Drug Resistant TB – A Clinician's Perpsective

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Case 1

- 32 year old single woman who works as a representative for a pharmaceutical company
- Trained as a dietician and did her final year and community service in a TB clinic
- 2006 diagnosed with PTB – 6 months treatment and was “cured”
- 2008 developed wheezing and tiredness – diagnosed with asthma - later diagnosed with PTB treated with SM and Rifafour

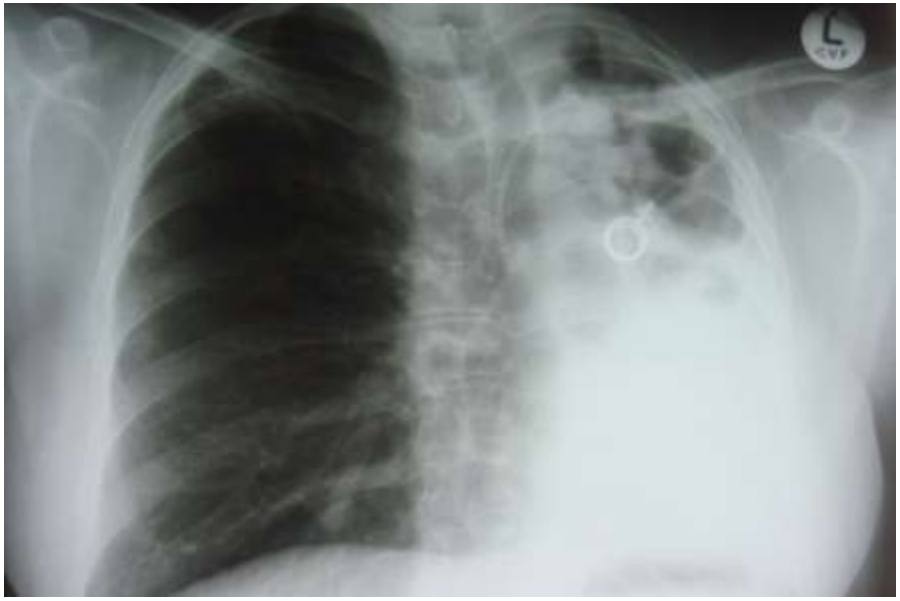
Case 1

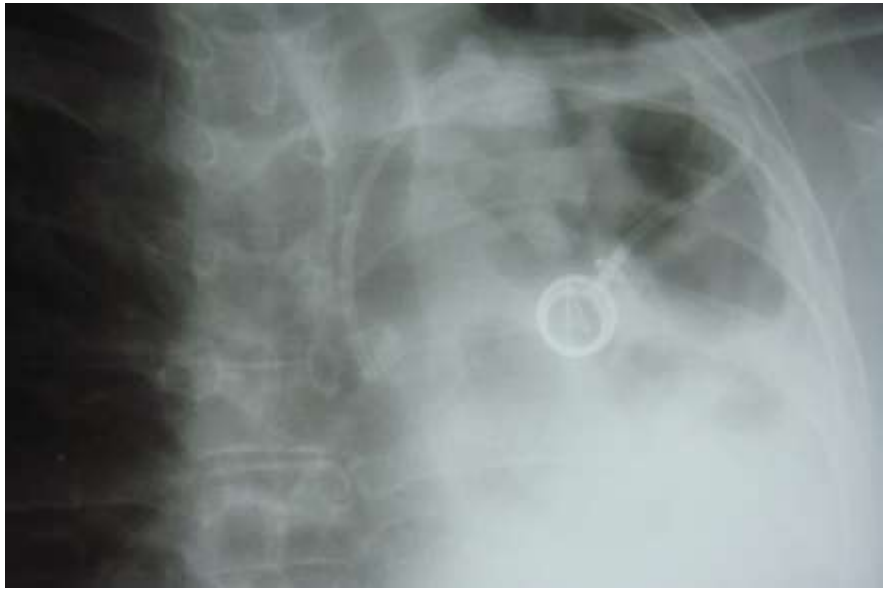
- September 2009 she “collapsed” – admitted to a hospital in Southern Cape where sputum showed she had MDR-TB but left on Rifafour and given iv moxifloxacin
- TB treatment was then stopped and she was left on cough syrup!
- October 2009 seen a northern suburbs TB clinic and started on MDR-TB treatment (KAN,OFX,EMB,PZA,ETH)
- Started to improve
- May 2010 she started to vomit her meds on a regular basis

