Section 14

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Abstract

Drug-resistant tuberculosis is an important impediment to successful TB control in any country. India has the highest number of MDR-TB cases in the world. Diagnosis and management of such cases are difficult; drugs are costly, of longer duration, and are associated side effects that are sometimes unacceptable. Further, treatment outcomes are not very encouraging. However, with availability of newer diagnostic opportunities, specifically CBNAAT, LPA for both the standard and second-line drugs and liquid culture and drug susceptibility testing have changed the approach. Further developments with availability of newer and efficacious drugs like bedaquiline, delamanid, and pretomanid have changed the paradigm of our approach for treating these cases with better outcomes. The duration of therapy has further come down with these new drugs and now we have the option of shorter courses of therapy to 6–9 months and the all oral longer duration of therapy for 18 months are now realities with success rates of more than 80%. Another important advantage is the no necessity of injectables so that patients accept these injection-free, all oral regimens with better compliance.

Introduction

The Revised National Tuberculosis Control Program (RNTCP), now known as the National Tuberculosis Elimination Program (NTEP) has notified around a total of 2.41 million TB patients of all types in 2019 according to the Nikshay dashboard.1 More than a quarter of TB patients in India have drug resistance to one or the other anti-TB drug as per the 1st National Anti-TB Drug Resistance Survey (NDRS) of India (1914–1916).

A case of presumptive DR-TB includes the following:
- Positive sputum smear during any follow-up visit while on treatment with first-line ATT;
- Pediatric TB non-responders;
- If the patient is a contact of a known DR-TB case;
- Earlier treated patient;
- TB-HIV coinfection;
- All notified new TB patients.

Results from a RNTCP (NTEP) accredited laboratory is taken as confirmed case of DR-TB. These patients are then classified according to the following definition:

Mono-resistance TB (MR): Biological sample—sputum or fluid or tissue shown to be resistant to any one anti-tubercular drug of the first-line only.

Polydrug resistance TB (PDR): When the biological sample shows resistance to more than 1 first-line anti-tubercular drug other than both INH (H) and rifampicin (R).

Rifampicin resistance (RR): When the sputum or the biological specimen shows resistance to rifampicin, when tested using phenotypic or genotypic methods and with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR, or XDR. Most of the rifampicin resistant cases will also show H-resistance, hence the
RNTCP (NTEP) has taken a considered decision that all R-resistance cases will be treated as MDR-TB cases.

**Multidrug resistance TB (MDR):** In this form of tuberculosis, the biological specimen is resistant to both INH and rifampicin with or without resistance to other first-line anti-TB drugs. These patients may also have additional resistance to any/all fluoroquinolones or any/all second-line injectable (amikacin, kanamycin, and capreomycin) anti-TB drug.

**Pre-XDR-TB:** MDR TB with demonstrable resistance to any one of the second-line injectable anti-TB drugs like amikacin, kanamycin, or capreomycin OR to any one of the fluoroquinolones.

**Extensive drug resistance (XDR):** When there is additional resistance to at least any fluoroquinolone (like ofloxacin, levofloxacin, moxifloxacin, etc) and a second-line injectables (like amikacin, kanamycin, or capreomycin) in a case of MDR TB.

The following technologies are used nowadays (besides culture and DST methods):
- Line Probe Assay (LPA) for detection of MTB complex and detection of resistance to first-line drugs rifampicin, isoniazid, and second-line drugs (fluoroquinolones, second-line injectables);
- CBNAAT (Cartridge Based Nucleic Acid Amplification Test) Xpert MTB/Rif testing by using the Gene X pert platform; and
- TrueNat TB test.²

Drug-resistant tuberculosis is a great impediment to the achievement of End TB strategy because of the complexity of drug regimes against this form of tuberculosis, treatment outcome, and cost involved. However, with availability of newer drugs particularly bedaquiline (BDQ), delamanid, and pretomanid and experience of success with shorter durations of therapy have raised hope to handle this form of the disease. An estimated 484,000 incident cases of MDR/RR-TB were reported in 2018 globally. MDR/RR-TB was reported in 3.4% of all new cases and 18% in all previously treated cases of TB. The three high burden countries for this form of TB were India (27%), China (14%), and the Russian Federation (9%). Around 123 countries of the world have reported the presence of XDR-TB (extensive drug-resistant TB) in their population. The proportion of XDR-TB among MDR-TB patients is 6.2% worldwide.³ About 214,000 deaths occurred from MDR/RR-TB in the word in 2018. INH mono-resistance was reported in 7.2% of cases of new TB and 11.6% in previously treated cases of TB globally in 2018. India in collaboration with WHO carried out the first National Anti-TB Drug Resistance Survey (NDRS) between 2014–1916. The survey carried out drug susceptibility testing (DST) for 13 anti-TB drugs using the automated liquid culture system, (the mycobacteria growth indicator tube, MGIT 960). The main findings were: MDR-TB in 6.19% of cases (2.84% among new and 11.60% among previously treated TB patients). Additional resistance to any fluoroquinolones was observed in 21.82%, and 3.58% of cases to any second-line injectable drugs amongst all MDR-TB cases. XDR TB was present in 1.3% of cases.⁴ During 2007–2018, India tested 2,798,599 patients using CB-NAAT and line-probe assays (LPAs). These tests detected 236,725 drug-resistant TB patients. In 2019, the program notified a total of 66,359 Multi Drug Resistant/Rifampicin Resistant (MDR/RR) TB cases and 56,500 (85%) of them put on treatment, which is an improvement of 7.6% over last year as reported by the India TB Report, 2020.

**Approach to Treatment of DR-TB**

Drug resistance emerges when anti-TB drugs are used inappropriately, poor TB control program, delayed diagnosis, inappropriate drug regimen, inadequate initial therapy, incomplete duration of therapy, inappropriate treatment modifications, addition of a single drug to an already failing regimen, improper use of chemoprophylaxis, poor adherence and incomplete follow up, failure to isolate MDR TB, failure to employ DOTS, availability of over the counter anti-TB drug, and faked drugs. Use of second-line drugs can cure MDR TB cases. However, second-line treatment options are limited and require long durations (up to 2 years of treatment). Besides the longer duration of therapy, other problems associated with these drugs are that they are expensive and toxic. More severe drug resistance can develop in some cases.

An independent expert panel of the WHO reviewed the latest evidence for treatment of drug-resistant TB in July 2018. The committee recommended certain key changes and issued a rapid communication.⁵

The programmatic management of drug-resistant TB (PMDT) was initiated in India in 2007 and the National Guideline scaled up the same which was achieved...
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Flowchart 1: Diagnostic algorithm for drug-resistant TB

TABLE 1
Conventional drug regimen (previously used) for MDR/RR; and XDR-TB

<table>
<thead>
<tr>
<th>Category of TB case</th>
<th>Drug regimen (intensive phase)</th>
<th>Treatment regimen (continuation phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR TB/RR-TB</td>
<td>(6–9 m) Kanamycin, Levofloxacin, Ethionamide, Cycloserine, Pyrazinamide, Ethambutol (duration 6–9 months)</td>
<td>(18 m) Levofloxacin, Ethionamide, Cycloserine, Ethambutol (duration 18 months)</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>(6–12 m) Capreomycin; PAS-para Aminosalicylic Acid; Mfx-Moxifloxacin; High dose INH; Czf-Clofazimine; Lzd-Linezolid; Amx/Clv-Amoxicillin-Clavulanic acid</td>
<td>(18 m) PAS-para aminosalicylic Acid; Mfx-Moxifloxacin; High dose INH; Czf-Clofazimine; Lzd-Linezolid; Amx/Clv-Amoxicillin-Clavulanic acid</td>
</tr>
</tbody>
</table>

by March 2013. However, the success rate of MDR TB treatment has been around 46% consistently with a death rate of approximately 20% while the same figures at the global level has been 52% and 17%, respectively. Fluoroquinolone resistance in Indian patients was responsible for such high rates of treatment failure and death rates.6

The diagnostic algorithm for DR-TB is shown in Flowchart 1.

The conventional DR-TB regimens consisted of the following drugs, which many countries including India continued to use till recently. These are shown in Table 1. However, this regimen is no more used by the National program.

All MDR-TB isolates are subjected to liquid culture DST for kanamycin and levofloxacin at baseline to rule out pre-XDR and XDR-TB. Appropriate modifications have to be made if there is additional drug resistance. Pretreatment investigations are carried out and drugs are dispensed in patient-wise boxes on monthly basis. Follow-up is done with culture every month in intensive phase and every quarter in the continuation phase. However, the major issues with these regimens are the longer duration of therapy (24–27 months) resulting in poor compliance, side effects, and the overall success rate was below 50% with approximately 20% death rates. These regimens were continued till 2016 starting from 2007 when PMDT (Programmatic Management of Drug-resistant TB) was initiated in the country. With discovery and availability of BDQ (2012) and delamanid (2014) the situation changed. Bedaquiline (BDQ) is a newly developed drug and is a diarylquinoline derivative. It targets the mycobacterial
ATP synthase. It has strong bactericidal activity and tissue distribution is quite extensive and the distribution in the tissue can be there for up to 5.5 months after BDQ is stopped. The most significant benefit with the drug is that it shortens the time for culture conversion quite significantly. However, there was concern about cardiac toxicity with QTc prolongation, but subsequently it was found to be tolerated in most patients. The drug is given in the following doses:

- Week 0–2: BDQ in a dose of 400 mg (4 tablets of 100 mg) per day (all 7 days of the week) along with an optimized background regimen (OBR)
- Week 3–24: BDQ 200 mg (2 tablets of 100 mg) 3 times per week + optimized background regimen (OBR)
- After 24th week, and from Week 25 (start of month 7): Other drugs in OBR is to be continued

*Delamanid* (DLM) is a nitro-dihydro-imidazooxazole compound and acts by inhibiting the key mycolic acid synthesis of the *Mycobacterium tuberculosis*. The drug is administered orally as 100 mg twice daily (BID) for 2 months followed by 200 mg once daily (QD) for 4 months and is administered along with an optimized background regimen (OBR).

A number of societies, the WHO and the NTEP of India have recommended regimens for treating different forms of DR tuberculosis. These recommendations are for the treatment of MDR-TB, XDR-TB, INH-resistant tuberculosis, or a mixed form of drug-resistant TB cases.

The WHO published the consolidated guidelines for DR TB in 2019 that include a set of comprehensive recommendations for the DR TB care and treatment. It includes eight guideline documents developed by WHO over a period extending from 2011 till 2018. The document includes a consolidated policy recommendations for treatment regimens meant for INH-mono-resistant TB, (HrTB) and MDR/RR-TB. The treatment for the latter category includes both the longer and shorter regimens, monitoring guidelines using culture and the timing of starting antiretroviral therapy when this is associated. It also includes the recommendations for surgery for MDR-TB cases and an optimal model of care and treatment of such patients.

The recommended treatments of drug-resistant TB are in four groups:

- Treatment of INH-resistant cases
- Long duration (standardized) of therapy
- Shorter duration of therapy
- Treatment of mixed drug-resistant cases

The regimen may or may not include bedaquiline/delamanid and can be classified as treatment of:

- MDR/RR-TB
  - Shorter MDR-TB regimen
  - Conventional regimens for MDR-TB
  - MDR or RR TB and additional resistance to any or all fluoroquinolones or second line injectable drugs
  - XDR-TB
- DR-TB (Mixed pattern)
  - with H mono + FQ/SLI/Lzd resistance
  - with MDR/RR-TB + FQ/SLI + Lzd resistance
- H-Mono/Poly Drug-Resistant TB

### Treatment Regimens for INH-resistant Tuberculosis (HrTB)

The INH and other drug resistance produce significant problem in the success of TB treatment. Table 2 shows the importance with various patterns of resistance that can ultimately lead to MDR/RR TB.

The World Health Organization (WHO) after reviewing many observational studies (~33 database, n=5418 INH mono-resistant cases) and individual patient data (IPD) came up with these specific guidelines for resistance to isoniazid in the absence of R-resistance. Rifampicin, levofloxacin, pyrazinamide, and ethambutol combination therapy is recommended for confirmed R-susceptible and H-resistant TB patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis. The treatment is for a period of 6 months. Streptomycin injection or other injectable drug is no more needed in this regimen. The duration can be extended up to 9 months. This will be true for extrapulmonary TB cases and TB with HIV also.

### Conventional MDR-TB Regimen of MDR/RR-TB—Longer Duration Therapy

The regimen shown in Table 1 is recommended for R-resistant (RR) + H sensitive/unknown Or MDR-TB which was used till 2016. With the availability of new drugs, WHO has now grouped the anti-TB drugs used for DR-TB for longer MDR-TB regimens into three groups and has recommended how to include these drugs in...
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When a longer regimen is used for MDR/RR TB, all the three drugs in Group A and at least one agent from Group B must be included so that the treatment is ensured and is commenced with at least four anti-TB drugs which are likely to be effective, and at least three drugs should be included for the rest of the duration after BDQ is stopped after 6 months. If the regimen includes only one or two drugs belonging to Group A, then both the drugs listed in Group B are to be used. If it is not feasible and the regimen cannot include drugs from Group A or B, then Group C drugs are to be added so that the regimen is complete. Injectable agents like kanamycin and capreomycin are no more recommended in the longer regimen since BDQ is a part of the drug therapy. Levofloxacin or moxifloxacin are now a part of the longer treatment regimen for MDR/RR TB. BDQ can be and should be a part of the regimen for MDR/RR TB in patients above the age of 6 years. If susceptibility is demonstrated, amikacin can be used in adults above the age of 18 years with adequate measures for safety monitoring. Streptomycin may be considered if amikacin is not available.

The conventional regimen as indicated above (with BDQ for 6 months) is indicated in MDR/RR-TB with treatment duration of 24–27 months. If fluoroquinolone is used for more than 1 month or a second-line injectable drug like amikacin, kanamycin, or capreomycin, which is not a part of the shorter MDR-TB treatment regimen as described below, but that may cause cross resistance, then it should be excluded. However, if a reliable DST has excluded drug resistance to these two classes of drugs, the shorter regimen is a choice. BDQ is contraindicated (not administered) in pregnancy and extrapulmonary case. Drug susceptibility tests for pyrazinamide, isoniazid, ethambutol, ethionamide, and fluoroquinolones are not recommended to decide therapy because of unreliability of these tests.

Longer regimen for MDR/RR-TB is usually 18–20 months duration and can be used as a standardized one or in an individualized form. These regimens usually consist of at least five medicines that are considered to be effective. The following factors are taken into consideration to determine the choice of drugs:

### TABLE 2
Issues associated with H-mono- and polydrug-resistant TB (RNTCP data)

<table>
<thead>
<tr>
<th>DST pattern</th>
<th>Total No. with DST available = 2,422 (%age out of 2,422)</th>
<th>Success (%)</th>
<th>Failure (%)</th>
<th>Progressed to Rif resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-Mono (LJ/MGIT) n=819 (34%)</td>
<td>31</td>
<td>49</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>SH n=611 (25%)</td>
<td>25</td>
<td>54</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>SHE n=323 (13%)</td>
<td>16</td>
<td>67</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>S Mono n=442 (18%)</td>
<td>26</td>
<td>49</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>HE n=100 (4%)</td>
<td>31</td>
<td>54</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>SE n=68 (3%)</td>
<td>24</td>
<td>49</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>E Mono n=59 (2%)</td>
<td>29</td>
<td>56</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>H Mono (LPA) n=6426</td>
<td>53</td>
<td>24</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 3
Grouping of drugs recommended for use in MDR-TB (longer regimens)

<table>
<thead>
<tr>
<th>Group and steps</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>All the three drugs to be included</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin, Moxifloxacin</td>
</tr>
<tr>
<td></td>
<td>Bedaquiline</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
</tr>
<tr>
<td>Group B</td>
<td>Add one or both drugs</td>
</tr>
<tr>
<td></td>
<td>Clofazimine</td>
</tr>
<tr>
<td></td>
<td>Cycloserine, Terizidone</td>
</tr>
<tr>
<td>Group C</td>
<td>Add to complete the regimen and when drugs from Group A and B cannot be used</td>
</tr>
<tr>
<td></td>
<td>Delamanid</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td></td>
<td>Imipenem-cilastatin OR Meropenem</td>
</tr>
<tr>
<td></td>
<td>Amikacin (OR Streptomycin)</td>
</tr>
<tr>
<td></td>
<td>Ethionamide or Prothionamide</td>
</tr>
<tr>
<td></td>
<td>p-aminosalicylic acid</td>
</tr>
</tbody>
</table>
Oral drugs are preferred over injectable drugs;
drug-susceptibility test (DST results);
reliability of the methods used for DST;
drug resistance levels in the population;
previous history of medicine used by the patient;
tolerability of the drugs used; and
issues pertaining to drug-drug interactions.

NTEP Recommendations for Longer All Oral Regimen

This longer all oral regimen (there is no injectable now) is now recommended for patients who are not suitable for receiving shorter MDR-TB regimen (see later) due to:

- Exclusion criteria for the shorter regimen
- Adverse drugs reactions to any component of the shorter regimen
- If there is resistance to any of the drugs in the regimen (for inh A mutation ethionamide cannot be given, or pyrazinamide resistance obtained from a certified lab).

The all oral longer regimen consist of the following:
6–8 months of Bedaquiline (Bdq), Levofloxacain (Lfx), Linezolid (Lzd), Clofazimine (Cfz) Cycloserine (Cs)/12 Levofloxacain (Lfx), Linezolid (Lzd), Clofazimine (Cfz), Cycloserine (Cs).

All regimens under RNTCP (NTEP) of longer duration (conventional MDR/MDRFQ/SLI/XDR-TB) are to be replaced with this longer oral regimen in adults. The regimen can be used in children more than 6 years. If resistant to FQ class on SL-LPA, levofloxacain is to be replaced with high dose moxifloxacain.

This is the standard drug regimen now for all MDR/RR TB and XDR TB under the program.

Delamanid (Dlm) in DR-TB

WHO has given a conditional recommendation for the use of delamanid after reviewing all data and pending further review later. The recommendation states that delamanid should only be added to the longer regimen for MDR TB only when the said treatment regimen cannot be constituted according to the recommendations by the WHO. It further emphasizes that delamanid should not be added to an otherwise well tolerated and effective longer MDR regimen. WHO does not recommend delamanid to be a part of the shorter regimen for MDR TB as sufficient data for the same is not there.

