Multi-Drug and Extensively Drug Resistant Tuberculosis

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National Jewish Health
Disclosures

None
Tuberculosis is a *Social Disease*

With a *Medical Aspect*

Sir William Osler, 1902
Nomenclature for Drug Resistant Tuberculosis Cases

- Drug Resistant Tuberculosis
- Multi-Drug Resistant Tuberculosis (MDR-TB)
- Rifampin Resistant Tuberculosis (RR-TB) (New definition as of May 2016)
- Pre-XDRTB (Resistant to INH, Rif, either quinolone OR a second line injectable but not both)
- Extensively-Drug Resistant Tuberculosis (XDR-TB)
Multi-drug resistant tuberculosis (MDRTB) is defined as a strain of *M. tuberculosis* which is resistant to AT LEAST isoniazid AND rifampin
MDRTB

• In 2015 there were an estimated 480,000 new cases of MDRTB worldwide and an estimated 1.4 million TB deaths and additional 400,000 deaths resulting from TB disease among people living with HIV.

• Only about 20% of the estimated 580,000 cases of MDRTB were treated.

• India, China and the Russian Federation accounted for 45% of the 480,000 (MDR-TB) and 100,000 (RR-TB) cases in 2015 report.
TB stats

• India accounts for more than ¼ of the world’s TB cases and deaths.

• Treatment success rate for MDR-TB (2013 cohort) 52%

• Treatment success rate for extensively drug-resistant (2013 cohort) 28%

• At least 23 countries in Africa and Asia have introduced shorter regimens for treatment of MDR-TB or RR-TB with high success rates 87-90% under tight research conditions

2016 WHO Report
TB Stats

• Standardized regimen of 9-12 months is recommended by WHO for all patients (excluding pregnant women) with pulmonary MDR/RR-TB that is NOT resistant to second-line drugs

• At least 70 countries have started using bedaquiline and 39 countries have started using delaminid by the end of 2015
MDR-TB op 20 + 10

- Bangladesh
- China
- DPR Korea
- Congo
- Ethiopia
- India
- Kazakhstan
- Kenya
- Indonesia
- Mozambique
- Myanmar
- Nigeria
- Pakistan
- Philippines
- Russian Federation
- South Africa

- Thailand
- Ukraine
- Uzbekistan
- Viet Nam
- Angola
- Azerbaijan
- Belarus
- Kyrgyzstan
- Papua New Guinea
- Peru
- Republic of Moldova
- Somalia
- Tajikistan
- Zimbabwe
# Short Course Standardized Regimen for MDR-TB

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Intensive</th>
<th>Continuation</th>
<th>Number</th>
<th>Cum. %</th>
<th>Treatment Success %</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>3KCOEHZP</td>
<td>12 OEHZP</td>
<td>59</td>
<td>13.8</td>
<td>68.9</td>
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<td>2</td>
<td>3(+)KCOEHZP</td>
<td>12 OEHZP</td>
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<tr>
<td>3</td>
<td>3(4)KCOEZP</td>
<td>12 OEZP</td>
<td>35</td>
<td>8.2</td>
<td>57.1</td>
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<tr>
<td>4</td>
<td>3(+)KCOEHZP</td>
<td>12 OHEZ</td>
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<td>10.5</td>
<td>66.7</td>
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<td>5</td>
<td>3(+)KCOEHZP</td>
<td>12 OHEZC</td>
<td>38</td>
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<td>84.2</td>
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<tr>
<td>6</td>
<td>4(+)KCGEHZP</td>
<td>5 GEZC</td>
<td>206</td>
<td>48.2</td>
<td>87.8</td>
</tr>
</tbody>
</table>

C = clofazimine, E = ethambutol, G = gatifloxacin, H = isoniazid, K = kanamycin, O = ofloxacin, P = prothionamide, Z = pyrazinamide

3(4) = minimum of 3 mos, prolonged to 4 months if no conversion by end of 3 mos
3(+) = minimum of 3 mos, prolonged until conversion achieved
4(+) = minimum of 4 mos, prolonged until conversion achieved

Primary MDR–TB, United States, 1993–2015*

* As of June 9, 2016.

