MMed and DCH Lectures

Weekly by Zoom

Prof Trevor Duke

MMed and DCH Lectures

Diagnosis of tuberculosis

August 3, 2020

Prof Trevor Duke

Is the diagnosis of TB difficult in children?

- TB is paucibacillary
  - “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 likely 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

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

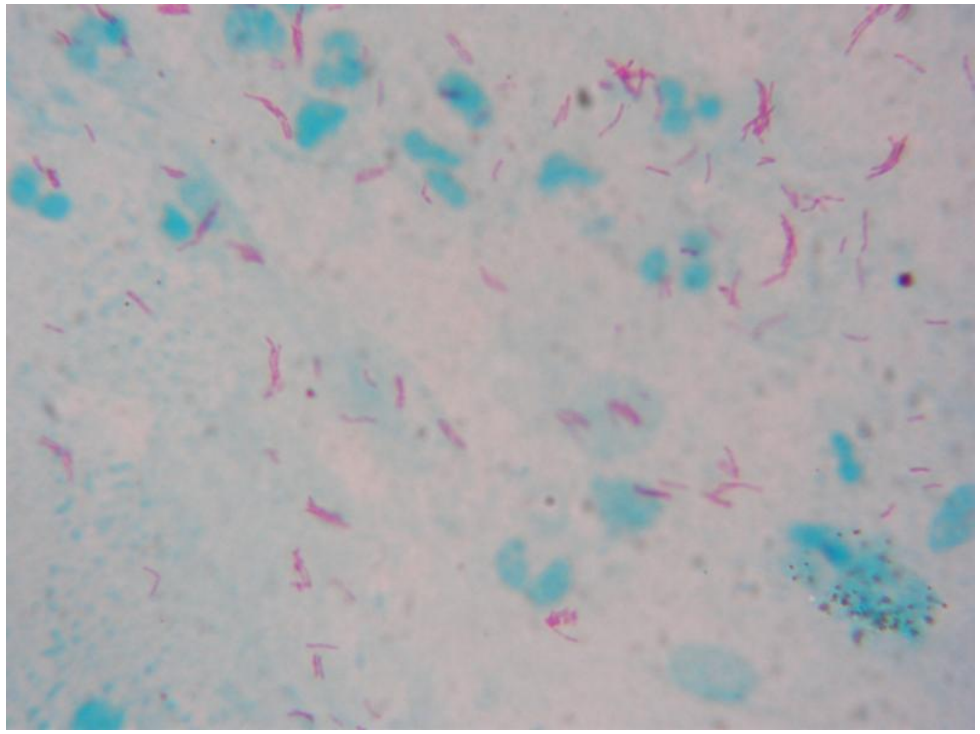
Feature	0	1	2	3	4	Score
Length of illness (weeks)	< 2	2-4		> 4		
Nutrition status (weight for age)	Above the -2 line	Between the -2 and -3 line		Less than the -3 line		
Recent close contact with an infectious TB case (adult with PTB or sputum smear positive case)	None	Verbal history of TB contact		Proven 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) Send to hospital if possible				Yes		
					TOTAL	

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 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)
  - *Retains red dye* in-spite of being exposed to acid alcohol
  - Makes mycobacterium hardy – survives on dry surfaces for prolonged periods
  - Other bacteria don’t have such a waxy cell wall, so the red dye washes out with acid-alcohol



