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Advanced Concepts in Pediatric Tuberculosis: Diagnosis Old and New Tools & Challenges

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Advanced Concepts in Pediatric Tuberculosis

1. Mycobacteriology, Pathogenesis and Epidemiology
2. Latent TB Infection
3. **Diagnosis: Old and New Diagnostic Tools and Challenges**
4. Clinical Manifestations
5. TB and HIV
6. Pharmacotherapeutics of TB drugs
7. Treatment of TB, including MDR
8. Infection Control, Source Case and Contact Investigation

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Diagnostic Tools and Challenges
Objectives

At the end of this presentation, attendees should be able to:

- Describe old and new tools used in the diagnosis of TB in children
- Understand advantages and limitations of each tool in detection and diagnosis of TB.
- Know the different samples that can be used to diagnose TB
- Identify the indications for examination of the cerebrospinal fluid in a patient with symptomatic tuberculosis
- Evaluate a patient with suspected TB infection

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TB in Children

- Most children who develop tuberculosis disease experience pulmonary manifestations
- 25-30% have an extrapulmonary presentation

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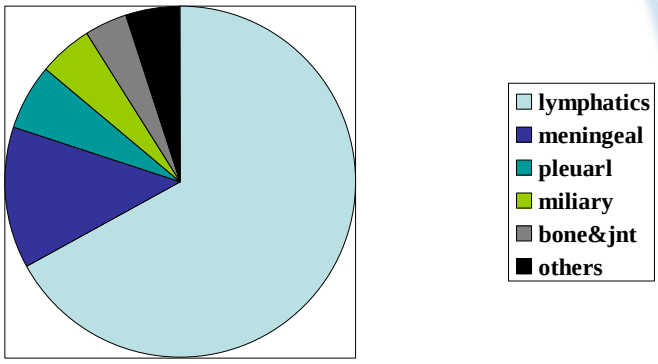
Extra-Pulmonary TB in Children



Pediatric Infectious Diseases, Jenson & Baltimore

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Challenges of diagnosing TB in children

- Not considered in the differential diagnosis in children, especially in low-endemicity settings.
- Can mimic many common childhood diseases, including pneumonia, viral infections, malnutrition, and HIV.
- The physical manifestations of disease tend to differ by the age of onset
- Paucibacillary nature of the disease in children result in low diagnostic yield

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Cases

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Case 1

- 5 year-old Egyptian girl
- Longstanding FTT + Anorexia
- Persistent cough associated with wheeze : partial response to bronchodilator
- Has recurrent febrile illness
- Treated as bronchial asthma for 6 months → NO improvement
- How would you manage this girl?

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Case 2

- A 2 year- old boy from the Philippines with right cervical lymphadenopathy of 2x3 cm for the last one month.
- He has received PO clindamycin x 1 week and IV cefuroxime for another week without much improvement .
- Weight: 75% , height 50%.
- Developed stridor in the last week.
- He was vaccinated with BCG vaccination at birth.

What should be done next?

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Case 3

- A 1 year-old girl with vomiting & deterioration of level of consciousness in the last 24 hours.
- She has unexplained febrile illness x 1 month
- A nanny from Ethiopia has been taking care of her for the last 3 months.

What will be the best diagnostic test to perform on this girl?

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Diagnostic priority

Diagnosis of active TB

Diagnosis of latent TB

Diagnostic tools for TB

LTBI	Active TB
• Skin testing (TST) • IGRAs	• Symptom-based approaches • Radiology-based approaches • Immune-based approaches • Organism-based approaches

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Symptom-based approaches

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Clinical scoring systems

- Can be used in
  - Endemic countries with limited resources
  - Low-risk children (immunocompetent children >3 years) in whom TB is usually a slowly progressive disease.
- Disadvantage: severely limited by the absence of standard symptom definitions & inadequate validation.

Hesseling AC, et al .Int J Lung Dis 2002; 6: 1038–1045.

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Clinical scoring systems

- Well-defined symptoms with a persistent, non-remitting character
- Most helpful symptoms :
  (1) Persistent, non-remittent coughing or wheezing
  (2) Documented failure to thrive despite food supplementation
  (3) Fatigue or reduced playfulness

Marais BJ, et al . Arch Dis Child 2005; 90: 1162–1165.
Marais BJ. et al. Pediatrics 2006; 118: e1350–e1359.

