Innovations in Tuberculosis Therapy

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Objectives

• Review history of tuberculosis (TB) and its treatment
• Review trends in tuberculosis incidence/prevalence
• Review diagnosis of LTBI and TB disease
• Review treatment options for LTBI
• Review treatment options for active TB
• Discuss treatment options for MDR and XDR TB
• Discuss new medications, phase 1-3 trials for new TB treatment regimens and DOT options

• Presentation focuses on current recommendations for the diagnosis and treatment of pulmonary tuberculosis only
History of Tuberculosis

• The Bible, ancient Greek literature, literature from the far East all make reference to variations of “Phthisis,” “White Plague,” and “Consumption.”

• 1834 standards of treatment included creating a pneumothorax to give the lung “rest.”

• In 1882, Robert Koch utilized a new staining method and identified *Mycobacterium tuberculosis* for the first time.

• BCG vaccine first used in 1921 in France

• Streptomycin first used in 1944
  • Significant side effects as monotherapy

• Isoniazid hit the market in 1952
History of Tuberculosis cont’d.

- TB Sanitorium 1926 - remained the mainstay of “treatment” until the mid 1950s-1960s when multidrug therapy was used with success
- Ototoxicity with injectibles still an issue
- Hepatotoxicity required close monitoring
Trends in Tuberculosis

- In 2013 a total of 9,588 new TB cases were reported in the US
  - Incidence of 3.0 cases per 100,000 people
  - Decrease from incidence of 4.2% in 2012

- Incidence among foreign-born is 13x greater
  - 64.6% of all TB cases

- Half of all cases of TB in 2013 occurred in California, Texas, New York, and Florida
  - 4,917 total cases

- 86 total cases of MDR TB were identified in 2012
Tuberculosis cases from the top 12 countries of origin, 1993 – 2009

- Mexico
- Philippines
- Vietnam
- India
- China
- Haiti
- Korea, Republic of
- Guatemala
- Peru
- El Salvador
- Ethiopia
- Honduras
Diagnosis

• Tuberculin skin test (Mantoux TST)
  • Positive testing is induration at 48-72 hours after test placement
    • >15mm in the general population
    • >10mm in healthcare workers and those at high risk for exposure
    • >5mm in HIV+ patients and the immunocompromised
Diagnosis cont’d.

• TB blood testing – Interferon Gamma Release Assay
  • QuantiFERON TB Gold In-Tube test (3rd gen 2007)
  • T-spot TB test (2008)
  • Updated guidelines for use June 25, 2010

• POSITIVE – Patient has been infected with TB bacteria. Additional testing is needed to determine if patient has active TB or LTBI

• NEGATIVE – Infection with TB bacteria is unlikely

• INDETERMINATE – Patient status could not be ascertained, testing should be repeated
  • Possible mishandling, possible patient immunosuppression, concurrent drug effect, poor mitogen response
IGRAs cont’d.

- June 25, 2010 – MMWR published guidelines on the use of IGRAs for TB testing
- How it works:
  - The QFT-GIT assay is an ELISA-based, whole-blood test that uses peptides from three TB antigens (ESAT-6, CFP-10, and TB7.7) in an in-tube format. The result is reported as quantification of IFN-gamma in international units (IU) per mL. An individual is considered positive for M. tuberculosis infection if the IFN-gamma response to TB antigens is above the test cut-off after subtracting the background IFN-gamma response in the negative control.
  - Sensitivity and specificity are similar to a properly placed PPD test, with some advantages and disadvantages
Advantages/Disadvantages

**Advantages of the test:**
- Requires a single patient visit to draw a blood sample.
- Results can be available within 24 hours.
- Does not boost responses measured by subsequent tests, which can happen with tuberculin skin tests (TST).
- Is not subject to reader bias that can occur with TST.
- **Is not affected by prior BCG vaccination.**

**Disadvantages and limitations of the test:**
- Blood samples must be processed within ~24 hours after collection while white blood cells are still viable.
- There is limited data on the use of QFT-GIT in children younger than 17 years of age, among persons recently exposed to M. tuberculosis, and in immunocompromised patients.
- Errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease the accuracy and potentially lead to indeterminate results.
- False positive results can occur with Mycobacterium szulgai, Mycobacterium kansasii, and Mycobacterium marinum.
Skin Testing and IGRA Discordance?

• What if Mantoux TST is negative and quantiferon is positive?
• What if Mantoux TST is positive and quantiferon is negative?

