Tuberculosis 2019: What’s New?

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Learning Objectives

• To understand TB epidemiology in the U.S. & globally

• To know the diagnostic algorithms for latent TB infection and active TB disease

• To be able to manage patients on treatment for latent TB infection and active TB disease

• To know about treatment monitoring, be aware of complications including drug toxicities & interactions
**TB IS THE TOP INFECTIONOUS KILLER IN THE WORLD**

**IN 2017**

1.6 MILLION PEOPLE DIED

**REACHING ALL PEOPLE WITH TB WITH QUALITY CARE**

**IN 2017**

10 MILLION PEOPLE FELL ILL WITH TB

6.4 MILLION PEOPLE WERE OFFICIALLY RECORDED BY NATIONAL REPORTING SYSTEMS

3.6 MILLION PEOPLE WERE UNDIAGNOSED, OR DETECTED BUT NOT REPORTED

Better reporting, diagnosis and access to care will close this gap.

**TACKLING THE MDR-TB CRISIS**

ONLY ONE IN FOUR PEOPLE HAD ACCESS TO MDR-TB TREATMENT

OF THOSE TREATED ONLY 55% WERE TREATED SUCCESSFULLY
Cascade of care analyses show gaps in delivery of high quality TB care

- 760,000 (25%) patients never seek government TB care
- 520,000 (20%) seek government care but are never started on treatment
Case 1 - diagnosis

• 30 year old male from Russia admitted from clinic with cough, fever, and 20 lb weight loss.

What initial TB test would you do?
A) TST or IGRA
B) Sputum smear and culture
C) Xpert MTB/RIF
D) Chest X-ray

Would this differ if he had been previously treated?
A) Yes   B) No
Active TB Diagnosis: Xpert MTB/RIF and Ultra

- Automated nucleic acid amplification assay, initial test per WHO
- Detects MTB and RIF resistance

Xpert MTB/RIF sensitivity 85%, specificity 98%
- 98% sensitivity for smear + culture + TB
- 67% sensitivity for smear – culture + TB
Xpert Ultra sens 88% (vs 83%), spec 96% (vs 98%)

- HIV+ 81% versus HIV- 88% sensitivity
- 96% sensitivity for RIF resistance (N.B. PPV), 98% specificity
Active TB Diagnosis: AFB smear & culture

- Smear sensitivity varies (~50-70%), 15% ↓ with HIV
- Typically 2-3 smears, 8 hours apart
- False + with NTMs/other AFBs

- Solid culture (LJ) takes 4-8 weeks
- Liquid culture (MGIT, BacTec) takes 2-4 weeks
- ALL TB patients need drug susceptibility testing

- ~20% culture negative TB (early, EPTB, sample)
Drug resistant TB

MDR (RIF + INH), XDR (MDR + FQ + SLID)

Think about DR-TB if:

• Known exposure to an individual with drug-resistant TB
• Residence/Origin in area with high rates of primary DR-TB
• History of previous TB treatment, particularly if interrupted
• Persistently positive smear or culture at or after 2-4 months

• Perform Xpert MTB/RIF to evaluate for RIF resistance
• If RIF-R or negative Xpert but high clinical concern, should have second line LPA/ CDC MDDR testing
Drug Resistant TB

Percentage of new TB cases with MDR/RR-TB

Figures are based on the most recent year for which data have been reported, which varies among countries. Data reported before 2002 are not shown.
Active TB Diagnosis: Imaging

- **CXR**: High sensitivity, specificity more variable, PPV ~60%
- **CT**: Preferred for lymphadenopathy, bronchogenic spread and abdominal TB
- **MRI**: Preferred for tuberculous spondylitis and CNS TB
- **Use of PET/CT**: Being studied for treatment monitoring
First Line TB Treatment

- Rifampin 600mg daily (consider ↑ dose if severe dz)
- Isoniazid 300mg daily
- Pyrazinamide 15-30mg/kg daily
- Ethambutol 15-25mg/kg daily (stop if fully susceptible)
- plus Pyridoxine 25-50mg daily
- Above for 2 months followed by 4 months RIF/INH for PTB & 9-12 months RIF/INH for EPTB (spinal/CNS)

- INH resistance – RIF/PZA/EMB + FQ x 6 months
Side Effects of TB treatment

- Hepatotoxicity (PZA, INH, RIF)
- Optic neuritis with Ethambutol:
  - Dose-dependent risk, higher risk with renal insufficiency (19.2/1000, permanent 2.3/1000)
- Peripheral neurotoxicity with INH: > Vit B6 (burning sensation, pricking pain, numbness or tingling)
- Lupus-like syndrome with INH
- Poliarthralgias with RIF and PZA
- Gout flare in patients with pre-existing dx with PZA
- Warn pts - orange discoloration of body fluids with RIF
Case 1 - treatment

• 30 year old Russian male with smear + pan-sensitive PTB with cavitary disease
• 3 weeks into treatment with RHZE she develops nausea / raised LFTs (AST 400, ALT 200, ALP 400)
• Meds held. How would you re-introduce?