Case 1

- TB symptoms recurred – tiredness, SOB, cough, night sweats, weakness, general body aches
- Continued on OFX,EMB,PZA,ETH – from BCH MDR-TB OP clinic
- Continued to work!
- Seen by me 29/09/10 – had 11 months MDR-TB treatment
- Weight 44kg, height 163cm, BMI 17
- Clinically evidence of a destroyed left lung
- Sputum – Smear 3+ pos, culture pos MTB – resistant to INH,RMP,EMB,AG

Case 1





Drug resistance

- Clinical situation where the patient is not expected to respond to standard treatment
- Usually a laboratory diagnosis but not always the case – can have so-called “clinical resistance”

Classification of drug resistance

- Mono-resistance
- Poly-resistance
- Multi-drug resistance
- Pre extensively drug resistance
  - Resistance to isoniazid and rifampicin plus either a second line aminoglycoside or capreomycin or a quinolone.
- Extensively drug resistance
  - Resistance to isoniazid and rifampicin plus either a second line aminoglycoside or capreomycin and a quiniolone.
- Total drug resistance – super XDR TB

Risk factors for DR TB

- Contact with a patient with DR TB
- Previous treatment for TB
- 50% or more DR TB patients have no previous history of TB and majority have no contact history
- In South Africa MDR TB occurs in 1-2% new cases of TB and 7% patients previously treated for TB

Challenges in management of drug resistant TB

- Suspect drug resistant TB
- Correctly diagnose drug resistant TB
- Select an effective and tolerable regimen
- Maintain patient on treatment until end of treatment
- Prevent patient from further transmitting disease – initial infection control measures

When to suspect drug resistance

- Patient is a contact of patient with drug resistant TB
- Patient is a HCW
- Patient has history of TB – DS or DR
- Failure to respond to standard TB treatment

Importance of diagnosing DR rapidly

- Patient can be put on appropriate treatment promptly
- This will improve his immediate health and prevent the development of destructive lung disease
- Prevent transmission

Diagnosis

- Collect 2 sputums
- Submit for Gene Xpert or LPA
- Ideally need 2 positive sputums showing DR before starting DR treatment
- Second line DST should be requested immediately to exclude pre and XDR TB
- No patient should be started empirically on an M(X)DR regimen unless reviewed by an expert in DR TB

Pitfalls in diagnosing DR-TB

- False positive laboratory results of TB and DR-TB do occur
- Causes of false positive result:
  - Incorrect labeling
  - Laboratory contamination
- In general false positive rate is 3% but may be higher in a very busy laboratory
- DS testing most reliable for INH and RMP and less so for other drugs
- Laboratory is a guide but there may be a disconnection between DST and clinical response
- No reliable DS tests for many of the drugs we use in XDR TB
- Can be differences in DST between laboratories
- Gene Xpert test can overcall rifampicin resistance – 1 in 5 or 1 in 6 cases – confirm with conventional DST or LPA

Don’t act on a laboratory report in isolation!

LABORATORY REPORT

Tests ordered TB Bactec,TB PCR,TB Sens L1*
* results to follow

TUBERCULOSIS INVESTIGATION

Direct microscopic examination for acid and alcohol fast bacilli (AAFBs) (Fluorochrome method)
Reported on 31/08/09 — **Positive for acid-fast bacilli**

Positive +++ (more than 10/immersion field)

This test was referred to a laboratory that does not have SANAS accreditation

PCR: MYCOBACTERIA
Result ..... **Positive for MTB complex**

Sensitivity Test
INH ..... **Resistant**
Rifampicin ..... **Resistant**

[redacted]

