MYCOBACTERL INFECTIONS

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MYCOBACTERIOLOGY

- Non-motile, nonspore – forming
- Acid Fast positive (Ziehl–Neelsen stain)

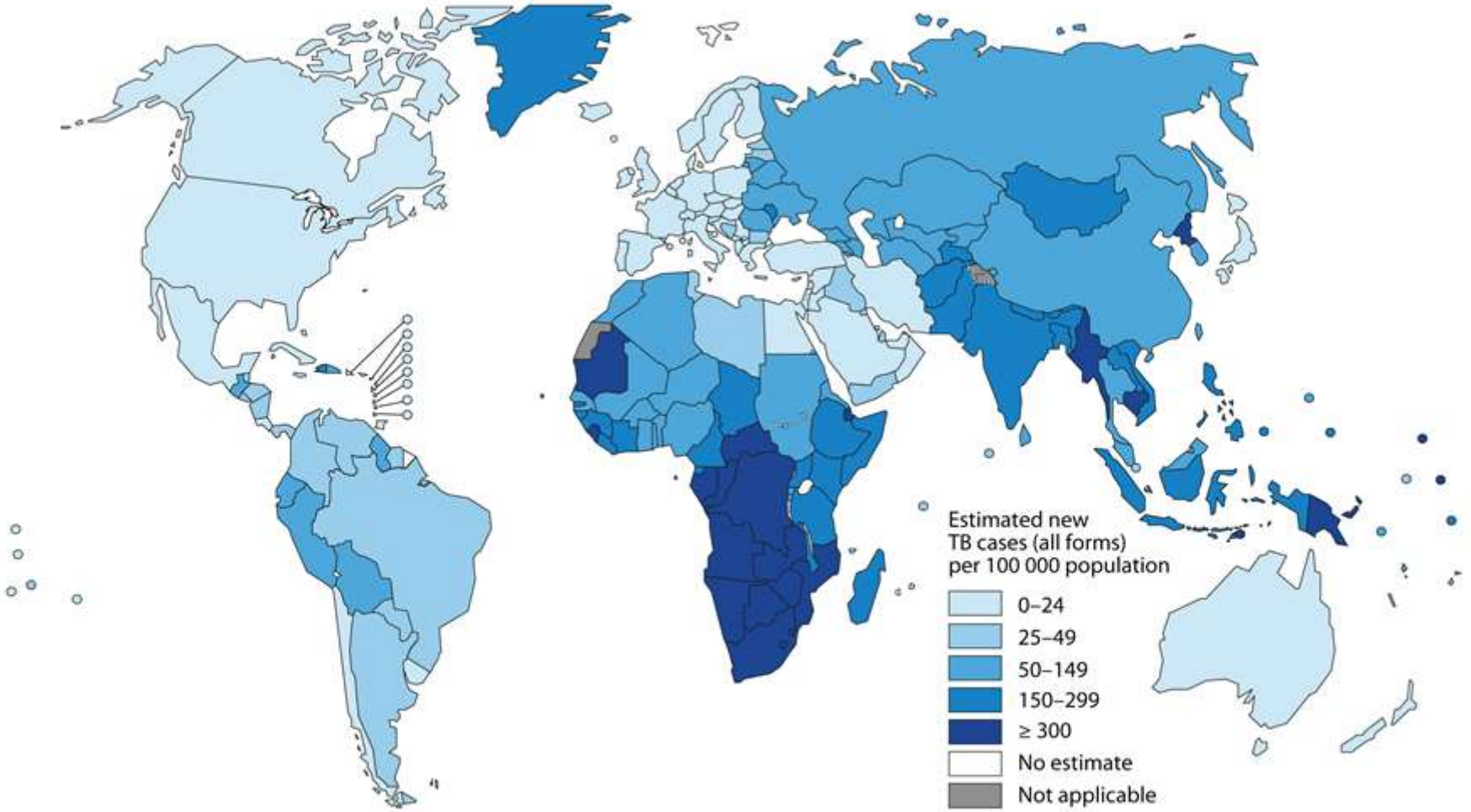
MYCOBACTERIOLOGY

- Obligate aerobes
- Cell wall: 20 to 60 percent lipids
- generation time of 12 to 48 hours (except rapid growers)

EPIDEMIOLOGY OF TUBERCULOSIS IN THE WORLD

- 10 million cases per year
- 2-3 million deaths per year
- 600,000 cases dual TB/HIV
- 2 billion infected individuals
- $30 – $50 billion per year direct impact

