Disclosure / Disclaimer

• No financial conflicts of interest

• Mention of off-label use of FDA-approved medications
Objectives

• Definitions:

• Discuss the epidemiology and pathogenesis of MDR TB

• Discuss MDR TB treatment regimens and new drugs

• Review special situation
Photojournalist James Nachtwey - TED Prize wish come true
37 photographs in 3 minutes
Millions of lives saved: XDR TB

James Nachtwey:
Moving photos of extreme drug-resistant TB

TED Prize Wish · 5:52 · Filmed Oct 2008
Subtitles available in 27 languages
 □ View interactive transcript

https://www.youtube.com/watch?v=SLhcngIcDNk
MDR TB (Multidrug Resistant)

- *M. tuberculosis* isolate that is resistant to at least INH and RIF
- Can be resistant to other drugs as well
ODR TB (Other drug resistant)

- Resistant to **INH**, sensitive to RIF, with or without resistance to other first or second-line drugs

OR

- Resistant to **RIF**, sensitive to INH, with or without resistance to other drugs

OR

- Resistance to any (1 or more) first-line drugs (**EMB, PZA, SMN**) other than INH or RIF
XDR TB (Extensively drug resistant)

- Resistance to at least **INH and RIF** from among the 1\(^{st}\)-line anti-TB drugs (MDR TB)
- **Plus** resistance to any fluoroquinolone
- **And** to at least one of 3 injectable 2\(^{nd}\)-line anti-TB drugs used in TB treatment
  - Capreomycin
  - Kanamycin
  - Amikacin
Epidemiology

The image

The dandelion is a plant which propagates itself by airborne means. In the same way, social action can spread and take root, carried on the winds of our efforts and the global determination to overcome this disease.

The image also represents the vulnerability of where the disease, located anywhere, and everywhere.

Preventable and curable. GLOBAL PLAN TO STOP TB.

WORLD TB DAY

Mayo Clinic Center for Tuberculosis
The Global TB Situation

Estimated number of cases, 2013

- All forms of TB: 9 million
- HIV-associated TB: 1.1 million
- Multidrug-resistant TB: 480,000 notified pulmonary TB patients
- Children: 550,000

Estimated number of deaths, 2013

- 1.5 million*
- *Including 360,000 deaths among HIV+
- 80,000 HIV negative

2013 MDR-TB Cases (Absolute numbers)
Percentage of New Cases with MDR-TB
1994-2012

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.

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a Figures are based on the most recent year for which data have been reported, which varies among countries.
Percentage of Previously Treated TB Cases with MDR-TB
1994-2012

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.

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* Figures are based on the most recent year for which data have been reported, which varies among countries. The high percentages of previously treated TB cases with MDR-TB in Bahrain, Bonaire – Saint Eustatius and Saba, Cook Islands, Iceland, Sao Tome and Principe, and Lebanon refer to only a small number of notified cases (<10).
Reported TB Cases
United States, 1982–2014*

No. of Cases

Year

2014,
9,412 Cases
3.0 Cases/100,000

*Updated as of June 5, 2015.
Primary MDR TB, United States, 1993 – 2014*

- 1993: 407 (2.5%) to 132 in 2002
- 2003-2013: 87-103 cases, ~1%
- 2014: 91 cases (1.3%)

*Updated as of June 5, 2015.

Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.
Primary MDR TB in U.S.-born vs. Foreign-born Persons
United States, 1993 – 2014*

Foreign-born: Between 1.2 and 1.8% since 1995. 1.3% in 2014
US-born: 1% since 1997 and was 0.5% in 2014.

*Updated as of June 5, 2015.
Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.
Primary Anti-TB Drug Resistance, United States, 1993 – 2014*

INH-R 8.2% in 1993; 9.8% in 2014

MDR TB 2.5% in 1993; 1.0% in 1998; 1.3% in 2014.

*Updated as of June 5, 2015.
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 in U.S.-born vs. Foreign-born Persons, United States, 1993 – 2014*

Foreign-born: 12.1% in 1993 to 10.2% in 2014.

U.S.-born persons: 6.7% in 1993 to 4.2% in 2007, but has increased since then to 7.5% in 2014.