Authorised by : Rule review
Dr CN Beylis Pathologist Test(s): TB PCR

for Director

--- End of Laboratory Report ---

Principles of treatment of DR-TB

- Patients need to be counselled about the duration of treatment and side effects, importance of adherence and infection control measures at home particularly with M(X)DR-TB
- Use at least 5 or 6 drug regimen initially with M(X)DR-TB
- Never add single drug to failing regimen
- Daily dosing
- DOT therapy
- Intensive phase 6 - 8 months (12 with XDR) with an injectable followed by a continuation phase of 12 to 18 months. (WHO/Dept Health Guidelines recommends18 months post sputum conversion or 24 months treatment)
- Total treatment time:
  - Minimum 12 months after the first negative culture in a series of negative cultures
  - Majority patients 18 – 24 months (24 months with XDR)
- Intensive phase should include an injectable (6-8 months; 12 months with XDR) and FQ
- Fast track ART in M(X)DR-TB regardless of CD4 count
- Optimise ARV's if already on ART to avoid potential toxicity with AG's/CAP

Drugs available to treat drug resistant TB

- WHO Group 1

  Ethambutol

  Pyrazinamide

- WHO Group 2

  Aminoglycosides – streptomycin, kanamycin, amikacin

  Capreomycin

- WHO Group 3

  Fluoroquinolones – ofloxacin, moxifloxacin, gatifloxacin, levofloxacin

- WHO Group 4

  Ethionamide, prothionamide, PAS, cycloserine/terizidone

- WHO Group 5

  Linezolid, clofazamine, meropenem, co-amoxyclav, macrolides, thiacetazone, rifabutin

Treatment of mono-resistant TB

- Isoniazid resistance
  - RHZE (FDC)
  - FQ can be added with severe disease
  - Duration 6 months after sputum culture conversion – total 9 months
- Rifampicin resistance
  - As for MDR TB and add isoniazid

Treatment of poly-resistant TB

- Usually means isoniazid and ethambutol resistance
- Rifampicin, pyrazinamide, moxifloxacin and streptomycin

Treatment of MDR-TB

- Kanamycin (im) or amikacin (iv)
- Moxifloxacin (or levofloxacin)
- Ethionamide
- Terizidone
- Pyrazinamide
- Ethambutol (if still susceptible)

Treatment of MDR-TB

Intensive Phase: Standardised Regimen for Adult and Children 8 years and older (MDR-TB Treatment)

Patient Weight	Drug	Dosage
<33kg	Kanamycin	15-20 mg/kg
	Moxifloxacin	400 mg (children: 7.5-10 mg/kg)
	Ethionamide	15-20 mg/kg
	Terizidone	15-20 mg/kg
	Pyrazinamide	30-40 mg/kg
33 - 50 kg	Kanamycin	500-750 mg
	Moxifloxacin	400 mg
	Ethionamide	500 mg
	Terizidone	750 mg
	Pyrazinamide	1000-1750 mg
51 - 70 kg	Kanamycin	1000 mg
	Moxifloxacin	400 mg
	Ethionamide	750 mg
	Terizidone	750 mg
	Pyrazinamide	1750-2000 mg
>70 kg	Kanamycin	1000 mg
	Moxifloxacin	400 mg
	Ethionamide	750-1000 mg
	Terizidone	750-1000 mg
	Pyrazinamide	2000-2500 mg

Continuation Phase: Standardised Regimen for Adults and Children 8 years and older (MDR-TB Treatment)

Patient Weight	Drug	Dosage
<33 kg	Moxifloxacin	400 mg
	Ethionamide	15-20 mg/kg
	Terizidone	15-20 mg/kg
	Pyrazinamide	30-40 mg/kg
33 - 50 kg	Moxifloxacin	400 mg
	Ethionamide	500 mg
	Terizidone	750 mg
	Pyrazinamide	1000-1750 mg
51 -70 kg	Moxifloxacin	400 mg
	Ethionamide	750 mg
	Terizidone	750 mg
	Pyrazinamide	1750-2000 mg
>70 kg	Moxifloxacin	400 mg
	Ethionamide	750-1000 mg
	Terizidone	750-1000 mg
	Pyrazinamide	2000-2500 mg

* Pyridoxine (Vit B6) 150 mg (maximum 200mg) to be given daily to patients on Terizidone.
** Adults who may not tolerate moxyfloxacin will be given levofloxacin at the following dosage: 750 mg for patient weighing below 51 kg, and 1000 mg for patients with a weight equal or above 51 kg.