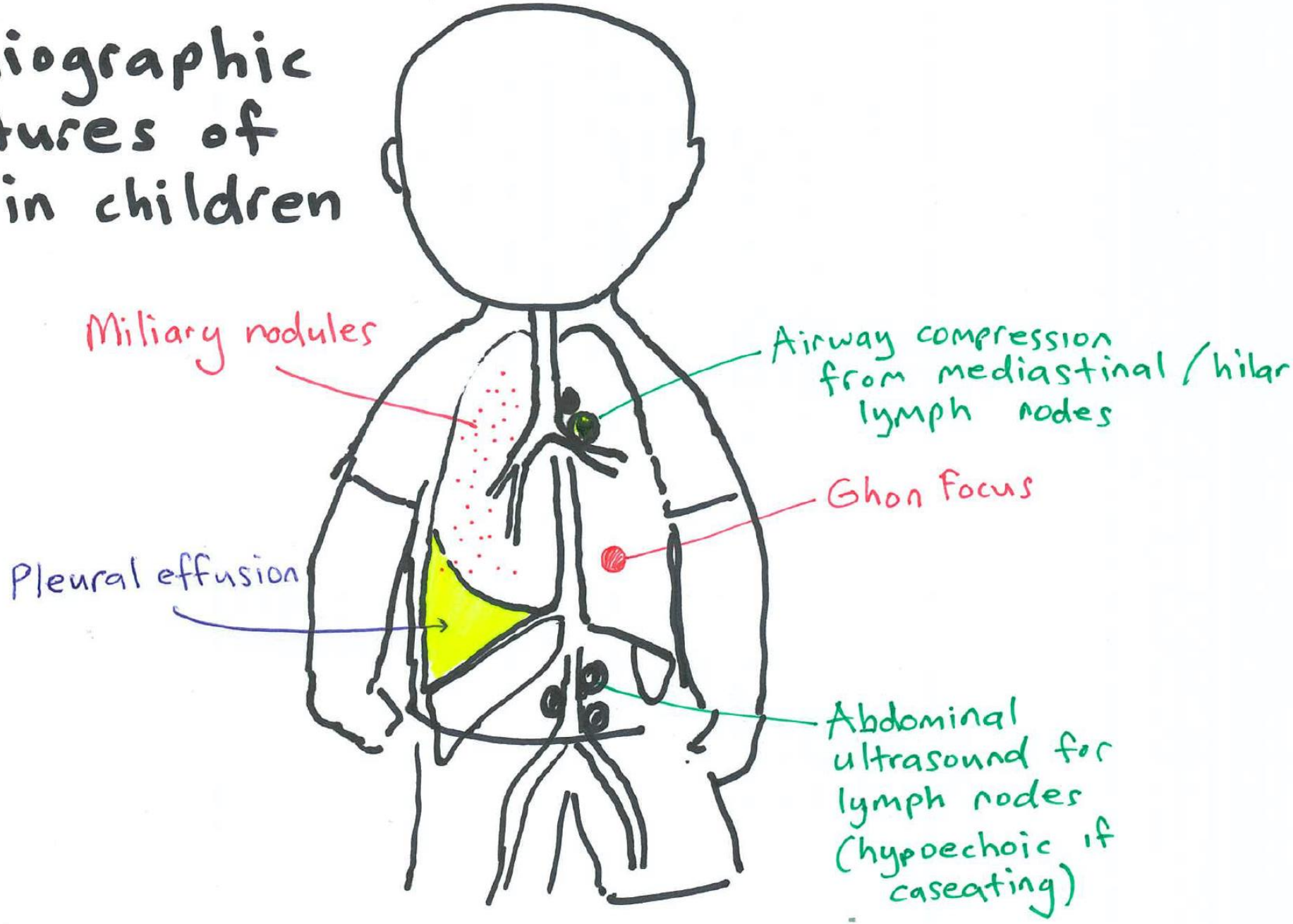
GeneXpert MTB / Rif

- 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

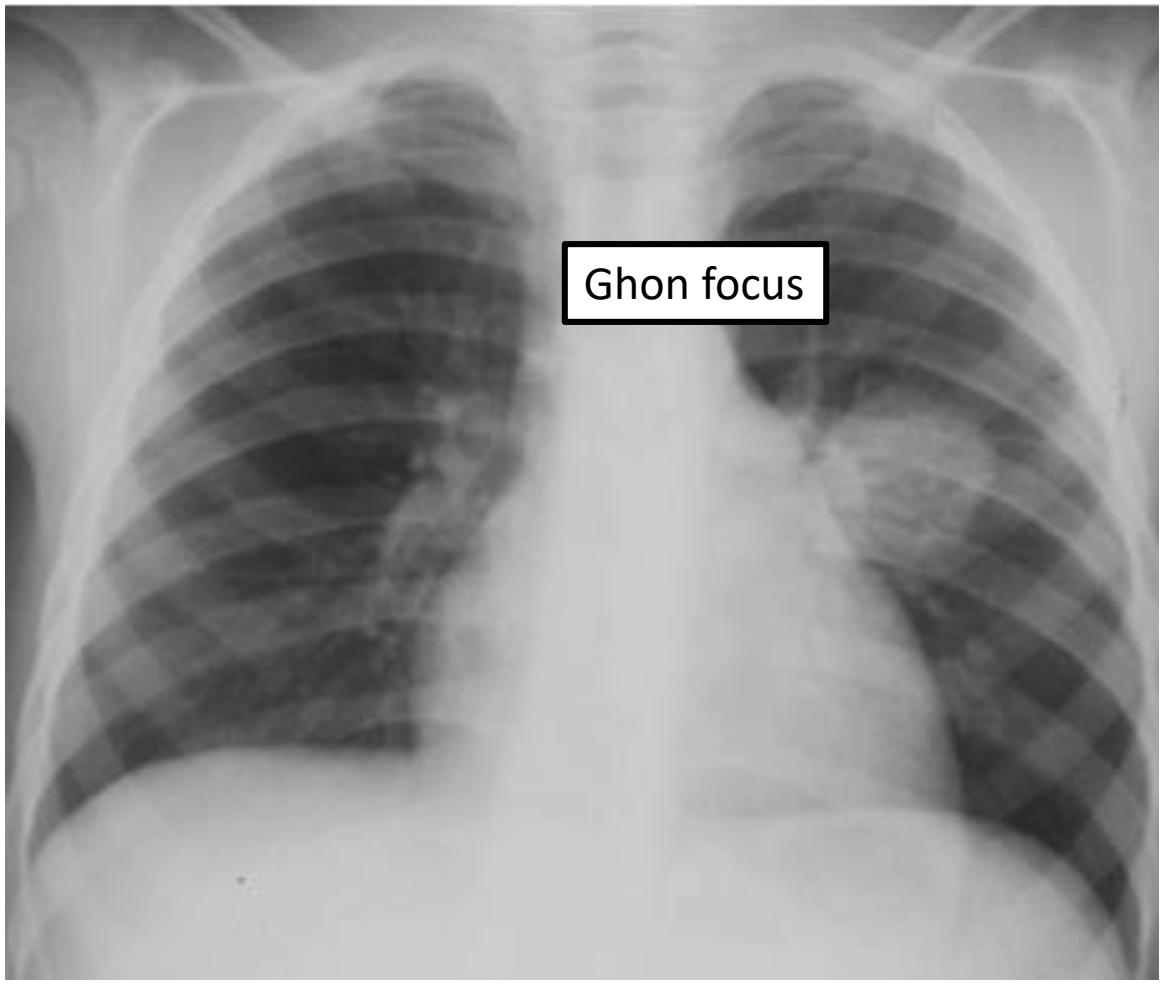


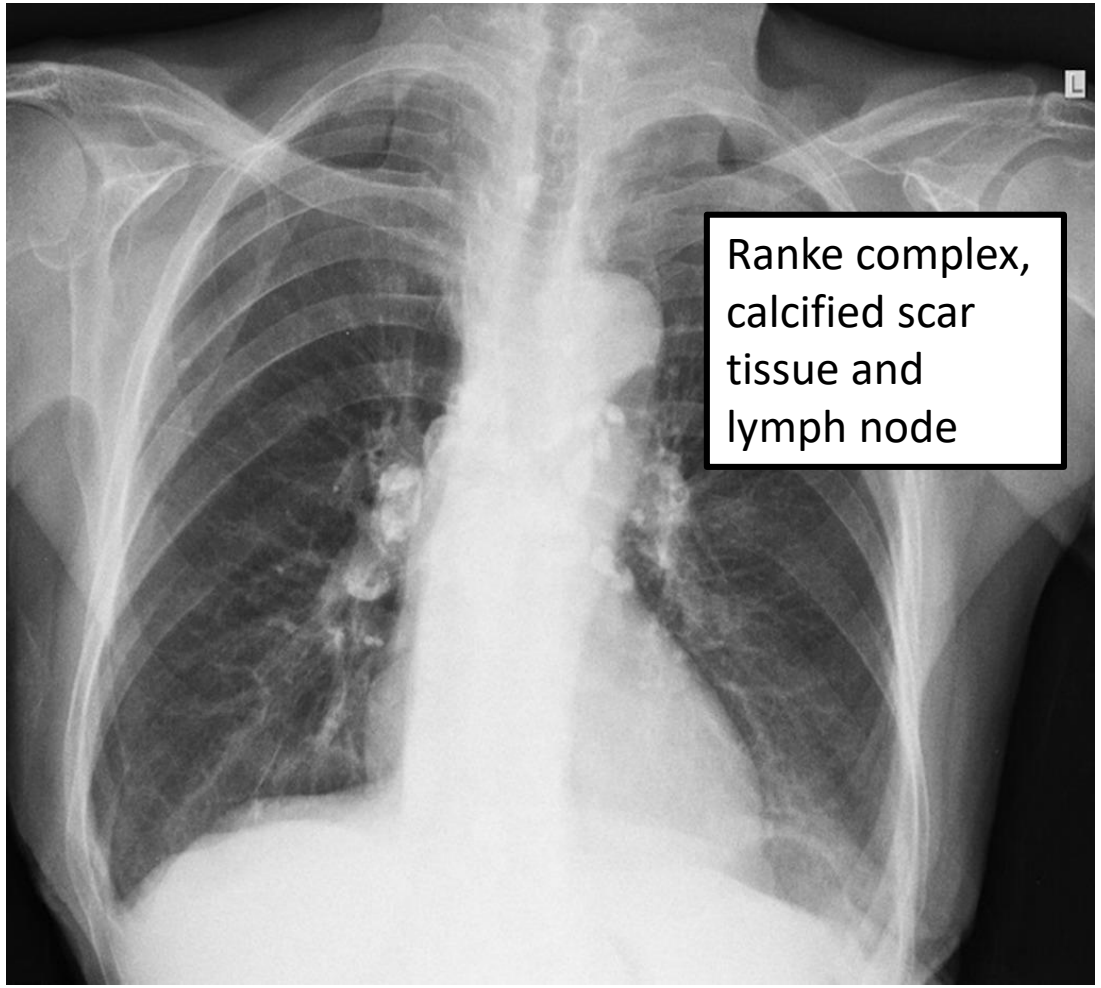
Chest x-ray changes in MDR TB