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Clinical scoring systems

- Diagnosis of TB cervical lymphadenitis:
  1) Persistent (longer than 4 weeks)
  2) Size: 2 x 2 cm or more
  3) No visible local cause
  4) No response to first-line antibiotics

Lindeboom Jaet al. Clin Infect Dis 2006; 43: 1547–1551

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Radiology-based approaches

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Chest X-ray

- Remains the most practical and helpful test in everyday practice.
- It usually provide an accurate diagnosis with suspicious symptoms, if evaluated by an experienced clinician
- Limitation: subjective interpretation

Marais BJ et al. Am J Resp Crit Care Med 2006; 173: 1078–1090.

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Chest X-ray

- **Sensitivity:**
  70% to 80%
- **Specificity:**
  60% to 70%.
- **Inter-reader variability:**
  - Chest x-ray interpretation is highly variable.

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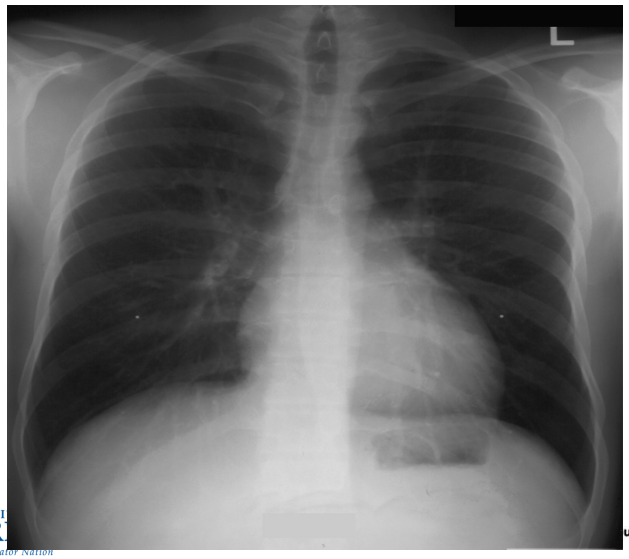
Normal CXR



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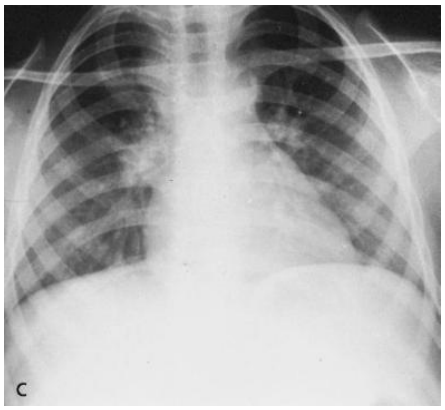
Primary TB



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Hilar & mediastinal lymphadenopathy

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Atelectasis

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Obstructive emphysema

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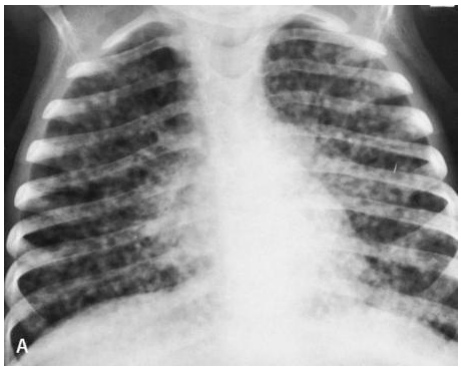
Miliary TB



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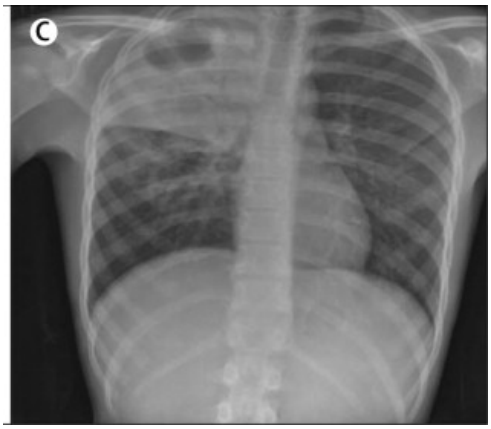
Cavitating lung disease



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Chest CT scan

- High-resolution computed tomography is the most sensitive tool currently available to detect hilar adenopathy and/or early cavitation.

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Immune-based approaches

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Immune-based diagnosis

- Complicated by:
  - Wide clinical disease spectrum (LTBI → different forms of active disease)
  - Factors that influence the immune response such as BCG vaccination
  - Exposure to environmental mycobacteria
  - HIV co-infection

Pai M et al. Exp Rev Mol Diag 2006; 6: 423–432.

