

# **MMed and DCH Lectures**

## **Diagnosis of tuberculosis**

October 4, 2021

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# Is the diagnosis of TB difficult in children?

- TB is pauci-bacillary
  - “Pauci” = few / minimal (i.e. *paucity*)
- Symptoms are non-specific (chronic cough, fever, weight loss)
- Signs are non-specific
  - Chest crackles, wasting
- Tests are insensitive (sputum, GA) or non-specific (chest x-ray)
  
- Diagnosis made by careful clinical assessment and deductive reasoning
- Difficult to *confirm* TB in many cases, but OK to make a clinical diagnosis of probable TB

# Integrated diagnosis of paediatric TB

- History
- Examination
- Radiology
  - Plain x-ray
  - CT scan
- Test for *M. tuberculosis* bacilli
  - Z-N stain
  - Culture
  - Histopathology
  - PCR (GeneXpert)
- Tuberculin skin test (Mantoux)
  - Test of immune response to TB

## Types of specimens

Sputum  
Gastric aspirate  
Pleural fluid  
Fine needle aspirate of lymph node  
CSF  
Ascites

# History and examination

## History

- Duration and consistency of symptoms
  - Cough for >2 weeks, daily and frequent, no response to a course of antibiotics
  - Fever daily >2 weeks, night sweats
- Fatigue, reduced playfulness
- Nutritional history, documented weight loss, FTT
- Immunization history (BCG and others)
- Social history, including TB contact (likely, proven, describe exactly what type)
  - The risk of TB infection to the infant of a mother with TB is extremely high
  - Risk of TB disease highest in first year after contact
  - Adults with reactivation TB most infectious

## Examination

- Chest: signs suggesting chronic respiratory distress, such as
  - Chest deformity
  - Course crackles
  - Large pleural effusion in a non-septic child
  - Wheezes and unilateral airway obstruction
- Growth and nutritional assessment
- Signs of extra-pulmonary TB
  - Lymphadenopathy
  - Ascites
  - Hepatosplenomegaly
  - Kyphoscoliosis
- Signs of comorbidities
  - Anaemia
  - HIV

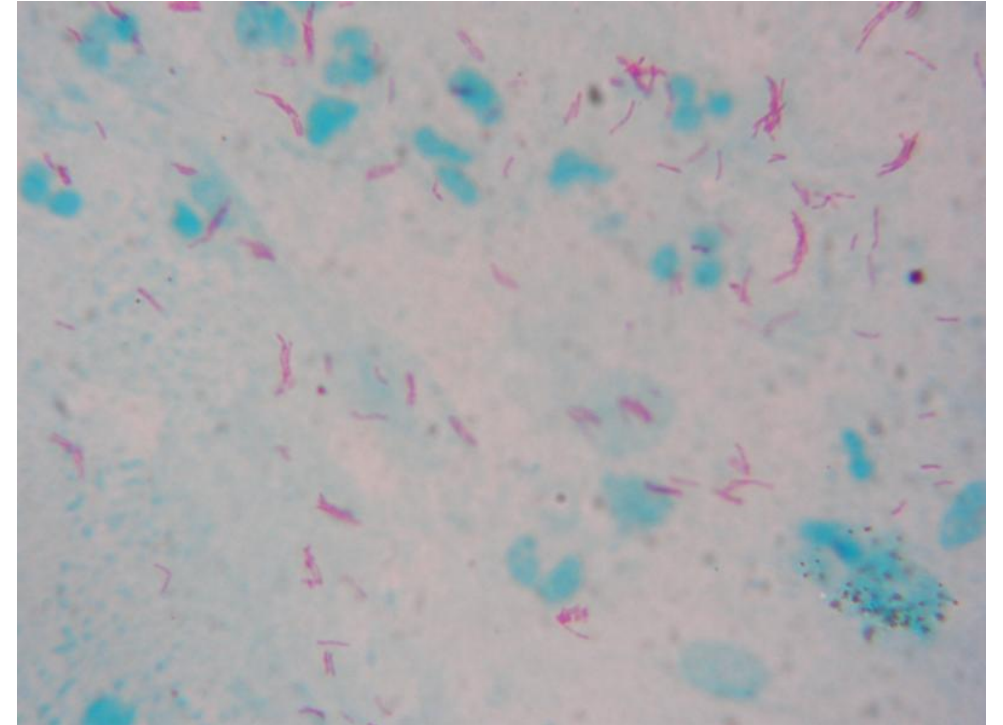
Feature	0	1	2	3	4	Score
Length of illness (weeks)	< 2	2-4		> 4		
Nutrition status (weight for age)	Above the -2 line	Between the -2 and -3 line		Less than the -3 line		
Recent close contact with an infectious TB case (adult with PTB or sputum smear positive case)	None	Verbal history of TB contact		Proven sputum positive contact		
Lymph nodes: large, painless, firm, soft sinus in neck/axilla				Yes		
Night sweats, unexplained fever			Yes			
Angle deformity of spine					Yes	
Malnutrition, not improving after 4 weeks of treatment				Yes		
Joint swelling, firm, non-fluid, non-traumatic				Yes		
Unexplained abdominal mass, ascites				Yes		
Coma for more than 48 hours (with or without convulsions)				Yes		
Send to hospital if possible						
					<b>TOTAL</b>	

# TB score

- Good screening test
- Very useful in rural areas with no diagnostic tests
- *Non-specific*, many other conditions can have a TB score >7, but TB is still often *the most likely* cause of the symptoms.
- Other conditions that can have a TB score >7
  - HIV
  - Bronchiectasis
  - Cancer (e.g. lymphoma)
  - Other chronic infections (e.g. chronic osteomyelitis)
- → Integrate TB score with diagnostic tests, and consider and exclude other conditions

# Ziehl Neelsen staining for AFB

- Process of Ziehl Neelsen staining
  - Dry smear → heat (60°C) → **corbol fuschin** (red) → heat (5')
  - Water wash → 3% acid alcohol until stain pale pink (2-5')
  - Water wash → **Methylene blue** (1-2')
  - Water wash → air dry
- **Waxy cell wall (mycolic acid)**
  - *Makes mycobacterium hardy – survives on dry surfaces for prolonged periods*
  - *Retains red dye in-spite of being exposed to acid alcohol*
  - Other bacteria don't have such a waxy cell wall, so the red dye washes out with acid-alcohol



