Barbara J. Seaworth, M.D.
November 20, 2015

Tuberculosis Intensive
November 17-20, 2015
San Antonio, TX

Barbara Seaworth, MD has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity
Strategies for Successful Treatment of Drug Resistant Tuberculosis in the U.S.
Barbara J. Seaworth, M.D.
Professor of Medicine
UT Health Northeast
Medical Director, Heartland National TB Center

Tuberculosis Intensive
November 17-20, 2015
San Antonio, TX

Objective -
Improved Management of MDR/XDR TB

Recognize which patients are at risk of MDR/XDR

Discuss the recommendations for management of MDR/XDR TB

– Should I start treatment before I know the 2nd line susceptibility results?
– How many drugs? Which ones? How long?
– How do I monitor for treatment response?

Identify the management of close contacts
Multiple Drug Resistant TB (MDR TB) is resistant to both INH and Rifampin.

Extensively Drug Resistant TB (XDR TB) includes MDR TB with additional resistance:
- Any fluoroquinolone
- Second line injectable (Capreomycin, Kanamycin, or Amikacin)

Pre-XDR TB includes MDR TB with resistance to:
- Any fluoroquinolone
- Second line injectable (Capreomycin, Kanamycin, or Amikacin)

The Costly Burden of Drug-Resistant TB in the U.S.

CDC March 2014
WHO 2014 Report: TB Epidemic

“Even Bigger Than We Thought”

- 9.0 million new cases of TB
  - 500,000 more TB cases than previously estimated
- 1.5 million deaths (4000 each day)
- Estimated 480,000 new MDR TB cases in 2013 (9% are XDR)

Pathway to Drug Resistance

Gandhi Lancet May 2010
CLASSIFICATION OF DRUG RESISTANCE

• PRIMARY DRUG RESISTENCE
  – No previous treatment
  – First isolate a person has is drug resistant

• ACQUIRED DRUG RESISTENCE
  – Resistance develops during inadequate treatment

Why Do We Have Drug Resistant TB?
## Increase in Streptomycin-Resistant Mutants During Monotherapy

<table>
<thead>
<tr>
<th>Weeks of treatment</th>
<th>SM-resistant mutants</th>
<th>SM-resistant mutants (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (before)</td>
<td>1 / 88,750</td>
<td>0.0011</td>
</tr>
<tr>
<td>2</td>
<td>1 / 13,174</td>
<td>0.0075</td>
</tr>
<tr>
<td>3</td>
<td>1 / 817</td>
<td>0.12</td>
</tr>
<tr>
<td>4</td>
<td>1 / 588</td>
<td>0.17</td>
</tr>
<tr>
<td>5</td>
<td>1 / 367</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Pyle M. Proc Mayo Clinic 1947;22:465

## Isoniazid Resistance After 2 Months of Isoniazid Monotherapy

- Retrospective analysis from isoniazid treatment trial 1952 among patients with drug-susceptible isolates before starting

<table>
<thead>
<tr>
<th>#Patients</th>
<th>Cavities</th>
<th>%Cult +</th>
<th>% resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>0</td>
<td>40%</td>
<td>22%</td>
</tr>
<tr>
<td>57</td>
<td>1+</td>
<td>44%</td>
<td>40%</td>
</tr>
<tr>
<td>89</td>
<td>2+</td>
<td>70%</td>
<td>61%</td>
</tr>
<tr>
<td>43</td>
<td>3+</td>
<td>88%</td>
<td>87%</td>
</tr>
</tbody>
</table>

Fox W, Sutherland I. Thorax 1955;10:85-98
WHO and National TB Program Policies Led to High Rates of MDR TB

- Global standard practice- diagnosis by smear only
  - No cultures or susceptibility tests

- Drug resistance is not recognized
  - Inadequate treatment is continued

- Standardized treatment regimens for failure
  - This allows further AMPLIFICATION of resistance

Predicting the Growth of XDR TB

Inadequate treatment of MDR TB leads to more XDR TB !
Countries that had reported at least one XDR-TB case by Oct 2013

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

© WHO 2013. All rights reserved.

