Diagnosis of drug-resistant tuberculosis disease in children: A practical approach

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Classification of DR-TB disease according to certainty
(research definitions [Seddon et al, 2013])

Confirmed:
• at least 1 of the signs and symptoms suggestive of TB disease, \textit{and}
• detection of \textit{M. \textit{tb}} from the child with \textit{demonstration of genotypic or phenotypic resistance}.

Probable:
• diagnosis of probable TB disease, \textit{and}
• DR-TB contact

Possible:
• diagnosis of probable TB disease, \textit{and}
• either (a) contact of a source case with TB disease who has risk factors for drug resistance, or (b) failure of first-line TB treatment
Determinants of bacteriological confirmation

- Pre-Test Probability
- Specimen sampling
- Handling & processing of sample
- Microbiologic test

Bacteriologic confirmation
Pre-Test Probability: Definition of Probable TB disease

(Research definitions [Graham et al, 2012])

• At least 1 of the signs and symptoms suggestive of TB disease, and
• CXR consistent with intrathoracic TB disease, and
• Presence of 1 of the following:
  (a) a positive clinical response to TB treatment
  (b) documented exposure to a source case with TB disease
  (c) immunological evidence of TB infection
**M. tb** detection & Drug Susceptibility Testing (DST)

Phenotypic: Cultures

- **Preferred Methods:** culture method that detects *M. tb* and DST simultaneously
  - Solid media (eg, Middlebrook 7H10 or 7H11)
  - Liquid media (eg, BACTEC MGIT 960)

- **Minimum threshold for detection:** 10-100 CFU/mL

- **Advantages**
  - Gold-standard for DST to essentially all TB meds
  - Treatment response monitoring

- **Disadvantages:**
  - Labor-intensive, time-consuming, expensive, requires specialized equipment and biosafety level 3 facility.
  - Results may take 2-6 wk; direct DST is preferred, as indirect DST adds ~8 days.
**M.tb** detection & drug resistance testing (DRT)

**Genotypic: Nucleic Acid Amplification Tests (NAATs)**

- **Preferred Methods**: automated NAAT that detects *M.tb* complex and DR simultaneously
  - Real-Time Polymerase Chain Reaction (eg, Xpert MTB/RIF)
    - Minimal threshold: 100-150 CFU/mL (c.w. 10,000 CFU/mL for microscopy)
    - Advantages: Useful in smear microscopy (+) & (-) samples; **rapid** (2 hr, vs. 2-8 wks for cultures); very practical (a self-contained, fully integrated, automated, requiring minimal technical expertise to operate); useful in various types of specimens; useful for “ruling in” (not for ruling out”)
  - Disadvantages: *Currently* only identifies Rmp (rpoB); not useful for treatment response monitoring (detect dead bacilli)

- Line Probe Assays (eg, GenoType MTBDRplus **version 2**)
*M. tb* detection & drug resistance testing (DRT)

**Genotypic: Nucleic Acid Amplification Tests (NAATs)**

- **Preferred Methods**
  - Real-Time Polymerase Chain Reaction (eg, Xpert MTB/RIF)
  - Line Probe Assays (eg, GenoType MTBDRplus *version 2*)
    - **Minimal threshold**: 100-150 CFU/mL (c.w. 10,000 CFU/mL for microscopy)
    - **Advantages**
      - Useful in smear microscopy (+) & (-) samples
      - **Rapid** (5 hr)
      - Can be done manually or automated
      - Useful for “ruling in” (not for ruling out”)
    - **Disadvantages**
      - *Currently* only identifies Rmp (rpoB), low-level INH (inhA), & high-level (katG) resistance
      - not useful for treatment response monitoring (detect dead bacilli)
**M. tb detection & drug resistance testing (DRT):** Xpert MTB/RIF vs GenoType MTBDRplus

**Study:** Barnard et al, 2012 (*J Clin Microbiol* 50(11):3712)

**Design:** Comparison of performance of Xpert MTB/RIF and GenoType MTBDRplus (v.2.0) on microscopy (+) & (-) patient specimens, using culture as gold-standard.