# GeneXpert MTB / Rif

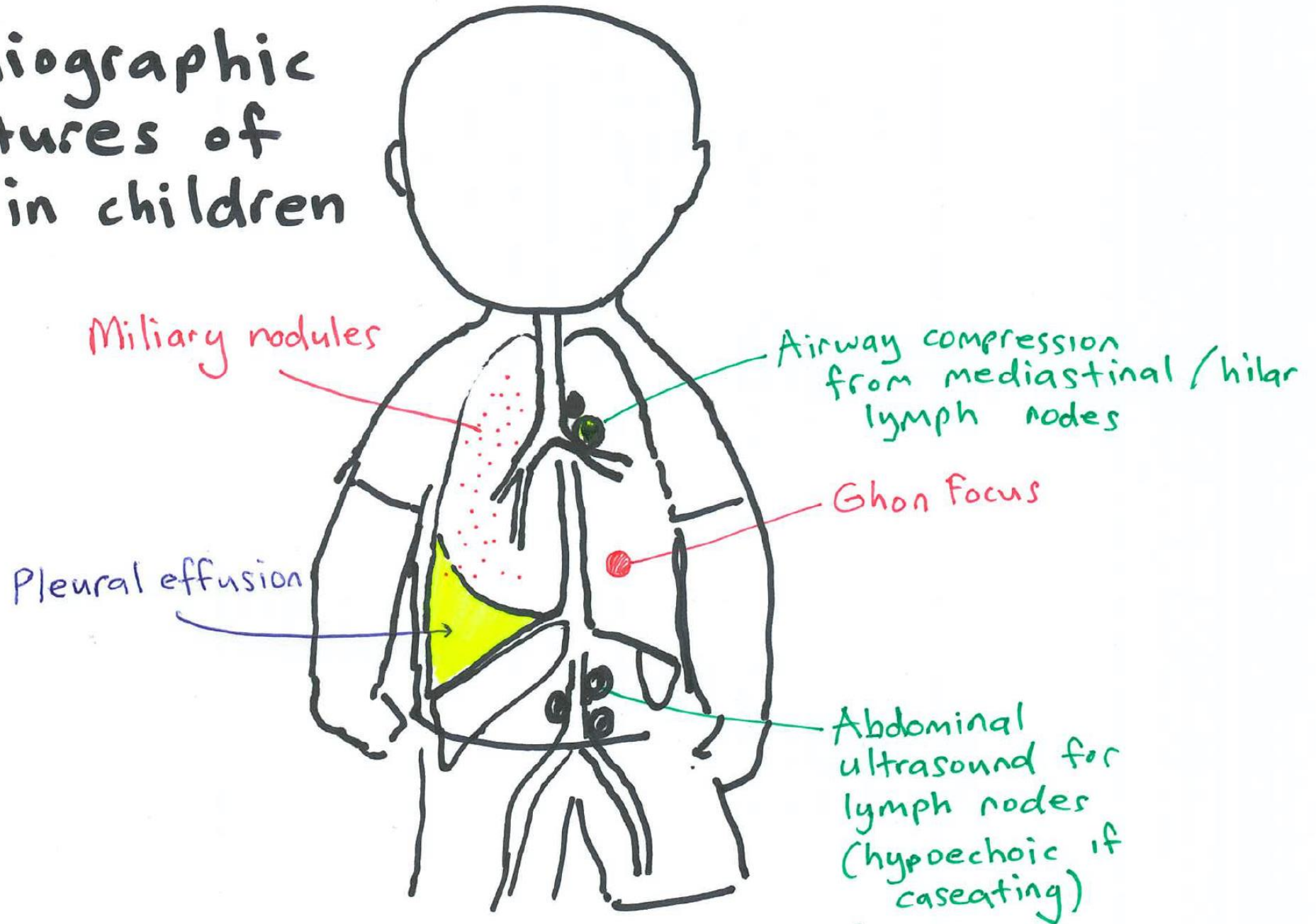
- Nucleic acid amplification test (PCR)
  - Concentrates Mycobacterium tuberculosis bacilli from sputum samples, isolates genomic material from the bacteria and amplifies the genomic DNA by PCR
  - Detects Mycobacterium tuberculosis rpoB gene and mutation resistance genes to rifampin (RIF)
- May remain positive during and even after treatment (not a follow-up test)
  - Cannot distinguish between alive and dead bacilli
- Less sensitive than sputum culture in adults



# Xpert Ultra

- Next generation GeneXpert MTB/Rif
- Slightly more sensitive on sputum than initial GeneXpert
- Depends on the specimens:
  - Sensitive for lymph nodes (higher than AFB staining)
  - Not much different for TBM (limiting factor still CSF volume)

