Multi-Drug Resistant (MDR) TB : Rational Approach to Management

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ABSTRACT

Multi drug resistant tuberculosis (MDR-TB) is defined as resistance to both Isoniazid (INH) and Rifampicin (RMP), alone or in combination with other drugs. MDR-TB typically occurs due to acquired or secondary resistance though it may occasionally occur in patients who have not had any prior treatment with anti-tuberculous drugs (primary resistance). Thus primary drug resistance (PDR) is defined as drug resistance occurring in an individual who has never taken ATT in the past. In patients with inadequate previous treatment, the bacterial resistance is acquired or secondary drug resistance (ADR). There has been a global resurgence of TB, together with human immunodeficiency virus (HIV) and TB co-epidemic. MDR-TB has reached epidemic proportions in some parts of the world. In a study in Delhi the incidence of MDR-TB was 14%, hence India is declared a "hot zone" of MDR-TB.

The treatment of MDR-TB with second-line drugs is expensive and less effective and this form of TB carries a very high morbidity and mortality even in immunocompetent individuals. WHO (World Health Organization) has suggested that second-line drug treatment should be provided by specialized units in close connection with a laboratory able to carry out reliable culture and sensitivity and has provided guidelines for the same.

INTRODUCTION

That resistance could emerge in antituberculosis therapy (ATT) was recognized right from the start of introduction of chemotherapy in the late 1940s. Multidrug resistant tuberculosis (MDR-TB) is defined as resistance to both Isoniazid (INH) and Rifampicin (RMP), alone or in combination with other drugs and has been reported from different regions of the world since the 1990s. It is the most severe form of bacterial resistance today and hence an important cause for concern in tuberculosis control.[1, 2] The treatment of MDR-TB with second-line drugs is expensive and less effective and this form of TB carries a very high morbidity and mortality even in immunocompetent individuals. The alarming worldwide threat imposed by multidrug resistant (MDR) TB is likely to have serious impact on TB control.

DEFINITION

Resistance to at least Isoniazid (INH) and Rifampicin (RMP) is considered as MDR-TB. However, the consequence of RMP mono resistance (though rare) is the same, i.e. failure of first-line treatment.

TYPES OF RESISTANCE

MDR-TB typically occurs due to acquired or secondary resistance though it may occasionally occur in patients who have not had any prior treatment with anti-tuberculous drugs (primary resistance). Thus primary drug resistance (PDR) is defined as drug resistance occurring in an individual who has never taken ATT in the past. If after clinical assessment, the history of prior anti-tuberculous drugs is doubtful, then the individual is said to have initial drug resistance. Initial drug resistance is a mixture of primary resistance and undisclosed acquired resistance. In patients with some record of previous treatment, the bacterial resistance is acquired or secondary drug resistance (ADR). Acquired drug resistance reflects failure of the present TB control programme, while primary resistance occurs due to poor TB control programmes in the past. PDR is more often resistance to one drug (streptomycin or isoniazid) than to two drugs (usually streptomycin and isoniazid). PDR to three drugs and primary multidrug resistance are exceptional. By contrast ADR usually concerns two or more drugs, and multidrug resistance is relatively frequent. This is the reason why PDR hardly affects the outcome of treatment with a WHO standard regimen containing four drugs in the initial phase of treatment in new smear positive cases.

PREVALENCE OF MDR-TB

The emergence of strains of *M. tuberculosis* that are resistant to anti-mycobacterial agents is a worldwide problem whose global magnitude is not well described. The highest rate of MDR-TB have been reported in Nepal (48.0%), Gujarat (India 33.8%), New York City (30.1%), Bolivia (15.3%) and Korea (14.5 %).[6] In a study in Delhi the incidence of MDR-TB was 14%, hence India

is declared a "hot zone" of MDR-TB. There has been a global resurgence of TB, together with human immunodeficiency virus (HIV) and TB co-epidemic. MDR-TB has reached epidemic proportions in some parts of the world.

DIAGNOSIS OF MDR-TB: WHEN TO SUSPECT MDR-TB

Clinical situations

- History of poor tuberculous treatment (poor compliance with WHO's directly observed treatment short course (DOTS) therapy, irregular drug therapy, inadequate doses, addition of a single drug to a failing regimen leading to step-wise emergence of poly-resistance)
- History of contact with a case of MDR-TB (PDR)

Laboratory situations

- Persistent smear positive at the end of 5 months of WHO category II regimen or smear positive at completion of 8 months of category II regimen.
- Worsening sputum status while on therapy.
- "Fall and rise" phenomenon- It is a smear phenomenon. The initial "fall" in sputum bacillary content is due to a rapid decrease in the drug sensitive bacillary population and the "rise" is due to the overgrowth of resistant strain.

Confirmation

- Culture susceptibility (C/S) showing "HR" resistance

Misdiagnosis of MDR-TB due to laboratory related errors

Misdiagnosis of MDR-TB due to laboratory related errors has been reported recently. The possible explanation has been cross-contamination, contamination with *M. avium* complex, suspected mislabeling and discrepant susceptibility tests due to poorly standardized techniques in different laboratories. Another important issue is the reliability of the techniques currently used to measure drug resistance. Isoniazid (IHH) and Rifampicin (RMP) resistance can be reliably measured however; resistance to pyrazinamide (PZA), Ethambutol (EMB) and Streptomycin (SM) is more difficult due to limitations of technique. The therapeutic index for a given drug, which is the difference between in vitro minimal inhibitory concentration (MIC) and the drug levels obtained in blood is low for certain second-line drugs Hence, in case Ethionamide (ETA), cycloserine (CYC), viomycin (VM) and para-amino salicylic acid (PAS) laboratory results fail to distinguish between sensitive and resistant strains. Susceptibility results alone should not dictate treatment and careful clinical correlation is necessary in making the diagnosis of MDR-TB.