Risk of Acquired Drug Resistance During Treatment

- Does inadequate treatment of MDR XDR-?
- PETTS Study n(%) Cure/Comp Failure Death
  - Green Light 585 (65) 47 (5.2) 82 (9.1)
  - Programatic 373 (52.7) 55 (7.8) 145 (20.5)

- Emergence of XDR GLC 21% __ non GLC 51%
- Emergence of FQN R GLC 10.1%____ non GLC 20.8%

• PETTS: Preserving Effective TB Treatment Study,
• Dalton et al. Lancet epub August 30, 2012
Figure 2. Risk of acquired drug resistance in Green Light Committee (GLC)-approved and non-GLC programs, stratified by baseline resistance to second-line drugs, in 5 countries, 2005-2010. Abbreviations: CI, confidence interval; GLC, Green Light Committee.


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Category</th>
<th>XDR: aOR 95% CI</th>
<th>P Value</th>
<th>FQ: aOR 95% CI</th>
<th>P Value</th>
<th>SLT: aOR 95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green Light Committee</td>
<td>Yes</td>
<td>0.21 (0.07-0.62)</td>
<td>.004</td>
<td>0.23 (0.09-0.59)</td>
<td>.001</td>
<td>0.74 (0.28-2.17)</td>
<td>.53</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>No. of hospitalizations for this episode of tuberculosis</td>
<td>0</td>
<td>1.36 (0.43-4.25)</td>
<td>.77</td>
<td>0.78 (0.31-1.99)</td>
<td>.35</td>
<td>1.48 (0.54-4.06)</td>
<td>.50</td>
</tr>
<tr>
<td>1</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>2</td>
<td>Ref</td>
<td>1.19 (0.45-3.13)</td>
<td>.43</td>
<td>3.75 (1.44-9.69)</td>
<td>.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of SLDs to which the isolate was susceptible</td>
<td>0-2</td>
<td>32.02 (14.47-70.89)</td>
<td>&lt;.0001</td>
<td>13.95 (7.42-26.22)</td>
<td>&lt;.0001</td>
<td>15.63 (2.84-94.70)</td>
<td>.006</td>
</tr>
<tr>
<td>3-4</td>
<td>Ref</td>
<td>2.25 (1.13-4.48)</td>
<td>.10</td>
<td>1.97 (1.09-3.57)</td>
<td>.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline ethambutol resistance</td>
<td>Res</td>
<td>1.40 (0.69-2.84)</td>
<td>.35</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Sus</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>baseline streptomycin resistance</td>
<td>Res</td>
<td>1.54 (0.84-2.81)</td>
<td>.16</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Sus</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>baseline fluoroquinolone resistance</td>
<td>Res</td>
<td>7.51 (2.83-19.94)</td>
<td>&lt;.0001</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Sus</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>baseline KAN or AMK resistance</td>
<td>Res</td>
<td>13.59 (4.73-39.09)</td>
<td>&lt;.0001</td>
<td>6.32 (2.58-15.49)</td>
<td>&lt;.0001</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Sus</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>baseline capreomycin resistance</td>
<td>Res</td>
<td>1.65 (0.62-4.39)</td>
<td>.32</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Sus</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>baseline ethionamide resistance</td>
<td>Res</td>
<td>1.09 (0.52-2.30)</td>
<td>.82</td>
<td>1.45 (0.71-2.96)</td>
<td>.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sus</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>baseline PAS resistance</td>
<td>Res</td>
<td>0.60 (0.19-1.91)</td>
<td>.39</td>
<td>0.08 (0.36-2.63)</td>
<td>.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sus</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Pneumonia score</td>
<td>Sus</td>
<td>0.96 (0.30-2.87)</td>
<td>.93</td>
<td>0.92 (0.29-3.03)</td>
<td>.63</td>
<td>0.85 (0.21-3.34)</td>
<td>.30</td>
</tr>
</tbody>
</table>
Emergence of New Forms of Totally Drug-Resistant Tuberculosis Bacilli
Super Extensively Drug-Resistant Tuberculosis or Totally Drug-Resistant Strains in Iran

Background: The study documented the emergence of new forms of resistant bacilli (totally drug-resistant [TDR] or super extensively drug-resistant [XDR] tuberculosis [TB] strains) among patients with multidrug-resistant TB (MDR-TB).

Methods: Susceptibility testing against first- and second-line drugs was performed on isolated Mycobacterium tuberculosis strains. Subsequently, the strains identified as XDR or TDR M. tuberculosis were subjected to spoligotyping and variable number tandem repeat (VNTR) analysis.