**Note:** Based on initial isolates from persons with no prior history of TB; multidrug resistant TB (MDR-TB) defined as resistance to at least isoniazid and rifampin.
As of June 9, 2016.

Note: Based on initial isolates from persons with no prior history of TB; multidrug resistant TB (MDR-TB) defined as resistance to at least isoniazid and rifampin.
XDR-TB* Case Count, Defined on Initial DST,† by Year, 1993–2015 §

* XDR-TB, extensively drug-resistant TB.
† DST, drug susceptibility test.
§ As of June 9, 2016.

Note: XDR-TB is defined as resistance to isoniazid and rifampin, plus resistance to any fluoroquinolone and at least one of three injectable second-line anti-TB drugs.
Roughly half of the global burden of MDR-TB is in 3 countries

2016 WHO Report
WHO MDRTB 2016 REPORT

Percentage of new TB Cases with MDR-TB/RR-TB

Percentage of previously treated TB cases with MDR/RR-TB*

* MDR = multidrug-resistant; RR = rifampicin-resistant
MDR/RR-TB = RR-TB cases including MDR-TB cases

Figures are based on the most recent year for which data have been reported, which varies among countries. Data reported before the year 2001 are not shown.

Figures are based on the most recent year for which data have been reported, which varies among countries.

Data Source: Global Tuberculosis Report 2016, WHO.
MDRTB

Ilya Pitalev/Kommersant Photo via Getty Images

WHO fact sheet 2015

2016 WHO Report
Short Course Standardized Regimen for MDR-TB

4(+)KCGEHZP/5 GEZC

Completion – 5.3%  Death – 5.3%
Cure – 82.5%  Default – 5.8%
Success – 87.8%  Failure – 0.5%
Failure – 0.5%
Relapse – 0.5%

WHO 2011 MDRTB Treatment Recommendations for Optimized Background Regimen (OBR)

- Treatment with a fluoroquinolone should be used (strong)

- A later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used (conditional)

- Ethionamide (or prothionamide) should be used (strong)

- (4) second-line anti-tuberculosis drugs likely to be effective (including a parenteral agent) as well as pyrazinamide, should be included in the intensive phase (conditional)

- Regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or PAS (p-aminosalicylic acid) if cycloserine cannot be used (conditional)

- Treatment duration for 24 months
Treatment Outcomes in Patients with MDR-TB, 2007-2012 Cohorts

WHO, Global Tuberculosis Report 2015
### New Grouping of MDR-TB Drugs 2016

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolone</td>
<td>Second-line injectable</td>
<td>Other Core Second-line</td>
<td>Add-on agents</td>
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<tr>
<td>Levofloxacin</td>
<td></td>
<td>Ethionamide/Prothionamide</td>
<td>D1: Pyrazinamide Ethambutol High-dose INH</td>
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<tr>
<td>Moxifloxacin</td>
<td></td>
<td>Cycloserine/Terizidone/Clofazimine</td>
<td>D2: Bedaquiline Delamanid</td>
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<tr>
<td>Gatifloxacin</td>
<td></td>
<td>Linezolid</td>
<td>D3: \textit{P-}aminosalicylic acid</td>
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<td></td>
<td></td>
<td></td>
<td>Imipenem/meropenem</td>
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<tr>
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<td></td>
<td>Amoxacillin/Clavulanate/Thioacetazone</td>
</tr>
</tbody>
</table>
## Building a Treatment Regimen with 2016 Update

