Module 6

MDR-TB IN CHILDREN
MDR TB disease in children: epidemiology

• Very limited data available

• The burden of MDR TB in children is likely to reflect that which occurs in adults, so.....

• MDR TB is common in children in settings where MDR TB is common

• MDR TB is increasing in children in settings where overall MDR TB is increasing
India, China, Russia, Pakistan and Ukraine have 60% of all MDR-TB cases

Proportion of MDR among new TB cases
Latest available data, 2013

Figures are based on the most recent year for which data have been reported, which varies among countries.
Insert some national MDR TB prevalence data
MDR TB disease in children: epidemiology

- MDR TB in children will mainly be from transmission of drug-resistant TB to the child, rather than acquired from prior exposure to TB treatment.

- Early diagnosis and effective treatment of MDR TB cases (usually adults) is the most effective tool available to reduce transmission.

- Children with MDR TB are not major contributors to the spread of MDR TB in the community.

- MDR TB in children is associated with increased morbidity and mortality compared to drug-sensitive disease.
1. Careful history
   - includes history of TB contact
   - symptoms suggestive of TB

2. Clinical examination
   - includes growth assessment

3. Tuberculin skin test

4. Bacteriological confirmation whenever possible

5. Investigations relevant for suspected PTB or suspected EPTB

6. HIV testing
Approach to diagnose MDR TB in children

- **Careful history**
  - History of contact with MDR TB case is critical information
  - Consider in child failing first-line TB treatment despite adherence
- **Clinical examination**
- **Investigations relevant for suspected PTB or EPTB**
  - Important to try to get samples for culture and DST
- **HIV testing**
  - Failure to respond to TB treatment should consider HIV-related lung disease that is not TB as well as the possibility of MDR TB
- **Bacteriological confirmation and drug susceptibility testing whenever possible**
  - Sputum (or other relevant samples e.g. lymph node aspiration) should be collected in all children with suspected MDR TB for culture with drug sensitivity testing (or LPA or Xpert MTB/RIF)
Poor response to TB treatment in HIV-infected child should consider possibility of other HIV-related lung disease as well as possibility of DR TB

<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent pneumonia</td>
<td>Recurrent episodes of cough, fever and fast breathing that usually respond to antibiotics</td>
</tr>
</tbody>
</table>
| LIP                          | Unusual before 1 year of age  
Associated with generalised symmetrical lymphadenopathy, clubbing, parotid enlargement.  
Nutritional status variable.  
CXR: diffuse reticulonodular pattern and bilateral perihilar adenopathy. No compression of airways |
| Drug resistant tuberculosis   | Persistent symptoms not responding to first-line TB treatment (usually by 2 months) despite good adherence.  
History of contact with known or suspected DR TB case.                                                                                       |
| Bronchiectasis               | Cough productive or purulent sputum; clubbing  
CXR: honeycombing usually of lower lobes  
Complicates recurrent bacterial pneumonia, LIP or TB                                                                                         |
| PcP                          | Common cause of severe, fatal pneumonia especially in infants.  
Persistent hypoxia is common  
Unusual after 1 year of age  
CXR: diffuse interstitial infiltration or hyperinflation                                                                                   |
| Mixed infection              | Common problem: LIP, bacterial pneumonia, TB  
Consider when poor response to first-line empiric management                                                                                   |
| Kaposi sarcoma               | Uncommon  
Characteristic lesions on skin or palate                                                                                                      |
Confirmed DR TB is a laboratory diagnosis: culture with DST or nucleic acid amplification test (e.g. Xpert MTB/RIF)

Probable DR TB is diagnosed in a child with TB and a recent close contact with DR TB

Suspected DR TB is when a child fails to improve while adherent to first-line anti-TB treatment OR if the adult source case is a treatment failure, a retreatment case or recently died from TB
Children with suspected MDR TB should ideally be referred to a facility that can do culture and drug susceptibility testing - usually a tertiary facility.

