Approach to Tuberculosis in the Developing World

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The scope of tuberculosis

• Over 2 billion people (1/3 population) in the world are infected with *M. tuberculosis*
  • ~10-15 million active tuberculosis cases
  • 3 million deaths each year.

• 22 countries carry 80% of world’s TB burden
  • 17 of these countries have gross national product per head < $760 (US) – defined by World Bank as ‘low income country’

• Poor countries bear most of global TB burden
  • 54% if TB cases occur in Africa and Asia
Burden of Tuberculosis - International

WHO: Global health report 2009, fact sheet (per 100,000 persons)
Estimated TB incidence rate, 2006
New cases per 100,000 population

Estimated new TB cases (all forms) per 100,000 population

- No estimate
- 0-24
- 25-49
- 50-99
- 100-299
- 300 or more

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Microbiology Challenges of *M. tuberculosis*

- **Slow growing mycobacteria**
  - Replicates every 12-24 hours
  - Delay in culture results
  - AFB smears not specific for MTB (but suggestive)

- **Requires specialized media for in vitro growth**
  - Not readily available in field clinics

- **Antimicrobial drug susceptibility testing available only in select labs**
Treatment Challenges of *M. tuberculosis*

- Combination therapy required
- Prolonged treatment
- 2nd-line TB drugs
  - Expensive
  - Poorly tolerated
  - Less effective
Common Lack of Medical Resources in 3rd World Setting

**Unavailable or typically not done:**
- Mycobacterial cultures
- Drug susceptibility/resistance testing
- Tuberculin skin testing
  - High % positive – from TB infection and/or prior BCG vaccination

**Limited availability**
- CXR – if hospital/clinic accessible
- 2nd-line TB drugs
- Directly Observed Therapy (DOT)
Clinical disease Challenges of *M. tuberculosis*

- Clinical presentations not specific for MTB
  - F/C, weight loss, sweats – common with malaria, select malignancies, HIV &/or HIV-associated Opport. Infections
  - Respiratory symptoms & CXRs – similarities with select fungal, other mycobacterial, select parasitic infections
    - HIV (+) pts with even less specific present
Approach to TB patient abroad

• **Do NOT** treat yourself
  • You’re temporary
  • Lack of access to drugs, DOT and personnel

• Refer to government-sponsored (WHO affiliated) TB treatment clinic/center
  • Go find one!! – or
  • Refer to local TB provider

• Only in very unusual circumstances treat TB yourself
TB Treatment in Underserved Community – *Need to refer* to Regional TB treatment center / clinic

- TB Drug availability
- AFB monitoring
- CXR availability
- DOTS (if available)
- Isolation (if applicable) – depending upon setting
Problems of Global Tuberculosis Containment

- Lack of Involvement of clinicians outside of public health TB control programs
  - E.g. private physicians
- Clinician deviation from standard internationally accepted DOTS TB management
- Under-use of sputum AFB smear microscopy
  - Over-reliance on CXRs
- Use of non-recommended TB drug regimens and combinations
- Mistakes in drug dosing and treatment duration
- Lack of supervised patient adherence

Hopewell. Lancet Inf Dis 2006;6:710
Distribution of MDR-TB diagnosed among previously treated TB cases

Zignol, Jour Inf Dis 2006:194
World Health Organization, 2006
MDR-TB Underreporting in Africa

A. Data from Third Global report on Anti-TB Drug Resistance in the World, WHO, 2004

B. Data from WHO publications, peer-reviewed journal articles and WHO’s Fourth Global report

C. Formulaic estimates JID 2006;194:479

Emerg Inf Dis 2008, 14(9): 1345
Standardized WHO approach towards TB management

• All patients with cough x 2-3 weeks should be evaluated for TB

• All patients with abnormal CXRs suggestive of TB should be further evaluated

• TB evaluation includes at least 2-3 sputum specimens for AFB smear

• Consideration for TB in patients with neg. sputa smear if CXR and symptoms c/w TB

• Test for HIV infection

• Assess high risk contacts (HIV+ patients, children) for LTBI and TB disease

• Ensure patient adherence to Tx (DOT)

Hopewell. Lancet Inf Dis 2006;6:710
Challenges with WHO approach to TB Diagnosis & Mgmt

- Chronic respiratory conditions common (asthma, bronchitis, bronchiectasis)
- Smoking, cooking
Challenges with WHO approach to TB Diagnosis & Mgmt.

• Lack of microscopy or radiology facilities

• Proper sputum collections
  • Esp. in children
  • Best when collected in early AM
  • 2\textsuperscript{nd} sputum smear increases AFB smear yield by 13%
  • 3\textsuperscript{rd} sputum smear ~ 4%
  \[\rightarrow\text{At least 2 quality sputa samples recommended}\]

Mase. Int J Tuberc Lung Dis. 2007 May;11(5):485-95
Challenges with WHO approach to TB Diagnosis & Mgmt.