*Updated as of June 5, 2015.
Note: Based on initial isolates from persons with no prior history of TB.
• Extensively drug-resistant TB (XDR-TB) occurs
  • MDR-TB + resistant to FQ + inject able agent
  • Fatality in 52/53 patients with median of 16 days
Killer TB tightens fatal grip

Despite indications that SA is in the forefront of infection, health ministers try to put a clamp on news and smuts global conference

New XDR TB ward at Brooklyn Chest Hospital in Cape Town
Countries that had reported at least one XDR TB Case by July 2014

- XDR TB had been reported by 92 countries by the end of 2013
  - 13 countries had >10 XDR TB cases
  - On average, 9.6% of MDR TB cases have XDR TB

- Highest in:
  - Azerbaijan (Baku city: 12.8%)
  - Belarus (11.9%)
  - Lithuania (24.8%)
  - Tajikistan (Dushanbe city and Rudaki district: 21%)

Extensively drug-resistant TB (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.
Emergence of New Forms of Totally Drug-Resistant Tuberculosis Bacilli

Super Extensively Drug-Resistant Tuberculosis or Totally Drug-Resistant Strains in Iran

Ali Akbar Velayati, MD; Mohammad Reza Masjedi, MD; Parissa Farnia, PhD;
Payam Tabarsi, MD; Jalladein Chahvari, MD; Abol Hassan ZiaZarifi, PhD;
and Sven Eric Hoffner, MD

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 numbers of tandem repeats (VNTR).

Results: Of 146 MDR-TB strains, 8 XDR isolates (5.4%) and 15 TDR isolates (10.3%) were identified. The remaining strains were either susceptible (67%) or had other resistance 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 [RF], streptomycin, ethambutol, and pyrazinamide). The median of in vitro drug resistance for all studied cases was INH and RF. The XDR or TDR strains were collected from both immigrants (Afghan, 30.4%; Azerbaijani, 8.6%; Iraqi, 4.3%) and Iranian (56.5%) MDR-TB cases. In such cases, the smear and cultures remained positive after 18 months of medium treatment with second-line drugs (ethionamide, para-aminosalicylic acid, cycloserine, ofloxacin, amikacin, and ciprofloxacin). Spoligotyping revealed Haarlem (39.1%), Beijing (21.7%), FAI (21.7%), and CAS (17.3%) superfamilies of M tuberculosis. These superfamilies had different VNTR profiles, which eliminated the recent transmission among MDR-TB cases.

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

(CHEST 2009; 136:420–425)
Emergence of Totally Drug Resistant (TDR) TB

- XDR TB plus cycloserine, PAS, all injectables
- 15 TDR isolates; 56% Iranian, 30% Afghani
- Cases + smear/culture after 18 months Rx
- 95% XDR/TDR had history of prior TB treatment
- 10% had resistance to all second line drugs (Iranian)
  - Believed due to exposure to aminoglycosides and FQ for treatment of other respiratory diseases
- Recent transmission was not the reason for emergence of TDR

Chest 2009; 136:420-425
2012: Totally drug-resistant TB?

WHO meets in Geneva; Central TB Unit sending team

Panic and chill in the air as TDR-TB claims 3 of 12 lives

India only the third country where the deadliest form of tuberculosis has struck

People the 12 patients came in contact with to be identified and tested for TB

Less than a week after top chest physician Dr Zarin F Udawatta broke the news of presence of totally drug resistant tuberculosis (TDR-TB) cases in the city, it was revealed on Friday that three of the 12 patients he studied have died in the past two weeks.

Nobody would have known of three deaths if the Directorate of Health Services and BMC’s health officers, completely taken aback by Dr Udawatta’s research, had not launched a drive to visit the 12 patients to collect sputum samples of their family members.

While the identities and addresses of the 12 patients are not available, Mumbai Mirror traced one of the dead patient’s family to its Patilwadi, Ranade Road, Dadar (west) home.

Supriya Daware, 20, died on January 5 after three years of being treated for TB across four hospitals. She was first diagnosed with TB when she was in class 12.