- 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

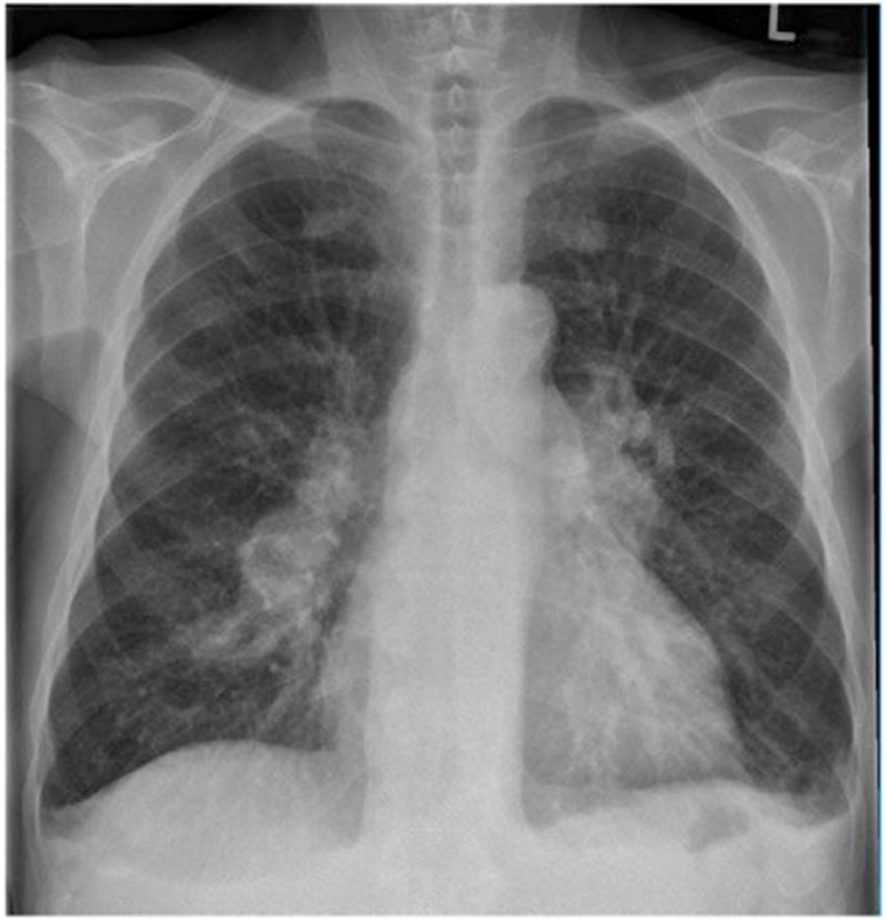




Hilar masses

Enlarged peri-hilar lymph nodes

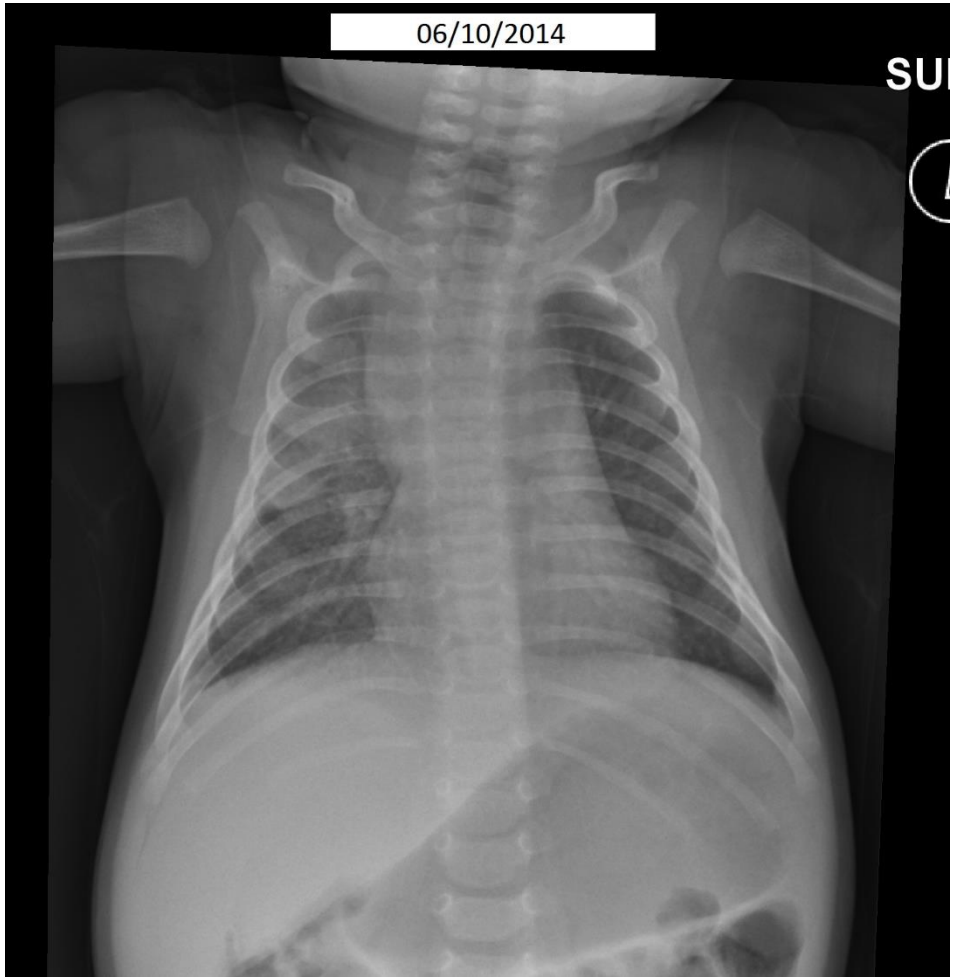
Discrete opacities: TB, lymphoma



Enlarged pulmonary arteries

