Tuberculosis for primary care pediatricians

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National Vice President Indian Academy Of Pediatrics 2011
TB IN CHILDREN - WORLD STATISTICS-2014

• Among the top ten causes of death globally
• 9 million new cases and 1.5 million deaths in 2013
• 0.55 million cases & 80000 TB deaths among children
• India & China account for 26% & 12% of total cases respectively.

WHO Global TB report 2014
Infants: 43%
Toddlers (1-5 years): 24%
Adolescents (11-15 years): 15%
Adults: 5-10%

Latent tuberculosis infection (90%)

Primary disease (10%)
If the immune system CANNOT keep tubercle bacilli under control, bacilli begin to multiply rapidly and cause TB disease.
SPECTRUM OF TUBERCULOSIS

Pulmonary Tuberculosis

Extrapulmonary tuberculosis

Lymph node tuberculosis
TB Effusions (pleural, pericardial, peritoneal)
Gastrointestinal tuberculosis
CNS tuberculosis
Skeletal tuberculosis
Genitourinary tuberculosis
Cutaneous tuberculosis
Congenital tuberculosis
Constitutional Symptoms

- Persistent fever
- Night sweats
- Weight loss/no weight gain
- Malaise
- Tiredness
- Loss of appetite
CLINICAL FEATURES

Pulmonary TB

- Fever and/or cough lasting >2 wks.
- Recurrent symptoms with normal intervening period - less likely to be TB.
- Cough can be dry or wet.
  - Chest pain
  - Dyspnoea
  - Haemoptysis
  - Wheezing
  - Respiratory distress
Lymph node tuberculosis

• Slowly enlarging lymph nodes in cervical, axillary, inguinal area
• Size >2 x 2cm
• Lymph nodes may be of varying sizes discrete or matted
• Firm or cystic in consistency usually non tender
• Abscess may burst open leading to chronic non healing sinus and ulcer
TB CERVICAL LYMPHADENITIS

Most common form of extra-thoracic TB
Abdominal tuberculosis spectrum

Abdominal tuberculosis

- Gastrointestinal
- Nodal
- Peritoneal (27-40%)
  - Ascitic
  - Dry
- Visceral

Small bowel
Large bowel
ABDOMINAL TUBERCULOSIS: CLINICAL PRESENTATION

• Abdominal pain most common symptom
• Colicky or cramp like character
• Some patients may have diarrhoea alternating with constipation
• Malabsorption is also common
• Ascites
• Other symptoms include anorexia, nausea, vomiting, melena
ASCITES
CNS TUBERCULOSIS SPECTRUM

- T.B Meningitis
- Space occupying lesions (Tuberculoma)
- Tubercular encephalopathy
- Vasculopathy
- Spinal TB
- Compressive myelopathy (Pott’s spine, tuberculoma, abscess)
- Arachnoiditis, meningitis
CNS TUBERCULOSIS: CLINICAL PRESENTATION

- Tuberculous meningitis presents with history of irritability, apathy, anorexia and behavioural changes.
- Fever, headache, vomiting, features of raised intracranial pressure, focal neurological deficit, convulsions.
SPINE TB

SITES – Affected in decreasing order:
Spine most common (thoracic > lumber > cervical) 50-60%
Multiple vertebral involvement with skip lesions may be seen (70-80%)

• Constitutional symptoms present
• Cold abscess-neck, chest wall, groin, inguinal areas and thighs
• Gibbus or kyphosis
• Paraplegia
DIAGNOSIS OF TUBERCULOSIS

- H/O Contact
- Clinical Evidence
- Bacteriological Tests—Smear, Culture (LJ Medium, Bactec, MB/BacT)
- Radiological Examination
- Immunodiagnosis
- Molecular diagnosis
BACTERIOLOGICAL TESTS
Sample Collection