# Radiographic features of TB in children

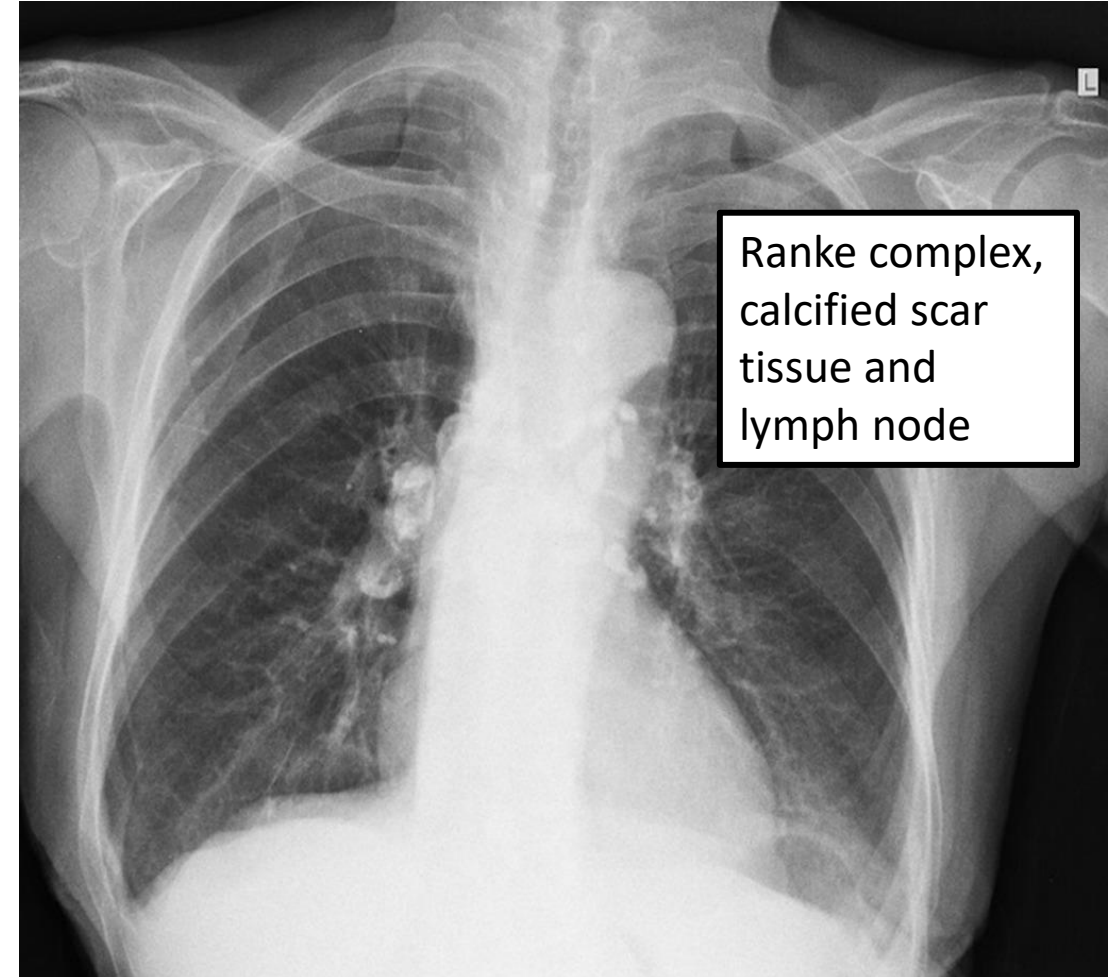
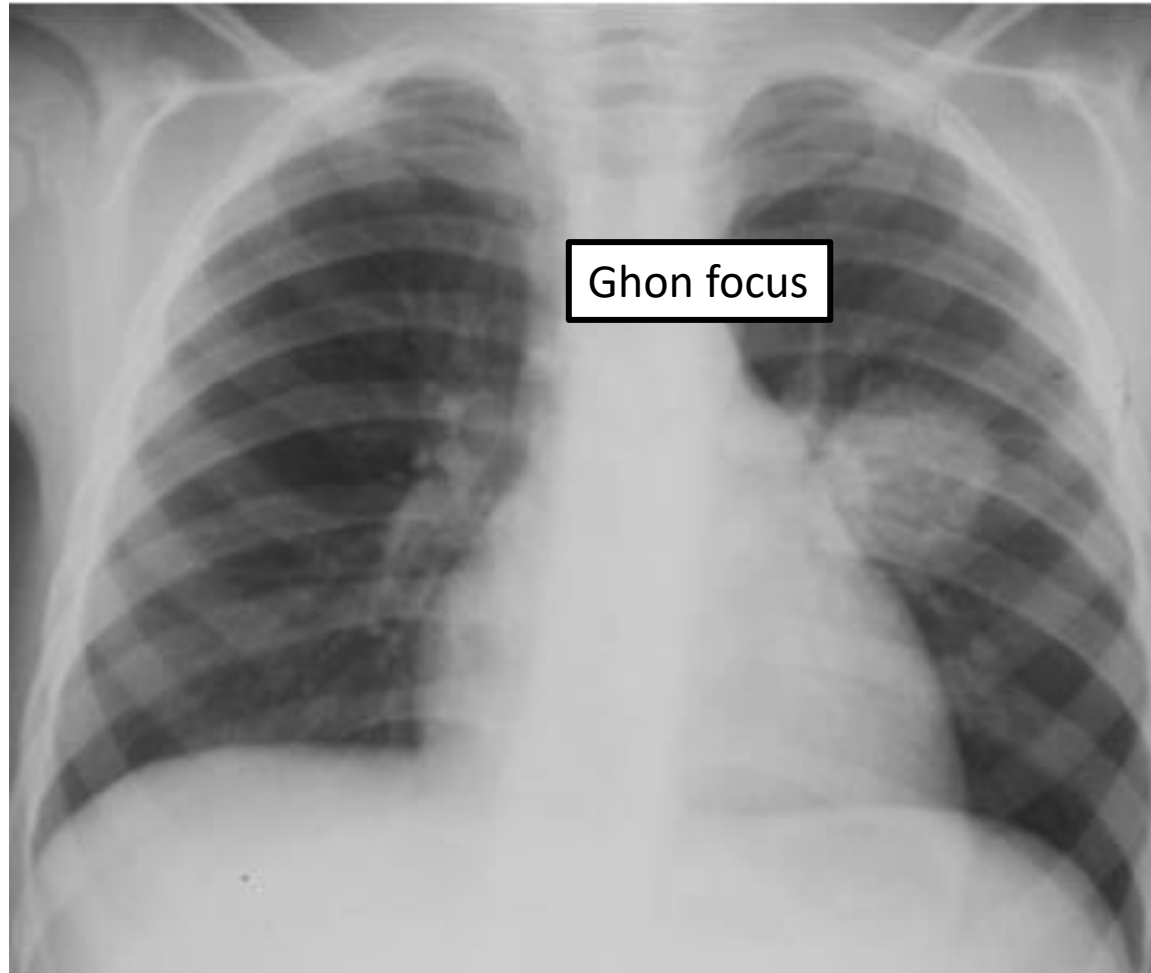


# Chest x-ray changes in MDR TB

- Consolidation
  - Segmental / lobar (50%)
  - Broncho-pneumonic consolidation (33%)
- Hilar / mediastinal lymphadenopathy (35%)
- Pulmonary cavities (30%)
- Miliary opacification (13%)
- Pleural effusions (11%)

Mannikkam S. Chest X-ray patterns of pulmonary multidrug-resistant tuberculosis in children in a high HIV-prevalence setting. SA Journal of Radiology 2016