Opacities with vascular marking extending outwards

Miliary pattern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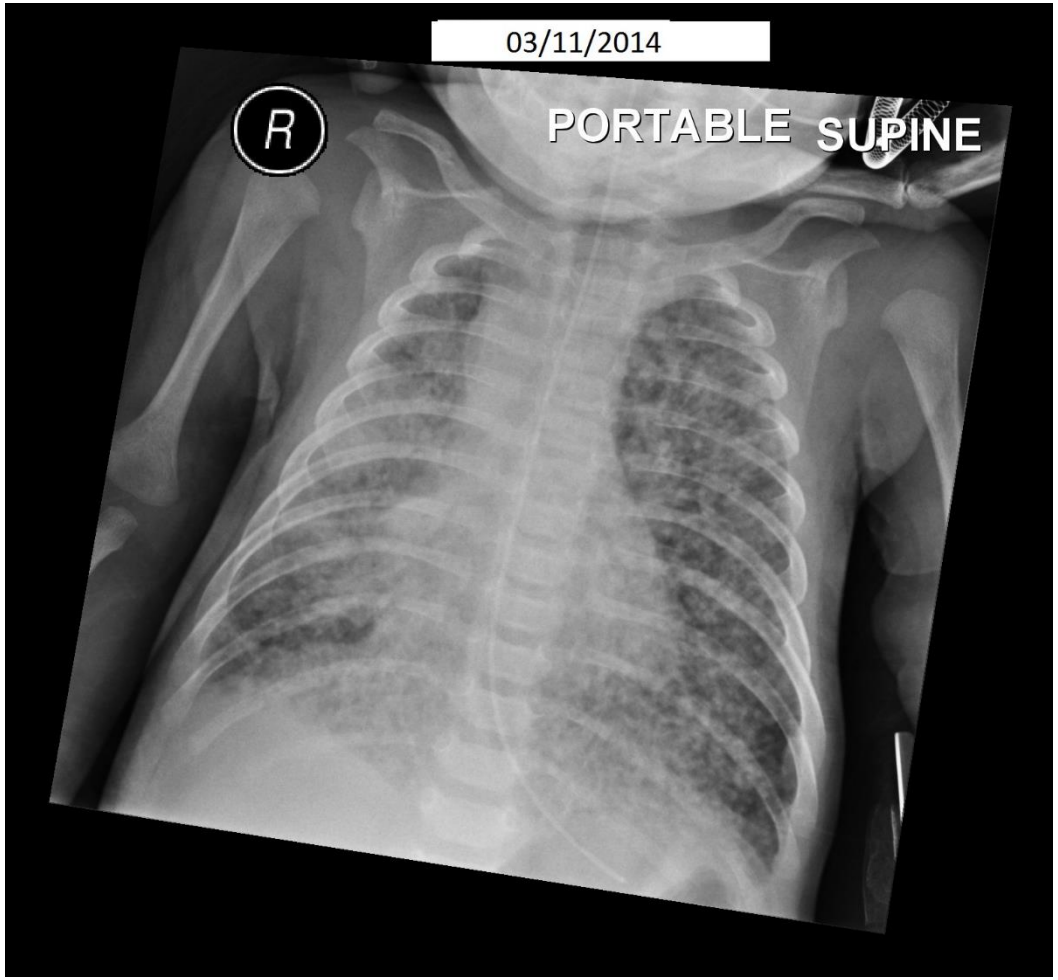
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Mantoux test