The drug is indicated in patients who are 18 years of age or above and can be a part of the combination therapy for MDR TB. Of course, now it is also recommended for children of 6 years age more.

The drug is recommended under RNTCP under the following conditions:

- Patients who are aged 6 years or above; and can also be used in patients with HIV, and who are not eligible for short course MDR TB treatment regimen due to resistance, other contraindications or inability to tolerate.
- Patients with MDR/RR TB and additional resistance to any or all fluoroquinolones and all second line injectable anti-TB drugs
- Extensively Drug Resistance TB (XDR TB)
- Patients with mixed pattern of Drug-Resistant TB and who are failing to any regimen for a drug-resistant TB regimen or who are not tolerating the drugs or there are other reasons of contraindication or those patients who come back after disruption or any new criteria of exclusion for shorter regimen or if the disease is extensive or advanced and when there is a possibility of poor outcome at the baseline risk (Table 4).

Shorter MDR-TB Regimen

To reduce the duration of therapy, a shorter duration of therapy, and known as The Bangladesh regimen was first tried in Bangladesh. The duration of therapy was for a minimum period of 9 months of treatment. The regimen consisted of gatifloxacin, clofazimine, ethambutol, and pyrazinamide all throughout the treatment period of 9 months and was supplemented by prothionamide, kanamycin injection, and high-dose isoniazid for a minimum of 4 months (intensive phase). The relapse-free cure was 87.9% (95% confidence interval, 82.7–91.6) observed among 206 patients. The regimen was well tolerated and infrequent major adverse drug reactions were observed and they could be manageable. The only issue with this regimen was that it was not a case control study, but an observational study. To establish the effectiveness further, a case control study was carried out subsequently. This short regimen consisted of high dose moxifloxacain, clofazimine, ethambutol, and pyrazinamide administered over a 40-week period, with additional kanamycin, isoniazid, and prothionamide in the first 16 weeks. There was provision of extension of the intensive
phase to 20 or 24 weeks for those who did not have sputum conversion by 16 or 20 weeks, respectively. The regimen was similar to that of the Bangladesh Regimen except that moxifloxacin was substituted for gatifloxacin because quality-assured gatifloxacin was not available. A similar prospective observational study was carried out in nine African countries in 1,006 MDR-TB patients. The regimen similarly comprised of a standardized 9-month regimen (moxifloxacin, clofazimine, ethambutol) (EMB) and pyrazinamide (PZA) throughout and additional kanamycin, prothionamide, and high-dose isoniazid during the intensive phase of 4–6 months. The cohort included 200 (19.9%) patients who were infected with the human immunodeficiency virus (HIV). Of these 1,006 patients, 728 (72.4%) were cured and 93 (9.2%) completed therapy; thus causing a success rate of 81.6%. Failure rate was 5.9%, 78 (7.8%) died, and 48 patients (4.8%) were lost to follow-up. Death among HIV positive cases was more (19.0% vs. 5.0%). The treatment success rate was not affected by HIV status. The main factor of failure was fluoroquinolone resistance. The bacteriological outcome was not affected by resistance to other drugs like pyrazinamide, ethambutol, or ethionamide. Hearing impairment of 11.4% was the most important adverse drug reaction with severe deterioration after 4 months. The observations of the trial supported the efficacy, and hence the use of shorter regimens.

The WHO recommends the use of short regimens of 9–12 months in place of long regimens in MDR/RR TB patients provided that the patient has not received second-line drugs for more than 1 month and there is no resistance to fluoroquinolones and second-line injectable anti-TB drugs.4

The National Technical Expert Group (NTEG) of the NTEP, India, has now recommended the use of shorter regimens in all cases of MDR TB except under the situations discussed in Table 5.

**BPAl Regimen**

Pretomanid, a new anti-TB drug was approved by the US FDA in August 2019 for use along with BDQ and linezolid (high dose); this regimen, referred to as the *BPAl regimen*, is administered for 6 months (extendable to 9 months) to treat adults with pulmonary form of the extremely drug-resistant TB (XDR-TB), or treatment-intolerant or non-responsive multidrug resistant TB (MDR-TB). It inhibits the biosynthesis of mycolic acid, thus blocking the production of cell wall by the**

<table>
<thead>
<tr>
<th>Resistance pattern</th>
<th>DST-guided regimen class</th>
<th>Intensive phase</th>
<th>Continuation phase</th>
<th>Principle of regimen design</th>
</tr>
</thead>
</table>
| **Regimen with new drugs for MDR-TB + FQ/SLI resistance:**
| MDR/RR + resistance to FQ class OR SLI class | MDR/RR + res to FQ class | (6–9) Km Eto Cs Z Lzd Cfz + (6) Dlm | (18) Eto Cs Lzd Cfz | 0 GpA + 1 GpB + 2 GpC + Z + add on 2 GpD |
| MDR/RR + res to SLI class | (6–9) Lfx Cm Eto Cs Z Lzd D Cfz + (6) Dlm | (18) Lfx Eto Cs Lzd | 1 GpA + 1 GpB + 2 GpC + Z + add on 2 GpC + 1 GpD2 |

| **Regimen with new drugs for XDR-TB:**
| XDR-TB (res to both FQ and SLI) | XDR-TB | (6–12) Cm Eto Cs Z Lzd D Cfz + (6) Dlm | (18) Eto Cs Lzd Cfz E | 0 GPA + 1 GPB + 2 GpC + Z + add on 2 GpC + 1 GpD1 + 1 GpD2 |

| **Regimen with new drugs for mixed pattern DR-TB:**
| Mixed pattern DR-TB | MDR/RR-TB + res to FQ/SLI + Lzd or more | Modify the regimen with new drugs for XDR-TB |

**TABLE 4** Use of delamanid according to drug resistance
mycobacteria. It acts in non-replicating mycobacteria as a respiratory poison releasing nitric oxide under anaerobic situation. The regimen of the three drugs was investigated in three sites in South Africa. The drug regimen was as follows:

- **BDQ** in a dose of 400 mg once daily for 2 weeks that was to be reduced to 200 mg thrice weekly for a period of 24 weeks;
- **Pretomanid**—200 mg daily for a period of 26 weeks; and
- **Linezolid** of 1,200 mg daily for up to 26 weeks.

The dose was adjusted according to toxicity. The study enrolled 109 patients (XDR TB and unresponsive MDR TB patients). After 6 months of the trial, an intention to treat analysis was done. Around 98 patients (90%; with CI of 83–95) showed favorable and 11 patients (10%) had unfavorable outcomes. There were 7 deaths. One patient withdrew consent during treatment, relapse occurred in two cases, and one patient was lost to follow-up. The linezolid toxicity included peripheral neuropathy (81%) and myelosuppression (48%). Although these were common toxicities, they were manageable. Very often reduction of dosages or in some cases interruption of linezolid resolved the toxicities. The trial is named as the *Nix-TB Trial*. This BPaL regimen consisting of BDQ, pretomanid and linezolid continued to show favorable outcome till 6 months after treatment completion in most cases even with high degrees of DR TB although some toxic effects were observed.

### Table 5

**Contraindications for shorter duration therapy**

<table>
<thead>
<tr>
<th>DST-based criteria</th>
<th>Non-DST-based criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>If DST/DRT result for FQ or SLI is resistant or presence of INH A mutation (for Eto) or resistance to Z (whenever available)</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>If result for DST (FQ, SLI, INH A mutation, Cfz &amp; Z) is not available, history of use of high dose moxifloxacin (Mfx(h)), Kanamycin (Km), Ethionamide (Eto) or Clofazimine (Cfz) for &gt;1 month</td>
<td>Any extrapulmonary disease in HIV positive cases</td>
</tr>
<tr>
<td></td>
<td>If the tuberculosis is disseminated, or TB meningitis, or tuberculosis of the central nervous system</td>
</tr>
<tr>
<td></td>
<td>If the patient does not tolerate any drug in the shorter MDR TB regimen or if there is a risk of toxicity to a drug in the regimen like drug-drug interactions</td>
</tr>
</tbody>
</table>

### Salvage Regimen

In spite all the above approaches, some patients continue to have sputum-culture-positive despite therapy with second-line TB drugs. For them treatment options are limited, especially if there is no scope of resectional surgery because of advanced and bilateral disease. Salvage therapy may be an option. Salvage therapy refers to the design of a regimen that combines both new and previously used drugs in a final effort to attain sputum conversion before declaring treatment to have failed. A combination of BDQ and delamanid along with other drugs may sometimes help with good results.

### General

Surgery in very few cases will be required and whenever possible, should be offered. It is imperative that pretreatment evaluation including detailed drug history, confirmation of DR TB using molecular methods, or liquid culture is a must to ascertain the type of drug-resistant TB. Pretreatment evaluation will need complete blood count, liver, and kidney function tests including thyroid function test, audiometry, cardiac assessment (for BDQ and DLM) and psychosocial evaluation. Nutrition is also important. The Government of India is providing Rs. 500 every month to these patients through direct transfer (DBT). Provision of ancillary drugs, initial admission (not mandatory now), and prescribing appropriate drugs is very essential. Besides, adverse drug reactions monitoring is equally important. Whenever there are associated conditions like HIV, diabetes, COPD, or other ailments they need to be looked after with equal emphasis. Treatments of these cases are usually carried out at the DR-TB center or DR-TB nodal center.

**Major Recommendations of NTEG (National Technical Expert Group) for the treatment of MDR/XDR TB are as follows:** (held from 9-11 September 2020)

**There will be only two types of regimens for treating MDR/XDR-TB** —

- All oral Longer MDR-TB regimens (12-18 months); and
- Shorter all oral bedaquiline (BDQ) containing regimen.
Shorter all oral bedaquiline (BDQ) containing regimen, (4-6) Bdq (6 m) Lfx Czf Z E Hh Eto/ (5) Lfx Czf Z E ( (recommended by WHO) in adults (>18 yrs) in individuals confirmed with pulmonary MDR/RR-TB, uncomplicated extra-pulmonary TB disease and in PLHIV to be introduced in a phased manner starting with an implementation pilot in selected states to gain programmatic experience to guide future expansion. This recommendation may be considered for children (6-17 years) given their special needs pan-India in consultation with NTEG for paediatric TB.

Only those patients with mutations in both inhA and katG will not be eligible for shorter regimen. However, patients with only inhA or only katG mutations will be eligible for the shorter regimen provided other conditions are met.

Preventive treatment among close contacts of MDR-TB index patients (in whom FQ resistance has been ruled out) using 6Lfx for all age groups to be introduced in a phased manner starting with an implementation pilot in selected states to gain programmatic experience to guide future expansion. This recommendation may be considered for children given their special needs pan-India in consultation with NTEG for paediatric TB.

For all oral longer MDR-TB regimen, the revised replacement drugs sequence recommended would be Delamanid, Amikacin, Pyrazinamide, Ethionamide, PAS, Ethambutol, Carbapenems.

Extension of BDQ beyond 6 months to be considered in patients in whom an effective regimen cannot be otherwise designed if only 2 of 5 drugs are available from Groups A & B and adequate number of Group C drugs are not available due to high background resistance, non-availability or unreliability of DST.

Use of BDQ in pregnancy needs further discussion with the concerned experts before taking a policy decision for its use under the program setting.

Combined use of BDQ and DLM in the regimen is recommended for those M/XDR-TB patients in whom an appropriate regimen cannot be designed using all 5 drugs from Group A and B.

BPaL research proposal may be considered with flexibility to adapt with anticipated results of ZeNix trial and submitted to the National Operational Research Committee for approval and implementation. BPaL can be considered as a last resort by NTEP under prevailing ethical standards in individual patients for whom the design of an effective regimen not possible as per recommendations.

Post-treatment completion follow-up of all successfully treated TB patients at 6th, 12th, 18th and 24th months to be initiated under NTEP. Plan and expedite introduction of Xpert-XDR test and drug susceptibility testing for the drugs Lzd, Z, Czf, Bdq, Dlm

Consider second line drugs procurement adjustments and forecasting (including child friendly formulations) and capacity building planning.

Strengthen mechanisms for improved patient follow-up and implementation of aDSM (Active TB drug-safety monitoring and management) as per the PMDT guidelines.

 Expedite up-gradation of Nikshay for diagnostic module, DR-TB case finding report and aDSM module for improving monitoring of DR-TB patients.

Build capacity of all providers (labs, DR-TBC, field staff) in optimally utilizing Nikshay (electronic data monitoring system) for real-time data entry as well as monitoring at state and district level in order to improve the quality of care and timely regimen change in DR TB patients.

Programme to issue DO to all DRTB Centres to consider admitting children requiring in-patient care for management of DRTB as per PMDT guidelines and proactively engage the available paediatricians (in-house/honorary) for the management of paediatric DR-TB patients.

Programme to issues Demi-Official letter for use of BDQ in children in the age-group 12-17 years for management of DR-TB

National Task Force (NTF) mechanism to support the establishment and functioning of DR-TB centres in remaining Medical Colleges across India (also engaging Paediatric Dept. for management of paediatric DR-TB patients).

Programme to establish the mechanism to ensure dissemination of any policy change to all stakeholders especially Nodal/District DR-TB sites including medical colleges. NTEP website to have all important communications sent to states periodically uploaded so that it can be easily accessed by all concerned.
Conclusion

The previously used longer but less effective drug regimen that contained an injectable drug has now been replaced with all oral, injection free short-course and longer duration (~18 months) therapy and is more effective. The National TB Elimination Program has quickly adopted these changes and has introduced these forms of therapy throughout the country so that DR-TB cases are treated more successfully. These are important developments that have been adopted by the program so that marching toward End TB will be a reality. However, prevention, early diagnosis, and completion of therapy are important keys to success.

References

Abstract

Drug resistant-tuberculosis (DR-TB) is relatively difficult to treat than drug-sensitive-TB. Nearly 27% of global multi-drug resistant/rifampicin resistant-TB (MDR/RR-TB) patients are in India. National guidelines for the treatment of DR-TB in India [programmatic management of drug resistant-TB (PMDT)] have been essentially adapted from ‘WHO consolidated guidelines for DR-TB treatment (2020)’. These national guidelines emphasize access of universal DST to all TB patients and categorize DR-TB into rifampicin susceptible but isoniazid monoresistant-TB (Hr-TB), MDR/RR-TB, and extensively drug resistant-TB (XDR-TB). As per PMDT guidelines, patients should be examined for Hr-TB and should be treated with uniphasic rifampicin, ethambutol, pyrazinamide, and levofloxacin regimen for 6 months. Preferably, 7-drug injection-free, pan-oral shorter (9–11 months) or 5-drug pan-oral longer (18–20 months) DST-guided, bedaquiline-containing individualized MDR-TB treatment regimen should be constituted for intensive phases and 4-drug regimen for continuation phases, respectively. Monthly smear and culture should be done during follow-up. Active TB drug-safety monitoring and management (aDSM) is strongly recommended. Post-treatment, follow-up at 6th, 12th, 18th, and 24th months of all successfully treated DR-TB cases under national-TB elimination programme (NTEP) is recommended.

Introduction

National Guidelines on drug resistant-tuberculosis (DR-TB) in India [programmatic management of drug resistant-TB (PMDT)] have been adapted from WHO Consolidated Guidelines on DR-TB treatment (2020). Recently, American Thoracic Society/Centers for Diseases Control and Prevention/European Respiratory Society/Infectious Diseases Society of America (ATS/CDC/ERS/IDSA) have jointly published comprehensive guidelines on treatment of DR-TB. Table 1 compares various differences between these three guidelines.

DR-TB Definitions

The term DR-TB is a broader one encompassing several subentities, and is primarily a laboratory diagnosis confirming the presence of Mycobacterium tuberculosis (Mtb) and subsequently demonstrating its resistance to first-line and second-line anti-tuberculosis drugs on drug-susceptibility testing (DST). Various sub-entities of DR-TB are defined in Box 1.

Epidemiology

DR-TB is highly prevalent and continues to be a serious public health threat. According to the WHO Global TB report 2020, worldwide there were 465,000 people (range 400,000–535,000) with new rifampicin resistant-TB (RR-TB) diagnosis and 78% of these had multdrug resistant-TB (MDR-TB). India (27%), China (14%), and Russian Federation (8%) contributed to almost half of these cases in 2019. Globally, 3.3% of new and 17.7% of previously treated patients had MDR/RR-TB.
### TABLE 1: Comparison of WHO, ATS/CDC/ERS/IDSA and PMDT, India guidelines for the treatment of drug-resistant TB (DR-TB)

<table>
<thead>
<tr>
<th>Types of DR-TB</th>
<th>WHO consolidated guidelines, 2020</th>
<th>ATS/CDC/ERS/IDSA guidelines, 2019</th>
<th>PMDT, India, 2019-20</th>
</tr>
</thead>
<tbody>
<tr>
<td>DST if Mtb isolated</td>
<td>Comprehensive DST if Mtb isolated</td>
<td>Microbiological data are required to constitute an individualized treatment regimen based on DST of the Mtb strain isolated</td>
<td>Universal DST is strongly recommended to constitute treatment regimen for DR-TB</td>
</tr>
<tr>
<td>Hr-TB</td>
<td>Information on katG and inhA mutations on genotypic (molecular) DST is essential.</td>
<td>No specific recommendation for genotypic DST</td>
<td>Recommendation for genotypic DST is similar to WHO 2020 guidelines</td>
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<td></td>
<td>For HR-TB patients should be treated with rifampicin, ethambutol, isoniazid and pyrazinamide for 6 months. Duration of pyrazinamide can be shortened to 2 months in selected situations such as non-cavitary disease, low-burden disease, or intolerance to pyrazinamide</td>
<td></td>
<td>About 10% of the Indian patients have inhA mutations where H can be administered and Ethambutol can’t be used because of cross-resistance</td>
</tr>
<tr>
<td></td>
<td>About 90% have katG mutations and ethambutol can be used. Addition of levofloxacin (Lfx) is done without a split for 6 months.</td>
<td>Recommendations: STRONG FOR: Bdq, later generation fluoroquinolones (Lfx and Mfx) CONDITIONAL FOR: Lzd, Cff Cs/Trd, E, Z (provided susceptibility to Z). CONDITIONAL AGAINST: Ethambutol, Km and Cm, PAS. STRONG AGAINST: macrolides (azithromycin and clarithromycin), Amx-Clv</td>
<td>About 90% have katG mutations and ethambutol can be used. Addition of levofloxacin (Lfx) is done without a split for 6 months.</td>
</tr>
<tr>
<td>Classification of Drugs</td>
<td>Drugs are classified into ABC groups depending on safety and efficacy profiles. Treatment regimen is preferably constituted from Groups A and B and if it is not possible then from drugs can be added from Group C</td>
<td>Recommendations: STRONG FOR: Bdq, later generation fluoroquinolones (Lfx and Mfx) CONDITIONAL FOR: Lzd, Cff Cs/Trd, E, Z (provided susceptibility to Z). CONDITIONAL AGAINST: Ethambutol, Km and Cm, PAS. STRONG AGAINST: macrolides (azithromycin and clarithromycin), Amx-Clv</td>
<td>*Grouping of drugs has been adapted from WHO guidelines 2020</td>
</tr>
<tr>
<td>Pan-oral Bdq-containing longer regimen (based on DST)</td>
<td>Intensive phase = at least 4 drugs Continuation phase = 3 drugs Pan-oral 5-drug longer regimen is constituted from Group A and B drugs and if it is not possible then Group C drugs are included from the replacement sequence depending upon drug susceptibility profile and tolerance</td>
<td>Intensive phase = 5 drugs Continuation phase = 4 drugs</td>
<td>Intensive phase = 5 drugs Continuation phase = 4 drugs</td>
</tr>
<tr>
<td></td>
<td>Regimen: (6-8) Bdq (6) Lzd Lfx Cff Cs/12 Lfx Lzd Cff Cs</td>
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### PAN-ORAL Bdq-CONTAINING SHORTER REGIMEN

A shorter all-oral Bdq-containing 7-drug regimen of 9-12 months duration is recommended in eligible patients with confirmed MDR/RR-TB who have not been exposed to treatment with second-line TB medicines used in this regimen for > 1 month, and in whom resistance to FQs has been excluded.