Treatment of pre and XDR-TB

- Capreomycin (im or iv)
- PAS
- Clofazamine
- Moxifloxacin (or levofloxacin)
- Terizidone
- Ethionamide
- Pyrazinamide
- High dose INH (10mg/kg)
- If funding available:
  - Linezolid
  - Meropenem +co-amoxyclav

Treatment of XDR-TB

Standardised Regimen for Adult XDR-TB Treatment

Patient weight	Drug	Dosage
Intensive Phase: Treatment taken daily for at least 6 months, guided by TB culture conversion		
<33 kg	Capreomycin	15-20 mg/kg
	Moxifloxacin	400 mg
	Ethionamide	15-20 mg/kg
	Terizidone	15-20 mg/kg
	Pyrazinamide	30-40 mg/kg
	PAS	150 mg/kg
	Clofazimine	3-5 mg/kg
33 - 50 kg	Capreomycin	500-750 mg
	Moxifloxacin	400 mg
	Ethionamide	500 mg
	Terizidone	500 mg
	Pyrazinamide	1000-1750 mg
	PAS	8000 mg
	Clofazimine	200 mg
51 -70 kg	Capreomycin	1000 mg
	Moxifloxacin	400 mg
	Ethionamide	750 mg
	Terizidone	750 mg
	Pyrazinamide	1750-2000 mg
	PAS	8000 mg
	Clofazimine	300 mg
>70 kg	Capreomycin	1000 mg
	Moxifloxacin	400 mg
	Ethionamide	750-1000 mg
	Terizidone	1000 mg
	Pyrazinamide	2000-2500 mg
	PAS	8000-12000 mg
	Clofazimine	300 mg

Continuation Phase: Treatment Taken Daily for at Least 18 Months after TB Culture Conversion

Patient Weight	Drug	Dosage
<33 kg	Moxifloxacin	400 mg
	Ethionamide	15-20 mg/kg
	Terizidone	15-20 mg/kg
	Pyrazinamide	30-40 mg/kg
	PAS	150 mg/kg
	Clofazimine	3-5 mg/kg
33 - 50 kg	Moxifloxacin	400 mg
	Ethionamide	500 mg
	Terizidone	500 mg
	Pyrazinamide	1000-1750 mg
	PAS	8000 mg
	Clofazimine	200 mg
51-70 kg	Moxifloxacin	400 mg
	Ethionamide	750 mg
	Terizidone	750 mg
	Pyrazinamide	1750-2000 mg
	PAS	8000 mg
	Clofazimine	300 mg
>70 kg	Moxifloxacin	400 mg
	Ethionamide	750-1000 mg
	Terizidone	1000 mg
	Pyrazinamide	2000-2500 mg
	PAS	8000 -12000 mg
	Clofazimine	300 mg

Treatment of preXDR-TB

- INH, RMP and FQ resistance
  - Treat for MDR-TB and add PAS
- INH, RMP and AG resistance
  - Treat for XDR-TB

Linezolid and treatment of XDR-TB

- Study population – 41 patients with failed XDR-TB
- Linezolid 600mg **added** to present treatment
- Patients were randomised to start immediately or after a delay of 2 months
- After culture conversion or 4 months further randomised to 600mg/day or 300mg/day
- Further 18 months treatment

Lee M et al. N Eng J Med 2012;367:1508-18

Linezolid and treatment of XDR-TB

- By 4 months 79% immediate start group had cultured converted v's 35% in delayed group
- 87% had culture converted by 6 months
- Patients on 300mg/day had fewer side effects
- 11% developed acquired resistance

Lee M et al. N Eng J Med 2012;367:1508-18

Meropenem and treatment of XDR-TB

- 6 patients XDR-TB failed treatment M-C combination
- 4/6 patients culture conversion by 6 months

Payen MC et al. Int J Tuberc Lung Dis 2012;16:558-60

Case 2

- 28 year old HIV negative married woman presented with a cough, weight loss and an abscess in left axilla.
- Sputum showed MTB resistant to INH,RMP,EmB and FQ
- Pus from abscess MTB resistant INH,RMP,AMIK,FQ,EMB
- Admitted BCH – standard XDR treatment
- Deteriorated – lost 13kg, "gave up"– signed "red ticket"
- Reluctantly continued treatment at TB clinic; collapsed at home
- Admitted UCT PAH; unable to stand, apathetic, wouldn't eat, weighed 38kg; pouring pus from multiple sinuses in left axilla; CXR mediastinal glands and RLL infiltrate
- Corrected severe electrolyte abnormalities, tube fed, port inserted
- **CAP ivi, moxifloxacin ivi, linezolid ivi, meropenem ivi, PAS, clofazamine, terizidone, high dose INH, PZA**
- In UCT PAH for 6 months
- Currently continuing on treatment at local TB clinc and injecting herself daily with capreomycin via port
- Looks "picture of health" -weight 56 kg, abscesses healed up months ago, CXR almost normal, sputums negative for 10 months