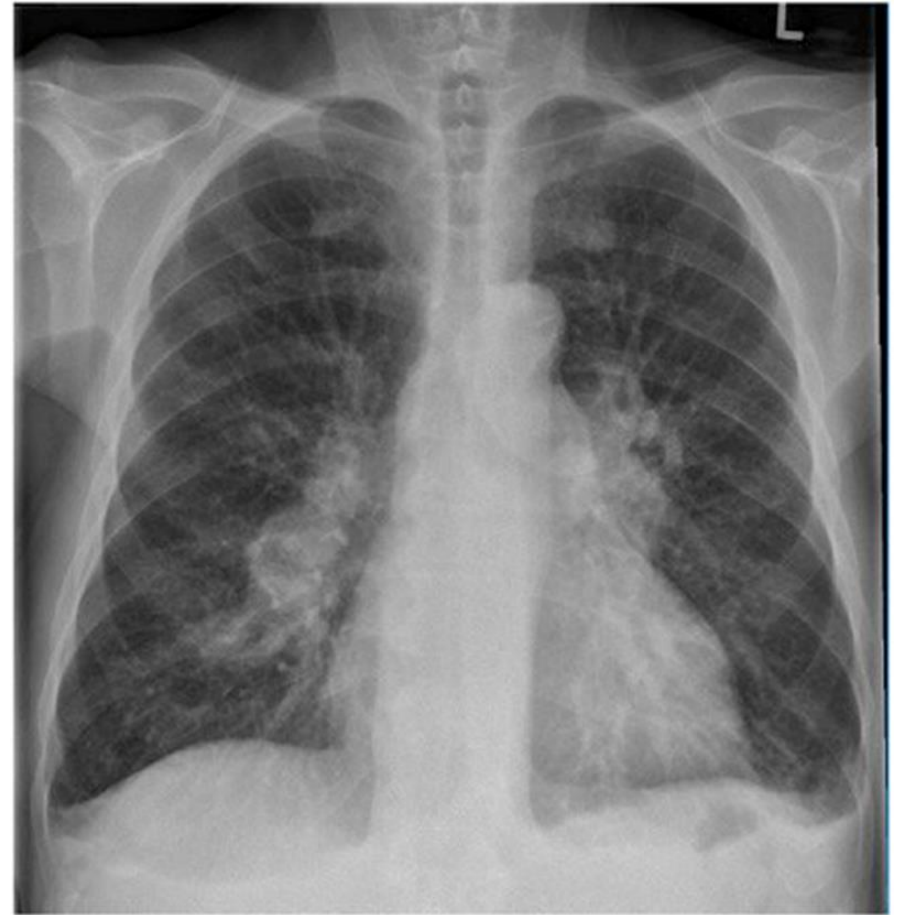
# Signs of primary TB



# Hilar masses



Enlarged peri-hilar lymph nodes  
Discrete opacities: TB, lymphoma



Enlarged pulmonary arteries  
Opacities with vascular marking extending outwards

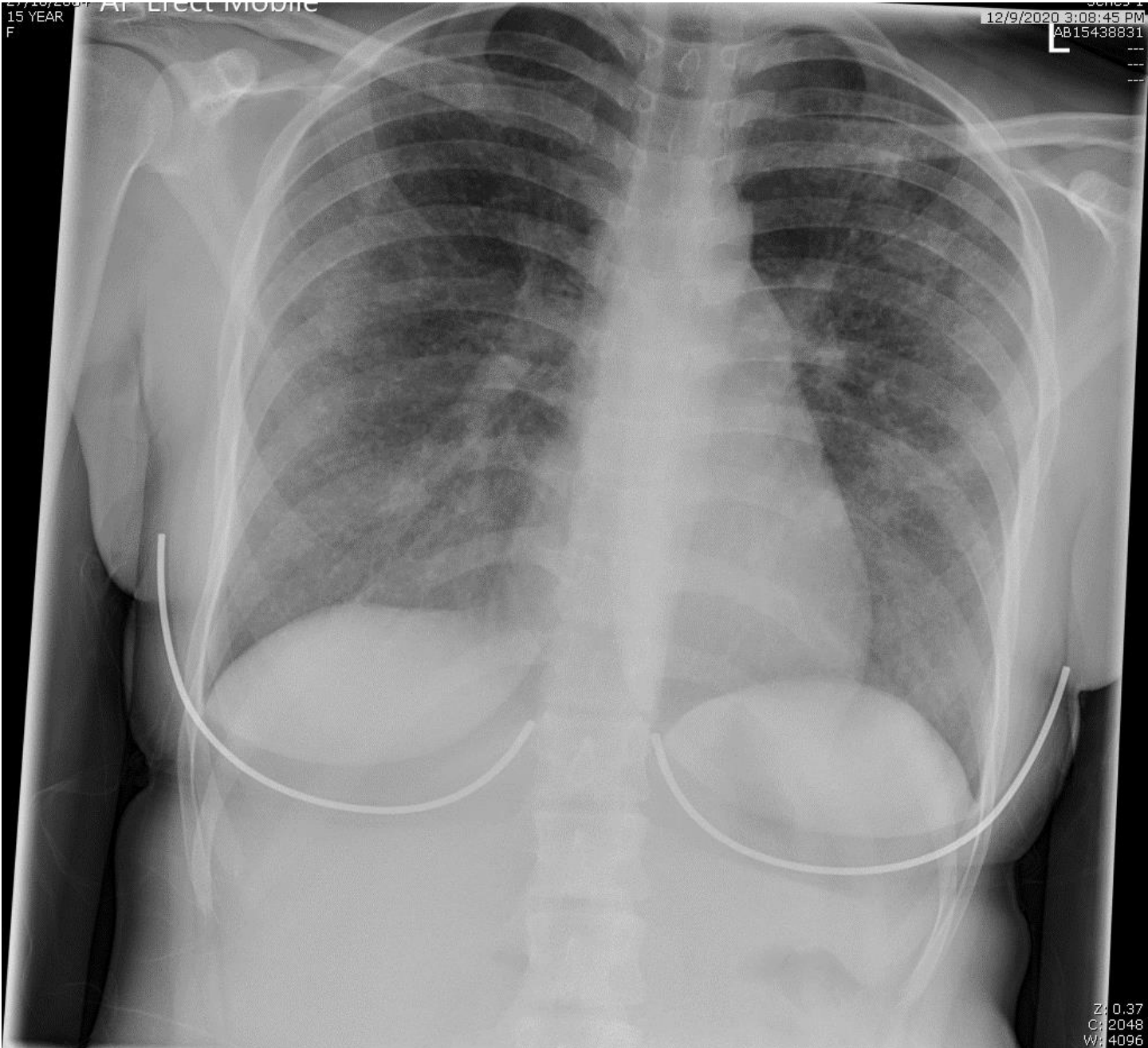
# Miliary pattern



12/9/2020  
15 YEAR  
F

AP EFFECT MOBILE

12/9/2020 3:08:45 PM  
AB15438831



Z: 0.37  
C: 2048  
W: 4096



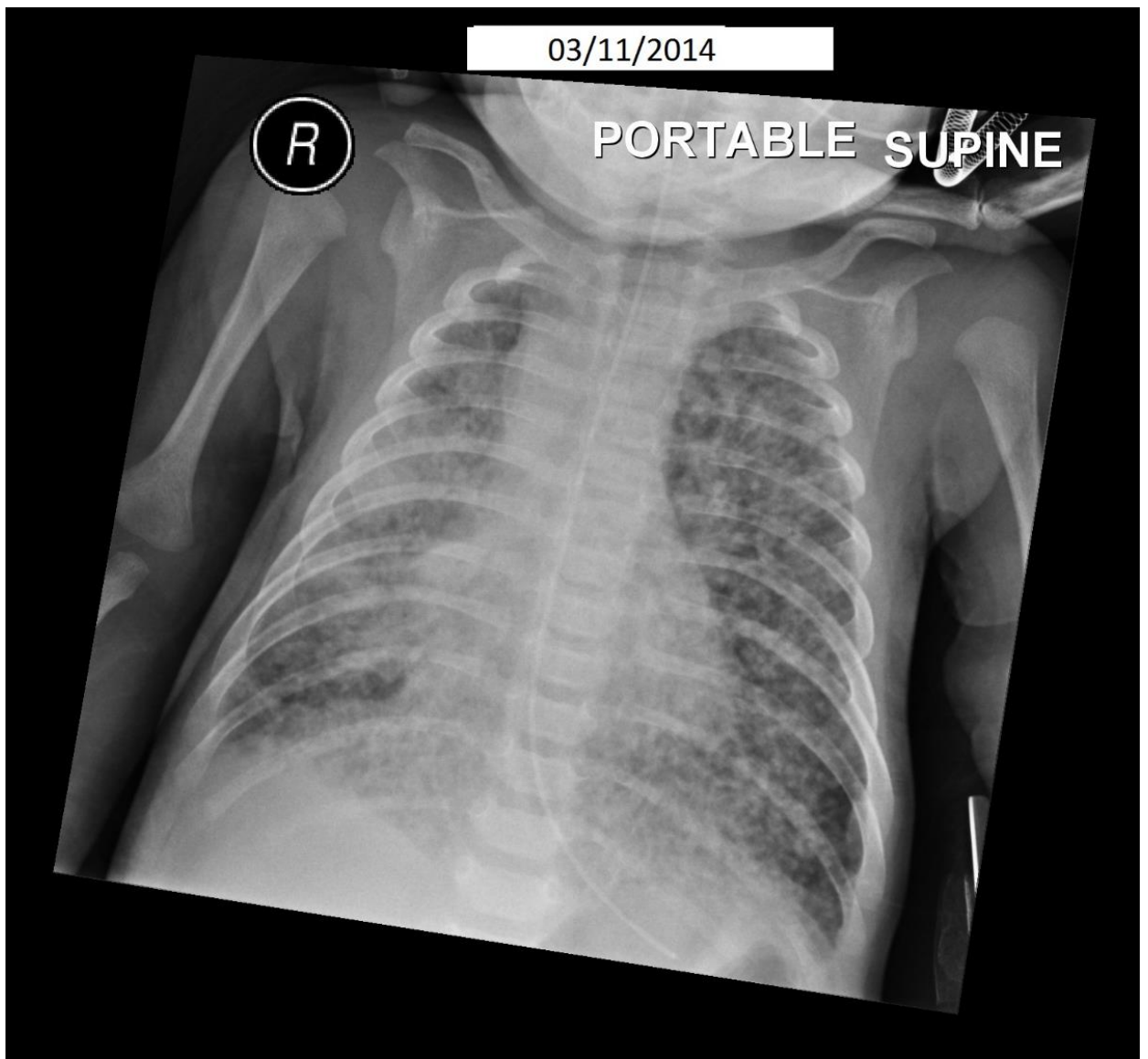
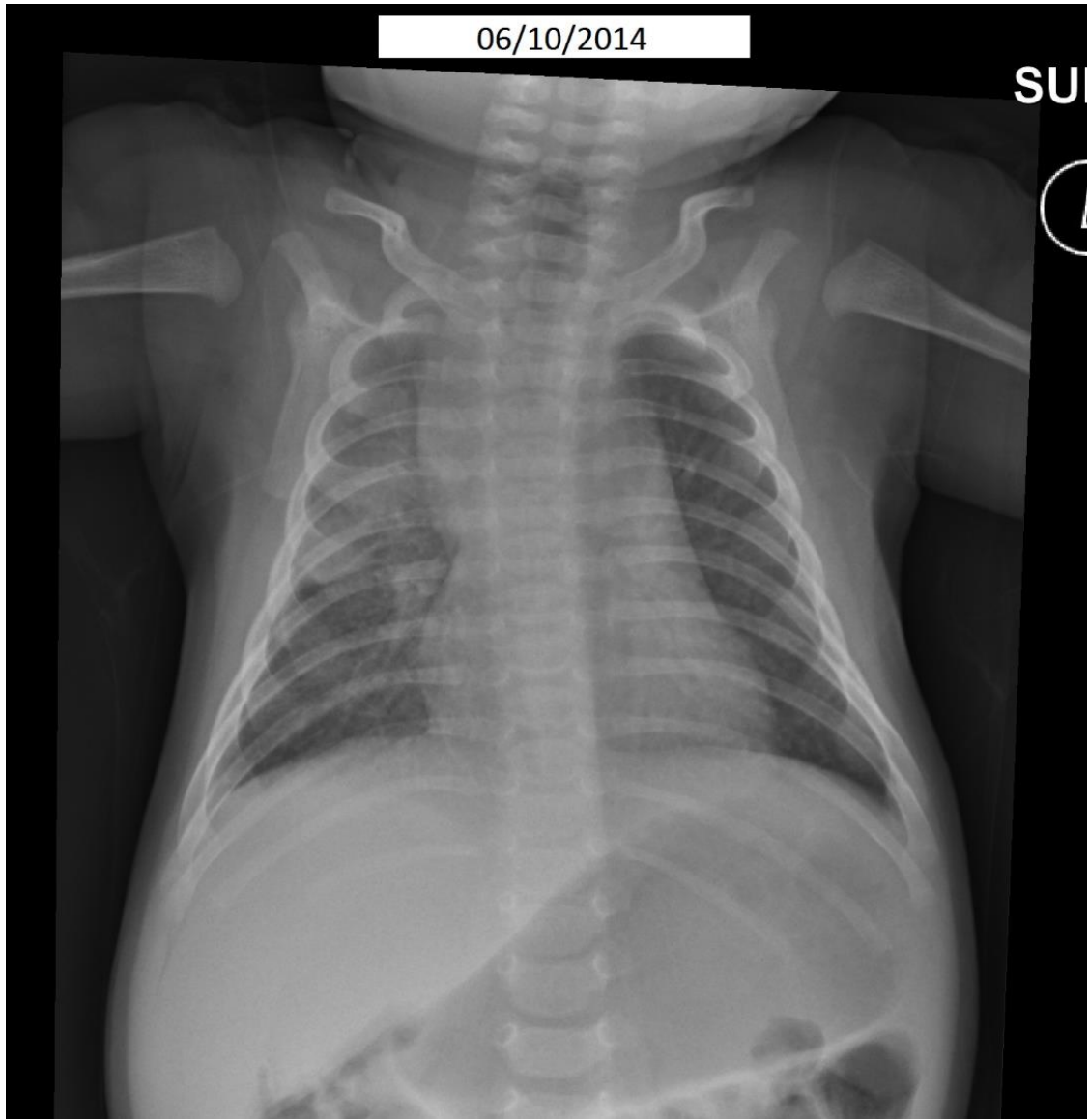
06/10/2014

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03/11/2014

PORTABLE SUPINE





# Mantoux test

- Tuberculin: extract of the tubercle bacillus mixed in glycerine  
0.1ml *intra-dermal*



# Interpreting a Mantoux test

- “Delayed-type hypersensitivity” response. T-cell mediated memory response.
- TB endemic countries:  $\geq 10\text{mm}$  induration is positive, *in the setting of clinical features of TB* (chest x-ray consistent with TB, known smear positive contact, HIV)
- A Mantoux test cannot be interpreted alone because it does not differentiate between active and latent TB
- *Other* mycobacterial infections also lead to +ve Mantoux (M. Leprae, MAIS complex)

# Interpreting a Mantoux test

## **False positive**

- BCG vaccine (usually <5mm)
- If injected area is touched, causing irritation

## **False negative**

- Malnutrition
- Recent TB infection (less than 8–10 weeks)
- Glandular fever (EBV infection)
- Live virus vaccine - within 3 weeks of live virus vaccination (measles, MMR, Sabin)
- Corticosteroid therapy
- HIV and low CD4 T cell counts