**Setting:** National Health Laboratory Service, Cape Town, South Africa.

**Results:** 282 consecutive specimens were tested by both Xpert MTB/RIF and Genotype MTBDRplus
- Similar sensitivities c.w. MGIT culture, ie, GenoType MTBDRplus (v2) and Xpert MTB/RIF were 73.1% and 71.2%, respectively
- Similar sensitivities c.w. microscopy(-) / culture(+) specimens: 57-58%
- Same specificities (100%) for M.tb detection
**M. tb** detection & drug resistance testing (DRT): INH-resistance / Rmp-susceptibility

**Study:** Smith et al 2012 (*Int J Tuberc Lung Dis* 16:203)

**Question:** *To what extent Rmp resistance is an adequate marker for MDR-TB?* [implications for Tx & surveillance]

**Design:** Retrospective analysis of data (WHO/The Union Global DRS data 1994–2007) from >81 countries and subnational settings.

**Results**

- In settings with relatively low MDR-TB prevalence (one third of all countries and subnational settings): >40% of Rmp-resistant isolates from *new* TB cases did not display resistance to INH.

- Among the third of countries or settings in the middle tertile, >24% of Rmp-resistant *new* TB cases had INH-susceptible TB.

**Conclusion:** INH susceptibility testing -- in addition to RMP susceptibility testing – may be indicated…
Induced sputa using Xpert MTB/RIF in children

**Study**: Nicol et al, 2011 (*Lancet Infect Dis* 11:819)

**Setting**: high burden of both TB and HIV (Cape Town, South Africa)

**Study Design**: prospective clinical study

**Inclusion criteria**: hospitalized/inpatient, range up to 15 years, pulm. TB suspected on the basis of having cough for >14 days, plus one of the following:

- TST-positive, or household contact infected with TB; or
- Failure to gain weight, or CXR suggestive of pulm. TB.

**Specimens**: 2 induced sputum (IS) samples

**Number recruited (n)**: 385 with 2 IS; 452 with at least 1 IS

**Ages**: median 19 months

**Results**: Culture(+): 16% (70/452)  
Xpert MTB/RIF(+): 13% (58/452)  
Smear microscopy(+): 6% (27/452)  

Incremental yield of 2nd IS by culture: 13.8% (8/58)  
Incremental yield of 2nd IS by Xpert MTB/RIF, *in smear (-) cases*: 27.8%
IS & SS using Xpert MTB/RIF in children

Study: Rachow et al, 2012 (Clin Infect Dis 54:1388)

Setting: high burden of both TB and HIV (Mbeya, Tanzania)

Study Design: prospective clinical study.

Inclusion criteria: inpatient & outpatient, <14 y.o., with at least 1 of the following symptoms:
(a) Persistent, unremitting cough for 21 days
(b) Repeated episodes of fever within the last 21 days
(c) Weight loss or failure to thrive within the previous 3 months; or,
(d) Signs and symptoms suggestive of extrapulmonary TB.

Specimens: 3 sputum samples – spontaneous (58.5%) & induced (41.5%).

Recruitment: 164; median age 5.8 years

Results: Culture(+): 17.1% (28/164)
Xpert MTB/RIF(+): 15.2% (25/164) -- 21 (75%) of 28 culture(+); 4 of 47 culture(-)
Smear microscopy(+): 4.3% (7/164)
Bacteriological confirmation:
Incremental gain per additional sample analyzed

Rachow et al, 2012 (Clin Infect Dis. 54:1388)
NPA vs. IS using Xpert MTB/RIF in Children

Study: Zar et al, 2012 (Clin Infect Dis 54:1388)

Setting: high burden of both TB and HIV (Cape Town, South Africa)

Study Design: prospective clinical study

Inclusion criteria: hospitalized/inpatient, up to 15 y.o., pulm. TB suspected on the basis of having cough for >14 days, plus one of the following:

- TST-positive, or household contact infected with TB; or
- Failure to gain weight, or CXR suggestive of pulm. TB.

