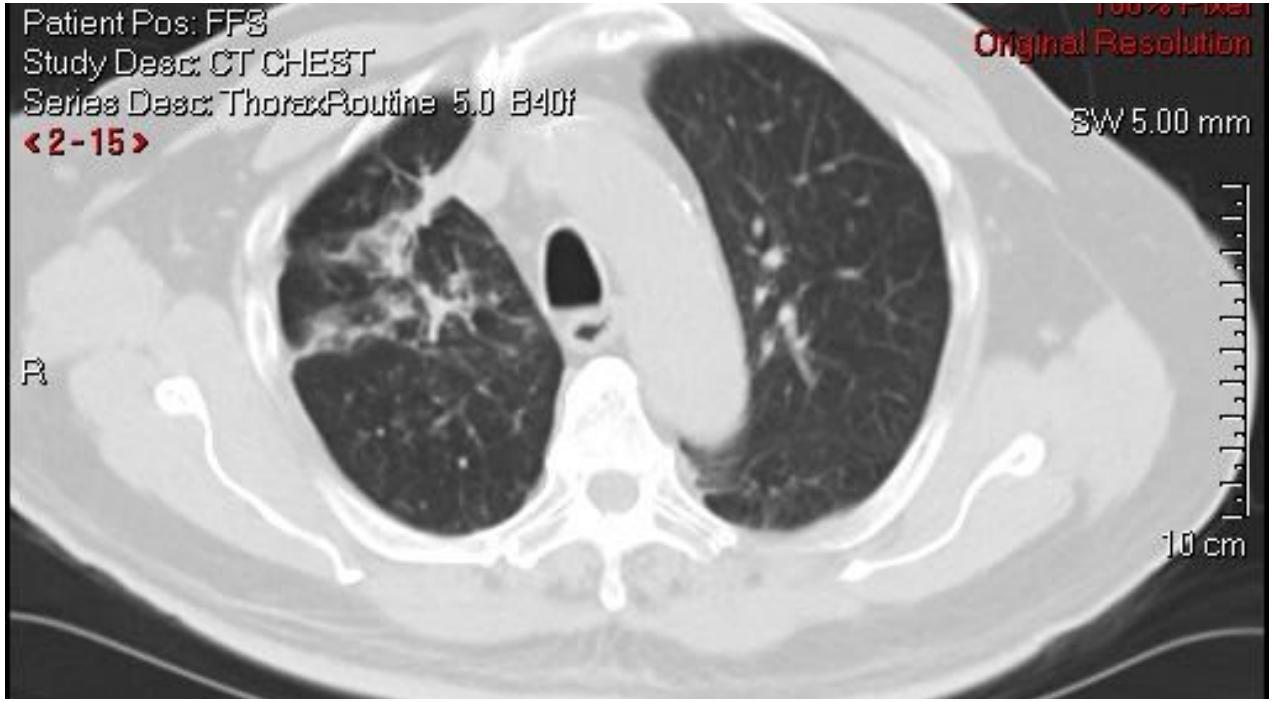
Drug Resistant Tuberculosis

Debra D. Poutsiaka, MD, PhD
Tufts Medical Center
Tufts University School of Medicine
Boston, Massachusetts