# Investigations for extra-pulmonary TB

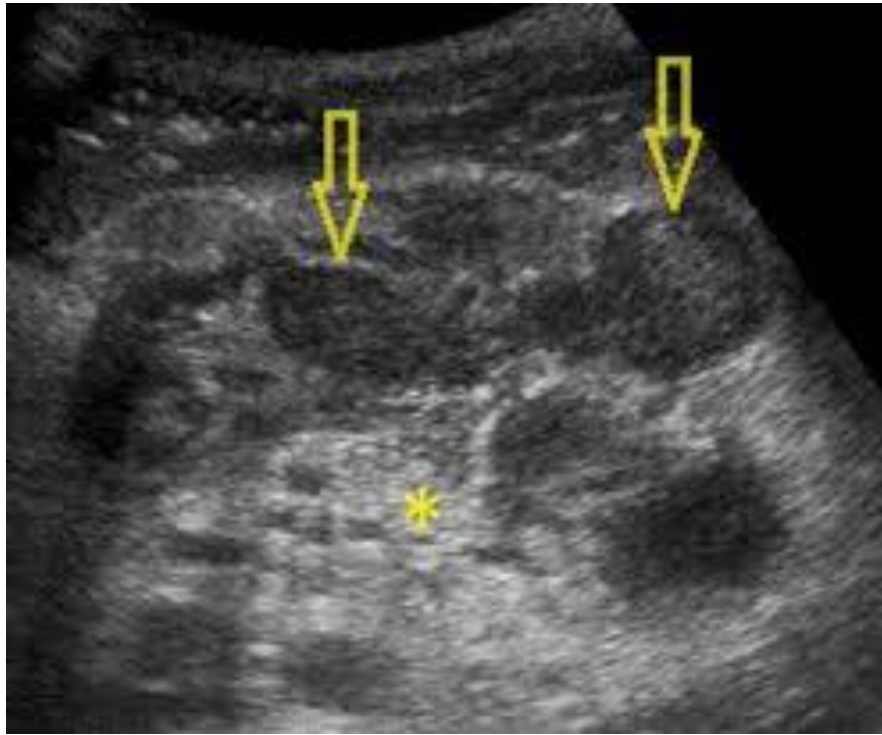
- Kidneys – sterile pyuria (high WCC in urine, bacterial culture negative)
- Lumbar or thoracic vertebra – Pott's disease
- Adrenal glands – Addison's disease
  - lethargy, hypotension, shock, ↓Na, ↑K
- Lymph nodes of neck – scrofula
- CSF / brain – CNS TB
- Gastrointestinal tract

Scrofula, matted, caseating  
cervical lymph nodes and  
sinus

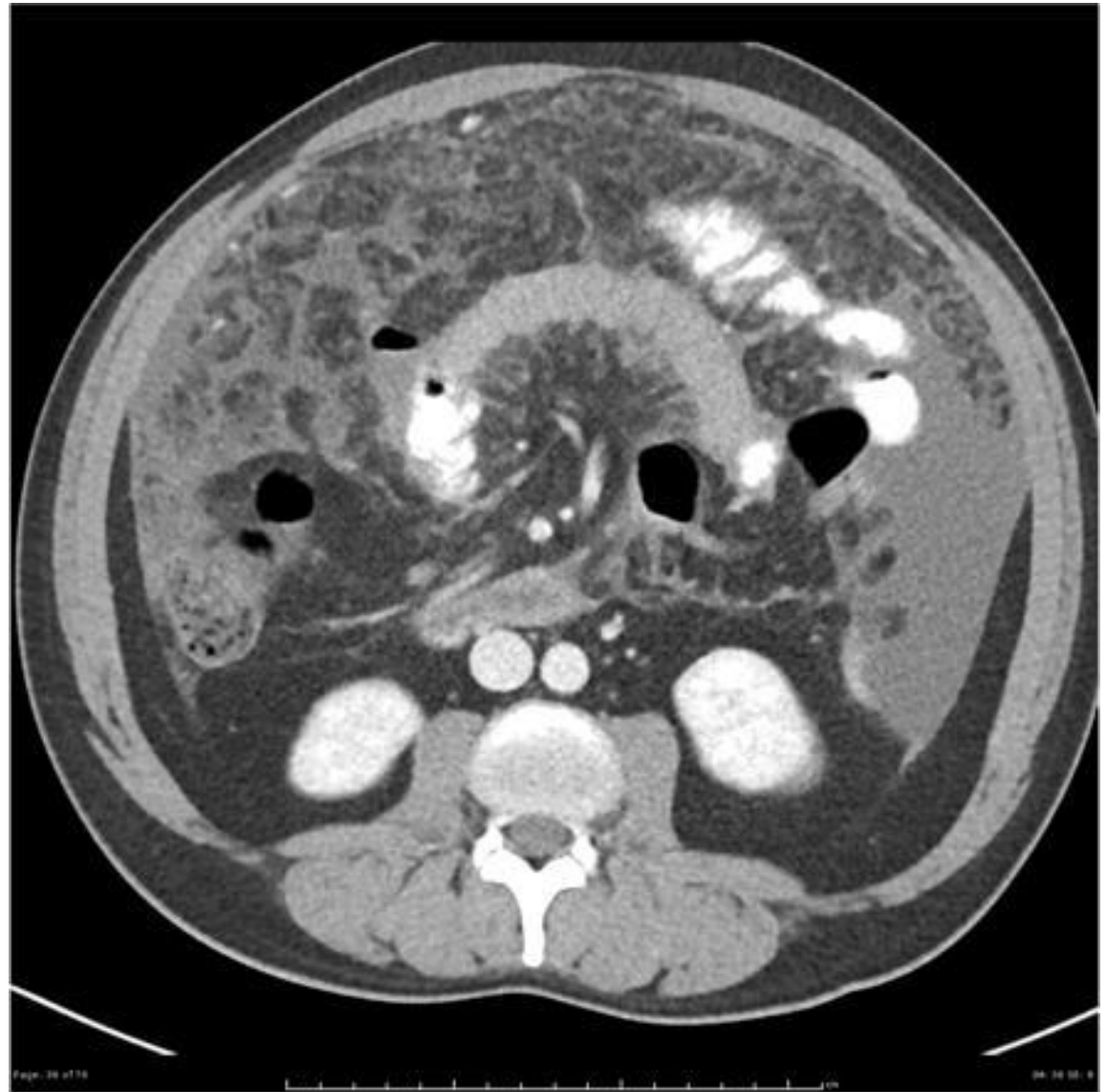


# Abdominal TB

- Ascitic fluid: leukocyte count of 150 to 4000 cells/mL, mostly lymphocytes
- CT scan
  - Thickening of peritoneum, omentum, and bowel wall
  - Lymph nodes: rim enhancement (white) and hypodense (black) centres due to caseous necrosis.
  - Ascites with strands, debris, and septation
- Ultrasound
  - **Hypoechoic** lymph nodes
  - Thickened multi-layered mesentery



