

A Team Approach to TB Management

Sabrina Roberts, MD

Jonathan Fine, MD

Pulmonary/Critical Care Medicine

Norwalk Hospital affiliated with Yale University

Case

- A 24 year old female is seen by her PCP on four separate occasions during the summer and fall of 2010 for fever and cough productive of purulent blood-tinged sputum.
- Each time she was treated with antibiotics for presumed recurrent lower respiratory tract infection.
- On two occasions she was treated with Avelox, following which her cough and fever transiently decreased.
- A chest x-ray was at some point obtained, which reportedly showed a left upper lobe opacity and prompted sputum to be sent to a commercial laboratory for AFB.

Case

- Past Medical History
 - BCG vaccinated
 - School TST negative at age 16 by history
- Medications: None
- Social History
 - Raised in the former Soviet Union
 - Works as an au pair since December 2009
 - Nonsmoker, no alcohol use, no IDU

Case

- Sputum smear positive for AFB and culture positive for *Mycobacterium tuberculosis complex*
- Patient advised by primary care physician to contact the Department of Health
- Susceptibilities were not performed by the commercial lab (CT state law does not require it)
- Treatment begun with the standard 4 drugs of isoniazid, rifampin, ethambutol, and pyrazinamide. Repeat sputum culture sent by health department.
- After 4 weeks of treatment, drug sensitivities by genotyping returned

CDC
12/10

INH -R, RIF-R, EMB -R, OFX-R, PZA -S

INH=Isoniazid, RIF=Rifampicin, PZA=Pyrazinamide, EMB=Ethambutol, OFX=Ofloxacin

Case referral

- TB should be treated by a clinical team experienced in management of the disease.
- TB management is a multidisciplinary approach involving the expertise of pulmonologists, infectious disease specialists and TB nurse specialists with close liaison with microbiology services.
- Regarding this case, the public health nurse redirected the patient to the experienced local TB team.

Genotyping

- Useful in confirming suspected transmission links
- Useful in identifying unsuspected transmission
- Useful in confirming false-positive culture (laboratory contamination)

- What type of resistance pattern might we be dealing with?

CDC
12/10

INH-R, RIF-R, PZA-S, EMB-R, OFX-R, SM-R

MDR- TB

Definitions

- **Monoresistant:** resistant to only one anti-tuberculosis drug
- **Multidrug-resistant:** resistant to at least isoniazid and rifampin
- **Polyresistant:** resistant to more than one anti-tuberculosis drug but not the combination of INH and RIF
- **Extensively drug-resistant:** resistant to at least INH and RIF, any fluoroquinolone, and at least one of three injectable second-line drugs (amikacin, kanamycin or capreomycin)

How common are MDR and XDR-TB?

- In 2008, the World Health Organization (WHO) estimated that around 40,000 cases of MDR-TB emerged worldwide, of these , only around 7% were identified.
- Only 1/5th were treated to WHO standards.
- In 2008 there were an estimated 150,000 deaths from MDR-TB.
- In 2010 there were 53,000 notified cases of MDR-TB worldwide.