• Age >50
• HIV status?
• Foreign born? BCG vaccine?
Typical Scenario

• A 45yo woman with a h/o joint pain and inflammation is seen by a rheumatologist who diagnoses rheumatoid arthritis and begins some anti-inflammatory therapy

• Patient is a candidate for possible biologics in the near future and baseline QFT-GIT is performed and results as a positive test

• Patient has never been out of the country and is perplexed as to why they have been sent to an infectious disease physician for evaluation
Consult cont’d.

• If not yet done, patient needs to be sent for a CXR to evaluate for any evidence of active disease or possibly scarring
  • If negative CXR, LTBI is the working diagnosis and treatment can be considered
  • If evidence of possible active infection, patient needs to be sent for sputum sample collection/staining
  • If evidence of scarring, further history to be obtained as patient may warrant multidrug therapy given a h/o possibly active disease
• Once the likelihood of LTBI is established, treatment can be discussed
Who should be treated?

• Everyone should be offered treatment
  • Especially immunocompromised hosts, HIV+ patients, and those about to start immunosuppressive medications for other conditions

• What are the risks if no LTBI treatment is taken?
  • Lifetime risk of ~10% to develop active infection
  • Greatest risk within the first 1-2 years after exposure

• Currently 4 treatment protocols are approved for LTBI treatment
### 4 LTBI Treatment Regimens

<table>
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<tr>
<th>Drug(s)</th>
<th>Duration</th>
<th>Dose</th>
<th>Frequency</th>
<th>Total Doses</th>
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<tr>
<td>Isoniazid (INH)</td>
<td>9 months</td>
<td>Adult: 5 mg/kg&lt;br&gt;Children: 10-20 mg/kg&lt;br&gt;Maximum dose: 300 mg</td>
<td>Daily</td>
<td>270</td>
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<td></td>
<td></td>
<td>Adult: 15 mg/kg&lt;br&gt;Children: 20-40 mg/kg&lt;br&gt;Maximum dose: 900 mg</td>
<td>Twice weekly</td>
<td>76</td>
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<tr>
<td></td>
<td>6 months</td>
<td>Adult: 5 mg/kg&lt;br&gt;Children: Not recommended&lt;br&gt;Maximum dose: 300 mg</td>
<td>Daily</td>
<td>180</td>
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<tr>
<td></td>
<td></td>
<td>Adult: 15 mg/kg&lt;br&gt;Children: Not recommended&lt;br&gt;Maximum dose: 900 mg</td>
<td>Twice weekly</td>
<td>52</td>
</tr>
<tr>
<td>Isoniazid (INH) and Rifapentine (RPT)</td>
<td>3 months</td>
<td>Adults and Children 12 and over:&lt;br&gt;&lt;br&gt;<strong>INH:</strong> 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum&lt;br&gt;&lt;br&gt;<strong>RPT:</strong>&lt;br&gt;10.0–14.0 kg 300 mg&lt;br&gt;14.1–25.0 kg 450 mg&lt;br&gt;25.1–32.0 kg 600 mg&lt;br&gt;32.1–49.9 kg 750 mg ≥50.0 kg 900 mg maximum</td>
<td>Once weekly</td>
<td>12</td>
</tr>
<tr>
<td>Rifampin (RIF)</td>
<td>4 months</td>
<td>Adult: 10 mg/kg&lt;br&gt;Maximum dose: 600 mg</td>
<td>Daily</td>
<td>120</td>
</tr>
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Active TB Treatment Review

• 5 basic “first line” drugs
  • Isoniazid
  • Rifampin
  • Pyrazinamide
  • Ethambutol
  • Streptomycin

• In general, historically, these drugs have the greatest activity against TB bacteria and should be the “core” to a TB drug regimen whenever possible

• Always send susceptibility cultures
  • New, non-foreign born cases presumed to be pansusceptible
  • Consider MDR in foreign born,
Usual algorithm

FIGURE 1. Treatment algorithm for tuberculosis.
TB Treatment

- Standard treatment involves a two month “intensive” treatment phase followed by a four month “continuation” phase
  - Phase 1 should include dose appropriate:
    - Isoniazid, rifampin, pyrazinamide, and ethambutol
    - Dosed daily or DOT
  - Phase 2 should include a continuation of:
    - Isoniazid and rifampin alone
    - Dosed daily or DOT
  - Never treat with a single agent

- Isolation for active cases?
  - Considerable evidence states essentially no longer infectious after 2 weeks of therapy
MDR and XDR-TB

• MDR Tuberculosis
  • MDR-TB is a form of drug-resistant TB in which TB bacteria can no longer be killed by at least the two best antibiotics, INH and RIF.

