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Treatment of Multidrug Resistant Tuberculosis

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Approaches to the treatment of multi- and extensively drug resistant tuberculosis

- Tailored drug regimens
- DOT
- Resectional surgery

Designing a treatment regimen for MDR/ XDR-TB

- Regimen should be based on:
  - Meticulous history of drugs taken by the patient
  - Knowledge of the epidemiology of drug resistance in the community
  - Drug susceptibility testing
- Ideally include at least 4 new drugs to which the isolate is (or should be) susceptible
- Never add a single drug to a failing regimen
- DOT is essential
- Consider surgery any time resistance to H + R + S is confirmed
- Treat for 18-24 months after culture conversion
- Consult an expert

Drugs for MDR-TB

Group name	Anti-tuberculosis agent	Abbreviation
Second-line parenteral agent (injectable anti-tuberculosis drugs)	kanamycin amikacin capreomycin	Km Amk Cm
Fluoroquinolones	levofloxacin moxifloxacin gatifloxacin ofloxacin	Lfx Mfx Gfx Ofx
Oral bacteriostatic second-line anti-tuberculosis drugs	ethionamide prothionamide cycloserine terizidone *p*-aminosalicylic acid	Eto Pto Cs Trd PAS
Group 5 drugs	clofazimine linezolid amoxicillin/clavulanate thioacetazone clarithromycin imipenem	Cfz Lzd Amx/Clv Thz Clr Ipm

Revised WHO guidelines for management of MDR-TB: general principles

- Rapid drug susceptibility testing (DST) of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis of TB, subject to available resources
- The use of sputum smear microscopy and culture rather than sputum smear microscopy alone is recommended for the monitoring of patients with MDRTB during treatment

WHO Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update

Revised WHO guidelines for management of MDR-TB: drug regimens

- In the treatment of MDR-TB, a fluoroquinolone should be used and a later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used
- In the treatment of MDR-TB, ethionamide (or prothionamide) should be used
- In the treatment with MDR-TB, four second-line antituberculosis drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase
- In the treatment of MDR-TB, regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or PAS (*p*-aminosalicylic acid) if cycloserine cannot be used
- Group 5 drugs may be used but are not included among the drugs making up the standard regimen.

WHO Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update

Revised WHO guidelines for management of MDR-TB: duration of treatment

- In the treatment of patients with MDR-TB, an intensive phase of at least 8 months' duration is recommended
- In the treatment of patients with MDR-TB, a total treatment duration of at least 20 months is recommended in patients without any previous MDR-TB treatment

WHO Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update

Outcomes of medical therapy for multidrug resistant tuberculosis

	Goble[1], Denver	Chan[2], Denver	Chiang[3], Taiwan	Mitnick[4], Peru
Years	1973-1983	1984-1998	1992-1996	2000-2002
Cases	171	205	299	75
Mean no. of drugs resistant	6	6	3	6
Culture conversion	65%	85%	51.9%	83%
Attributable mortality	22%	12%	9.4%	8%

1. NEJM 1993; 328: 527-532
2. AJRCCM 2004; 169: 1103-1109
3. Eur Respir J 2006; 28: 980-985
4. NEJM 2003; 348: 119-128

Linezolid in the treatment of tuberculosis

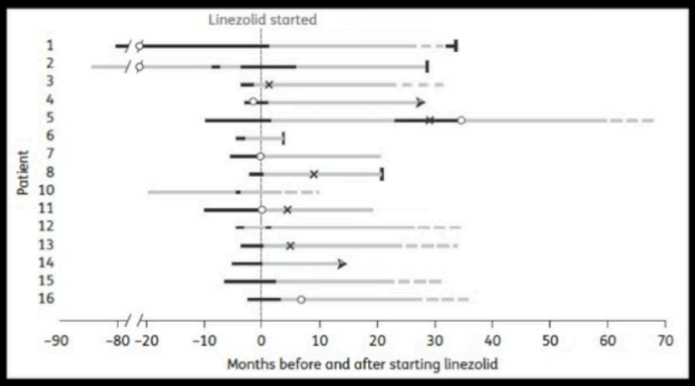
- Oxazolidinone
- Approved for the treatment of gram-positive infections
- Good *in vitro* activity against *M. tuberculosis*, with MIC in the 0.5-1 μg/ml range
- Expensive
  - Drugstore.com price for 60 tablets $4,279.36 (i.e. $71.30/ tablet)

Linezolid in the treatment of tuberculosis

- Usual dose given: 600 mg b.i.d., with reductions to 600 q. day or 300 b.i.d. if needed
- Cure reported in 14/23 (61%) patients in the literature after addition of linezolid
- Three of 23 (13%) patients died despite addition of linezolid
- Serious adverse events common:
  - 75% of all patients had an SAE
  - Neuropathy (peripheral, optic): 45.8%
  - Anemia: 41.7%
  - Eleven (47.8%) ultimately had treatment limited side effects

Ntziora and Falagas, Int J Tuberc Lung Dis 2007; 11: 406-411

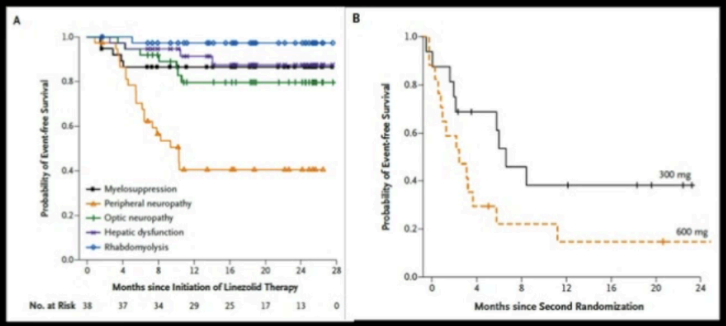
Utility of linezolid in the treatment of MDR and XDR TB: New York City experience