• 2 sputum samples sufficient (WHO)
• Hypertonic saline induced sputum
• Gastric Aspirate/NPA/BAL
• Efforts to be made to obtain specimen from any body cavity in which the organism may reside like: whole blood, bone marrow (in miliary disease), FNAC (lymph node), biopsy specimen (lymph node, bone), CSF, pleural fluid, ascitic fluid, first morning urine.
SMEAR MICROSCOPY

1. Ziehl Nielsen: mainstay in detection of M.TB
2. Conventional Fluorescence microscopy:
   • 10% more sensitive with same specificity
   • Less time consuming
TB MICROSCOPY-PITFALLS

- Difficult to obtain sputum samples from children
- Insensitive technique: detects only $10^4$ AFBs/ml
- Less than 20% of children with proven TB will have a sputum or gastric aspirate sample positive on ZN staining, compared to 75% in adults
- It cannot differentiate between live and dead mycobacteria & between M. tuberculosis & other mycobacteria
CULTURE

• Gold standard for M. Tb detection
• LJ Medium: Most widely used but may take 4-6 wks.
• BACTEC: Improves yield & takes 9-14 days
• MGIT: less than 8 days
• Septi-Check AFB system (3 wks): More sensitive as shown in adults
• Microscopic Observation Drug Susceptibility (MODS): utilizes Middlebrook 7H9 broth culture & is more sensitive than LJ media
TB CULTURE METHODS-PITFALLS

- Sensitivity is low ranging from 30 to 50%.
- LJ medium: results available after 8-12 weeks and drug susceptibility testing are not reliable.
- High cost of equipment, inability to observe colony morphology and risk of overgrowth of contaminants are limitations of newer culture techniques such as BACTEC, Septicheck AFB system.
• “Special features for HIV-infected TB patients included lower detection by SM and culture. New microbiological assays, such as the automated liquid culture system, showed increased accuracy and speed of detection”.

  *Dr. R. Dayal  Plos One -2012*
CHEST X-RAY

• Chest X-ray: no pathognomonic radiological signs of TB.
• Pulmonary infiltrates with hilar lymphadenopathy, pleural effusion, cavitatory lesion, miliary lesions may be seen.
• Non-resolving chest shadows despite adequate antibiotic therapy in symptomatic child is significant.
• A study by Soumya et al,( Indian Pediatrics, Vol 45, 2008) showed that only 50% of the bact/histopath proven PTB cases had positive X-ray findings.
• Lateral view also advisable.
Progressive Primary Disease
PRIMARY PROGRESSIVE TB :
PARENCHYMAL DISEASE WITH PNEUMATOCELE
PITFALLS: CHEST X RAY

- Problems in interpretation are i) exposure in expiration ii) excessive lordosis iii) rotation of thorax iv) faulty exposure.

- In children < 3 years a normal thymus may deceptively broaden the mediastinum / mimic right upper lobe consolidation.

- Persistent lung shadow often investigated / treated as koch’s.

USG

Pulmonary TB
- Persistent/unusual opacities, pleural abnormalities and mediastinal widening.
- Follow up in pleural effusion/empyema.
- Guided interventions e.g. empyema drainage & mediastinal lymph node sampling.

Abdominal TB
Mesentric thickness of 15mm or more, ascites, mesentric lymphadenopathy (>10mm along short axis), dilated & matted bowel loops, granuloma & abscesses in liver and spleen.
HRCT

• Detect lymph nodes undetected on CXR.
• More sensitive than CXR for miliary TB and small cavitation.
• Can differentiate old fibrotic lesions from active TB lesions.
• Detect earlier stages (thickening of caecum & terminal ileum) of abdominal TB

Limitation

Very high radiation exposure
CECT scan in tuberculous meningitis demonstrating marked enhancement in the basal cistern and meninges, with dilatation of the ventricles.