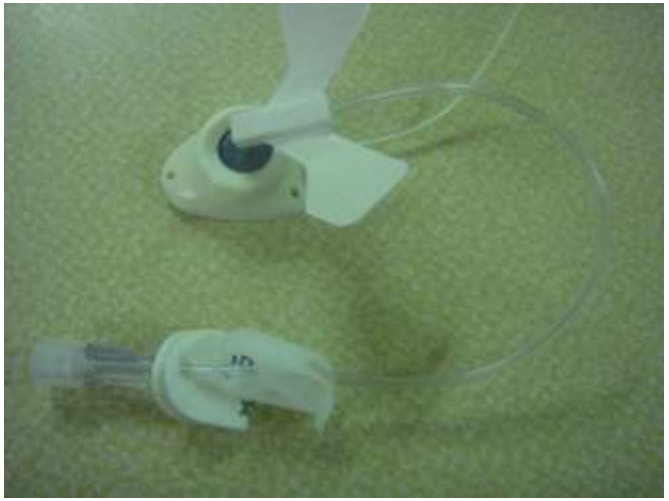
Side effects of treatment of M(X)DR-TB

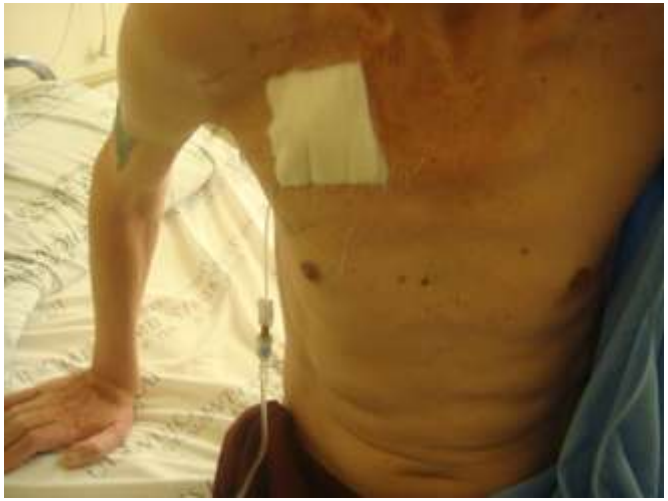
- Hearing loss
- Joint and muscle pain
- Renal impairment
- Hypokalaemia, hypocalcaemia, hypomagnesaemia
- Nausea and vomiting
- Diarrhoea
- Abdominal pain
- Fatigue
- Hair loss
- Depression
- Psychosis
- Peripheral neuropathy
- Rash
- Insomnia
- Skin pigmentation

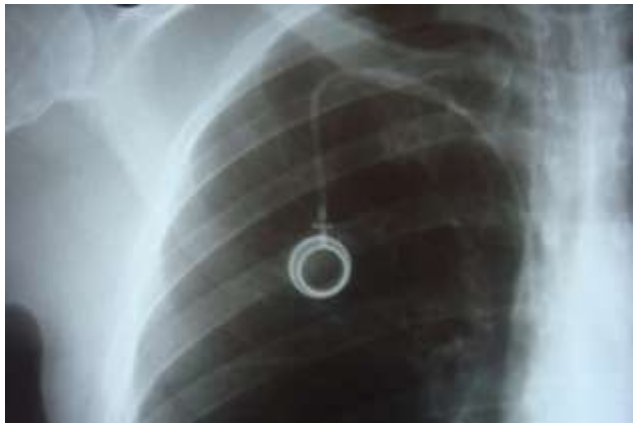
Practical aspects of AG/CAP administration

- Painful prolonged im injections
  - Local anaesthetic
  - Ultrasound
- Intravenous therapy
  - Peripheral veins
  - Portacath
- Monitor hearing 2-4 weekly
- Monitor renal function, potassium, magnesium and calcium