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TST

Lack both sensitivity and specificity

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T-cell assays
T-Spot. TB and Quantiferon-TB Gold

- Advantage:
  - more specific than the TST
- Limitations:
  - Fail to differentiate LTBI from active disease.
  - Blood volume required (3–5 ml)
  - Limited data in children (reservation in very young children)
  - Expensive

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New diagnostic approaches

Immune-based			
Antibody-based assays	Diagnosis of probable active TB	Simple, point-of-care testing, variable accuracy and difficulty in distinguishing LTBI from active TB	Not validated
MPB-64 skin test	Diagnosis of probable active TB	Simple, point-of-care testing, requires a second visit to read the result	Not sufficiently validated No studies in children

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Organism-based approaches

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Microscopic Examination

- Cornerstone of TB diagnosis & control
- Two stains are widely used:

  1) Ziehl-Neelsen, requires a light or bright field microscopy

  2) Auramine stain, requires fluorescence microscopy.
- In most high income countries fluorescence microscopy is standard practice

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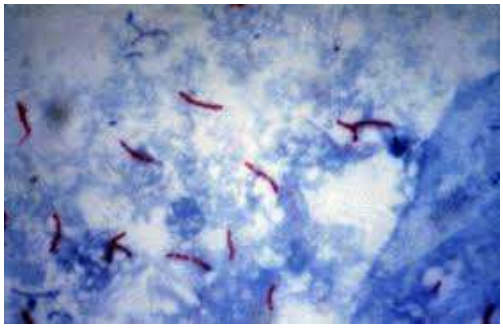
Ziehl-Neelsen stain



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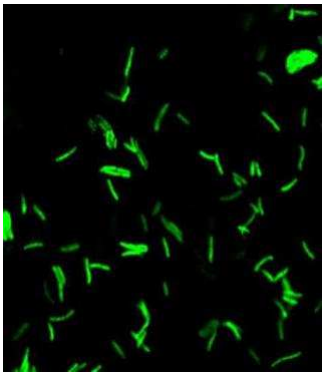
Auramine stain



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Microscopic Examination- Advantages

- Rapid
- Inexpensive
- Identifies the most infectious TB patients.

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Microscopic Examination- Limitations

- Sensitivity (20%-80%)
  1. Type of specimen, Sensitivity is higher for respiratory samples
  2. Patient population (could be NTM in low TB incidence)
  3. Stain used
     ZN stain 100,000 bacteria/ml,
     Fluorescent 10,000 bacteria/ml
  4. Experience of the microscopist.
  5. Age of patient: lower in children

- Smear microscopy cannot be used to determine drug resistance.

Steingart KR t al. *Lancet Infect Dis* 2006;6(9):570-81.
Steingart KR et al,. *Lancet Infect Dis* 2006;6(10):664-74.

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Culture

- Positive culture is the 'gold standard test' for diagnosis of TB in a symptomatic child.
- Solid or liquid broth media
- Limitations:
  - Slow turnaround time
  - Excessive cost (automated liquid broth systems)
  - Poor sensitivity in children with active TB.

  (culture is –ve in 70% of cases with probable tuberculosis)
  - Expensive in poor resource countries

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HJ Zar, et al. Lancet, 365 (2005), pp. 130–134

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New Diagnostic Approaches

Organism-based			
Colorimetric culture systems (e.g. TK-Medium)	Bacteriological confirmation of active TB	Simple and feasible, limited resources required; potential for contamination in field conditions	Not well validated in children
Phage-based tests (e.g. FASTPlaque-TB)	Diagnosis of probable active TB and detection of resistance to rifampicin	Requires laboratory infrastructure; performs relatively poorly when used on clinical specimens	Not well validated in children
Microscopic observation drug susceptibility (MODS) assay	Diagnosis of probable active TB and detection of drug resistance	Simple and feasible, limited resources required	Not well validated in children
PCR-based tests	Diagnosis of probable active TB and detection of resistance to rifampicin	Rarely available in endemic areas; sensitivity poor in paucibacillary TB; specificity a concern in endemic areas where LTBI is common, except if specimen collected from a "sterile" source; requires adequate quality control systems	Extensively evaluated, but evidence not in favour of widespread use

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Marais & Pai . Peds Resp Reviews 2007

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Samples for TB diagnosis

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Gastric Aspirate (GA)

- Indicated in children with possible TB who cannot expectorate sputum (< 7 years).
- Collection of two or three fasting, early morning gastric aspirate specimens.