Results: Of 140 MDR-TB strains, 9 XDR isolates (6.4%) and 15 TDR isolates (10.7%) were identified. The remaining strains were either susceptible (67.7%) or resistant to different patterns (20%). Overall, the median of treatments and drugs previously received by MDR-TB patients was two courses of therapy of 15 months’ duration with five drugs (isoniazid [INH], rifampicin [R], streptomycin, ethambutol, and pyrazinamide). The median of 245 drug-resistant TB cases in such studies was INH and R. The XDR or TDR strains were collected from both immigrants (Afghanistan, 50.2%; Azerbaijan, 8.6%; Iran, 4.2%) and Iranian patients (36.8%) MDR-TB cases. In such cases, the smear and cultures remained positive after 15 months of medium treatment with second-line drugs (etambutol, para-aminosalicylic acid, cycloserine, ethionamide, amikacin, and capreomycin). Spoligotyping revealed Haarlem (50.7%), Beijing (27.7%), EAI (21.7%), and CAS (17.7%) superfamily M. tuberculosis. These superfamilies had different VNTR profiles, which eliminated the recent transmission among MDR-TB products.

Conclusions: The isolation of TDR strains from MDR-TB patients from different regional sources is alarming and underlines the possible dissemination of such strains in Asian countries. The next question is how should one control and treat such cases.

World Report
January 2012
CID

India reports cases of totally drug-resistant tuberculosis

Researchers in Mumbai have identified 12 patients with a violent strain of tuberculosis that seems to be resistant to all known treatments. The cases of totally drug-resistant tuberculosis (TDR-TB) have been detected in the city in the past 3 months. WHO, the only other episode of TDR-TB reported were in China in 2000 and Italy in 2007.

“Initially, it is a failure of public health, and that has to be accepted in this country,” said Zahir F Ikubida, who has been treating the patients at the P D Hinduja National Hospital and Medical Research Centre, and who, in turn, will be treated by a team of experts at the hospital.

India reports cases of totally drug-resistant tuberculosis

Researchers in Mumbai have identified 12 patients with a violent strain of tuberculosis that seems to be resistant to all known treatments. The cases of totally drug-resistant tuberculosis (TDR-TB) have been detected in the city in the past 3 months. WHO, the only other episode of TDR-TB reported were in China in 2000 and Italy in 2007.

“Initially, it is a failure of public health, and that has to be accepted in this country,” said Zahir F Ikubida, who has been treating the patients at the P D Hinduja National Hospital and Medical Research Centre, and who, in turn, will be treated by a team of experts at the hospital.

Research in Mumbai. There is “poor infection control at most of these settings,” said Ikubida, and people with resistant tuberculosis could well be infecting patients with a normal tuberculosis infection. A 5-year study done by the Foundation with the Ministry of Health found that most patients were resistant to two or three of the first-line drugs, and some to all four. The city could have as many as 8500 cases of multi-drug-resistant tuberculosis (MDR-TB) each year, but lacks the laboratory infrastructure in the public system to identify and confirm
• Proposed definitions are ambiguous. No evidence that proposed totally resistant TB differs from XDR TB.

• Susceptibility tests for several drugs are poorly reproducible. Few laboratories can test all drugs.

• No consensus list of all anti-TB drugs. Many drugs are used off-label. New drugs would render the proposed category obsolete.

• Labeling TB strains as totally drug resistant might lead providers to:
  • think infected patients are untreatable.

Susceptibility Studies

First Line
• Resistant
  – INH
  – Rifampin
  – Rifabutin
  – PZA
  – Ethambutol
  – Streptomycin

Second Line
• Resistant
  – Amikacin
  – Kanamycin
  – Capreomycin
  – Ethionamide
  – Ofloxacin
  – PAS
Susceptibility Studies

- Susceptible
  - Linezolid < 0.4
  - Cycloserine
  - Clofazimine < 0.06 mcg/ml
- Moxifloxacin = 1.0 mcg/ml
  - Usually has MIC < 0.5
  - MIC of 1.0 is resistant but drug may have some efficacy due to ability to get high blood levels

DST Coverage Among New Cases and Enrolment on MDR TB Treatment
Compared to Global Stop TB Targets 2011-2015

WHO Global TB Report 2014
Treatment Outcomes for MDR
2007 2011 Global Cohorts

Treatment success overall 2011 48%
WHO 2014 Global TB Report

How Can We Do Better?

