Drug Resistant TB: Prevent it Don’t make it worse

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Detroit TB Program / Wayne State University School of Medicine
Tri-State TB Intensive Workshop
Columbus, Ohio
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Disclosures

• Financial – none
• 10 medications are approved by the FDA for TB
  – INH, RIF, Rifapentine, PZA, EMB, Streptomycin, Cycloserine, Ethionamide, PAS, Bedaquiline

  – All other drugs discussed here are NOT FDA approved for TB
Objectives

• When you think TB you will think drug resistance
• When your patient has a higher than normal chance of having drug resistant TB you will know to rapidly confirm it or rule it out
• When you suspect or know that your patient has drug resistant TB you will know how to develop a treatment plan

Topics

• Introduction – uncertainties, resources, definitions
• Epidemiology / costs
• Origin of drug resistant TB – man made
• Diagnostic testing – rapid
• Building a treatment regimen
  – Mono, Poly, and Multi-Drug Resistant TB
INTRODUCTION

Introductory Remarks

• Adequate data in the form of randomized controlled trials is lacking
• Recommendations for treatment are often based on expert opinion, which can vary
• Each case has its own complexities and complications should be expected, anticipated, and discussed
• This is a moving field
  – WHO Guideline Development Group convened July 16-20, 2018 to update 2016 guidelines
The White House National Action Plan

- December 2015, 5 year plan
  - Strengthen domestic capacity to combat Multidrug-Resistant TB (MDR-TB)
  - Strengthen state & local capacity to prevent transmission of drug-resistant TB
  - Ensure that patients with drug-resistant TB receive treatment until cured

Published 2016
Represents best practice in 2015
New ATS, CDC, IDSA MDR guidelines are in process
**Definitions (1)**

- **DST**: Drug susceptibility testing
- **DS-TB**: Drug-susceptible TB
- **DR-TB**: Drug-resistant TB
- **MDR-TB**: Multidrug-resistant TB
  - Any TB resistant to at least isoniazid (INH) and rifampin (RIF)
- **Pre-XDR-TB**: Pre-extensively drug-resistant TB
  - A type of MDR-TB that is also resistant to either a fluoroquinolone or 1 of 3 injectables (amikacin, kanamycin, capreomycin)
- **XDR-TB**: Extensively drug-resistant TB
  - A type of MDR-TB that is also resistant to both a fluoroquinolone and 1 of 3 injectables (amikacin, kanamycin, capreomycin)

**Definitions (2)**

- **RR-TB**: Rifampin-resistant TB
- **MDR/RR-TB**: WHO guidelines refer to rifampin or rifampin and isoniazid resistant TB
- **Transmitted drug resistance (primary)**: TB in a person not previously treated for TB (new* TB case)
- **Acquired drug resistance (secondary)**: TB in a person previously treated for TB (previously treated* TB case)
  - New case* = < 1 month treatment
  - Previously treated* = treatment for ≥1 month
  - Resistance can be created by 1 month of inappropriate treatment
  - Primary & secondary are old terms
Definitions (3)

• Mono or isolated resistance – resistance to 1 drug
  – INH mono-resistance is common, rifampin less so
  – PZA mono-resistance suggests *M. bovis* (including BCG), or other mycobacteria (*M. canettii*)

• Poly-resistant TB – resistance to >1 drug, but not INH and RIF
Epidemiology - Global

• 490,000 cases of MDR-TB in 2016 globally
  – 110,000 additional cases of RR-TB
• 47% of the MDR/RR-TB cases were from India, China, and the Russian Federation
  – 6.2% were XDR-TB
• 4.1% new and 19% previously treated TB cases were MDR/RR
• 240,000 MDR/RR cases died
• 130,000 MDR/RR cases started treatment
  – 54% who started treatment in 2014 were successfully treated

Figures are based on the most recent year for which data have been reported, which varies among countries. Data reported before 2002 are not shown.
Epidemiology – U.S.A. 2016

• 97 cases of MDR (including 1 XDR) = 1% cases
• 78 of the MDR cases were new / primary drug-resistant
• 18 of the MDR cases had prior TB treatment
  – 1 had unknown TB history
• 89 of the MDR cases, including the XDR one, were in non-U.S. born persons
• 1.4% of all TB cases in 2016 were MDR

Primary Anti-TB Drug Resistance, United States, 1993–2016*

* As of June 21, 2017.
Note: Based on initial isolates from persons with no prior history of TB; multidrug-resistant TB (MDR-TB) is defined as resistance to at least isoniazid and rifampin.
Primary Isoniazid Resistance Among U.S.-Born versus Non-U.S.–Born Persons, United States, 1993–2016*

* As of June 21, 2017.
Note: Based on initial isolates from persons with no prior history of TB.

