Drug Resistant Tuberculosis: Pearls and other Considerations

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Disclosure

• None
Objectives

• Describe factors responsible for delayed response and/or treatment failure
• Describe treatment and management strategies for multidrug-resistant TB
• Define drug resistant TB
• Review the epidemiology and pathogenesis of MDR TB
• Review MDR TB treatment principles and new drugs
TB Therapy Drug Resistance Definitions

• **Poly-resistant TB**
  - Resistance to >1 drug
    - but not isoniazid and rifampin

• **Multi-Drug Resistant (MDR) TB**
  - Resistance to at least isoniazid and rifampin

• **Extensively Drug Resistant (XDR) TB**
  - MDR (INH & rifampin) + plus:
    - Resistance to a fluoroquinolone + plus:
    - Resistant to an injectable (kanamycin, streptomycin, amikacin)
MDR-TB Prevalence in the United States

- MDR TB cases
  - Totals
    - 1.4% (96 cases) in 2013
    - 1.3% (91 cases) in 2014

- Foreign born:
  - 31% (149 of 484) in 1993
  - 88% (80 of 91) in 2014.

Risk Factors for Drug-resistant TB

1. Previous TB therapy – especially with
   • Prior non-DOT based therapy
   • Patient non-compliance
   • Incomplete treatment, lack of documentation
   • Non-CDC, non-WHO endorsed standard regimens

   • Acknowledging for a patient – *TB therapy is difficult*
     • Prolonged treatment program
     • Many pills
     • Common drug intolerances

2. Contact with a patient with drug-resistant TB

Seaworth B. IDCNA Vol 16, No. 1, 73-105. March 2002
3. Persons from countries with higher rates of drug-resistant/MDR TB cases

More than 6% of new TB cases are MDR-TB in these locations:
- Azerbaijan, Baku City (22.3%)
- Kazakhstan (20%)
- Republic of Moldova (19.4%)
- Ukraine, Donetsk (16%)
- Russian Federation, Tomsk (15%)
- Uzbekistan, Tashkent (14.8%)
- Estonia (13.3%)
- Russian Federation, Mary El (12.5%)
- Latvia (10.8%)
- Lithuania (9.8%)
- Armenia (9.4%)
- Russian Federation, Orel (8.8%)
- China, Inner Mongolia (7.3%)
- China, Heilongjiang (7.2%)
- Georgia (6.8%)

Risk Factors for Drug-resistant TB - cont’d

4. Lack of response while on therapy:
   a. Clinical or radiologic progression
   b. MTB cultures remain (+) after 3 mo.

5. International TB endemic regions:
   a. Prolonged hospitalization (TB endemic regions / international)
   b. HIV co-infection (TB endemic regions / international)
   c. Lack of sustainable drug availability to patients through inadequate pharmaceutical supply chain and/or failure to provide free treatment

6. Overuse of fluoroquinolones in other infection syndromes that propagates fluoroquinolone-resistant TB (Respir inf., UTI)

7. Delays in diagnosing TB (inappropriate abx exposure)

Diagnosing Drug-Resistant TB

• Conventional Growth-based Drug-Susceptibility Testing (DST)
  • Solid media (e.g. agar proportion method)
    • ~3-4 weeks
  • Liquid broth system – require:
    • 1-2 weeks after setting up for DST
    • > 4 weeks from time of specimen receipt in lab
MTB - Solid Media
Drug Resistance Testing

- Agar proportion is the current gold standard for all drugs except pyrazinamide
  - not rapid (14-21 days)
  - labor-intensive, technically complex
  - no FDA-cleared, commercially-available kit

Organism is resistant to drug A in the upper right compartment (>1% of inoculum shown by upper left control quadrant is growing in presence of drug). Organism is susceptible to drugs B & C in the lower compartments. Control quadrant in upper left contains no drugs.
Rapid Broth Susceptibility Testing for MTB
FDA-cleared, semi-automated with MGIT or VersaTREK systems

Compare growth rates in bottles/tubes +/- critical concentrations of drug

CDC goal is results for first-line drugs reported within 15-30 days after receipt of the specimen
**M. tuberculosis** complex resistant isolates

- If the isolate is resistant to any agent – Consider:
  - Confirming resistance by 2\textsuperscript{nd} method or 2\textsuperscript{nd} lab
  - Initiating testing of secondary agents to avoid delays

- If the isolate is resistant to only PZA consider:
  - Mycobacterium speciation
    - *M. bovis* is mono-PZA-resistant
      (most isolates of *M. tuberculosis* are PZA-susceptible)
  - Sequencing for *pncA* gene mutation
Pyrazinamide resistance – Sequencing of \textit{pncA}