Ashok Daware, her distraught father, said she was last taken to the TB Hospital in Sewri on December 29. “They told her she was in the last stage. My daughter shrank from 42 kg to 18 kg in the three years she was being treated.”
Impact of MDR TB

- Enormous resource sink
- Prolonged treatment/monitoring required
- Large cost incurred (drugs, hospitalization, DOT, lab testing)
- Major impact to individual health
- Prolonged isolation, inability to work
- Pool of clinical experts diminishing
- Increasingly complex healthcare systems to navigate
- Therapy for contacts?
Treatment for LTBI in contacts of MDR-TB patients, Federated States of Micronesia, 2009-2012.

Bamrah S¹, Brostrom R¹, Dorina F², Setik L², Song R¹, Kawamura LM³, Heetderks A¹, Mase S¹.

Abstract

SETTING: Few studies have shown the operational feasibility, safety, tolerability, or outcomes of multidrug-resistant latent tuberculous infection (MDR LTBI) treatment. After two simultaneous multidrug-resistant tuberculosis (MDR-TB) outbreaks in Chuuk, Federated States of Micronesia, infected contacts were offered a 12-month fluoroquinolone (FQ) based MDR LTBI treatment regimen.

DESIGN: Between January 2009 and February 2012, 119 contacts of MDR-TB patients were followed using a prospective observational study design. After MDR-TB disease was excluded, 12 months of daily FQ-based preventive treatment of MDR LTBI was provided by directly observed therapy.

RESULTS: Among the 119 infected contacts, 15 refused, while 104 began treatment for MDR LTBI. Of the 104 who initiated treatment, 93 (89%) completed treatment, while 4 contacts discontinued due to adverse effects. None of the 104 contacts who undertook MDR LTBI treatment of any duration developed MDR-TB disease; however, 3 of 15 contacts who refused and 15 unidentified contacts developed MDR-TB disease.

CONCLUSION: Providing treatment for MDR LTBI can be accomplished in a resource-limited setting, and contributed to preventing MDR-TB disease. The Chuuk TB program implemented treatment of MDR LTBI with an 89% completion rate. The MDR LTBI regimens were safe and well tolerated, and no TB cases occurred among persons treated for MDR LTBI.

Comment in
Treatment Costs

- Direct costs, mostly covered by the public sector
- $134,000 per MDR TB patient (average)
- $430,000 per XDR TB patient (average)
- $17,000 per non-MDR TB patient

Estimated cost per patient treated for drug-susceptible TB, 2013

- **TB caseload (notified TB cases)**
  - 1,500,000
  - 1,000,000
  - 250,000

- **Cost per patient treated (2014 US$, log scale)**
  - 10,000
  - 5,000
  - 1,000

- **GDP per capita (2014 US$, log scale)**
  - 20,000
  - 10,000
  - 5,000
  - 2,000

- **WHO region**
  - Africa
  - Americas
  - Eastern Mediterranean
  - European
  - South-East Asia
  - Western Pacific

Countries included: Afghanistan, Bangladesh, Brazil, Cambodia, China, Colombia, DR Congo, Ethiopia, India, Indonesia, Kenya, Kyrgyzstan, Mauritania, Netherlands, Nigeria, Pakistan, Russia, South Africa, Thomson Morocco, Uganda, Vietnam, Zimbabwe.
Estimated cost per patient treated for MDR-TB, 2013

The diagram illustrates the estimated cost per patient treated for multi-drug resistant tuberculosis (MDR-TB) in 2013, plotted against GDP per capita (2014 US$, log scale). Each country is represented by a circle whose size is proportional to the MDR-TB caseload (notified cases). The WHO regions are color-coded as follows:

- African
- Americas
- Eastern
- Mediterranean
- European
- South-East Asia
- Western Pacific

Countries with high MDR-TB caseloads and relatively low GDP per capita are more heavily emphasized in the graph.
Which Patients are at Risk of Drug Resistant TB?

- Birth/ residence in country with high incidence of drug resistant TB
- U.S. residents who travel to high risk areas
- Exposure to patient with relapse or failure
- Prior treatment for TB
- Treatment failure
- Relapse in a patient not on DOT
- Poor adherence
- Clinical deterioration during 4 drug therapy
Why Do We Have Drug Resistance?