- **WHO consolidated guidelines, 2020**
  - Standardized 9- to 11-month shorter MDR-TB regimen is not preferred as it has injectables. A research recommendation has been given for the conduct of RCTs to evaluate the efficacy, safety and tolerability of newer oral drugs.

- **ATS/CDC/ERS/IDSA guidelines, 2019**
  - 9- to 11-month shorter pan-oral Bdq-containing 7-drug regimen comprising of (4-6) Bdq (6) Lfx Lfz Cff Z E H Eto/ (5) Lfx, Cff Z E to be administered if there are no contraindications.

- **PMDT, India, 2019-20**
  - Combined use of Bdq and Dlm is recommended for M/XDR-TB patients in whom an appropriate regimen can’t be made using all 5 drugs of groups A and B.

- **BPaL regimen**
  - Bdq, Pa and Lzd (BPaL) for pre-XDR-TB (MDR-TB plus FQs) under operational research (OR) conditions who have no previous exposure or <2 weeks exposure to Bdq and Lzd.

- **Use of injectable**
  - Amikacin may be included in patients aged ≥ 18 years on longer regimens to constitute a regimen. Use of injectables (especially Kanamycin and Capreomycin) is avoided as far as possible. Although, if all other options are exhausted, for the use of streptomycin in vitro drug sensitivity must be demonstrated.

- **Duration of treatment for longer MDR-TB**
  - Intensive phase= 6-7 months
  - Total duration= 18-20 months
  - After culture conversion= 15-17 months
  - In MDR/RR-TB patients, on longer regimens containing amikacin or streptomycin an intensive phase of 6-7 months is suggested for most patients. However, the duration may be modified according to response to treatment.

- **Use of injectables**
  - Use of injectables is not recommended. However, Am/S may be included if one is unable to constitute a 5-drug regimen and Mtb is drug-sensitive.

- **Amikacin or streptomycin can be used to constitute a 5-drug regimen in patients with aged >18 years, if it is essential and Mtb is susceptible to the drug depending upon tolerance of drugs and in vitro drug resistance.**
### Contd...

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<thead>
<tr>
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<tbody>
<tr>
<td>In patients with RR-TB or MDR-TB, elective partial lung resection (lobectomy or wedge resection) may be done along a constituted drug regimen in a centre with a skilled and experienced thoracic surgeon and with careful selection of candidates</td>
<td>According to guidelines, an elective partial lung resection (e.g., lobectomy or wedge resection) with a DST-guided MDR-TB treatment regimen is more beneficial compared with medical therapy alone when clinical judgment, supported by bacteriological and radiographic data, suggests a strong risk of relapse or treatment failure. Pneumonectomy is not recommended</td>
<td>Lung resection surgery is not done usually due to lack of infrastructure and well-trained and skilled thoracic surgeons</td>
<td></td>
</tr>
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</table>

### Preventive therapy

<table>
<thead>
<tr>
<th>WHO consolidated guidelines, 2020</th>
<th>ATS/CDC/ERS/IDSA guidelines, 2019</th>
<th>PMDT, India, 2019-20</th>
</tr>
</thead>
<tbody>
<tr>
<td>No specific recommendation for LTBI</td>
<td>For LTBI for MDR-TB patients’ contacts, 6 to 12 months of treatment with a later-generation fluoroquinolone alone or with a second drug, on the basis of DST of the <em>Mtb</em> isolate of the source-case</td>
<td>No specific recommendation for LTBI</td>
</tr>
</tbody>
</table>

*Replacement drugs sequence consists of the following order: delamanid (Dlm), amikacin (Am), pyrazinamide (Z), ethionamide (Eto), para-aminosalicylic acid (PAS), ethambutol (E), penems. Use of Bdq during pregnancy is under consideration. Bdq may be used beyond 6 months if only 2 of 5 drugs from Groups A and B are available and adequate no. of Group C drugs are not available due to high background resistance non-availability or unreliability of DST.

**Note:** ATS/CDC/ERS/IDSA guidelines (2019) and WHO Consolidated DR-TB guidelines (2020) categorise following drugs, Am, S and H differently whereas in PMDT, 2019-20 PAS has been preferred over E and carbapenems.

Am, amikacin; Amx/Cln, amoxicillin-clavulanic acid; ATS/CDC/ERS/IDSA, American Thoracic Society, U.S. Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America; Bdq, bedaquiline; Cfk, clofazimine; Cln, cilastatin; Cs, cycloserine; Dlm, delamanid; DST, drug-susceptibility testing; E, ethambutol; EPTB, extrapulmonary TB; Hh, high-dose isoniazid; Hr-TB, rifampicin sensitive but isoniazid resistant-TB; Imp, imipenem; Km, kanamycin; Lfx, levofloxacin; LTBI, latent TB infection; Lzd, linezolid; Lzdl, low dose linezolid (300mg); MDR/RR-TB, multidrug-resistant/Rifampicin resistant-tuberculosis; Mfx, moxifloxacin; P: pretomanid; PAS, para-aminosalicylic acid; PLHIV, people living with HIV; PMDT, programmatic management of drug-resistant tuberculosis; S, streptomycin; WHO, World Health Organisation; XDR-TB, extensively drug-resistant TB; Z, pyrazinamide.

In FL-LPA, mutations in test system made in India.

TrueNat is a chip based battery operated nucleic acid amplification and in SL-LPA the mutations for FQs (Mfx and Lfx) and injectables MDR/RR-TB and 30% of XDR-TB cases were initiated on treatment. In India 48% of laboratory confirmed only one in three diagnosed MDR/RR-TB accessed DR-TB previously treated patients had MDR/RR-TB.4 Globally, tuberculosis in India, 2019–2055.5% of these were tested for second-line anti-TB drugs other than both isoniazid and rifampicin. Extensively drug resistant TB (XDR-TB): Refers to Mtb resistant to both rifampicin and isoniazid. DST-guided treatment is strongly recommended in the revised DR-TB treatment guidelines.

Factors related to previous treatment
Incomplete and inadequate treatment
Inadequate treatment adherence
Vulnerence of Mtb strain, e.g., W-Beijing genotype is well-known for multidrug resistance
Presence of multidrug transporter proteins may lead to drug resistance in Mtb strain
Lower anti-TB drugs levels due to either malabsorption of anti-TB drugs or drug-drug interactions like rifampicin and moxifloxacin
Male gender
Older age
Low BMI
Diabetes mellitus
HIV/AIDS
Factors such as psychiatric illness, alcoholism, drug addiction, and homelessness do predict non-adherence to treatment

Risk factors for drug-resistant tuberculosis

BMI, body mass index; HIV/AIDS, human immunodeficiency virus acquired immunodeficiency virus; Mtb, Mycobacterium tuberculosis.

Source: Adapted from Sharma SK, Mohan A. Multidrug-resistant tuberculosis: a menace that threatens to destabilize tuberculosis control. Chest. 2006;130:261-72.

Integrated Diagnosis of DR-TB

According to National Guidelines,1 it is essential to rapidly characterize Mtb sensitivity or resistance to H, FQs, and second-line injectables (SLIs) with first line-line probe assay (FL-LPA) and second line-line probe assay (SL-LPAs) respectively after receiving nucleic acid amplification tests (NAAT) amplification report and treat according to DST report in order to avoid further amplification of DR-TB. Subsequently, although time-consuming, phenotypic culture with DST is required to establish the diagnosis. DST-guided treatment is strongly recommended in the

India had 66,255 laboratory-confirmed MDR/RR-TB in 2019, 55.5% of these were tested for second-line anti-TB drugs and 3.5% had extensively drug-resistant-TB (XDR-TB). MDR-TB developed among 2.8% of new and 14% of previously treated patients had MDR/RR-TB.4 Globally, only one in three diagnosed MDR/RR-TB accessed DR-TB treatment, and in India 48% of laboratory confirmed MDR/RR-TB and 30% of XDR-TB cases were initiated on
National TB Elimination Program (NTEP)\(^1\)–\(^3\) erstwhile known as Revised National TB Control Program (RNTCP) known to avoid further amplification of resistance and the integrated diagnostic algorithm (Flowchart 1) can be used for this. As mentioned previously, it is established that rapid molecular tests such as NAAT and LPAs provide early diagnosis of DR-TB and are helpful when used in tandem with phenotypic methods (solid and liquid cultures) as latter take longer for DST results.

The standard smear microscopy test has some inherent limitations as it is usually difficult to diagnose TB when the bacillary load in the sputum specimen is <10\(^3\)/mL\(^8\). The DST can be growth-based (phenotypic DST) on liquid culture (Bactec MGIT 960) or solid culture (Lowenstein-Jensen culture) or genotypic DST which employs rapid molecular tests for the diagnosis of DR-TB. Various molecular tests include NAAT (cartridge based NAAT or chip based TrueNat) and FL-LPAs (GenoType MTBDR\(^\text{plus}\) V1, GenoType MTBDR\(^\text{plus}\) V2) and Nipro (NTM \text{MDRTB} detection kit) and SL-LPAs (MTBDR\(^\text{sl}\) V1 and MTBDR\(^\text{sl}\) V2).\(^9\) The NAAT test uses real time-polymerase chain reaction (RT-PCR) principle and the result is reported as \textit{Mtb} detected/not detected with additional finding of \textit{Mtb} rifampicin sensitive or resistant. Under programmatic conditions where the laboratory capacity is limited and facilities for FL-LPAs and SL-LPAs are not available, the report of NAAT as RR-TB is considered as a surrogate marker of MDR-TB and the patient is treated as MDR-TB as phenotypic tests with DST usually take from weeks to months. While the test report from FL-
LPAs provides additional information of Mtb sensitivity or resistance to H, SL-LPAs provide additional information on resistance to fluoroquinolones and SLIs.9

LPAs are a family of deoxyribonucleic acid (DNA) strip-based tests that determine the drug-resistance profile of an MTB1 complex strain through the pattern of binding of amplicons (DNA amplification products) to probes targeting the most common resistance associated with the mutations to first- and second-line agents and to probes targeting the corresponding wild type (WT) DNA sequence.9 LPAs are WHO-approved tests for rapidly detecting drug resistance to the first- and second-line agents. They can be used for testing of culture isolates (indirect testing) and direct testing of acid-fast bacilli (AFB) smear microscopy specimens (FL-LPA), and both smear positive and smear negative sputum specimens (SL-LPA). Mutations are detected by the binding of amplicons to probes targeting the most commonly occurring mutations (MUT probes) or inferred by the lack of hybridization (lack of binding) of the amplicons to the corresponding WT probes.9 The post-hybridization reaction leads to the development of the colored bands on the test strip detecting probe binding. LPA results are reported as “Resistance not detected” instead of “Susceptible” to define the bacteria resistance profile.9

Given the limitations of LPA and in particular the fact that the resistance cannot be completely excluded even in the presence of all WT probes as not all mutations that confer resistance are covered by these tests or mutations that are covered may be below the limit of detection, it is more appropriate to report the result as “resistance detected” or “resistance not detected.”9 The term “resistance detected” is used whenever one or more MUT probes identifying specific mutations conferring resistance to the drugs are developed regardless of whether WT probes are developed or not.9 The term “resistance inferred” is used whenever one or more WT probes in regions of the gene known to confer resistance to the drug are not developed and none of the MUT probes in the corresponding region is developed. In this case the precise mutation cannot be reported, only the region where the mutation lies is identified.9

FL-LPA showed sensitivity and specificity for the detection of rifampicin resistance 96.7% and 98.8%, respectively, and for the detection of resistance sensitivity and specificity 90.2% and 99.2%, respectively.10 SL-LPA (GenoType MTBDRsl V1) showed pooled sensitivity and specificity for the detection of fluoroquinolone resistance by direct testing of 86.2% and 98.6% respectively, and a pooled sensitivity and specificity for the detection of second-line injectable drugs resistance of 87% and 99.5%, respectively.9

**Treatment of DR-TB**

**Treatment of Isoniazid-resistant Tuberculosis (Hr-TB)**

Substitution of H with levofloxacin (Lfx) is recommended for the treatment of Hr-TB. Drug regimen consisting of rifampicin, ethambutol, pyrazinamide, and levofloxacin (REZ-Lfx) is administered for 6 months without split of intensive and continuation phases.2 Although, moxifloxacin (Mfx), arguably more potent than Lfx, has several limitations due to drug-drug interactions,2 and QTc-prolonging ability when coadministered with drugs with similar properties. Further, Mfx peak plasma concentration and exposure declines when coadministered with rifampicin, however, unlike Lfx, does not require dose modifications in chronic kidney disease. Recent ATS/CDC/ERS/IDSA guidelines provide option of shortening the duration of pyrazinamide (Z) to 2 months in presence of non-cavitary and low-burden disease, intolerance, or toxicity to Z.9

Treatment can be extended to 9–12 months as per clinical, radiological, and microbiological responses, especially in extrapulmonary TB involving bone, central nervous system (CNS) and/or miliary TB. Use of injectable agents like streptomycin and others is not recommended in the guidelines.1-3 In case of additional resistance, intolerance or toxicity to a drug, its substitution can be effected by, in order of preference with linezolid (Lzd), clofazimine (Cfz), or cycloserine (Cs).

**Treatment of MDR/RR-TB**

Two evidence-based guidelines on DR-TB treatment have been published in 2019. A propensity score-matched meta-analysis of an individual patient data meta-analysis (IPDMA) from 12,030 patients in 50 studies from 25 countries was used for making recommendations in these guidelines. Major differences between WHO Consolidated Guidelines, ATS/CDC/ERS/IDSA Guidelines, and current Indian Guidelines, 2019–20, are listed in Table 1. Current
BOX 3  Principles of drug-resistant TB management

- Drug susceptibility testing (DST)-guided treatment is recommended for DR-TB and universal DST should be available to all TB patients.
- A bedaquiline-based 5-drug regimen (3 drugs from Group A, two from Group B and if not possible from Group B then one or two drugs from Group C; refer Table 2) should be constructed for MDR/RR-TB.
- A fully oral regimen is preferred and injectables like kanamycin and capreomycin are no longer recommended.
- Long-term bedaquiline-based drug regimen should have at least 5 drugs for initial 6 months and afterwards 4 drugs should be continued for rest of the treatment duration.
- The individualized, longer MDR-TB regimen is to be administered for the duration of 18–20 months, and the duration is primarily based on patient’s response to treatment or 15–17 months after culture conversion.
- In addition to smears, monthly follow-up cultures should be done from 1st month till the end of intensive phase. Decision on treatment extension should be based on culture reports at 4th, 5th and 6th month.
- If patient’s culture is positive after 8 months from the specimen submitted at the end of 6th month, treatment failure will be declared.
- If drugs need to be discontinued due to intolerance or resistance on DST, then sequence of drug replacement should be according to the guidelines.
- If fluoroquinolone (FQ) class resistance is detected on SL-LPA, replace Lfx with high dose moxifloxacin (Mfxh).
- Fluoroquinolone should not be used, if resistance to high dose moxifloxacin with LC-DST (MIC, 1.0 μg) is reported.
- In case of fluoroquinolone-resistant pre-extensively drug resistant (pre-XDR)-TB, a second line injectable drug (SLID) may be considered.
- Duration of XDR-TB treatment should be longer than MDR/RR-TB.
- Cascades of training are recommended for implementation and adoption of rapid changes in DR-TB management integrated with efficient mechanism of active drug-safety monitoring and management (aDSM).
- aDSM should focus on QTc monitoring (along with observation of serum K+, Mg2+, and Ca2+ levels), myelosuppression, optic and peripheral neuropathy and lactic acidosis.
- Ensure treatment adherence by different methods complemented with information and communication technology based adherence monitoring and reminder systems.

Note: As per WHO consolidated guidelines on drug-resistant tuberculosis treatment, duration of standardized shorter MDR-TB regimen is 9-12 months which is one month more than the original standardised shorter MDR-TB regimen used in trial, given that some patients required slightly more than 11 months to complete a shorter regimen owing to brief interruptions.

Indian guidelines for MDR/RR-TB have been primarily adapted from WHO Consolidated Guidelines, 2020 (Box 3).

