DRUG RESISTANT TUBERCULOSIS IN CHILDREN

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Nearly one-third of the global population is infected with mycobacterium tuberculosis and is at risk of developing the disease. More than eight million people develop active tuberculosis (TB) every year and about two million die (1). More than 90% of TB cases and deaths occur in the developing world. Co-infection with human immunodeficiency virus (HIV) significantly increases the risk of developing TB (2). At the same time, multidrug resistance, which is caused by poorly managed TB treatment, is a growing problem of serious concern in many countries around the world (3).

Children are usually infected with TB by an adult or an older child with sputum smear-positive pulmonary TB (PTB), often a family member. Less commonly, they may be infected by contact with smear-negative (often culture positive) cases. They may also be infected with mycobacterium bovis by drinking untreated milk from infected cows. The commonest type of TB in children is extrapulmonary TB (EPTB) and commonly includes TB lymphadenopathy, TB meningitis, TB effusions and spinal TB with ratio of PTB:EPTB being 1:3. PTB in children is usually smear-negative. Children with TB can present at any age, but most common age is between 1-4 years of age (4). Children are susceptible to drug-resistant as well as drug-sensitive TB. Drug resistant TB is a laboratory diagnosis. However, drug resistant TB should be suspected if any of the features below are present (5).

1. Features in the source case suggestive of drug-resistant TB:
   • Contact with a known case of drug-resistant TB
   • Remains sputum smear positive after 3 months of treatment
   • History of previously treated TB
   • History of treatment interruption

2. Features of a child suspected of having drug-resistant TB:
   • Contact with a known case of drug-resistant TB
   • Not responding to the anti-TB treatment regimen
   • Recurrence of TB after adherence of treatment.

Causes of drug resistant (DR) – TB
The causes are as follows:-
1. Inappropriate guidelines or non compliance with guidelines for management of TB
2. No monitoring of treatment
3. Poor quality of drugs or poor storage of drugs
4. Wrong dose or combination
5. Unavailability of certain drugs
6. Poor adherence to treatment
7. Adverse effects of drugs leading to poor intake of medicines.

Drug resistance is strongly associated with previous treatment and probability is over 10 fold higher than for untreated patients \(^6\).

**Magnitude of drug resistance**: China and India carry approximately 50% of global DR-TB with the Russian Federation a further 7%. It is estimated that 489139 cases of drug resistant TB have emerged in 2006 globally \(^7\) and nearly half a million cases emerge every year.

**History of drug resistance**: Strains resistant to streptomycin were first reported in 1940s and by mid 1990s, most countries reported resistance to isoniazid and rifampicin. In 2006, extensively drug resistant TB (XDR-TB) emerged with resistance to first and second line drugs which is a serious emerging threat to global health.

**Types of drug resistant TB**
- Mono-resistance: resistance to one antituberculosis drug
- Poly-resistance: resistance to more than one antituberculosis drug, other than both isoniazid and rifampicin.
- Multi-drug resistance (MDR): Resistance to at least isoniazid and rifampicin.
- Extensive drug resistance (XDR): Resistance to any fluoroquinolone and at least one of three injectable second line drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance \(^7\).

**Classes of antituberculosis drugs**: Antituberculosis drugs are traditionally divided into first and second line drugs. The first line drugs are
- **(Group 1 agents)**:
  - Isoniazid (H)
  - Rifampicin (R)
  - Pyrazinamide (Z)
  - Ethambutol (E)

The second line drugs include
- **(Group 2 agents): Injectable agents**
  - Streptomycin (S)
  - Kanamycin (Km)
  - Amikacin (Am)
  - Capreomycin (Cm)

- **Group 3 agents**: Fluoroquinolones
  - Moxifloxacin (Mfx)
  - Levofoxacin (Lfx)
  - Ofloxacin (Ofx)
**Group 4 agents**: Oral bacteriostatic second line agents
- Ethionamide (Eto)
- Protionamide (Pto)
- Cycloserine (Cs)
- Terizidone (Trd)
- P-aminosalicylic acid (PAS)

**Group 5 agents**: Agents with unclear efficacy
- Clofazimine (Cfz)
- Linezolid (Lzd)
- Amoxicillin/Clavulanate (Amx/Clv)
- Thioacetazone (Thz)
- Imipenem/Cilastalin (Ipm/Cln)
- High-dose isoniazid (high-dose H) [defined as 16-20 mg/kg/day]
- Clarithromycin (Clr).