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Gastric Aspirate (GA)

- Advantages:
  - Microscopy: +ve 0%-21% (median 7%)
  - Culture: +ve 0%-75% (median 20%) of children with a clinical diagnosis of likely TB.
- Disadvantages:
  - Uncomfortable & unpleasant for patients
  - Difficult implementation: performed immediately upon the patient awakening (need hospitalization)

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Marais BJ et al . Clin Infect Dis 2006; 42: e69–e71.
Marais BJ et al. Am J Resp Crit Care Med 2006; 173: 1078–109

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Induced Sputum

- Collection of a single 3% hypertonic saline-induced sputum specimen seems to provide the same yield as three gastric aspirate specimens
- Sensitivity: detects 75-100% of culture-positive TB cases
- Yield higher for sputum induction than nasopharyngeal aspiration and gastric lavage

Zar HJ et al. Lancet 2005; 365: 130–134
Hepple P et al. *Int J Tuberc Lung Dis* 2012;16(5):579-88

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Induced Sputum

- Limitations:
  - Patient must be hospitalized
  - Sputum induction may pose a nosocomial transmission risk if adequate infection control measures are not in place

Marais BJ, et al. Indian J Med Microbiol 2006; 24: 249–251
.

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Sputum

- At least three sputum specimens of 5-10 mL each should be collected and tested with microscopy as well as culture.
- Only 10–15% of sputum samples revealing acid-fast bacilli.
- Yield of the third sputum smear is only about 2%-5%, the yield of the third culture may be as high as 5%-10%, especially in HIV-infected people.

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Bronchoalveolar Lavage (BAL)

- Used when spontaneous sputum and induced sputum are unavailable, or all samples are smear-negative.
- Disadvantages:
  - Discomfort for the patient
  - expensive
  - Contribute to nosocomial spread of TB if not performed in an appropriate environment with protection of staff.
- Yield is only 77%.

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Pleural fluid

- Yellow, occasionally tinged with blood.
- Chemistry :
  - Protein: 2 to 4 g/dL
  - Glucose: 20-40 mg/dL.
  - WBC : 100-1000 cells/mm^3 (↑PMN)
  - AFB smears: usually negative (because of the relative paucity of organisms).
  - Cultures: +ve in 30 - 70% of cases.
- Biopsy of the pleura is more likely to yield a +ve AFB stain or culture, & evidence of granuloma formation

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Urine

- Not invasive; excretion of Mycobacterium tuberculosis well documented
- To be considered with new sensitive bacteriological or antigen-based tests

Bone marrow

- Good sample sources to consider in the case of probable disseminated TB

Cerebro-spinal Fluid (CSF)

- Fairly invasive
- Bacteriological yield low, but CSF analysis is important
- To be considered if there are signs of tuberculous meningitis*

*Signs can be very subtle in young children.

*Need for high index of suspicion.

Cerebro-spinal Fluid (CSF)

- WBC 10 - 500 cells/mm3 (↑Lymphocytes)
- Glucose < 40 mg/dL (can go as low as 20 mg/dL).
- Protein 400-5000 mg/dL

- In 5 - 10 mL of CSF:
  - AFB smear: +ve in 30%
  - Culture : +ve in 70%.

Fine needle aspiration

- Excellent bacteriological yield
- Minimal side-effects
- Procedure of choice in children with superficial lymphadenopathy

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Conclusion

- AFB microscopy & culture remain the gold standard for TB diagnosis .
- If the child has +ve TST, clinical or radiographic findings suggestive of TB, H/O contact with an adult with TB, the child should be treated for tuberculosis disease. Drug susceptibility similar to adult.
- PCR may be an aid in the diagnosis of extrapulmonary tuberculosis
- Novel biomarkers in blood or urine that can reliably distinguish active from LTBI in children .

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Cases

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Case 1

- 5 year-old Egyptian girl
- Longstanding FTT + Anorexia
- Persistent cough associated with wheeze : partial response to bronchodilator
- Has recurrent febrile illness
- Treated as bronchial asthma for 6 months → NO improvement
- How would you manage this girl?