A new feature of guidelines is regrouping of DR-TB drugs into A, B, and C categories and the ranking is based on the efficacy profiles of drugs (Table 2). Based on 6-month culture conversion results in the Delamanid (Dlm) Phase III trial, Dlm has been placed in group C. Dosages of drugs for MDR/RR-TB treatment as per weight categories are detailed in Table 3. Interim analysis of an Indian study on safety and efficacy of bedaquiline under conditional access program (CAP) for MDR-TB in India was recently published. This feasibility study was conducted between June 2016 and August 2017 under programmatic conditions in the field settings at six sites of India. Of 620 MDR-TB patients, 57% patients had MDR-TB with additional drug resistance to fluoroquinolones (MDR_{FLQ}) and 5% with additional second-line injectable (MDR_{SLI}) and 16% had extensively drug-resistant TB (XDR-TB). 39% had severe malnutrition [body-mass index (BMI<16)]. After 6 months of treatment, the Mtb culture conversion was achieved in 83% of patients. The median time to culture conversion was 60 days, higher BMI was associated with faster culture conversion. Mortality was 12% and a majority of deaths (56%) occurred within the first 6 months of treatment. While Bdq was permanently discontinued in about 2%, its administration was temporarily interrupted in about 3% due to QTc interval prolongation and after correction of abnormalities of Mg2+, Ca2+, and K+, it could be successfully reintroduced. Based on these results it was concluded that Bdq-based treatment for MDR/RR-TB is safe and can be scaled up with careful monitoring of QTc interval. According to WHO Guidelines, decisions to start the standardized shorter MDR-TB regimen should be made according to patient preference and clinical judgment (Box 4). Since some geographical areas in India are still implementing standardized shorter MDR/RR-TB, a pan-oral, injection-free drug regimen is strongly recommended in the current National Guidelines of India.
Current Indian guidelines recommend bedaquiline-based, preferably pan-oral 5-drug regimen as per DST in the Intensive Phase and 4-drugs in the Continuation Phase: 6–8 Bdq (6) Lfx, Lzd, Cfz, Cs/12 Lfx, Lzd, Cfz, Cs (Box 5). Similar regimens have been endorsed in the ATS/CDC/ERS/IDSA Guidelines (Table 4). Bedaquiline should be stopped after 6 months and linezolid dose should be reduced to 300 mg once daily. Monthly sputum smear and cultures should be done. In case sputum culture positivity persists after 3 months then treatment failure should be strongly suspected and the DST should be repeated.

If SL-LPA detects FQ class resistance, then addition of two drugs is preferred in the previous regimen from class C drugs. High dose Mfx (Mfx³) is effective provided susceptibility is proven in LC-DST to Mfx³ (MIC,1.0μg) in many settings SL-LPA detects specific mutations such as A90V, S91P, D94A (gyrA) which contribute to low-level Mfx resistance. In all MDR/RR-TB patients, SL-LPA is recommended which clarifies the additional FQ class resistance and second-line injectable drugs resistance. Management of extrapulmonary TB (EPTB) is similar to pulmonary MDR/RR-TB and patients are monitored for clinical, radiological, and microbiological outcomes.

### TABLE 2

<table>
<thead>
<tr>
<th>Group and steps</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Include all three drugs</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin or Moxifloxacin</td>
</tr>
<tr>
<td></td>
<td>Bdq</td>
</tr>
<tr>
<td></td>
<td>Lzd</td>
</tr>
<tr>
<td>Group B</td>
<td>Add one or both drugs</td>
</tr>
<tr>
<td></td>
<td>Clofazimine</td>
</tr>
<tr>
<td></td>
<td>Cycloserine or Terizidone</td>
</tr>
<tr>
<td>Group C</td>
<td>Add to complete the regimen and when drugs from Groups A and B can’t be used because of drug intolerance, toxicity or some other contraindication</td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
</tr>
<tr>
<td></td>
<td>Delamanid</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td></td>
<td>Imipenem-cilastatin or Meropenem</td>
</tr>
<tr>
<td></td>
<td>Amikacin (or Streptomycin)</td>
</tr>
<tr>
<td></td>
<td>Ethionamide or Prothionamide</td>
</tr>
<tr>
<td></td>
<td>3-aminosalicylic acid</td>
</tr>
</tbody>
</table>

This table is intended to guide the design of individualized, longer MDR-TB regimens. Group C drugs are ranked by decreasing order of usual preference for use subject to other considerations. The 2018 Individual Patient Data-Meta-analysis (IPD-MA) for longer regimens included no patients on thioacetazone (T) and too few patients on gatifloxacin (Gfx) and high-dose isoniazid (H) for a meaningful analysis. Evidence on the safety and effectiveness of Bdq beyond 6 months and below the age of 6 years was insufficient for review. Evidence on the concurrent use of bedaquiline and delamanid was insufficient for review. Use of linezolid for at least 6 months was shown to increase efficacy, however, drug toxicity may limit use. The analysis suggested that using linezolid for the whole duration of treatment would optimise its effect (about 70% of patients on Lzd with data received it for >6 months and 30% for 18 months or the whole duration). From the IPD-sub-analysis no patient predictors for early cessation of Lzd could be identified. Evidence on the safety and efficacy of delamanid beyond 6 months, below the age of 3 years was insufficient for review. Pyrazinamide is to be used only if DST results confirm susceptibility. Every dose of Imp-Cln and meropenem is administered with clavulanic acid, which is only available in formulations combined with amoxicillin (Amx-Clv). Amx-Clv is not counted as an additional effective TB agent and should not be used without Imp-Cln or meropenem. Amikacin and streptomycin are only to be considered if DST results confirm susceptibility and high-quality audiometry monitoring for hearing loss can be ensured. Streptomycin is to be used only if amikacin cannot be used (unavailable or documented resistance) and if phenotypic DST results confirm susceptibility (streptomycin resistance is not detectable with second-line molecular line probe assays). Kanamycin and capreomycin are no longer recommended for use in MDR-TB regimens. These agents only showed effectiveness in regimens without bedaquiline, linezolid, clofazimine or delamanid, and therefore only proposed when other options to compose a regimen are not possible.

TABLE 3  Dosage of MDR/RR-TB drugs in adults

<table>
<thead>
<tr>
<th>Drugs</th>
<th>16–29 kg</th>
<th>30–45 kg</th>
<th>46–70 kg</th>
<th>&gt;70 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin (R)*</td>
<td>300 mg</td>
<td>450 mg</td>
<td>600 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>High-dose H (H⁺)</td>
<td>300 mg</td>
<td>600 mg</td>
<td>900 mg</td>
<td>900 mg</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td>400 mg</td>
<td>800 mg</td>
<td>1200 mg</td>
<td>1600 mg</td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td>750 mg</td>
<td>1250 mg</td>
<td>1750 mg</td>
<td>2000 mg</td>
</tr>
<tr>
<td>Levofloxacin (Lfx)</td>
<td>250 mg</td>
<td>750 mg</td>
<td>1000 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Moxifloxacin (Mfx)</td>
<td>200 mg</td>
<td>400 mg</td>
<td>400 mg</td>
<td>400 mg</td>
</tr>
<tr>
<td>High-dose Mfx (Mfx⁺)</td>
<td>400 mg</td>
<td>600 mg</td>
<td>800 mg</td>
<td>800 mg</td>
</tr>
<tr>
<td>Bedaquiline (Bdq)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid (Lzd)</td>
<td>300 mg</td>
<td>600 mg</td>
<td>600 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>Clofazimine (Cfz)</td>
<td>50 mg</td>
<td>100 mg</td>
<td>100 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>Cycloserine (Cs)†</td>
<td>250 mg</td>
<td>500 mg</td>
<td>750 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Delamanid (Dlm)</td>
<td>50 mg twice daily (100 mg) for 24 weeks in 6–11 years of age</td>
<td>100 mg twice daily (200 mg) for 24 weeks for ≥12 years of age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipenem/cilastatin (Imp/Cls)†</td>
<td>1000 mg imipenem/1000 mg cilastatin twice daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meropenem (Mpm)†</td>
<td>1000 mg three times daily (alternative dosing is 2000 mg twice daily)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin (Am)†</td>
<td>500 mg</td>
<td>750 mg</td>
<td>750 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Capreomycin (Am)†</td>
<td>500 mg</td>
<td>750 mg</td>
<td>750 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Kanamycin (Km)†</td>
<td>500 mg</td>
<td>750 mg</td>
<td>750 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Ethionamide (Eto)</td>
<td>375 mg</td>
<td>500 mg</td>
<td>750 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Na-PAS (60% weight/vol)†</td>
<td>10 g</td>
<td>14 g</td>
<td>16 g</td>
<td>22 g</td>
</tr>
<tr>
<td>Amoxyclov (Amx-Clv) (In child: WHO 80 mg/kg in two divided doses)</td>
<td>875/125 mg BD</td>
<td>875/125 mg BD</td>
<td>875/12 mg (2 morning plus 1 evening)</td>
<td>875/125 mg BD (2 morning plus 1 evening)</td>
</tr>
<tr>
<td>Pyridoxine (Pdx)</td>
<td>50 mg</td>
<td>100 mg</td>
<td>100 mg</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

*For H mono/poly resistant TB
†Drugs can be given in divided doses in a day in the event of intolerance
‡For adult more than 60 yrs of age, dose of SLI should be reduced to 10 mg/kg (max up to 750 mg)
†Phenotypic DST for some medicines included in the regimen (ethambutol and ethionamide) is not considered reliable and reproducible.
§Extensive TB disease: bilateral cavitary disease or extensive parenchymal damage on chest X-ray. In children under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest X-ray.


BOX 4  Criteria to decide when the shorter MDR-TB regimen may be offered

A shorter all-oral Bdq-containing regimen (4–6) Bdq (6m) Lfx Cfz E H⁺ Eto/(5) Lfx Cfz Z E of 9–12 months duration is recommended in eligible patients with MDR/RR-TB in the following situations:
- Without resistance or suspected ineffectiveness of a medicine in the shorter regimen (except H resistance)*
- Without exposure to previous treatment with second-line medicines in the regimen for >1 month (unless DST confirms susceptibility to these medicines)†
- No pregnancy
- Age >6 years
- No extensive TB disease§ and with no severe EPTB
- PLHIV

*H resistance determined by mutations in either inhA or katG genes (not both) or phenotypic DST. The presence of both mutations suggests that isoniazid at high dose and thioamides are not effective and therefore, in such patients, shorter regimen should not be used.
†Phenotypic DST for some medicines included in the regimen (ethambutol and ethionamide) is not considered reliable and reproducible.
‡Extensive TB disease: bilateral cavitary disease or extensive parenchymal damage on chest X-ray. In children under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest X-ray.

Bdq, bedaquiline; Cfz, clofazimine; DST, drug susceptibility testing; E, ethambutol; EPTB, extrapulmonary TB; H, isoniazid; H⁺, high-dose isoniazid; Lfx, levofloxacin; MDR/RR-TB, multidrug-resistant/ Rifampicin resistant-tuberculosis; PLHIV= people living with HIV; Z, pyrazinamide

### Table 4: ATS/CDC/ERS/IDSA criteria to build an individualized treatment regimen for MDR-TB

- **Constitute a drug regimen consisting of five or more drugs to which the \( \text{Mt} \) isolate is susceptible (or has low likelihood of resistance), preferably with drugs that have not been used to treat the patient previously.**
- **Choice of drugs is contingent on capacity to appropriately monitor for significant adverse effects, patient comorbidities, and preferences/values (choices therefore subject to program and patient safety limitations).**
- **In children with TB disease who are contacts of infectious MDR-TB source cases, the source case’s isolate DST result should be used if one is unable to obtain from the child.**
- **TB expert medical consultation is recommended (ungraded good practice statement).**

<table>
<thead>
<tr>
<th>Step 1: Choose one of the later-generation fluoroquinolones</th>
<th>Lfx, Mfx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2: Choose both of these prioritized drugs</td>
<td>Bdq, Lzd</td>
</tr>
<tr>
<td>Step 3: Choose both of these prioritized drugs</td>
<td>Cfz, Cs/Trd</td>
</tr>
<tr>
<td>Step 4: If a regimen can’t be assembled with five effective oral drugs, <em>and the isolate is susceptible</em>, use one of these injectable agents*</td>
<td>Am, S</td>
</tr>
<tr>
<td>Step 5: If needed or if oral agents preferred over injectable agents in Step 4, use the following drugs†</td>
<td>Dlm‡, Z, E</td>
</tr>
<tr>
<td>Step 6: If limited options and cannot assemble a regimen of five effective drugs, consider use of the following drugs</td>
<td>Eto or Pto§, Imp–Cln or Mpm-Cln</td>
</tr>
</tbody>
</table>

The following drugs are no longer recommended for inclusion in MDR-TB regimens: Cm and Km, Amx/Clv (when used without a carbapenem), Azithromycin and clarithromycin.

---

*Amikacin and streptomycin should be used only when the patient’s isolate is susceptible to these drugs. Because of their toxicity, these drugs should be reserved for when more-effective or less-toxic therapies cannot be assembled to achieve a total of five effective drugs in the intensive phase.

†Patient preferences in terms of the harms and benefits associated with injectables (the use of which is no longer obligatory), the capacity to appropriately monitor for significant adverse effects, consideration of drug–drug interactions, and patient comorbidities should be considered in selecting Step 5 agents over injectables. Ethambutol and pyrazinamide had mixed/marginal performance on outcomes assessed in our PS-matched IPDMA; however, some experts may prefer these drugs over injectable agents to build a regimen of at least five effective oral drugs. Use pyrazinamide and ethambutol only when the isolate is documented as susceptible.

‡Data on dosing and safety of delamanid are available in children ≥3 years of age.

§Mutations in the \( \text{inh}A \) region of the \( \text{Mycobacterium tuberculosis} \) genome can confer resistance to ethionamide/prothionamide as well as to INH. In this situation, ethionamide/prothionamide may not be a good choice unless the isolate is shown to be susceptible with in vitro testing.

|| Divided daily intravenous dosing limits feasibility. Optimal duration of use not defined.

¶Fair/poor tolerability and low performance. Adverse effects reported to be less common in children.

**Data not reviewed in our PS-matched IPDMA (propensity score-matched individual patient data meta-analyses), but high-dose isoniazid can be considered despite low-level isoniazid resistance but not with high-level INH resistance.

*Note: pepQ mutations were associated with low-level resistance to Bdq and cross-resistance to Cfz. These mutations reduced the efficacy of both drugs in vivo but did not lead to complete resistance to these drugs. The value of using loading doses and the optimal dosing for Cfz requires additional research.

Am, amikacin; Amx/Clv, amoxicillin -clavulanic acid; Bdq, bedaquiline; Cfz, clofazimine; Cln, cilastatin; Cm, capreomycin; Cs, cycloserine; Dlm, delamanid; DST, drug susceptibility testing; E, ethambutol; Hh, high-dose isoniazid; Imp, imipenem; INH, isoniazid; IPDM, individual patient data meta-analyses; Km, kanamycin; Lfx, levofloxacin; Lzd, linezolid; MDR, multidrug-resistant; PS, propensity score; Mfx, moxifloxacin; PAS, p-aminosalicylic acid; S, streptomycin; TB, tuberculosis; Trd, terizidone; Z, pyrazinamide.

### TABLE 5  Sequence of using replacement drugs to modify the regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Sequence of using replacement drug to modify the regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>All oral H mono/poly</td>
<td>If SL LPA detects Lfx resistance; replace Lfx with Mfx if Z cannot be used; substitute with Lzd. If Lzd cannot be administered, replace with Cfz. If both Lzd and Cfz cannot be given, use Cs as replacement. If both Mfx and Z cannot be used; add two drugs of these Lzd, Cfz, Cs in the order of preference. Treat for 9 months. Replacement situations proposed composition of regimen after replacement. Initiate treatment. If Lfx cannot be used, replace Lfx with Mfx if SL LPA pattern suggests. If Mfx cannot be used, replace it with Dlm. If Mfx &amp; Dlm both cannot be used, add two drugs from replacement sequence. If Bdq cannot be used, replace with Dlm. If Dlm cannot be used, replace with two drugs from replacement sequence. If one of Lzd, Cfz or Cs cannot be used, no replacement. If two or all three of Lzd, Cfz or Cs cannot be used, replace with two or three drugs from replacement sequence. After 6 months of treatment. If one of the drugs from Lfx, Lzd, Cfz, Cs cannot be used; no replacement is required. If two drugs from Lfx, Lzd, Cfz, Cs cannot be used, replace with two drugs from Z*, Eto*, PAS, E in given order to complete the four drugs regimen.</td>
</tr>
</tbody>
</table>

*Use Dlm: if available, no history of prior use and no exclusion criteria for its use, Z: if resistance not detected, Eto: If inhA mutation not present, Am: if SL LPA pattern suggests. DST for Bdq, Dlm, Lzd, Cfz, and Z will be considered whenever it is available. DST for E and Eto is not reliable and reproducible.

†Replacement sequence: Dlm, Am*, Z*, Eto*, PAS, E, Imp/Cln or Mpm plus Amx/Clv Am, amikacin; Amx/Cln, amoxicillin-clavulanic acid; Bdq, bedaquiline; Cfz, clofazimine; Cln, cilastatin; Cm, capreomycin; Cs, cycloserine; Dlm, delamanid; DST, drug-susceptibility testing; E, ethambutol; H, high-dose isoniazid; Hr-TB, rifampicin sensitive but isoniazid resistant-TB; Imp, imipenem; Km, kanamycin; Lfx, levofloxacin; Lzd, linezolid; MDR/RR-TB, multidrug-resistant/Rifampicin resistant-tuberculosis; Mfx, moxifloxacin; Pa, pretomanid; PAS, p-aminosalicylic, acid; S, streptomycin; Z, pyrazinamide.


Depending on EPTB site and the treatment duration is 18–20 months. Drug treatment preferably a regimen containing FQ, Bdq, Lzd, and Cs (injectables Am/S only if Mtb is susceptible); Cfz, Eto (provided inhA mutations are absent) may be used if required. Efavirenz may be replaced with nevirapine in patients with HIV/AIDS. Treatment of MDR/RR-TB patients with pregnancy is done with a 4-drug regimen according to the DST and with drugs having a low-teratogenic potential. In children with seizures Mmp is preferred over Imp.