Case Presentation

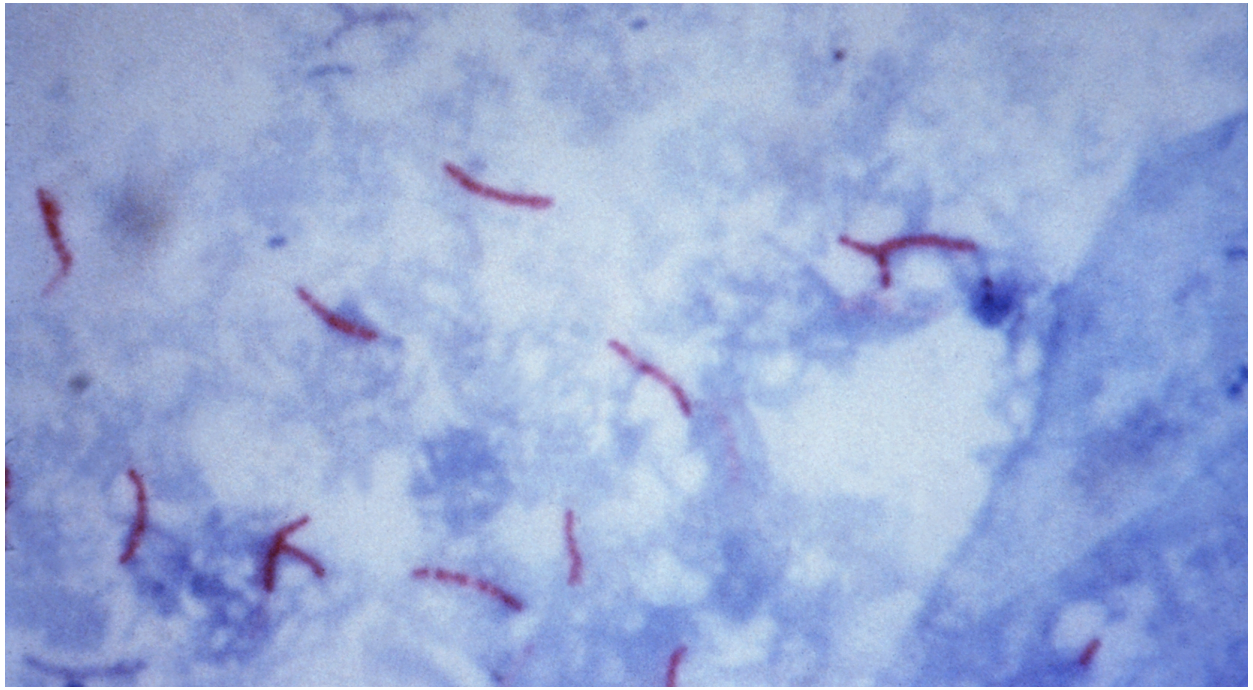
- 73 year old Asian man was admitted to Tufts Medical Center after 2 days of hemoptysis on December 27, 2003
- Past medical history
  - Tuberculosis 1996 treated for 12 months
  - Tuberculosis 2001 treated with 3 drug for 9 months
- Social history: The patient had recently arrived from Myanmar
- Physical and laboratory examinations were unremarkable

CT scan of the chest



Based on the history and presentation, tuberculosis was suspected. The patient underwent bronchoscopy.

Acid-Fast Smear



Conventional Ziehl-Neelsen Stain

Source: Wikipedia.com

Subsequent Course

Patient was started on

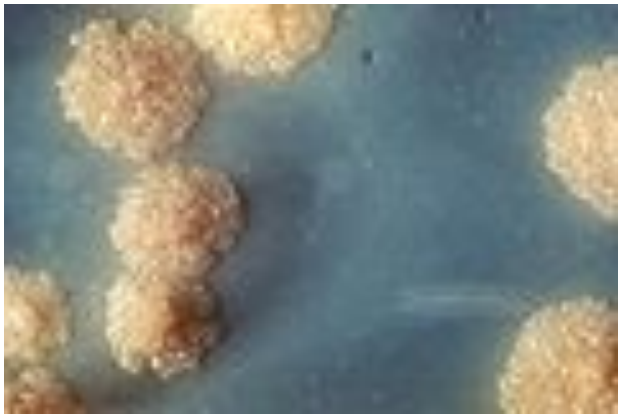
- isoniazid
- rifampin
- pyrazinamide
- ethambutol
- levofloxacin

Pending – cultures and drug susceptibility testing (DST)

[redacted]e and Drug Susceptibility Testing (DST) Results *8 weeks later*

Mycobacterium tuberculosis

capreomycin	S
ciprofloxacin	S
cycloserine	S
ethambutol	R
ethionamide	S
isoniazid	R
kanamycin	S
pyrazinamide	R
rifampin	R
streptomycin	R



M. tuberculosis colonies

Source: Wikipedia

Multi-Drug Resistant (MDR) TB

Current World Health Organization definition:

M. tuberculosis resistant to isoniazid and rifampin

Case

Based on DST, the patient's treatment (DOT) was changed to:

- Levofloxacin (a fluoroquinolone)
- Para-aminosalicylic acid
- Capreomycin (an injectable)
- Cycloserine

His sputum cultures converted to negative prior to this change.

History of MDR-TB

Early to mid-1990's:

Outbreaks of MDR-TB noticed in the United States
(New York, Florida, Texas)

2007 world-wide estimate:

Of 17,690 M. tuberculosis isolates, 20% were MDR-TB
(Shah, Emerging Infections Disease, 2007)

2008 WHO estimates:

Each year 424,000 people develop MDR-TB (50% in China, India)
100,000 people treated for MDR-TB (only 28% of MDR cases)
MDR-TB deaths – 150,000 in 2008
12 countries – at least 6% of new TB cases are MDR-TB
5 countries – MDR-TB in 50% or more among previously treated