CECT in a child with TBM showing hydrocephalus with periventricular ooze and meningeal enhancement.
MRI

- MRI is superior to CT for detection of basal meningeal enhancement, small tuberculomas, infarcts of basal ganglia.
- MRI spectroscopy helps in differentiating tuberculoma (lipid peak) from other lesions.
- Highly sensitive in osteoarticular tuberculosis for detecting marrow infiltration & assessment of extradural disease, spinal disease.
IMMUNODIAGNOSIS OF TB

• Mantoux test (Tuberculin skin test)
• Interferon Gamma Release Assays
• Serology
• CD4:CD8 ratio
• BCG Test – No longer recommended
TUBERCULIN TEST

• 1-5 TU PPD-RT 23 used. Cut off value of 10mm.
• Correct method of administration & reading- raise a wheal of about 6mm, read within 48-72hrs, max. 7 days.
• False negative: viral infections, PEM, lymphoreticular malignancies, immunosuppressive drugs, improper storage and dilution of vaccines, faulty administration and faulty reading.
• False positive: s/c admin and booster effect on repeat tuberculin testing in the same place, MOTT infections.
PITFALLS: MANTOUX TEST

- Test becomes positive in 3 to 6 weeks of acquiring the infection (rarely after 3 months)
- Technique important for the end result
- BCG vaccinated children - TST +ve in most of them
- Distinction between the infected & diseased?
AAP RECOMMENDATIONS FOR TST & IGRA

Children who should have annual TST/IGRA
• those infected with HIV
• Incarcerated adolescents

Who should have immediate TST/IGRA
• Contacts of patients with confirmed/suspected TB
• Immigrants from endemic countries
• With radiographic/clinical features suggesting TB
Positive TST Results: AAP

- **Induration ≥ 5mm**
  
a) Children in close contact with person with known / suspected TB
b) Findings on chest X ray consistent with active / previous TB
c) Clinical evidence of tuberculosis
d) Immunocompromised state
Positive TST Results: Contd...

- **Induration ≥ 10 mm**
  a) Children younger than 4 yrs
  b) Those with other medical conditions
  c) Those born in high prevalence regions of the world
  d) Who travel to endemic regions of the world

- **Induration ≥ 15 mm**
  Children ≥ 4 yrs of age without any risk factors

*American Academy of Pediatrics: Red Book; 2009: 684*
QUANTIFERON TB GOLD IN TUBE

- Detects IFN-gamma in blood in response to antigens such as ESAT-6 & CFP10

- **Advantages**: More specific than PPD, no boosting effect, unaffected by previous BCG vaccine & exposure to atypical bacteria, better in HIV and malnourished children

- **Limitations**: Sample to be processed within 12 hours of collection, can’t differentiate b/w latent or active tuberculosis, sharing of antigens with Non Tuberculous Mycobacteria (M. kansas, M. szulgai and M. marinum)
Comparison of diagnostic methods *(Dayal: Ind Pediatrics, 2012)*

<table>
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<th>Specificity %</th>
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Comparison of QFT GOLD In Tube with other tests for Pulmonary & Extra Pul Tuberculosis

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SUMMARY

• QFT sensitivity = 51.2% ; specificity = 48.0%. Latent infection responsible for low specificity.
• QFT-G may be negative in patients with more advanced disease and malnutrition due to diminished immune response.
• Children showing positive results with both ELISA & QFT-G in tube should be considered for follow up.
• Further studies recommended.
• “QFT-GIT and TST have similar accuracy for active-PTB diagnosis. Moreover, in HIV-infected patients, a combination of smear microscopy with both immunological tests significantly increases the sensitivity for active disease diagnosis compared to smear microscopy alone”.

Dr. R. Dayal, Plos One - 2013
WHO recommendation for IGRAs (2014)

- Interferon-gamma release assays (IGRAs) should not replace the tuberculin skin test (TST) in low and middle-income countries for the diagnosis of latent TB infection in children or for the diagnostic work-up of children (irrespective of HIV status) suspected of TB disease in these settings.
Diagnosis by serology in T.B

• Sensitivity of ELISA(PGLTb1) is 49.2% & specificity 96.3% which was comparable with PCR-IS6110 (40% and 100%)

  Dayal et al, J Trop Pediatr 2006)

• Sensitivity & specificity of ELISA (ESAT 6) was 53% & 100% respectively which was comparable with PCR (IS-6110)

  (Dayal et al J Trop Pediatr 2006)

• Sensitivity and specificity of ELISA(Ag 85) was 59.1% and 71.9% that was higher then conventional culture methods.