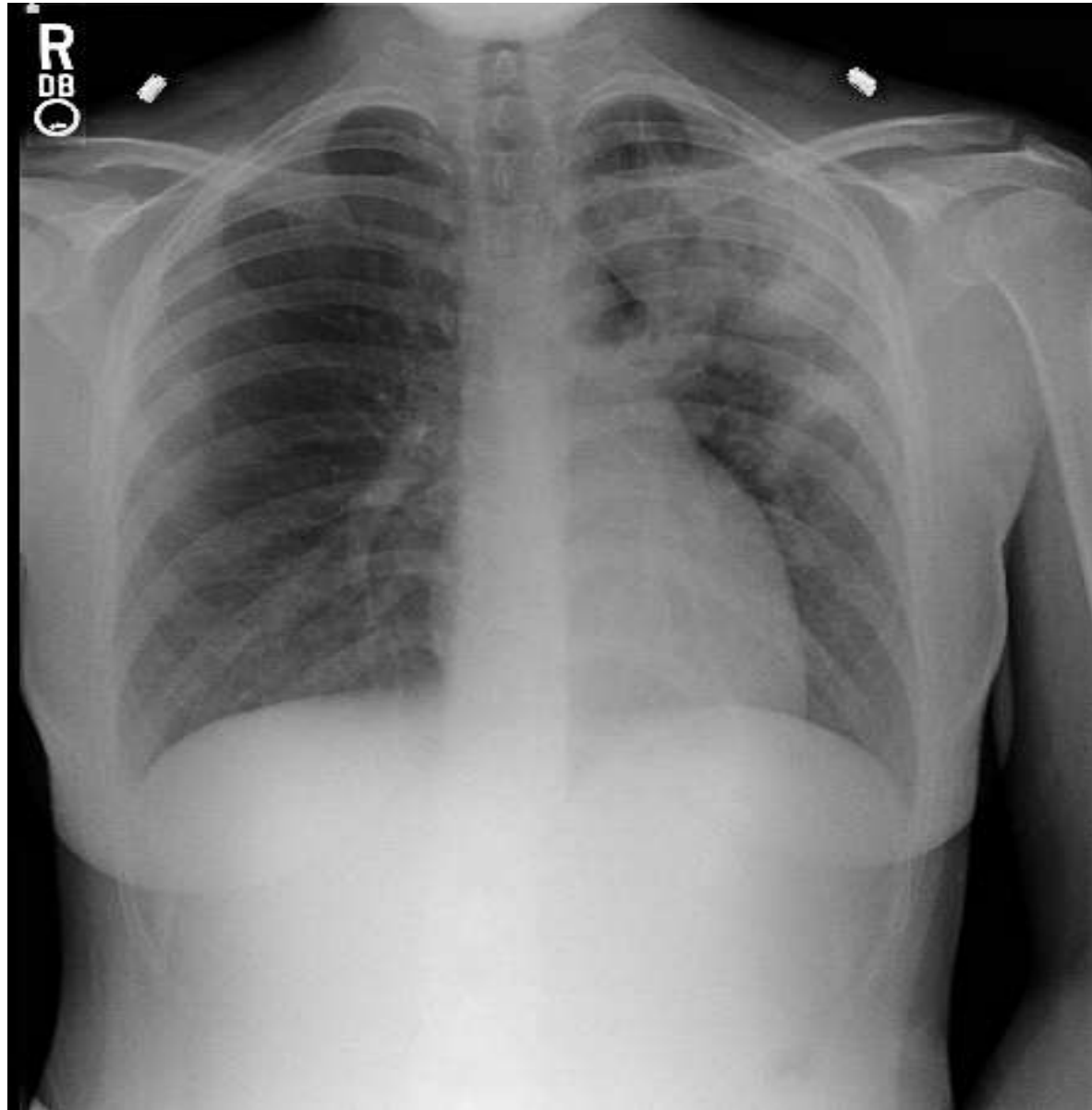
MDR-TB Morbidity, Connecticut 2005–2010

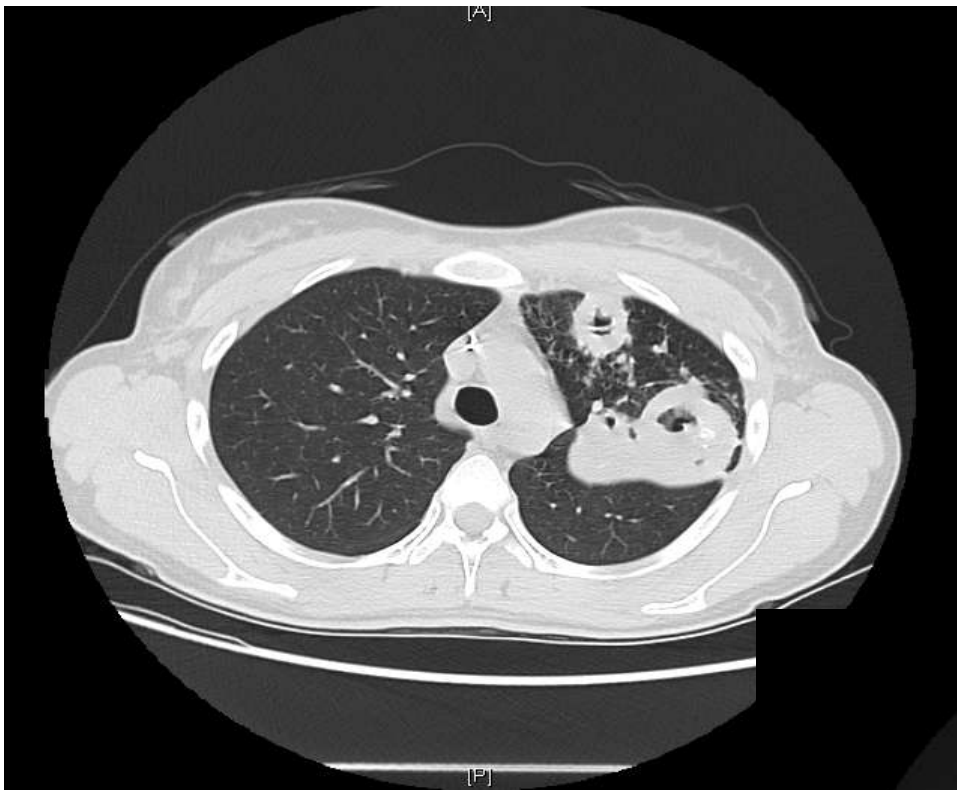
| Year | Number of Cases | Country of Birth |
|-------------|------------------------|---|
| 2005 | 0 | |
| 2006 | 1 | USA (travel to SE Asia) |
| 2007 | 3 | Mexico, Ecuador, India |
| 2008 | 2 | Niger, Vietnam |
| 2009 | 0 | |
| 2010 | 5 | Nigeria, Vietnam, Congo, Thailand, India |

Source: Lynn Sosa, MD, CT DPH

Our patient..