- Tuberculin is a glycerol extract of the tubercle bacillus, intradermal, 0.1ml *intra-dermal*

Interpreting a Mantoux test

- Delayed-type hypersensitivity response. T-cell mediated memory response.
- In endemic countries ≥10mm 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

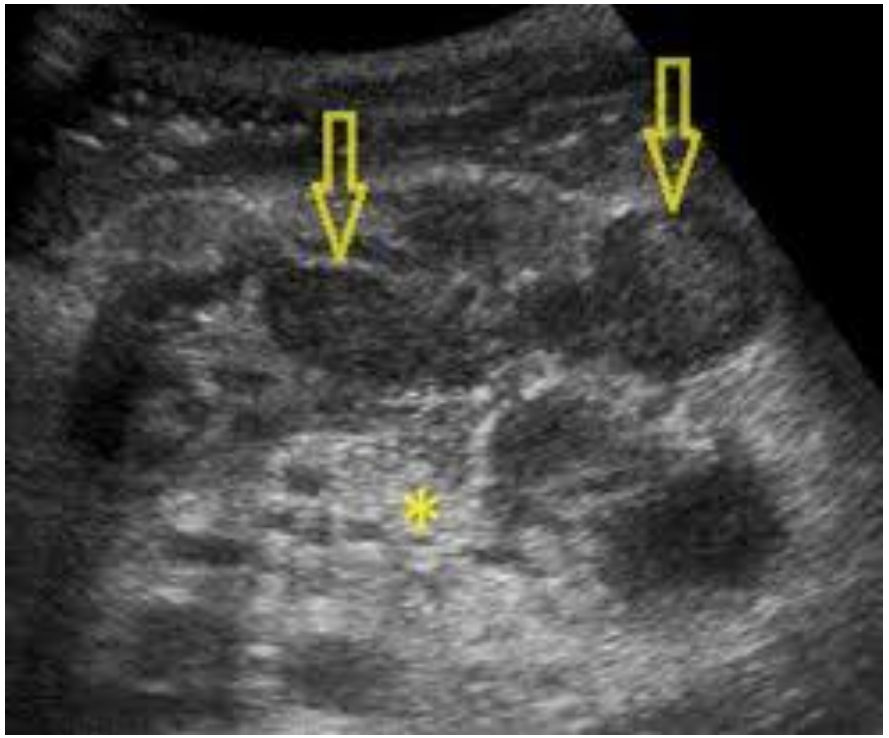
- Malnutrition
- Recent TB infection (less than 8–10 weeks)
- Glandular fever (EBV infection)
- Live virus vaccine - within 3 weeks of live virus vaccination (measles, MMR, Sabin)
- Corticosteroid therapy
- HIV and low CD4 T cell counts