- Inadequate treatment
  - Incorrect regimen (lack of drugs or knowledge)
  - Poor adherence
  - Malabsorption

Treatment failure / relapse with drug resistant TB

Transmission of drug resistant TB
Transmission of Drug-Resistant TB

- Transmitted same way as drug-susceptible TB

- Drug resistance is divided into two types
  - **Primary resistance** develops in persons initially infected with resistant organisms
    - Healthcare-associated transmission
    - Community transmission
  - **Secondary resistance** (acquired resistance) develops during TB therapy
    - Nonadherence to therapy
    - Inappropriate therapy
Pathogenesis of Drug Resistance

Spontaneous mutations develop as bacilli proliferate to $>10^8$

<table>
<thead>
<tr>
<th>Drug</th>
<th>Natural Resistance Mutation Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>$10^8$</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>$10^6$</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>$10^6$</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>$10^5$</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>$10^6$</td>
</tr>
<tr>
<td>INH and RIF</td>
<td>$10^{14}$</td>
</tr>
</tbody>
</table>
Drug-resistant mutants in large bacterial population

Multidrug therapy:
No bacteria resistant to all 3 drugs

Monotherapy:
INH-resistant bacteria proliferate
Spontaneous mutations develop as bacilli proliferate to $>10^8$.

INH resistant bacteria multiply to large numbers.

INH mono-resistant mutants killed, RIF-resistant mutants proliferate $\rightarrow$ MDR TB.
What Do Patients with MDR TB Need?

• Patients with MDR TB need to have
  • Accurate and prompt identification
  • Notification to the field staff and provider(s)
  • Appropriate case management
  • Appropriate treatment based on drug susceptibility test results
  • Appropriate infection control measures instituted
## Treatment Strategies

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standardized treatment</strong></td>
<td>Regimen is designed based on <strong>Drug Resistance Surveillance (DRS)</strong> data from a <strong>representative patient population</strong>.</td>
</tr>
<tr>
<td><strong>Empirical treatment</strong></td>
<td>Regimen is individually designed based on patient’s <strong>previous history of TB treatment</strong> and <strong>DRS data as above</strong>.</td>
</tr>
<tr>
<td><strong>Individualized treatment</strong></td>
<td>Regimen is designed based on the patient’s <strong>previous history of TB treatment</strong> and <strong>individual DST results</strong>.</td>
</tr>
</tbody>
</table>
## Antituberculosis Drugs

<table>
<thead>
<tr>
<th>First-Line Drugs</th>
<th>Second-Line Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Streptomycin</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Cycloserine</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>p-Aminosalicylic acid</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Ethionamide</td>
</tr>
<tr>
<td>Rifabutin*</td>
<td>Amikacin or kanamycin*</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>Capreomycin</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin*/Moxifloxacin*</td>
</tr>
</tbody>
</table>

* Not approved by the U.S. Food and Drug Administration for use in the treatment of TB
What is Bedaquiline?

- BDQ is a proton pump inhibitor for ATP synthase that is a diarylquinoline
- the first new class of drugs to obtain FDA approval for a TB indication in 40 years
Linezolid

- Oxazolidinone
  - Bacteriostatic; binds rRNA; inhibit protein synthesis
- Since 2000- selected cases, recently a 2\textsuperscript{nd} or 3\textsuperscript{rd} line drug
- Adverse effects:
  - **Pancytopenia and peripheral/optic neuritis**
    - May or may not be reversible
    - May or may not be ameliorated by vitamin B\textsubscript{6}
  - Risk of serotonin syndrome with selective serotonin reuptake inhibitors (SSRIs)- use with caution
  - Lactic acidosis
- Consider using 600 mg daily (300mg/day being studied)

Lee et al., NEJM 2012;367
Third-Line Drugs Used in MDR TB Treatment -2

- **Clofazimine**
  - More commonly used in patients with leprosy
  - Used in selected cases
  - Needs Investigational New Device (IND) from FDA