Management Strategies Must be
Individualized by Patient and Drug Susceptibility
Early Recognition of Which Patients are at Risk of MDR/XDR TB

• Those who were:
  – Born/reside in a country with high incidence of drug resistant TB
  – Exposed to a patient with relapse or failure

• Those with a history of
  – Prior treatment for TB
  – Treatment failure
  – Clinical deterioration during 4 drug therapy

Bad Bugs – Primary XDR TB

• 56 yr old male, born in US- no history of TB
• TST positive, abnormal CXR,
• Cough, fever, sweats, weight loss
• Culture + M TB Resistant to:
  • INH,
  • Rifampin, Rifabutin
  • PZA
  • Ethambutol
  • Streptomycin, Capreomycin, Amikacin
  • Levofloxacin
  • Ethionamide
Acquired XDR TB

Contact to father who died with MDR TB in 1994

- Father’s culture resistant to:
  - INH,
  - Rifampin, Rifabutin
  - PZA
  - Ethambutol
  - Streptomycin, Capreomycin, Amikacin
  - Ofloxacin
  - Ethionamide

Father was drug susceptible at first diagnosis!

XDR-TB
Extensively Drug Resistant Tuberculosis

Isoniazid
Ethambutol
Rifampin

Streptomycin
Ethionamide
Ofloxacin

Rifabutin
Kanamycin
Capreomycin
INH and Ethambutol Resistant TB

- Initial culture resistant to: INH, ethambutol

- At 10 weeks of therapy patient remains ill and AFB +
  - Providers ask to add moxifloxacin

- Best approach?
  - Always plan treatment so that further resistance does not occur

  - **Know what the current resistance pattern is now**

  - Stop therapy if possible and wait
11/24/2015

Always Use At Least 2 Drugs To Which The TB Is Susceptible.

Never Treat Active TB With A Single Drug!

Never Add a Single Drug to a Failing Treatment Regimen!

PZA only works on slowly growing M TB; it should not be counted as a 2nd drug to protect Rifampin.
INH and Ethambutol Resistant TB

• Initial culture resistant to:
  
  **Streptomycin, kanamycin, amikacin, and capreomycin**
  plus INH and ethambutol

• At 10 weeks of therapy patient is still quite sick cough, poor appetite, no energy and positive smears

• Best approach?
  – Be aggressive but – know where you are starting new treatment from

  ![Add Moxifloxacin?](image)

  Get a New Culture and Susceptibility Test

Pre XDR TB

• After two months of RIPE treatment, - 2\textsuperscript{nd} culture
  – new Rifampin resistance
  – Resistance to INH, ethambutol
  – Streptomycin, kanamycin, amikacin, and capreomycin

  \textbf{PRE XDR TB!}

• Aggressive new treatment regimen needed

• Adding Moxifloxacin would have been adding a single drug to a failing regimen and created XDR!
New Immigrant – Sick on Plane

Burmese teenager with prior history of TB

Case Study: New Immigrant

- Coughing during flight to U.S., weight 76 pounds
  - History of prior treatment in country of origin
  - Sputum smear and later culture was positive for M TB

- Treatment: INH, Rifampin, EMB, PZA plus Moxifloxacin

- Resistant: INH, Rifampin, EMB, PZA
- Susceptible: ethionamide, levofloxacin, amikacin

A key drug has been compromised
New Immigrant

• Patient improves clinically after MDR regimen starts
  – Gains 25 pounds
  – Cough, fever, and night sweats resolve

• Smears and cultures convert at 12 weeks

• Last positive culture Moxifloxacin resistant
  – Moxifloxacin can’t be the strong drug to anchor treatment

Repeat sensitivity on last positive culture to look for further resistance
to plan treatment based on effective drugs!