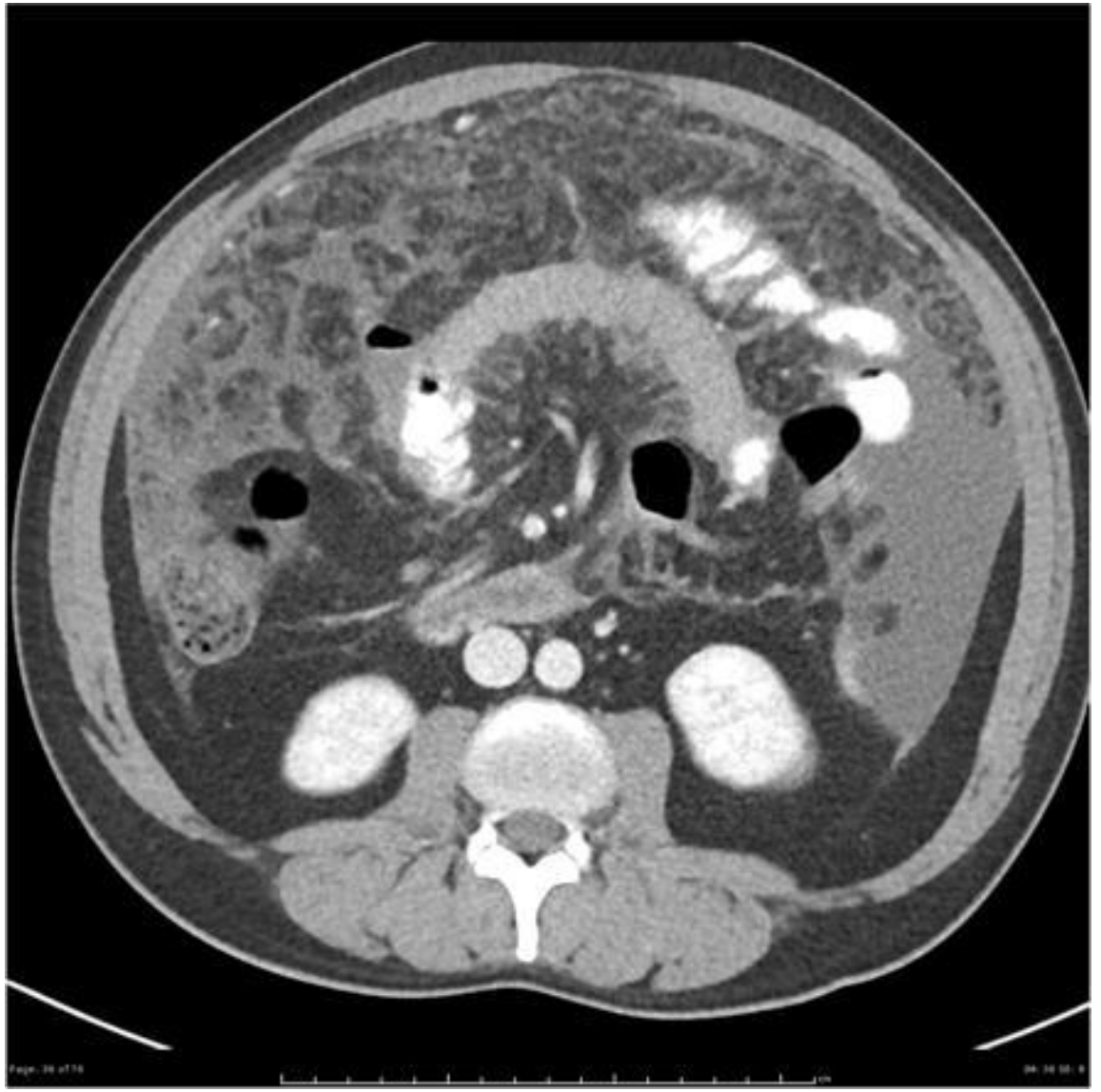
Investigations for extra-pulmonary TB

- 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

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 (“club sandwich”)





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 NPV 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

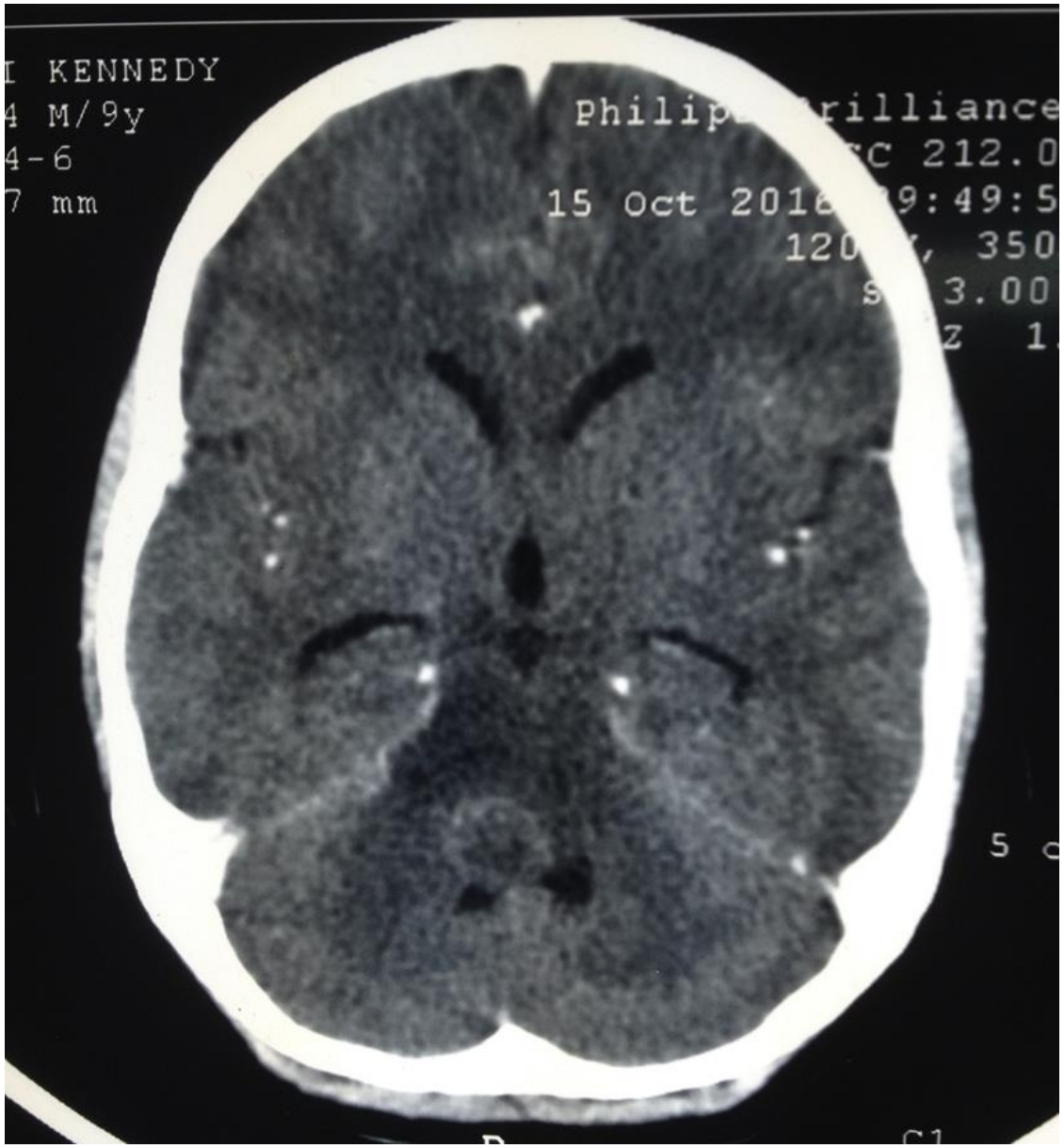
0.25ml **Gram stain**
0.5ml protein glucose
0.2ml **bacterial culture**