**Nix-TB Trial: Bedaquiline, Pretomanid, and Linezolid (BPaL) Regimen for MDR-TB Treatment**

Nix-TB is a clinical trial, conducted by TB alliance in three South African sites (April, 2015 to November, 2017) in which the 3-drug pan-oral BPaL regimen, consisting of...
### TABLE 6
Characteristics of drugs used for DR-TB

<table>
<thead>
<tr>
<th>Group</th>
<th>Dosage</th>
<th>Adverse events</th>
<th>Special precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Include all three medicines (unless they cannot be used) | Levofloxacin (Lfx) or Moxifloxacin (Mfx) | 500–1000 mg daily | In advanced CKD, class effect of fluoroquinolones may pose a higher risk of neurotoxicity, peripheral neuropathy, and optic neuropathy. Dosing should be decreased to 500 mg daily in patients with creatinine clearance (CrCl) 60 mL/min. Biweekly dosing is preferred. | Dose adjustment required in CrCl 
< 30 mL/min = 750–1000 mg daily<br> < 30 mL/min = 750–1000 mg thrice weekly<br> No dose adjustment in CrCl ≥ 30 mL/min. Monitoring required for QTc prolongation when co-administered with Clindamycin, Ctx, Lfx, Mfx. |
| | Bedaquiline (Bdq) | 400 mg daily | QTc prolongation, arthralgias, hepatitis, headache, anorexia, nausea | Monitoring required for QTc prolongation; QTc monitoring required when co-administered with Clarithromycin, Cfx, Lfx/Mfx. |
| | Linezolid (Lzd) | 600 mg once daily; the dose can be decreased to 300 mg after 3–6 months; linezolid should be discontinued in case of toxicity | Hematological toxicity, lactic acidosis, peripheral and optic neuropathy and serotonin syndrome. Drug toxicity is related to dose and duration. Lactic acidosis occurs early in few weeks to months while neurological toxicity occurs late after 3–4 months. | CrCl ≥ 30 mL/min: no dose adjustment required; < 10 mL/min: 250 mg daily or 500 mg on alternate days; therapeutic drug monitoring is recommended if facility is available. Avoid l-dopa in patients with history of epilepsy. Skin reactions like rash, pruritus, fever, and eosinophilia can be avoided by application of sunscreen and moisturizers. |
| **Group B** | | | |
| Add both medicines (unless they cannot be used) | Clofazimine (Cfx) | 100 mg daily | Ichthyosis and dry skin, sunburn, pink-brownish-black discoloration of skin, corneal and retinal deposits, anemia; acne flare | Monitoring of skin problems is required. Skin problems can be prevented by application of sunscreen and moisturizers. |
| | Cycloserine (Cs) OR Terizidone (Trd) | 10–15 mg/kg/day in divided dose<br> 250 mg morning<br> 500 mg evening | Dizziness, slurred speech, convulsions, headache, tremor, insomnia, confusion, depression, and altered behavior. Seizure activity in some patients. No CNS toxicity in cases treated with 10 mg/kg/day. | CrCl ≥ 30 mL/min: no dose adjustment required; < 10 mL/min: 250 mg daily or 500 mg on alternate days; therapeutic drug monitoring is recommended if facility is available. Avoid l-dopa in patients with history of epilepsy. Skin reactions like rash, pruritus, fever, and eosinophilia can be avoided by application of sunscreen and moisturizers. |
| | | | | Mu-190.indd 1239 | 29-01-2021 15:17:56 |
### Group C

Add to complete the regimen and when medicines from Group A and B cannot be used

<table>
<thead>
<tr>
<th>Medication (E)</th>
<th>Dosage</th>
<th>Adverse events</th>
<th>Special precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethambutol (E)</td>
<td>15–25 mg/kg/day</td>
<td>Dose dependent optic (retrolubar) neuropathy (&gt; 30 mg/kg/day or 15–25 mg/kg in CKD); generally, reverses on prompt discontinuation; hyperuricemia Uncommon: interstitial nephritis, cholestatic jaundice, neutropenia and thrombocytopenia, reversible cutaneous hypersensitivity disappearing on desensitization</td>
<td>Cr cl ≥ 30 mL/min, no dose adjustment required; &lt; 30 mL/min: 15–25 mg/kg twice weekly. Patients should be monitored at baseline and regularly thereafter for visual acuity and red-green color discrimination</td>
</tr>
</tbody>
</table>

Delamanid (Dlm) 100 mg twice weekly for 6 months (can be administered longer) QTC prolongation, nausea vomiting and abdominal pain dizziness QTC monitoring at baseline, 2, 12, and 24 weeks. Stop if > QTC 500 ms; monitor serum K⁺, Mg²⁺ and Ca²⁺

Pyrazinamide (Z) 25–30 mg/kg/day (1.5 g for 50 kg, 2 g for > 50 kg) GI upset, hyperuricemia, arthralgia, hepatotoxicity (not dose related) Cr cl ≥ 30 mL/min: no dose adjustment required; < 30 mL/min: 25–30 mg/kg three times/week

Imipenem - cilastatin (Imp-Cln) OR Meropenem Amoxicillin-Clavulanate (Mpm/Amx-Clv) 1g IV every 12 h 1g every 8–12 h IV administered with clavulanate (as amoxycillin clavulanate 250/125 mg every 8–12 h) GI upset, transaminitis Do not adjust dose in CKD Do not adjust dose in CKD

Amikacin (Am) 15 mg/kg-maximum 1 g; five to seven times weekly or 20–25 mg/kg 2–3 times/week Vestibular, auditory and renal toxicities Baseline audiogram and renal functions. Dose adjustment required in CKD. Prefer to avoid if possible. Periodic monitoring of audiogram and renal functions every 2-4 weeks

Ethionamide (Eto) Or Prothionamide (Pto) 15–20 mg/kg/day in divided doses. The usual dose is 250–1000 mg/day. Most patients should be started on 250 mg doses daily or twice daily and gradually increased over several days to 750 or 1000 mg total daily dose Pto is generally considered to be less unpleasant and better tolerated than Eto. However, profile of adverse events is similar. GI disturbances, metallic taste and sulphurous belching; psychotic reactions, hypoglycemia (especially in diabetes mellitus patients); hepatitis. Other rare side-effects include gynaecomastia, menstrual disturbance, impotence in males, acne, alopecia and peripheral neuropathy Should not be administered in pregnancy (teratogenicity in animals). Careful monitoring is required if administered in patients with diabetes mellitus, liver disease, alcoholism or mental instability. No dose adjustment required in CKD. Serum TSH monitoring required periodically especially when co-administered with PAS

p-aminosalicylic acid (PAS) 150 mg/kg or 10–12 g daily in 2-3 divided doses GI disturbances (diarrhea is self-limiting), hypothyroidism (more chances if given along with ethionamide), hypokalemia, hepatitis, thrombocytopenia, aggravation of metabolic acidosis in patients with CKD Although no dose adjustment required in CKD. However, caution should be exercised, since main route of excretion is renal. Periodic serum TSH monitoring required especially when co-administered with ethionamide

*All are bactericidal except Cs and PAS which are bacteriostatic; Cfz and Eto are weak bactericidal

Note: Creatinine clearance (CrCl) is best calculated with estimated glomerular filtration rate (eGFR) using CKD Epidemiology Collaboration (CKD-EPI) creatinine equation. CKD, chronic kidney disease; CKD, chronic kidney disease; Cr Cl, creatinine clearance; ECG, electrocardiogram; GI, gastrointestinal; SSRIs, selective serotonin reuptake inhibitors; TB, tuberculosis; TSH, thyroid stimulating hormone

<table>
<thead>
<tr>
<th>Description</th>
<th>Responsible ARV drugs</th>
<th>Responsible anti-TB drugs</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal toxicity</td>
<td>TDF</td>
<td>Aminoglycosides, Cm</td>
<td>- TDF causes renal failure with hypophosphatemia and proteinuria&lt;br&gt;- Avoid TDF in patients receiving aminoglycosides and Cm&lt;br&gt;- Serum creatinine should be checked before switching patients onto TDF after completion of aminoglycoside&lt;br&gt;- Caution is advised when administering TDF or aminoglycosides in patients with underlying co-morbidities, such as, diabetes mellitus or in patients who are receiving concomitant nephrotoxic agents such as NSAIDs and amphotericin B&lt;br&gt;- If TDF is necessary, close monitoring of serum creatinine is required</td>
</tr>
<tr>
<td>Electrolyte abnormality</td>
<td>TDF</td>
<td>Aminoglycosides, Cm</td>
<td>- Exclude exacerbating factors, such vomiting, diarrhoea, dehydration, diuretics, etc.</td>
</tr>
<tr>
<td>Hepatitis/hepatotoxicity</td>
<td>NVP, EFV, PI (especially RTV), NRTI</td>
<td>Z, Bdq, PAS, FQ</td>
<td>- When severe stop both ARVs and anti-TB agents, restart TB drugs first&lt;br&gt;- Assess for other contributing factors such as alcohol abuse, viral aetiologies and other drugs like co-trimoxazole&lt;br&gt;- Avoid concomitant use of NVP and Z&lt;br&gt;- The risk of NVP hepatotoxicity is highest in the first 3 months of starting therapy with higher risk in patients with CD4+ &gt;250/mm³, the risk of NVP hepatotoxicity is lower if VL is suppressed</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>AZT</td>
<td>Lzd, H</td>
<td>- Stop Lzd if myelosuppression occurs. Blood transfusion is indicated if haemoglobin falls below 8 g/dL&lt;br&gt;- Avoid co-administration of AZT and Lzd&lt;br&gt;- Adverse events should be managed with a combination of temporary suspension of linezolid, dose reduction and/or symptom management&lt;br&gt;- Reduction dose of 300 mg daily may be associated with fewer neuropathic effects but is not supported by pharmacokinetic data&lt;br&gt;- Consider stopping cotrimoxazole</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>ddl, d4T</td>
<td>Lzd, Cs, H, Eto, E</td>
<td>- Avoid use of D4T or ddl in combination with Cs or Lzd&lt;br&gt;- Use pyridoxine as prophylaxis in patients receiving Cs, H and Lzd</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>Bdq, Mfx, Cfz Lfx, Ofx</td>
<td>Close monitoring of QTc is recommended when using these agents in combination</td>
<td></td>
</tr>
<tr>
<td>Description</td>
<td>Responsible ARV drugs</td>
<td>Responsible anti-TB drugs</td>
<td>Considerations</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>------------------------</td>
<td>---------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Central nervous system toxicity</td>
<td>EFV</td>
<td>Cs, H, Eto/Pto, FQ</td>
<td>• EFV toxicity occurs in first 2–3 weeks of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Concurrent use of EFV with CS needs close monitoring</td>
</tr>
<tr>
<td>Headache</td>
<td>AZT, EFV</td>
<td>Cs, Bdq</td>
<td>• Headaches may be self-limited in case of AZT, EFV and Cs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Advice analgesia and hydration</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>RTV, d4T, NVP</td>
<td>Eto, PAS, H, Bdq, E, Z</td>
<td>• Most drugs will cause some degree of nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• If persistent consider drug-induced pancreatitis, hepatitis</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>d4T, ddl, AZT, 3TC</td>
<td>Lzd</td>
<td>• High index of suspicion needed to detect hyperlactatemia to prevent overt</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>symptoms of lactic acidosis</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>d4T, ddl</td>
<td>Lzd</td>
<td>• Avoid co-administration where possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• If pancreatitis occurs discontinue the ARVs completely</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>PI, ddl</td>
<td>PAS, FQ, Eto</td>
<td>• For mild diarrhea anti-motility drugs can be used</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• May be self-limited. Exclude opportunistic infections</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>ddl</td>
<td>E, Lzd, Eto</td>
<td>• Stop all suspected agents causing optic neuritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Screen patients using the Snellen chart and Ishihara chart</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>d4T</td>
<td>Eto, PAS</td>
<td>Monitor serum TSH for patients receiving these agents</td>
</tr>
<tr>
<td>Joint pain</td>
<td>PI (Indinavir)</td>
<td>Z, Bdq</td>
<td>Mild symptoms can be managed with simple analgesics</td>
</tr>
</tbody>
</table>

ARV, anti-retroviral drugs; ARVs, anti-retroviral drugs; AZT, zidovudine; Bdq, bedaquiline; Cfz, clofazimine; Cm, capreomycin; Cs, cycloserine; d4T, stavudine; ddl, didanosine; DR-TB, drug-resistant tuberculosis; E, ethambutol; EFV, efavirenz; Eto, ethionamide; FQ, fluoroquinolones; Gfx, gatifloxacin; H, isoniazid; HIV, human immunodeficiency virus; Lfx, levofloxacin; Lzd, linezolid; Mfx, moxifloxacin; NRTI, nucleoside reverse transcriptase inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs; NVP, nevirapine; Ofx, ofloxacin; PAS, para-aminosalicylic acid; PI, protease inhibitor; Pto, prothionamide; RTV, ritonavir; TB, tuberculosis; TDF, tenofovir disoproxil fumarate; TSH, thyroid stimulating hormone; VL, viral load; Z, pyrazinamide

bedaquiline, pretomanid, and linezolid was administered in 109 XDR-TB patients. Patients received bedaquiline 400 mg once daily for 2 weeks followed by 200 mg three times a week for 24 weeks, plus pretomanid 200 mg daily for 26 weeks and linezolid 1,200 mg daily for up to 26 weeks. Ninety-six percent of patients were successfully treated after 6 months of treatment with BPaL drug regimen and 6 months of post-treatment follow-up. With the advantages of pan-oral shorter treatment duration and very low rates of adverse drug reactions, the BPaL regimen can be adopted as a standard DR-TB regimen.

**Active TB Drug-safety Monitoring and Management**

Several drugs used for the treatment of MDR-TB have additive toxicities and may cause adverse events (AEs) and serious adverse events (SAEs). Active TB Drug-Safety Monitoring and Management (aDSM) has been strongly recommended for better adherence and successful treatment outcome. Table 6 details serious adverse reactions of the drugs and special precautions required while treating MDR/RR-TB patients. During treatment of HIV DR-TB patients, clinicians should be careful and need to carefully monitor additive drug cotoxieties and drug-drug interactions (Table 7). Linezolid is a very potent anti-TB drug and its irrational use because of its free availability over-the-counter for other bacterial infections such as staphylococcus should be avoided.

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Conclusion

All efforts should be made to have quality laboratory network with regular accreditation. Universal DST is strongly recommended to enable individualized pan-oral long-term MDR/RR-TB regimens to prevent further amplification of drug resistance. Smear and mycobacterial cultures should be done monthly during follow-up, aDSM should be rigorously followed to have good adherence for better treatment outcome. All these concerted efforts will go a long way toward achieving the goal of TB-free world.

References

Abstract
Diabetes is one of the largest causes of non-communicable morbidity and mortality worldwide and in India. Tuberculosis is the leading infectious disease in India and some other Asian countries including China. Tuberculosis and diabetes are frequently encountered together. About 10% of TB cases are globally linked to diabetes. Diabetes affects the presentation and treatment outcomes of tuberculosis. On the other hand tuberculosis also affects the treatment of diabetes due to significant drug interaction and some other factors. So, theoretically, treatment of both diseases needs to be modified. In this context many studies have been published which indicates that TB-diabetes need special considerations in treatment. It will help in improving the treatment outcome and preventing the emergence of drug resistance cases.

Introduction and Epidemiology
Globally tuberculosis is the leading cause of death from an infectious disease and in India the incidence of tuberculosis in 2018 has been estimated to be 27 lakhs, about 16% increase from previous year.\textsuperscript{1,2} Recent estimation of diabetic population worldwide is about 463 millions.\textsuperscript{3} The proportion of people with diabetes are increasing in many countries. India has an estimated 77 million people with diabetes, which makes it second most affected country after China. India alone contributes to about 17% of world diabetic population.

TB and Diabetes Comorbidity
About 10% of TB cases globally are linked to diabetes. The precise biological mechanism is still not very clear but it has been observed that diabetes accounts for 20\% of smear-positive pulmonary TB. Recent analysis have indicated that increase in diabetes prevalence in India has been an important obstacle in reducing TB incidence.\textsuperscript{4} More recent studies suggest that DM increases the risk of active TB up to three- to fourfold. In an Indian study the prevalence of DM among TB patients was 13.1\% (known diabetic 9.1\% and new diabetic 4\%). TB and diabetes when present together affects each other in various ways:
- Diabetics have weaker immune system so they are at higher risk of progressing latent TB to active TB.
- Diabetes can lengthen the time for sputum culture conversion and thus may be potential cause for development of MDR-TB.
- People with TB and diabetes have four times higher risk of death during treatment and higher risk of relapse. Higher reported rate of mortality in TB patients with diabetes may be caused by cardiovascular complications rather than by TB itself.\textsuperscript{6}
- Diabetes is complicated by the presence of infectious diseases, including TB. It is important that proper care for diabetes should be provided to patient suffering from TB-diabetes comorbidity.
- TB is associated with worsening of glycemic control in diabetics; good glycemic control can improve the outcome. Furthermore diabetics may have many other
How Diabetes Affects Clinical Spectrum of Tuberculosis?

Clinical Presentation

Major biochemical manifestation of diabetes is hyperglycemia which favors growth, viability, and pathogenicity of the tubercle bacilli. Increased production of glycerol, and nitrogenous substance further aids to the growth of tubercle bacilli. Tuberculosis runs more aggressive course in a diabetic. In diabetic subject increased prevalence of pulmonary TB and relatively infrequent extrapulmonary form of TB have been noticed. In a series of studies 82.6% of diabetics with TB were found to be above 45 years with male preponderance. In another Indian study it has been observed 55% of TB-DM group were underweight and age group was above 45 years. In DM-TB group prolonged duration of illness and more significant weight loss has been observed than in non-diabetic subjects. Low grade fever and productive cough were observed with almost equal frequencies in both groups.

Diagnosis

Sputum microscopy and X-ray chest are two most important investigations used for the diagnosis of pulmonary tuberculosis in RNTCP. Apart from that we have CBNAAT for detection of RR, LPA, and culture sensitivity test for individual DST. Now RNTCP has a well designed program structure from national level to PHI level. RNTCP was launched in 1997 and achieved full nationwide coverage by March 2006. DMC is the most peripheral laboratory under RNTCP. There are 13,000 DMCs across the country. HIV screening of all patients undergoing sputum examination has also been included. In 2010, an integrated National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease, and Stroke (NPCDCS) has been launched.

Effect of Diabetes on Sputum Examination

Sputum positivity indicates the infectivity of pulmonary tuberculosis and culture conversion the effectiveness of treatment. In a study it has been found that diabetics are five times more prone to develop sputum positive pulmonary tuberculosis than non-diabetics. These factors were analyzed in a recent Turkish study containing 737 pulmonary tuberculosis patients hospitalized during 2000 to 2005. They concluded that those who are diabetic, radiologically having extensive and cavitory lesions, take longer sputum and culture conversion time than the other group. Another larger study concluded that pulmonary tuberculosis patients with diabetes had a higher bacillary load before initiation of treatment and DM was found to be an independent risk factor for more AFB on sputum smear examination.