• XDR Tuberculosis
  • XDR-TB is a less common form of MDR-TB in which TB bacteria are able to circumvent the two best antibiotics, INH and RIF, as well as most of the alternative drugs used against MDR-TB. This includes resistance to any fluoroquinolone and at least one of the injectable anti-TB drugs.

Percentage of new tuberculosis cases with MDR-TB*

* MDR-TB: multidrug-resistant tuberculosis (resistance to, at least, isoniazid and rifampicin)
Note: Figures are based on the most recent year for which data have been reported, which varies among countries.

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Suggested MDR-TB Treatment

- **INH resistance:**
  - Rifampin + pyrazinamide + ethambutol +/- fluoroquinolone
    - 6 months of therapy
- **Rifampin resistance:**
  - Isoniazid + ethambutol + fluoroquinolone + pyrazinamide for the first 2 months (+/- injectable agent if severe disease)
    - 12-18 months of therapy
- **INH+rifampin resistance:**
  - Fluoroquinolone + pyrazinamide + ethambutol + an injectable agent +/- an alternative agent
    - 18-24 months of therapy
Suggested XDR-TB Treatment

- Therapy requires administration of 4-6 drugs in combination to which the resistant organism is susceptible
- These regimens generally include multiple second line drugs and should include all available “first line” drugs
- Use of newer agents, trial agents remain an option for severe resistant disease
- Treatment anticipated 18-24 months
New Innovative Treatments

- At least 10 compounds are currently in various stages of development or are being redeveloped or repurposed for the treatment of TB
- June 24, 1998 brought FDA approval of the first drug with a new indication for the treatment of TB, rifapentine (Priftin®)
  - Rifapentine is dose 600mg p.o. 2x/wk x 8 weeks then q weekly thereafter for 18 weeks
  - Also can be used as DOT for LTBI with INH
Rifapentine cont’d.

- Rifamycin class with known potent mycobacteriacidal activity
- Same class as rifampin, rifabutin
- Potential upcoming role as first line treatment for TB
  - Potential to shorten treatment
  - Weekly DOT use
  - Trials ongoing
First NEW Drug in 40 years

• Bedaquiline (Sirturo ®) was released by Janssen and approved December 28, 2012
  • Diarylquinolone agent approved in combination to treat MDR-TB when no other alternatives are available
    • Targets proton pump for ATP synthase
  • Black box warning for cardiac arrhythmias
  • Numerous adverse events reported

• Phase 3 trials are ongoing, compassionate use currently in Europe and South Africa
  • Restricted use in the United States
  • Drug enrollment hotline 1-800-526-7736 for patient candidates
Next up, Delamanid

• Delamanid is a product from the existing nitroimidazole class which is currently being developed as a potential TB drug
• Being developed by Otsuka pharmaceuticals specifically for the treatment of MDR-TB

• Phase 2b trials ongoing with nearly double the clinical effectiveness at two months (sputum culture conversion negative) in combination therapy when compared to placebo

• Most likely next-to-market candidate
The others...

- PA-824 and TBA-354
  - Both also in the nitroimidazole class
  - Trials ongoing for drug sensitive and drug resistant TB
  - TBA-354 said to be longer lasting with greater activity against resistant strains
    - Has been selected for human trials based on in-vitro and animal studies

- AZD5847
  - Potential new TB drug being developed by AstraZeneca
  - December 2012, first human patients in a phase 2a trial in South Africa
  - Potential application for this drug in TB and HIV co-infected patients
Summary

• Nearly 10,000 annual cases of active TB in the US each year
  • Currently a downward trend, however with increased immigration certain areas are seeing a climb in positive cases
• 4 viable LTBI regimens including DOT options if necessary
  • All LTBI patients should be offered treatment for LTBI infection
• Weekly DOT therapy administered by the health department remains the preferred method of treatment for most TB positive patients
• All positive smears/cultures should be sent for susceptibility testing. MDR and XDR isolates require multiple drugs for very long treatment courses.
• One new drug, bedaquiline, on the market as of December 2012 with at least 10 additional agents being developed or repurposed for TB treatment
References

- American Thoracic Society, CDC, IDSA. *Treatment of Tuberculosis.* MMWR. June 20, 2013. 52(RR11);1-77.