Primary MDR-TB, United States, 1993–2016*

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Note: Based on initial isolates from persons with no prior history of TB; multidrug-resistant TB (MDR-TB) is defined as resistance to at least isoniazid and rifampin.

November, 2017

Direct costs
DS-TB $18,000
MDR-TB $160,000
XDR-TB $513,000
First Conclusions

- Rates and numbers of MDR-TB cases are low but costs, morbidity, and mortality are staggeringly high
- Preventing or recognizing DR should be part of initial TB management
- Estimating likelihood of DR is essential to good care
  - Country of origin and residence helps determine risk
  - Persons treated previously for TB have a higher risk
- **Consider risk of resistance before initiating TB therapy**

**ORIGINS OF DRUG RESISTANT TB**

Genetic mutations. Selective pressure. Made by humans.
How TB drug resistance develops

• Mechanism: Spontaneous mutations in resistance gene
  – Single nucleotide substitutions lead to mutations in a gene, conferring resistance to a specific antibiotic
• Selective pressure
  – Inappropriate treatment => acquired DR
  – Clinical drug resistance is man-made
• Transmission to contact => transmitted DR

Adenine  Thymine  Guanine  Cytosine

• Spontaneous mutations develop as bacilli proliferate to >10^8 (100,000,000)
• Typical TB cavity contains 10^7 to 10^9 organisms
• Without selective pressure from inappropriate antibiotic use, a single bacillus will not be resistant to 2 antibiotics.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>PREVALENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISONIAZID</td>
<td>3.5 x 10^{-6}</td>
</tr>
<tr>
<td></td>
<td>0.0000035</td>
</tr>
<tr>
<td>RIFAMPIN</td>
<td>1.2 x 10^{-8}</td>
</tr>
<tr>
<td></td>
<td>0.000000012</td>
</tr>
<tr>
<td>PYRAZINAMIDE</td>
<td>1.0 x 10^{-5}</td>
</tr>
<tr>
<td></td>
<td>0.00001</td>
</tr>
</tbody>
</table>

• The prevalence of resistance to INH and Rifampin would be $3.5 \times 10^{-6} \times 1.2 \times 10^{-8} = 4.2 \times 10^{-14}$

Some Resistance Genes

- INH
  - KatG
  - inhA
  - kasA
  - 80% of resistance
- RIF
  - rpoB
  - >95% of resistance
- PZA
  - pncA
- EMB
  - embB
  - ubiA
- SM (aminocyclitol glycoside)
  - rrs
  - rpsL
- Fluoroquinolones*
  - gyrA, gyrB
- Kanamycin*, Amikacin*
  - its
- Linezolid*
  - rplC
- Ethionamide (analog INH)
  - ethA
- PAS
  - thyA
  - ribD
Creation of MDR-TB
“Previously Treated” or “Acquired”

Transmission of MDR TB
“MDR in New Case” or “Transmitted MDR”

2\textsuperscript{nd} Set of Conclusions (1)

- One should suspect resistance in those with prior treatment that was inappropriate
  - Wrong drugs, doses, regimens
  - Intermittent therapy with missed doses
  - Interrupted, erratic treatment
  - Noncompliance, no DOT, patient taking some medicines & not others
  - Possibility of malabsorption
    - Critically ill patient given oral medications
  - Bad medications

2\textsuperscript{nd} Set of Conclusions (2)

- Consider resistance most likely in these circumstances
  - Extensive cavitary disease (more organisms)
  - Poor clinical response to therapy after 2 months
  - Positive cultures after 3 months of therapy or after conversion
  - Contact with a person with resistant disease
  - Emigration from or travel to (>1 month) region with high prevalence/incidence of DR
  - HIV – higher rates of RR-TB
- Taking a good history is essential to preventing or worsening DR and for selecting drugs for treatment
2\textsuperscript{nd} Set of Conclusions (3)

- Never treat TB with a single agent
- Never add a single agent to a failing regimen (patient not improving or getting worse) unless you know the drug susceptibilities

IF YOU SUSPECT RESISTANCE
TEST FOR RESISTANCE

Contact laboratory. Work with local health department / state. Consult experts, COE.
Think resistance? Test for resistance! (1)

- Conventional, growth-based DST is a gold standard, but
  - Slow
  - Growth detection and identification takes several weeks; DST an additional 1-3 weeks
- DST for 1st line drugs (INH, RIF, EMB, PZA) should be done for
  - All new TB isolates
  - Positive cultures after 3 months of therapy
  - Positive cultures after a period of negative ones

