Treatment of Drug Resistant Tuberculosis

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Case

- 21 yo from China, no prior TB, asymptomatic, incidentally found to have LUL nodular opacities, underwent bronchoscopy
- BAL: smear few AFB
- GeneXpert: MTB positive; rpoB mutation = rifampin resistant
- No household or high-risk contacts, can self-isolate, does not want to start rx
- 1. What would you do:
  - RIPE
  - Wait for CDC MDDR on the specimen
  - BPaL
  - BPaLM
  - Other

Drug Resistant TB

- Only ~9% of TB we see

Tuberculosis Cases and Percentages by Drug Resistance[1]: United States, 1993–2023

Year	Total cases[2]	Isoniazid (INH)-resistant[3]		Fluoroquinolone resistant[4]		Multidrug-resistant (MDR)[5]		Pre-extensively drug-resistant (Pre-XDR)[6]		Extensively drug-resistant (XDR)[7]	
		No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
2023	6,964	589	(8.5)	45	(0.6)	100	(1.4)	15	(0.2)	1	(0.0)

(INH and RIF R)

(>plus FQ or INJ R)

(>plus FQ R and INJ,BDQ, or LZD R)

Drug Resistant TB

- Only ~9% of TB we see
- Important because regimens change when drug resistant or drug intolerant
- Standard “pan-susceptible” RIPE for RIP-susceptible TB (E doesn’t matter)
  - RIPE 2 months, RI 4 months
- INH mono-resistant TB (RPE susceptible)
  - Drop the I
  - Continue the RPE, usually add a quinolone (levo 750 qd/moxi 400)
  - 6 months duration of all 4 drugs
  - Other options possible
- PZA mono-resistant TB (RIE susceptible)
  - Drop the P
  - Continue the RI
  - 9 month duration

Drug Resistant TB

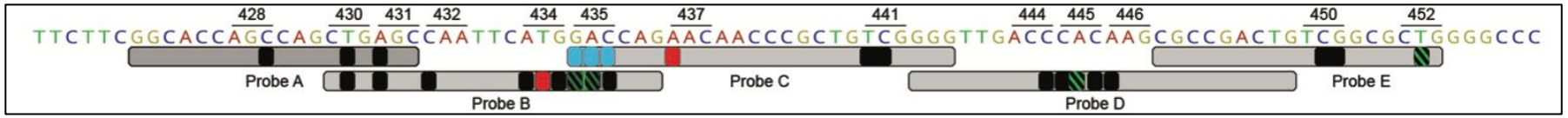
- Rifampin resistance is a big deal
  - Rifampin intolerance, if not severe, try rifabutin
- Rifampin mono-resistant (IPE susceptible)
  - Less common
  - Option 1: BPaL or BPaLM for 6 months
  - Option 2: Drop the R, continue IPE, add quinolone, 12 month duration of all 4 drugs
  - Some other options possible
- Rifampin AND INH resistant = Multi drug resistant TB
  - More common
  - Currently BPaL or BPaLM for 6 months

Drug Resistant TB

- Bedaquiline or Linezolid or Pretomanid resistant
  - Very rare fortunately
  - Starting to occur, esp BDQ R in South Africa
  - Susceptibility test methods and mutations less clear
  - INH and RIF and FQ and (B or L) Resistant = “XDR TB”
  - Can’t use BPaLM
  - Individualized longer regimen

Confirm the diagnosis of Rif R

- Higher concern in those with prior TB treatments or from high-risk countries (esp former USSR)
- Suspicion usually starts with rpoB mutation by GeneXpert on specimen: “rifampin resistance”



  - Send specimen to CDC for MDDR to confirm: will identify the exact rpoB mutation, also INH mutations, quinolone mutations
  - Up to 86% of Xpert Rif R can be false positive with low bacillary load (Ngabonziza, Lancet Micr 2020)
  - Silent mutations (probe B)

- Upon culture growth, confirm rapid molecular (CDC MDDR) and phenotypic susceptibilities on isolate

- Consider likelihood of MDR to decide whether to treat for MDR (versus waiting)
  - Sick, high likelihood of MDR: generally start treating with a BPaL regimen
  - Not sick, low likelihood of MDR, low transmission risk: consider waiting for confirmation
  - Would not treat with RIPE

Back to Case 1

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  - BPaL
  - BPaLM
  - Other

Case 2

- 63 yo DM from India, no prior TB, cough, nonspecific patchy airspace RLL
- sputum: smear +
- GeneXpert: MTB positive; rpoB resistant

MDDR

Rifampin (RIF)	**Result**	**Interpretation**
RIF interpretation		RIF resistant
rpoB*	Ser450Leu	

Comments and Disclaimers

* DTBE Reference Laboratory has transitioned from the E. coli to the M. tuberculosis numbering system for reporting rpoB gene mutations.