Hypoechoic (black=no echos) lymph nodes



Thickening of peritoneum, omentum, and bowel wall  
Ascites with strands, debris, and septation

# CNS Tuberculosis

- Integrated diagnosis clinical and laboratory tools
- History of meningitis 5 days



# CNS tuberculosis

- For a test to adequately rule out a life-threatening disease, a high sensitivity is needed.
- Xpert: sensitivity 28-79%, depending on study and CSF volume. Large CSF volumes (ideally 8–10 mL) needed for Xpert testing, centrifuged.
- Small volumes, e.g. 2ml, have lower sensitivity
- 84% NPV → Negative Xpert test does not exclude TBM
- CSF Ziehl-Neelsen staining is rapid, but sensitivity is poor (10%–20%)

Meningitis symptoms >5 days

No LP

Check for signs of ↑ICP  
papilloedema  
extensor posturing  
sun-setting eyes

LP

Measure pressure with manometer

8 ml of CSF

Centrifuge at 1000-3000 g for 20 min  
Remove supernatant, leave 4 ml

0.25ml **Gram stain**  
0.5ml protein glucose  
0.2ml **bacterial culture**

**2ml GeneXpert**  
0.5ml TB Culture  
0.1ml AFB stain

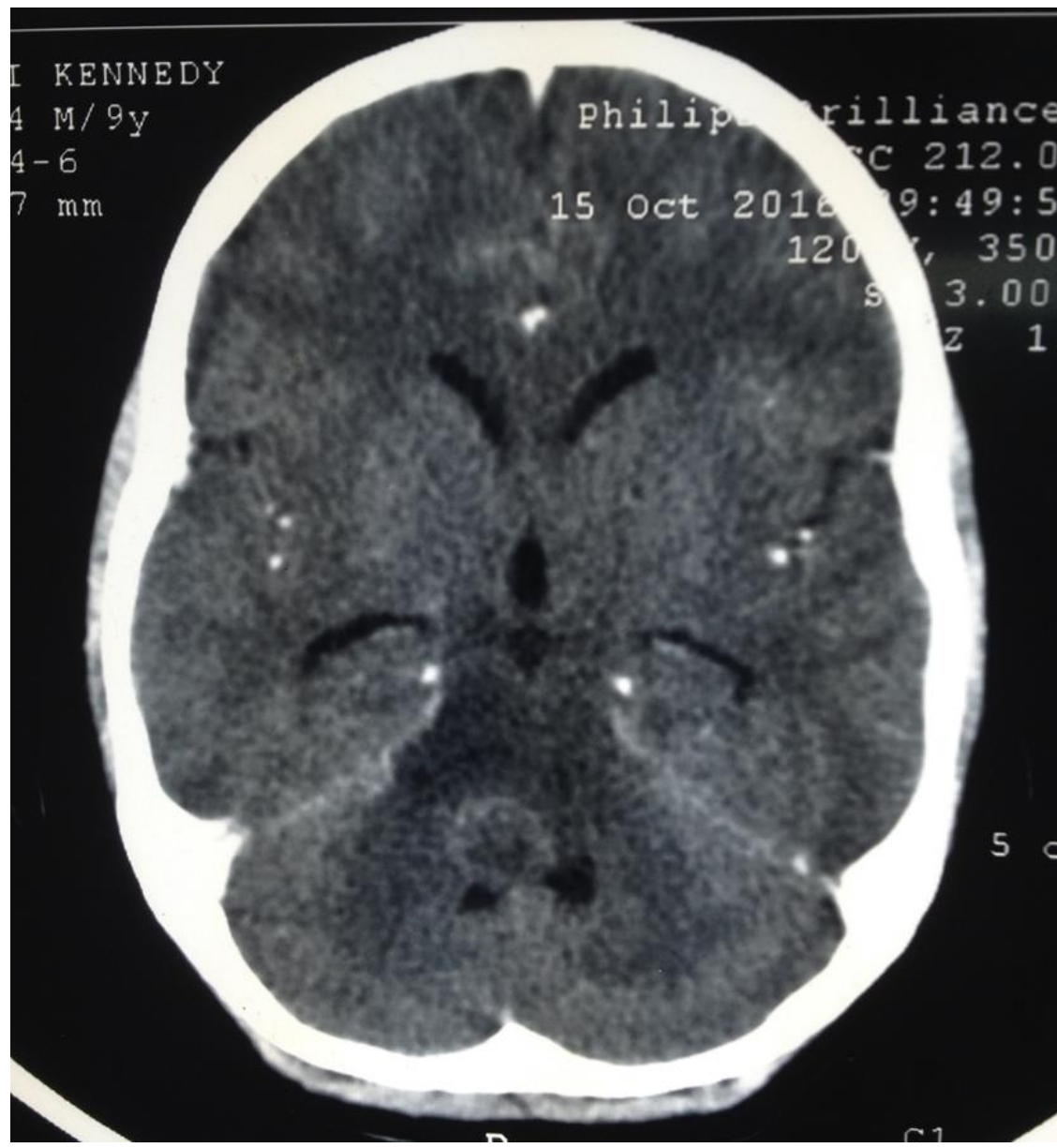
0.1ml Indian Ink stain  
0.5ml Cryptococcal Ag

# CSF volume and diagnostic tests

If <0.5 ml of CSF available, all the specimen is needed for microscopy of Gram stain, and bacterial culture.

KENNEDY  
4 M/9y  
4-6  
7 mm

Philip Brilliance  
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120 kV, 350  
S 3.00  
Z 1



5

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The Royal Children's Hospital  
CT Brain With IV Contrast  
C+ Head 4.5 H31s  
2/10/2009 14:48:44  
09065873CTBRWC