Specimens: Paired nasopharyngeal aspirate (NPA) and induced sputum (IS)

Number recruited (n): 535 (21.9% HIV-infected) at least one pair; 396 two pairs; median age 19 months
NPA vs. IS using Xpert MTB/RIF in Children

Study: Zar et al, 2012 (Clin Infect Dis 54:1388)

Results:

- Overall very low bacteriological yield of 1-2 paired NPA + IS
  - Culture(+): 16.3% (87/535)
  - Xpert MTB/RIF(+): 15.1% (81/535)
  - Smear microscopy(+): 5.6% (30/535)
- Of culture(+), IS yield (84/87, 96.6%) higher than NPA yield (61/87, 70.1%) [P < .001].
- Of Xpert(+), IS yield (71%; 45/63) similar to NPA yield (65%; 41/63) [P=0.44].
- Xpert complementary to culture: Bacteriologically confirmed 5 IS & 7 NPA that were culture(-)
- A 2nd sample increases yield: Incremental yield of 2nd IS & of 2nd NPA by:
  - Liquid culture (MGIT): IS 17.6%; NPA 26.3%; NAAT (Xpert MTB/RIF): IS 25%; NPA 36.7%
- Amongst children with two paired specimens, 63 culture-confirmed cases occurred [60 (95.2%) IS vs 48 (76.2%) NPA, P = .002].
GA using Xpert MTB/RIF in children

Study: Bates et al, 2013 (The Lancet Infectious Diseases 13:36)
Setting: High burden of both TB and HIV (Lusaka, Zambia).
Study design: Prospective clinical study.
Inclusion criteria: hospitalized/inpatient with suspected pulmonary TB, 15 years or younger
Number Recruited: 930
Specimens: 1 spontaneous sputum (SS) in 142 (15%)
  1 gastric lavage aspirate (GLA) in 788 (85%)
Results:
• Overall yield was low
  – cultures were positive in 58 children (6%).
• Xpert MTB/RIF performed similarly on GLA & sputum *(p=0.1649)
  – Xpert MTB/RIF on GLA had a sensitivity of 69% (33/48)
  – Xpert MTB/RIF on SS had a sensitivity of 90%* (9/10)
Stool using Xpert MTB/RIF in children

Study: Nicol et al, 2013 (Clinical Infectious Diseases 57:e18)
Setting: high burden of both TB and HIV (Cape Town, South Africa)
Study design: Prospective clinical study
Age: median age 31 months (interquartile range 19–57 months)
Inclusion criteria: hospitalized/inpatient, pulm. TB suspected on the basis of having cough for >14 days, plus one of the following:
  - TST-positive, or household contact infected with TB; or
  - Failure to gain weight, or CXR suggestive of pulm. TB.
Recruitment: 115 children, of whom 17 (14.8%) were HIV infected and 67 (58.3%) were hospitalized.
Specimens: 1 stool; 2 induced sputa (IS)
Results:
  • Overall yield was low
    - cultures were positive in 14.8% (17/115)
  • Xpert MTB/RIF c.w. liquid culture (BACTEC MGIT)
    - 1 stool had a sensitivity of 47% (8/17)
    - 2 IS had a sensitivity of 65% (11/17)
    - Sensitivity of Xpert on stool versus IS was not significantly different (p=0.30); however, sample size very small.
Potential specimens for bacteriological confirmation of PTB

- Nasopharyngeal aspirate
- Oral swab
- Tracheal aspirate
- Bronchoalveolar lavage
- Laryngopharyngeal aspirate
- String test
- Gastric aspirate/lavage
- Stool
Variety: Combination of specimens
"intensive" specimen collection