Think resistance? Test for resistance! (2)

- DST should be done for 2o drugs for all cases of RIF resistance – treat as if this is MDR-TB
- Talk to lab to make sure appropriate testing for 2o drugs is done
Think resistance? Test for resistance! (3)

• Xpert® MTB/RIF (FDA approved) and Xpert® MTB/RIF Ultra
  – Point of care assay to detect MTB complex and mutations of the
generepoB, known to confer RIF-R
  – Does not involve gene sequencing; Molecular Beacon
  – Time to result is 1.5-2 hours
  – Ultra – better detection of MTB complex in paucibacillary specimens;
more reliable detection ofrepoBmutations that => RIF-R
  – If RIF-R is detected, confirmation should be obtained with a
sequencing-based method unless patient has clear risk
  • “Silent” mutations which don’t => resistance may be picked up (false positive)

Think resistance? Test for resistance! (4)

• Line-probe assays
• Sequencing-based assays
  – Pyrosequencing
    • California Public Health Lab
  – CDC Molecular Detection of Drug Resistance (MDDR) service
    • Sanger sequencing
  – Whole Genome Sequencing
• Communicate – local lab, public health lab, local health
department, state TB program, COE to make sure proper and
timely testing is done!
Pyrosequencing (PSQ) for XDR TB Screening

At MDL, CA Department of Public Health

Contact: Dr. Desmend (ed.desmend@cdph.ca.gov; 510-412-3781) or Grace Liu (grace.liu@cdph.ca.gov; 510-412-3929)

PSQ is a rapid screening technique for molecular detection of drug resistance. For confirmation of PSQ results, culture-based drug susceptibility testing should be performed.

Intended use
- Identification of M. tuberculosis complex (MTBC).
- Screening for resistance to INH, RIF, quinolones and injectable drugs.

Date of implementation
3-26-2012

Testing schedule
The assay is performed 3-4 times a week. If urgent, additional runs can be scheduled.

Turnaround time: 1-3 days.

Principle
The test involves two steps:
1. Use PCR to amplify the target sequences.
2. Use pyrosequencing technology to perform realtime sequencing.

The sequencer, PyroMark Q24, deposes one kind of dNTP at a time according to the order specified by the assay. If the dNTP being deposited is complementary to the first available base in the DNA template, the dNTP will anneal to the template and pyrophosphate (ppi) will be generated. The ppi will trigger a cascade of chemical reactions and result in the emission of light. The light generated is proportional to the dNTP incorporated. The identity of dNTP incorporated represents the base(s) sequenced. The sequence genes when the incorporation of dNTP complementary to the DNA template occurs will end the dispersion of dNTPs.

Specimens
- Solid media or broth (0.5-1.0 ml). Ship at room temperature or with cold packs.
- Cultures: solid media or broth (0.5-1.0 ml). Ship at room temperature or with cold packs.

Molecular targets
- INH: katG (codon 312-316), inhA promoter and clpC-oxfR intergenic region
- RIF: rpoB core region from codons 567 to 553.
- Ethambutol: embB (gene)
- PZA: pncA
- Fluoroquinolones: gyrA, gyrB, parC, parE
- Amikacin, Kanamycin, Capreomycin: rrs, eis, tlyA
- RIF: rpoB

Performance characterization

<table>
<thead>
<tr>
<th>DST results by MGIT 960 (KAN: by agar proportion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH (n=345)</td>
</tr>
<tr>
<td>0 (149)</td>
</tr>
</tbody>
</table>

**Drugs Tested**

**INH**: inhA, katG

**RIF**: rpoB

**Ethambutol**: embB

**PZA**: pncA

**Fluoroquinolones**: gyrA

**Amikacin, Kanamycin, Capreomycin**: rrs, eis, tlyA
<table>
<thead>
<tr>
<th>Gene (region) examined</th>
<th>Result</th>
<th>Interpretation (based on in-house evaluation of 850 clinical isolates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rrs (rrdA)</td>
<td>Mutated</td>
<td>Rifampin resistant; (66% of isolates in our in-house evaluation of 850 clinical isolates with this mutation are RIF-R)</td>
</tr>
<tr>
<td>fabI (promoter)</td>
<td>Mutated</td>
<td>Isolated resistance; (100% of isolates in our in-house evaluation of 850 clinical isolates with this mutation are RIF-R)</td>
</tr>
<tr>
<td>fabI (internal ORF)</td>
<td>No mutation</td>
<td></td>
</tr>
</tbody>
</table>

* A negative result (e.g., no mutation) does not rule out contributory mutations present elsewhere in the genome.