Isoniazid (INH)	**Result**	**Interpretation**
INH interpretation		INH resistant
inhA	No mutation	
fabG1	No mutation	
katG	Partial amplification, Ser315Thr	

Ethambutol (EMB)	**Result**	**Interpretation**
EMB interpretation		Likely EMB resistant
embB	Met306Ile	

Pyrazinamide (PZA)	**Result**	**Interpretation**
PZA interpretation		Likely PZA resistant
pncA	Ile90Thr	

Fluoroquinolones (FQ)	**Result**	**Interpretation**
FQ interpretation		Cannot rule out FQ resistance.
gyrA	No mutation	
gyrB	No mutation	

Case

- 63 yo DM from India, no prior TB, cough, nonspecific patchy airspace RLL
- sputum: smear +
- GeneXpert: MTB positive; rpoB resistant
- 2. What would you do:
  - RIPE
  - Wait for culture
  - BPaL
  - BPaLM
  - Other

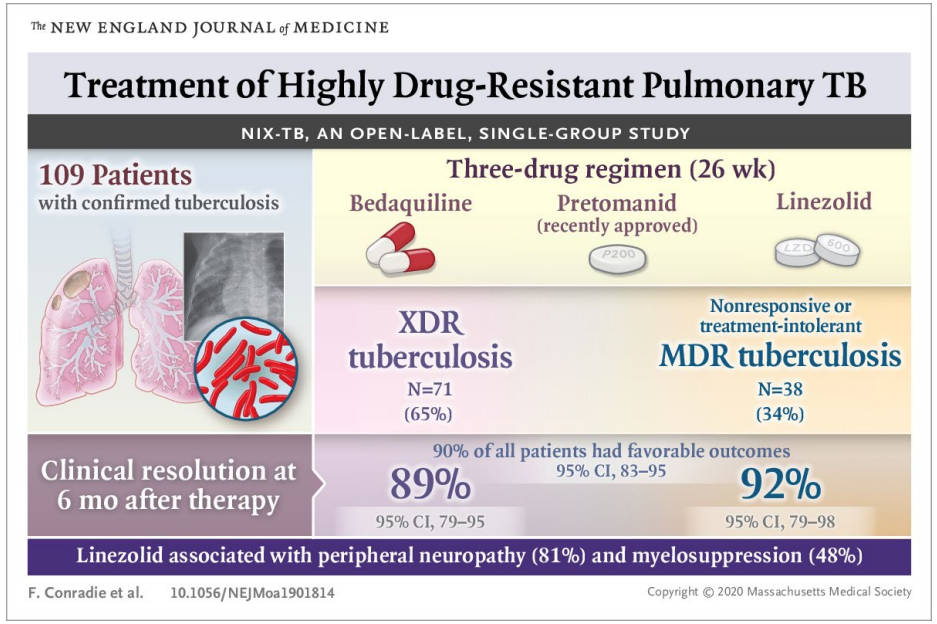
MDR TB treatment history in US

- Pre 2018
- Individualized regimen of 4-5 active drugs, prioritizing Fluoroquinolone and injectable
- Based on susceptibility testing
- Usually treat for 12+ months after culture conversion
- Patients did well, >80% cure
- Ototoxicity with injectable, use N-acetyl cysteine 600mg po bid (Kranzer, Thorax, 2015)

- 2019-2021
- Meta-analysis of observational data, 12030 patients, showed that treatment success higher with Lzd, Levo/Moxi, Bdq, Clofaz (Ahmad et al., *Lancet* 2018)
- Led to a regimen of Bdq,Cfz,Lzd,Moxi/Levo,Cyc
- Confirm FQ susceptibility
- All oral: usually treat for 15 months after culture conversion (associated with higher treatment success)

MDR TB treatment – current options

- Option 1: BPaL
- 2021 - present
- NIX trial: 90% favorable outcome (n=109) with Bedaquiline, Pretomanid, LZD 1200mg daily x 6 months (Conradie, NEJM 2020)
- All oral: 6 months. Susceptibility testing less important.
- ZeNix trial: BPaL with LZD 600mg daily x 6 months OK (Conradie, NEJM 2022)



Option 2: BPaLM

- BPaLM x 6 months
- TB-PRACTECAL trial: 89% favorable vs 52% with standard care treatment lasting 9-20 months. LZD 600 daily x 16 weeks, then 300mg daily for 8 weeks (Nyangwa, NEJM 2022)

Option 3:

- 9 mo regimens: BCLLfxZ, BLMZ, and BDLLfxZ (Guglielmetti, NEJM 2025)

Most MDR TB rx currently…

- Confirm MDR
- BPaL(+/-M)
  - Bedaquiline- 400mg daily x 2w, then 200mg 3x MWF
  - Linezolid- 600mg daily
  - Pretomanid- 200mg daily
  - Moxifloxacin- 400mg daily
  - B6- 100mg daily