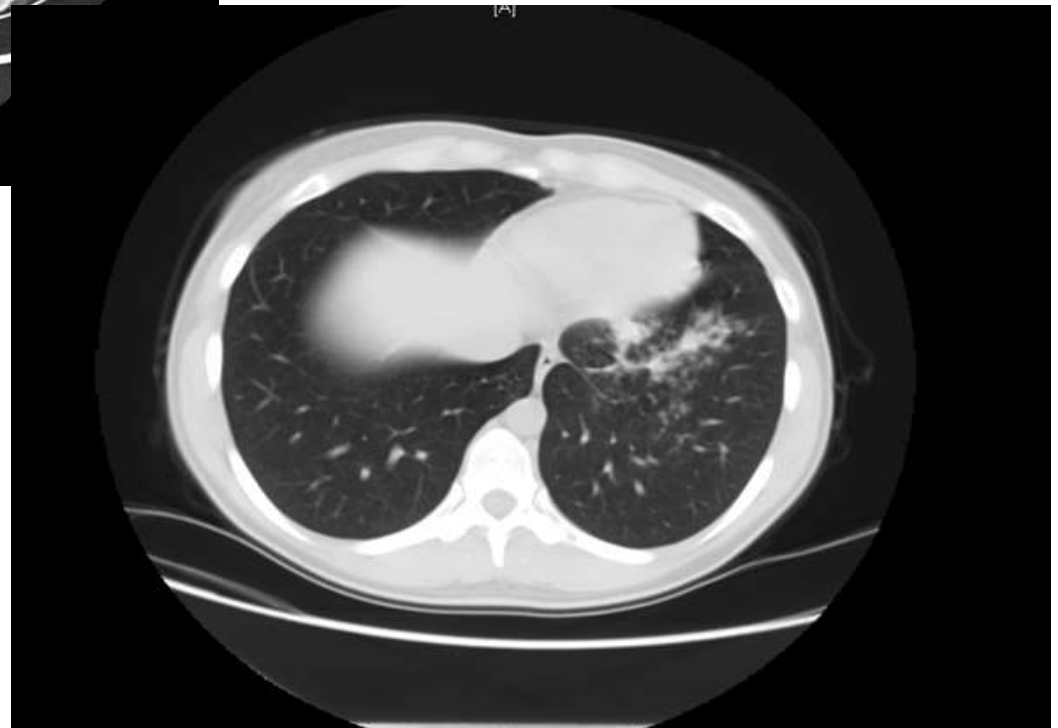
- Upon recognition of resistance the patient was withdrawn from the home and admitted to the hospital.
- HIV negative
- ROS – Weight loss 10 lbs
- Physical examination – Robust appearing female, otherwise unremarkable.





Left upper lobe cavitating masses, with left lower lobe consolidation.

12/2010



Hospitalization

- Patients should be isolated ideally until all cultures are negative.
- Prior to discharge from hospital, arrangements should be discussed with the local Department of Public Health.
- Arrangements for the supervision and the administration of all anti-TB therapy should be discussed with the patient.

How would you treat this patient?



Building a Treatment for MDR-TB

STEP 1

Begin with any 1st line agents to which the isolate is susceptible + FQN based on susceptibility

1st line drugs

PZA
EMB



fluoroquinolones

Levofloxacin
Moxifloxacin



Injectable agents

Amikacin
Capreomycin
Streptomycin
Kanamycin

Drug
ramping

Oral second-line drugs

Cycloserine
Ethionamide
Para aminosalicylate

STEP 2

Add 2nd line drug until you have 4-6 drugs to which the isolate is susceptible and preferable which have not been used to treat the pt previously

STEP 3

If 4-6 drugs not available above, the consider third-line in consultation with TB expert

Third-line drugs

| | |
|-------------|---------------|
| Clofazimine | Imipenem |
| Linezolid | Macrolides |
| Augmentin | High-dose INH |

Case

- Treatment initiated 12/7/10- with the following state Department of Health and CDC recommended regimen.
- Cycloserine 250mg by mouth b.i.d.
- Ethionamide 250mg b.i.d. with meals
- Linezolid 600mg by mouth daily
- PAS 4g by mouth b.i.d.
- Pyrazinamide 1500 mg by mouth daily
- Capreomycin 1g IV daily
- The patient discharged to continue with directly observed therapy.