WHO recommendations for serological tests (2014)

- Commercial serodiagnostics should not be used in children suspected of active pulmonary or extrapulmonary TB, irrespective of their HIV status.
ADA Test

• Simple and inexpensive.
• Activity is increased in diseases where there is a cell mediated immune response.
• False +ve: bacterial infections, rheumatologic d/s, lymphoproliferative d/s.
• Determination of ADA isoenzymes (ADA-2) helps in differentiation of TB from other causes.
• The sensitivity & specificity of ADA:
  **CSF**: 62.5-73% & 71-92% (Cut of value 5-10 IU/L)
  **Body fluids (pleural, pericardial & ascitic)**: 81% & 75% (cut of value 38 IU/L)
MOLECULAR METHODS TO DIAGNOSE TUBERCULOSIS
POLYMERASE CHAIN REACTION

• Various types – Conventional PCR, Real time PCR, PCR- Restriction Fragment Length Polymorphism, DNA strip assays etc.

• 3 common basic steps - Sample preparation, Amplification and Detection.

• Automated Nucleic Acid Amplification Tests: very sensitive & detect as few as 10 bacilli/ml.

• PCR based on target sequences of MPB64, 16sRNA, TRC4, 38kD, IS6110 has been found to be sensitive & specific.
LINE PROBE ASSAY

• Screening test for rapid detection of MDR-TB & resistance to Rifampicin and/or Isoniazid.

• Meta-analyses to evaluate assay performance results against conventional DST methods showed:
  
  (sensitivity $\geq$ 97%, specificity $\geq$ 99%) for the detection of rifampicin resistance,

  (sensitivity $\geq$ 90%; specificity $\geq$ 99%), resistance to rifampicin in combination with isoniazid

  “on smear-positive sputum specimens”
Line Probe Assay

Disadvantages:

• Not a complete replacement for conventional culture and DST (Drug Susceptibility Testing) - culture is still required for smear-negative specimens

• Conventional Drug Susceptibility Testing is still necessary to confirm XDR-TB

WHO. Policy statement on Molecular Line Probe Assays for rapid screening of patients at risk of MDR-TB. June 2008; 1-9
**Xpert MTB/RIF**

- Use of Nucleic Acid Amplification Technique (NAAT)
- Hemi-nested real time PCR based
- Screening test for diagnosis of M. tuberculosis and rifampicin resistance
- Rapid results – 1 hr 45 min
- Sensitivity for diagnosis among culture positive cases- 92.2% to 97.6%
- Sensitivity for diagnosis among culture negative cases- 72.5% to 85.1%
- Sensitivity and specificity in detecting Rifampicin resistance- 99.1% and 100% respectively
WHO recommendations for Gene Xpert test (2014)

• Xpert MTB/RIF **should be used** rather than conventional microscopy and culture as the initial diagnostic test in children suspected of having MDR TB, HIV-associated TB and TB meningitis.

• Xpert MTB/RIF **may be used** as initial test in suspected TB cases.

• Xpert MTB/RIF **may be used** as a replacement test for testing of non-respiratory specimens from extrapulmonary TB cases.
WHO recommendation for HIV testing (2014)

- Routine HIV testing should be offered to all patients with presumptive and diagnosed TB.
- In settings of high HIV prevalence, all household and close contacts of people with TB should be counselled and tested for HIV.
- In settings of low HIV prevalence, all household and close contacts of people with TB who have symptoms compatible with TB disease may be offered counselling and testing for HIV.
Diagnostic algorithm for Paediatric Pulmonary Tuberculosis
Persisten Fever and/or Cough >2 weeks AND/OR Loss of weight/No weight gain¹ AND/OR History of contact with infectious TB case