Most MDR TB rx currently…

- After a couple weeks, check a Linezolid trough (and 2h peak)
- If LZD trough < 2 mcg/ml, continue
- If LZD trough >2 mcg/ml, reduce to 600mg tiw

Clinical Infectious Diseases

MAJOR ARTICLE

Association Between Increased Linezolid Plasma Concentrations and the Development of Severe Toxicity in Multidrug-Resistant Tuberculosis Treatment

Johannes Eimer,[1,©] Mathilde Fréchet-Jachym,[2] Damien Le Dû,[2] Eric Caumes,[3] Najoua El-Helali,[4] Dhiba Marigot-Outtandy,[2,5] Frédéric Mechai,[6,7] Gilles Peytavin,[8] Valérie Pourcher,[3] Christophe Rioux,[9] Yazdan Yazdanpanah,[9] Jérôme Robert,[1,10] and Lorenzo Guglielmetti[1,10]; for the LZDM group

Linezolid side effects

- **Neurotoxicity**
- Can occur late
- Peripheral neuropathy (glove and stocking) and optic neuropathy
- May or may not be reversible
- Ask about for neuropathy symptoms

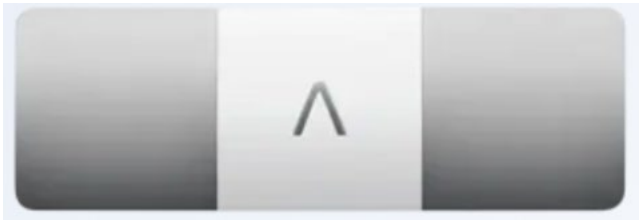
- **Bone marrow toxicity**
- Can occur early
- Can be anemia, thrombocytopenia, leukopenia
- Monthly CBC and chemistry (lactic acidosis)

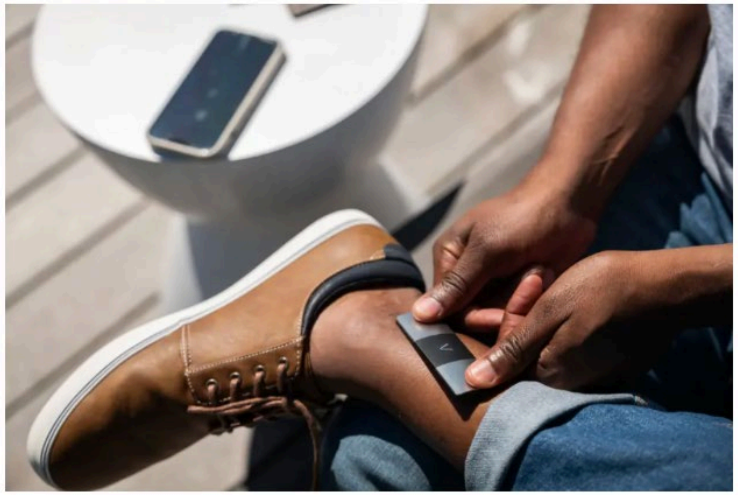
Linezolid side effects

- In the NIX trial, LZD was 1200qd with dose adjustment if toxicity
  - 81% developed neuropathy
  - Only 34% completed 26 weeks of LZD
  - Only 15% completed 1200 qd
  - Still did well from TB standpoint
- Room to go down on LZD to 300mg qd or tiw if needed
- Quinolones can also cause neuropathy – stop the quinolone
- We use B6 100mg (but no evidence that it works)
- Caution concurrent use of SSRI or MAOI antidepressants – serotonin syndrome
- If can’t use LZD then can’t use BPaL 6 month regimen > longer more complex regimen

Bedaquiline – QTc prolongation

- Recommend EKG monitoring at baseline, and at 2, 12, and 24 weeks
- Often use Kardia device if can't get EKG





- Probably discontinue bedaquiline if QTc >500 msec develops
  - Correct potassium, calcium, and magnesium
  - Discontinue other QT prolonging drugs (Moxi)
- If can't use BDQ then can't use BPaL 6 month regimen > longer more complex regimen

MDR TB rx exposure/LTBI/window prophylaxis

- Generally use Levofloxacin 750mg qd x 6 months
- ~60% reduction in TB in household contacts (Duong NEJM Evid 2025)

MDR TB isolation in the community

- Used to be wait until documentation of culture conversion (few months)
- Now, generally follow NTCA guidance of at least 5 days with active drugs – depending on individual circumstances

Drug Resistant TB key points

- GeneXpert Rif R, esp smear negative/low likelihood > confirm rifampin resistance (CDC MDDR)
- Usually use BPaL(M)
- 6 months all oral
- Usually well tolerated but monitor for side effects of LZD and QT prolongation