

Chapter IX: Management of Relapse, Treatment Failure, and Drug Resistance

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A. Relapse

Relapse refers to the circumstance in which a patient becomes culture-positive again or experiences clinical or chest x-ray deterioration consistent with active tuberculosis after successful completion of treatment. In such cases, vigorous efforts should be made to establish a diagnosis and obtain sputa specimens to test for drug resistance. True relapses are due to failure of chemotherapy to sterilize the host tissues, enabling the original infection to reestablish itself. In locations where TB is highly endemic, a new strain of *M. tuberculosis* may be responsible for the apparent relapse.

Patients who are most likely to have true relapses are those with at least two of the following risk factors:

- Cavitory pulmonary tuberculosis
- Positive sputa cultures after 8 weeks of chemotherapy
- Being underweight at diagnosis (less than 90% of ideal body weight or BMI < 18.5).

Most patients relapse within the first 6-12 months after completion of treatment. Acquired drug resistance is rare among patients relapsing following DOT treatment of drug-susceptible tuberculosis using standard regimens. In cases of relapse in patients who received self-administered therapy or a non-rifamycin regimen, the risk of acquired drug resistance is substantial.

Additionally, if initial drug susceptibility testing was not done and the patient fails or relapses with a rifamycin-containing regimen given by DOT, there is a high likelihood that the organisms were resistant from the beginning.

B. Treatment Failure

Treatment failure is defined by continued or recurrently positive cultures in a patient receiving appropriate chemotherapy. Among patients with drug-susceptible pulmonary tuberculosis, even with extensive lung cavitation, over 95% will be culture-negative after 3 months of treatment with a regimen that contains INH and rifampin. During this time the vast majority of patients show clinical improvement. Patients whose sputum cultures remain positive after 4 months of treatment are considered to have failed treatment.

There are multiple potential reasons for treatment failure that should be considered:

- Patients on self-administered therapy who don't take their medications consistently or on DOT who spit out or deliberately regurgitate the pills
- Unrecognized drug resistance
- Malabsorption because of prior resectional surgery or taking TB medications with antacids or other drugs or substances that bind or interfere with absorption
- An extreme biologic variation
- Lab error should also be considered as a possible reason for a patient who is otherwise doing well.

A fundamental principle in managing patients who have failed treatment is that a single new drug should never be added to a failing regimen. So doing may lead to acquired resistance to the added drug. In such cases it is generally prudent to add at least 3 new drugs to which susceptibility could logically be inferred to lessen the probability of further acquired resistance.

C. Management of Drug-Resistant TB

Tubercle bacilli are continually undergoing spontaneous mutations that create resistance to individual tuberculosis drugs. However, the frequency of these single mutations is sufficiently low that, with appropriate combination chemotherapy that is reliably ingested, clinically significant resistance will not develop.

Acquired drug resistance is much more likely to occur in cavitary pulmonary tuberculosis when there is a large bacillary population and an inadequate drug regimen is prescribed (inappropriate drugs, insufficient dosage) or when there is a combined failure of both the patient and the provider to ensure that an adequate regimen is taken. Patients with acquired drug resistance may transmit their strains to others who, if they develop tuberculosis, will have primary drug resistance.

Drug resistance in a patient with newly diagnosed tuberculosis may be suspected on the basis of historical (previous treatment) or epidemiological information (contact with a known drug-resistant case or coming from a part of the world where drug resistance is common). Multi-drug resistance has been found in approximately 7% of foreign-born patients with a history of prior tuberculosis treatment, a high-risk subgroup accounting for about 5% of reported cases. Most cases of MDR-TB are reported among patient without prior TB treatment, so obtaining drug-susceptibility results is important for all patients. Patients with strains of *M. tuberculosis* that are resistant to both INH and RIF (multi-drug resistant TB or MDR TB) are at high risk of treatment failure and further acquired resistance. Fluoroquinolones such as levofloxacin or moxifloxacin have become key components of regimens used to treat MDR-TB. MDR TB isolates with resistance to drugs in the fluoroquinolone class are associated with poor treatment outcomes, and the term extensively drug-resistant has been coined for MDR-TB isolates with resistance to both a fluoroquinolone and at least one of the injectable second-line drugs (amikacin, kanamycin or capreomycin).

Consultation with experts in the management of MDR-TB should always be sought. In addition, useful information for clinicians is provided by the Curry International Tuberculosis Center both as printed and on-line resources.

The following principles should guide treatment for drug-resistant TB:

- A single new drug should never be added to a failing regime.
- When initiating or revising therapy, always attempt to employ at least 3 previously unused drugs.
- Do not limit the regimen to 3 agents if there are other previously unused drugs that are likely to be active against the tuberculosis.

- DOT is mandatory.
- Intermittent therapy should not be used, except for injectable agents after an initial period (usually 2-3 months) of daily therapy.
- Resistance to rifampin is nearly always associated with cross-resistance to rifabutin and rifapentine.
- There is no cross-resistance between SM and the other injectable agents: amikacin, kanamycin, and capreomycin (although resistance to all may occur as independent events). However, cross-resistance between amikacin and kanamycin is universal.
- Simultaneous use of 2 injectable agents is not recommended.
- Resistance to PZA is uncommon in the absence of resistance to other first-line drugs. If mono-resistance to PZA is observed, consideration must be given to the possibility that the patient is infected with *M. bovis* and not *M. tuberculosis*.

D. Surgery

Surgery is not a first-line option in the treatment of TB because, in most cases, pulmonary TB is curable using modern drug regimens. Surgery is, however, one of the last alternatives available for individuals with severe drug resistance (on average, having resistance to more than 5 drugs). These individuals appear to benefit from the resection of cavitary or badly damaged lung tissue. Even with successful surgery, 12-24 months of chemotherapy using drugs to which there is demonstrated susceptibility should be given.

E. Lab Consideration in Determining Drug Resistance

Drug susceptibility testing for INH, rifampin, and EMB should be performed on an initial isolate of *M. tuberculosis* from all patients. Susceptibility testing for first-line and second-line drugs should be performed for all patients with possible treatment failure or relapse, if the patient has a positive culture after 3 months of therapy or if the patient develops positive cultures after a period of negative cultures. Due to the importance of initiating an effective regimen for patients with drug-resistant TB, rapid molecular testing for rifampin resistance (strongly associated with MDR-TB) is provided by the CDPHE laboratory. In addition, rapid molecular testing for additional first and second line TB drugs can be obtained from the CDC laboratory by referrals through CDPHE and are also being done in a number of referral laboratories.

References

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