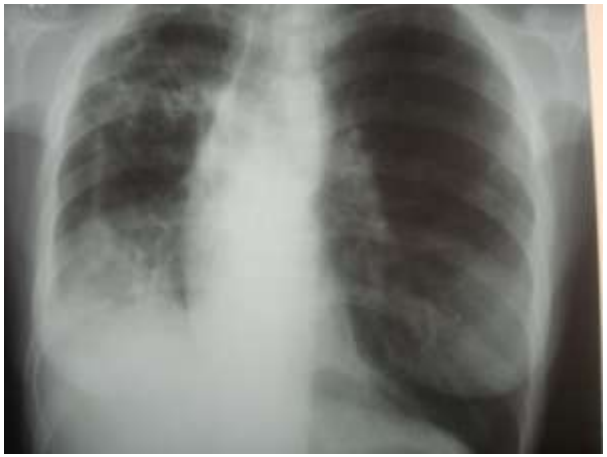
Aminoglycoside/capreomycin use: Portacath

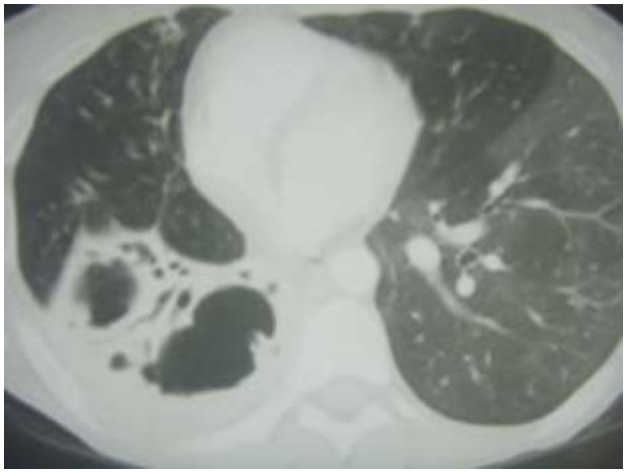


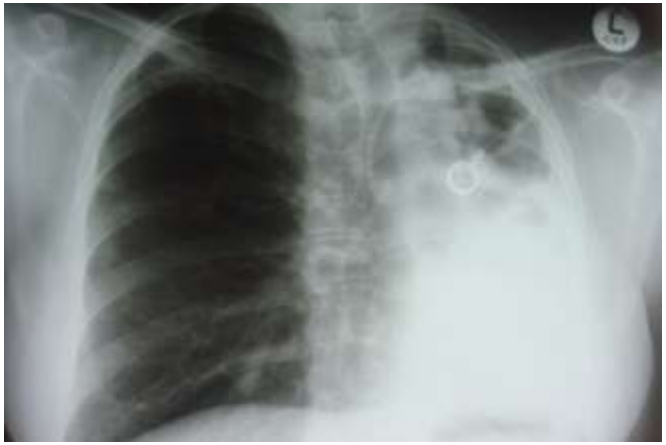




Surgery in M(X)DR-TB





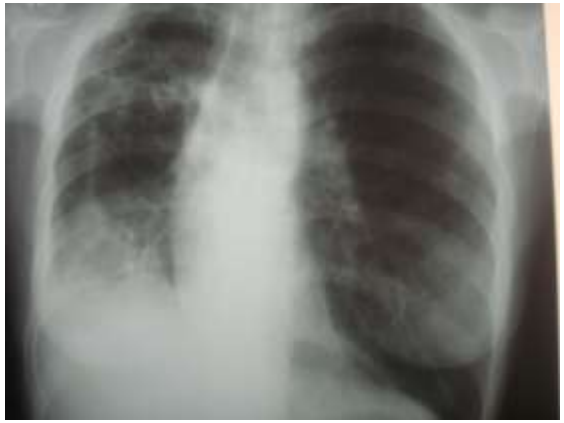


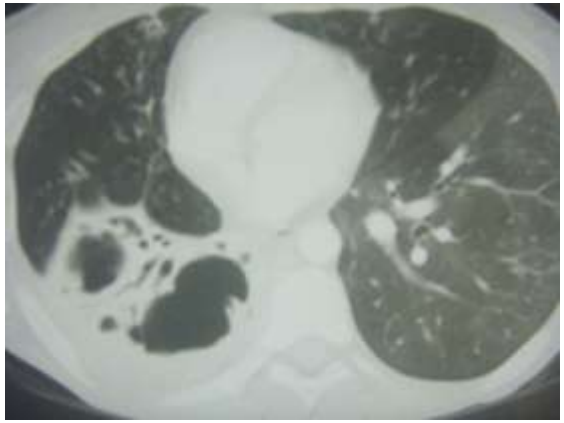
Which patients will benefit from surgery?