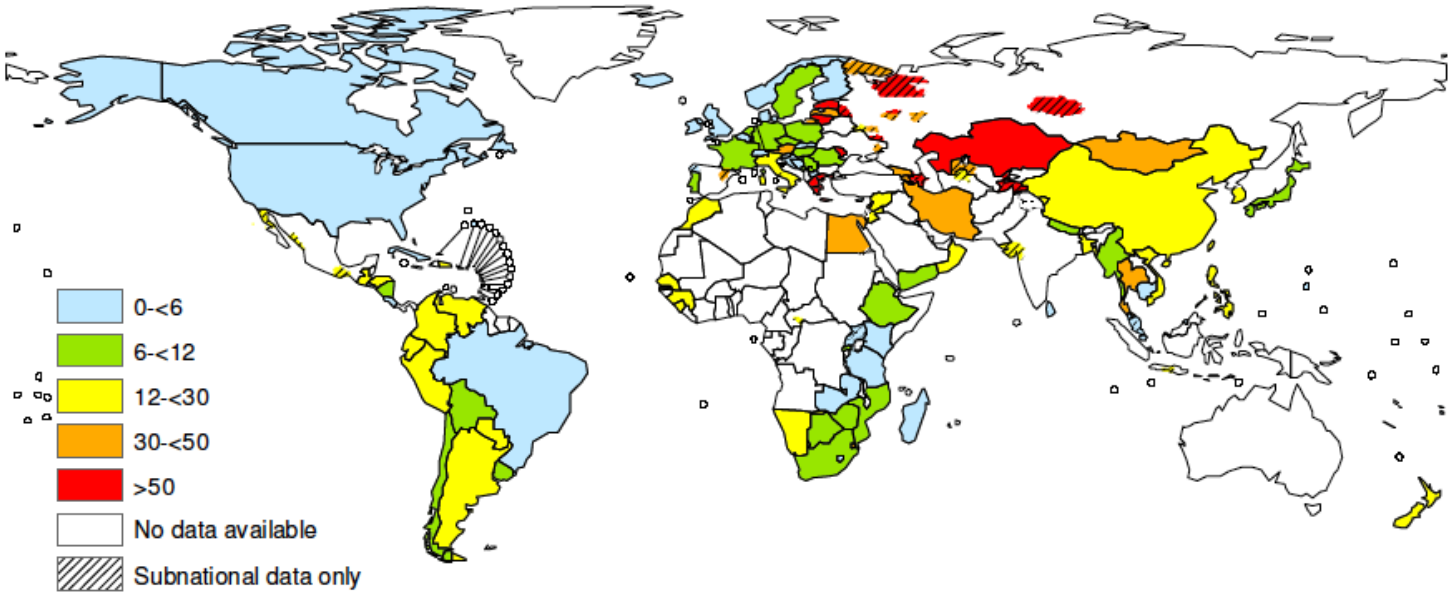
http://www.who.int/tb/challenges/xdr/xdr_mdr_factsheet_2007_en.pdf

World-wide MDR-TB Among the Previously Treated

Proportions of MDR among previously treated TB cases, 1994-2010

World Health Organization

THE STOP TB DEPARTMENT



Emergence of Extensively Resistant (XDR) Tuberculosis

1990's to 2000's, increased resistance detected

2007 revised WHO definition of XDR-TB:

- MDR-TB (resistant to INH and rifampin) also resistant to
  - Any fluoroquinolone
  - At least one injectable second line agent (amikacin, kanamycin or capreomycin)

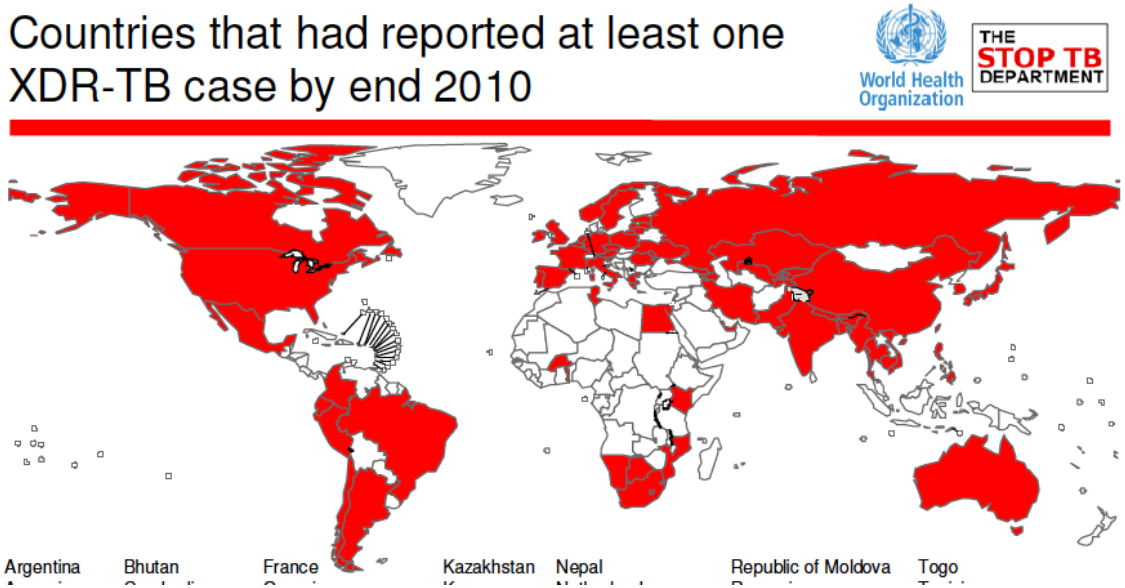
Risks: previous TB treatment, HIV infection, homelessness, alcoholism, bilateral and cavitary lesions, failure to take at least 80% of doses