Risk factors for the development of MDR-TB in persons without prior TB history

- Residence in or travel to an endemic region*
- Treatment of pulmonary disease with a prolonged course of multiple antibiotics or an injectable agent for more than a few weeks in a foreign country*
- Treatment of a pulmonary problem with a fluoroquinolone*
- Inappropriate treatment of active TB as LTBI
- Exposure to a person with documented drug-resistant TB
- Residence or work in a setting in which drug-resistant TB is documented

Risk factors for the development of MDR-TB in patients with history of TB

- Large bacillary load with extensive (bilateral or cavitary) disease
- Lack of conversion of cultures to negative during therapy
- Slow resolution of symptoms
- Worsening radiographic findings
- Nonadherence or erratic taking of medications
- Lack of DOT
- History of an inappropriate regimen*

Subsequent susceptibilities one month later from National Jewish Hospital

CDC

1/11

INH-R, RIF-R, PZA-R, EMB-R, ETA-R, AVELOX-S, CIP-R, RFB-R, SM-R, CM-S, PAS-S

INH-Isoniazid, RIF-Rifampicin, PZA-Pyrazinamide, EMB-Ethambutol, ETA-Ethionamide, CIP-Ciprofloxacin, RFB-Rifabutin, SM-Streptomycin, CM-Capreomycin, PAS- Para-amino-salicylate

Smear +
MTB

Smear+
MTB

Smear+
MTB

Smear +
Few MTB

Smear +
few AFB-
NTM

Smear +

10/10

12/10

1/11

2/11

3/11

4/11

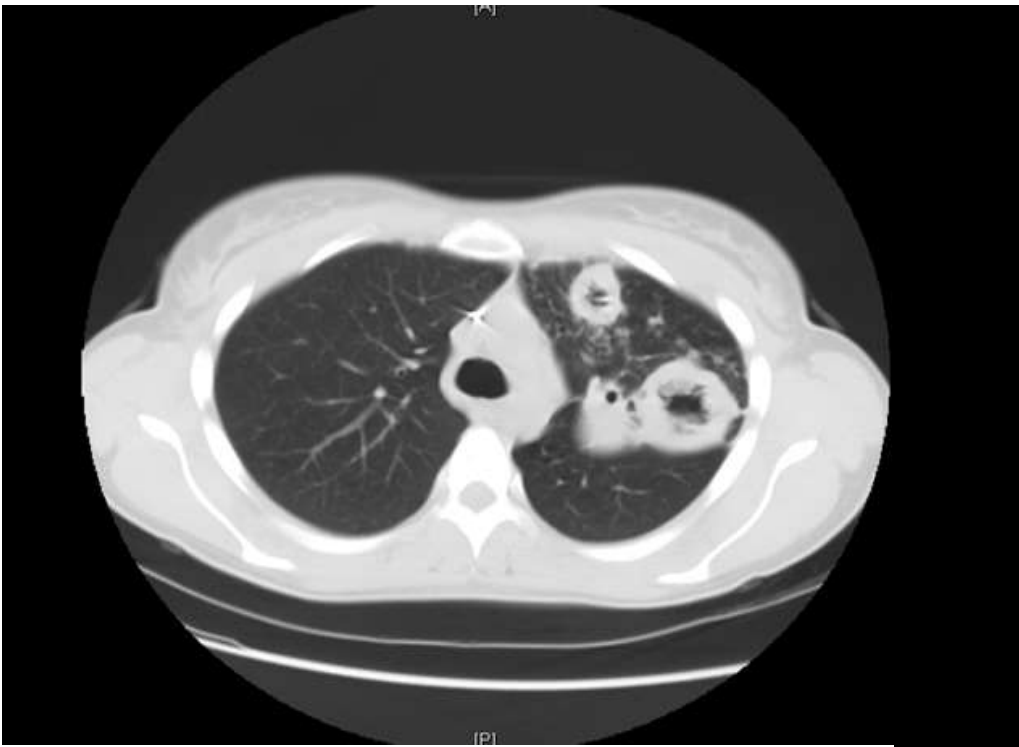
Isoniazid
Rifampin
Pyrazinamide
Ethambutol