Sputum Examination

Sputum Smear positive

- Smear positive Pulmonary TB
- Treat according to Guidelines

Sputum Smear Negative/Sputum not available for examination

Child has:
1. Already received a complete course of appropriate antibiotics OR
2. Sick look, OR
3. Severe respiratory distress, OR
4. Any other reason for X-Ray chest OR

Yes

X-Ray chest (XRC) & Tuberculin Skin test (TST)

XRC - Suggestive of TB² AND TST positive³

Smear positive

- GL/IS/BAL⁴
- Smear negative

Smear negative Pulmonary TB
- Treat According to Guidelines

Either or Both Negative

Follow Flowchart 2

A 7-day course using antibiotic which has no anti-TB activity e.g. Amoxicillin. (Do not use quinolones).

No

¹ History of unexplained weight loss or no weight gain in past 3 months; Loss of weight defined as loss of more than 5% body weight as compared to highest weight recorded in last 3 months.
² Radiological changes highly suggestive of TB are Hilar/paratracheal lymphadenitis with or without parenchymal lesion, miliary TB, fibro-cavitary pneumonia.
³ If the radiological picture is highly suggestive of TB, then proceed to do further investigations irrespective of the TST result as the sensitivity of the test is not 100%.
⁴ All efforts including Gastric Lavage (GL)/Induced sputum (IS) or Bronchoalveolar lavage (BAL) should be made to look for Acid fast bacilli (AFB) depending upon the facilities.
All efforts including Gastric lavage (GL)/Induced sputum (IS) or Bronchoalveolar lavage (BAL) should be made to look for Acid fast bacilli (AFB) or for Mtb rapid culture or GeneXpert® wherever facilities are available.
Further investigations in Pediatric pulmonary TB suspect who has persistent symptoms and does not have highly suggestive chest x-ray.

- X-ray normal, TST negative:
  - Review for an alternative diagnosis.

- X-ray nonspecific shadows, TST positive/negative:
  - Repeat chest x-ray after a course of antibiotic (if not already received).
    - X-ray persistent nonspecific shadows, TST positive/negative:
      - GL, IS, BAL.
        - Smear positive:
          - Smear positive Pulmonary TB. Treat according to guidelines.
        - Smear negative:
          - Look for alternative diagnosis.
          - If no alternative diagnosis found – treat as smear negative Pulmonary TB.
      - Alternate diagnosis established:
        - Yes: Give specific therapy.
        - No: Review for alternate diagnosis.

- X-ray normal, TST positive:
  - Review for alternate diagnosis.

- Gl, IS, BAL:
  - Smear positive:
  - Smear negative:
    - Look for extra-pulmonary site TB.
    - If no then:
      - Seek expert help.
      - CT chest & other investigations may be needed.
Diagnostic algorithm for diagnosis of Lymph Node Tuberculosis

1. Enlarged lymph node - Matted, cold abscess with or without a discharging sinus
2. Lymph node enlargement of > 2 cm in one or more sites
   - Prescribe a course of antibiotics for 7 days (Do not use Quinolones).
   - Review after 2 weeks
   - In case of non-response, suspect TB as the cause for lymphadenitis

   * Smear examination for AFB by ZN Staining of the pus from discharging sinus / aspirate from lymph node
   * Aspirate for fine needle aspiration for cytology (FNAC), where facilities exist.

   - Diagnosis confirmed if the pus / aspirate from FNAC show: (i) ZN stain +ve for AFB, and/ or (ii) granulomatous changes

3. If no granulomatous changes and no AFB, consider alternative diagnosis;
   - Go for lymph node biopsy.
   - Isolated Mantoux test positivity without suggestive findings on FNAC should not be treated with ATT

Treat as Case
The following dosages of anti-TB medicines should be used daily for the treatment of TB in children:

- Isoniazid (H) 10 mg/kg (range 7–15 mg/kg); maximum dose 300 mg/day
- Rifampicin (R) 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day
- Pyrazinamide (Z) 35 mg/kg (range 30–40 mg/kg)
- Ethambutol (E) 20 mg/kg (range 15–25 mg/kg)
WHO recommendations for treatment of pulmonary and extrapulmonary T.B.(2014)

Pulmonary TB or tuberculous lymphadenitis children living in settings:

• with low prevalence of HIV & low INH resistance and who are HIV-negative can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months.
Treatment Continued....