How Does Detection of Genetic Mutations Causing Resistance Fit Into Management of a New TB Case?
2011 WHO Guidelines

Rapid drug susceptibility testing of INH and Rifampin or Rifampin alone is recommended

- On all before treatment - most cost-effective strategy to avert deaths and prevent additional resistance

- For both INH and Rifampin if MDR –TB prevalence is > 1% and INH resistance is > 2% (U.S. qualifies)

- Should provide a diagnosis within two days of testing

- Only molecular tests meet this criterion

CDC - Molecular Detection of Drug Resistance (MDDR) Testing (Sanger sequencing)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>rpoB</td>
<td>96.1</td>
<td>97</td>
</tr>
<tr>
<td>INH</td>
<td>inhA + katG</td>
<td>88.6</td>
<td>98.7</td>
</tr>
<tr>
<td>FQ</td>
<td>gyrA</td>
<td>82.2</td>
<td>97</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>rrs + eis</td>
<td>86.8</td>
<td>96.9</td>
</tr>
<tr>
<td>Amikacin</td>
<td>rrs</td>
<td>87.9</td>
<td>99</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>rrs + tlyA</td>
<td>44.6</td>
<td>85.9</td>
</tr>
</tbody>
</table>
When Should an Empiric Treatment Regimen for MDR TB Be Started?

• If patient is stable and no high risk contacts in the home, it is best to wait until molecular tests suggest a viable regimen or 2nd line susceptibility tests are available.

• If patient is unstable or small children in home, start treatment

• Most experts would often start with an aggressive regimen using molecular testing to guide choices

38 year old woman admitted in respiratory failure along U.S./Mexico border
rpoB mutation – GAC>GTC; Asp516Val

Mutation predicts Rifampin resistance but Rifabutin susceptibility

• Some rpoB mutations can cause low-level resistance to rifampin*

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Rifampin MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>511 Leu → Pro</td>
<td>0.5 ug/ml</td>
</tr>
<tr>
<td>516 Asp → Tyr</td>
<td>0.25 ug/ml</td>
</tr>
</tbody>
</table>

• Strains with these 2 mutations test as susceptible in MGIT broth (test concentration is 1 ug/ml) may be resistant on agar
  – Significance of these mutations not yet clear

“Low Level” Resistance to Rifampin
Do MICs from 0.25-0.5 lead to treatment failure?

- Williamson article* cites 3 treatment failure cases
  - Retrospective study of INH resistant patients (49 cases)
    - 3/3 with rpoB mutation failed
    - 2/49 without rpoB mutation failed

- Van Deun looked at difficult isolates in CDC performance tests
  - Those with rpoB mutations failed in 6 of 14 instances and relapsed after initial cure in 5/14. Clinical information not available in 2, one cure.

- Increased rifampin exposure (20mg/kg/day) will likely overcome some low level resistance


Molecular Detection of Drug Resistance Shows XDR TB

- 24 yr immigrant-prior TB therapy
- PZA resistance detected
  - suspected INH, rifampin, EMB
- 3 days later MDDR notes XDR
  - Ofloxacin resistant Ala90Val
  - Moxifloxacin?
  - Resistant to all injectable drugs
- Case about to start graduate school at time of diagnosis
  - Hospitalized in isolation
When Can DNA Sequencing Help Better Characterize Susceptibility of an Isolate?

- Resistance to rifampin (*rpoB*)
  - Low level rifampin resistance may be missed (treatment failure)
  - Rifabutin susceptible strains may be missed

- May help predict susceptibility or resistance to moxifloxacin in cases of ofloxacin resistance

- PZA results on MGIT may give false resistance
  - Repeat susceptibility test and request molecular test (*pncA*)

- Confirm EMB susceptibility for INH-Resistant cultures
  - MGIT may give falsely susceptible ethambutol results

MDR TB Reported After 2 Months of Treatment with INH, Rifampin, Ethambutol, and PZA

March 29, 2011 after 2 mo RX

Smear negative – but culture quickly becomes positive
F/U of MDR TB 4 Years After Standardized First Line Therapy

- New and retreatment MDR TB cases managed by standard treatment – all treated 3 x/week
  - RIPE x 2, Rif/INH x 4: for new cases 83% cure
  - RIPES x 2, Rif/INH/EMB x 6: for retreatment 66% cure

- 4 years later:
  - Recurrence: 61%
  - Death due to TB: 36%

- Treatment with FLD is highly ineffective in curing MDR – TB even if the reported cure rate is high initially
  - Patients were evaluated for cure with sputum smears only

He GX et al, PloS ONE, May 2010
2011 WHO Guidelines

- Recommendations on the number of drugs in the regimen, use of specific drugs, and duration of therapy were:
  
  - Guided by a meta-analysis from 32 studies with >9000 treatment episodes using pooled individual patient data
    - XDR TB patients excluded
    - Many studies used DST results to adjust drug regimen
  
  - Quality of evidence was judged to be low or very low
    - No cohorts with randomized controlled trials
    - Bias likely to be substantial “certain drugs used for sicker patients”

Ahuja et al; Plos Medicine 2012

2011 WHO Guidelines

In MDR TB, at least four second line antituberculosis drugs likely to be effective should be included in the intensive phase

- Use of ≥4 drugs in intensive phase and throughout therapy associated with a statistically significant peak in cure.

