Drug resistant Tuberculosis

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Management of drug-resistant TB :

- Difficult
  and may
- Necessitate use of second-line drugs
- Surgical resection.
- Need expertise in this area
- Need supportive public health infrastructure .

DOTs

- In a patient with drug-susceptible TB who receives rifamycin-based DOT, relapse is likely due to a drug-susceptible organism. Such patients usually respond again to the initial regimen.

- If compliance has been irregular, particularly if the patient has not received DOT, resistant organisms will probably be present.

Good patient outcomes

- depend upon:
  1.rapid and accurate diagnosis
  2 .administration of proper therapy
  3.close monitoring
  4.adherence to the treatment regimen and patient safety.

- Drug-resistant TB refers to TB caused by an isolate of Mycobacterium tuberculosis that is resistant to one or more antituberculous drugs.

Types of drug-resistant TB

- Monoresistant TB refers to TB caused by an isolate of M. tuberculosis that is resistant to a single antituberculous agent.
- Poly-resistant TB refers to TB caused by an isolate of M. tuberculosis that is resistant to more than one antituberculous agent; the isolate may be resistant to either isoniazid (INH) or rifampin but not both.
- Multidrug-resistant TB (MDR-TB) refers to TB caused by an isolate of M. tuberculosis that is resistant to both INH and rifampin and possibly additional agent.

- **Pre-extensively drug-resistant TB** (pre-XDR-TB) refers to an isolate of M. tuberculosis that is resistant to INH and rifampin and either quinolones or all injectable agents (streptomycin, amikacin, kanamycin, or capreomycin).
- **Extensively drug-resistant TB** (XDR-TB) refers to TB caused by an isolate of M. tuberculosis that is resistant to at least INH, rifampin, and fluoroquinolones as well as either aminoglycosides (amikacin, kanamycin) or capreomycin or both .
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Totally drug-resistant TB (TDR-TB)

- Isolate of M. tuberculosis resistant to all locally tested medications .
- However, the published studies initially describing TDR-TB did not include susceptibility testing for less frequently used agents with activity against TB (including cycloserine, terizidone, clofazimine, linezolid, or carbapenems)

  or

- more recently introduced agents (including bedaquiline, pretomanid, and delamanid) and therefore is a term that may be inconsistent (depending on local susceptibility capacity) or misleading.

- **Primary drug resistance** refers to TB caused by a drug-resistant isolate of M. tuberculosis in a patient who has not previously received antituberculous therapy, strongly suggesting that the patient was infected with an already drug-resistant isolate.
- **Secondary drug resistance** (in contrast to primary drug resistance) refers to the development of drug resistance during or following antituberculous therapy in patients who had previously had drug-susceptible TB, suggesting that the patient acquired drug resistance after the start of antituberculous therapy.

MDR-TB treatment

- Which of them is worst?
- INH resistance
- Or
- RIF resistance

MDR-TB treatment

- Surprisingly, studies of four-drug, 6-month chemotherapy demonstrated that initial INH or STM resistance did not compromise outcome
- but
- Results were very poor (>50% lack of conversion or relapse) when initial RIF resistance was present.
- In a meta-analysis, treatment failure and relapse were substantially higher in the presence of initial drug resistance.

MDR ----------XDR

combatting the development of XDR

- Access to effective second-line agents
- Increased sputum culture
- Susceptibility testing

  and
- Genotypic data

MDR treatment:

- For therapy for TB that is resistant to both INH and RIF,
- Susceptibility testing for second-line drugs should be performed
  and
- treatment individualized according to the susceptibility test results.
- the role of PZA may be limited in MDR-TB
- The injectable agents are particularly important for good outcomes, although nephrotoxicity and ototoxicity are concerns.

- If a **suboptimal regimen** is prescribed, resistance to additional drugs may emerge and the opportunity for success may be lost.

Fluoroquinolones in MDR:

- For TB that is INH and RIF resistant but fluoroquinolone susceptible, a fluoroquinolone should always be administered along with other drugs to which the organism is susceptible.
- The risk for treatment failure is increased if the M. tuberculosis isolate is also resistant to fluoroquinolones.
- Levofloxacin may be preferred over ofloxacin, but moxifloxacin has the greatest in vitro activity against M. tuberculosis

- Companion drugs may include aminoglycosides (STM, kanamycin, or amikacin) or capreomycin, ethionamide, and cycloserine.
- Capreomycin or amikacin can replace STM.
- Kanamycin is less effective and more toxic and is used as a last resort.
- There is usually no cross-resistance between capreomycin and STM, amikacin, or kanamycin, but amikacin and kanamycin are usually cross-resistant

Newer therapies

- The uncertain efficacy of newer therapies is underlined by the report of the development of resistance to bedaquiline and delamanid during treatment of MDR-TB.

Extensively Drug-Resistant Tuberculosis

- Resistance to INH, RIF, any fluoroquinolone, and at least one of three injectable second-line drugs (amikacin, kanamycin, or capreomycin)
- Treatment is difficult and usually associated with poor outcomes.
- The risk for treatment failure and death has been higher than in patients with MDR-TB in some series, but not all.
- Cure rate in a report from South Africa was 5%, and mortality was 78% at 60 months.

XDR-TB

- Treatment with at least five drugs to which the organism is susceptible is recommended.

linezolid

- In a study of 41 patients with treatment-refractory XDR-TB, **linezolid** was associated with sputum culture conversion, but 82% of patients had clinically significant adverse events attributable to linezolid.
- The cure rate 1 year after the end of treatment was 78%.
- A similar trial in China also found a significantly higher cure rate (70% vs. 34% in the control group), but again with an adverse event rate in the linezolid group of 82%.

clofazimine

- A retrospective report in a predominantly HIV-infected South African population noted improved culture conversion with **clofazimine** (40% vs. 29% in the comparator group), with only minor adverse effects

Summary

- When drug resistance is suspected:
- The treatment regimen should include:
- INH, RIF, PZA, EMB, a fluoroquinolone, and an injectable agent (e.g., capreomycin),
- Pending susceptibility results.

MDR-TB

- TB resistant to INH and RIF (i.e., MDR-TB)
- Should be treated with a fluoroquinolone, ethionamide (or protionamide), PZA, and probably an injectable agent plus either cycloserine or PAS.
- The intensive phase of treatment is for 8 months, and the total treatment duration is 20 months.

XDR-TB

- TB resistant to INH, RIF, an injectable agent, and a fluoroquinolone (i.e., XDR-TB)
- Should be treated with at least four second-line antituberculosis drugs likely to be effective, in addition to PZA during the intensive phase of treatment.
- Surgical resection may be required.
- A prolonged course of treatment is necessary, but the optimal duration is unknown.