All patients resistant to H/R; 10/16 resistant to injectables; 6/16 resistant to quinolones

Anger et al. J Antimicrob Chemother 2010; 65:775-783

Adverse effects associated with administration of linezolid for tuberculosis



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

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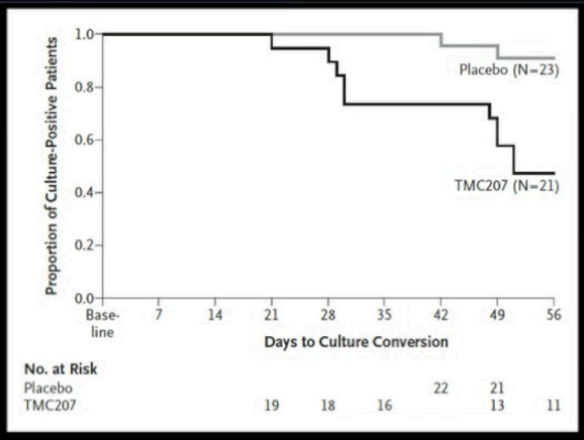
TB drugs in development

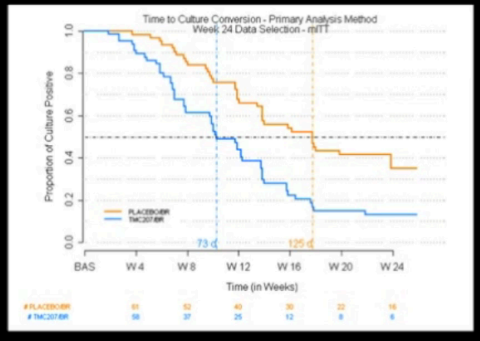
Sponsor	Drug	Stage
Sanofi-Aventis	Rifapentine	Phase 4
Bayer/GA	Moxifloxacin	Phase 2/3
EU, WHO	Gatifloxacin	Phase 2/3
Tibotec	TMC207	Phase 2
Otsuka	OPC67683	Phase 2
Global Alliance	PA-824	Phase 1
Sequella	SQ-109	Phase 1
Lupin	Pyrrole, LL-3858	Phase 1
Pfizer	PNU100480	Phase 1

Bedaquiline (TMC207), an ATP synthase inhibitor, in the treatment of MDR-TB



Diacon et al. N Engl J Med 2009; ;360:2397-405.

Time to culture conversion in patients with MDR-Tb treated with bedaquiline: C208 trial



Source: Janssen briefing document prepared for FDA hearing, Nov. 28, 2012

Excess deaths in experimental arm of C208, bedaquiline clinical trial in MDR-TB

C208 Stage 2[a]	N = 79	N = 81
During Trial	6	1
Follow-up of Premature Withdrawals	4	1
Total	10	2

Source: Janssen briefing document prepared for FDA hearing, Nov. 28, 2012

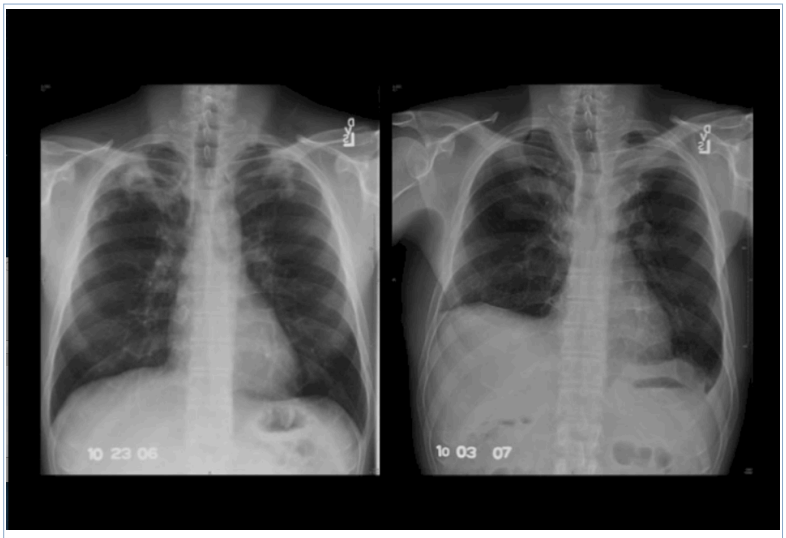
Outcomes of surgical therapy for tuberculosis

	Pomerantz[1], Denver	Somocurcio[2], Peru	Kir[3], Turkey	Shiraishi[4], Japan
Years	1983-2001	1999-2004	1993-2005	2000-2002
Cases	172	121	79	30
Surgical mortality	3.3%	5%	2.5%	0%
Major complications	12%	16%	25.3%	33%
Treatment success rate	98%	74.8%	94.5%	93%

1. J Thoracic Cardiovasc Surg 2001; 121: 448-453
2. Thorax 2007; 62: 416-421
3. J Thoracic Cardiovasc Surg 2006; 131: 693-696
4. J Thoracic Cardiovasc Surg 2004; 128: 523-528

Selection of patients for surgery

- Localized disease
- Good nutritional and overall status
- Availability of drugs for medical treatment post-surgery
- Experienced and willing surgeon



Treatment of drug resistant tuberculosis: summary and conclusions

- Complex and often multimodality
- Expensive
- High morbidity, both from tuberculosis itself and therapeutic approaches
- Mortality is appreciable
- DOT essential
- Expert consultation required
- Good outcomes can be achieved in many cases