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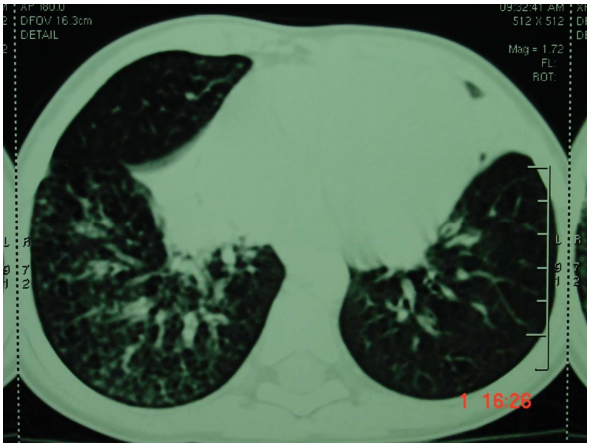
CT scan of chest



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Other investigations

- TST : 7 mm induration
- Admitted for early morning gastric aspirate x 3
  - AFB : negative
  - TB culture positive

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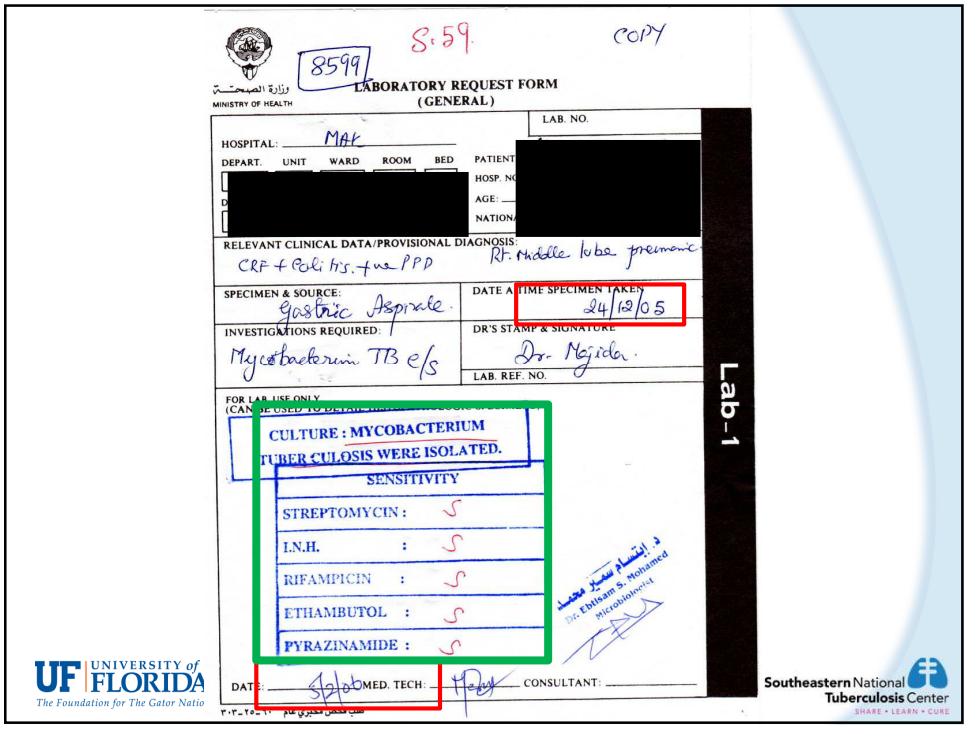

Case 2

- A 2 year- old boy from the Philippines with right cervical lymphadenopathy of 2x3 cm for the last one month.
- He has received PO clindamycin x 1 week and IV cefuroxime for another week without much improvement .
- Weight: 75% , height 50%.
- Developed stridor in the last week
- He was vaccinated with BCG vaccination at birth.

What should be done next?

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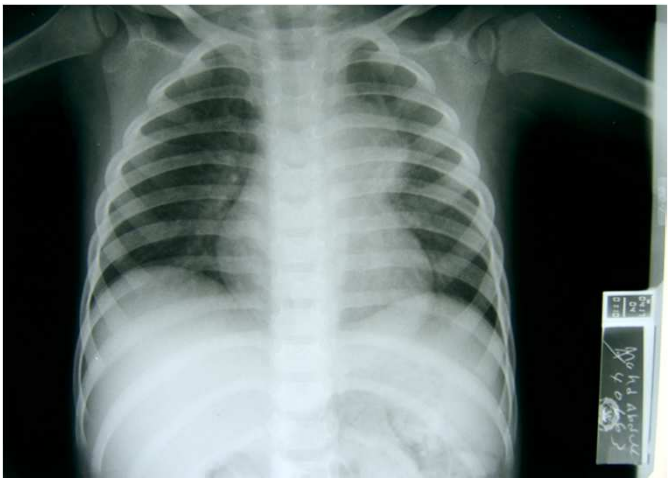
CXR