In MDR TB, regimens should include at least PZA, a fluoroquinolone, a parenteral agent, ethionamide, and cycloserine (or PAS)

- Use of drugs that were part of failing prior regimens or that are reported as resistance is probably not beneficial.
In MDR TB, the intensive phase should last at least 8 months

In MDR TB, the total treatment duration should be at least 20 months in those with no prior MDR TB treatment

- Peak in cure was later for those with prior therapy
  - 27.6 – 30.5 months

In MDR TB, ethionamide should be used (strong recommendation)

- Among the oral bacteriostatic drugs, the association with cure was higher with ethionamide > cycloserine > PAS.

- Ethionamide showed little effect in patients who were treated previously for MDR-TB.
  - (I suspect this was due to ethionamide resistance).
Treatment Issues Not Addressed

- Pediatric TB
- XDR TB
- Use of Linezolid
- Non-MDR-TB polydrug-resistance
- Chemoprophylaxis for contacts of MDR
- Treatment for adverse reactions

**Step 1**
Use any available
First line agents to
Which the isolate is
Susceptible
Add a
Fluoroquinolone
And an injectable
Drug based on
susceptibilities

**Step 2**
Pick one or more of these
Oral second line drugs
Cycloserine
Ethionamide
PAS

**Step 3**
Consider use of these
Third line drugs
Imipenem
Linezolid
Macrolides
Amoxicillin/Clavulanate
Clofazamine
**Culture and Smear Outcomes in MDR TB**

- **Levofloxacin 750mg Vs Moxifloxacin 400mg**

**When should Linezolid be Added?**

- Extensive Drug Resistance, including XDR TB
- Failed MDR TB therapy
- **To make the strongest possible initial regimen?**
- Patients on individualized therapy who have had 2nd line drug susceptibility testing done
- Linezolid when included in a regimen was associated with culture conversion in most by 2 – 3 months and 81.8% were successfully treated

Migliori ERJ 2012,
34 (89%) of 38 patients culture converted ≤ 6 months; median 75 days on LNZ
3 (8%) of 38 patients had treatment failure: 2 patients in 300 mg group; 1 patient in 600 mg group
1 (3%) of 38 patients had treatment relapse
4 patients developed resistance

Linezolid Added as Single Drug to Chronic MDR TB Culture Conversion

Linezolid 600 mg daily added as only change in regimen at study start or after 4 months
Timing of Linezolid Toxicity

Predictors of Poor Outcome for MDR Patients Treated at DOTS-Plus Projects

• Independent predictors of death and failure:
  – HIV positive, low BMI
  – Prior treatment, more resistance
  – Extensive disease, positive smear
  – Positive culture after 3 months of treatment

  • Consider augmenting treatment if possible

Kurbatova et al. Tuberculosis, 2012
Long-term outcomes of patients with XDR TB in South Africa: a cohort study


Prospective F/U of 107 XDR patients treated from 3/2008–8/2012, empirically as inpatients with a median of 8 drugs

44 patients (41%) had HIV. 36 (64%) of 56 isolates were resistant to at least eight drugs

• At 24 months of F/U, 17 (16%) had a favorable outcome, 49 (46%) had died

• At 60 months, 12 patients (11%) had a favorable outcome, 78 (73%) had died, 11 (10%) had failed treatment.

• 45 patients were discharged, of whom 26 (58%) had achieved sputum culture conversion and 19 (42%) had failed treatment.

Aggressive Regimen is Associated with Improved Outcomes

• Individualized based on 1st/2nd line susceptibility test results

• Use of drugs with proven or likely susceptibility, including
  – 5 drugs including an injectable for 6 months after culture conversion
  – 4 oral drugs including a FQN which should be given for 18-24 months after culture conversion

   Mitnick, PLoS One, March 2013
Aggressive Regimen Outcomes

• Cure or completion in 66.1% of 669 patients
  – Patients resistant to average of 5.4 drugs
  – Only two had no prior therapy

• Such a regimen previously shown to decrease relapse (Frank, CID 2013)

Treatment Outcomes Among Patients with MDR TB: Systematic Review and Meta-analysis

• Bayesian random-effects meta-analysis Successful treatment outcome was defined as cure or treatment completion.
• 34 clinical reports with a mean of 250 patients per report met the inclusion criteria.