A) RIF +/- EMB followed by INH then PZA
B) RIF +/- EMB followed by INH then FQ/LZD
C) INH followed by RIF followed by PZA then EMB
D) EMB followed by RIF then INH then PZA
Approach to TB Drug-Induced Hepatotoxicity

**Figure 3.** Monitoring for hepatotoxicity during treatment of TB disease. Dotted lines signify management according to physician’s discretion. ALT = alanine aminotransferase; AST = aspartate aminotransferase; HCV = hepatitis C virus; HepBsAg = hepatitis B surface antigen.
Treatment monitoring

- Monthly sputum smears and cultures
- Culture conversion = 2 consecutive negative cultures
- Adverse events common with HIV/TB treatment including GI reactions and rashes
- Fever may represent TB, IRIS, another infection
- 20% have an increase in AST with first-line Rx
- DILI = ≥3 x ULN AST if Sx or ≥5 x ULN AST if no Sx
- If disproportionate ↑ in Bil &/ ALP plus AST -> RIF
- Re-introduction: RIF +/- EMB then INH, may avoid PZA

ATS TB Guidelines 2003
WHO TB Treatment Guidelines 2009
Saukkonen AJRCCM 2006
Progress towards shorter less toxic regimens?

- NIX-TB open label study in South Africa (bedaquiline, pretomanid and linezolid) for XDR-TB: 66/74 (89%) patients with favorable outcome.

- STREAM trial results—RCT compared shorter MDR Rx to standard (78% vs. 80% treatment success), data on all oral MDR-TB regimen including BDQ is pending.

- WHO now recommends new/repurposed drugs like bedaquiline & linezolid over aminoglycosides for DR-TB.
**FIG. 8.2**
The global development pipeline for new anti-TB drugs and regimens, August 2017

<table>
<thead>
<tr>
<th>Phase Ia</th>
<th>Phase IIa</th>
<th>Phase IIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK-3036656b</td>
<td>Delpazolid (LCB01-0371)</td>
<td>Bedaquiline</td>
</tr>
<tr>
<td>OPC-167832b</td>
<td>PBTZ169b</td>
<td>Delamanid</td>
</tr>
<tr>
<td>Q203b</td>
<td>SQ109b</td>
<td>Pretomanid</td>
</tr>
<tr>
<td>Sutezolid</td>
<td>Levofloxacin</td>
<td>Clofazimine</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Linezolid (high dose)</td>
<td>Rifampicin (high dose)</td>
</tr>
<tr>
<td>Nifazoxamide</td>
<td>Rifapentine</td>
<td>Rifapentine</td>
</tr>
<tr>
<td>Rifampicin (high dose)</td>
<td>Rifapentine</td>
<td></td>
</tr>
<tr>
<td><strong>Bedaquiline</strong></td>
<td><strong>Pretomanid</strong></td>
<td><strong>Linezolid</strong>, with or without moxifloxacin or clofazimine for MDR-TB or XDR-TB (TB PRACTECAL trial)</td>
</tr>
<tr>
<td><strong>Bedaquiline</strong></td>
<td><strong>Pretomanid</strong></td>
<td><strong>Linezolid</strong> (NIX-TB trial)</td>
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<tr>
<td><strong>Bedaquiline</strong></td>
<td><strong>Pretomanid</strong></td>
<td><strong>Pyrazinamide</strong> regimen</td>
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<td><strong>Bedaquiline</strong></td>
<td><strong>Pyrazinamide</strong> regimen</td>
<td><strong>STREAM</strong> trial</td>
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<tr>
<td><strong>Bedaquiline</strong></td>
<td><strong>Pyrazinamide</strong> regimen</td>
<td><strong>MDR-END</strong> trial</td>
</tr>
<tr>
<td><strong>Delamanid</strong></td>
<td><strong>Linezolid</strong></td>
<td><strong>Moxifloxacin</strong> for drug-susceptible TB (TB Trial Consortium Study 31/A5349)</td>
</tr>
</tbody>
</table>

a New drug compounds are listed first, followed by repurposed drugs and then by regimens.
b New chemical class.

Source: Adapted from the Stop TB Partnership Working Group on New TB Drugs pipeline. More information on these products and other ongoing projects can be found at http://newtbdrugs.org
Case 2

• 36 year old female from Vietnam referred to clinic due to new HIV diagnosis (asymptomatic). What is your TB testing approach?