2ml GeneXpert
0.5ml TB Culture
0.1ml AFB stain

0.1ml Indian Ink stain
0.5ml Cryptococcal Ag

CSF volume and diagnostic tests

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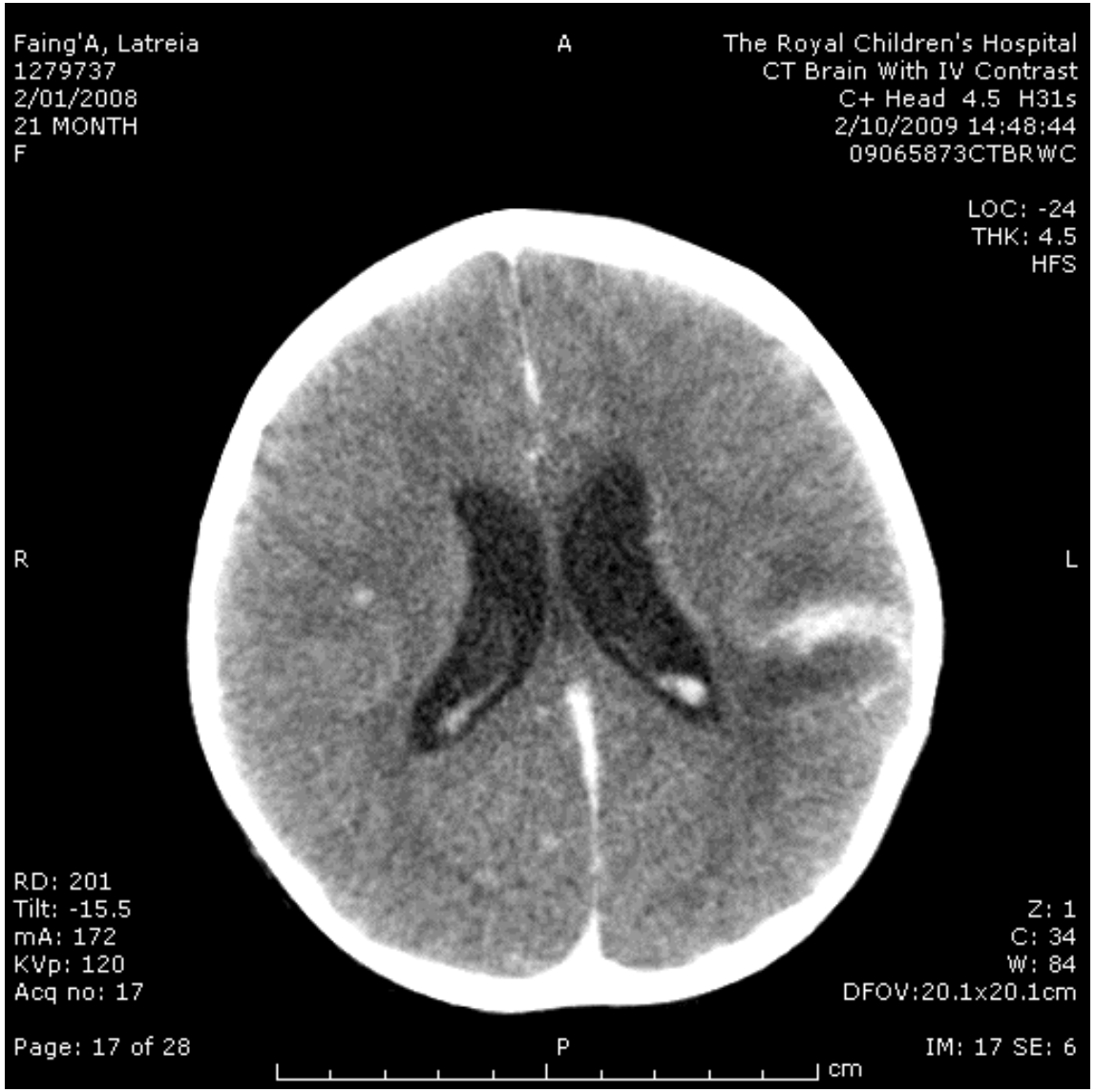
