Recognizing MDR-TB in Children

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Objectives

- Review the definitions and categorization of drug-resistant tuberculosis
- Understand the emergence of drug resistance
- Know the global and local MDR TB situation
- Learn how to recognize and diagnose MDR TB
Definitions

**MDR TB:** TB isolate that is resistant to both isoniazid and rifampin

**XDR TB:** MDR + resistance to fluoroquinolone and 1 of the 3 injectable drugs (amikacin, kanamycin, capreomycin)
Definitions

• **Primary drug resistance:**
  – Infected with TB which is already drug resistant
  – New case

• **Secondary (acquired) drug resistance:**
  – Drug resistance develops during treatment
  – Retreatment case – relapse, lost to follow up, treatment failure
The Universe of TB

- **All TB**
  - **TB with any drug resistance**
  - **MDR TB***
    - with drug resistance to at least the first-line drugs isoniazid and rifampin
  - **XDR TB****
    - with drug resistance to the first-line drugs isoniazid and rifampin and to specific second-line drugs

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* Often resistant to additional drugs
** Resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin)
Spontaneous mutations develop as bacilli proliferate to $>10^8$

<table>
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<th>Drug</th>
<th>Mutation Rate</th>
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<td>Pyrazinamide</td>
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Drug-resistant mutants in large bacterial population

Multidrug therapy: No bacteria resistant to all 3 drugs

INH
RIF
PZA

Monotherapy: INH-resistant bacteria proliferate

INH
INH resistant bacteria multiply to large numbers

Spontaneous mutations develop as bacilli proliferate to $>10^8$

INH mono-resist. mutants killed, RIF-resist. mutants proliferate $\rightarrow$ MDR TB
DR TB can occur when drugs are misused or mismanaged

- Patients do not complete the full course of treatment
- Health care providers prescribe the wrong treatment, the wrong dose, or wrong length of time for taking the drugs
- Drug supply is not always available
- Drugs are of poor quality
Drug-Resistance Among TB Cases

- About 3.6% of new tuberculosis (TB) patients in the world have multidrug-resistant strains.

- Levels are much higher – about 20% - in those previously treated for TB.

- About 10% of MDR-TB cases are also resistant to the two most important second-line drug classes, or XDR-TB.
High risk of infection in children who are contacts of MDR-TB patients

- In 119 South African children less than 5 years of age who had contact with an adult with MDR-TB in the prior 30 months:
  - 12% had active TB
  - 51% had latent infection (TST+)
  - 37% had no evidence of infection

Household contacts of MDR-TB patients almost always have MDR-TB

- A Peru study looked at 4503 household contacts of 693 MDR-TB and XDR-TB index patients:
  - 117 (2.6%) had active TB at the time the index patient began MDR-TB treatment;
  - 242 contacts developed TB during 4-year follow-up;
  - Of the 359 cases of active TB, 142 had DST, of whom 129 (91%) had MDR-TB.

Global TB situation in 2014

- 9.6 million people fell ill with TB and 1.5 million died from the disease.
- An estimated 1 million children became ill with TB and 140,000 children died of TB.
- An estimated 480,000 people developed multidrug-resistant TB (MDR-TB).
- The TB death rate dropped 47% between 1990 and 2015.
TB situation in children

- In 2014, 359,000 new and relapse cases among children were reported, an increase of about 30% compared with 2013.
- The largest increases were in India (about 30,000) and the Philippines (about 10,000).
MDR TB in the Philippines
National Drug Resistance Survey Data

- **2004 DRS**
  - 4% among new cases
  - 21% among re-treatment cases

- **2012 DRS**
  - 2% among new cases
  - 21% among re-treatment cases
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## National DR TB Prevalence Data

(DOH-NTP: Dr. Celine Garfin and Ms. Donna Gaviola)

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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)
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.

When DR-TB is suspected, every effort should be made to confirm the diagnosis by obtaining specimens for culture and DST.

Rapid DST of iNH and RIF or of RIF alone is recommended over conventional testing or no testing at the time of diagnosis.
Criteria for Suspected MDR-TB

- History of previous treatment within the past 6-12 months
- Close contact with a person known to have MDR-TB, including household and school contacts
- Close contact with a person who has died from TB, failed TB treatment, or is non-adherent to TB treatment
- Failure to improve clinically after 2-3 months of first-line TB treatment, including persistence of positive smears or cultures, persistence of symptoms, and failure to gain weight (radiological improvement is frequently delayed)

No

Continue evaluation for susceptible TB

Yes

Clinical assessment and MDR-TB diagnostic work-up including sputum, rapid tests, fluid sampling, biopsy
Results of diagnostic workup available

Yes

MDR-TB confirmed
Treatment based on DST

DS-TB confirmed
First-line TB treatment

No diagnosis confirmed

Clinically stable without concerning signs or symptoms
Await diagnosis and monitor closely

