Chapter 5:
Treatment of Pulmonary Tuberculosis
What Every GP Should Know

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Suspicion

- High incidence of TB in India
- Every GP in India must have a high index of suspicion for the disease in all patients with cough for more than two weeks
  - And in all patients with chest x-ray abnormalities.

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If TB Is Suspected...

• Important to order sputum tests that can microbiologically confirm TB
  – Smear microscopy
  – Cultures
  – GeneXpert (Molecular tests)

• These tests are all endorsed by the World Health Organization (WHO) and available at more affordable prices in the private sector, via the IPAQT initiative ([www.ipaqt.org](http://www.ipaqt.org))
  – 75 accredited private labs across India.

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Blood Tests are NOT reliable for Pulmonary TB

• Pulmonary TB cannot be reliably detected by any blood test

• Sputum is the most important sample to collect

• Chest x-rays helpful, but they are not specific for TB
  – Must be followed by microbiological tests

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Key Steps

• Once TB is diagnosed, there are several key steps to ensure that patients have good outcomes
Key Steps

• Assessment for multi drug-resistant TB (MDR-TB) risk factors
• Selection of correct first-line drug regimen, duration and dosage
• Ensuring treatment adherence
• Monitoring treatment success
• Management of adverse events
• Notification of TB cases
• Referral of patients with suspected MDR-TB

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The Effective Treatment of TB has 3 aims

1. The rapid reduction of bacillary load to ensure clinical improvement and to arrest transmission

   - This is achieved through the use of potent bactericidal drugs such as isoniazid and rifampicin

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The Effective Treatment of TB has 3 aims

- 2. The prevention of the emergence of drug resistant strains.
  - The emergence of such strains is dependent on bacillary load and spontaneous mutations occurring in multiplying bacilli within the lungs
  - The concurrent use of multiple anti-tuberculous drugs is aimed at suppressing the growth of such mutants, and is an important component of an adequate regimen for treatment

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The Effective Treatment of TB has 3 aims

• 3. Prevention of relapse
  – This is achieved through prolonged treatment, especially with a regimen that includes rifampicin, and monitoring of adherence to ensure elimination of any residual, persistent organisms, which are known to be responsible for relapse

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Standards for Care

- Two important standards for TB care were released in March 2014:
  - 3rd edition of the International Standards for TB Care (ISTC)
  - 1st edition of Standards for TB Care in India (STCI)
- These standards establish the best practices for TB diagnosis, treatment and follow-up
  - Must be followed by all practitioners

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Assessment for MDR-TB Risk Factors

• Before TB treatment is started, practitioners must assess the patient for MDR-TB risk
According to the ISTC...

• An assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance (if known), should be undertaken for all patients.

• Drug susceptibility testing should be performed at the start of therapy for all patients at a risk of drug resistance.

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According to the ISTC...

- Patients who remain sputum smear-positive at completion of 3 months of treatment, patients in whom treatment has failed, and patients who have been lost to follow-up, or relapsed following one or more courses of treatment should always be assessed for drug resistance
According to the ISTC...

• For patients in whom drug resistance is considered to be likely an Xpert MTB/RIF (GeneXpert) test should be the initial diagnostic test

• If rifampicin resistance is detected, liquid culture and testing for susceptibility to isoniazid, fluoroquinolones and second-line injectable drugs should be performed promptly

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Selection of Correct First Line Drug Regimen

• In India, several studies have shown widespread use of incorrect and irrational TB drug prescriptions, especially in the private sector

• Incorrect prescriptions can lead to emergence of drug-resistance and result in poor patient outcomes

• This underscores the importance of clinician education and adherence to standards
WHO-approved first-line treatment regimen

• According to the ISTC, all patients who have not been treated previously and do not have other risk factors for drug resistance should receive a WHO-approved first-line treatment regimen using quality assured drugs

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Initial Phase

- The **Initial phase** should consist of two months of isoniazid, rifampicin, pyrazinamide and ethambutol
Continuation Phase

- The **Continuation phase** should consist of isoniazid and rifampicin given for 4 months
- The doses of anti-tuberculosis drugs used should conform to WHO recommendations
- Fixed dose combination drugs may provide a more convenient form of drug administration
- The STCI recommends that the continuation phase should consist of three drugs (isoniazid, rifampicin and ethambutol) given for at least four months
  - This is because of the high levels of isoniazid resistance in India

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• Evidence suggests that both daily and thrice-weekly intermittent drug regimens are acceptable for first-line TB therapy, provided mechanisms are put in place to ensure adherence

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• Intermittent drug therapy makes it easier to implement directly observed therapy (DOT), while daily treatment provides a great margin of safety

• Dosages of drugs must be based on body weight and acceptable ranges are shown in Table 1 (based on ISTC)