• Passive TB case diagnosis much more common than active investigations

• TB disease and infection screening variably practiced
  • Often limited to HIV, high risk contacts / children
  • Contact investigation often only performed with AFB smear (+) index case

• Symptoms commonly not assessed

Bothamley. Eur Respir Jour 2008;32:1023
A New Approach to TB Investigation in Underserved Location:
4 Steps to Success:

Defining / characterizing:

1. The **Host**
2. The **Syndrome**
3. The **Microbiology**
4. The **Treatment**
1st - Define the Host
Defining the Host

• Immunocompetent vs. Immunosuppressed
  – **Especially HIV status
    • Higher rates of primary TB disease
    • More atypical pulmonary findings
    • Higher rates of extrapulmonary disease & dissemination

• Other medical comorbidities: Diabetes

• Adult vs. Child

• Living status: community vs., hospital, jail, shelter etc.
  • Other cases of TB reported, pattern of spread?
Adult: Reactivation Pulmonary TB

More common presentation in immunocompetent, HIV-neg. adults

Typical Symptoms - nonspecific:

- Dry, NP cough
- Hemoptysis
- Hoarseness
- Chest pain, pleurisy
- Dyspnea
- Constitutional symptoms: (malaise, feverish, sweats, weight loss)

Predilection for upper lung zones
CXR of Pulmonary TB Disease – Reactivation
Typically in Immunocompetent Adult

- **Location:** apical and/or posterior segment of RUL; apicoposterior segment of LUL or superior segment of either lower lobe
- **Infiltrate:** fibronodular, irregular with variable coalescence and cavitation
- **Cavities:** thick, moderately irregular walls
- **Volume loss:** progressive, can be rapid

**PLEASE NOTE:**
- **“Atypical”** lung findings in approx. 1/3 patients
- **Infiltrates can appear anywhere!!**
Presentation of TB Commonly Different in HIV / Immunosuppressed Pts

TB in an immunosuppressed patient

• Can be more of a “Systemic” illness

• More extrapulmonary involvement - up to 60% cases in HIV (+) pts:

  • More atypical presentations:
    • Diarrhea
    • Hepatosplenomegaly
    • Lymphadenopathy
Pulmonary TB with immunosuppression

- CXR findings - advanced HIV/AIDS (↑variable):
  - Confluent pneumonia
  - Lower zone infiltrates
  - Hilar / paratracheal adenopathy
  - Risk for Miliary spread / pattern

- “Primary Complex pattern” common with HIV/AIDS
  - Hilar adenopathy
  - Lower / mid lung infiltrates, unilateral
  - Pleural effusions
A global view of HIV infection
39.5 million people [34.1-47.1] living with HIV in 2006

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Data Source: WHO/UNAIDS
Map Production: Public Health Mapping and GIS
Communicable Diseases (CDS)
World Health Organization
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Tuberculin skin testing & HIV infection

• Reactivity of TST decreases as CD4 count decreases:
  • 15-25% false-neg. (-) in normal host (HIV neg.) with pulmonary TB (disease)
  • 50-90% false-neg. (-) in pts. with early HIV (no other OI’s)
  • 80-100% false-neg. (-) in pts. with advanced HIV

• In USA/UK, consider preventative INH therapy for HIV & immunosupp. pts regardless of TST for:
  • Close contacts to “infectious” cases
Risk of tuberculosis after untreated MTB infection

• Normal adults: 5-10% in lifetime
• HIV infected adults: 7-10% per year
• Older children: 5-10% (delayed)
• Infants: 40% within first 2 years

Infants and HIV patients at highest risk of TB disease
Clinical Presentations of Pediatric TB is NOT the same as with Adult TB

Distinction between TB infection and disease more clear in adult than in children / infants

- **Adult**: disease usually follows reactivation of previously dormant organisms and almost always have
  - Significant symptoms and CXR abnormalities.

- **Infants & children**: disease more often complicates initial “primary” infection
  - CXR findings can be subtle and symptoms are lacking in up to 50% children
  - Typically lower MTB burden - Less contagious; AFB smear commonly negative
Manifestations of Primary Pulmonary TB in children

- Hilar or mediastinal adenopathy
- Paucity of SSx relative to CXR
- Usually no cavities
2nd - Define the Syndrome the “-itis”
Define the Syndrome – the “itis”

- Pneumonitis – clinical sx’s or via CXR?
- Lymphadenitis, meningitis / cerebritis, pericarditis, hepatitis, peritonitis, pyelonephritis, etc.

Is the syndrome consistent with TB?

Is this new vs. recurrent TB?

Is drug-resistant TB possible? Prev trx?

Treatment approaches based the syndrome – not all the same
Considerations Depending upon the Type of Tuberculosis – “The Syndrome”

• **Infectiousness** to others – more of a concern with pulmonary disease

• Role of **Steroids** – meningeal and pericardial disease

• **Extensions** in duration of therapy – e.g. bone/joint (vertebral), CNS TB

• Presentations of **IRIS**
Miliary Tuberculosis

Granulomas from Mycobacterium tuberculosis
Lymphatic TB (Scrofula)
Pleural TB
Pleural TB – Advanced, calcified
Genitourinary TB
Pericardial TB
Chest X-ray Residuals of Primary Infection

Apical fibronodular scarring due to inflammation after bacillemia; known eponymically as *Simon's focus*.