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Group A (one)</th>
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<tr>
<td></td>
<td>Levofloxacin</td>
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<tr>
<td></td>
<td>Moxifloxacin</td>
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<tr>
<td></td>
<td>Gatifloxaxin</td>
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<tr>
<th>Step 2</th>
<th>Group B (one)</th>
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<tr>
<td></td>
<td>Kanamycin</td>
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<tr>
<td></td>
<td>Amikacin</td>
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<tr>
<td></td>
<td>Capreomycin</td>
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<thead>
<tr>
<th>Step 3</th>
<th>Group C (two)</th>
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<tbody>
<tr>
<td></td>
<td>Ethionamide/Prothionamide</td>
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<tr>
<td></td>
<td>Clofazimine</td>
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<tr>
<td></td>
<td>Cycloserine/Terizidone</td>
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<tr>
<td></td>
<td>Linezolid</td>
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<tr>
<th>Step 4</th>
<th>Group D1</th>
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<tr>
<td></td>
<td>Pyrazinamide (include)</td>
</tr>
<tr>
<td></td>
<td>Ethambutol*</td>
</tr>
<tr>
<td></td>
<td>High-dose INH*</td>
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</table>

<table>
<thead>
<tr>
<th>Group D2</th>
<th>Bedaquiline</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Group D3</th>
<th>Imipemen/Meropenem</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Amoxacillin/Clavulanate</td>
</tr>
<tr>
<td></td>
<td>P-aminosalicylic acid</td>
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</tbody>
</table>
Short(er) Course Regimen for MDR-TB

- Isoniazid*
- Moxifloxacin*
- Pyrazinamide
- Ethambutol
- Clofazimine
- Prothionamide
- Isoniazid* (High dose)
- Kanamycin

Initial Phase (7 drugs)
Continuation Phase (4 drugs)

(months)
WHO Policy Recommendation
Shorter Course MDR-TB Regimen

Recommendation:

In patients with RR or MDR-TB
  • who have not been treated with second-line drugs and
  • in whom resistance to FQNs and SLI agents has been excluded or is considered to be highly unlikely
a shorter MDR-TB regimen of 9-12 mos may be used instead of a conventional regimen

(conditional recommendation, very low certainty in the evidence)
Countries Using Short(er) Course MDR-TB Regimen
# Treatment Success*

## Shorter vs. Conventional Regimens

<table>
<thead>
<tr>
<th>Resistance pattern</th>
<th>Shorter MDR-TB Regimen (N=1116)</th>
<th>Conventional MDR-TB Regimen (N = 5850)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>90.3%</td>
<td>78.3%</td>
</tr>
<tr>
<td>PZA susceptible; FQN susceptible</td>
<td>96.8%</td>
<td>83.5%</td>
</tr>
<tr>
<td>PZA resistant; FQN susceptible</td>
<td>88.8%</td>
<td>81.4%</td>
</tr>
<tr>
<td>PZA susceptible; FQN resistant</td>
<td>80.0%</td>
<td>64.4%</td>
</tr>
<tr>
<td>PZA resistant; FQN resistant</td>
<td>67.9%</td>
<td>59.1%</td>
</tr>
</tbody>
</table>

*Treatment success – cure or completed

*WHO 2016 Update*
Eligibility For Short-course Regimen for MDR-TB in Europe

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>SLID</th>
<th>FQ</th>
<th>Pto/Eto</th>
<th>E</th>
<th>Z</th>
<th>N</th>
<th>%</th>
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<tbody>
<tr>
<td>Austria</td>
<td>80</td>
<td>41</td>
<td>25</td>
<td>48</td>
<td>64</td>
<td>63</td>
<td>8</td>
<td>10</td>
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<tr>
<td>France</td>
<td>114</td>
<td>30</td>
<td>32</td>
<td>71</td>
<td>65</td>
<td>59</td>
<td>7</td>
<td>6</td>
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<tr>
<td>Germany</td>
<td>70</td>
<td>23</td>
<td>27</td>
<td>57</td>
<td>80</td>
<td>73</td>
<td>6</td>
<td>9</td>
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<tr>
<td>Portugal</td>
<td>200</td>
<td>51</td>
<td>48</td>
<td>83</td>
<td>52</td>
<td>75</td>
<td>9</td>
<td>5</td>
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<tr>
<td>TBnet*</td>
<td>148</td>
<td>28</td>
<td>21</td>
<td>47</td>
<td>54</td>
<td>62</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>612</td>
<td>37</td>
<td>33</td>
<td>64</td>
<td>60</td>
<td>67</td>
<td>48</td>
<td>8</td>
</tr>
</tbody>
</table>

