

# TB DISEASE IN CHILDREN AND PREGNANT WOMEN



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- Discuss the unique aspects of TB disease in children
- Highlight the clinical presentation and laboratory findings
- Review the diagnosis and treatment of TB disease in children and pregnant women
- Go over the new short-course therapies for tuberculosis in children



Disclosure: I have no conflicts of interest

#### RISK OF DISEASE WITH NO TREATMENT BY AGE INFECTED OR MEDICAL CONDITION



### **RISK OF PROGRESSION TO TB DISEASE BY AGE**

Age @ primary infection	Risk of Disease	
Birth-12months	Disease	50%
	Pulmonary Dis	30-40%
	Miliary or TBM	10-20%
1-2 years	Disease	20-25%
	<b>Pulmonary Dis</b>	75%
	Miliary or TBM	2-5%

Marais BJ. Int J Tuberc Lung Dis 2004;8:392-402





**FIGURE 101–5** The timetable of tuberculosis.

#### \*Feigin & Cherry, Text of Pedi ID

## TB DISEASE

#### Adult TB Disease

#### **Pediatric TB Disease**



## TB EXTRAPULMONARY DISEASE

Adult Extrapulmonary Disease 15% Pedi Extrapulmonary Disease 25%



## **REACTIVATION DISEASE**

- Occurs <u>years</u> after primary infection
- Typical of adult disease
- Also seen in teens
- Often cavitary disease
- High numbers of organisms (AFB +)
- Usually symptomatic and contagious



# PRIMARY TB DISEASE

Typical of childhood TB
May be seen in adults
Usually not cavitary

Classic x-ray:

- > Hilar lymphadenopathy
- Infiltrates or
- Miliary pattern

Low numbers of organisms

- ▹ AFB smears negative in 95%
- Cultures negative in 60%

 Most children <10 years are not contagious
 Half asymptomatic (50%)





## COMMON SYMPTOMS OF TB DISEASE IN CHILDREN

- Cough and/or other respiratory symptoms
- Wheezing, crackles or decreased breath sounds on lung examination
- Lymphadenopathy / lymphadenitis
- Persistent fever (FUO)
- Weight loss or failure to thrive
- Signs and symptoms of meningitis
  - Headache, vomiting, irritability, lethargy or seizures
- Unlike adults, half of children with TB disease have no symptoms

# Diagnosis of TB in Children

#### 💠 Gold Standard –

Positive TB Culture, OR

#### **Clinical Diagnosis (most common):**

- Abnormal CXR or laboratory or physical examination consistent with TB <u>AND</u>
  - 1 or more of the following:
  - Positive tuberculin skin test or IGRA
  - Contagious adult contact identified
  - Clinical course consistent with TB disease
  - Improvement on TB therapy





### Diagnostic Triad Pediatric TB Disease

- Positive TB skin test or IGRA
- Abnormal CXR
- Infectious contact







# Radiographic Findings in Pediatric TB Disease

#### **Classic in TB disease**

- Hilar and interthoracic lymphadenopathy
- Miliary pattern
- Apical cavitary lesions in adults and teens
- Basilar meningitis

#### Not specific but seen in TB

- Lobar pneumonia in any lobe
- Pleural effusion more common in teens and adults

# Hilar Lymphadenopathy

## Hallmark of Pediatric TB Disease

## Six week old with respiratory failure



## Miliary Tuberculosis





## Peripheral Lymphadenopathy

Central hypodensity

Peripheral enhancement on contrast CT

## **Cavitary Disease**

- Common in adults and teens
- Occasionally in infants with severe
   TB disease



# Source of Infection

- Contact Investigation may support diagnosis and guide treatment of a child with negative cultures
  - Source: Adult or teen with contagious TB
    - Usually symptomatic with cough
    - AFB smear positive pulmonary TB
    - NAAT, Xpert, cultures and susceptibilities
      - Should help guide treatment of pediatric contacts



## PERIPHERAL LYMPHADENOPATHY

- Physical exam, carefully check for
  - Cervical, supraclavicular, axillary and inguinal nodes
- TB disease of lymph nodes usually measure > 1 cm
- Diagnosis: Fine needle aspirate or excisional biopsy for pathology and culture recommended
- May progress to necrosis, caseation or chronic drainage
- Node may become more inflamed with TB treatment