(Kliiman, Ann Int Med, 2009, study in Estonia; Shin, Am J Resp Crit Care Med, 2010)

XDR-TB Worldwide

2008 data

- Data from 48 countries – 5.4% of MDR-TB was XDR
- In 8 countries, >10% of MDR-TB was XDR



http://www.who.int/tb/challenges/mdr/drs_maps_feb2011.pdf

MDR-TB in Haiti

- Data is sparse and possibly not representative of the entire country.
- Surveys from 1982-1996:
  - <1% of TB cases were MDR

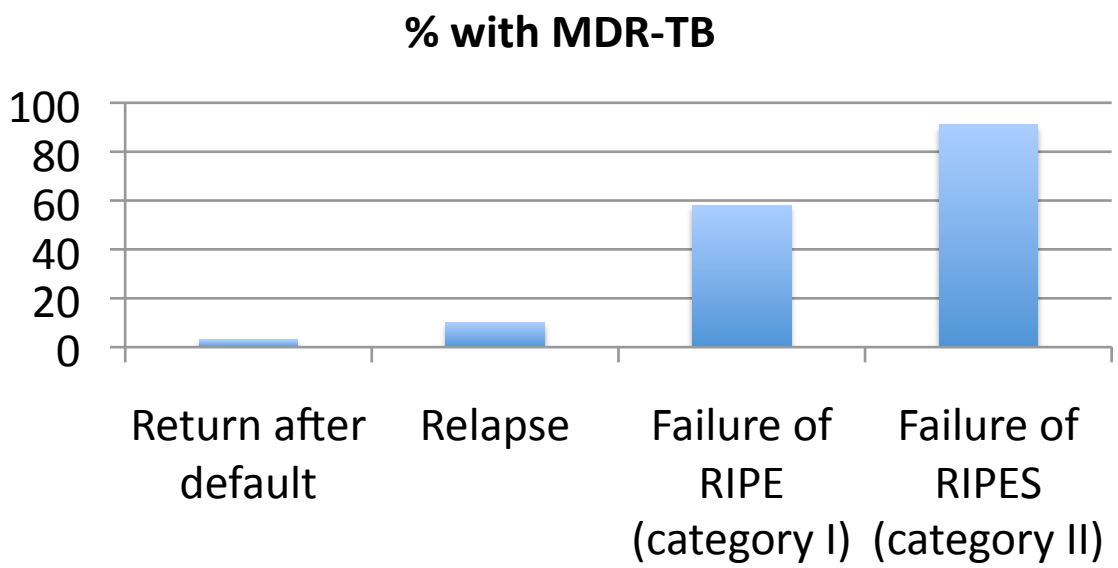
    (Pitchenik NEJM 1982) Scalcini Am Rev Resp Dis 1990, Malone CID 1994, Chaisson Am J Resp Crit Care Med 1996)
- 2000-2002 survey of one HIV testing site:
  - Of 330 isolates, 8% were MDR
  - 6% of new cases
  - 20% of recurrent cases
  - "Hot Zone" – sites with >5% resistant TB in first episodes where transmission to the general population is likely

(Joseph AIDS 2006)

WHO Data and Estimates for Haiti

- 2008
  - 14,662 cases of TB countrywide
  - 44 reported as MDR (0.3%)
- 2010 estimates and data
  - Estimated 260 new TB cases are MDR-TB (2.1%)
  - Estimated 44 of retreatment cases are MDR (12%)
  - However, only 41 cases were reported
  - Estimated 0.5 DST for 23,000 cases of TB per 10,000,000
- Under-reporting