**Hospitalisation** is usually required for treatment because it includes injectables.

Follow-up and **management of adverse events** should ideally be managed by experienced paediatrician at tertiary level.
All children with suspected MDR TB should be referred

Never add a single drug to a failing regimen

Treat according to DST results from child or from likely source case (if results from child not available)

Give at least 3 drugs, preferably 4, to which patient or adult source case is susceptible

All treatment daily and under direct observation

Caregivers need counselling and support regarding adverse effects, treatment duration and adherence

Careful monitoring for clinical response and adverse events
1. Choice of treatment will be influenced by availability of DST in child or contact, and drug resistance surveillance in a particular setting
2. Minimum of 4 active drugs if extensive pulmonary or disseminated disease
3. Start with first-line drugs to which DST results show susceptibility (e.g. ethambutol, PZA)
4. Add an injectable (e.g. amikacin)
5. Add fluoroquinolone (e.g. levofloxacin or moxifloxacin)
6. Duration 18 months – limited evidence
7. Hospitalisation for 4-6 months for injectable
8. DOT by health worker
Drugs used for treatment of MDR TB in children

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Drug name</th>
<th>Daily dosage in mg/kg</th>
<th>Maximum dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: Oral first-line drugs</td>
<td>Ethambutol</td>
<td>20-25</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>30-40</td>
<td>2000</td>
</tr>
<tr>
<td>Group 2: Injectable agents. Aminoglycosides</td>
<td>Streptomycin (1st-line)</td>
<td>15-20</td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td>Amikacin</td>
<td>15-20</td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td>Kanamycin</td>
<td>15-20</td>
<td>1000</td>
</tr>
<tr>
<td>Cyclic polypeptide</td>
<td>Capreomycin</td>
<td>15-20</td>
<td>1000</td>
</tr>
<tr>
<td>Group 3: Fluoroquinolones</td>
<td>Ofloxacin</td>
<td>15-20</td>
<td>800</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin</td>
<td>7.5-10</td>
<td>750</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>7.5-10</td>
<td>400</td>
</tr>
<tr>
<td>Group 4: Second-line oral drugs</td>
<td>Ethionamide (or prothionamide)</td>
<td>15-20</td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td>Cycloserine (or terizidone)</td>
<td>10-20</td>
<td>1000</td>
</tr>
<tr>
<td>*Para-aminosalisylic acid (PAS; 4gr sachets)</td>
<td></td>
<td>150</td>
<td>12g</td>
</tr>
<tr>
<td>Group 5: Drugs of uncertain value</td>
<td>High-dose INH</td>
<td>15-20</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>10-12 twice daily</td>
<td>300 once/twice daily</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin/clavulanate</td>
<td>15 amoxicillin 3 x daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>7.5-15 twice daily</td>
<td>500 twice daily</td>
</tr>
<tr>
<td></td>
<td>Thioacetazone</td>
<td>3-4</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td>Imipenem/cilastatin</td>
<td>(only IV)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clofazimine</td>
<td>3-5</td>
<td>300</td>
</tr>
</tbody>
</table>

a. DST could be unreliable – use as additional drug if DST result susceptible or not done²⁵
b. Choose one drug in each of these groups; amikacin preferred to kanamycin in children
c. Choose one or more of these drugs to make up total of 4 new drugs
d. Consider use of these drugs if insufficient drugs to build an acceptable regimen with previous groups. Each drug only considered as half a drug, therefore 2 drugs in this group counts as one additional drug.
e. PAS is administered in acidic base (e.g. yoghurt or orange juice) for improved absorption
f. Linezolid dosage for TB is uncertain, but lower doses (300mg twice daily or even 300mg daily in adults) cause less adverse effects and still seem effective.³³
g. Thioacetazone should NOT be used in HIV-infected patients

