Surgery for MDR/XDR Tuberculosis and Non-Tuberculcous Mycobacterial Disease

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Surgery for Drug-Resistant Tuberculosis

**Indications**

**Eradicate TB Infection:**
- Localized disease amenable to resection
- Persistent cavitary disease
- Persistent positive sputum with/without cavity
- Destroyed lung

**Complications of TB Infection:**
- Massive hemoptysis
- Bronchopleural fistula
- Bronchial stenosis
- Trapped lung
Worldwide Incidence of Tuberculosis
December, 2011

Multidrug and Extensively Drug Resistant Tuberculosis

9 million TB cases

Drug Susceptible

Any Drug Resistance

MDR-TB

XDR-TB

Resistance to at least isoniazid and rifampin (MDR) plus resistance to fluoroquinolones and one of the second-line injectable drugs (amikacin, kanamycin, or capreomycin)
## Worldwide Incidence of Tuberculosis
### December, 2011

<table>
<thead>
<tr>
<th>Category</th>
<th>Estimated number of cases, 2011</th>
<th>Estimated number of deaths, 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>All forms of TB</td>
<td>8.7 million (8.3–9.0 million)</td>
<td>0.99 million* (0.8–1.1 million)</td>
</tr>
<tr>
<td>HIV-associated TB</td>
<td>1.1 million (1.0–1.2 million)</td>
<td>430,000 (400,000–460,000)</td>
</tr>
<tr>
<td>Multidrug-resistant TB</td>
<td>630,000 (460,000–790,000)</td>
<td>out of ~12 million prevalent TB cases</td>
</tr>
</tbody>
</table>

* Excluding deaths attributed to HIV/TB

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Multi-Drug Resistant Tuberculosis
December, 2011

Percentage of cases

- 0-2.9
- 3-5.9
- 6-11.9
- 12-17.9
- ≥ 18
- No data
- Subnational data only
- Not applicable

Extreme-Drug Resistant Tuberculosis
Fall, 2012

MDRTB Treatment
Percentage of MDRTB Cases receiving treatment

Overall: 20%

Adequate: < 10%

Worldwide MDRTB Treatment Success
2009

THE STOP TB STRATEGY
Building on and enhancing DOTS to meet the TB-related Millennium Development Goals

THE GLOBAL PLAN TO STOP TB 2011–2015
Transforming the Fight
TOWARDS ELIMINATION OF TUBERCULOSIS
Designing a Treatment Regimen

General Principles

• Early DR-TB detection/prompt initiation of therapy

• Regimens should be based on:
  • the history of drugs taken by the patient
  • drugs and regimens used in the country and
  • the prevalence of resistance

• Regimens should consist \( \geq 4 \) effective drugs

• When possible, once daily dosing is recommended

• Drug dosage should be determined by body weight

WHO Guidelines for the Programmatic Management of Drug-Resistant TB2008
Building a Treatment Regimen in MDRTB

Step 1
- Group 1
  - Ethambutol
  - Pyrazinamide

Step 2
- Group 2
  - Streptomycin
  - Kanamycin
  - Amikacin
  - Capreomycin

Step 3
- Group 3
  - Levofloxacin
  - Moxifloxacin
  - Ofloxacin

Step 4
- Group 4
  - Ethionamide
  - Protonamide
  - Cycloserine
  - Terizidone
  - P-aminosalicylic acid

Step 5
- Group 5
  - Clofazimine
  - Imipemen
  - Amoxacillin/Clavulanate
  - Macrolides
  - Linezolid
  - Thioacetzone
  - High-dose INH