- **Bedaquiline**
  - 1\textsuperscript{st} new class of TB medication approved since RIF
  - New class of antibiotics, diarylquinolones
  - Given as part of MDR combination therapy
  - New mechanism of action: inhibits ATP synthase
Step 1

Begin with any 1st-line agents to which the isolate is susceptible

Add a fluoroquinolone and an injectable drug based on susceptibilities

**First-line drugs**
- Pyrazinamide
- Ethambutol

**Fluoroquinolones**
- Levofloxacin
- Moxifloxacin

**Injectable agents**
- Amikacin
- Capreomycin
- Streptomycin
- Kanamycin

Adapted from Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd Ed., available from Curry International Tuberculosis Center
Step 1

Begin with any 1st-line agents to which the isolate is susceptible.

Add a fluoroquinolone and an injectable drug based on susceptibilities.

**First-line drugs**
- Pyrazinamide
- Ethambutol

**Fluoroquinolones**
- Levofloxacin
- Moxifloxacin

**Injectable agents**
- Amikacin
- Capreomycin
- Streptomycin
- Kanamycin

PLUS

Step 2

Pick one or more of these

Add 2nd-line drugs until you have 4-6 drugs to which isolate is susceptible (which have not been used previously).

**Oral second-line drugs**
- Cycloserine
- Ethionamide
- PAS

Step 1

Begin with any 1st-line agents to which the isolate is susceptible

Add a fluoroquinolone and an injectable drug based on susceptibilities

First-line drugs
- Pyrazinamide
- Ethambutol

Fluoroquinolones
- Levofloxacin
- Moxifloxacin

Injectable agents
- Amikacin
- Capreomycin
- Streptomycin
- Kanamycin

PLUS
One of these

PLUS
One of these

Step 2

Pick one or more of these

Oral second-line drugs
- Cycloserine
- Ethionamide
- PAS

Add 2nd-line drugs until you have 4-6 drugs to which isolate is susceptible (which have not been used previously)

Step 3

Consider use of these

Third-line drugs
- Linezolid
- Clofazimine
- Bedaquiline
- High-dose isonizid
- Imipenem
- Amoxicillin/Clavulanate

Adapted from Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd Ed., available from Curry International Tuberculosis Center
Principles for Managing MDR TB

• MDR TB should never be treated without expert consultation of a specialist in MDR TB treatment

• Patients must be treated with a regimen of at least 3-5 anti-TB medications to which the strain is likely to be susceptible (4-6 or better)
Principles for Managing MDR TB - 2

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

• When initiating or revising therapy, always attempt to use at least 3 previously unused drugs to which there is *in vitro* susceptibility
  • One agent should be an injectable agent
  • A good response does not justify continuation of an inadequate regimen
Principles for Managing MDR TB - 3

• Injectable agents can be given 5 days/wk initially
  • After culture conversion, dosing can be 2-3x/wk

• With extensive disease or slow conversion of sputum cultures, the injectable should be used for longer periods after culture conversion

• Streptomycin resistance may accompany INH resistance

• Surgery should be considered if a patient’s cultures fail to convert to negative after 4 months of appropriate treatment
Principles for Managing MDR TB - 4

• Some experts use EMB at a dose of 25 mg/kg daily when used as treatment of patients with MDR TB
  • If this higher dose is used, monthly visual monitoring is recommended

• Fluoroquinolones:
  • Oral agents, well tolerated
  • One of the two most important agents in MDR treatment
Specific Drug Resistances

• If isolates show resistance to INH only at a low concentration, INH 900 BIW (high intermittent dose) can be used
  • Do not rely on its effectiveness as a main agent

• There is cross-resistance between amikacin and kanamycin

• Determination of resistance to PZA is problematic, but is uncommon in the absence of resistance to other 1\textsuperscript{st}-line drugs
  • If mono-resistance to PZA is found, consider the specimen may be \textit{M. bovis}, not \textit{M. tb}
Rifampin Resistance

- Resistance to RIF is generally associated with cross-resistance to rifabutin and rifapentine
  - When RIF resistance is present but *in vitro* sensitivity to rifabutin is reported, treatment should still be the same as if RIF-resistant