Cycloserine
Ethionamide
Linezolid
PAS
Pyrazinamide
Capreomycin

Cycloserine
Ethionamide
Linezolid
PAS
Capreomycin

Avelox
Cycloserine
Linezolid
PAS
Capreomycin

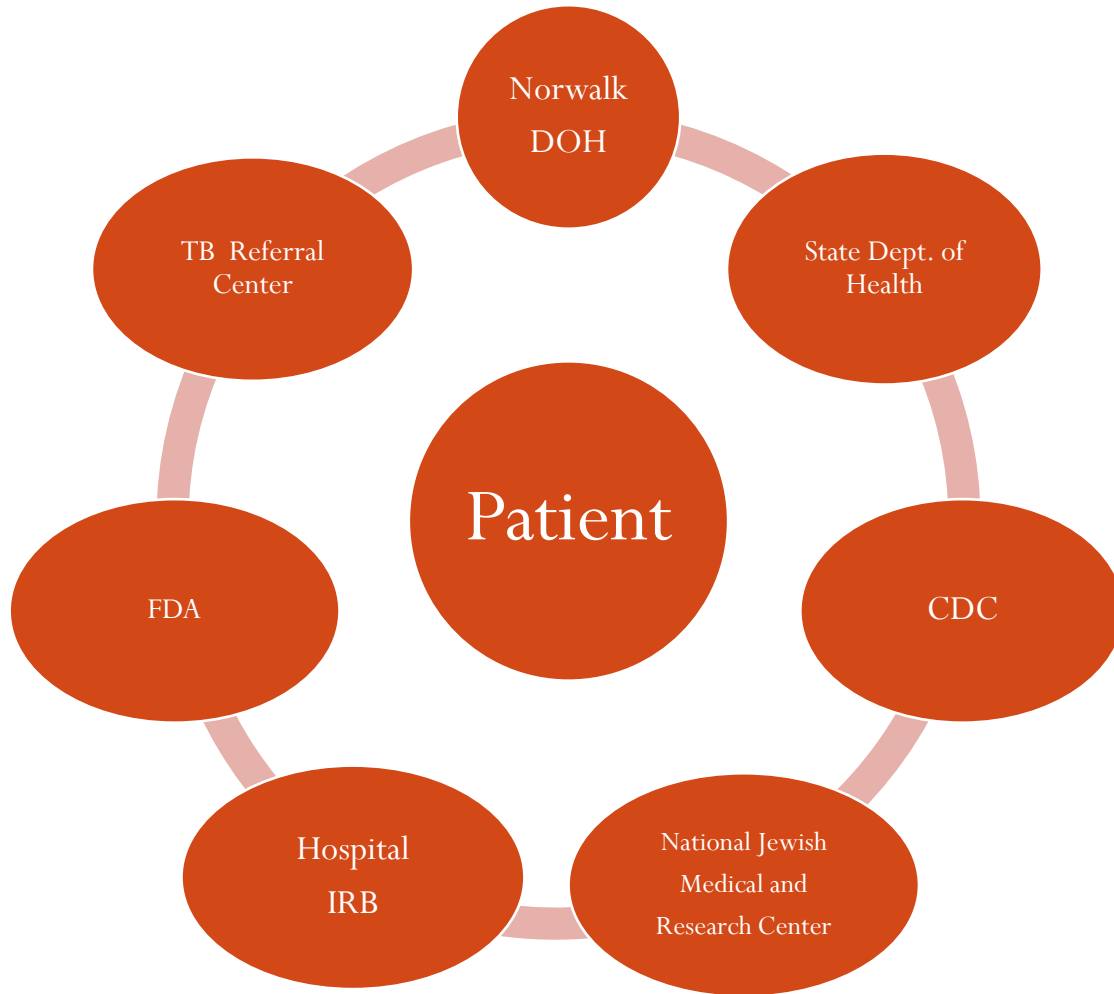
Clofazamine
Cycloserine
Avelox
Linezolid
PAS
Capreomycin



- Multifocal and multicentric cavitating masses
- New lingula infiltrate
- Slightly improved left lower lobe infiltrate

3/2011





- **Treat for at least 18 months after culture conversion**
- Patients with MDR-TB should have prolonged follow up post-treatment period

- The number of drugs required to cure MDR-TB is not known.
- Recommendations are based on expert opinion rather than data from RCTs.
- Most studies used 4-to 6-drug regimens with cure rates of **56% to 83%**