Effect on Chest X-ray

Comparative studies of radiological findings in TB-diabetes with tuberculosis alone group have yielded contrasting results. In a study by Perenez-Guzman et al. in Mexico, 192 diabetic patients were compared with radiological findings of tuberculosis alone. They found that the TB-DM patients were older and have a decreased frequency of upper (17% vs. 56%), and an increased frequency of lower (19% vs. 7%) and increased frequency (64% vs. 36%) both upper and lower lung field lesions. In TB-DM group cavitory lesions were more (82.5% vs. 59%) than control and that were more often in lower lung field (29% vs. 3%). Cavities were more often multiple in the TB-DM patients (25% vs. 2%).

Treatment Outcome and Complications

At the end of intensive phase treatment a slightly lower sputum conversion rates were observed in diabetics as compared to non-diabetic group. Regarding treatment outcome some reports suggest adverse effects of diabetes on treatment outcome of TB patients with increased rate of failure, death, defaults, and relapses. Mortality rates in these patients are reported to be several times higher than the non diabetic TB patients. However, in contrary recent study concludes that as far as tuberculosis is concerned, the survival rate and socioeconomic rehabilitation of adequately treated patients with diabetes and pulmonary TB are the same as that of TB patients without diabetes.

How to Tackle?

Screening for Diabetes

Ideally WHO and International Union against Tuberculosis and Lung Disease recommend that all adult TB patients...
should be screened for diabetes. But in country like India where resources are tight it may be more cost effective to go for the targeted screening policy for high risk patients; above 40 years of age, those who are overweight or obese, those with family history of diabetes, those who consume excess alcohol, those with a previous history of gestational DM or previous pre-DM.

When to screen a tuberculosis patient for diabetes is very important aspect for the ease of programmatic management and to alleviate fallacies like stress related diabetes. It has been recommended that TB patients should be screened for diabetes at the time of diagnosis and registration. The fasting blood glucose and HbA1c are the two most suitable tools in programmatic setting and in those patients who have symptoms of diabetes—polyuria, polydipsia, and polyphagia. In asymptomatic persons fasting after glucose both should be done (Table 1).

Treating a diabetic-tuberculosis has many challenges with treatment of tuberculosis as well as treatment of diabetes. Both diseases alter each other management in many ways. Medications used for their management affect each other in terms of—efficacy, drug interaction, adverse reactions. More over TB adversely affects control of diabetes too. Diabetics have often cardiovascular complications and risk factors which may be worsened by tuberculosis. So there are some considerations which must be taken into account while dealing with this complex duel problem:
  - Inflammation related with TB can lead to temporarily elevated blood suger—“stress induced hyperglycemia,” sometimes quite pronounced but usually improve during TB treatment.
  - Our initial priority should be successful initiation of TB treatment and with optimizing blood glucose control.
  - Referral of TB patients to specialized DM treatment centre is not recommended in the early phase of treatment because of the risk of transmission of tuberculosis.

### Treatment of Tuberculosis

For treating diabetic tuberculosis patients, under RNTCP a National framework for joint TB-diabetes collaborative activities has been launched in 2017 in co-ordination with NPCDCS (National Program for Cancer, Diabetes, Cardiovascular Diseases and Stroke). Currently recommended anti-tuberculosis treatment is similar for patients with combined TB and diabetes compared to those with TB only. This strategy needs proper evaluation because DM is associated with ATT drug resistance, slower treatment response, higher rate of toxicity, treatment failure, and recurrent TB. Points to be considered for ATT in diabetics:
  - The length of ATT might have to be adjusted. This is common practice in some countries including China. In a retrospective cohort study in Taiwan, a 9-months treatment regimen was associated with a lower rate of recurrent TB than the 6 months regimen.\(^{19}\)
  - Higher dose of ATT may be needed, especially rifampicin due to interaction with sulphonyl urea derivatives. In an observational study in the USA it has been found that therapeutic drug monitoring for INH and rifampicin, after 2 weeks of treatment was associated with significantly shorter time of sputum culture conversion among patients with combined TB and DM.\(^{20}\)
  - TB-DM should be prioritized for DST at least for RR by CBNAAT. Nowadays CBNAAT is recommended as initial DST for all patients with high MDR/TB burden.

### TABLE 1

<table>
<thead>
<tr>
<th>Blood test</th>
<th>Diabetes mellitus</th>
<th>Pre-diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 hrs plasma glucose after oral glucose tolerance test (OGTT)</td>
<td>≥11.1 mmol/L</td>
<td>7.8–11.0 mmol/L</td>
</tr>
<tr>
<td></td>
<td>≥200 mg/dL</td>
<td>140–199 mg/dL</td>
</tr>
<tr>
<td>Fasting plasma glucose (FPG)</td>
<td>≥7.0 mmol/L</td>
<td>6.1–6.9 mmol/L</td>
</tr>
<tr>
<td></td>
<td>≥126 mg/dL</td>
<td>110–125 mg/dL</td>
</tr>
<tr>
<td>Glycosylated hemoglobin (HbA1c)</td>
<td>≥6.5%</td>
<td>6.0–6.4%</td>
</tr>
<tr>
<td></td>
<td>≥48 mmol/mol</td>
<td>42–47 mmol/mol</td>
</tr>
</tbody>
</table>
but on ground level this is not happening due to resource issues.

- Close monitoring of ATT is needed due to risk of side effects and drug interaction particularly if more toxic second line drugs used for MDR-TB.
- Close monitoring for renal, hepatic function, and neuropathic sign and symptoms because OHA and ATT may have combined toxicity or diabetes may have impaired renal function. INH may aggravate neuropathic symptoms.
- Drug compliance needs more close observation because of high pill burden (Table 2).

### Treatment of Diabetes

Treatment of diabetes itself is a vast subject but here while treating a diabetic patient with tuberculosis following points to be considered:

- It should be noted that TB-diabetes form a heterogeneous group consisting of previously diagnosed (known) diabetic and “New” diabetic. In the TANDEM cohort, around 74% of TB-DM patients have previously diagnosed DM (74%), while 26% were newly detected as a result of screening. The relationship between tuberculosis and diabetes is bidirectional. TB is a known cause of pancreatitis and tuberculosis pancreatitis might reveal itself only after the development of diabetes.
- Management of diabetes should be aggressive and optimal glycemic control results in a better patient outcome. If tuberculosis is not extensive or severe there may not be much difference for treatment of diabetes alone, i.e., it may be treated as per general guideline for the treatment of diabetes. Some important drug interaction should be kept in mind while adjusting the dose of OHA.
  - Refampicin, through enzyme induction, accelerates the metabolism of sulphonylureas and biguanides, reducing their plasma level and thereby leading to hyperglycemia. Isoniazid antagonizes the action of sulphonylureas and worsen glycemic control. Isoniazid also inhibits the release of insulin even among none diabetics and causes hyperglycemia. Metformin is the drug of choice having no clinically relevant drug interaction. It has some anti-tuberculous activity also. DPPIV inhibitors causes immune paresis and probably worsen treatment outcome of tuberculosis. Thiazolidinediones efficacy may be decreased by enzyme inducing effect of refampicin.
  - Insulin is the preferred agent for type 2 DM treatment with TB. The rational for the choice of insulin includes:
    - Severe TB infection
    - Body tissue loss
    - The need for increased anabolism
    - Pancreatic hypofunction
    - Interaction between OHA and ATT
    - Possibility of associated liver disease which would preclude the use of oral agent

So, usually in case of severe TB-DM with profound systemic sign and symptoms patient is switched over to insulin. After few weeks of treatment tuberculosis get controlled then dose requirement of insulin falls, patient may again be switched over to OHA. Choice of insulin should be based on safety, effectiveness, cost, and patient characteristics.

### TABLE 2 Important drug interactions in TB-DM patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>Refampicin</th>
<th>Isoniazid</th>
<th>Aminoglycosides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>No clinically relevant Interaction</td>
<td>No important interaction</td>
<td>May worsen neuropathic symptoms</td>
</tr>
<tr>
<td>Sulfonylurea (Glyburide, Glipizide, Glimepiride)</td>
<td>Decreased Glyburide level (39%), Glipazide (22%), Glimepiride (30%)</td>
<td>↑ Sr Conc. of Glimepiride and my cause Hypoglycemia</td>
<td>My worsen renal toxicity</td>
</tr>
<tr>
<td>DPP IV inhibitor (Sitagliptin, Saxagliptin)</td>
<td>May ↓ blood level of gliptines</td>
<td>Not significant</td>
<td>No significant interaction</td>
</tr>
<tr>
<td>Thiazolidinedione (Pioglitazone)</td>
<td>↓ Pioglitazone level (54%)</td>
<td>No interaction</td>
<td>No significant interaction</td>
</tr>
<tr>
<td>Insulin</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Source: Adopted from www.heartlandntbc.org
Cardiovascular risk assessment is very important in patients with TB-DM. The higher reported rate of mortality in TB patients with diabetes may be caused by these cardiovascular complications rather than TB itself. Cohort study in Taiwan has shown that patients with newly diagnosed pulmonary TB have a 40% increased risk of ACS and a 50% higher risk of ischemic stroke.26,27

Conclusion

Our country India has very large number of tuberculosis cases as well as diabetics. Clinical presentation as well as treatment outcome of tuberculosis is largely affected by other comorbidities. Diabetes is an important comorbidity which affects all aspects of tuberculosis management and vise-versa. TB-DM is a commonly encountered situation which needs special attention in RNTCP (NTEP) to improve the treatment outcome and prevent complications.

References

Abstract

Tuberculosis remains a major public health problem in developing countries like India due to undue diagnostic delay in diagnosis, and hence treatment of TB. While diagnosis of TB has entered into an era of molecular detection of tubercle bacilli which is faster and rapid, we are still sticking to sputum microscopy as initial test for diagnosing TB, which has comparatively less sensitivity. WHO has recommended molecular assays (Gene X-pert MTB/RIF, Gene X-pert Ultra, and TrueNat) as initial tests for diagnosis of TB and rifampicin resistance in a recent communication, which will bring a paradigm shift in to End TB program.

Introduction

A tribute to Robert Koch is the discovery of tubercle bacilli as a causative organism of tuberculosis (TB) on 24th March, 1882, but the mystery of TB continues even today. TB attacks lungs in 80% of cases called pulmonary tuberculosis (PTB), but it can also affect any extrapulmonary organ named extrapulmonary TB. Global burden of TB is still quite high. In 2018, 10 million people contracted TB and 1.5 million died. There are more than 0.5 million new cases of multidrug resistant TB. Globally, diagnosis of TB and drug-resistant TB remains a challenge, because a third of people with TB and two-thirds of people with drug-resistant TB are not being detected. Accelerated efforts to diagnose TB and drug-resistance are crucial to end the global TB epidemic. India which accounts for 1/5 of global burden of TB needs adequate policy reforms and a high-quality laboratory system which utilizes modern diagnostics for early and rapid diagnosis of TB and rifampicin (RIF) resistance.

Diagnosis of TB

Standards of TB care in India (STCI) have laid down clear diagnostic criteria for different types of TB:

- **Pulmonary TB:** Any adult patient complaining of cough more than 2 weeks, fever more than 2 weeks, significant weight loss, and any abnormality in chest X-ray must be evaluated for TB.
- **Pediatric TB:** Children with persistent fever and/or cough more than 2 weeks, loss of weight/or no weight gain, and/or contact with pulmonary TB cases must be investigated for TB.
- **Extrapulmonary TB:** For all patients with presumptive EPTB, appropriate specimens from the presumed site of involvement must be obtained for microscopy/culture and drug sensitivity/molecular assay to pathological examinations.

WHO urges countries to expand access to rapid molecular tests for detection of TB. Molecular assay (CBNAAT) is already the preferred first diagnostic tool for childhood TB and TB-HIV coinfection. A systemic review of 23 studies has shown that TB is diagnosed in India after a delay of about 2 months. Molecular assay as initial test will lead to early diagnosis. It will also promote reduction in transmission and faster life-saving treatment of this deadly communicable disease.
Paradigm Shift

There has to be a paradigm shift in the approach to TB diagnosis by using newer molecular tests in place of conventional sputum microscopy, if we want to achieve the ambitious goal of ending TB early and accurate diagnosis of TB and RIF resistance is a prime step in this direction.

- **Sputum microscopy:** It has been a diagnostic tool for TB for over a century and still most conventional method for diagnosing TB in India. It takes less than an hour during the examination. At least 5–10 thousand tubercle bacilli per mL of sputum (limit of detection LOD) are needed to demonstrate bacilli in the sample. But this methodology lacks sensitivity and so misses many TB cases.

- **Mycobacterium culture:** Culture of mycobacterium TB is the gold standard for diagnosis of TB. In contrast to sputum microscopy only 10–100 tubercle bacilli are needed for culture positivity. Conventional LJ Media takes longer time (4–8 weeks), but liquid culture media like BACTEC or non-radiometric MGIT (mycobacterium Growth Indicator Tube) takes 2–3 weeks times. But this process is cumbersome and time consuming. Hence, there is a dire need of a diagnostic tool which can provide a rapid and confirmed diagnosis of TB. Molecular assay is most suitable to perform this role.

- **Molecular assays:** Science is moving from biology to microbiology and from microbiology to molecular biology. Molecular assay have ushered to a new era of rapid and early diagnosis of not only TB, but also RIF resistance.

  - **Probe-based Methods/DNA Chip-based Methods:**
    - Cartridge Based Nucleic Acid Amplification Test (CBNAAT): Gene X-pert, Gene X-pert Ultra, and TrueNat are endorsed by WHO
    - Line Probe Assay (LPA)
    - Loop-mediated isothermal amplification (LAMP)

  - **Rapid Molecular Tests:**
    - Nucleic Acid Amplification Test (NAAT) is a molecular system that detects pathogenic DNA (deoxyribonucleic Acid) of *Mycobacterium tuberculosis* (MTB).

Molecular assays have several advantages in their arms:

- NAAT amplifies mycobacterium specific DNA sequences using a nucleic acid probe
- It increases the rate of detection
- It requires only 16–131 bacilli to give positive results in a given sample
- It lessens the time of detection
- It is more accurate diagnosis with sensitivity at least 80% in most studies and specificity 98–99%

**Disadvantage:** It has one disadvantage that it is not able to differentiate active infections from old ones as DNA from a dead organism can be detected and amplified by PCR.

X-pert MTB/RIF (USA) is an automated PCR test, which detects MTB and RIF resistance within 2 hours of starting the test. X-pert Ultra is the new version of X-pert MTB/RIF, which is much more sensitive than X-pert. Its sensitivity is comparable to liquid TB culture. Gene Ultra is an advanced version of Gene X-pert with better TB detection capabilities and more definitive identification of RS and RR bacilli. Gene Ultra can be used as an alternative to Gene X-pert for initial testing in pts with s/s of TB. It is also planned to phase out Gene X-pert to be replaced by Gene Ultra.

- **Line Probe Assays (LPAs) are active molecular tools.** LPA of TB was endorsed by WHO in 2008. Meta analyses have shown that LPAs are highly accurate for the detection of first-line drug resistance of isoniazid (INH), RIF, and other first line drugs in sample positive specimens. By using LPA it is possible to diagnose MDR early and rapidly within 2 days.

INH and RIF drug resistant strains are identified by detecting the most common single nucleotide polymorphism associated with resistance.

- **Loop-mediated isothermal amplification (LAMP):** LAMP is an isothermal nucleic acid amplification technique. It was recommended by WHO in 2016 for diagnosis of TB as a replacement of smear microscopy. Characteristics of TB-LAMP have been compared to those of Gene X-pert and LPA (Table 1).

### Evidences of Molecular Assays as Initial Test for TB Diagnosis

- **X-pert TB/RIF:** WHO in 2010 has approved X-pert MTB/RIF machine, which utilizes molecular technique for
rapid diagnosis of TB and RR. 70 studies involving more than thirty thousand patients from 37 countries have shown high diagnostic accuracy of gene X-pert in pulmonary TB (Table 2).

If a patient is rifampicin resistant (RR), can Gene X-pert give false rifampicin sensitive (RS) results? Answer is yes and this paradox is caused by silent mutation. Data from JLNMCH, Bhagalpur, confirm clear-cut superiority of cartridge based NAAT (CBNAAT) over sputum microscopy. 14 Conventional approach using LED microscopy SP was 10.3% while CBNAAT detected 22% positivity. An addition advantage was 19% positivity in SN samples.11,14

Molecular assays are pillars in diagnosis of EPTB: Difficulties were always encountered in confirming the diagnosis of EPTB because of its paucibacillary nature and obtaining tissues from unreachable sites. By using Xpert MTB increased numbers of bacteriologically confirmed EPTB cases were found.

Xpert MTB/RIF ultra: Xpert MTB/RIF-ultra is much more sensitive than Xpert MTB/RIF.10 Table 3 shows the limit of detection (LOD) of different diagnostic tests of TB.

In samples where MTB detected was very low false RMP resistance was seen in Gene X-pert, not in Gene Ultra. Such sample must be subjected to Gold Standard test of TB diagnosis-culture DST. For HIV-positive patients sensitivity of Ultra was 90% versus 77%, i.e., 13% more.

It is as sensitive as mycobacterial culture. In other words Ultra will result in greater TB case detection rate in subjects with paucibacillary TB such as smear negative-culture-positive TB, those with HIV coinfection, pediatric TB, and those with extrapulmonary TB. High diagnostic accuracy of Gene X-pert Ultra in adults with PTB: 5 studies from 12 countries (including high-burden TB countries) overall sensitivity was found to be 90%, which includes all specimens smear-positive and smear-negative ones. Overall specificity was 96% in both types of specimens.

Pediatric TB: There are difficulties in obtaining sputum specimens in children and due to this limitation various non-pulmonary specimens (gastric, nasopharyngeal, and stool) are used for bacteriological confirmation. Data from 21 countries involving more than 6,000 patients show.

In pediatric TB these are variable sensitivity in different specimens (nasopharyngeal—46%, stool—61%, sputum—65%, and gastric—73%) and Specificity 98–100%.

