Errors in Dx and Rx of TB

David Schlossberg, MD, FACP
Professor of Medicine
Temple University School of Medicine
Medical Director, TB Control Program
Philadelphia Department of Public Health

TB – Still a threat

• 1/3 of the world infected
• 2-3 million deaths/year
• Diagnosis is slow
• Rx is long and complicated
• Many pitfalls in Dx and Rx

“It might be TB; let’s do a PPD”
False-negative PPD

- Active tuberculosis (~25%)
- Miliary tuberculosis (~50%)
- Immunosuppression, e.g. AIDS, Steroids
- Waning with age (~5% per year)
- Vaccination, viral illness

IGRAs

Sensitivity ~ PPD. Remember, it is an immunologic test, also

“Sputum Smear is usually positive”
SPUTUM STAIN vs. CULTURE

Φ Smear: 5000-10,000 AFB
Φ C+S: 10-100 AFB

False Φ Sputum Smear

As many as 50% of cases

Negative Sputum Smear

“Smear-negative TB is not contagious”

Φ sputum much more contagious
- but: 1/6 cases smear-negative contact
Culture-negative TB

- Sputum: 17% in US
- Extra-pulmonary variable:
  - Cerebrospinal fluid: 30-50%
  - Urine: 20%
  - Peritoneal fluid: 75%
  - Consider PCR – urine, fixed tissue

Culture-negative TB – 17%!

- Empiric TB Rx
- Alternative Dx – Stop TB Rx
  - No improvement by 2 mos - stop Rx
- Prove TB - Rx
- TB cultures negative
  - Improvement – Rx for 4 months

"Negative cultures rule out TB"
“A Normal CXR rules out TB”

**TB in Advanced AIDS**

**Frequently atypical:**
- CXR: clear; lower-lung zone infiltrates; adenopathy
- Extrapulmonary involvement up to 70%: lymphatic, meningeal, pleural, hepatic, renal, splenic, spinal, cutaneous, miliary dissemination
- PPD negative in majority
- May have no symptoms (5% of one cohort of HIV pts)
- African post mortem studies: TB was cause of death in ~40%, but was suspected in only 50% pre-mortem
"TB Pleural effusions persist if untreated"

Beware the self-limited Pleural effusion!

"Negative pleural fluid culture rules out TB"

Body Cavities: Tissue > Fluid

Tuberculosis of:
- Pleura
- Pericardium
- Synovium
- Peritoneum
Miliary TB
CXR may be negative initially
If in doubt, repeat it.
Sputum smear/culture SHOULD be negative
--unless pulm TB present also
The Ten Commandments

How TB is treated with one drug

1. Treating LTBI with “stable” CXR
2. Adding one drug to a failing regimen
3. Starting Rx with only 2 drugs before sensitivity known

“The CXR can determine if disease is active”
LTBI = R/O active TB: Beware the Misleading X-ray Reports:
“Stable”
“inactive”
“healed”
“fibrotic”
“old”
“scarring”

Can not tell activity from CXR. If in doubt, wait for C&S or begin Rx with 4 drugs

“If regimen is failing, add one new drug”

Never Add Just One!

<table>
<thead>
<tr>
<th>Treatment</th>
<th>March</th>
<th>June</th>
<th>October</th>
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</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td></td>
<td></td>
<td>R</td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
<td></td>
<td>R</td>
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<tr>
<td>Ethambutol</td>
<td></td>
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<td>R</td>
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</tbody>
</table>

Smear
+ + + +

Culture
+ + + +

Susceptibility
Isoniazid R R R
Rifampin S R R
Ethambutol S S R

That’s why we begin Rx with at least 4 drugs:

- INH
- Rifampin
- PZA (shortens Rx to 6 months)
- Ethambutol (in case of INH Resistance)
Starting with just 2 drugs...

PZA does not protect against resistance. Therefore, assume INH resistance and don’t start, e.g. with INH plus rifampin.

INH Resistance

- Japan 3% new 19% prior Rx
- USA 8% new 14% prior Rx
- Korea 12%
- China 13%
- Philippines 14%
- Russia 16%
- Vietnam 19%

“Isolation can be discontinued once Rx is begun”

Infectiousness

- Isolation in hospital
  - Clinical response
  - 3 consecutive AFB-negative smears
  - Two weeks of Rx (5-7 days if smear negative)

- Can leave hospital while still contagious
  - “Home Isolation”
Home Isolation

Can discharge patients while still contagious
– Clinical judgment: what is home situation, regarding susceptibles, e.g. children, immunosuppressed, etc.
– “Isolate” at home: no visitors, ventilation, cough into tissues, mask for doctor visits, etc.
– Isolate until criteria satisfied, i.e. 3 negative smears and 2 weeks of Rx with clinical response

IRIS

Known TB may appear to worsen on Rx
**OR** Unsuspected TB may be unmasked
• Both HIV-positive and HIV-negative patients
• Seen with TNF-alpha antagonists
• Described post-partum
  • lymphocyte reactivity normalizes in 24 hours

IRIS Epidemiology

• Normal patients – during anti-TB Rx
• HIV infection – ART
• Transplantation – ↓ immunosuppressive Rx
• Pregnancy – post-partum
• Neutropenia – rapid recovery after colony-stimulating growth factor
• After Rx with TNF-alpha antagonists

“Worsening on Rx = Rx Failure”
Subcutaneous abscess – Immune Reconstitution in patient with AIDS And Miliary TB, on HAART


<table>
<thead>
<tr>
<th>Days of anti-TB Rx prior to ART</th>
<th>Incidence of IRIS</th>
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</thead>
<tbody>
<tr>
<td>0-30</td>
<td>100%</td>
</tr>
<tr>
<td>31-60</td>
<td>33%</td>
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<tr>
<td>61-90</td>
<td>14%</td>
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<tr>
<td>91-120</td>
<td>7%</td>
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<tr>
<td>&gt;120</td>
<td>0%</td>
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IRIS Risk: Timing of Rx

Early ART reduces morbidity and mortality

NIH: CD4 count <500 cells/mm$^3$: within 2–4 weeks of TB Rx
CD4 count >500 cells/mm$^3$: within 8 weeks of TB Rx

WHO: “ASAP” (within 8 weeks)
Can defer for 2 months with high IRIS mortality rate, e.g. CNS

Timing of ART in TB
Balancing IRIS/pill burden/drug tox vs. OIs, Mortality

Aidsinfo.nih.gov 2011
Management of IRIS

- Rule out other causes
- Continue ART and anti-TB Rx
- Treat symptomatically
  - NSAIDS
  - Corticosteroids
  - Recent report: TNF-alpha inhibitors

Summary

- Smear, PPD, CXR, culture: can be negative
- Tissue > Fluid for culture (e.g. pleura)
- Never treat with one drug
  - adding one drug to a failing regimen
  - starting with INH/RIF
  - Treating LTBI without ruling out TB disease
- IRIS can mimic Rx failure or resistance

THANK YOU!