- with extensive pulmonary disease living in areas with high HIV prevalence +/- high isoniazid resistance should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months.
Treatment Continued....

• During the continuation phase of treatment, thrice-weekly regimens can be considered for children known not to be HIV-infected and living in settings with well-established directly-observed therapy (DOT)

• Streptomycin should not be used as part of first-line treatment regimens for children with pulmonary TB or tuberculous peripheral lymphadenitis.
• Children with suspected or confirmed tuberculous meningitis and osteoarticular TB should be treated with:
  (HRZE) for 2 months, followed by
  (HR) for 10 months,
  total duration of 12 months.
CASE DEFINITIONS

- **New case**: who have never been treated for TB or have taken anti-TB drugs for less than 1 month.

- **Relapse**: patients previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB.

- **Cured**: A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.

- **Treatment failed**: A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
PREVENTION

Close contact: A person who is not in the household but who shared an enclosed space, such as a social gathering place, workplace, or facility, with the index case for extended daytime periods during the 3 months before the start of the current treatment episode.
WHO recommendation for BCG vaccination (2014)

• In settings where TB is highly endemic or where there is high risk of exposure to TB, a single dose of BCG vaccine should be given to all infants.

• In children who are known to be HIV-infected, BCG vaccine should not be given.

• In infants whose HIV status is unknown and who are born to HIV-positive mothers and who lack symptoms suggestive of HIV, BCG vaccine should be given after considering local factors.
WHO recommendations for contact tracing (2014)

Clinical evaluation of household and close contacts for active T.B should be done for contacts who are:

- children with symptoms suggestive of TB,
- children <5 years of age,
- immunocompromised patients (especially those living with HIV), and
- child contacts of index cases with MDR-TB or XDR-TB (proven or suspected)
• Children <5 years of age who are household or close contacts of people with TB and who, after an appropriate evaluation, are found not to have TB disease should be given 6 months of IPT (10 mg/kg per day, range 7-15mg/kg, maximum dose 300 mg/day)
WHAT IS MDR TB?

• Confirmed MDR-TB case: An MDR-TB suspect who is sputum culture positive and whose TB is due to M.TB that are resistant in-vitro to at least isoniazid and rifampicin with or without resistance to other anti-tubercular drugs based on DST results.
Probable MDR TB

Children with signs and symptoms of active TB diseases who in addition have the following risk factors should be considered as having “probable” MDR-TB and started on MDR-TB treatment even in the absence of bacteriological confirmation:

1) Close contact with MDR-TB;

2) Close contact with a person who died while on TB treatment;

3) Close contact with a person who failed TB treatment;

4) Failure of a first-line regimen, recognizing that both bacteriologic and clinical definitions of failure should be used (see RNTCP guidelines);

5) Previous treatment with second-line medications
MDR TB Prevalence: Global scenario

• Globally, 5% of TB cases were estimated to have had MDR-TB in 2013 (3.5% of new and 20.5% of previously treated TB cases)

• In 2013, there were an estimated 480,000 new cases of MDR-TB worldwide, and approximately 210,000 deaths from MDR-TB.

• Among patients with pulmonary TB who were notified in 2013, an estimated 300,000 had MDR-TB.

• More than half of these patients were in India, China and the Russian Federation.

WHO Global TB report 2014
Drug-resistant TB should be suspected when:

- there is contact with known DR-TB;
- there is contact with suspected DR-TB, i.e. source case is a treatment failure or a retreatment case or recently died from TB;
- a child with TB is not responding to first-line therapy despite adherence;
- a child previously treated for TB presents with recurrence of disease.
DIAGNOSIS OF MDR-TB

DR-TB

- Clinical: Least reliable
- Radiological: Less reliable
- Mol. Bio.: Very Good
- Bacteriological C/S: Gold Standard
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

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

Suspected DR-TB

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

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

Check DST results
MANAGEMENT

Management principles:

• Never add a single drug to a failing regimen; this may lead to amplification of resistance.