**X-Pert MTB/RIF to Detect RIF Resistance in Pediatric TB**

Using Gene X-pert when RIF resistance was tested with reference to phenotypic drug sensitivity testing it was found to have high overall sensitivity (90%) and specificity.
CHAPTER 192
Molecular Assays as Initial Tests for the Diagnosis of Tuberculosis

TABLE 3
Limit of detection (LOD) Diagnostic tests for TB Limit of detection (bacilli per mL of sample)

<table>
<thead>
<tr>
<th>Test</th>
<th>Limit of Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum microscopy</td>
<td>5,000–10,000</td>
</tr>
<tr>
<td>Mycobacterium culture</td>
<td>10–100</td>
</tr>
<tr>
<td>Gene X-pert</td>
<td>131</td>
</tr>
<tr>
<td>Gene Ultra</td>
<td>16</td>
</tr>
<tr>
<td>TrueNat</td>
<td>29</td>
</tr>
</tbody>
</table>

(98%). Data from six studies which involved 200 patients from four high-burden countries supported the above findings.

EPTB: Similar to pediatric TB difficulties are faced in obtaining extrapulmonary specimens and in aiding bacteriologically confirmed diagnosis in EPTB.

Gene X-Pert as Initial Test for EPTB

Data was assessed from 59 studies from 26 countries, which used MTB/RIF in adults with extrapulmonary TB. Sensitivity and specificity of extrapulmonary TB varied with specimen types (Table 4).

Another studies group using X-pert Ultra showed high performance of detection of RIF resistance sensitivity 96-97% and specificity 99%.

TrueNat as Initial Test for Diagnosis of TB

TrueNat TB test is a new molecular assay, which is in fact a real time PCR system. It is simple and user friendly. It is a point of care (POC) tool and battery operated. Therefore, it is suitable for diagnosis of TB and RIF resistance for poor countries like India where it can be used in rural primary health centers (PHC).

WHO Endorses TrueNat Test

In December 2019, WHO considered the latest evidence on the use of Molbio TrueNat MTB/RIF test. Multicentric study of TrueNat assays done in India, Peru, Ethiopia, and Papua-New Guinea involving 744 patients examined the performance of TrueNat MTB, MTB plus, and MTB RIF Dx assays, which showed comparable efficacy to X-pert MTB/RIF and X-pert Ultra in TB diagnosis and RIF resistance. Overall sensitivity of the TrueNat MTB assay was 83% and that of MTB plus 89% while specificity for MTB and MTB Plus assay was 99% and 98%, respectively. The endorsement of TrueNat by WHO will help the low and middle income countries to use TrueNat in elimination of the disease (TB).

To evaluate the performance of TrueNat assay in comparison with Gene X-pert, 274 samples were processed. The overall sensitivity of TrueNat and Gene X-pert was 94.7% and 96%, respectively.

Conclusion

- There are robust data to support that molecular assays (X-pert MTB/RIF and X-pert Ultra) should be used as initial tests for diagnosis of pulmonary TB in adults.
- A large number of studies support the use of X-pert MTB/RIF and X-pert Ultra as initial diagnostic work-up of extrapulmonary TB.
- These molecular assays show clear superiority over conventional sputum microscopy in the diagnosis of pediatric TB.
- Both molecular assays X-pert and X-pert Ultra show high accuracy in the simultaneous detection of RIF resistance.
- Low cost and Indian molecular assay TrueNat MTB, MTB plus, and MTB-RIF Dx show comparable accuracy with both Gene X-pert and Gene X-pert Ultra in diagnosis of TB and RIF resistance.

References


TABLE 4
Sensitivity and specificity of extrapulmonary samples by Gene X-pert

<table>
<thead>
<tr>
<th>Samples</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph nodes</td>
<td>84.9</td>
<td>92.5</td>
</tr>
<tr>
<td>CSF</td>
<td>79.5</td>
<td>98.6</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>43.7</td>
<td>98.1</td>
</tr>
<tr>
<td>Gastric lavage</td>
<td>83.8</td>
<td>98.8</td>
</tr>
</tbody>
</table>


Abstract
COPD and Tuberculosis are common respiratory diseases in our country. Past history of Tuberculosis is considered an important risk factor for COPD. Chronic airflow obstruction in tuberculosis patients occurs due to tuberculosis-associated lung damage leading to COPD. A number of factors associated with COPD may increase the progression of Tuberculosis in these patients, most important factors are- use of inhaled/oral corticosteroids in the treatment of COPD and smoke related exposure related altered protective response to \textit{M. tuberculosis}. There is bidirectional relationship between tuberculosis and COPD. Early diagnosis and standardized treatment of Tuberculosis and COPD is essential. Action to increase awareness regarding COPD is essential.

Introduction
Tuberculosis and chronic obstructive pulmonary disease (COPD) are major causes of morbidity and mortality worldwide. As per recent reports the prevalence of COPD is increasing worldwide. Past history of tuberculosis is an important risk factor of COPD. It is well known that COPD patients have an increased risk of developing tuberculosis. Thus, there is bidirectional relationship between COPD and tuberculosis. It is alarming for our country since both these diseases are prevalent in our country. These diseases have adverse impact on each other as far morbidity and mortality is concerned. We are committed to eliminate TB, if we have to fulfill our commitment, timely intervention and action for early diagnosis and institution of appropriate treatment of tuberculosis is essential. In addition to adequate steps for diagnosis and treatment of tuberculosis, common risk factors for tuberculosis and COPD must be addressed properly to prevent development of both these diseases in future, otherwise we cannot achieve the target of TB elimination.

COPD and pulmonary tuberculosis are two very important disease of respiratory system, worldwide. These diseases primarily affects lung, COPD is a non-communicable disease, and pulmonary tuberculosis is an infective disease caused by Mycobacterium tuberculosis. As per a number of studies conducted worldwide, there is bidirectional relationship between two diseases and effects each other adversely.

Due to recent advancement in medical field incidence of infective diseases are showing decreasing trend. Due to economic development epidemiological transition is going on globally, the incidence of infective diseases are decreasing, but there is increase in the incidence of non-communicable diseases like COPD. But due to rapid urbanization, overcrowding, lack of awareness, weak health-care system in our part of world (low and middle income countries), there is double burden of infective diseases like tuberculosis and non-communicable diseases like COPD.

We are committed to eliminate tuberculosis, from India by 2025, 5 years ahead of global target, if we have to achieve the target we must take steps to control both COPD and tuberculosis simultaneously. Early diagnosis and proper and standardized treatment of tuberculosis
is mandatory to reduce the future burden of COPD and tuberculosis both. Similarly, steps must be taken to reduce air pollution and other common risk factors, which may help in prevention of these diseases. Fortunately a number of programs are going on in our country, so we can expect favorable results in near future.

**Current Global Burden of Tuberculosis**

As per global TB report (2019), this is one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent. About a quarter of the world’s population is infected with *Mycobacterium tuberculosis* and thus at risk of developing TB disease. Globally, an estimated 10 million people fell ill with TB in 2018, and there were about 1.5 million death due to this disease. With timely diagnosis and treatment, most people who develop TB can be cured and transmission of infection reduced in the society, thus decreasing mortality and morbidity.

**Current Global Burden of COPD**

COPD is a major public health problem worldwide, due to its high prevalence, morbidity and mortality. Mortality due to COPD is showing an increasing trend. At present it is the third leading cause of death globally. Chronic obstructive disease is a progressive disease, treatment can relieve symptoms and thus, improve quality of life and reduce the risk of death. Air pollution and smoking both active and passive is very important risk factor. Use of conventional fuel is prevalent in our country, this is also an important risk factor. By risk reduction measures we can reduce the burden and socioeconomic consequences. Fortunately, a number of initiatives have been taken in our country, this may have a positive impact and reduce the burden of COPD in our country.

**Tuberculosis and COPD Different Aspects of Association**

**COPD and Tuberculosis Shared Risk Factors**

There are some common risk factors for COPD and Tuberculosis, that is, they share some of the risk factors and these are shown in Figure 1.

**Tuberculosis as the Risk Factor for COPD**

Past history of tuberculosis is well recognized as risk factor for development of COPD, particularly in developing countries. This relationship of TB and COPD is dangerous for our country since the prevalence of both diseases are high in our country. The pathological process due to tuberculosis leads structural changes in the lungs. These structural damage of the lungs increases with increasing number of episodes and they persists despite anti-tubercular chemotherapy.

The structural damage leads to air flow obstruction and impairment of lung function. Impairment in airflow can occur during active phase of tuberculosis or may be detected after the treatment. Patients usually develop maximum loss of lung function within 6 months of diagnosis of tuberculosis and generally stabilize about 18 months after the completion of treatment. Antitubercular treatment leads to improvement in lung function, but the residual lung function impairment depends on both pre- and post-treatment radiological extent of disease. Delay in initiation of treatment lead to more extensive disease and more structural damage leading to more impairment of lung function.

**Mechanism of Airflow Obstruction Due to Tuberculosis**

The sequence of pathological process leading to chronic airflow obstruction in post-tuberculosis patient is not clear, following mechanisms have been proposed:
Role of macrophages: Macrophages are one of the key cells concerned in the pathological process of tuberculosis, these cells play an important role in wound healing and resolution, they may cause remodeling of airways, leading to chronic airflow obstruction.

Small airway involvement: The pathological process undergoing in lungs in tuberculosis may involve the small airways leading to airflow obstruction. The observation of Allwood et al. during their study supports this concept, they observed that patients with chronic airflow obstruction with definite previous TB had higher gas trapping, fibrosis, and emphysema score than subjects with no previous tuberculosis. The diffusion capacity was also significantly lower in patients with definite previous TB.11

Bronchiectasis: Post-tuberculosis bronchiectasis is very common finding and probably most common cause of Bronchiectasis in our country. Endobronchial obstruction or peribronchial fibrosis or obstruction by enlarged lymph nodes found in tuberculosis, may lead to bronchiectasis and chronic airflow obstruction.12

Accelerated parenchymal destruction: Lung parenchymal inflammation occurs in tuberculosis, this leads to destruction of pulmonary extra-cellular matrix (ECM). As described earlier remodeling occurs in the lung due to ongoing pathological and healing process, Matrix metalloproteinases (MMP) are considered to mediate tissue remodeling in tuberculosis. MMPs are a family of calcium dependent zinc containing endopeptidases. There are different kinds of MMPs. Different MMPs plays different role in Mycobacterial infection. MMP-9 is concerned in the formation of stable granuloma, thus containing the infection. Reactivation of latent TB leads to MMP-1 secretion, which causes alveolar destruction and is responsible for cavitation in tuberculosis.13 Type II pneumocyte makes MMP-1.14 MMPs lead to degradation of ECM and thus involved in the pathogenesis of both tuberculosis and COPD, the scaffold of alveolar wall.

The pathological process in tuberculosis leading to chronic airflow obstruction maybe summarized in the Flowchart 1.

Impact of COPD on Tuberculosis

It is well known that patients suffering COPD have increased risk of developing tuberculosis. Lee et al. in his study observed that COPD is an independent risk factor for tuberculosis.15

Exact mechanism or the factors which leads to increased risk is not well known, inhaled and oral corticosteroids are used for the treatment of COPD. Corticosteroids are known to produce immune-suppression; this may increase the risk of tuberculosis.16

Use of corticosteroids is not the only factor responsible for immune impairment in COPD and tuberculosis, but other factors also involved in immune impairment in these cases are:

- Cigarette smoke exposure: According to study conducted by patients Shang et al., the cigarette smoke exposure alters the protective response to M. tuberculosis.17
- High levels of cytokines: High levels of some of cytokines like sIL-2R, IL-6, TNF-alpha, IFN-y are found in COPD patients. These cytokines by producing an exuberant inflammatory response may cause progression of tuberculosis in COPD patients.18
- Dysfunction of alveolar macrophages: In patients suffering from COPD, dysfunction of alveolar macrophages develops, which is considered independent of steroids, this leads to an additional risk of developing tuberculosis.19,20
Conclusion

COPD and tuberculosis are most common respiratory problem in our country. As per different studies conducted, past history of tuberculosis is considered an important risk factor for COPD. Chronic airflow obstruction in tuberculosis patients occurs due to tuberculosis associated lung damage leading to COPD. A number of factors related to COPD may increase the risk of progression of tuberculosis in these patients—use of inhaled and oral corticosteroids in the treatment of COPD, may increases the risk of progression of tuberculosis by causing immune suppression. Other factors are—smoke exposure related altered protective response to M. tuberculosis, high levels of some of the cytokines and dysfunction of alveolar macrophages observed in COPD patients, which is independent of steroids. Thus, above mentioned facts indicates that there is bidirectional relationship between two diseases.

Early diagnosis and timely initiation of standardized and complete of treatment of tuberculosis and COPD is essential. Government of India under ‘National Tuberculosis Elimination’ has increased facility for early diagnosis and proper treatment of tuberculosis, definitely this will have a positive impact. Diagnosis of COPD is based on clinical suspicion, confirmed by respiratory function tests, it is essential to increase general awareness regarding this disease and improvement in facility for diagnosis of COPD. Action to reduce shared risk factors for COPD and tuberculosis is the prerequisite to reduce the burden of both tuberculosis and COPD in our country. These steps may improve the quality of life, morbidity, and mortality due to these diseases.

References

Abstract

The exudative pleural effusion caused either by infections like tuberculosis or due to other diseases like cancer, is associated with a lot of complications and even mortality. The proper history and pleural fluid examination is the first step in differential diagnosis of exudative pleural effusion, but sometimes other investigation techniques like imaging, closed pleural biopsies, and pleuroscopy or video associated thoracoscopy are needed to clinch the diagnosis and proper management.

Introduction

Pleural effusion is a common condition in day to day practice. It develops when more fluid enters the pleural fluid than is removed. The first step in the evaluation of pleural effusion is to determine whether it is exudate or transudate. In cases of exudative effusion the stepwise approach to find out the etiology is needed. Thoracentesis and pleural fluid examination are useful in differential diagnosis of such cases. Other tests like CT scan, Pleuroscopy, etc. may help in reaching an etiological diagnosis.

Pleural effusion may be caused by variety of diseases. Traditionally to simplify the diagnostic approach the pleural effusion is first dichotomized as transudative or exudative. Exudative effusion usually develops due to inflammatory or malignant disorders. The basic pathophysiological mechanism of exudative pleural effusion is increased capillary permeability, which leads to accumulation of large molecular weight compounds in the pleural space.

There are numerous causes of exudative pleural effusion. The most common cause of this in areas where tuberculosis is endemic is secondary to pleural TB. The other common causes are pneumonic, malignancy (primary or secondary) and pulmonary embolus with infarction. The less common causes are—rheumatoid arthritis, other connective tissue diseases, pancreatitis, esophageal rupture, post coronary artery bypass surgery, etc.

Initial Evaluation

The careful history, including the occupational history & history of past illness, symptoms, and signs on physical examination are the first vital measure in guiding the evaluation of pleural effusion.

Pleuritic chest pain, cough, and dyspnea are three basic symptoms of exudative pleural effusion besides other symptoms like fever may be present. Pleuritic chest pain is due to inflammation of parietal pleurae and it likely indicates some infectious cause, while dull aching chest pain is very much suggestive of pleural malignancy. Non-productive cough is also a common symptom. Although the exact mechanism of cough is not clear, but pleural inflammation is again implicated as possible cause.

The third symptom dyspnea is basically due to space occupying process in the thoracic cavity and reappearance
of fluid quickly after therapeutic thoracentesis is most likely due to malignant involvement of pleura.

**Thoracentesis and Examination of Pleural Fluid**

After the initial evaluation, the next step is diagnostic thoracentesis and examination of pleural fluid. It not only settles the issue of transudative versus exudative effusion, but also diagnoses the cause of exudative effusion in most cases.

The usual tests that should be performed on fluid obtained during diagnostic thoracentesis are—cell counts and differentials, glucose, adenosine deaminase (ADA) estimation, and cytologic analysis. The pH measurement and bacterial cultures should be done when acute infection is suspected. The routine pleural fluid tests are summarized in Table 1.

For proper total white blood cell count and differential cell count, it is necessary to send the pleural fluid in anti-coagulated tube. Otherwise the fluid is likely to clot leading to an inaccurate count.³

The main WBC cell type is determined by the mechanism of pleural injury and the time interval between the onset of pleural pathology and thoracentesis. So, the neutrophil-rich fluid is highly suggestive of an acute process like parapneumonic effusion, while lymphocyte predominant fluid profile is indicative of chronic process like tuberculosis or malignancy.

A low pH value of fluid has important therapeutic and prognostic implications with parapneumonic and malignant pleural effusion. Low pH value less than 7.20 in patients with parapneumonic effusion is indicative of drainage of the fluid.⁴

In the unavailability of pH value determination, a pleural fluid glucose concentration of less than 60 mg% helps in detecting complicated parapneumonic effusion.⁴

The enzyme ADA plays a very important role in lymphoid cell differentiation. Pleural fluid ADA level greater than 40 U/L is highly sensitive and specific marker for the diagnosis of tuberculous pleural effusion. The sensitivity varies between 90% and 100%, while specificity is as high as 85% and 95%.⁵

Pleural fluid culture for both aerobic and anaerobic bacteria may identify the culprit microorganism in almost 40% of parapneumonic effusion.²

Pleural fluid smears for mycobacterium are positive very rarely found in about 5% of cases² and about one third of patients with tuberculous pleural effusion have negative tuberculin skin test.⁶

Pleural fluid cytology is very important to diagnose malignant pleural effusion. Cytology positivity is almost 60% in malignant pleural effusion.⁷

The test result negativity are related to different factors such as type of tumor (usually negative in mesothelioma, sarcoma, and lymphoma), the tumor burden in pleural space and the expertise of the person performing the job. An amount of 10 mL of pleural fluid is adequate for cytologic processing. Additional pleural taps increase the diagnostic yield further.

A second thoracentesis may be considered in suspected malignant effusion and the initial pleural fluid cytology examination is negative for malignancy.