*16 countries in Europe

Lange C, et al. AJRCCM 2016;194:1029
Line Probe Assays for the Detection of Resistance to SLD

The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs
WHO Policy Recommendation
Use of Second-line Line Probe Assays

• For patients with confirmed rifampin-resistant TB or MDR-TB, second-line-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to *fluoroquinolones*

(conditional recommendation, moderate certainty in evidence for direct testing of sputum; low certainty in evidence for indirect testing of cultures)
WHO Policy Recommendation
Use of Second-line Line Probe Assays

• For patients with confirmed rifampin-resistant TB or MDR-TB, second-line-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to second-line injectable drugs (conditional recommendation, low certainty in evidence for direct testing of sputum; very low certainty in evidence for indirect testing of cultures)
## Accuracy of MTBDRs\(s\) for Fluoroquinolones and Second-Line Injectable Drug Resistance

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indirect Testing</th>
<th>Direct Testing</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pooled Sensitivity</td>
<td>Pooled Specificity</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>85.6%</td>
<td>98.5%</td>
</tr>
<tr>
<td>Second-line injectable</td>
<td>76.5%</td>
<td>99.1%</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>70.9%</td>
<td>98.8%</td>
</tr>
</tbody>
</table>

Conventional phenotypic DST should be used in the follow-up evaluation of patients with a negative result especially in settings with a high pre-test probability for resistance.
Second-line Line Probe Assays
Implementation Considerations

- SL-LPA cannot determine resistance to individuals groups in the class of FQN
- Mutations in some regions may cause resistance in one drug more than another
- SL-LPA should be used for direct testing of smear negative or positive sputum specimens
- SL-LPA are suitable for use at central or national reference laboratories with appropriate infrastructure
- Culture and phenotypic DST should be available
STREAM Trial

Regimen A: WHO-approved MDR-TB Regimen

- Intensive phase: KM+INH+PTO+
- Continuation phase: MFX+CFZ+EMB+PZA

Regimen B: KM+INH+PTO+

- Intensive phase: MFX+CFZ+EMB+PZA
- Continuation phase: BDQ+LFX+CFZ+EMB+PZA

Regimen C: INH+PTO+

- Intensive phase: BDQ+LFX+CFZ+EMB+PZA
- Continuation phase: BDQ+LFX+CFZ+EMB+PZA

Regimen D: KM+INH+BDQ+

- Intensive phase: BDQ+LFX+CFZ+PZA
- Continuation phase: BDQ+LFX+CFZ+PZA

May 2016 WHO MDRTB Short Course Treatment for MDR-TB/RR-TB

- Exposure to >1 second-line medicines in the shorter MDR-TB regimen for >1 month
- Intolerance to >1 medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- Pregnancy
- Extrapulmonary disease
- At least one medicine in the shorter MDR-TB regimen not available in the programme

---

**NO**

Shorter MDR-TB regimen

- Intensive phase: Duration 4-6 months, Composition: 4 second-line drugs
- Continuation phase

**YES**

Individualised ("conventional") MDR/RR-TB regimens

- Intensive phase: Duration: Up to 8 months, Composition: 4 or more second-line drugs
- Continuation phase
Shorter Course MDR-TB Regimen
Implementation Considerations

• Patients should be tested for susceptibility to FQNs and SLI agents before starting the regimen
• WHO recommends that MTBDRs/sl be used as the initial direct test instead of phenotypic culture-based DST
• In settings in which laboratory capacity for DST to FQN and SLI agents is not yet available, treatment decisions would need to be based on likelihood of resistance
• Clofazimine and high-dose INH may be difficult to procure in some countries.
• Development of an active pharmacovigilance program
MDRTB

PREVENT SELECTION OF RESISTANT BACTERIA

– PRESCRIBE AN ADEQUATE REGIMEN
– ASSURE COMPLIANCE
Prior partial gastrectomy contributed to medication malabsorption.
CAUSES OF MDRTB