Clinically unstable with concerning signs and symptoms present (temp.>40, hypoxia, respiratory distress, hemoptysis, severe anorexia, indicators of meningeal or disseminated TB)
Consider empiric MDR-TB therapy while awaiting diagnosis
Case scenarios
Case scenario 1

S> A 7-year-old boy is brought to the OPD

- “lumps” in neck and “coughing all the time”
- Father died of TB last year, even though he took his medications every day

O> P.E. - Cachectic, febrile 39°C, HR 137, multiple cervical LN, cool to touch, round and rubbery

- chest retractions, minimal expansion of the right hemithorax, right side of chest is dull to percussion, and no breath sounds

A> critically ill, MDR TB considered

P> emergency thoracentesis with removal of 600 cc of straw-colored fluid; sputum sample sent for smear, culture, and rapid DST.; regimen for MDR TB started
Case scenario 1

- 2 days later: Xpert MTB/RIF test showed Rifampicin resistance to RIF (RR)
- Final culture results: resistance to INH, RIF, EMB, and SM

- After 2 years: because he was started on treatment quickly, patient fully recovered and remains an active, playful 9-year-old (having completed 2 years of treatment when he was seven) at the top of his class in school.
Case scenario 2

- An 11-yo girl being treated for TB (cough, fever, weight loss, hemoptysis)
- (+) AFB smear, was started on HRZE and received DOT at a LHC, compliant
- 1st mo: smear (-), feeling “better”, cough and fever resolved
- 2nd mo: recurrence of cough, night sweats, smear(-)
- 3rd mo: symptoms worsened, daily fevers, smear showed “rare AFB,” (was felt to be a “contamination” when a repeat smear was negative)
- Continued on HR with good compliance
Case scenario 2

- She now presents to the OPD after having coughed “two cups” of blood. She also notes a 6 kg weight loss, daily fevers, severe cough, and shortness of breath.
- P.E
  - ill-appearing, cachectic, and tachycardic, diffuse crackles and wheezes all fields.
  - sputum is streaked with blood
  - smear shows AFB
- A repeat history is taken, no history of contacts with other TB patients and specifically state that they have no known MDR-TB contacts or risk factors. A rapid HIV test is negative.
Case scenario 2

- deemed to be at high risk for MDR-TB, as she is failing a first-line regimen given under strict DOT.
- Her sputum is sent for culture and DST.
- Empirical MDR TB regimen is started; she is hospitalized for the first 2 weeks of therapy and then returns to the PMDT Treatment Center.
- She receives daily medications under strict DOT.
- Her symptoms improve, and 2 months later, her smear is negative.
- Her DST results: resistance to INH, RIF, EMB, and SM.
- Her MDR TB regimen is continued and she is monitored closely for compliance and adverse events.
Case scenario 3

- 4-year-old boy brought to the hospital clinic at the end of the 6th mo of anti-Tb treatment
- Persistent cough, shortness of breath; failure to thrive
- PMHx: His mother had past history of TB
- hospitalized 7 mos ago: 4 mos of cough, fever, anasarca
- Chest xray: left upper lobe infiltrate, bilateral hilar opacities.
- Hospital staff could not obtain a sputum sample for lab tests
- He was discharged on a 6-mo course of anti-TB regimen
- The patient did poorly over the next few months with worsening cough and failure to thrive.
Case scenario 3

- P.E. (present):
  - General wasting, weight 9 kg, RR 30 bpm
  - Chest diffuse bilateral crackles
- Laboratory: Renal function normal, Liver function normal, Hgb 6.0 g/dL WBC 18.8 x 10^9/L, HIV test test, negative
- Current diagnostics: Gastric lavage - AFB 3+ and culture grew M. tuberculosis, DST showed resistance to isoniazid, rifampin, ethambutol, and streptomycin.
Case scenario 2

- This child received a regimen for MDR TB.
- He received nutritional upbuilding
- Smear and culture converted to negative after the first month of treatment.
- After 6 months of intensive phase treatment, his weight was 11.5 kg. Chest X-ray showed improvement. His weight continued to improve. He completed treatment at 22 months. Final weight was recorded at 15.3 kg.
Take home message

- A high index of clinical suspicion is needed for timely diagnosis of MDR-TB in children.
- Risk factors include a history of previous treatment, failure to improve on first-line TB treatment, known MDR-TB contact, contact with a patient who died on TB treatment or failed TB treatment.
- Empiric treatment should be considered based on the DST of the contact or based on DST results from the child’s own specimens (if available).
- Early initiation of appropriate treatment is essential to ensure good outcomes.
“All providers who undertake evaluation and treatment of patients with tuberculosis must recognize that, not only are they delivering care to an individual, they are assuming an important public health function.”
Acknowledgement
Thank You