Estimated tuberculosis (TB) incidence rates, 2011



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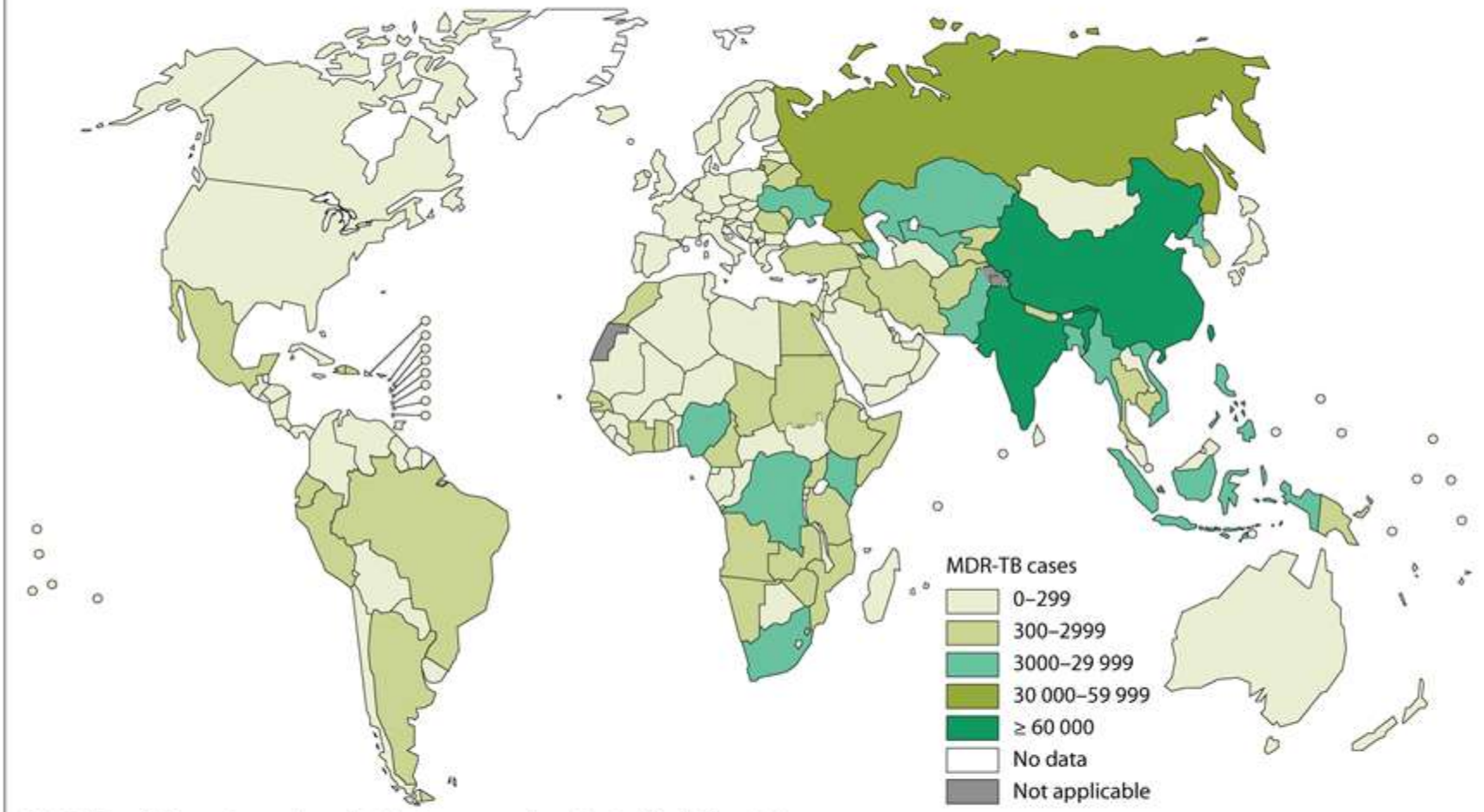
Source: *Global Tuberculosis Report 2012*. WHO, 2012.

World Health Organization

Number of MDR-TB* cases estimated to occur among notified pulmonary tuberculosis cases, 2011



* MDR-TB: multidrug-resistant tuberculosis (resistance to, at least, isoniazid and rifampicin)

Source: *Global Tuberculosis Report 2012*. WHO, 2012.

World Health Organization

RISK FACTORS FOR TUBERCULOSIS

Increased risk of acquiring or having infection

- Foreign born from high prevalence country
- Some healthcare workers
- Family history of TB (2-3 generations)
- Intravenous drug or crack cocaine user
- Contact with HIV- infected individuals
- Contact with inmates of prison or jail (past or present)
- Some nursing homes, residential living\ \

RISK FACTORS FOR TUBERCULOSIS

Increased risk of developing disease after infection

- Extremes of ages: infants, elderly
- Recent (<3 years) infection
- HIV infected
- Immune suppression - drugs or disease
- Certain diseases: silicosis, diabetes mellitus

TRANSITIONS INTUBERCULOSIS

- Susceptible
- Exposed
- Infected
- Diseased
- Sick
- Diagnosed
- Treated
- Cured

STAGES OF TUBERCULOSIS

Exposure

- **Defined by contact investigation - recent (< 3months) contact with an infectious case**
- **Negative ST, physical exam and chest radiographs**
- **Period during which the skin test may be negative in an infected person**
- **Children < 5 years old should be treated (usually INH) because they may develop disease rapidly**
- **Older children and adults often not treated, but repeat skin test 3 months after exposure over**

STAGES OF TUBERCULOSIS

Infection

- Hallmark is a “positive” skin test
- “Germs in the body”
- Chest radiograph is normal
- No symptoms, physical exam is normal