A) No TB testing
B) Tuberculin Skin Test (TST)
C) Quantiferon-Plus (IGRA)
D) T Spot TB (IGRA)
E) Sputum testing (microscopy, culture, Xpert)
F) Chest X-ray
LATENT TB

- Estimated that ~1.7 billion worldwide have latent TB
- ~13 million (4%) of US population has latent TB
- 5-10% of those infected will develop active TB

Higher risk of reactivation in patients with immunosuppression including HIV (3-12 fold higher)

PEOPLE WHO SHOULD BE TESTED FOR TB INFECTION INCLUDE:

- Contacts of people with TB disease.
- People from countries where TB disease is common.
- People with health problems that make it hard to fight TB disease.
- People who spend time in places where TB is more common.
Cascade of care analyses show gaps in delivery of high quality latent TB care
Tuberculin Skin Test (TST)

- 0.1 ml of tuberculin PPD injected into inner forearm with a tuberculin syringe, with bevel facing upward
- Injection should cause a pale 6-10mm elevation of skin (wheal)
- TST should be read after 48-72 hrs
- Measure induration not erythema
- Positive test depends on risk e.g. PLHIV or child contacts = 5mm
Interferon-Gamma Release Assay (IGRA) - Quantiferon PLUS

- Test measures IFN-γ produced by lymphocytes to TB antigens and test controls coated on tube
- Increasing data demonstrates CD8 response in active TB, including early phase of infection
- Additional TB2 tube includes short peptide antigens (MHC-1) to stimulate CD8 cells
- Positive result if TB1-nil OR TB2-nil > 0.35iU/ml
- Results: positive, negative, indeterminate
Interferon-Gamma Release Assay (IGRA) - T Spot TB

**The Science Behind T-SPOT Technology**

1. Collect the blood sample. At the lab, PBMCs are separated from whole blood, washed, counted, and inoculated into 4 separate microwells.
2. PBMCs (●) and specific TB antigens (□) are added to wells pre-coated with antibodies to IFN-γ (▲) and incubated 16 to 20 hours (27°C ± 2°C).
3. IFN-γ (▲) is released from activated T cells and captured. Wash wells, add secondary conjugated antibody (λ). Incubate for one hour.
4. Wells are washed. A substrate is added which produces spots (□) where interferon gamma was secreted by T cells. Spots are counted.

**Interpreting Tuberculosis Test Results with the T-SPOT TB test:**
- Interferon-gamma is captured and presented as spots from T cells sensitized to TB infection
- Results are interpreted by subtracting the spot count in the negative (NIL) control from the spot count in Panels A and B:
  - Positive > 8 spots
  - Negative < 4 spots
  - Borderline 5, 6, or 7 spots
  - Invalid

**Negative Result**
- Nil Control

**Positive Result**
- ESAT-6 Panel A
- CFP 10 Panel B
- Positive Control

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CDC IGRA Factsheet
Choice of LTBI test (CDC)

- IGRA preferred
  - Groups with low rate of returning for TST read
  - Those who have received BCG (vaccine/cancer Rx)

TST preferred
- Children aged <5 years (potentially IGRA plus TST)
- Either
  - Contact tracing (baseline IGRA/TST -> 8-10 wks post exposure)
  - Occupational screening
- Both
  - Initial negative in high risk groups, indeterminates
  - To increase acceptance

Important to emphasize that TARGETED TESTING IS RECOMMENDED i.e. for persons at risk of LTBI based on exposure, or at risk of progression to TB (e.g. PLHIV), or poor outcomes (NOT for persons at low risk)
The following tool estimates the risk of active tuberculosis for an individual with a tuberculin skin test reaction of $\geq 5$ mm, based on his/her clinical profile. It is intended for adults tested with standard tuberculin (5 TU PPDS, or 2 TU RT-23), and/or a commercial Interferon Gamma release assay (IGRA). For more details about the algorithm used, go to the About page. The current version of the algorithm contains modifications of the original version, which was detailed in a paper by Menzies, et al. (2008). For further information see references, or contact dick.menzies@mrcill.ca

Please select the best response for each field:

<table>
<thead>
<tr>
<th>TST Size:</th>
<th>IGRA Result:</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-9 mm</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Age at immigration (if person immigrated to a low TB incidence country):

- **Age:** 40

Country of birth:

- Haiti

For more info, visit: BCG World Atlas.