**Group 1 drugs**: They are the most potent and best tolerated and should be used if there is good laboratory evidence and clinical history to suggest that a drug from this group is effective. However rifampicin has high cross-resistance to newer generation rifamycins such as rifabutin and should not be used if there is resistance to rifampicin.

**Group 2 drugs**: All patients with MDR-TB should receive a Group 2 injectable agent if susceptibility is documented. Kanamycin or Amikacin should be the first choice, given the high rates of streptomycin resistance. Also both these agents are economical and have less ototoxicity than streptomycin. Amikacin and Kanamycin have cross-resistance and if an isolate is resistant to both Streptomycin and Kanamycin, then Capreomycin should be used.

**Group 3 drugs**: All patients with MDR-TB should receive a Group 3 agent if the sensitivity report suggests susceptibility to quinolones. Ciprofloxacin is no longer recommended to treat TB. Currently the most potent fluoroquinolones in descending orders are: moxifloxacin = gatifloxacin > levofloxacin > ofloxacin. Ofloxacin is commonly used for low cost. Gatifloxacin is associated with serious cases of hypoglycemia, hyperglycemia and new onset diabetes and thus is not commonly used. Also long term safety of moxifloxacin is not established. Thus levofloxacin remains an effective quinolone.

**Group 4 drugs**: Group 4 agents are used to treat MDR & XDR-TB based on susceptibility pattern, efficacy, cost and side effects. Ethionamide or Protionamide is often added because of low cost; however they have cross-resistance with isoniazid. If cost is not an issue, PAS can be given as it has no cross-resistance to other drugs. However combination of ethionamide or protonamide and PAS often causes gastrointestinal side effects and hypothyroidism and this combination should only be used if more than two Group 4 drugs are needed. As a second drug, cycloserine is often used in combination with either PAS or ethionamide/protonamide. Group 4 drugs should be started at low dose and then escalated over two weeks to avoid early adverse effects.
**How to identify drug resistance TB**

On suspicion of drug resistance TB, drug susceptibility testing (DST) should be done on the infected material ideally for both first and second line antituberculous drugs. In children with active TB who are contacts of patients with DR-TB, they can be started on treatment according to the regimen and sensitivity pattern in the source contact. For initial screening, rapid DST methods should be used as far as possible. If DST is not possible for all drugs, one can do DST for rifampicin (Rifampicin is the most potent anti TB drug and rifampicin resistance most commonly occurs with concomitant isoniazid resistance). Thus rifampicin resistance is a strong indicator that a patient may have MDR-TB\(^{(13,14)}\). As per the DST report, the treatment regimen has to be devised.

Different techniques are available for DST. Phenotypic testing is routinely done and involves culturing M. tuberculosis in the presence of antituberculosis drugs to detect inhibition of growth. This allows detection of drug resistance regardless of mechanism or molecular basis\(^{(15)}\). Genotypic testing detects specific mutations that lead to resistance and involves polymerase chain reaction (PCR).

**Devising a treatment regimen for MDR-TB**

The following basic steps are necessary when dealing with drug resistant TB:

- Regimen should be devised based on previous drug history, prevalence of resistance pattern in the area and drug susceptibility report.
- Regimen should consist of at least 4 drugs with good effectiveness.
- When possible pyrazinamide, ethambutol and fluoroquinolones should be given once per day as high peaks attained with once a day dosing are more efficacious.
- PAS, cycloserine, thionamide/protonamide should be given in split doses to avoid adverse effects.
- An injectable drug (aminoglycoside or capreomycin) should be used for a minimum of six months and at least 4 months past negative culture report.
- Minimum length of treatment is 18 months after culture becomes negative.

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Thus MDR-TB treatment would consist of
Use any first line drug (P or E) based on sensitivity
+
Injectable Agent (Avoid Streptomycin)
+
Fluoroquinolones. (In case of XDR-TB, use higher generation of fluoroquinolone)
And/or
Group 4 agent (one or more)
↓
To add to at least 4 efficacious drugs for the treatment regimen.
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**Special situations:** In case of central nervous system (CNS) drug resistant TB, drugs with good CNS penetration such as rifampicin, isoniazid, pyrazinamide, protonamide/ethionamide and cycloserine should be considered. Aminoglycosides and capreomycin penetrate CNS only in presence of meningeal inflammation. Higher generation fluoroquinolones also have good penetration of CNS. PAS and ethambutol do not cross the blood brain barrier.
Devising a treatment regimen for XDR-TB

The following basic steps are:

- Use any Group 1 agent that may be effective.
- Use an efficacious injectable agent for 12 months or for entire treatment regimen.
- Use a higher generation fluoroquinolone such as moxifloxacin.
- Use all 3 Group 4 agents that are effective.
- Use 2 or more agents from Group 5.
- Consider high dose isoniazid if low level resistance is found.
- Consider surgery for localized disease.