Risk Factors for MDR-TB



R: rifampin

I: isoniazid

P: pyrazinamide

E: ethambutol

S: streptomycin

Default: 2 month or more interruption of therapy for any reason

Relapse: Redevelopment of smear-positive TB after previous treatment and cure

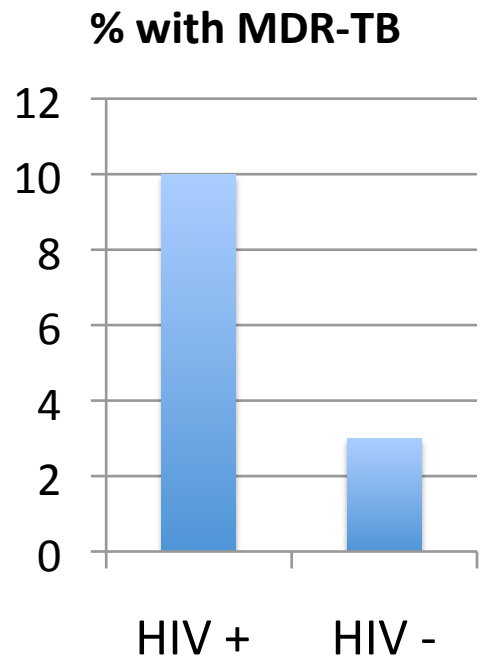
Failure: While on treatment, persistence of positive smears, or reversion of negative smears to positive

http://whqlibdoc.who.int/publications/2010/9789241599191_eng.pdf

Is HIV a Risk Factor for MDR-TB?

Data is scarce

- Estimated three-fold increased risk for MDR-TB in HIV patients
  - Study done at a Haitian HIV testing center therefore the results might not be representative of the country, world.
- WHO: too little data but it appears that HIV positive people are more likely to harbor MDR-TB



http://whqlibdoc.who.int/publications/2010/9789241599191_eng.pdf; Joseph, AIDS 2006

Approach to the MDR-TB Patient

Suspect MDR-TB in a patient with symptoms of TB (cough, hemoptysis, fever/chills, weight loss)

and…

A history of prior treatment for TB

or

Who is a close contact of an MDR-TB patient

Barriers to treatment: cost, duration

Approach to the Patient with MDR-TB

Care is based on

- Appropriate triage and infection control
- Education
- Support
- Patient's medical history
- Appropriate testing
- Directly observed therapy
- Adherence
- Close follow up assessments

Appropriate triage and infection control

- Suspected (or known) MDR patients should
  - Wait in a well-ventilated area
  - Cover mouth with tissues when coughing if smear-positive or a new case
  - If HIV-positive and smear-positive or a new case, should not be seen in the HIV/HAART area

Educate the Patient about MDR-TB

- It develops when medications are not taken regularly
- It can be transmitted to others, especially patients with HIV
- It is most infectious at the start of therapy so good ventilation at home is important
- Treatment lasts at least 2 years
  - Consists of 2nd line agents, which are weaker
  - No other treatment exists
  - Side effects occur but are usually manageable
- Coughing close contacts should be tested
- Notify program of plans to travel or move

Form a contract with the MDR-TB Patient

- The patient will undergo treatment for at least 2 years
- The patient is willing to undergo directly observed therapy (DOT)
- Agree upon the person who is to be the "treatment supporter"
- The patient will come to the TB clinic monthly
- Treatment will stop if the patient does not take medications as directed

Directly Observed Therapy (DOT)

- Observation and recording of patient taking medication
- Medication checks for correct medication
- Monitor for side effects
- Provide encouragement
- Respond quickly (within 24 hours) if patient misses a dose
  - Visit home
  - Assess for reason
  - Give medication
  - Contact healthy facility if problem continues
- Collect monthly sputum samples
- Treatment supporter can function as the DOT agent

Treatment Supporters

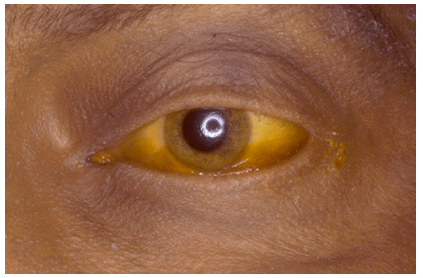
- Should live geographically close to patient
- Must be accepted by the patient
- Must be committed
- Has received MDR-TB specific training
- Supports no more than 2 patients
- Is not immunosuppressed

Support by the health facility

- Discuss integration of medications into daily routine
- Dispense and record medications
- Provide food packages
- Provide support for transportation
- Refer to a support group
- Arrange for injections to be given at a local health center
- Arrange for education of the treatment supporter