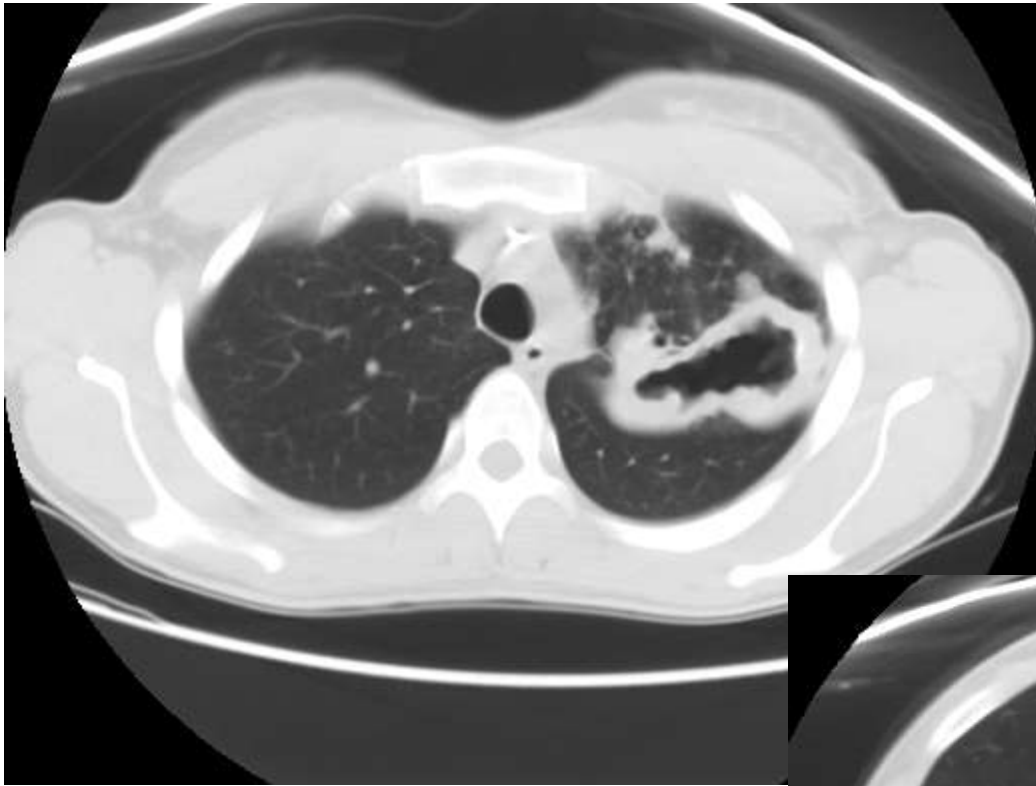
Which agents should we use for the treatment of multidrug-resistant Mycobacterium tuberculosis? J Antimicrob Chemoth 2004; 54: 593–602

Predictors of good outcome include:

- Susceptibility to and use of PZA and/or EMB
- **Susceptibility to and use of a FQN**
- **Use of >5 drugs for treatment**
- Sputum culture conversion by 2 months of treatment
- Surgical resection

Predictors of failure include:

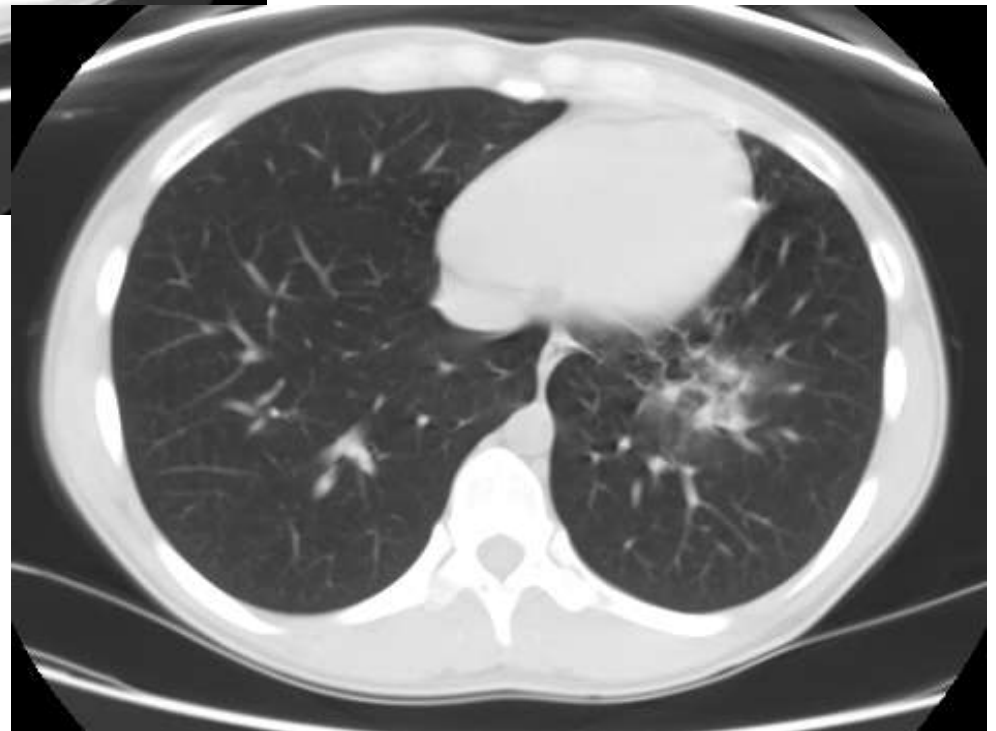
- History of previous therapy
- **Greater number of drugs to which the organism is resistant**
- **Presence of cavitation on the CXR**
- **Positive cultures after 2-3 months of treatment**
- HIV infection



Mild decrease in size
of left upper lobe
cavitary mass

8/11

There is ill-
defined airspace disease surrounding the
lower lobe segmental bronchi extending
to the lateral and posterior segments