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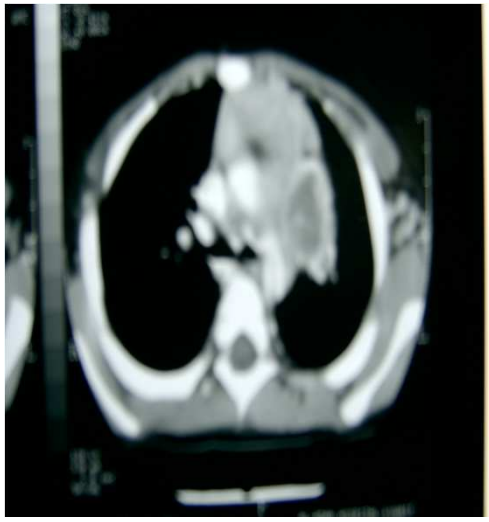
CT chest



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Fine needle aspiration of the cervical lymph node

- Direct microscopy: +ve AFB
- Pathology : granulomas & AFB +ve
- Culture : Mycobacteria TB, sensitive to 1st line antiTB

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Case 3

- A 1 year -old girl with vomiting & deterioration of level of consciousness in the last 24 hours.
- She has 1 month history of recurrent unexplained febrile illnesses.
- A nanny from Ethiopia has been taking care of her for the last 3 months.

What will be the best diagnostic test to perform on this girl?

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CT scan of head

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Further management

- Admitted to the ICU
- Neurosurgeon : VP shunt
- CSF:
  - WBC : 548 cells/µL (80% lymphocytes)
  - Protein: 2500 mg/dl
  - Glucose : 20 mg/dl
  - Gram stain: Negative
  - AFB stain : Positive

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Clinical Progress

- Started on anti TB medication
- CSF for TB PCR TB +ve
- Remained in coma x one week
- Nanny:
  - Was coughing x 2 months, seen several doctors
  - CXR: right middle lobe pneumonia
  - Sputum: +ve AFB
- TB culture in CSF of the girl (after 1 month) : positive

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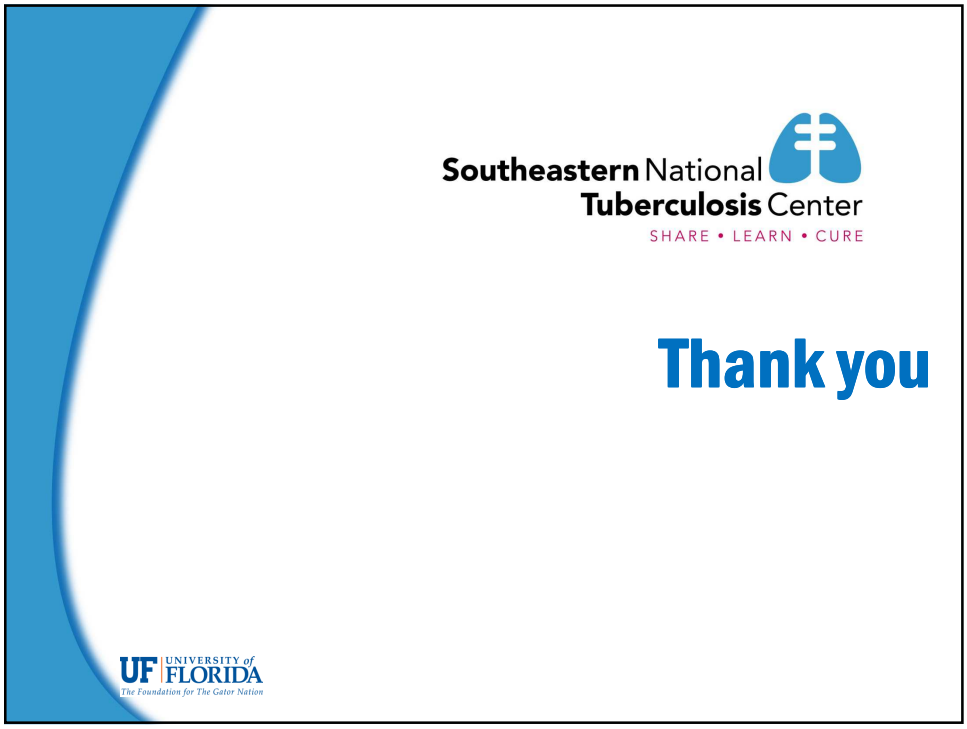
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