- Failed chemotherapy (XDR-TB treatment); must have essentially unilateral disease
- Previous MDR-TB; relapsed in same site; essentially unilateral disease
- All XDR-TB patients who have sputum converted; localised residual disease

Approach to patient who is failing MDR-TB treatment

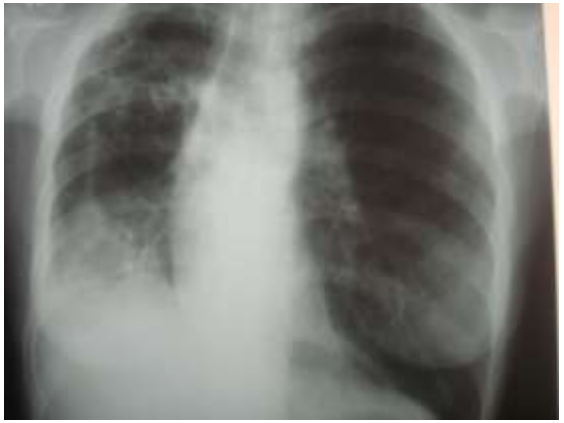
- Review diagnosis
- Assess compliance
- Repeat DST
- DST shows XDR-TB treat accordingly
- If diagnosis is correct and compliance adequate despite DST still showing only INH and RMP resistance treat for XDR-TB

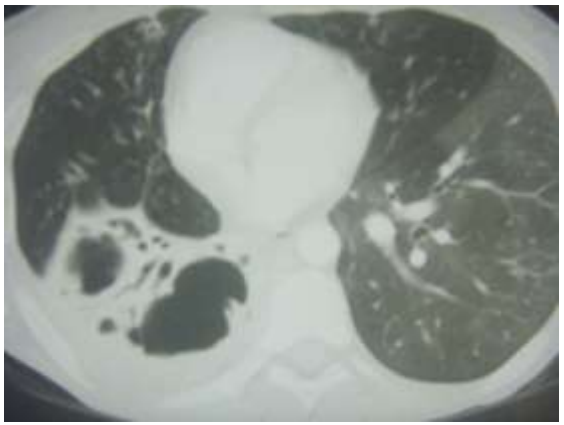




Approach to patient who is failing MDR-TB treatment

- If surgically operable still initially treat for XDR-TB and then perform surgery when and if converted
- If fail treatment still perform surgery if still operable





Failed XDR-TB patient

- Persistent positive cultures after 12 months of confirmed treatment
- AND:
  - Extensive and bilateral lung disease with no option for surgery
  - Extensive drug resistance with no option to add additional agents

The failed patient with XDR-TB

- Majority of patients with XDR-TB will fail treatment and there will not be a surgical option
- What happens to these patients?
- In Western Cape they are not dying rapidly as those are in KZN
- Many are relatively well and fully ambulant – chronic excretors
- Tended to remain in TB hospitals for years blocking beds

Review Board

- All failed XDR TB patients are presented to the Western Cape Department of Health Review Board
- If decision that no further treatment will be of help discharged from BCH with advice regarding infection control
- XDR-TB “hospice” established at Nelspoort in Karoo

Special situations

- Elderly
- Pregnant patient
- Renal failure
- DR-TB meningitis
- Abdominal DR-TB

Case 1

- Admitted to UCT PAH
- Port inserted
- IV capreomycin, oral moxifloxacin, PAS, terizidone, linezolid (6 months), high dose INH, clofazamine. NO ethionamide!
- Potassium supplements
- Vomiting controlled with iv anti-emetics

Case 1

- TB symptoms resolved
- Weight 44 – 60kg
- Sputum cultures negative from month 4
- Month 9 left pneumonectmy
- Remains on XDR TB treatment with iv capreomycin, PAS, moxifloxacin, high dose INH, PZA and terizidone aiming for 24 months treatment
- Very well – returned to work as a drug rep