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Drugs Dosages

Table 1 – Doses of first-line antituberculosis drugs in adults and children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended dose in mg/kg body weight (range)</th>
<th>Three times weekly regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily regimen</td>
<td>Range</td>
</tr>
<tr>
<td>Isoniazid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>10</td>
<td>(7-15),</td>
</tr>
<tr>
<td>Adults</td>
<td>5</td>
<td>(4-6),</td>
</tr>
<tr>
<td>Rifampicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>15</td>
<td>(10-20),</td>
</tr>
<tr>
<td>Adults</td>
<td>10</td>
<td>(8-12),</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>35</td>
<td>(30-40),</td>
</tr>
<tr>
<td>Adults</td>
<td>25</td>
<td>(20-30),</td>
</tr>
<tr>
<td>Ethambutol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>20</td>
<td>(15-25),</td>
</tr>
<tr>
<td>Adults</td>
<td>15</td>
<td>(15-20),</td>
</tr>
</tbody>
</table>

Source: ISTC, 3rd edition (reference 6)
Fixed Dose Drug Combinations (FDC)

• Where possible, according to STCI and ISTC, fixed dose drug combinations (FDC) should be used
  – They reduce the number of pills taken daily
  – Increase patient convenience
  – Reduce the potential for medication errors

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Duration

• With respect to duration of therapy, 6 months is the standard for first-line therapy.
• The STCI recommends that the duration of the continuation phase can be extended by 3 – 6 months in special situations like bone and joint TB, spinal TB, and central nervous system involvement.

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Ensuring Treatment Adherence

• Since drug-sensitive TB requires at least 6 months of continuous therapy, ensuring adherence is a big challenge.

• Providing support for, and making every effort to ensure adherence should be considered to be part of the prescription for the treatment of TB.

• Important to develop an approach that is tailored to each patient and one that involves an agreement between the GP and the patient.
• Every TB patient should receive counseling at the start of TB treatment
• They should be informed that they have a curable disease called TB, and that completion of the entire 6 month course is critically important to prevent poor outcomes

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• Patients should also be informed about likely adverse drug events, and they should get a clear plan on when to come back for follow-up visits

• Mobile phone reminders may help with improving adherence and follow-up visits

• Patients also need to be advised about diet, return to work, smoking and alcohol cessation, and may need to be screened for co-morbid conditions like diabetes and HIV

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• Doctors can also work with local community-based and non-governmental organizations, and enlist community health workers as ‘treatment supporters’ to supervise and support the patient with treatment completion.

• To ensure treatment adherence, it is also important that doctors maintain some written record on what treatment was started, when, dosages, adverse reactions, results of follow-up lab tests, etc.

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Monitoring Treatment Success

• Weight of the patient should ideally be monitored on a monthly basis, and drug dosages adjusted to reflect the change in weight.

• The STCI recommendation states that
  – ‘Response to therapy in patients with pulmonary tuberculosis, new as well as retreatment cases, should be monitored by follow-up sputum microscopy (one specimen) at the time of completion of the intensive phase of treatment and at the end of treatment.’

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Management of Adverse Effects

• Drug-induced hepatitis is the most common major adverse reaction associated with ATT
• Severe nausea, jaundice or confusion should make the physician suspect the possibility of hepatitis
• Advancing age and pre-existing liver disease are known risk factors, and special monitoring and care needs to be exercised in these groups of patients

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Hepatitis

• All TB drugs should be stopped when hepatitis is suspected
• The monitoring of the drug-induced hepatitis, and re-introduction of drugs is beyond the scope of this article and can be found elsewhere

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Management of Adverse Effects

• Any reported visual impairment should warrant the stopping of ethambutol
• Severe skin rashes may have to be treated by stopping all drugs and re-introducing them one at a time under observation, to identify the offending agent
• Common minor side effects include nausea and anorexia
  – Can be minimized by taking the medications with small meals or just before bedtime

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Management of Adverse Effects

• Joint pains caused by pyrazinamide can be treated with non-steroidal anti-inflammatory drugs
• Pyridoxine supplements may be used to alleviate the mild tingling and numbness in the hands and feet that may be caused by isoniazid

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Notifications of TB Cases

• As per Government of India order and STCl recommendations:
  – “All health establishments must report all TB cases and their treatment outcomes to public health authorities (District Nodal Officer for Notification)”

• By notifying all TB cases to the local health authorities, private practitioners can seek help from the RNTCP to help follow-up patients who default

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Referral of Patients with Suspected MDR-TB

• All patients with risk factors for drug-resistance (e.g. patients with a history of previous TB treatment) must be investigated for MDR-TB using drug-susceptibility testing

• Since MDR-TB requires long-term and specialized management, patients should be referred to chest specialists
  – Either in the private sector, or in the public sector where free treatment is available under the programmatic management of drug-resistant TB

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Critical Role

• In conclusion, GPs have a critical role to play in the control of TB at a community level
  – Especially in India, where a majority of TB patients seek care in the private sector

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Ensuring the Best Standards

• Ensuring the best standards of TB treatment comprises:
  – The prescription of the right drugs in the right regimens
  – Monitoring patients for signs of response to treatment and signs of adverse reactions to medications
  – Supporting the patient in maintaining adherence to treatment

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References

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