• All treatment should be given daily and under direct observation.

• Treat the child according to the DST results from the likely source case, unless M. *TB culture and DST results are available from the child.*
• Do second-line DST in all MDR-TB cases to exclude resistance to the fluoroquinolones and/or second-line injectables.
• Give at least three or preferably four drugs to which the patient or adult source case is naive or their isolates susceptible.
• Assessment of the child should be undertaken as a minimum:
  - symptom assessment;
  - assessment of treatment adherence;
  - enquiry about any adverse events; and
  - weight measurement.
• Clinical, radiographic and culture response to treatment should be monitored
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<th>Group Name</th>
<th>Drugs</th>
<th>Dosage* (mg/kg)</th>
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<td>Injectable agents</td>
<td>Kanamycin</td>
<td>15–30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amikacin</td>
<td>15–22.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Capreomycin</td>
<td>15–30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Streptomycin</td>
<td>15–20</td>
</tr>
<tr>
<td>3</td>
<td>Fluoroquinolones</td>
<td>Ofloxacin</td>
<td>15–20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ciprofloxacin</td>
<td>20 twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Levofloxacin</td>
<td>7.5–10†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moxifloxacin</td>
<td>7.5–10</td>
</tr>
<tr>
<td>4</td>
<td>Oral bacteriostatic second-line</td>
<td>Ethionamide</td>
<td>15–20</td>
</tr>
<tr>
<td></td>
<td>agents</td>
<td>Prothionamide</td>
<td>15–20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cycloserine</td>
<td>15–20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Terizidone</td>
<td>15–20</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Para</em>-aminosalicylic acid</td>
<td>150</td>
</tr>
<tr>
<td>5</td>
<td>Agents with unclear efficacy</td>
<td>Clofazimine</td>
<td>3–5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linezolid</td>
<td>10†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amoxicillin-clavulanic acid</td>
<td>10–15 (amoxicillin component) three times a day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imipenem/cilastatin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thiacetazone</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High dose isoniazid</td>
<td>15–20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clarithromycin</td>
<td>7.5–15 twice daily</td>
</tr>
</tbody>
</table>
1) Use any Group 1 first-line oral drugs that have certain, or almost certain, susceptibility in DST. These drugs should be administered for the duration of therapy.

2) Add one Group 2 injectable agent based on DST results and treatment history. This agent is normally given for a minimum of 6 months and for 4 months after culture conversion. Preferably, it should be an aminoglycoside such as amikacin. Do not use streptomycin (unless other Group 2 drugs are unavailable) – high rates of resistance with DR-TB strains and higher incidence of ototoxicity.

3) Add one Group 3 fluoroquinolone based on DST results and treatment history, for the duration of therapy. Levofloxacin and moxifloxacin are preferred to ofloxacin ciprofloxacin is not recommended.
4) **Group 4 second-line oral drugs** should be added for the **duration of therapy**, until there are at least four drugs in the regimen to which the isolate is likely to be susceptible.

5) If a regimen of four effective drugs cannot be built from Groups 1-4, consider adding at least two **Group 5 third-line** drugs. **DST** is not standardized for Group 5 drugs.
Treatment duration depends on the extent of the disease; in most cases the intensive phase will last at least 8 months and total duration of treatment will be at least 10 months.

All treatment should be given daily and under direct observation.
Conclusions

- The conventional methods of diagnosis are still extremely important.
- Always attempt to demonstrate Mycobact. TB.
- Imaging has great value in diagnosis & monitoring of disease.
- IGRA have limited value in endemic countries.
- Gene Xpert preferred over microscopy & culture when available.
- Commercial serodiagnostics not recommended.
- Look out for MDR–TB: it’s on the rise!!