• Primary (Initial) Resistance
• Secondary (Acquired) Resistance
  – Malabsorption (Surgery/HIV)
  – Poor adherence to medical regimen
  – Inadequate treatment regimen
MDRTB

IF YOU DON’’T SUSPECT DRUG RESISTANCE YOU DEFINITELY WON’’T FIND IT!
NEVER, NEVER, NEVER

ADD A SINGLE DRUG TO A FAILING REGIMEN
### ANTI-MYCOBACTERIAL DRUG HISTORY

**ORGANISM ID:** MDR TB  
**DRUG SUSCEPTIBILITY:** ETA/SM/CM/KM/AK/CS/PAS  
**DRUG RESISTANCE:** INH/RIF/EMB/S

**PATIENT HX:** 53 Y old man from Houston with NIDDM, HTN, Alb, with MDRTB.

<table>
<thead>
<tr>
<th>DATE</th>
<th>8/88</th>
<th>4/90</th>
<th>7/90</th>
<th>9/90</th>
<th>1/91</th>
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</tbody>
</table>

**Comments:** 8 months FUO  
Resp failure  
7 etiology  
Began on Biweekly RX  
5/cough  
N/V/malaise with SM  
CT chest RUL cavity

**2110-112 9/92**
“An ounce of prevention is worth a pound of cure”

• Case fatality rate
What about Vitamin D?

Martineau et al; J Steroid Biochem Mo Biol; 2007
Wejse et al; Am J Resp Crit Care Med; 2009
Maratineau et al; Lancet; 2011
“An ounce of prevention is worth a pound of cure”

• Case fatality rate
• Administration of therapy
PAS granules

Must be taken with acidic beverage
“An ounce of prevention is worth a pound of cure”

- Case fatality rate
- Administration of therapy
- Duration of therapy
“An ounce of prevention is worth a pound of cure”

- Case fatality rate
- Administration of therapy
- Duration of therapy
- Toxicity of medications
“An ounce of prevention is worth a pound of cure”

- Case fatality rate
- Administration of therapy
- Duration of therapy
- Toxicity of medications
- Cost
Cost of Treatment for MDR-TB

2016 WHO Report
Cost of Drug Therapy for MDRTB

Capreomycin 1 gm IV TIW x 6 months  2,500
Moxifloxacin 400 mg po QD x 2 yrs  11,600
Ethionamide 500 mg po QD x 2 yrs  5,500
Cycloserine 500 mg po QD x 2 yrs  8,200
PAS 4 gms po BID x 2 yrs  6,500
Ethambutol 800 mg QD x 2 yrs  5,000

Levothyroxin 100 mcg po QD x 1.5 yrs  240
Pyridoxine (Vit. B6) 50 mg po QD x 2 yrs  60

$ 39,600

Bedaquiline 400mg/day x 2wks → 200mg 3x/week x 22 weeks
High income country  $ 30,000
Middle income country  $ 3,000
Low income country  $ 900
# MDRTB Treatment at NJC

## Use of Fluoroquinolones (FQN’s)

<table>
<thead>
<tr>
<th>Period</th>
<th>Cases</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973–1983</td>
<td>0/171</td>
<td></td>
</tr>
<tr>
<td>1984–1998</td>
<td>163/204</td>
<td></td>
</tr>
</tbody>
</table>

MDRTB TREATMENT AT NJC

Use of RESECTIONAL SURGERY

1973-1983

6/171 (4%)

1984-1998

130/205 (63%)

New WHO 2016 Treatment Guidelines for MDRTB/ RR-TB

- 9-12 months of treatment that is NOT resistant to second-line drugs (Except for pregnant women)
- All RR-TB cases are to be treated with a MDR-TB regimen, regardless of isoniazid susceptibility
- Clofazimine and Linezolid are now recommended as core second-line medicines
- PAS is an add-on agent
- MACROLIDES ARE NO LONGER INDICATED
Left bronchopleuralcutaneous fistula
MDRTB SURGICAL MANAGEMENT