• Collection of various specimens
  – Gastric aspirate (or gastric lavage)
  – Spontaneous/induced sputum or laryngopharyngeal aspirate
  – Swallowed sputum in esophagus (on string)
  – Nasopharyngeal swab
  – Oral swab
  – Fine-needle aspirate of lymph nodes
  – Cerebrospinal fluid
  – Blood
  – Urine
<table>
<thead>
<tr>
<th>Specimen</th>
<th>Collection procedure</th>
<th>Age group</th>
<th>Minimum volume</th>
<th>Best collection time</th>
<th>Other comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous sputum</td>
<td>Cough up sputum without prior saline nebulization</td>
<td>&gt;7 years</td>
<td>3 ml</td>
<td>Early morning</td>
<td>If unable to produce enough sputum, consider sputum induction</td>
</tr>
<tr>
<td>Induced sputum/laryngo-pharyngeal aspirate</td>
<td>hypertonic saline nebulization before cough up sputum</td>
<td>Any age</td>
<td>3 ml</td>
<td>Early morning</td>
<td>If child unable to cough, consider laryngo-pharyngeal suctioning</td>
</tr>
<tr>
<td>Gastric aspirate</td>
<td>Nasogastric aspiration of gastric juice containing swallowed sputum</td>
<td>&lt; 7 years</td>
<td>5 ml</td>
<td>Early morning before out of bed</td>
<td>After waking up and sitting and standing, stomach begins to empty, losing volume of aspirate</td>
</tr>
<tr>
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<tr>
<td>Gastric Lavage</td>
<td>Nasogastric instillation of solution to wash off and recover sputum adhered to walls of stomach</td>
<td>&lt;7 years</td>
<td>10 ml</td>
<td>Early morning</td>
<td>Use only if at least 3 ml of gastric aspirate can not be obtained</td>
</tr>
<tr>
<td>String Test</td>
<td>Esophagogastr-duodenal nylon yarn that can absorb swallowed sputum</td>
<td>&gt; 4 years</td>
<td>N/A</td>
<td>Unknown, duration probably more important</td>
<td>Consider when good quality or quantity of sputum and aspirate can not be obtained</td>
</tr>
<tr>
<td>Nasopharyngeal aspirate</td>
<td>Nasopharyngeal suctioning to collect secretions from URT, but may also collect from LRT if cough reflex is stimulated</td>
<td>&lt; 6 years</td>
<td>2 ml</td>
<td>Unknown, probably higher yield in morning</td>
<td>Yield tends to be similar to or lower than that of induced sputum or gastric aspirate/lavage</td>
</tr>
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</tr>
<tr>
<td>Stool</td>
<td>Uncontaminated by toilet bowl or urine</td>
<td>Any age</td>
<td>1 tablespoon (5 g)</td>
<td>Any time</td>
<td>Bacteriologic yield has been lower than that of sputum and gastric lavage and gastric aspirate</td>
</tr>
<tr>
<td>Bronchoalveolar lavage (BAL)</td>
<td>Bronchoscopy</td>
<td>Any age</td>
<td>3 ml</td>
<td>Any time</td>
<td>Bacteriologic yield of one sample is not superior to serial induced sputum or gastric lavage or gastric aspirate</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>Lumbar puncture</td>
<td>Any age</td>
<td>2 ml</td>
<td>Any time</td>
<td>Submit 3rd or 4th tube for culture to reduce chance of contamination from skin flora</td>
</tr>
</tbody>
</table>
## Types of Specimens

<table>
<thead>
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<tr>
<td>Serosal (pleura, pericardium, peritoneum, synovium)</td>
<td>Serosal fluid aspirate followed by serosal tissue biopsy</td>
<td>Any age</td>
<td>1 ml</td>
<td>Any time</td>
<td>Bacteriologic yield of tissue is much higher than fluid. Biochemical markers useful in all fluids</td>
</tr>
<tr>
<td>Urine</td>
<td>Clean catch, mid-stream urine</td>
<td>Any age</td>
<td>2 ml</td>
<td>1st morning urination</td>
<td>Yield low except in urinary tract TB. Lipoarab-inomannan antigen very sensitive in immuno-compromised HIV positive patients</td>
</tr>
<tr>
<td>Blood</td>
<td>Phlebotomy</td>
<td>Any age</td>
<td>5 ml</td>
<td>Any time</td>
<td>Yield very low, use in severely ill HIV infected patients</td>
</tr>
<tr>
<td>Fine needle aspiration</td>
<td>Fine needle aspiration and/or biopsy</td>
<td>Any age</td>
<td>Based on type</td>
<td>Any time</td>
<td>Useful because histopathological features consistent with TB can be diagnostic</td>
</tr>
</tbody>
</table>
Specimen collection Strategies: Pooling of Samples