---

**TABLE 1** Routine pleural fluid tests for pleural effusion

<table>
<thead>
<tr>
<th>Test</th>
<th>Test value</th>
<th>Suggested diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td>&gt;40 U/L</td>
<td>Tuberculosis (&gt;90%), Empyema (60%), complicated parapneumonic effusion (30%), malignancy (5%), Rheumatoid arthritis²</td>
</tr>
<tr>
<td>Cytology</td>
<td>Atypical cells/Malignant cells</td>
<td>Malignancy (primary or secondary)</td>
</tr>
<tr>
<td>Glucose</td>
<td>&lt;60 mg/dL</td>
<td>Acute infection like parapneumonic effusion, tuberculosis, malignancy, rheumatoid arthritis⁵</td>
</tr>
<tr>
<td>RBC count</td>
<td>&gt;100×10⁶/L</td>
<td>Malignancy, trauma, parapneumonic effusion, pulmonary embolism</td>
</tr>
<tr>
<td>WBC count &amp; differential</td>
<td>10×10⁹/L</td>
<td>Infection, empyema, etc.</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>&gt;50%</td>
<td>Tuberculosis-most likely, malignancy, and post-CABG</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>&gt;50%</td>
<td>Parapneumonic effusion, pulmonary embolism, abdominal diseases</td>
</tr>
</tbody>
</table>
Other Diagnostic Modalities

There are occasions when we need to further investigate the case in order to get a cause of exudative pleural effusion. The further work up includes:

- **Imaging techniques**: High resolution helical CT scan is the investigation that is used as first line modality for delineating pulmonary circulation in patients suspected to have pulmonary embolism. CT can distinguish malignant from benign pleural disease also as it detects nicely pleural nodules or nodular pleural thickening. The detection and differentiation of benign and malignant pleural disease is further enhanced using positron emission tomography scan.8

- **Bronchoscopy**: Endobronchial malignancy may lead to exudative pleural effusion also. Whenever this is suspected in chest radiography or CT scan images, or patient has symptoms of hemoptysis or there is massive pleural effusion or shift of mediastinum to the side of pleural effusion, bronchoscopy is useful.

- **Closed pleural biopsy**: In cases of undiagnosed exudative pleural effusion, percutaneous closed pleural biopsy (CPB) is recommended. Image guided biopsy is superior to blind closed biopsy. The sensitivity of image guided biopsy is much higher than closed biopsy. Histological examination associated with culture of pleural biopsy tissue confirms the diagnosis of tuberculosis in 90% of patients.5

- **Pleuroscopy**: Pleuroscopy, usually referred to as medical thoracoscopy, is gradually gaining importance and now recognized as procedure of choice both for diagnosing and treating exudative pleural effusion, which eludes diagnosis after thoracentesis. It is diagnostic in more than 90% of patients with pleural malignancy where cytology is negative.7 Pleuroscopy offers the additional benefit of effective pleurodesis during the procedure.

**Conclusion**

The careful stepwise approaches starting from proper history taking, evaluation of symptoms & signs, and diagnostic tests help in finding out the exact cause of exudative pleural effusion in majority of cases. Despite the best of efforts, approximately 15% of patients of pleural effusion remain undiagnosed.10

The suggested algorithm for the investigation of exudative pleural effusion is shown in **Flowchart 1**.
References

Abstract
Tubercular lymphadenitis is the most common form of extrapulmonary tuberculosis. The most common lymph node involved is cervical followed by Supraclavicular, Axillary, submandibular and, Inguinal region. Majority of patient presented as isolated chronic nontender lymphadenopathy. The regimen and duration of tuberculosis is same as pulmonary tuberculosis. Treatment is complicated by paradoxical reaction in almost 1/5th of patients, which does not require change in treatment and most of the patient subside by its own.

Introduction
We are living in the second-most populous country after China in the world and one-fourth of the global incident tuberculosis (TB) cases occur in India annually as per the WHO Global TB Report. Extrapulmonary TB (EPTB) is defined as occurrence of TB other than lung is more common in immunocompromised individual with HIV infection. Lymph node TB was found as most common EPTB (37.14%) found in 517 EPTB cases. Cervical lymphadenitis is also known as scrofula. Tubercular lymphadenitis is caused mainly in mycobacterium TB, rarely by nontuberculous mycobacteria (NTM), especially in children or patient who immunocompromised.

Pathogenesis
Tubercular lymphadenitis is considered as local manifestation of systemic disease while lymphadenopathy due to NTM is purely a localized disease. Tubercular bacilli generally enter the body via respiratory tract and undergo hematogenous and lymphatic dissemination. Hilar and mediastinal lymph node are first lymphoid organ involved when spread from lung parenchyma occur. This can occur during primary infection or may occur due reactivation of previous infection. In NTM lymphadenitis, the bacilli enter through oropharyngeal mucosa, salivary glands, tonsil, or conjunctiva.

There are five stages of lymph node TB described by Jones and Campbell:

- **Stage 1:** Enlarged, firm mobile discrete lymph nodes showing non-specific reactive hyperplasia
- **Stage 2:** Large rubbery lymph nodes fixed to surrounding tissue due to periadenitis
- **Stage 3:** Central softening due to abscess formation
- **Stage 4:** Collar stud abscess formation
- **Stage 5:** Sinus tract formation

Clinical Presentation
Most common clinical presentation as slowly enlarging lymph node. Constitutional symptoms like fever, weight loss, anorexia, and fatigue rarely found. We found almost one-fourth of study patients (25.38%) having a symptom for more than 1 year before getting diagnosed as tubercular lymphadenitis before putting on anti-tubercular treatment. Cervical lymph node is the most
commonly involved followed by axillary and inguinal lymph node. Fever has been reported in 20–50% of cases in HIV-negative patients and 60–80% in HIV-positive patients. Our study showed fever, anorexia, and weight loss in 72.30%, 50.76%, and 41.53%, respectively. More than half of study patients (55.38%) received homoeopathic or ayurvedic treatment before putting on anti-tubercular treatment that could be one of the causes of delayed presentation. Physical examination finding depends upon stage of disease. Enlarged lymph node may be firm, discrete mass or matted nodes fixed to surrounding structures; the overlying skin may be indurated. The lymph nodes are usually non tender unless secondary bacterial infection has occurred. Sometimes, lymph node abscess ruptured leading to non-healing sinus formation. The typical TB sinus appears thin, bluish, undermined edges with watery discharge. There is various complication occur especially due to mediastinal TB. These include dysphagia due to pressure on esophagus, esophagomediastinal fistula and tracheoesophageal fistula. Node may cause thoracic duct obstruction presenting as chylothorax, chylous ascites, or chyluria.

We found almost one-fourth of study patients (25.38%) having a symptom for more than 1 year before getting diagnosed as tubercular lymphadenitis before putting on anti-tubercular treatment.

**Differential Diagnosis**

- Hodgkin lymphoma and non-Hodgkin lymphoma
- Reactive lymphadenitis (secondary to bacterial or viral infections)
- NTM infection
- Cat scratch disease
- Fungal infection
- Sarcoidosis
- Kikuchi disease (idiopathic histiocytic necrotizing lymphadenitis)

**Diagnosis**

Diagnosis of tuberculous lymphadenitis is confirmed by histopathology showing caseating granuloma and/or bacteriological evidence in form of smear positive for acid-fast bacilli (AFB), molecular test, or culture positivity. Fine needle aspiration (FNA) is appropriate for initial evaluation of cervical lymphadenopathy to evaluate for tuberculous lymphadenitis. The yield of FNA appears to be highest in the setting of HIV infection and in regions where the prevalence of TB is high. Specimens should be subjected for microscopy, culture, cytology, and polymerase chain reaction/GeneXpert testing. Excisional lymph node biopsy is indicated when FNA is not diagnostic. The finding of caseating granulomas on histopathology is highly suggestive of TB but it is not confirmatory because other disease like sarcoidosis and fungal infection may have granuloma. Multiplicity, matting and causation are three features which help in differentiating TB from other differential. In our study among 130 study patients, 62 (47.69%) were classified as having confirmed TB based on AFB positivity in FNAC sample. The remaining 68 (52.30%) patients had probable TB.

**Treatment**

Treatment options for tubercular lymphadenitis are surgical excision of involved node and/or anti-tubercular treatment. It is generally agreed that anti-tubercular treatment is sufficient for majority of cases and surgical treatment required in selected cases. INDEX TB guideline recommends 6-month therapy with first-line anti-tubercular drug of isoniazid, rifampicin, ethambutol, and pyrazinamide. The studies evaluated 6–9 months regimen and found no difference as far as cure rates (89–94%) or relapse rates (3%) are concern. Anti-tubercular treatment may be complicated by paradoxical reaction or increase in size of primary lymph node and/or appearance of new lymph nodes in up to 20% of patients during or even after cessation of treatment. These nodes may show histopathological features characteristics of TB but sterile on culture. These phenomena are transient and nodes ultimately regress in size. We did a study to identify incidence of paradoxical reaction and residual lymph node at the end of 6 months of treatment. Forty-six (35.38%) patients out of 130 developed paradoxical reaction, and most of this occurred in the first 2 months of the initiation of anti-tubercular treatment. Fifty-eight patients (44.61%) had a residual lymph node of size more than 1 cm after 6 months of treatment. Only 9 patients out of 54 patients had significant reduction in the size of the lymph node with extended 9 months of treatment (Flowcharts 1 and 2). So, presence of residual lymph node at the end of treatment does not require extended duration of treatment rather just close observation required but if there is increase in size of lymph node, send sample for histopathological examination, GeneXpert, and AFB culture.
Lymph node TB is the most common forms of EPTB and is different from pulmonary TB in terms of diagnosis and treatment. Treatment regimen and duration is similar to pulmonary TB, but complicated by paradoxical reaction or residual lymph node at the end of treatment. So, patient might be given multidrug-resistant (MDR) treatment for paradoxical reaction and extended the duration of treatment for residual lymph node. Sample should always be processed for molecular test like GeneXpert and culture in all worsening lymph node with treatment to differentiate paradoxical reaction from drug resistance.

**Conclusion**


**Flowchart 1:** Treatment outcome of standard 6 months and extended 9 months of lymph node tuberculosis patients

**Flowchart 2:** Characteristics of paradoxical reactions (number in bracket showing number of patients)
Abstract
Tuberculosis of stomach is a very rare manifestation of mycobacterium tuberculosis and presents as a diagnostic challenge to physicians. Gastrointestinal tuberculosis is the sixth most common cause of extrapulmonary tuberculosis, and stomach is the sixth most common site of it. It mostly occurs as a part of disseminated tuberculosis or in an immunocompromised state and presents as non-healing gastric ulcer or gastric outlet obstruction. It’s mostly diagnosed after surgical intervention as yield of endoscopic biopsies is low due to submucosal location of granulomas. It’s treated with conventional antitubercular therapy, and surgery is only needed when it presents with complications.

Introduction
Tuberculosis is endemic and a major health problem in India. Gastric tuberculosis is a rare manifestation of gastrointestinal tuberculosis and usually occurs in association with pulmonary tuberculosis or in immunocompromised states. It mostly presents as a diagnostic dilemma and often masquerades as peptic ulcer disease or gastric malignancy.

Epidemiology
Pulmonary tuberculosis accounts for 85% and extrapulmonary tuberculosis accounts for 15% of all cases of tuberculosis in an immunocompetent person. Gastrointestinal tuberculosis is the sixth most common cause of extrapulmonary tuberculosis after lymph node, genitourinary, bone and joints, miliary, and meningeal tuberculosis.1 Tuberculosis can involve any part of gastrointestinal tract but it most commonly involves the ileocecal region followed by ascending colon, jejunum, appendix, duodenum, stomach sigmoid colon, and rectum.2 The incidence of tuberculosis reduces as we move proximally and distally from ileocecal region. Stomach is the sixth most common cause of gastrointestinal tuberculosis and it accounts for 0.5–3% of its all cases.3 The various sites of tuberculosis have been shown in Flowchart 1. It occurs mostly between ages of 15–62 years with a male preponderance.4

Pathogenesis
Gastric tuberculosis usually occurs as a part of disseminated disease or in immunocompromised states. Isolated gastric tuberculosis in immunocompetent person is very rare and only few case reports are published till date. We have published a case of isolated gastric tuberculosis in a healthy female presenting as non-healing gastric ulcer5 (Figs. 1A to C). Stomach as a site for tuberculosis is very rare due to bactericidal properties of gastric acid, absence of lymphoid tissue, and rapid transit of food in stomach due to its continuous motor activity.6 The possible routes of infection in stomach are: direct infection of mucosa due to swallowing of sputum, direct infection from neighboring tubercular lesion, hematogenous spread or...
Flowchart 1: Various sites of tuberculosis in an immunocompetent person

**Pathology**
Gastric tuberculosis can present as an ulcer, hypertrophic mass, or ulcerohypertrophic lesion in the stomach. Most commonly it presents with non-healing gastric ulcer. Hypertrophic lesions mimic gastric carcinoma and present with gastric outlet obstruction. It mostly involves the antrum or prepyloric region in the lesser curvature. The granulomatous lesions can involve the mucosa, submucosa, or serosa but most commonly it involves the submucosa. Granulomas in stomach can be caused by various disorders like tuberculosis, Crohn’s disease, sarcoidosis, fungal and parasitic infection, Whipple’s disease, xanthogranulomatous gastritis, lymphoma, Churg-Strauss syndrome, exposure to beryllium and silicates, but most commonly it is caused by tuberculosis and Crohn’s disease. Granulomas are more common in gastrointestinal tuberculosis compared to Crohn’s disease. Caseation is present in around 40% cases. Granulomas in tuberculosis are more in number, larger in size, and confluent compared to Crohn’s disease.

**Clinical Features**
Clinical presentation of gastric tuberculosis is nonspecific. Its most common symptom is abdominal pain followed by vomiting. Constitutional symptoms of tuberculosis like fatigue, evening rise of temperature, loss of weight and appetite, etc. can also be present in some patients. Due to delay in its diagnosis it can also present with its sequelae like:
- Gastric outlet obstruction, which presents with postprandial vomiting, pain, and distension of abdomen
- Gastrointestinal bleed in the form of hematemesis and melena
- Perforation peritonitis and rarely
- Gastrocolic and gastrobronchial fistula.
Gastric tuberculosis most commonly presents as a case of non-healing gastric ulcer, which is resistant to proton pump inhibitor and negative for helicobacter pylori or as
a case of a gastric outlet obstruction mimicking gastric malignancy but negative in histopathology. In both these clinical scenarios we should be highly suspicious of its diagnosis.

**Diagnosis**

Diagnosis of gastric tuberculosis is difficult and often delayed and it’s mostly diagnosed after surgical intervention. The gold standard for its diagnosis is presence of acid fast bacilli in the histopathology specimen which is very rare.

Upper gastrointestinal endoscopy is the most important initial investigation. It can detect
- solitary or multiple ulcers in prepyloric region in lesser curvature
- ulceroproliferative mass in antrum causing gastric outlet obstruction, or
- submucosal lesion with normal overlying mucosa.

Endoscopic biopsies have a low yield for granuloma as majority of lesions are submucosal in location. So it’s advisable to take multiple deeper biopsies during endoscopy to increase the yield. *Helicobacter pylori* should always be ruled out in tissue biopsy and by doing rapid urease test. Colonoscopy should always be done in suspected cases as ileocecal tuberculosis can coexist with it.

Endoscopic ultrasonography (EUS) is very helpful and should be performed when it presents with submucosal mass or if there are associated adjacent lymph nodes. EUS guided fine needle aspiration cytology (FNAC) and biopsies should be taken from submucosal lesions and lymphnodes as it has a high yield for its diagnosis.

Imaging modalities like ultrasonography (USG) and contrast enhanced computed tomography (CECT) of

**Figs. 1A to C:** Isolated gastric tuberculosis in an immunocompetent female. *(A) Endoscopic image showing large gastric ulcer; (B) Endoscopic biopsy showing granuloma with multinucleate giant cell; (C) Endoscopic image showing healing of ulcer after 2 months of antitubercular treatment.*

abdomen is not much useful in diagnosis as their findings are non-specific. They can show gastric wall thickening, hypodense lesion in antrum, multiple enlarge lymph nodes, peritoneal thickening, ascites, etc. CT or USG guided FNAC from enlarged lymph nodes should be done if they are accessible for making diagnosis. X-ray chest should always be done in any suspected patient as 25% of patients will have coexisting pulmonary tuberculosis. The yield of mycobacterial culture is from 0–69% in gastrointestinal tuberculosis in various studies. Bhargava et al. has suggested to do routine culture of biopsy specimen to increase the diagnostic yield. The sensitivity and specificity of polymerase chain reaction (PCR) in endoscopic biopsies for gastrointestinal tuberculosis is 44% and 95%, respectively. Kim et al. has suggested to do PCR testing as it also helps in ruling out Crohn’s disease. So, in any suspected cases of gastric tuberculosis, culture and PCR testing of biopsy should also be done to increase the yield of diagnosis.

Tuberculin test is non-specific test and is not done routinely for its diagnosis. There is no specific biochemical or hematological test for it.

Treatment

Treatment of gastric tuberculosis is conventional 6 months antitubercular therapy (ATT) with initial 2 months of intensive therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol followed by 4 months of continuation phase with isoniazid and rifampicin. Few guidelines recommend longer duration of treatment of 1 year for it. For uncomplicated cases ATT alone is sufficient for its treatment. Asia Pacific Association of Gastroenterology and Indian Society of Gastroenterology consensus on Crohn’s disease have suggested a trial of ATT in cases where there is doubt in diagnosis. Empirical ATT should always be given in any granulomatous lesion of stomach without a definitive diagnosis.

Surgery or endoscopic therapy is needed if it presents with complications.
- Surgery in the form of distal gastrectomy or primary closure is the main stay of treatment if it presents with perforation peritonitis.
- Gastric outlet obstruction secondary to tuberculosis can be dealt with endoscopic or surgical intervention. Endoscopic balloon dilatation followed by starting of antitubercular therapy should be the preferred initial treatment for it. For unresponsive cases surgery in the form of gastric resection with gastrojejunal anastomosis is usually done.
- Patient presenting with gastrointestinal bleedings should be initially managed with endoscopic hemostatic procedures like adrenaline spray, adrenaline injection, hemoclipping, etc. Non-responsive cases are treated surgically with partial gastrectomy.

Conclusion

Tuberculosis can involve any part of gut even in immuno-competent person. Gastric tuberculosis though rare should be kept as one of the differential diagnosis in any case of chronic infiltrative lesion of stomach like non-healing ulcers and gastric outlet obstruction. The yield of endoscopic biopsies is low for granuloma due to submucosal location of the lesion so deeper and repeated biopsies are advisable for making early diagnosis and avoiding surgical interventions. If diagnosed early, it responds very well to standard ATT.

References