MDDR assays were developed and the performance characteristics determined by the DTBE Reference Laboratory. They have not been cleared or approved by the Food and Drug Administration.
Criteria for MDDR testing (1)

1. Increased risk for DR
   A. Born in / lived in >1 month high prevalence country
   B. Contact to someone known to or suspected to have DR
   C. Patient not responding to Rx
   D. Patient with prior Rx and relapse

2. Public or personal health consequences
   A. Congregate setting, many contacts
   B. Age <5, immune compromised
   C. Case has contacts to patients in 2B who need window prophylaxis

Criteria for MDDR testing (2)

3. Lab issues
   A. Mixed cultures unlikely to yield results
   B. AFB smear positive / culture negative
   C. Pathology specimens not sent for culture

4. Program priorities

   Our patient: from S. Africa, did charity work in very poor areas, visited many homes there.
BUILDING AN EFFECTIVE REGIMEN

General Considerations (1)

- Teamwork; consult experts
- Treatment should be daily DOT (5 days/week), not intermittent, with exceptions of
  - Injectables
  - Adjustments for renal failure (PZA, EMB)
  - Specific studied regimens
- Anticipate problems. Discuss with patient. Have monitoring plan
- When to start treatment? For our patient we waited.
General Considerations (2)

• While waiting for test results, what drugs to use?
  – Expanded empiric treatment regimen
    • Four 1st-line drugs plus 2 or more additional ones (p. 67 in Survival Guide)
    – Avoid previously used drugs
    – Consider cross-resistance (p. 76 in Survival Guide)
  • Decision to treat empirically depends on factors such as
    – How ill the patient is; how contagious
    – How long you expect it to take to get results

Mono-Resistant TB
INH

• RIF, EMB, PZA +/- later generation fluoroquinolone (Levofloxacin, Moxifloxacin, not Ciprofloxacin)
  – 6-9 months (6 months requires PZA + RIF)
  – Confirm susceptibility of fluoroquinolone
• RIF, EMB, + later generation fluoroquinolone
  – 9-12 months (9 months requires RIF)
• Daily RIF, EMB, PZA, MFX 400mg X 2 months, then weekly Rifapentine 1200 mg + MFX 400 mg for 4 months
Isolated RIF Resistance

• Usually cross resistant to Rifabutin, always to Rifapentine
• Confirm Xpert result
• Preferred regimens
  – 1. INH, EMB, PZA, later generation fluoroquinolone daily for at least 2 months
  – Then PZA can be stopped or continued
  – Duration 12-18 months or
  – 2. INH, EMB, PZA for 18 months

Isolated EMB or PZA Resistance

• EMB makes no difference
• PZA: Think *M. bovis*, including BCG, or others (*M. canettii*)
• PZA is essential for shortening Rx time to 6 months
  – INH and Rifampin for 9 months
Poly-Resistant-TB

- INH & EMB: RIF, PZA, FLQ 6-9 months
- INH & PZA: RIF, EMB, FLQ 9-12 months
- INH, EMB, & PZA: RIF, FLQ, oral 2nd-line agent, for 9-12 months with injectable for 1st 2-3 months
- RIF & EMB: INH, PZA, FLQ for 12-18 months with injectable for 1st 2-3 months
- RIF & PZA: INH, EMB, FLQ for 12-18 months with injectable for 1st 2-3 months

MDR-TB
Principles (1)

- Evidence weak. New guidelines are being developed
- Number of drugs: 4-6 effective ones, aim for 5
  - Consider 6 in an intensive phase, 4 in the continuation phase
  - Intensive phase is initial period with injectable
    • Aim for at least 6 months after culture conversion
  - Total duration
    • Aim for at least 18 months after culture conversion
- Better outcomes occur with less severe disease, rapid clinical response, susceptibility to FLQ and/or PZA
MDR-TB
Principles (2)

- Drug ramping
  - Cycloserine, Ethionamide, PAS should be started at low doses and increase over a 1-2 week period of time
- Therapeutic drug monitoring
  - Amikacin
  - Cycloserine (at full dose)
- Malabsorption
- Poor clinical response / relapse
- Drug drug interactions

Comparison between standard U.S.-based classification and the WHO classification system for anti-tuberculosis drugs

1. Linezolid often used as 2nd-line agent in U.S.
2. Not available in the U.S.
3. Amoxicillin/Clavulanate is used as a source of Clavulanate (adjunctive agent)
**Building a Treatment Regimen 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.