• Pooling of spontaneous sputum in adults [Warren et al, 2000; AJRCCM]
  – By requiring minimum of 5 mL, and pooling daily samples until reached, yield increased 27% (72.5% to 92.0%)

  – GAs, 2 per day (AM & PM), x 3 days (total of 6 samples)
  – Morning sample provided the best culture results
  – Results: At least one positive culture was obtained from 12 of 13 children (ie, 92%).

• Pooling of swallowed sputum on string (preliminary) [Perez-Velez et al 2010, AJRCCM 181:A1775]
  – Using “home-brew” PCR as detection method, yield of 3 pooled strings > yield than 1 gastric aspirate or 1 induced sputum/laryngopharyngeal aspirate
Variability in the reported bacteriological confirmation rates of PTB in children: Possible explanations

Most “high-yield” studies tend to have higher thresholds for inclusion with criteria that are more refined:

- Younger children (↑ yield)
- Passive case finding
  - More likely to have CXRs & expert reading (↑ yield)
  - Longer course/history of illness (↑ yield)
- More likely to have CXRs & expert reading (↑ yield)
- More likely to have specimens collected (some with a hospitalization bias) that are...
  - Better quantity & quality (↑ yield)
  - More expeditious processing (↑ yield)
Specimen Collection Strategy

- ** Variety:** Collect multiple samples of different specimens
  - eg, GA (x 2) & IS (x 2) & LN-FNA(s)
- ** Quantity:** Do not self-impose limit to volume
  - eg, 5 mL of gastric aspirate, in early AM, usually possible
- ** Quality:** Collect samples properly
  - Use clean/sterile technique (to minimize contamination)
  - Avoid dilution (eg, GA preferred over GL)
  - Avoid adding preservatives (eg, use sterile water)
  - Neutralize ASAP (eg, < 30 minutes)
  - Avoid prolonged room temperature (eg, place in cooler)
Key points: Bacteriological Confirmation

• **Re. Overall bacteriologic confirmation rate of pulm. TB:**
  – very low with currently available diagnostic methods.

• **Re. Tests:** Culture and NAATs (eg, Xpert) are complementary
  – NAATs are far superior to microscopy as rapid tests.
  – NAATs do not replace culture methods.

• **Re. Specimens:**
  – Variety specimens: although some specimens may have higher yield than others by certain tests, no single specimen type confirms all cases (ie, combinations may be complementary)
  – Quality (eg, GA vs. GL; early morning vs. later)
  – Quantity: ↑ volume → ↑ bacillary load→ ↑ likelihood of surpassing minimum threshold for detection

• **Re. Samples:** Both by culture and by Xpert, there is an incremental gain from 1 sample to 2 samples, and from 2 to 3 samples
Challenges and barriers to diagnosing TB disease in children

- Only 19% of childhood TB cases were confirmed by culture in 2009.
- The trends over the last decade indicate a slight improvement in culture confirmation.
- Only 42% of the nearly 40 000 cases reported were tested by culture. Of these, fewer than 7000 (40%) were culture positive.

**Figure:** Number of culture-positive childhood TB cases and proportion of total childhood cases, 2000–2009

European Centre for Disease Prevention and Control, 2011
Diagnosis of DR-TB

**Question**

- *In clinical practice*, should the diagnosis of DR-TB be limited to only bacteriologically confirmed cases of drug resistance?
Diagnosis of DR-TB

Question

• *In clinical practice*, should the diagnosis of DR-TB be limited to only bacteriologically confirmed cases of drug resistance?

• Should patients at *significant risk* for DR-TB be treated as such?
Diagnosis of DR-TB

Case

1 y.o. child, brought by mom to local hospital in Buenaventura, Colombia, with 2-week history of a clinical syndrome consistent with acute meningitis, mother recently diagnosed with smear-positive pulm. TB, confirmed to be MDR. Child’s CSF predominantly lymphocytic pleocytosis; CXR reveals mediastinal lymphadenopathy & right mid-lung consolidation.