Table 1: Suggested regimens for mono & polydrug resistance (11)

<table>
<thead>
<tr>
<th>Pattern of drug resistance</th>
<th>Suggested regimen</th>
<th>Min. duration of treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>H (± S)</td>
<td>RZE</td>
<td>6-9 mths</td>
<td>For extensive disease, add fluoroquinolone</td>
</tr>
<tr>
<td>H and Z</td>
<td>RE and fluoroquinolone</td>
<td>9-12</td>
<td></td>
</tr>
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<td>RZ and fluoroquinolone</td>
<td>9-12</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>HE, quinolone + 2 mths of Z</td>
<td>12-18</td>
<td>An injectable agent may be used additionally for extensive disease</td>
</tr>
<tr>
<td>R and E (± S)</td>
<td>HZ, quinolone + Injection for first 2-3 mths</td>
<td>18</td>
<td>Injectable agent may be given for 6 mths for extensive disease</td>
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<td>18</td>
<td>Injectable agent may be given for 6 mths for extensive disease</td>
</tr>
<tr>
<td>H, E, Z (± S)</td>
<td>R, fluoroquinolone ± oral second line ± Inj for first 2-3 mths</td>
<td>18</td>
<td>Injectable agent may be given for 6 mths for extensive disease</td>
</tr>
</tbody>
</table>

Drug resistance in pregnancy: Since majority of teratogenic effects occur in first trimester, therapy may be delayed till second trimester and injectable agents and ethionamide should be avoided in view of fetal adverse effects.

Drug Resistance and breast feeding: When resources and training are available breast feeding should be avoided. However, breast feeding may be continued with mother receiving full antituberculous treatment as most drugs are found in breast milk in fraction of the therapeutic dose.

Table 2: Dosage of all second line antituberculosis drugs (7, 12)
HIV and DR-TB: Treatment of DR-TB in patients with HIV is very similar to that in patients without HIV. However, ART should be started early as mortality in these patients is high. Drug interactions are a common problem. Didanosine retards absorption of fluoroquinolone and should be given 2 hours after fluoroquinolone administration. Clarithromycin has multiple drug interactions with protease inhibitors and NNRTIs and should be avoided.

Monitoring patients on treatment for drug resistance TB

Smears and cultures from TB affected organ should be performed monthly till smear and culture become negative after which one can do smears monthly and cultures quarterly. However in children and in those patients with extrapulmonary TB it may not be possible to get material for smear and culture frequently in which case, treatment response may be monitored clinically and by other radiological or blood investigations.

Patients on Cycloserine should receive pyridoxine to prevent neurological adverse effects. Common adverse effects commonly seen are rashes, gastrointestinal symptoms, jaundice, ototoxicity, peripheral neuropathy and palpitations or muscle cramping due to electrolyte toxicity. Nephrotoxicity is a known complication of injectable agents and serum creatinine and electrolytes should be monitored monthly. Hypothyroidism is a problem caused by PAS and ethionamide and patients should be screened for thyroid stimulating hormone (TSH) every 6 monthly. Patients receiving pyrazinamide should undergo 1-3 monthly testing of liver enzymes. Patients exhibiting adverse effects can either have a lower dose of the drug or the drug may have to be replaced.

Outcome: A patient with drug resistant TB is said to be cured if the treatment has been completed according to the protocol and has at least 3 consecutive negative cultures in the final 12 months of treatment. In children it may not be possible to get the cultures done regularly in which one may consider successful treatment completion on basis of clinical, laboratory improvement and completes treatment as per protocol. Treatment may be considered to be failed if any one of the 3 final cultures is positive or there is poor clinical or radiological response. In such patients, a new regimen is started and surgery may be considered. Adding one or two drugs to a failing regimen should be avoided.
**Conclusion:** Both MDR & XDR TB is on the rise. Treatment outcomes are guarded as mortality is high in these patients. Timely diagnosis, adequate laboratory services to identify drug resistance, availability of second line antituberculous drugs and devising ideal regimen for treatment is essential for good outcome.

**References:**