## TEEN WITH NECK MASS

- 15-year-old African American boy with 5 week history of:
  - > Neck mass
  - Fever, 20 lb weight loss
  - > No foreign travel or known TB exposure
- Physical
  - > 100 kg, football player
  - > 5 cm cervical lymphadenopathy
  - Lungs clear
- PPD negative, O mm
- CXR normal



## NECK CT

Lymphadenopathy



## TEEN CASE OF LYMPHADENOPATHY

• Differential diagnosis

- ✓ Lymphoma, leukemia
- $\checkmark$  HIV, EBV, Cat scratch disease
- ✓ Tuberculosis
- ✓ Mycobacterium avium (MAC) or other NTM

• Laboratory

- $\checkmark\,$  CBC with peripheral smear negative
- ✓ HIV negative
- ✓ Node biopsy:
  - > Negative for cancer
  - > AFB smear negative
  - Granulomas seen on path
  - > TB culture positive at 5 weeks for MTB
  - > Susceptible to all drugs
- $\checkmark\,$  Quantiferon (IGRA) positive at 5 days
- All symptoms resolved on RIPE therapy

# **Collecting Specimens from Children**

# **Gastric Aspirates**

- Usually inpatient but can be collected outpatient
- Overnight fasting
- Lavage with normal saline
- Collected in morning x 3 days
- ♦ AFB smear yield: minimal <5%</p>
- TB Culture yield: 40% average (20-50% range)



Protocol: Curry International TB Center

https://www.currytbcenter.ucsf.edu/product/guide/pediatric-tuberculosis-a-guide-to-the-gastric-aspirate-procedure

# Induced Sputum

- Outpatient procedure
- 2-3h fasting period
- Pretreatment:
  - Nebulized bronchodilator and hypertonic saline
  - Chest physiotherapy (CPT)
- Nasopharynx suctioned
- One specimen sufficient
- Culture yield 40%
- May be successful in children
   3 years and over



Lancet. 2005;365:130

# **TB** Cultures from Children

- Bronchoalveolar lavage (BAL) or induced sputum
  - Single specimen with similar yield to 3 GA's
- Lymph nodes
  - Biopsy or FNA for path and culture
  - Sensitivity 30-70% yield on culture
- For TB meningitis
  - \* LP recommended for  $\leq$  12 months with TB disease
  - Sensitivity 20% average (12-50% range)
  - High volume (>6 ml) CSF sample improves culture yield but still low
- Bottom Line
  - Negative AFB smear, NAAT or culture does not rule out disease
- Culture and sensitivities from adult may guide treatment for child



## Molecular Tests including Nucleic Acid Amplification Tests NAAT

#### Gen-Probe, Xpert MTB/RIF and Xpert Ultra

- Highly specific, rapid results, Xpert detects rifampin resistance
- Not FDA approved in U.S. for smear negative samples
- Adults with AFB smear negative, culture positive pulmonary disease
  - Xpert on sputum samples: Sensitivity 66-79% Specificity 99%

#### Cochrane Review of Xpert & Xpert Ultra in <u>Children</u> with <u>culture positive TB</u>

- Sputum samples: Sensitivity 65-73% Specificity 98-99%
- Pulmonary TB: Gastric Aspirates > Sputum > Stool > Nasopharyngeal (lowest)
- Lymph node TB: Sensitivity 90% Specificity 90%
- TB Meningitis CSF: Sensitivity 54% Specificity 94%

Chakravorty S, et al. mBio 8:e00812-17, 2017. <u>https://doi.org/10.1128/mBio.00812-17</u>
 Kay AW et al. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD013359. DOI: 10.1002/14651858.CD013359.pub2.

## BABY EXPOSED TO TB DISEASE

- 6 month old infant
- Mother with TB disease
- How do you determine the risk to the baby?

- Mother's
- Chest x-ray
- AFB smears
- Treatment duration
- Contact with baby



## BABY EXPOSED TO TB DISEASE

- Mother AFB positive
- Mom just starting treatment
- Mother's CXR with severe cavitary disease



### **EVALUATION OF INFANT**

#### • History, baby with

- Cough and fever for 2 weeks
- Seen at clinic and urgent care x 2
   Diagnosed as viral illness
- Physical exam 2 weeks later
  - Alert infant with tachypnea and wheezing
  - Eye deviation and left sided weakness
- Laboratory and imaging
  - CXR
  - Lumbar puncture
  - Brain MRI

### DIFFUSE MILIARY DISEASE



### OUTCOME

#### • Diagnosis:

- Miliary TB and
- TB meningitis
  CSF: 27 WBC (80% L), 120 protein
- Brain MRI: multiple tuberculomas and stroke

