspected** of having TB (conditional recommendation acknowledging resource implications, very low quality evidence)

The end