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http://bcgatlas.org
IGRA vs. TST

<table>
<thead>
<tr>
<th></th>
<th>Menzies 2007</th>
<th>Kahwati 2016</th>
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</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TST</td>
<td>0.71 (0.74 for 5mm)</td>
<td>0.79 (both 5mm/10mm)</td>
</tr>
<tr>
<td>QFT</td>
<td>0.76 (0.8 for ESAT6/CFP-10)</td>
<td>0.8</td>
</tr>
<tr>
<td>TSPOT</td>
<td>0.88 (0.93 for ESAT-6)</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TST</td>
<td>0.66 (0.98 if no BCG)</td>
<td>0.97 (10mm)</td>
</tr>
<tr>
<td>QFT (GIT)</td>
<td>0.97</td>
<td>0.97</td>
</tr>
<tr>
<td>TSPOT</td>
<td>0.92</td>
<td>0.95</td>
</tr>
</tbody>
</table>

- Challenges: test variability, conversions, reversions
- IGRA cross-reactivity: M. bovis (not BCG), M. africanum, M. kansasii, M. marinum, M. szulgai
- Both tests have a low positive predictive value $\rightarrow$ 1-3% of IGRA+ contacts develop active TB over the next 2 years
- Neither is a test for active TB
What to do if latent TB test is positive

• Should trigger prompt evaluation for active TB
• Absence of any symptoms (cough of any duration, fever, night sweats, weight loss) has a 97% NPV for culture-positive TB, CXR further increases sensitivity
• Sputum culture is not recommended if asymptomatic and CXR is unrevealing for signs of TB

• If test positive and no evidence for active TB in PLHIV or if there is exposure to infectious TB regardless of test result, LTBI Rx is recommended
Case 2 - treatment

- How would you treat this patient for LTBI? (assuming no issues with other medications)

A) Isoniazid x 9 months
B) Rifampin x 4 months
C) Rifabutin x 4 months
D) Isoniazid / Rifapentine x 3 months
LTBI Treatment Choices

**Table 2. Latent TB Infection Treatment Regimens**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Duration</th>
<th>Interval</th>
<th>Minimum-doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months</td>
<td>Daily</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly*</td>
<td>76</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>6 months</td>
<td>Daily</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly*</td>
<td>52</td>
</tr>
<tr>
<td>Isoniazid and Rifapentine</td>
<td>3 months</td>
<td>Once weekly*</td>
<td>12</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4 months</td>
<td>Daily</td>
<td>120</td>
</tr>
</tbody>
</table>

*Use Directly Observed Therapy (DOT)

- 1HP non-inferior to 9H in multi-site phase 3 open-label RCT of PLHIV >13 years, fewer adverse effects and higher Rx completion rates
- Self administered therapy non-inferior to directly observed therapy
Monitoring on LTBI Treatment

- Monthly follow up suggested
- Ask re: nausea, anorexia, icterus, rash, parasthesias
- Baseline ALT, AST, Total Bilirubin, repeat if abnormal
- Should evaluate for co-existent viral hepatitis

- Stop if
  - Asymptomatic  >5 fold increase above ULN AST
  - Symptomatic  >3 fold increase above ULN AST
  - Baseline abnormal  >3 fold increase above ULN AST
Hold Your Breath

- Stigma is a major barrier to TB care

Paulina Siniatkina, Russia
I survived XDR-TB. It took me more than three years to get cured. I took 20 tablets a day. Injections every day for 6 months! The meds made me deaf.

I had to drop out of University. Drug-resistant TB is hard to treat but it is curable. I can hear now via cochlear implants. I am going to study at University of Cape Town.

-Phumeza Tisile
TB Survivor
TB Diagnostics
Take Home Points

- **Xpert MTB/RIF** has high sensitivity (smear positive cases, lower for smear negative) and specificity
- **EPTB** – relies on clinical suspicion, biopsy, TB PCR
- Drug susceptibility testing recommended for all

- Targeted LTBI testing & follow up for those at risk
- For most LTBI testing, IGRA has similar challenges & is not superior to TST but may offer some advantages
- Serial LTBI testing only if high risk
TB Therapeutics
Take Home Points

• Early initiation of effective Rx for active TB is essential to improve outcomes & ↓ transmission

• RIF based first line Rx causes drug-drug interactions
  • EFV or DTG based regimen preferred for PLHIV

• Monitor for treatment toxicity

• Adverse events common with TB/HIV, consider IRIS

• Treatment support, communication with DPH ⬆️

• Shorter LTBI regimens effective & can ↑ adherence
Key Points and Next Best Steps

• Majority of US TB cases due to reactivation rather than transmission ➔ identifying and treating latent TB is critical

• All patients being evaluated for active pulmonary TB should undergo Xpert MTB/RIF

• Treatment may be complicated by drug toxicities, drug interactions (e.g. RIF and HIV ART) and potentially IRIS

• Understand diagnostic approach for latent & active TB

• Understand approach to treatment choices including adverse effects, ART interactions, shorter LTBI regimens