HOW TO PROCEED WITH A SUSPECT CASE OF MDR-TB

1. Take a detailed history of previous chemotherapy
   - Ascertain the previous drugs taken, their doses, duration and regularity; correlate the past clinical, radiological and bacteriological status.
   - Reasons for failure of previous therapies.
2. Order C/S for *M. Tuberculosis*
   Sensitivity to first-line drugs is sufficient. Sensitivity testing for second-line anti-tuberculous drugs is not standardized and hence not reliable.
3. Test for associated diabetes mellitus (DM) and counselling for HIV testing
4. Start the patient afresh on WHO Category 2, DOTS wherein treatment should be strictly supervised

MDR-TB Treatment

WHO (World Health Organization) has suggested that second-line drug treatment should be provided by specialized units in close connection with a laboratory able to carry out reliable culture and sensitivity and has provided guidelines[3] for the same. Revised National TB Control Programme (RNTCP) based on WHO guidelines has categorized treatment of TB as shown in Table 1.

Steps in MDR TB treatment

- Start three new drugs, which the patient has never taken before and to which the tubercle bacilli are likely to be susceptible; and which have no cross-resistance to drugs taken in the past.
- Ensure compliance
- Repeat sputum smear examination at 2 months, then monthly, till smear turns negative
- Confirm with culture
- Continue all drugs for a period of 1 year after culture turns negative
- Evaluate for surgery in appropriate case

Characteristics of Second-line drug

- Drugs with bactericidal activity- Aminoglycosides, thioamides (Ethionamide and prothionamide)
- Drugs with low bactericidal activity- fluoroquinolones
- Drugs with bacteriostatic activity- Cycloserine, PAS

Cross-resistance profile

- Strains resistant to streptomycin are susceptible to kanamycin and amikacin
- Resistance to Kanamycin induces a complete cross-resistance to amikacin
- Resistance to Kanamycin and amikacin induces resistance to streptomycin
- Strains which are resistant to streptomycin, kanamycin and amikacin are still susceptible to capreomycin
- Ethionamide exhibits complete cross-resistance with prothionamide
- Ofloxacin and ciprofloxacin induce complete cross-resistance for all other fluoroquinolones
- Cycloserine does not exhibit cross resistance to any other anti-tuberculous drugs

PITFALLS IN DIAGNOSIS OF MDR-TB

Clinical suspicion of drug resistance of MDR-TB requires bacteriological confirmation. Diagnosis of MDR-TB should not be made hurriedly in the following situations:

- Persistence of fever on adequate ATT – Fever may persist up to 40 days while a patient is on effective ATT.
- Increase in the size of TB lesions while on ATT- Worsening of signs and symptoms or lesions on chest radiograph can occur while the patient is on adequate ATT. This is known as paradoxical reaction and is due to "immune-reconstitution phenomenon". In TB lymphadenopathy, appearance of new nodes, enlargement of nodes, cold abscess formation and sinus formation can occur while on effective chemotherapy. 10% of cases may be left with residual nodes at the end of chemotherapy. Enlarging tuberculomas, appearance of new tuberculomas or abscess formation may cause clinical deterioration despite adequate ATT, and do not indicate drug resistance. Pleural effusions may similarly increase in size or worsen due to fibrosis. No change in ATT is justified unless the pleural fluid or the biopsy material grows resistant mycobacteria.
- Mechanical complications like bronchopleural fistula, empyema and pleural thickening during the quiescent phase of pulmonary tuberculosis do not indicate drug resistance. Similarly TB meningitis may be complicated by hydrocephalus.
- Complications like fibrosis, collapse, cavity, bronchiectasis and broncholithiasis can occur in the residual TB lesions, which may predispose to infections, pneumothorax and hemoptysis.
- Recurrent bacterial infections in healed tuberculosis lesions and progressive obstructive airway disease can cause hypoxia and pulmonary hypertension.
- Renal amyloidosis can rarely occur causing nephrotic syndrome.
- Progressive upper lobe fibrosis may cause damage to the left recurrent laryngeal nerve and vocal cord paralysis.

These clinical situations can be mistaken for drug resistance despite absence of active tuberculosis and unnecessarily considered for second-line therapy.

CONCLUSIONS

It has also been suggested that the WHO recommended TB control programme using DOTS should have additional intervention for treatment of MDR-TB (DOTS plus). However, the potential of introducing drug resistance resulting from a failure to adhere to the principles of chemotherapy will never be overcome even by development of new drugs. The top priority therefore remains prevention, not treatment of MDR-TB.

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LEARNING POINTS

In order to prevent MDR-TB a physician

- Must diagnose TB by sputum smear or histology
- Must consider culture / sensitivity if suspected MDR cases (including extra-pulmonary tuberculosis)
- Must test for associated DM and counsel for HIV testing
- Must give DOTS in sputum positive patients
- If DOTS is not possible must use fixed-dose combination (FDC) which is adjusted for body weight
- Must persist with the prescribed regimen and not change drugs erratically
- Must never add one drug to a failing regimen
- Must refer cases of suspected drug resistance to specialized centers and not introduce second-line drugs

Pitfalls in treatment of MDR-TB

- Use of drugs other than the recommended as second-line drugs
- Failure to recognize cross-resistance for example use of amikacin after kanamycin has failed.
- Failure to ensure compliance by making provision for entire course of therapy
- "Addition syndrome" i.e. addition of one drug at a time to a failing therapy
- Failure to offer surgery to appropriate cases.