Dense, calcified hilar node; with Ghon lesion, constitutes *Ranke's complex*.

Site of primary pulmonary infection; *Ghon lesion*.
Risk of Tuberculosis (disease) after untreated MTB infection

• Normal adults: 5-10% *in lifetime*
• HIV infected adults: 7-10% *per year*
• Older children: 5-10% (delayed)
• *Infants: 40% in 1-2 years*
3rd - Define the Microbiology

Either confirmed or suspected
Defining the Microbiology
Questions to consider:

1. Is it Infection vs. Non-infection-driven inflammation?

If infection present:

2. Is the Infection mycobacterial, bacterial, fungal, viral, protozoan, helminthiic?

- AFB staining, KOH, Gram staining on sputum smear or tissue?
  • Easily done in most laboratories; rapid results
Defining the Microbiology

3. Is the infection caused by *M. tuberculosis* vs. Non TB mycobacteria (NTM)?
   - Presumptive TB in endemic regions and by clinical presentation
   - Mycobacteria cultures, probes and PCR usually not available in 3rd world setting

4. Drug susceptible vs. resistance (single drug, MDR, XDR-TB)
   - Often based on previous treatment and response (or lack of response)

** Note: MTB may not be confirmed when starting therapy
Diagnostic Considerations in HIV (+) pts with MTB Disease

- Sputum smear and culture somewhat less sensitive in HIV (+) pts
  - May be 2° to decrease tendency for cavitory disease (less organism load)
  - May need to collect additional sputum samples; consider gastric and urine samples – if resources available
- In USA - consider MTB probes on smear negative sputum samples
4th - Define the Treatment
# Anti-Tuberculosis Drugs

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<td>• Isoniazid</td>
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<td>• Rifamycin</td>
<td>• Streptomycin; Amikacin &amp; Kanamycin</td>
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<td>• Cycloserine (and Terizidone)</td>
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<td>• Para-Aminosalicylic Acid (PAS)</td>
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Treatment of Pulmonary TB
Programs may vary by country

Option 1:
Initiation: INH, RFP, PZA, EMB daily x 8wks
Continuation: INH, RFP daily or 2-3x/wk DOT x 16 wks

Option 2:
Initiation: INH, RFP, PZA, EMB daily x 2 wks, then
INH, RFP, PZA, EMB 2x/wk DOT x 6 wks
Continuation: INH, RFP 2x/wk x 16 wks DOT

Option 3:
INH, RFP, PZA, EMB 3x/wk DOT x 6 months

Special circumstances:

a) Pts. who cannot take PZA: INH, RFP x 9 months
   • EMB or SM added initially unless ↓ resist. Risk 2x/wk dosing can be given after 1-2 mo. if isolate sensitive

b) Pregnancy: INH, RFP, EMB x 9 months (PZA avoided in USA)
Practical Aspects of TB Management

- 1st line drugs should be administered together
  - Do not allow for “split dosing” - lower efficacy with decreased peak concentration
- Use “fixed dose” combination drugs when DOT not possible
  - Rifamate = INH + rifampin; Rifater = INH + rifampin + PZA
- GI upset common early in treatment (r/o hepatitis)
  - Administration with food preferable rather than split dosing for GI discomfort
DOTS – the WHO Recommended TB Control Strategy

1. Commitment of governments to a national tuberculosis program

2. Detection of cases through sputum smear microscopy of patients with suspected tuberculosis

3. Standardized short course chemotherapy with the 1st line drugs (isoniazid, rifampin, pyrazinamide, and ethambutol / streptomycin) given under direct observation

4. Regular, uninterrupted supply of all essential antituberculosis drugs

5. A monitoring system for program supervision and accountability

Sterling. BMJ 2003;326:574
DOTS additional points

• Mycobacterial cultures and drug susceptibility testing are not required
  • Drug resistance not detected
• Treatment is started on the basis of symptoms or a positive smear
• Second line drugs are not used
• Three categories of treatment regimens exist; all are directly observed
DOTS Performance

- Through 2005, DOTS implemented in 182 countries
  - Covering 77% of global population
  - Global TB case detection increased from 11% in 1995 to 45% in 2003
- High acceptance of DOTS in India, China
- Poor DOTS application in Africa
  - WHO focusing efforts on the Africa continent accepting DOTS
  - Effort to combine TB and HIV screening

Sharma. Lancet 2006; 367:951
MDR-TB: the *DOTS–Plus* Program

- Mycobacterial cultures and drug susceptibility testing performed – if available
- Second line antituberculosis drugs are used
  - The regimen includes ≥ 2 active drugs, including 1 IV agent for ≥ 6 months
  - Total duration of treatment 18-24 months
  - Treatment is directly observed
- Treatment regimen is either:
  - Individualized according to Abx susceptibility test results
  - Given as a standardized regimen to patients who fail supervised re-treatment (e.g. when culture and drug susceptibility testing not performed)

Bathamley. Eur Respir Jour 2008;32:1023
The End
Questions?