Clinical Assessment of the MDR-TB Patient

- History
  - Present illness
  - Past medical history, especially TB history
- Physical examination – to include:
  - Weight
  - Vital signs: heart rate, blood pressure, respiratory rate, temperature
  - Pallor
  - Scleral icterus
  - Thrush



http://hardinmd.lib.uiowa.edu/cdc/6053.html;
http://library.med.utah.edu/WebPath/jpeg2/EYE040.jpg

Testing of the MDR-TB Patient

- HIV testing if status is unknown
- Complete blood count
- Aspartate transaminase (AST)
- Alanine transaminase (ALT)
- Bilirubin
- Creatinine
- Potassium
- Pregnancy test (more on pregnancy later)

Initial Testing of the MDR-TB Patient: Sputum Collection of 2 Samples

- For microscopic examination, culture and DST (or molecular detection of resistance genes)
- Collect early morning specimen if possible
- Patient should rinse his or her mouth beforehand
- Goal – deep specimen, not saliva or nasal secretions
- Perform in an open space
- Both hands should be placed on pelvis, then sit or squat
- Open container and cough sputum into it

Empiric Therapy

- Therapy not yet guided by DST – a best guess
- Those who have relapsed during treatment or defaulted
  - Treat as MDR-TB or again with first-line agents??
  - Unclear guidance from WHO
- Those who have undergone prior treatment
  - Presume that the patient has MDR-TB
  - Start "Category 4" regimen – second-line agents
    - Standardized
    - Individualized

Standardized Category 4 Regimen

Z-Km-Lfx-Eto-Cs-PAS

Pyrazinamide: 3½ tablets (1750 mg)

Kanamycin: 1 injection (1000 mg)

Levofloxacin: 2 tablets (500 mg)

Ethionamide: 1 tablet (250 mg)

Cycloserine: 1 capsule (250 mg)

PAS: 1 sachet (4 g)†

Ethionamide: 2 tablets (500 mg)

Cycloserine: 2 capsules (500 mg)

PAS: 1 sachet (4 g)†

Pyridoxine: 6 tablets (150 mg)

model.pih.org/files/MDR-TB_A_Field_Guide_4web.pdf, doses for a 60 kg person

Individualized Category 4 Regimen

For patients with any of the following:

- Pregnancy
- Jaundice or liver disease
- Chronic illness (diabetes, heart or kidney disease)
- Household contact of MDR-TB patient
- History of receiving second line agents

This requires special consultation

Special Considerations for the Pregnant Patient

- Pregnancy NOT a contraindication to treatment
- Discuss risks and benefits of MDR-TB treatment
  - Benefit is potential cure of MDR-TB, healthy mother, healthy baby
  - Risks are drug-related
    - If possible, start in the second trimester since most teratogenicity occurs in the first trimester
    - Avoid injectables – toxic to the developing fetal ear
    - Capreomycin is the injectable of choice if one is needed
    - Avoid ethionamide – increases nausea, vomiting, teratogenic in animals

DST Aids in Adjusting the Regimen

Principles in DST-directed treatment:

- Use at least 5 drugs
- Include any first line agents to which strain is susceptible
- Include an injectable for a prolonged period
- Include a quinolone
- Consider drug resistance data of person, region and patient's treatment history

How Long to Treat MDR-TB

Treatment phases

	Duration	Characteristics
Initial phase	At least six months and until sputum smears and cultures are continuously negative	• Close monitoring for side-effects • At least five drugs • Includes injectable
Continuation phase	12-18 months	• Fewer side-effects • Usually only oral drugs

Duration of injectable:

- Consider stopping during continuation phase depending upon patient, smears, DST results and chest radiograph
- If strain is highly resistant, can opt to continue for entire course but consider reducing frequency to 3x/week

Following the MDR-TB Patient

Role of the treatment supporter/DOT staff

- Check drugs for correctness
- Witness patient taking drugs and record
- Be aware of possible side effects
- Response quickly if the patients misses a scheduled dose
- Accompany patient to health facility monthly
- Make arrangements if supporter or patient is to travel
- Assist patient in collecting sputum samples

Clinical Assessment

Every 2 weeks for the first 3 months then monthly thereafter

- History
- Physical examination
- Laboratory examination
- Sputum examination (two)

History: Ask About Interim Developments

- Any need for interim medical care?
  - If so, why?
  - Obtain records
- Reassess family status
  - Pregnancy if patient is a woman
  - Symptoms in household contacts
- Monitor for signs of treatment failure
  - Persistent or new TB symptoms (cough, hemoptysis, sputum production, fever, weight loss, night sweats)
  - Persistently positive sputum studies
  - Sputum culture that becomes positive after being negative

Adherence Monitoring

- Review medication list
- Review treatment record
- Ask questions

  Ex. “Many patients have difficulties taking these medications. What problems have you had?”