- Broth DST of PZA can overcall resistance
  - MGIT (up to 68\% false resistance)
    - Piersimoni C et al., 2013, J Clin Microbiol. 51:291-4
    - Simons SO et al., 2012, J Clin Microbiol. 50: 428-34
  - VersaTREK (~70\% false resistance)
    - Simner PS et al., manuscript in preparation

- Sequencing of the \textit{pncA} gene from culture isolates can help
  - Mutations associated with resistance occur throughout this 558bp gene so sequence entire gene and promoter region
  - Performed by CDC, Mayo or the NYS DOH Wadsworth Center
Xpert MTB/RIF and Rifampin resistance

- Target is rpoB: gene encoding beta subunit of bacterial RNA polymerase
- Mutations in an 81bp region of the rpoB gene are responsible for ~96% of RIF resistance in Mtb;
- also predicts MDR TB since the majority of RIF-resistant isolates will also be INH-resistant
- Some false positive RIF resistance with Xpert
  - PPV is lower in low prevalence settings
  - CDC recommends reporting Xpert RIF-R as a preliminary result pending confirmation with sequencing; growth-base DST is still required
Molecular resistance testing for MTB at the CDC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Locus/Loci examined</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>rifampin</td>
<td>rpoB</td>
<td>97.1</td>
<td>97.4</td>
</tr>
<tr>
<td>isoniazid</td>
<td>inhA &amp; katG</td>
<td>86.0</td>
<td>99.1</td>
</tr>
<tr>
<td>fluoroquinolones</td>
<td>gyrA</td>
<td>79.0</td>
<td>99.6</td>
</tr>
<tr>
<td>kanamycin</td>
<td>rrs &amp; eis</td>
<td>86.7</td>
<td>99.6</td>
</tr>
<tr>
<td>amikacin</td>
<td>rrs</td>
<td>90.0</td>
<td>98.4</td>
</tr>
<tr>
<td>capreomycin</td>
<td>rrs &amp; tlyA</td>
<td>55.2</td>
<td>91.0</td>
</tr>
<tr>
<td>ethambutol</td>
<td>embB</td>
<td>78.8</td>
<td>94.3</td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>pncA</td>
<td>86.0</td>
<td>95.9</td>
</tr>
</tbody>
</table>

Second Line TB Medications

- Less effective
- More expensive
- More toxic
Second Line TB Medications

- Fluoroquinolones
  - Moxifloxacin, Levofloxacin
- Aminoglycosides
  - Streptomycin, Amikacin & Kanamycin
- Capreomycin
- Linezolid
- Ethionamide
- Cycloserine
- Para-Aminosalicylic Acid (PAS)
New and other novel drugs for use (MDR- & XDR-TB)

→ a few other “arrows in the quiver”

New drugs

• Bedaquiline
• Delamanid

Older / less active

• Clofazimine
• Carbapenem/clavulanate
Principles of Drug-Resistant TB Management

• A single new drug should never be added to a failing regimen

• MDR/XDR treatment regimens are based on expert opinion, not clinical trials

• Several regimens exist based on different sites/guidelines
  • Drug Resistant TB, Survival Guide; Francis Curry TB Center / UCSF
  • New York City Dept. of Health, Clinical policies and protocols. *Bureau of Tuberculosis Control*, 2008
  • WHO Guidelines for the programmatic management of drug-resistant tuberculosis.
  • Union 2013: Int J Tuberc Lung Dis 2010; 14: 382–390
Treatment options, regimens and basic approaches for drug-resistant TB
Monoresistance – Isoniazid

- Rifampin, PZA, Ethambutol x 6-9 months

- Considerations for more extensive disease:
  - Treat 9 months
  - Add fluoroquinolone (moxifloxacin, levofloxacin) or injectable (e.g. amikacin)

- Examples: ND, Wisc. TB outbreaks
Monoresistance - Rifampin

NYCHD

• Option 1: Induction - INH/PZA/EMB/inj/FQ x 2-3 mo. after culture conversion
  Continuation: INH/PZA/EMB+-/FQ x 12-14 mo. (18 total mo. preferred)

• Option 2: Induction - INH/PZA/SM+-/-EMB 2-3 mo. after culture conversion
  Continuation - INH/PZA/SM+-/-EMB x 3-5 mo. (9 mo. total)

Curry/UCSF

• Option 1: INH/EMB/PZA/FQ x 2 mo. then INH/EMB/FQ to complete 12-18 mo.

• Option 2: Option 1 +injectable for first 2 mo.

• Option 3: INH/PZA/SM( or other inj) x 9 mo.

