Management of MDRTB

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Have a nice flight, sir.

Ha! He missed the TB.
It began here....
Management strategies evolved.
And evolved
Till now...
Today

- Global and Myanmar
- Principles of treatment
- MDRTB, XDRTB and TDRTB
MDRTB globally

• Globally, 5% of TB cases are estimated to have MDR-TB.
  • Primary TB - an estimated 3.5%
  • Secondary TB - an estimated 20.5%

• Levels of drug resistance among new cases are <3% in 108 (75%) of the 144 countries with drug resistance surveillance data

• Eastern European and central Asian countries have the highest levels of MDR-TB
  • Primary TB - an estimated 35%
  • Secondary TB - an estimated 75%
Epidemic of MDRTB
Percentage of new cases with MDRTB 1994-2012

Most recent data shown
Percentage of previously treated TB cases with MDRTB 1994-2012

Most recent data shown
MDR-TB treatment outcomes of Myanmar (July 2009 to September 2011) (N=303)

- Cured: 71%
- Died: 17.3%
- Defaulted: 10.3%
- Failed: 1%
- Refused Tx: 0.3%
Countries that have notified at least 1 patient of XDRTB by 2012
Estimated HIV prevalence in TB
Estimated TB mortality rates in non-HIV TB
Number of XDRTB started on treatment
Why has MDRTB occurred?
Current drug activity
Xpert MTB/RIF capacity

1. Sputum liquefaction and inactivation with 2:1 sample reagent
2. Transfer of 2 ml material into test cartridge
3. Cartridge inserted into MTB-RIF test platform (end of hands-on work)
4. Sample automatically filtered and washed
5. Ultrasonic lysis of filter-captured organisms to release DNA
6. DNA molecules mixed with dry PCR reagents
7. Seminested real-time amplification and detection in integrated reaction tube
8. Printable test result

Time to result, 1 hour 45 minutes
Other resistance will develop - genes associated with resistant MTB

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Kat G, Inh A, Kas A</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>rpo B</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>emb B</td>
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<tr>
<td>Streptomycin</td>
<td>rps L</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>pnc A</td>
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<tr>
<td>Fluoroquinolones</td>
<td>gyr A</td>
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</table>
Principles of MDR+ treatment

• Promptly suspect drug-resistant (DR) TB and do full TB screen AND initiate appropriate therapy early if likely

• Regimens should be based on the history of drugs taken by the patient

• Assume R if therapy given previously

• R prevalence in country of birth/residence MUST be taken into consideration

• If the evidence for drug sensitivity is unclear DO NOT rely on it being fully active
Basic rules..

• Give AT LEAST 4 active drugs (= 6-7 drugs usually because uncertain) while awaiting sensitivities

• Drugs are chosen with a stepwise selection process

• The duration of the intensive phase of treatment (when an injectable drug is given) should be at least 6 months (or 4 months after culture conversion).

• The continuation phase (without the injectable drug) should last until 18 months after culture conversion
Principles of MDR+ treatment

- When possible, give PZA, EMB, and MOX once per day as thought high peaks may be more efficacious.
- PRO, CYC, PAS usually split because decreases AE
- Monitor levels of AMIK/KAN as may be needed for up to six months
- The minimum length of treatment for XDR-TB will be 18 months after culture conversion
- PZA can be used for full course of treatment
- Consider surgery if localised disease
When to include..

- Group 1 drugs:
  - INH
  - Rifampicin
  - Pyrazinamide
  - Ethambutol
FIRST - 1\textsuperscript{st} line drugs

- Most potent and best tolerated
- MUST be used if MDRTB suspected but unconfirmed
- MUST not rely on and assume resistance is present and therefore add in additional drugs
- If RIF resistance then rifabutin will also be resistant in 85%
- If INH resistant then may be PRO/ETH resistant
When to include/which one..

- Group 2 drugs - injectables:
  - Streptomycin
  - Kanamycin
  - Amikacin
  - Capreomycin
SECOND - INJECTABLE

• All patients with possible MDR+ TB MUST receive an injectable agent
• All patients SHOULD receive AMIK or KAN if susceptibility is documented or presumed
• There are high rates of streptomycin resistance in DR-TB patients
• AMIK/KAN have low otoxicity rates but get BL audiometry
• AMIK/KAN usually X-resistant
• If an isolate is resistant to SM/AMIK/KAN, capreomycin should be used
When to include/which one..

• Group 3 drugs - fluoroquinolones
  • Ciprofloxacin
  • Ofloxacin
  • Levofloxacin (dose)
  • Moxifloxacin
THIRD – Quinolone

- All patients should receive quinolone unless R very likely.
- Ciprofloxacin should NO longer be used to treat TB
- Most potent: MOX = GAT > LEV > OFL
- MOX/LEVO may have activity against CIP/OFL R strains
- GAT is associated with SERIOUS glucose imbalance and should NOT be used if MOX S
- In fact GAT has been discontinued COMPLETELY
When to include/which one.

• Group 4 drugs – mixture of actions
  • Prothionamide
  • Ethionamide
  • Cycloserine
  • PAS
FOURTH – Older 2\textsuperscript{nd} line agents

• Generally more side effects & bacteriostatic
• Ethionamide = prothionamide for activity
• If ETH resistance then PRO resistant despite disparate sensitivity results
• ETH/PRO resistant then X-reactivity with INH resistance so also cannot rely on as fully active drug
• CYC + PRO or PAS common combination (check TSH)
• All neurotoxic – give high dose PYR
When to include/which one..