**Use any available**
- **First-line drugs**
  - Pyrazinamide
  - Ethambutol
- **Fluoroquinolones**
  - Levofloxacin
  - Moxifloxacin
- **Injectable agents**
  - Amikacin
  - Capreomycin
  - Kanamycin
  - Streptomycin

**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**
  - Cycloserine
  - Ethionamide
  - PA8
  - Linezolid

\[^{a}\]
Bedaquiline (BDQ)

- Diarylquinoline
- FDA approved 28 December 2012
  - 1st TB drug approved since Rifampin in 1971
- Phase IIb studies by Diacon, et al. 2014
  - Higher mortality (12.6%) than controls (4.9%)
  - 7 patients died, median of 386 days after the last dose
- In a study in France reported by Guglielmetti, et al., 35 patients received BDQ
  - 7 (20%) had increase of ≥60 milliseconds increase in QT interval
Bedaquiline (BDQ)

- Dose: 100 mg. capsules
  - 400 mg. daily for 14 days followed by
  - 200 mg. 3 times/week for 22 weeks
- Acquired resistance can occur
- Cross reaction (both directions) with Clofazimine

XDR-TB

- Use whatever you have left
- Duration 24 months after culture conversion
- Carefully consider surgery
# Adverse Effects

<table>
<thead>
<tr>
<th>SIDE EFFECT</th>
<th>DRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>Ethionamide, PAS</td>
</tr>
<tr>
<td></td>
<td>Quinolones, Clofazimine, Rifabutin, Linezolid</td>
</tr>
<tr>
<td>Hearing, Vestibular</td>
<td>Injectables</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>Linezolid, INH</td>
</tr>
<tr>
<td></td>
<td>Quinolones, Ethionamide, Cycloserine</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>PZA, PAS, Rifabutin, Ethionamide, Quinolones</td>
</tr>
<tr>
<td>Renal Insufficiency, Electrolytes</td>
<td>Injectables</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>Cycloserine, Quinolones, Ethionamide, Clofazimine</td>
</tr>
<tr>
<td>Rash</td>
<td>All. Clofazimine turns skin, tears, secretions orange</td>
</tr>
<tr>
<td>Vision</td>
<td>Ethambutol, Rifabutin, Linezolid</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Ethionamide, PAS, Quinolones (hypoglycemia)</td>
</tr>
<tr>
<td>Cardiac, QTc interval prolongation</td>
<td>Bedaquiline, Quinolones, Clofazimine</td>
</tr>
</tbody>
</table>

**DRUG RESISTANCE**

**ONLY 1 IN 5 PEOPLE NEEDING TREATMENT FOR MULTIDRUG-RESISTANT TB IN 2016 ACTUALLY RECEIVED IT**

**BETTER PREVENTION, DETECTION AND CURE WILL ADDRESS THE MDR-TB CRISIS**
<table>
<thead>
<tr>
<th>WHO 2016 Medicines Recommended for RR-TB and MDR-TB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A. Fluoroquinolones</strong></td>
</tr>
<tr>
<td>Levofloxacin</td>
</tr>
<tr>
<td>Moxifloxacin</td>
</tr>
<tr>
<td><em>Gatifloxacin NA in U.S.A.</em></td>
</tr>
<tr>
<td><strong>Group B. 2nd Line Injectable Agents</strong></td>
</tr>
<tr>
<td>Amikacin</td>
</tr>
<tr>
<td>Capreomycin</td>
</tr>
<tr>
<td>Kanamycin</td>
</tr>
<tr>
<td>Streptomycin</td>
</tr>
<tr>
<td><strong>Group C. Other Core 2nd-Line Agents</strong></td>
</tr>
<tr>
<td>Ethionamide</td>
</tr>
<tr>
<td>Cycloserine</td>
</tr>
<tr>
<td><em>Linezolid</em></td>
</tr>
<tr>
<td><em>Clofazimine</em></td>
</tr>
<tr>
<td><strong>Group D. Add-On Agents (Not core ones)</strong></td>
</tr>
<tr>
<td>D1 Pyrazinamide</td>
</tr>
<tr>
<td>Ethambutol</td>
</tr>
<tr>
<td>High dose Isoniazid</td>
</tr>
<tr>
<td><strong>D2 Bedaquiline</strong></td>
</tr>
<tr>
<td><em>Delamanid NA in U.S.A.</em></td>
</tr>
<tr>
<td><strong>D3 P-aminosalicytic acid (PAS)</strong></td>
</tr>
<tr>
<td>Imipenem-cilastatin</td>
</tr>
<tr>
<td>Meropenem</td>
</tr>
<tr>
<td>Amoxicillin-Clavulonate (to create carbapenem-clavulonate)</td>
</tr>
</tbody>
</table>