#### • Treatment:

- RIPE therapy x 12 months
- Prednisone x 2 months
- Baby did well with normal exam and development after treatment



# **TB VS BACTERIAL MENINGITIS**

#### Table 2

Multivariate logistic regression analysis, at various levels of the predictor variables, for TBM cases

Predictor variables	Р	OR	95% CI
History of illness >5 days	0.000	6.1	2.5-14.8
WBC count $< 1000/\text{mm}^3$	0.009	2.9	1.3 - 6.4
Lymphocytes >30%	0.000	10.1	4.5-22.6
Protein content >100 mg/dL	0.002	2.5	1.2 - 6.1
Headache	0.001	5.4	2.0-14.2
CSF appearance (clear)	0.002	2.4	1.2-5.9

CI = confidence interval.

Youssef FG, et al. Diagn Microbiol Infect Dis 2006;55(4):275-8

# TB MENINGITIS TREATMENT AND CLINICAL COURSE

- ♦ Rule out TBM in children ≤ 12 months with TB disease and patients with miliary TB
- ✤ 9-12 months RIPE therapy
- Steroids for 6-8 weeks with 2-3 week taper
  - decreases CNS inflammation
- Symptoms initially worsen then gradually improve over 2-4 weeks
  - Fever common for first month
- Possible complications
  - > Seizures
  - > Hydrocephalus
  - > SIADH
  - > CNS tuberculoma, stroke, intellectual disabilities, CP
  - > Mortality high (>90%) if not diagnosed and treated

# TB Disease in Pregnant Women



#### POTENTIAL MODES OF INOCULATION AND PATHOGENESIS OF TUBERCULOSIS IN THE NEWBORN INFANT



# Treatment for TB disease in Pregnant Women

- Women diagnosed or suspected of having TB disease
   Should start TB treatment without delay
- All first line drugs are considered safe in pregnancy
- Treatment regimen
  - PZA or not?
  - If PZA is <u>not</u> included, treat for 9 months with Rifampin, INH and EMB

Source: Dr. Lisa Armitige HNTC

# PZA in Pregnant Women

- The WHO and IUATLD recommend
  - Include PZA in the treatment of TB in pregnant women
- The CDC 2003 treatment guidelines
  - Did not recommend PZA in pregnancy
  - Due to lack of safety data
- Current (2016) CDC/IDSA/ATS treatment guidelines state
  - Evaluate risk/benefit of PZA
  - Benefits may outweigh risk
  - Women with HIV, extrapulmonary or severe disease should receive PZA in their treatment regimen



# **After-Delivery Concerns**

- Should mother and infant be separated?
  - Yes if mother is suspected of having MDR-TB
  - But if mother is infectious but not MDR disease:
    - Start baby on INH or Rifampin window prophylaxis
    - Minimize exposure
      - Mother can wear a mask while holding the baby
      - Sleep in separate rooms until mother is no longer infectious
- Can mother breastfeed?
  - Yes
  - TB drugs cross the placenta and breast milk in low but safe levels



# Take Home Points

- Treating a pregnant mother also protects her baby, her family and her community
- If a CXR is warranted, it should be performed
- Pregnant women can be safely treated for TB infection and TB disease
- PZA, though controversial, in most cases will add more benefit than harm to the treatment of pregnant women



# Treatment of TB in Children



# TREATMENT OPTIONS FOR PEDIATRIC TB DISEASE

• 6-9-month old standard RIPE therapy

#### NEWER

- 4-month RIP +/- E therapy for uncomplicated pediatric disease (SHINE study)
  - WHO endorsed
  - CDC expected to endorse
- 4-month Rifapentine, Moxifloxacin, INH and PZA
  - Adults and children  $\geq 12$  ys of age
  - For uncomplicated, mostly pulmonary TB, including cavitary disease
  - CDC and WHO endorsed



#### SHINE STUDY

4- vs 6-month treatment in children with TB disease

#### • Criteria:

• Smear-negative disease in children < 16 years of age, symptomatic, nonsevere, drug-susceptible TB

#### • Nonsevere TB defined as:

- No cavities, no miliary TB
- Pulm disease confined to 1 lobe, non-complex pleural effusions, no significant airway obstruction
- No drug resistant disease or drug resistant exposure



# • Randomized to 4 or 6 months first-line WHO fixed-dose regimens

- Daily, self administered, used check lists and pill counts with 94% adherence
- 95% study retention at 72 weeks