  – Our analysis shows that the proportion of patients treated successfully improved when treatment duration was at least 18 months, and if patients received directly observed therapy throughout treatment.

  – Pooled success 69% if 18 months of treatment with DOT throughout

Bacteriological Monitoring During MDR Therapy
2011 WHO Guidelines

- The use of sputum smear microscopy and culture rather than sputum smear alone
- Monthly sputum smear microscopy and culture performed best at identifying failures earlier
- Early identification of failure allows for institution of infection control measures and changes to drug regimen before resistance can be amplified.

Short, Highly Effective and Inexpensive Standardized Treatment of MDR TB

- Prospective cohorts treated in Bangladesh for minimum 9 months – Cohort #6 - 206 patients, mean BMI 16.1 kg
- Relapse free cure 87.9%

- Intensive phase 4 (+) months
  - High dose gatifloxacin (800 mg if 50 kg)
  - Kanamycin 4 months or until sputum conversion (17% extended)
  - Prothionamide, PZA, high dose INH (600mg), ethambutol, clofazamine

- Continuation phase 5 months
  - Gatifloxacin, PZA, ethambutol, clofazamine (50–100 mg)

Van Deun, Int J Resp Crit Care Med, 2010
Proportion with Successful Outcomes

Van Deun, Int J Resp Crit Care Med, 2010

Revised STREAM
Janssen co-sponsors

- All will get moxifloxacin (high dose), clofazimine, INH (high dose), PZA, EMB

- 9 Month Phase 3
  - Bedaquiline based completely oral regimen
  - Prothionamide

- 6 Month Phase 3
  - Bedaquiline x 6 months
  - Kanamycin x 2 months
  - No prothionamide
The medicine and syringes to treat one MDR-TB patient for one year. Patients need to undergo treatment from 18–24 months

IDSA fact sheet 2013

• Staggering Medication Burden

BDQ – The Hard Facts!

$23K for the 188 tablet/24 week course under 340B pricing.

Non 340B will be more expensive
CDC Recommendation # 1

- Bedaquiline may be used in the initial 24 weeks of treatment in adults with laboratory-confirmed pulmonary MDR TB when an effective treatment regimen cannot otherwise be provided.
  - Quality of evidence: low

CDC Recommendation # 2

- Bedaquiline may be used on a case-by-case basis in the populations listed below when an effective treatment regimen cannot otherwise be provided.
  - Quality of evidence: insufficient – expert opinion.
    - Children
    - HIV-infected persons
    - Pregnant women
    - Persons with extrapulmonary TB
    - Patients with co-morbid conditions on concomitant medications
CDC Recommendation # 3

• Bedaquiline may be used on a case-by-case basis for durations longer than 24 weeks when an effective treatment regimen cannot otherwise be provided.
  – Quality of evidence: insufficient – expert opinion.


Identification and Management of Contacts

- Transmission to household contacts similar to drug susceptible TB, active TB disease noted in:
  - 3.6% in South Africa (all MDR or XDR)
  - Mortality 14% if MDR, 52% if XDR
    Vella, Int J Tuberc Lung Dis 2011
  - 5% in Peru (80% MDR)
    - Constant rate per year over three years
    Grandjean, 2011 Int J Tuberc Lung Dis

- Contacts with active disease identified early in South Africa but in Peru required follow up for at least 12 months

Management of Contacts of MDR TB

- Evaluate possibility that source was MDR

- Discuss possible treatment with patient – no studies to guide

- CDC recommends clinical and radiographic follow up for 24 months whether individuals with LTBI presumed due to an MDR/XDR isolate are treated or not

- 2 drugs to which source is susceptible for 6 – 12 months
  - Levofloxacin or moxifloxacin and PZA or ethambutol and PZA
  - Some experts use fluoroquinolone alone for 9 – 12 months
  - Some experts use any two of the above that will work

  CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000;49(no. RR-6):1–51.
Only ~7% of MDR is diagnosed with DST

Only ~16% MDR is treated according to WHO standards