CDC/ATS

• INH/PZA/EMB x 12-18 mo. (consider + FQ or Inj. if extensive disease)

• INH/PZA/SM x 9 mo.
Mono resistance to EMB, PZA, or SM

- Little impact on treatment efficacy
- Loss of EMB/SM does not change efficacy or treatment duration
- Loss of PZA: extend duration with INH/RIF by 3 mo. (9 mo. total)
Poly-resistant TB

- Resistance to >1 TB drug, but not INH & RIF
- Treatment should include as many 1\textsuperscript{st} line drugs as possible + FQ and in some cases injectable
  - Composition and duration of therapy depended upon specific drug resistance profile
Approach to MDR-TB Management

• Include any active 1\textsuperscript{st} line drug, then add FQ and injectable (amikacin/kanamycin/SM/capreomycin)

• Add oral 2\textsuperscript{nd} line drugs to compose 4-6 drug regimen
  • Note: When restarting or revising therapy, always try to use at least 3 previously unused drugs to which there is demonstrated in vitro susceptibility (1 should be injectable)

• If there are not 4-6 active drugs available, then consider 3\textsuperscript{rd} line drugs (BDQ, clofazimine, carbapenem/clavulanate, high dose-INH)

• Surgery can be considered with complex cavitary disease or slow clinical response
Additional considerations

- “Low level” INH resistance
  - INH resistance at MIC 0.2 mg/L, but active at MIC 1.0 mg/L
  - Consideration for 900 mg INH BIW/TIW weekly
  - Would not count INH as an “active” drug in regimen

- ~10-15 % rifampin resistant MTB may be susceptible to rifabutin (in vitro)
  - Rifabutin can be considered, but would not count as active drug
Composing an Effective Drug Treatment Program for MDR-TB

**STEP 1**

Begin with any first-line agents to which the isolate is susceptible

Add a fluoroquinolone and an injectable drug based on susceptibilities

<table>
<thead>
<tr>
<th>First-line drugs</th>
<th>Fluoroquinolones</th>
<th>Injectable agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrazinamide</td>
<td>Levofloxacin</td>
<td>Amikacin</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Moxifloxacin</td>
<td>Capreomycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Streptomycin</td>
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<td></td>
<td></td>
<td>Kanamycin</td>
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Challenging
Composing an Effective Drug Treatment Program for MDR-TB

STEP 2

Add second-line drugs until you have 4–6 drugs (optimally at least 5) to which the isolate is susceptible (and preferably which have not been used to treat the patient previously)

Pick one or more of these

Oral second-line drugs

Cyclosorine
Ethionamide
PAS
Linezolid

More challenging

Composing an Effective Drug Treatment Program for MDR-TB

**STEP 3**

If there are not 4–6 drugs available in the above categories, consider third-line drugs in consultation with an MDR-TB expert.

### Consider use of these

<table>
<thead>
<tr>
<th>Third-line drugs</th>
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<tbody>
<tr>
<td>Bedaquiline</td>
</tr>
<tr>
<td>Delamanid[^4]</td>
</tr>
<tr>
<td>Clofazimine</td>
</tr>
<tr>
<td>Imipenem</td>
</tr>
<tr>
<td>Meropenem/Clavulanate</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanate</td>
</tr>
<tr>
<td>Clarithromycin</td>
</tr>
<tr>
<td>High-dose INH</td>
</tr>
</tbody>
</table>

[^4]: Most challenging
Extremely Drug resistant TB (XDR-TB)

- Resistance profile:
  - INH & rifampin = MDR strain) and:
  - A fluoroquinolone and:
  - One of injectables (kanamycin, streptomycin, amikacin)

- Similar approach to MDR TB but may need to use 3rd line drugs

- Surgery should strongly be considered

Other consideration:

• Delays in starting expanded therapy until DST available is occasionally considered:
  • A Judgement call – based on:
    • Stable disease in immunocompetent host
    • No vulnerable contacts at home
    • MDR or XDR-TB case when DST pending and construction of active regimen is in doubt
    • Patient is NOT a flight risk
The role of surgical resection

• Favorable results reported with resectional lung surgery in patients with MDR-TB

• Resective surgery considered for:
  • Patients with high-grade drug resistance (limited drug options)
  • Relatively localized lung disease
  • Lack of initial response

• NJMC, Denver with high experience
  • Dedicated surgeon / surgical team (Dr. M Pomeranz)
  • Pneumonectomy or lobectomy

Pomerantz et al. J of Thorac Cardiovasc Surg. 2001;121(3) 448-53
The role of surgical resection - timing

• When surgical resection is favored
  • e.g. cavitary disease, necrotic / avascular lung tissue

• Optimal timing for surgery can be difficult to determine

• Consider delaying surgery for a few months after start of combination drug therapy
  • Lower TB organism burden
  • Enhanced patient nutrition / weight gain
  • Improved postoperative tissue healing