V/Q scan

LEFT PERFUSION %: 1.3191
RIGHT PERFUSION %: 98.68
Post-op
apical air cap
MDRTB SURGICAL MANAGEMENT

NJC outpatient visit. C/O “gurgling” in left chest with nausea and vomiting
Herniation of intestine through left hemidiaphragm
Pt. underwent emergent transthoracic repair of the hernia and continues to do well. She completed 2 years of medical therapy post-operatively and remains disease free.
MDRTB Pre-op
MDRTB Post-op
Surgery for Pulmonary NTM Disease

“VATS” Approach

- Thoracoscopic Lobectomy
  - Two 1 cm incisions
  - One 4 cm “utility” incision
  - No rib spreading
- Operation otherwise identical to open approach
- Double lumen tube
- No epidural catheter
- Prior surgery not absolute contraindication
"C'mon, c'mon—it's either one or the other."
Thoracotomy

Sternotomy

Axillary thoracoplasty
TB infection on chest wall
Thoracoplasty


Permission to use photo
Post op 11/2006
Disseminated TB of sacrum 40 days after surgical debridement (12/06)
Disseminated TB rib 20 days surgical debridement (11/23/06)
MDRTB without surgery
MDRTB without surgery
Bedaquiline

• The need for new therapies to treat multidrug-resistant (MDR) tuberculosis is great

• The new compound TMC207, a diarylquinoline that inhibits mycobacterial ATP synthase, shows promising activity against MDR tuberculosis

• In this study involving 47 patients, the administration of TMC207, as compared with placebo, resulted in a shorter time to sputum-culture conversion and a significant increase in the proportion of patients achieving culture conversion to negative
Observations

1. Of the 10 deaths in the bedaquiline group, 8 patients converted.
2. The 2 patients who did not convert died from a TB-related cause.
3. Of the 8 who converted:
   - 4 relapsed:
     - 3 died from TB-related causes (1 from hemoptysis)
     - 1 discontinued and died from MVA
   - 4 did not relapse but died from non-TB related causes.
4. Two deaths in the placebo group did not convert and died from TB-related causes.
Hope on the Horizon

Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

Maria Tarcela Gler, M.D., Vija Skripconoka, M.D., Epifanio Sanchez-Garavito, M.D., Heping Xiao, M.D., Jose L. Cabrera-Rivero, M.D., Dante E. Vargas-Vasquez, M.D., Mengqiu Gao, M.D., Ph.D., Mohamed Awad, M.B., B.Ch., M.D., Seung-Kyu Park, M.D., Ph.D., Tae Sun Shim, M.D., Ph.D., Gee Young Suh, M.D., Manfred Danilovits, M.D., Hideo Ogata, M.D., Anu Kurve, M.D., Joon Chang, M.D., Ph.D., Katsuhiro Suzuki, M.D., Thelma Tupasi, M.D., Won-Jung Koh, M.D., Barbara Seaworth, M.D., Lawrence J. Geiter, Ph.D., and Charles D. Wells, M.D.

Not yet approved for in USA
Delamanid Use – WHO Recommendations 2016

• May now be used in patients age 6 and older and may be used in HIV infected patients
  – It is not currently recommended in pregnancy, breast feeding or children

• Do no use if corrected QT is >500ms

• It must be used in conjunction with WHO OBR
  – PZA, quinolone, second line injectable, plus 2 bacteriostatic agents (ethionamide, PAS, cycloserine)

• Use in first 6 months of treatment

• No current standardized DST for Delamanid

• No current recommendation for use of BOTH delamanid and bedaquiline in a treatment regimen

• Recommended dose of Delamanid is 100mg BID
Pretomanid and TBA-354

• Pretomanid (pree TOH mah nid)(formally PA–824) is a nitroimidazo–oxazine
  – Significant early bactericidal activity alone and in combination with bedaquiline or with PZA and moxifloxacin

• TBA–354 is a next generation nitroimidazo–oxazine that has in vitro potency superior to PA–824 and greater stability than the other nitroimidazole derivative, delamanid

Tasneen ; AAC; Jan 2015:129-135
Bull Moose near Walden, Colorado