Smear +
few
NTM

Off
isolation

M.
abscessus

M.
abscessus

No AFB

04/11

7/11

11/11

12/11

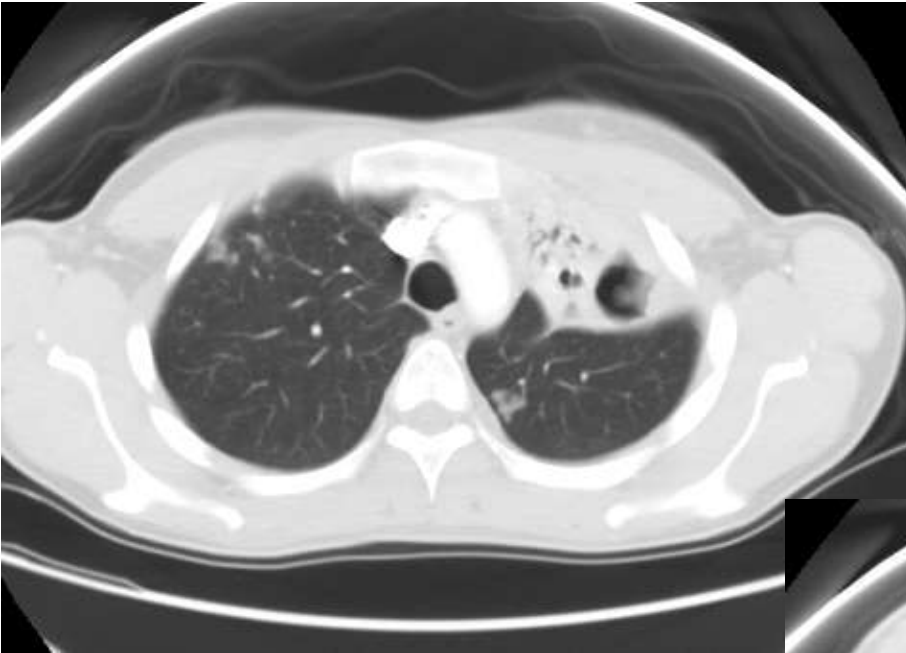
01/12

Cycloserine
Avelox
Linezolid
PAS
Capreomycin
Clofazamine

Cycloserine
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Linezolid
PAS
Capreomycin
Clofazamine

Cycloserine
Avelox
Linezolid
PAS
Capreomycin
Clofazamine

**Amikacin, Imipenem,
Azithromycin**
Cycloserine
Avelox
Linezolid
PAS
Clofazamine



2/12

Significant interval progression of the pulmonary disease with interval development of complete atelectasis of the entire left upper lobe, progressive nodular infiltrates the left lower lobe and new prominent nodular infiltrates within the right upper lobe.



What is the role for surgery?

Surgery and Tuberculosis

- The indications for surgery usually include management of complications of TB (including hemoptysis, bronchiectasis, bronchial stenosis, bronchopleural fistula and aspergilloma) and management of drug-resistant forms of the disease

Souilamas R, Riquet M, Barthers F, et al. Surgical treatment of active and sequelar forms of pulmonary tuberculosis. Ann Thorac Surg 2001;71:443–7.

TUBERCULOSIS

Surgery for patients with drug-resistant tuberculosis: report of 121 cases receiving community-based treatment in Lima, Peru

Jose G Somocurcio, Alfredo Sotomayor, Sonya Shin, Silvia Portilla, Maria Valcarcel, Dalia Guerra, Jennifer Furin

Thorax 2007;62:416-421. doi: 10.1136/thx.2005.051961

Table 2 Initial surgical procedures performed (n = 121)

| Procedure | Number (%) |
|----------------------------------|------------|
| Lobectomy | 76 (62.8) |
| Pneumonectomy | 27 (22.3) |
| Lobectomy and segmentectomy | 11 (9.1) |
| Segmentectomy or wedge resection | 3 (2.5) |
| Other | 4 (3.3) |

Table 3 Postoperative complications (n = 27)

| Complication | Number |
|---------------------------|--------|
| Major | |
| Bronchopleural fistula | 8 |
| Empyema | 6 |
| Pulmonary embolus | 2 |
| Haemorrhage | 2 |
| Wound dehiscence | 2 |
| Bronchopneumonia | 2 |
| Respiratory insufficiency | 5 |
| Minor | |
| Wound infection | 6 |
| Prolonged air leak | 5 |
| Recurrent nerve lesion | 2 |
| Pneumothorax | 1 |

- Before surgery, 20.7% of patients were culture-negative and 79.3% were culture-positive.
- Among the 115 patients for whom follow-up results were available, 78.3% were culture-negative in the early postoperative period and 74.8% remained culture-negative at long-term postoperative follow-up.
- Among the 91 individuals who were culture positive before surgery and who had follow-up results, 72.5% were culture-negative immediately after surgery and 68.1% were culture-negative at the time of analysis.(33 months post op.)
- Postoperative mortality within 1 month of surgery in this cohort was 5.0%.