Pomerantz et al. J of Thorac Cardiovasc Surg. 2001;121(3) 448-53
Successful MDR-TB outcomes not necessarily limited to surgical resection

- Inclusion of better 2\textsuperscript{nd} line drugs - e.g.:
  - Newer fluoroquinolones (Moxifloxacin / levofloxacin); Injectables (prolonged periods of time); Linezolid
  - Even better when PZA or EMB remain active

- Medical management a consideration when an active combination drug regimen can be composed
  - Inclusion of $\geq 5$ drugs with in vitro activity

- Pushing serum levels to upper limits of therapeutic window (roles for TDM)

Principles for MDR and XDR-TB management

• Providers need to be comfortable asking for assistance
  • Most providers are not overly experienced in drug-resistant TB management
• Our Mayo TB Center practice utilizes Region-5 MDR-TB Team consensus with more complex TB drug-resistant cases
• Such patients may not have a “2nd chance” for treatment success
Principles for MDR and XDR-TB management - II

Co. and State Public health departments need to be involved for case management:

- Directly observed therapy (DOT) is crucial
- Heightened monitoring for treatment response and drug toxicities
- Contact investigations
Pearls of Select 2nd-line TB Drugs
Aminoglycoside – associated Ototoxicity

Consider:
- Monthly audiology testing
- Monthly office-based vestibular testing

Note – CN8 toxicity is **irreversible**
GI Intolerance: Nausea/Vomiting

Especially common with:

- Ethionamide
- PAS
- Clofazimine
- **Any start-up program with many pills**
Endocrine problems:

Including:

- Hypothyroidism
- Hypoglycemia
- Other (esp. with ETA)
  - Gynecomastia, hair loss, menstrual irregularity

Especially common with:

- Ethionamide
- PAS
Dose Escalation Strategies: Ethionamide, Cycloserine, PAS

- Relevant Drugs:
  - Ethionamide
  - Cycloserine
  - Para-aminosalicylic acid

- Purpose:
  - Improved patient tolerance (gradual dose escalation)
  - More precise dosing for acceptable serum drug levels
Dose Escalation Strategies: Ethionamide, Cycloserine, PAS

• Ethionamide & cycloserine
  • Start with 250 mg daily x a few days
  • Increase to 250 mg bid x a few days
    • Check serum level
  • Increase to 250 mg/qAM and 500 mg q/PM

• PAS (Paser granules, sachet packets)
  • Start with 2 gm bid x a few days
  • Increase to 2 gm/qAM and 4 gm qPM x few days
  • Increase to 4 gm bid
    • Check serum level
Linezolid usage

• An oxazolidinone

• Toxicities – significant (> 50%) and include:
  • Neuropathies - peripheral & optic
  • Myelosuppression
  • Hyperlactatemia
  • Risk of serotonin syndrome with SSRIs

• Bacteriostatic; binds rRNA; inhibits protein synthesis

• Dosing: 600 mg daily successfully used

Linezolid usage

• Dosing of 300 mg /d can be effective for MDR-TB
  • Possibly lower adverse effects compared to 600 mg daily or bid

• 300 mg/d dosing can achieve serum concentrations greater than MIC values (≤0.25 mg/L)

• Favorable penetration into pulmonary & soft tissues

Bedaquiline (Situro) – a new diarylquinoline

- Inhibits mycobacterial ATP synthase
- Spectrum of activity includes: *M. tuberculosis* and select NTM (including MAC)
- Indications: treatment of pulmonary MDR-TB in pts ≥ 18 yo when optimal TB drug program cannot be constructed
- BDQ dosing: 400 mg daily x 2 weeks, then 200 mg TIW x 22 weeks – then off
Bedaquiline – concerns and limitations

- Increased risk of death (11.4% vs. 2.5% in comparator group)
- Elevated QTc (although not felt to be a major risk by CDC group meeting)
  - May be additive with other QTc prolonging drugs - *caution by FDA
- Higher hepatic adverse reactions
- Drug interactions via Hepatic CYP 3A
  - M2 is major metabolite (4-6x less potent)
  - BDQ does not increase or decrease 3A4 activity
  - Rifampin will decrease BDQ levels (via accelerated 3A4 metabolism)
- Limited data in HIV co-infected patients

CDC RTMCC meeting January 14-15, 2013
New drugs on the horizon

- OPC – 67683 (Delamanid)
  - Nitro dihydro imidazooxazole
- PA-824; nitroimidazole
  - Combinations with PZA and moxifloxacin
- AZD 5847; oxazolidinone
Remember – the negative stigma of drug-resistant TB is not simply abroad
• Drug resistant TB can be challenging to manage
• Some things in life seem very ‘unnatural’
• But if a basset hound can actually run…….then 
  together we can eliminate drug resistant TB!

The End

Questions?