You suspect disseminated (meningeal, pulmonary, & intrathoracic LN) TB disease.

Questions

1. [For clinical purposes] Would you begin empiric coverage for MDR-TB?
Diagnosis of DR-TB

Case
Second-line drugs were not available; a standard regimen of first-line drugs (INH+Rmp+Pza+Emb) was given. After an initial brief clinical improvement, the child soon deteriorated and 2 weeks later. Culture of gastric aspirate grew *M. tb* after 4 weeks; drug-susceptibility testing results were received 8 weeks later from the national reference lab and reported resistance to INH and Rmp.

- “Children are as susceptible to drug-resistant as to drug-sensitive TB.”
- “Drug-resistant TB is a laboratory diagnosis.”
- “Drug-resistant TB should be suspected if…”
- “The diagnosis and treatment of drug-resistant TB in children is complex and should be carried out at referral centres.”

Key Point
- WHO and many NTP guidelines suggest that presumptive diagnosis may be made, and hence respective treatment may be indicated, but do not explicitly state so.
DR-TB in children

Problems

• There are [too] many children with DR-TB disease that are not treated because diagnosis not confirmed.

• Prevalence (“market”) of DR-TB underestimated.
  – Governments do not proportionately/adequately fund pediatric program within NTP
  – Diagnostics companies not persuaded to develop and study new tests for children
  – Pharmaceutical companies not persuaded to develop pediatric formulations
One of the biggest obstacles to getting children into treatment for MDR-TB is delay in making the diagnosis

• Median delay of 36 weeks seen in a large cohort in South Africa.
  [Seddon et al., 2012, J. Trop. Peds.]

• Early diagnosis is linked with improved outcomes.
  [Ettehad et al., 2012, Lancet ID]
Challenges in diagnosing TB in children

Challenges for clinical diagnosis
- Clinical presentation:
  - Extrapulmonary disease (eg, intrathoracic LN disease)
  - Non-localized Sx/Si: ↓ playfulness; ↓ appetite; failure to thrive; fever
  - “Atypical” respiratory symptoms: eg, wheezing

Challenges for bacteriological confirmation
- Paucibacillary disease
- Difficulties in specimen collection
  - Spontaneous sputum not possible in young children
  - Invasive procedures (eg, gastric lavage/aspiration; sputum induction requiring laryngopharyngeal suctioning; nasopharyngeal aspiration)
    - Culturally not acceptable in some communities (eg, Amerindians; Armenians)
    - Operational barriers in some primary-level centers (trained personnel; equipment; space)
Challenges in diagnosing TB in children

Broad spectrum of clinical syndromes and severity of disease:
Presence and type of clinical manifestations depend on the stage of disease progression which in turn depends on the immune function

• the sooner disease is diagnosed and treated, the less morbidity.

— Early stages:
  • May have very mild symptoms (just constitutional and/or immunological symptoms and signs).
  • But... diagnosis in early stages requires a high index of suspicion.

— Later stages:
  • Localizing signs and symptoms of the affected organ/system/region begin to appear.
    — Intrathoracic TB is the most common clinical syndrome of TB in children.
Clinical Dx: Increasing probability of TB as etiology

- Microbiological studies (Culture; NAATs; Ag detection; microscopy)

- Histopathological studies

- Biological markers

- Immune-based tests

- Epidemiological risk factors suggestive of exposure

- Alternative DDx have been ruled out by appropriate tests
  - Comorbidity/coinfection under-recognized (esp. in immunocompromised)
  - Acute pneumonia due to M.tb also under-recognized (6% in cohort of young children in Medellin, Colombia—currently ongoing study).

- Alternative DDx have failed appropriate therapeutic trials
Increasing probability of drug-resistance: screening for risk factors

• Features in the source case suggestive of DR-TB
  – contact with a known case of DR-TB
  – remains sputum smear-positive after 3 months of Tx
  – history of previously treated TB
  – history of treatment interruption

• Features of a child suspected of having DR-TB
  – contact with a known case of DR-TB
  – not responding to the TB treatment regimen
DR-TB in Children: Dx & Tx

So... Question

In children...