When is surgery an option in drug-resistant TB?

- **Surgery should be considered:**
- When cultures continue to be positive beyond 4 to 6 months of treatment for MDR and /or
- When extensive patterns of drug resistance exist that are unlikely to be cured with chemotherapy alone.

- **To maximize the potential success of surgery:**
- The disease should be sufficiently localized to allow lobectomy or pneumonectomy and remaining tissue should be relatively disease-free.
- Should be performed by an experienced surgeon and only after several months of chemotherapy have been given - preferably after culture conversion.
- Even after successful lung resection, the patient should complete a full course of treatment.

Drug- Resistant Tuberculosis. A survival guide for clinicians. National Tuberculosis Center. California

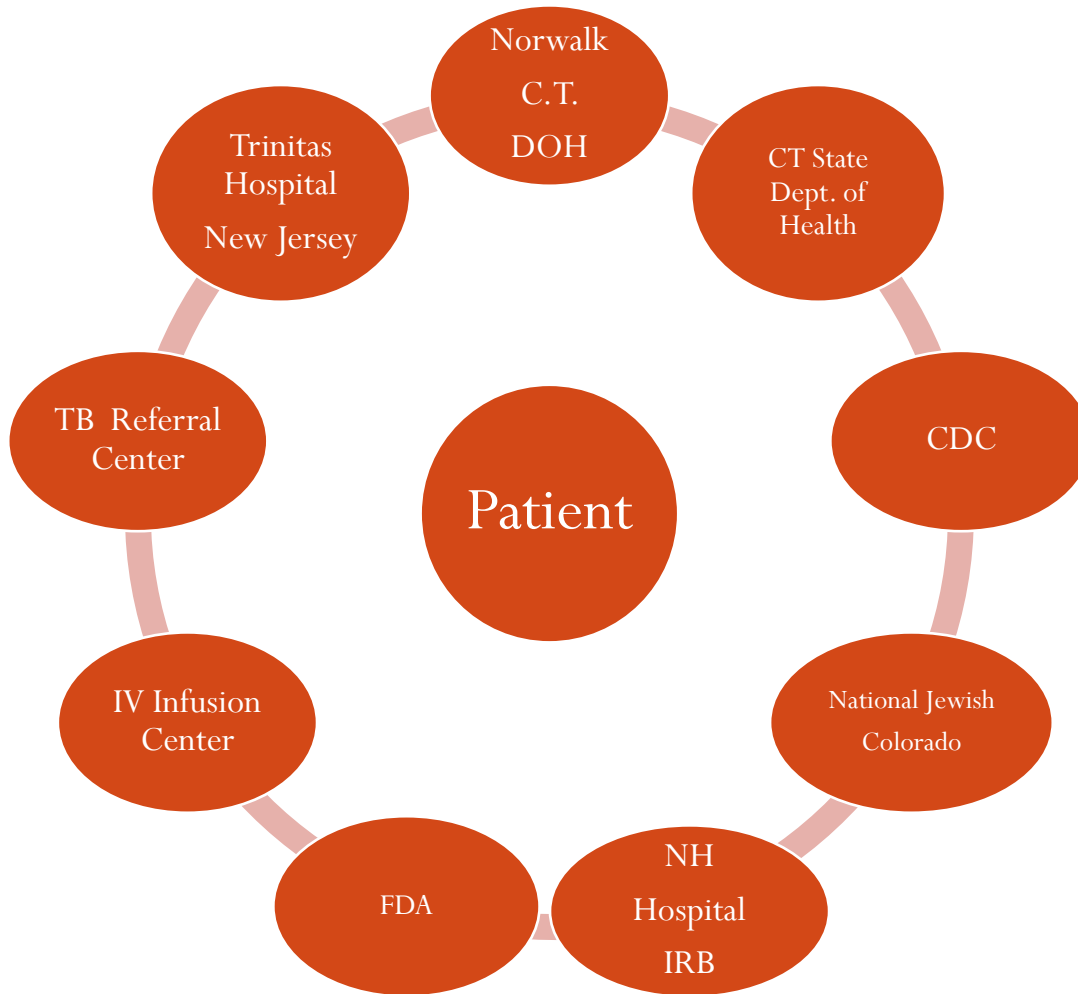
Surgery yes, but where?

- Experienced CT surgeon
- Negative pressure OR
- Willing hospital infection control dept.
- Reimbursable by the State
- Accessible to the patient



Case

- Patient subsequently had surgery 2/28/2012 at Trinitas Hospital in New Jersey
 - left upper lobe lobectomy
 - wedge resections of the left lower lobe



Patient's comments

- The difficulty in accepting a disease which carries significant stigma
- Who do I blame for this happening?
- The importance of psychotherapy
- Fear
- The lack of control
- The feeling of society not needing or wanting you
- Living with the daily side effects of all the medication

Special thank you

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