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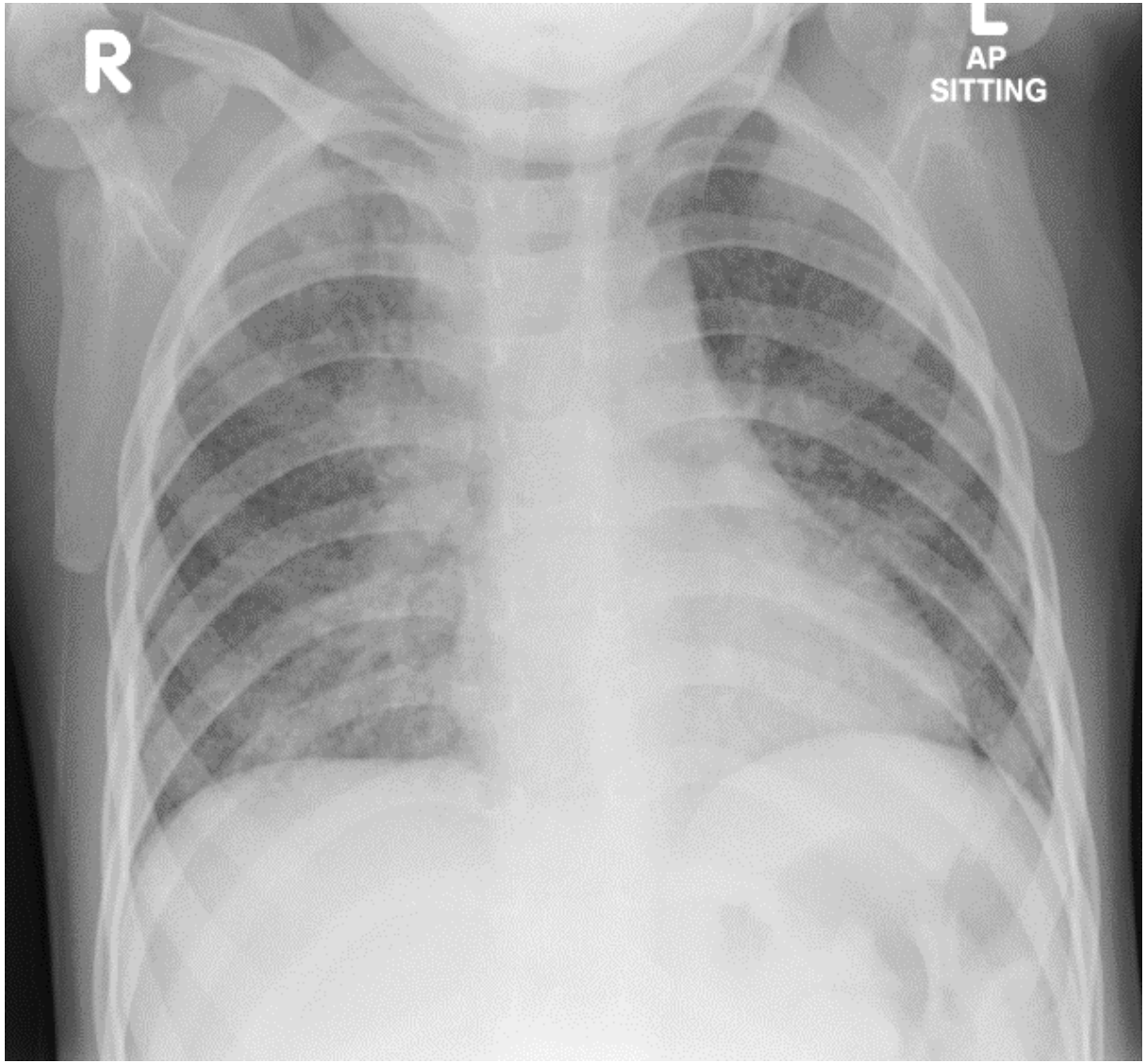
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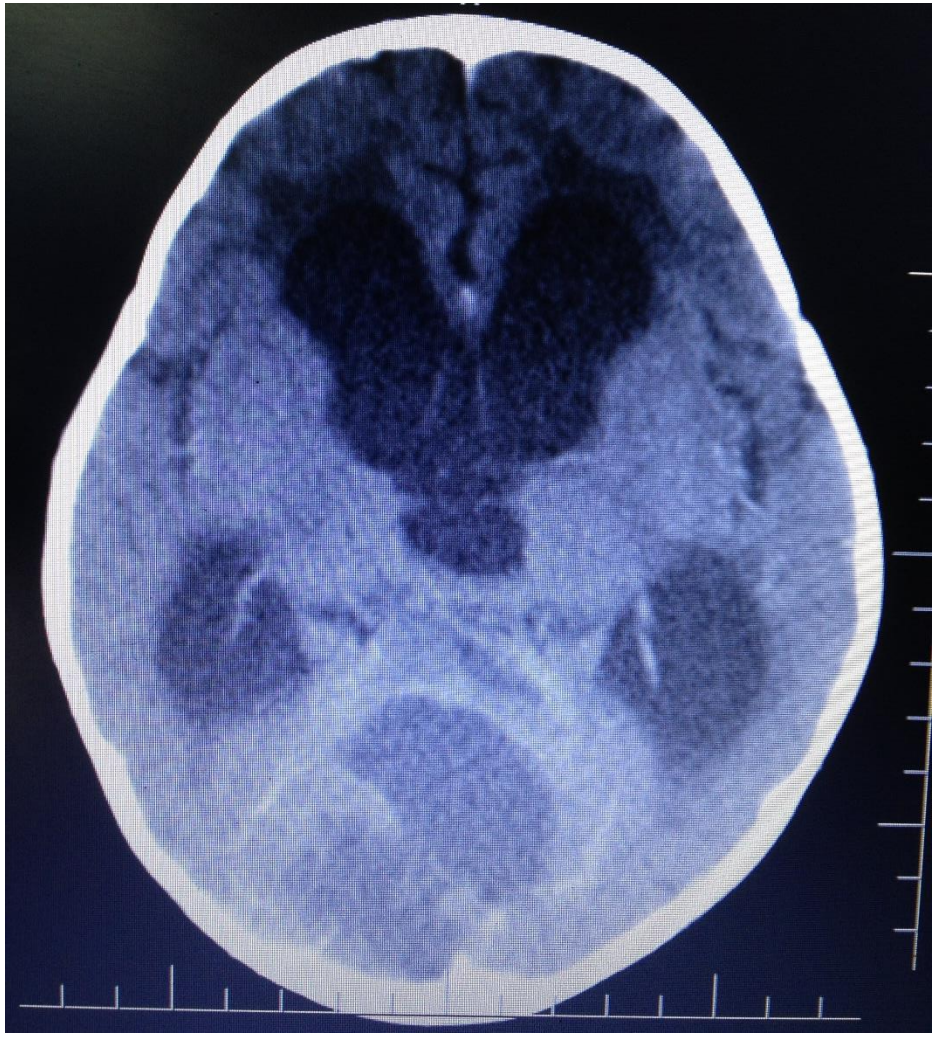

MDR TB

- 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