Goal: at least 4 effective drugs
## Drug Resistant Tuberculosis

### Predictors of Success and Failure

<table>
<thead>
<tr>
<th>Success</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Use of pyrazinamide and/or ethambutol, if susceptible</td>
<td>- Previous therapy</td>
</tr>
<tr>
<td>- Use of a fluoroquinolone</td>
<td>- Number of drugs resistant</td>
</tr>
<tr>
<td>- Use of &gt; 5 drugs</td>
<td>- Resistance to FQN</td>
</tr>
<tr>
<td>- Sputum conversion by 2 mos</td>
<td>- Resistance to capreomycin</td>
</tr>
<tr>
<td>- Surgical resection</td>
<td>- Presence of cavitation</td>
</tr>
<tr>
<td></td>
<td>- Low BMI</td>
</tr>
<tr>
<td></td>
<td>- HIV infection</td>
</tr>
<tr>
<td></td>
<td>- Poor adherence</td>
</tr>
<tr>
<td></td>
<td>- Positive cultures at 2-3 mos</td>
</tr>
<tr>
<td></td>
<td>- XDR-TB</td>
</tr>
</tbody>
</table>
Surgery for MDR-TB, XDR-TB

Factors favoring Surgery

• A pattern of drug-resistance so extensive that it compromises the likelihood of medical cure

• Localized lung damage (cavitation, destroyed lung) that might be a focus of persistent disease and/or further acquired resistance

• Allergies or intolerance to essential medications that might afford cure

• Lack of access to curative chemotherapy
Surgery for MDR-TB, XDR-TB

Risks/Benefits

• Benefits
  – Rapid bacteriologic conversion
  – Removal of bronchiectatic/fibrotic lung
  – Increased chance of cure in some patients

• Risks
  – Morbidity and mortality related to surgery
  – Potential long-term functional deficits
  – Transmission in the health facility
## Surgery for MDR-TB

### Current Results

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number</th>
<th>Operations</th>
<th>Mortality</th>
<th>Morbidity</th>
<th>Cure rate (negative sputum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Leuven</td>
<td>1997</td>
<td>62</td>
<td>62</td>
<td>1.6%</td>
<td>23%</td>
<td>80%</td>
</tr>
<tr>
<td>Sung</td>
<td>1999</td>
<td>27</td>
<td>27</td>
<td>0%</td>
<td>25.9%</td>
<td>96.3%</td>
</tr>
<tr>
<td>Pomerantz</td>
<td>2001</td>
<td>172</td>
<td>180</td>
<td>3.3%</td>
<td>12%</td>
<td>98%</td>
</tr>
<tr>
<td>Shiraishi</td>
<td>2004</td>
<td>87</td>
<td>95</td>
<td>0%</td>
<td>11.5%</td>
<td>93%</td>
</tr>
<tr>
<td>Naidoo</td>
<td>2005</td>
<td>23</td>
<td>23</td>
<td>0%</td>
<td>17.4%</td>
<td>95.6%</td>
</tr>
<tr>
<td>Dewan</td>
<td>2006</td>
<td>74</td>
<td>74</td>
<td>4.1%</td>
<td>32%</td>
<td>89.8%</td>
</tr>
<tr>
<td>Kir</td>
<td>2006</td>
<td>79</td>
<td>81</td>
<td>2.5%</td>
<td>25%</td>
<td>94.5%</td>
</tr>
<tr>
<td>Mohsen</td>
<td>2007</td>
<td>23</td>
<td>23</td>
<td>4.3%</td>
<td>34.7%</td>
<td>96.0%</td>
</tr>
<tr>
<td>Somocurcio</td>
<td>2007</td>
<td>121</td>
<td>121</td>
<td>5.0%</td>
<td>22.6%</td>
<td>63.0% at 6 months</td>
</tr>
</tbody>
</table>
Surgery for MDR-TB
Current Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Success (95% CI)</th>
<th>Failure (%)</th>
<th>Relapse (%)</th>
<th>Death (%)</th>
<th>Default (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pomerantz et al.</td>
<td>92 (87–96)</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Park et al.</td>
<td>94 (83–99)</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chan et al.</td>
<td>76 (68–83)</td>
<td>7</td>
<td>0</td>
<td>8</td>
<td>6</td>
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<tr>
<td>Somocurcio et al.</td>
<td>63 (54–71)</td>
<td>11</td>
<td>1</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Leuven et al.</td>
<td>77 (65–87)</td>
<td>10</td>
<td>10</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Sung et al.</td>
<td>74 (54–89)</td>
<td>19</td>
<td>7</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Chiang et al.</td>
<td>88 (70–98)</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Naidoo et al.</td>
<td>96 (78–100)</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Kwon et al.</td>
<td>89 (73–97)</td>
<td>9</td>
<td>0</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Park et al.</td>
<td>84 (60–97)</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kir et al.</td>
<td>89 (79–95)</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Mohseni et al.</td>
<td>91 (72–99)</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>88 (76–95)</td>
<td>9</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Shiraishi et al.</td>
<td>91 (80–97)</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Kang et al.</td>
<td>90 (81–96)</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Summary