Turkova A et al. N Engl J Med 2022;386:911-22. DOI: 10.1056/NEJMoa2104535

## SHINE STUDY 4-MONTH TREATMENT IN CHILDREN

#### • Population:

- 1204 children from Africa (88%) and India (12%)
- Median age 3.5 years (range 2 month 15 years)
- 11% with HIV
- 14% were culture or Xpert confirmed, 86% clinical diagnosis
   67% pulmonary TB
  - 29% mixed resp/lymph node TB
  - 3% peripheral lymph-node TB

#### • Outcome:

- Noninferiority of the shorter regimen with favorable outcome in 98% in 4-month and 97% in 6-month regimen
- Study Power 90%

Turkova A et al. N Engl J Med 2022;386:911-22. DOI: 10.1056/NEJMoa2104535



# Unfavorable Status by 72 Weeks Excluding Children Who Did Not Complete 4 Months of Treatment Noninferiority margin, 6 percentage points Adjusted difference, -0.4 percentage points (95% CI, -2.2 to 1.5)



Death from any cause: 7;12 patients Tx failure requiring extension: 9;5 Recurrence of TB: 6;4

## Pneumonia and/or Liver events 47;48 patients of 1204 total patients

## FIXED-DOSE COMBINATIONS FOR CHILDREN

- Intensive phase of TB treatment:
  - Rifampicin 75 mg + Isoniazid 50 mg + Pyrazinamide 150mg
- Continuation phase of TB treatment:
  - Rifampicin 75mg + Isoniazid 50 mg
- Ethambutol should be added in the intensive phase for:
  - Children with extensive disease or in areas with high prevalence of HIV or isoniazid resistance

	Number of tablets		
Weight	Intensive phase RHZ 75/50/150 *	Continuation phase RH 75/50	
4-7 kg	1	1	
8-11 kg	2	2	
12-15 kg	3	3	
16-24 kg	4	4	
≥25kg	Adult dose recommended	Adult dose recommended	

1) Global TB Programme, WHO http://www.who.int/tb/areas-of-work/children/ TB Alliance www.tballiance.org/children

2) Int J Tuberc Lung Dis. 2015 Dec;19 Suppl 1:3-8. doi: 10.5588/ijtld.15.0416.

# 4 MONTH REGIMEN FOR ADULTS AND CHILDREN $\geq$ 12-YRS

Rifapentine, Moxifloxacin, Isoniazid and Pyrazinamide daily

- Intensive phase daily 8 weeks of 4 drugs daily
- Continuation phase 9 weeks of daily RPT, MOX and INH
- Endorsed by WHO and CDC
- Eligible
  - Ages  $\geq 12$  years and weight  $\geq 40$  kg
  - Drug susceptible pulmonary TB disease
- <u>NOT</u> eligible
  - < 12 years of age
  - Pregnant women
  - Most extrapulmonary TB
  - Prolonged QT-syndrome
  - History of partial TB treatment in preceding 6 months
  - Drug resistant TB

Dorman SE, et al.: AIDS Clinical Trials Group; Tuberculosis Trials Consortium. N Engl J Med 2021;384:1705-18. PMID:33951360 https://doi.org/0.1056/NEJMoa2-33400

## MONITORING CHILDREN ON TB TREATMENT

Risk of drug toxicity very lowMonitor clinical signs

- Regular clinical visits (4-6 wks)
- Patient education



- Routine blood work not necessary unless
  - Signs or symptoms of toxicity
  - Risk factors for toxicity (obesity, other hepatotoxic medications)
- Follow up to monitor symptoms and reinforce adherence

When to follow up x-rays

- Pulmonary TB: beginning and end of therapy or anytime if clinical change
- ▶ For TB meningitis: MRI at beginning, 1-2 mo into tx and at end

Document completion of therapy

## PEDIATRIC TB DISEASE SUMMARY

- Higher risk for
  - Progression to disease
    - ${\scriptstyle \circ}$  Especially infants and children  $\leq 2$  years
  - Extrapulmonary and disseminated disease including TB meningitis
- Most common TB disease sites in children
  - Pulmonary and lymph nodes
- Symptoms may be subtle or absent in children
- Children  $\leq 10$  years
  - Have low bacterial load (paucibacillary disease)
  - Usually are not contagious
    - Unless cavitary or AFB smear positive disease
- AFB smears and TB cultures
  - Often negative in children
  - Clinical diagnosis most common





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## Questions?