• Group 5 drugs – very limited data/poor activity
  • Clofazimine
  • Co-amoxiclav
  • Linezolid
  • Meropenem
  • Clarithromycycin
FIFTH – desperate measures

• Efficacy often uncertain
  • Imipenem/Meropenem
  • Co-Amoxiclav
  • Linezolid

• Or weak and bacteriostatic
  • Clofazamine
  • Azithromycin/clarithromycin
  • Thioacetazone (NOT IN HIV)

• Expensive & may require IV admin
• High-dose INH can be considered if low level R
Evolution of TB drug resistance

- **Drug susceptible TB**
  - Sensitive
  - Treatable with 4 drug regimen

- **MDR-TB 1990**
  - Resistance to H&R
  - Treatable with 2nd line drugs

- **XDR-TB 2006**
  - Resistance to 2nd line drugs
  - Treatment options seriously restricted

- **TDRTB 2008**
  - Resistance to all available drugs
  - No treatment options
Extensively drug resistant TB (XDR-TB)

• Defined as resistance to:
  • At least rifampicin and isoniazid (=MDR) of the first line drugs
  • Plus
  • Resistance to any fluoroquinolone
  • Plus
  • Resistance to one or more injectable second line drugs (capreomycin, kanamycin, amikacin)
Myanmar MDR-TB Regimen

First-line Group 1
First line oral
- Isoniazid
- Rifampicin
- Ethambutol
- Pyrazinamide

Second-line Group 2
Injectable
- Streptomycin
- Kanamycin
- Amikacin
- Capreomycin

Group 3
Quinolone
- Ciprofloxacin
- Ofloxacin
- Levofloxacin
- Moxifloxacin

Group 4
Bacteriostatic 2nd-line drugs
- Ethionamide
- Cycloserine
- PAS

Group 5
Limited data of efficacy
- Clofazimine
- Linezolid
- AMX/CLV
- High dose INH

6 Am-Lfx-Eto-Cs-Z / 18 Lfx-Eto-Cs-Z
Begin with any first line agents to which the isolate is susceptible.

Add a fluoroquinolone and an injectable drug based on susceptibilities.

**First-line drugs**
- Pyrazinamide
- Ethambutol

**Fluoroquinolones**
- Levofloxacin
- Moxifloxacin
- Ofloxacin

**Injectable agents**
- Amikacin
- Capreomycin
- Streptomycin
- Kanamycin
Step 1

Begin with any First line agents to Which the isolate is Susceptible

Add a Fluoroquinolone And an injectable Drug based on susceptibilities

First-line drugs
- Pyrazinamide
- Ethambutol

PLUS

Fluoroquinolones
- Levofloxacin
- Moxifloxacin
- Ofloxacin

PLUS

Injectable agents
- Amikacin
- Capreomycin
- Streptomycin
- Kanamycin

Step 2

Add 2nd line drugs until you have 4-6 drugs to which isolate is susceptible (which have not been used previously)

Pick one or more of these

Oral second line drugs
- Cycloserine
- Ethionamide/ prothionamide
- PAS

PLUS
Step 1

Use any available

First-line drugs
- Pyrazinamide
- Ethambutol

PLUS

Fluoroquinolones
- Levofloxacin
- Moxifloxacin
- Ofloxacin

PLUS

Injectable agents
- Amikacin
- Capreomycin
- Streptomycin
- Kanamycin

Step 2

Pick one or more of these

Oral second line drugs
- Cycloserine
- Ethionamide
- PAS

PLUS

Step 3

Consider use of these

Third line drugs
- Imipenem
- Linezolid
- Macrolides
- Amoxicillin/Clavulanic A
- High-dose INH
- Meropenem
- Clofazamine
- Thiacetazone

If there are not 4-6 drugs available consider 3rd line in consult with MDRTB experts
### Step 3

**Consider use of these**

**Third line drugs**
- Imipenem
- Linezolid
- Macrolides
- Amoxicillin/Clavulanic A
- High-dose INH
- Meropenem
- Clofazamine
- Thiacetazone

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### Step 4

**Consider use of these**

**Expanded access drugs**
- TMC 207 – weekly dosing
- OPC-67683 – faster TB clearance than INH/EMB
- PA-824 – activity against MDRTB

HELP
Rich or poor, TDR-TB is a threat to everybody

Ones’ 10L with people infected by TB in 2011, and 2 half have died so far

TB scourge acquires a new dimension: Emergence of Totally Drug-Resistant (TDR) Tuberculosis in India
TDR-TB

- Resistant to all 2\textsuperscript{nd} line drugs
- Culture and smear remain +ve after 18m f 2\textsuperscript{nd} line therapy
- Described mainly in India but also elsewhere
New drugs - life cycle and drug activity
Public Health Law pre - 6 April 2010

• 1984 Act and TB:
• Section 35: compulsory medical examination
• Section 37: power to remove to hospital a person with a notifiable disease
• Section 38: power to detain in hospital a person with a notifiable disease
• Failure to comply leads to a level 1 fine = £100
Management of MDR-TB
Thank you

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