- Treatment success (%)
  - 84 (78–89)
  - $I^2 = 79$
  - $P < 0.001$

- Other statistics:
  - 6 (4–8)
  - 3 (1–4)
  - 5 (2–8)
  - 3 (1–5)

University of Colorado
Anschutz Medical Campus
Role of Surgery in MDR-TB
UCH-NJH Experience

• 205 patients between 1984-1998

• Resistance to median of 6 drugs

• Treated with a median of 6 drugs

• 130 patients had at least one resection

• Surgery, FQN associated with favorable response

Role of Surgery in MDR-TB
UCH-NJH Experience

Odds Ratios for Individual Variables

Drug resistance (#) \( p < 0.0001 \)

Current drug suscept. (#) \( p = 0.0004 \)

Surgery done \( p = 0.0008 \)

FQN used \( p = 0.02 \)

Non-extensive disease \( p = 0.48 \)

Role of Surgery in MDR-TB
UCH-NJH Experience

Chan ED, et al. AJRCCM 2004;169:1103
Surgery for MDR-TB
Istanbul, Turkey

- 252 MDR-TB patients

- Success related to:
  - Less drug resistance
  - Female
  - Younger age
  - Limited disease

- Results consistent with data from Japan, Korea, Tiawan, and Latvia

## Surgery for MDR/XDR-TB

Seoul, South Korea

<table>
<thead>
<tr>
<th>Treatment Outcome</th>
<th>MDR TB (n = 46)</th>
<th>XDR TB (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td>Probable cure</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Treatment completion</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Unfavorable outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failure</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>Default</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>Transfer out</td>
<td>...</td>
<td>1</td>
</tr>
</tbody>
</table>

MDR TB = multidrug-resistant tuberculosis; XDR TB = extensive drug-resistant tuberculosis.
Nontuberculous Mycobacteria (NTM)

• AKA: Atypical mycobacteria
  Environmental mycobacteria (EM)
  Mycobacteria other than tuberculosis (MOTT)

• Found in water, soils, food, on surfaces
• Resistant to chlorination, disinfectants
• Not obligate pathogens
• No person to person disease transmission
Nontuberculous Mycobacteria

Common NTM Species

• Slow growing mycobacteria
  – M. avium complex (MAC)
  – M. kansasii
  – M. xenopi
  – M. simiae

• Rapid growing mycobacteria
  – M. abscessus
  – M. fortuitum
  – M. chelonae
Nontuberculous Mycobacteria
Common NTM Species

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• Rapid growing mycobacteria
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  – M. fortuitum
  – M. chelonae
# Nontuberculous Mycobacteria

## Comparison with Tuberculosis

<table>
<thead>
<tr>
<th>Feature</th>
<th>TB</th>
<th>NTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFB (+)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Person to person transmission</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Reportable disease</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Incidence increasing in US</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Significant drug resistance seen</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Nontuberculous Mycobacteria

Diagnosis

• Presenting symptoms include chronic productive cough, dyspnea, hemoptysis, fatigue, recurrent pneumonias, fever

• Distinction between colonization, contamination and true infection can be difficult

• Diagnosis usually requires presence of symptoms, characteristic radiologic findings and repeated (2-3) positive cultures/smears after malignancy, TB and fungal disease excluded
Nontuberculous Mycobacteria