- For all with RIF-resistance (mono-RIF or MDR TB), consider extended therapy (up to 18-24 months) if:
  - There is cavitary or extensive disease
  - The patient is HIV-positive or has risk factors for HIV infection
  - The patient is immunosuppressed
  - Time to culture conversion is prolonged
Treatment of HIV-related MDR-TB

- Rapid diagnosis of drug resistance
- Important to treat with the most active anti-TB regimen available
- Initiate antiretroviral therapy based on CD$_4$ count and other individual patient variables
- Use therapeutic drug monitoring when drug interactions are possible or malabsorption is suspected
MDR TB in Pregnancy

• Most medications used to treat MDR TB are known to cause fetal abnormalities or have not been studied adequately regarding their safety in pregnancy

• PZA can be used as a main agent and is recommended by WHO & ATS
  • WHO recommends its use in pregnancy even for drug-susceptible TB patients
  • In the U.S., it is considered a category C agent

OK to use: INH, RIF, EMB, PZA, PAS, Cycloserine
Do not use: FQ, Aminoglycoside, Ethionamide
Monitoring Serum Drug Levels

- Serum drug level monitoring can be used in patients with the following medical conditions:
  - HIV positive/AIDS
  - Diabetes
  - Malabsorption syndromes
  - Renal failure
  - Failure to improve on treatment/relapse
  - MDR TB
Drug Intolerance

• In general, length of treatment for patients with drug intolerance is the same as for those who have drug resistance
DOT for MDR TB

- Essential that MDR TB patients be treated with Directly Observed Therapy (DOT)
  - Improved overall cure rates
  - Reduction in community prevalence of MDR
- Intermittent regimens should not be used
- All 2\textsuperscript{nd}-line agents must be administered daily
- Twice/day DOT should be used when feasible, and more frequent dosing than twice daily should be avoided
- All doses must be observed
Directly Observed Therapy
Indications for Surgery - 1

• Adequate 1\textsuperscript{st} and 2\textsuperscript{nd} -line regimens of anti-TB medications have failed to cure or cause \textit{M. tb} cultures to convert to negative within 4 to 6 months

• Sufficient medications are available to treat the patient postoperatively

• Disease is sufficiently localized to allow lobectomy or pneumonectomy

• Remaining lung tissue is relatively free of disease

• Acceptable surgical risk, with sufficient pulmonary reserve to tolerate the resection
Indications for Surgery - 2

• Additional possible indications for surgery:
  ✓ Major bronchial obstruction
  ✓ Severe hemoptysis
  ✓ Bronchopleural fistula (BPF)

• Even after lung resection, the patient must complete a full course of treatment (i.e., 18-24 months after culture conversion) with medications to which the *M. tb* strain is susceptible
Role of Public Health

Contact Investigation

All cases begin as a contact
Treatment of Contacts to Drug Resistant TB

• Persons exposed to INH-resistant TB:
  - Rifampin:
    – 4 months adults
    – 6 months children

• Persons likely infected with MDR TB:
  - 6-12 months FQ and EMB, or PZA and EMB (i.e., ≥ 2 drugs to which organism is susceptible)
  • Limited experience with FQ as single agent
Follow-up of MDR TB Patients after Treatment Completion

- Patients with TB resistant to INH and RIF or treated without RIF/RBT
  - Medical evaluation every 4 months during the 1\textsuperscript{st} year after treatment completion
  - Then every 6 months during the 2\textsuperscript{nd} year
- Months: 4, 8, 12, 18, 24 post treatment
- Educate about relapse and to return if they develop symptoms
Discharge

• What do you need to know?
  • About the patient
  • About the home setting
  • About visitors
Infection Control Issues Related to Multidrug Resistant TB Patients

• MDR TB patients should remain hospitalized or on home isolation if an outpatient until:
  • 3 sputum smears are AFB- negative
  • Clinically improved and near resolution of cough
  • Tolerating an appropriate treatment regimen
  • Patient agrees to DOT and it has been arranged
  • Proper arrangements have been made for follow-up
  • A home assessment should be done with evaluation for insertion of a HEPA filter in the residence
Returning MDR TB Patients to Work or School-Culture Conversion