Adapt a table depending on availability of drugs in your setting

## Adverse effects of drugs used for treatment of MDR and XDR TB in children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse effects</th>
<th>How to monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Hepatotoxicity, Rash, Peripheral neuropathy (rare), Psychosis</td>
<td>Jaundice, liver enzymes, Clinical observation for other adverse effects</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Hepatotoxicity, Arthralgia, Rash</td>
<td>Jaundice, liver enzymes, Clinical observation for other adverse effects</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Optic neuritis (rare)</td>
<td>Vision screening if possible</td>
</tr>
<tr>
<td>Second-line injectable drugs</td>
<td>Ototoxicity (starts with high frequency hearing loss and may continue after stopping culprit drug), Nephrotoxicity (Renal failure and severe hypokalaemia)</td>
<td>Hearing test (audiology)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Gastro-intestinal disturbance</td>
<td>Serum creatinine and potassium levels</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Insomnia, Arthralgia</td>
<td>Clinical observation and caregivers’ report</td>
</tr>
<tr>
<td>Capreomycin</td>
<td></td>
<td>Serum uric acid if used with pyrazinamide</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Gastro-intestinal disturbance</td>
<td>Clinical observation</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Insomnia</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Arthralgia</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Gastro-intestinal disturbance (nausea, vomiting, abdominal pain and anorexia)</td>
<td>Jaundice – serum alanine transferase and billirubin</td>
</tr>
<tr>
<td>Thioamides</td>
<td></td>
<td>Thyroid stimulating hormone and free T4 levels</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Hepatotoxicity</td>
<td>Clinical observation</td>
</tr>
<tr>
<td>Prothionamide</td>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Psychosis, convulsions, paraesthesia, depression</td>
<td></td>
</tr>
<tr>
<td>Terizidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Para-aminosalisylic acid (PAS)</td>
<td>Gastro-intestinal disturbance (mainly diarrhoea), Hypothyroidism</td>
<td>Clinical observation</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Myelosuppression</td>
<td>Thyroid stimulating hormone levels and free T4</td>
</tr>
<tr>
<td></td>
<td>Lactic acidosis</td>
<td>Full blood counts</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td>Serum lactate level</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis</td>
<td>Clinical observation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapt a table depending on availability of drugs in your setting

Diagnostic algorithm approach to suspected or confirmed DR TB in children

New child TB case

Confirmed DR-TB

DST known

No

Contact with infectious TB case?

Yes

Drug-resistant source case

Confirmed or Probable DR-TB

Treat as DR-TB according to DST result of child or source’s isolate
Do culture & DST if DR not confirmed

Suspected DR-TB

Do culture/DST on child & source’s specimens. Treat as DS-TB
Close follow-up essential

Check DST results
Check response to treatment
If DST shows DR or if failing adherent therapy, treat as DR-TB

Yes or No

Source case DST not done & child failing 1st-line treatment or source retreatment or chronic TB case

Confirmed DS-TB

No source case known or DST not done, no risk factor Drug-susceptible source case

Probable or Confirmed DS-TB

Do culture/DST on child’s specimens if DS not confirmed mainly if poor response to treatment

Check DST results

All children with suspected MDR TB should be tested for HIV

HIV-infected children are at high risk of severe disease and death due to DR TB

ART markedly improves outcome for MDR (and XDR) TB with no increase in adverse events - should be started early in treatment

Drug interactions are usually not a problem as regimens usually do not contain rifampicin

Patients should also receive pyridoxine and cotrimoxazole preventive therapy

Careful monitoring for clinical response and adverse events
Management of child contact of DR TB case

Identification and **symptomatic screening of all contacts** of DR TB cases is important

Symptomatic contacts require evaluation for possible TB

Investigation of symptomatic contacts should include sputum for culture and drug sensitivity (or LPA or Xpert MTB/RIF)

Asymptomatic contacts need to be followed and informed that prompt evaluation is required should symptoms develop
Management of child contact of DR TB case

There is very little evidence and no agreed consensus on the use of or optimal regimen for preventive therapy for asymptomatic contacts of drug resistant TB cases.

One approach is not to provide any preventive therapy and opt for careful, regular follow-up informing the contact about possible symptoms of TB and that prompt evaluation is needed if symptoms develop.

An alternative approach, especially for high-risk contacts such as HIV-infected or young children, is to choose a preventive therapy regimen that includes at least two drugs to which the DR TB index case is susceptible or naïve and treat for at least 6 months.
Management of Multidrug-Resistant Tuberculosis in Children: A Field Guide
A history of contact with a suspected or proven drug resistant TB case is critical in evaluation and management of child with suspected DR TB or an asymptomatic child contact.

Children with suspected DR TB should be referred if possible to specialist for investigation (culture and sensitivity), management (hospitalisation for injectables) and monitoring for toxicity to second-line drugs.

HIV test is routine in evaluation of suspected DR TB and early ART improves outcome.

Decisions regarding preventive therapy for at risk child contacts will be informed by drug sensitivity pattern of the index case.