Therapy

- Therapy directed in part by susceptibility testing, and should be continued 12 months after Culture (-)

- MAC: macrolide, rifampin, ethambutol, ± amikacin
- M kansasii: rifampin, ethambutol, INH ± macrolide
- M abscessus: macrolide, amikacin, cefoxitin, imipenum

- Indications for surgery include persistent, focal (cavitary or bronchiectatic) parenchymal disease after antimicrobial treatment
Surgery for Pulmonary NTM Disease

Presentation

• Middle-aged females, thin, Caucasian, nonsmokers, right middle lobe / lingular disease

• Isolated large, thick-walled cavitary disease.

• Elderly men, smokers, ETOH abuse, underlying COPD. Resembles TB, may progress to complete lung destruction.
Surgery for Pulmonary NTM Disease

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Surgery for Pulmonary NTM Disease
Results of Surgical Therapy

• Corpe, 1981: 131 cases, mortality 6.9%, BPF 5.3%, 93% sputum conversion rate

• Nelson, 1998: 28 cases, mortality 7.1%, BPF 3.6%, complication rate 32%, 88% sputum conversion rate

• Shiraishi, 2002: 21 cases, mortality 0%, complication rate 29%, sputum conversion 100% → 90% at 2 years

• Mitchell, 2008: 265 cases, mortality 2.6%, complication rate 18%, BPF 4.2%, 87% sputum conversion rate
Surgery for Pulmonary NTM Disease

BPF after Pneumonectomy

- Bronchopleural fistula rate 4.2 % (11/265)
- All had MAC; (+) sputum in 10/11 patients (91%)
- Right pneumonectomy in 9/11 patients (82%)
  - Right pneumonectomy 9/27 (33%)
  - Simple right pneumonectomy 4/16 (25%)
  - Completion right pneumonectomy 4/8 (50%)
- For right pneumonectomy, use of transposed muscle led to a lower rate of BPF formation (26%) than when muscle was not used (50%)
- Lobectomy/Segmentectomy BPF rate: 0.9%

Surgery for Pulmonary NTM Disease

BPF after Pneumonectomy

Shiraishi, 2004: 11 pneumonectomies (5 right, 6 left) for NTM disease

- No mortality; all patients achieved sputum conversion

- BPF rate 27% (3/11 patients)
  - all right side, all covered with muscle
  - Treated with re-closure successfully; one empyema

Shiraishi, 2010: MDR-TB vs. NTM pneumonectomy

- No operative mortality

- MDR-TB: 22 patients (7 right, 15 left)
  - Male 72%, Sputum negative 63%
  - BPF rate 4.5% (1 right)

- NTM: 11 patients (7 right, 4 left)
  - Female 72%, Sputum negative 9%
  - BPF rate 45% (4 right, 1 left)
Surgery for Pulmonary NTM Disease

BPF Reduction Strategies

• Maximize preoperative antibiotic regimen

• Bronchial stump closure

• Muscle flap transposition

• Omental transposition

• ? Eloesser flap
Lung Resection in MDRTB, NTM Cases

Things to Consider…..

- What is the goal of the operation?
- Encourage a multidisciplinary approach
- Is it the right time to operate?
- What is the nutritional status of the patient?
Lung Resection in MDRTB, NTM Cases

Things to Consider…..

• Choose best surgical approach

• Culture all specimens

• Address space issues within hemithorax

• Buttressing of bronchial closure
  – drug resistant organisms
  – poorly controlled infection
Conclusions

- Anatomic lung resection is clearly of benefit for those with MDRTB/XDRTB with acceptable morbidity and mortality

- Lung resection may be accomplished in those with NTM disease with acceptable morbidity and mortality, although further studies are needed to define the long term benefit

- Proper patient selection, multidisciplinary approach are keys factors for success

- Many patients may be amenable to thoracoscopic techniques

- Risk of BPF after right pneumonectomy in NTM patients is high