- MDR TB patients should be kept from returning to work or school, or transferring to another congregate setting such as a shelter or nursing home until culture conversion is confirmed
  - 2 consecutive negative cultures at least 2 weeks apart
- Culture conversion is necessary unless the patient will be transferred to an airborne infection isolation room in the congregate setting
- Exceptions can be made for certain types of work settings, if all the conditions in previous slide are met
  - Decided in consultation w/ Office of Medical Affairs
Situations Where Culture Conversion Should Be Confirmed Prior to Return to Work

- Work sites where individuals with drug susceptible TB and MDR TB should be excluded until culture conversion is confirmed:
  - Work sites where persons with HIV or other immunocompromised patients are cared for
  - Neonatal intensive care units
  - Patient care areas
  - Nursing homes
  - Congregate settings such as daycare and schools
# Drug Regimens for MDR TB

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Initial Phase</th>
<th>Continuation</th>
<th>Total length</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH/RIF + SMN</td>
<td>PZA/EMB/FQ &amp; IA, 5 days a week</td>
<td>6 months after culture conversion</td>
<td>18-24 months after culture conversion</td>
</tr>
<tr>
<td>INH/RIF/EMB + SMN</td>
<td>PZA/FQ/IA, 5 days a week plus at least 1-2 second-line agents*</td>
<td>PZA/FQ, plus at least 1-2 second-line agents</td>
<td>Extend therapy:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Cavitary disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- HIV positive or risk factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Immuno-suppressed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Prolonged time to culture conversion</td>
</tr>
<tr>
<td>INH/RIF/PZA + SMN</td>
<td>EMB/FQ/IA, 5 days a week plus at least 1-2 second-line agents*</td>
<td>EMB/FQ, plus at least 1-2 second-line agents</td>
<td></td>
</tr>
<tr>
<td>INH/RIF/PZA/EMB + SMN</td>
<td>FQ/IA, 5 days a week plus at least 2-3 second-line agents*</td>
<td>FQ plus at least 2-3 second-line agents</td>
<td></td>
</tr>
</tbody>
</table>
# Drug Regimens for MDR TB

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Initial Phase</th>
<th>Continuation</th>
<th>Total length</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INH/RIF/EMB/SMN/KAN/ETH/RBT + PZA</strong> (strain W and W variants)</td>
<td><strong>FQ/IA plus at least 2-3 other agents to which the organism is susceptible</strong></td>
<td><strong>FQ plus at least 2-3 second line agents to which organism susceptible</strong></td>
<td>18-24 months after culture conversion</td>
</tr>
<tr>
<td><strong>INH/RIF/EMB/SMN/FQ/+ 2\textsuperscript{nd}-line IA ±PZA</strong> (i.e. XDR TB)</td>
<td><strong>Any 3-4 drugs to which organism is susceptible. Consider Linezolid, Clofazimine, γ-Interferon &amp; Bedaquiline</strong></td>
<td><strong>Until culture conversion</strong></td>
<td><strong>Any 3-4 drugs to which organism is susceptible. Consider Linezolid, γ-interferon &amp; Clofazamine</strong></td>
</tr>
</tbody>
</table>

- At least 24 months after culture conversion
- Ideal therapy duration unknown
- Evaluate for early surgery
New Hope
Case #1

The DR Coordinator informs you that your patient at the private doctor’s office has INH resistant tuberculosis. The patient has a cavity in the RUL, and still has positive cultures into the 2nd month of therapy.

1. What are the different options for treatment, and the length of therapy?
2. Who should be informed?
3. How should the patient’s 4 year old and 10 year old children be treated for LTBI?
Case #2

Patient in the clinic is still infectious after 1 ½ months of INH/RIF/PZA/EMB. The report comes back from the lab that the patient is resistant to INH/RIF/PZA and sensitive to EMB.

1. How should this patient be treated initially and for how long?
2. When can the patient return to work/school?
3. What should be discussed in the case management meeting about this patient?
4. How long should the patient be followed after completing therapy 18 months later?
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