• with clinical diagnosis of TB disease,
• with risk factors for DR-TB,
• with negative [final] test results (cultures & PCRs-DRT)
• who remain “stable” (ie, without complicated disease)...

...should we wait for complications before considering DR-TB Tx?
...should we initiate Tx for presumed pansusceptible TB?
...should we initiate Tx for presumed DR-TB disease?
DR-TB in Children: Dx & Tx

Question
In children...
- with clinical diagnosis of TB disease,
- with risk factors for DR-TB,
- with negative [final] test results (cultures & PCRs-DRT)
- who remain “stable” (ie, without complicated disease)...

...should we wait for complications before considering DR-TB Tx?

...should we initiate empiric Tx for presumed pansusceptible TB?

...should we initiate empiric Tx for presumed DR-TB disease?

Answer
No evidence base to guide decision making...
DR-TB in Children: Dx & Tx

*My* opinion regarding when to initiate empiric coverage for DR-TB disease...

- In clinically unstable children: initiate ASAP

  *and*

- In clinically stable, but with *higher risk* for progression to complicated disease

  - *In 167 children with TBM, the mean period between recognition of first symptoms of TBM and death was 19.5 days*

  [Lincoln et al, 1960; *J Pediatr* 57:807]
Risk factors for progression from infection to disease to death

*Why are they relevant?*

- The identification of risk factors for progression from infection to disease, and from disease to death, is important to:
  
  - *Increase the index of suspicion* for the Dx of TB disease (both pulmonary and extrapulmonary), and expedite the diagnostic evaluation.
  
  - *Expedite the initiation of TB Tx* if there is sufficient evidence from findings consistent with TB disease.
  
  - May affect TB *treatment response or outcome*. 
Diagnostic Specimen Management: Principles

• **Biosafety:**
  – Children can be smear-positive & have a cough effective enough to transmit TB
  – Health care workers should wear N95 masks

• **Contamination:**
  – Avoid contamination from adjacent secretions or tissues
  – Sterilize all equipment after use

• **Quality:**
  – Collect respiratory specimen at optimal times (pref. early AM) to maximize yield
  – Avoid Fasting 3-6 hours (depending on diet and age)
  – Avoid gastric lavage if aspirate >2-3 mL

• **Quantity:** minimum quantity unknown
  – In adults, more than 5 mL increased yield ~more than 25% [Warren et al, 200]
  – Principle: the more organisms collected, the higher the likelihood of detection
Diagnostic Specimen Management: Principles (cont.)

• **Minimize risk of false-negatives culture:**
  – Collect specimen before starting Tx
  – When TB in DDx, avoid agents with antimycobacterial activity
  – Avoid saline solution with antimycobacterial preservatives

• **Preservation:**
  – Confirm neutral pH of potentially acidic specimens (eg, gastric aspirate)
  – Use appropriate transport media
  – Minimize transport time
  – Store specimens appropriately
Key Points

1. **We’re not there yet!...** As long as the majority of DR-TB disease cases in children are not bacteriologically confirmable, presumptive diagnosis of DR-TB disease should be made when risk factors—as stipulated by WHO—are present.
   - should be the “norm”—*not the “exception”—most especially in TB programs that are not diagnosing (and treating) a similar proportion of children with DR-TB as adults

2. Appropriate empiric DR-TB treatment should be...
   - *Initiated* when clinically unstable (and, of course, when Tx failure)
   - *Very seriously considered* when there are risk factors for progression to TB disease and death (eg, immunocompromising conditions, persisting “infecting inoculums”, decreasing effectiveness of available Tx options (ie, MDR/XDR).

3. A systematic approach is needed for the *prudent* presumptive diagnosis DR-TB disease

4. Optimize specimen collection strategy: *variety, quantity, quality*
   - In cases of severe/complicated TB disease, do not delay the initiation of *empiric* TB treatment just to collect specimens—do both *concomitantly!*