LOC: -24  
THK: 4.5  
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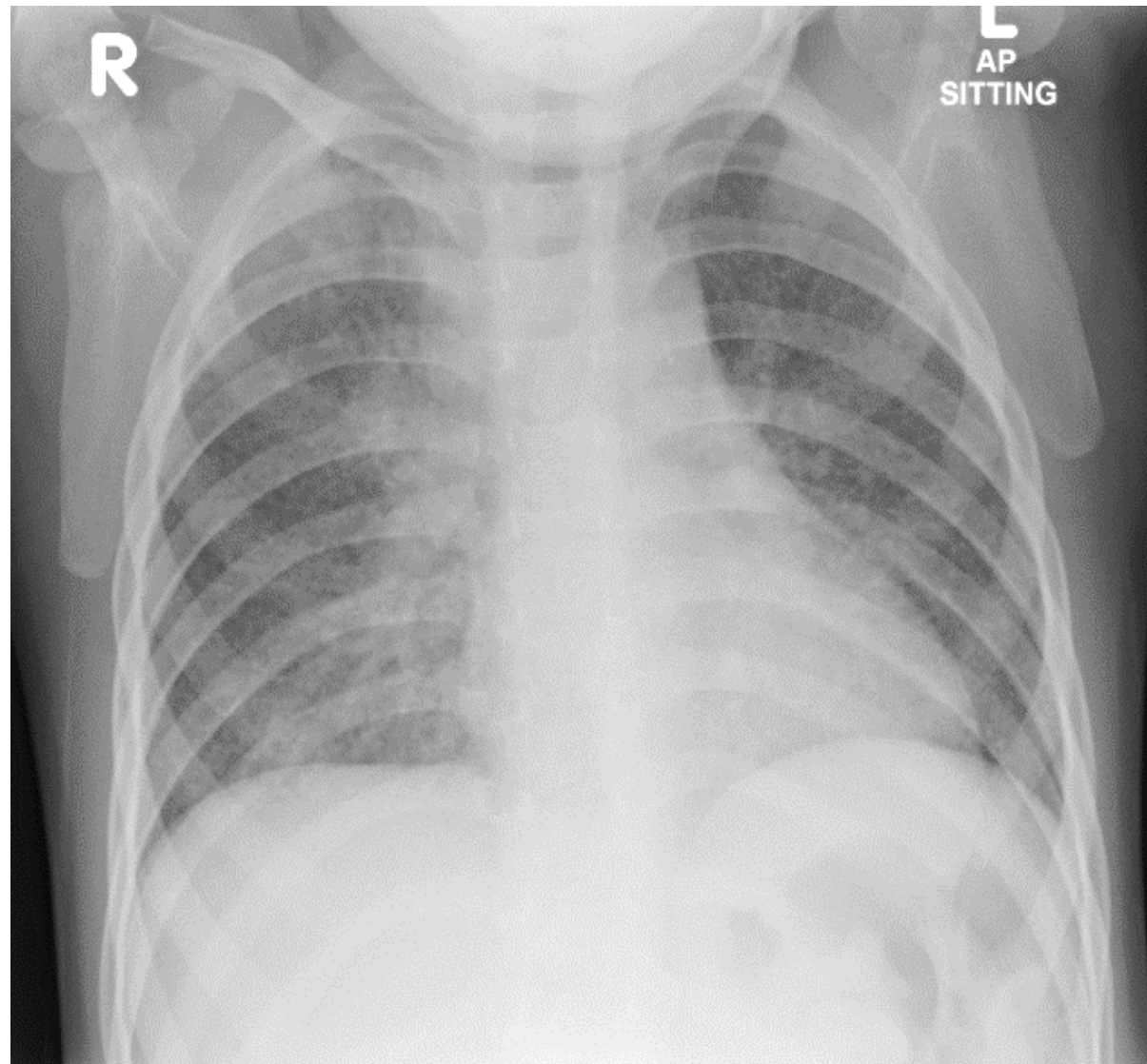
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Tilt: -15.5  
mA: 172  
KVp: 120  
Acq no: 17

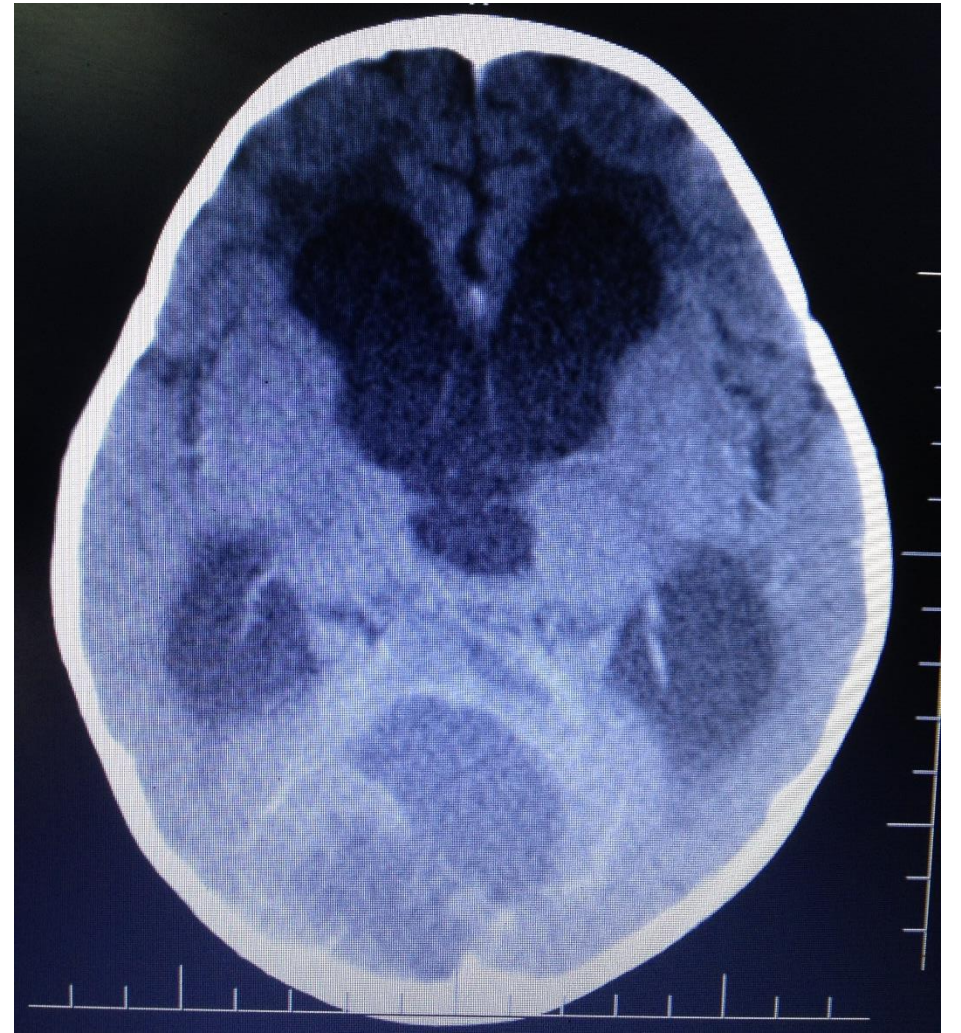
Z: 1  
C: 34  
W: 84  
DFOV: 20.1x20.1cm

Page: 17 of 28

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# MDR TB

- Most acquired from adults
  - Selective anti-TB pressure on paucibacillary TB rare
- MDR-TB is a bacteriological diagnosis
  - The organism must be identified and drug susceptibility testing done to confirm the diagnosis of MDR-TB
  - But criteria for investigating for MDR TB...

# Criteria for considering MDR TB

- Close contact with a known case of drug resistant TB
- Early treatment failure - any child or adolescent who at the end of the Intensive phase, despite adherence:
  - Remains sputum or gastric aspirate smear-positive OR
  - Is showing no or inadequate clinical improvement OR
  - Failures to gain weight despite provision of adequate food
- Recurrence of TB after adherence to treatment