- If poor adherence, determine why:

  Side effect? Forgot? Treatment supporter problem? Financial? Hunger? Work? Disorganized? Depressed? Other medical problems? Substance use?

Side Effect/Toxicity Assessment

Remember, these might be due to other medications, conditions, especially in HIV!

Symptom	Agent	Comments/Response
Nausea/vomiting	Eth, PAS	Rehydrate if necessary
Diarrhea	PAS	Rehydrate if necessary
Fatigue	Hypokalemia from injectables	Bananas, potassium supplements
	Hypothyroidism Eth, PAS	Is reversible. Supplement with thyroxine
Depression, anxiety, nightmares, psychosis	Cs	Consider reduced dose
Jaundice	Z, Eth	Check LFT's, stop drugs and obtain consult
Muscle cramps, spasms		See hypokalemia above

Side Effect/Toxicity Assessment

Symptom	Agent	Comments/Response
Numbness, tingling, paresthesias	Neuropathy from INH, Cs, injectable	Patient taking pyridoxine? Treat symptoms with amitriptyline or carbamazepine
Swelling, decreased urine output, hypertension	Renal failure from injectable	Stop injectable and obtain consultation
	Hypothyroidism Eth, PAS	Is reversible. Supplement with thyroxine
Rash, skin peeling, mucosal ulceration	Many possibilities	Stop all drugs and obtain consultation for careful reintroduction of medications
Dizziness or loss of balance	Vestibular toxicity from injectable	Check LFT's, stop drugs and obtain consult
Hearing loss	Ototoxicity from injectable	Obtain consultation

Clinical Assessment of the MDR-TB Patient

Physical Examination

As per the initial assessment

Clinical Follow up Schedule

Month	Clinical consult	Smear	Culture	DST	AST, ALT, bili†	Cr, K†	TSH
1	Every 2 weeks	√			√	√	
2		√			√	√	√*
3		√	√		√	√	
4	Monthly	√					
5		√					
6		√	√	√			√
7		√					
8		√					
9		√	√				
10		√					
11		√					
12		√	√	√			√
until completion		Monthly	Every three months	Every six months			

Case Presentation (continued)

- Due to the localized nature of the infection and the presence of MDR-TB, the patient underwent right upper lobe resection.
- Pathology showed the presence of caseating granulomas and acid-fast bacilli.
- He completed 24 months of therapy and remains tuberculosis-free 5 years later.

Role of Surgery in Treating MDR-TB

An adjunct to medical therapy

Seemed beneficial in several studies

ex. 4-fold increased chance of success (Chan, Am J Resp Crit Care Med, 2004)

Consider if:

- Extensive resistance and therefore a high likelihood of failure
- Localized cavitary disease within 1 lobe or total destruction of one lung
- Predictable adequate postoperative lung function

Outcomes

Data is varied and difficult to compare

- Different populations studied
  - proportion with HIV varied
  - geographic differences
- Treatment differences
  - surgery
- Different endpoints
- Different follow up and analytical methods

Outcome Definitions (per Normes Pour La Tuberculose Multi Resistante)

Cured: Treatment protocol completed and 5 negative cultures were obtained during the last year of treatment

Completed treatment: Completed treatment protocol but did not meet definition of cured or treatment failure due to an inadequate number of cultures performed

Interrupted treatment: MDR-TB interrupted for 2 or more consecutive months

Treatment failure: 2 or more positive cultures among 5 cultures collected during the last year of treatment or one positive culture of the last 3 collected.

Also, treatment stopped due to poor response or severe side effects

Outcomes

Favorable outcomes from MDR-TB associated with

- Use of FQ (8-fold increased likelihood of success)
- Surgical intervention (4-fold increased likelihood of success

(Chan, Am J Resp Crit Care Med 2004, Dheda Lancet, 2010)

Poor outcomes associated with

- Resistance to FQ or streptomycin

(MMWR 55:1176, 2006)

Outcomes

Delay or lack of sputum conversion to culture negative is predicted by

- previous treatment for MDR-TB
- heavy growth on initial sputum culture
- bilateral cavitations
- # of drugs resistant to at treatment initiation

Lack of sputum conversion to negative cultures is related to outcomes:

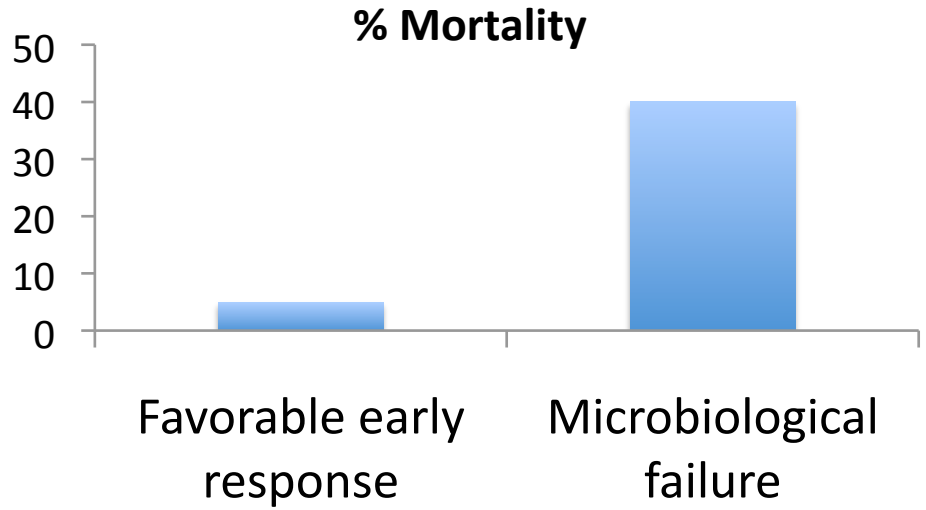
Conversion	% cured	% failed	% died
Yes (77%)	81	2	4
No (23%)	0	68	21

(Holtz, Ann Int Med, 2006, study in Latvia, no mention of HIV)

Outcomes

US study of 205 patients with MDR-TB:

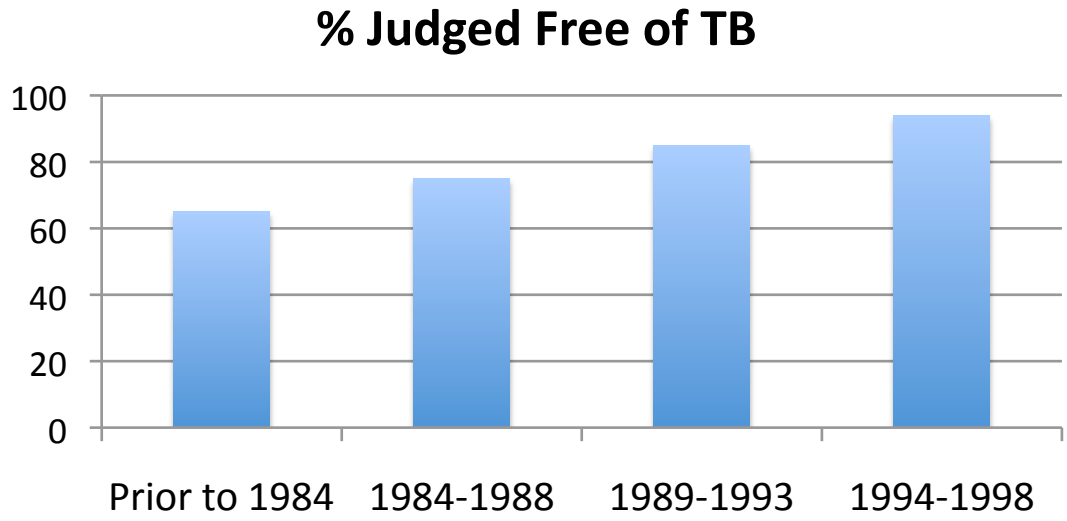
- 85% achieved "early favorable response" (sputum conversion within 3 months)
- Mortality was related to microbiological response



Chan, Am J Resp Crit Care Med, 2004

Outcomes

Outcomes improved over time (from Chan):



WHO data for Haiti 2006:

- 86% survival of patients treated for MDR-TB
- Outcome of the remaining 14% not evaluated

(https://extranet.who.int/sree/Reports?op=vs&path=/WHO_HQ_Reports/G2/PROD/EXT/MDRTB_Indicators)

Outcomes

Outcomes in HIV

- No data for Haiti and many other places
- Poor data when available suggest a trend toward increased mortality in HIV
- Less mortality with HAART

Outcomes with XDR-TB vs non-XDR MDR-TB

- Data suggests increased mortality but again information is sparse and often of poor quality

Summary

- MDR-TB and XDR-TB are a serious problem in Haiti and world-wide
- Treatment is multifaceted and depends upon
  - Suspecting MDR-TB and making the diagnosis
  - Supporting the patient in their community
  - Appropriate clinical and microbiological assessment
  - Appropriate, aggressive treatment
  - Adherence and toxicity monitoring

Summary (continued)

- Outcomes are variable
- Outcomes appear to be improving
- With appropriate treatment, long-term survival and cure can be achieved

Thank you to Dr. Edouard Vannier for help in translation!

Dudley, Massachusetts 10/31/11, www.boston.com