SKIN-TESTING, INFECTION AND DISEASE

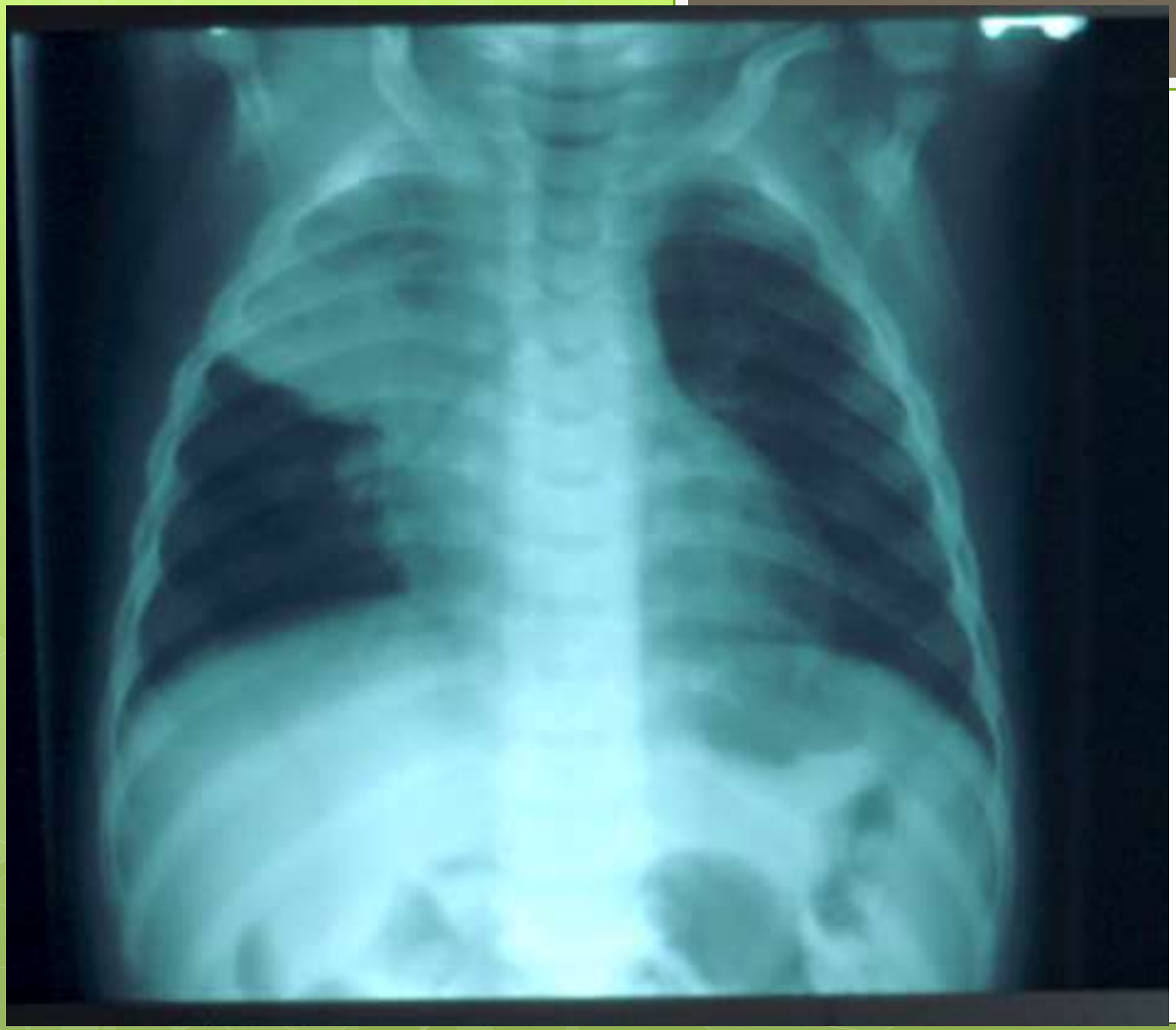
- Tuberculin Skin Test (TST) takes 3 weeks to 3 months to turn positive after infection has occurred

Risk of disease after untreated infection:

- Normal adults: 5-10 percent in lifetime (half of risk in first 2-3 years)
- HIV-infected adults: 5-10 percent per year
- Infants: 40 percent in 1-2 years
- Older children: 5-10 percent (delayed)

STAGES OF TUBERCULOSIS

- Disease
  - Clinical and/or radiographic manifestations of progressive tuberculosis infection
  - Primary: complication of initial infection
  - Reactivation: disease occurs after period of dormancy of the infection
  - TST is negative in 10 % of disease cases (50 % of meningeal or miliary disease)



TIMETABLE OF PEDIATRIC TUBERCULOSIS

- Miliary and meningeal develop rapidly (1-12 months)
- Lymph node (cervical) 2-12months
- Pleural effusion 3-9 months
- Skeletal 6months - 2 years
- Renal 1-5 years

ARE CHILDREN WITH TUBERCULOSIS EVER CONTAGIOUS?

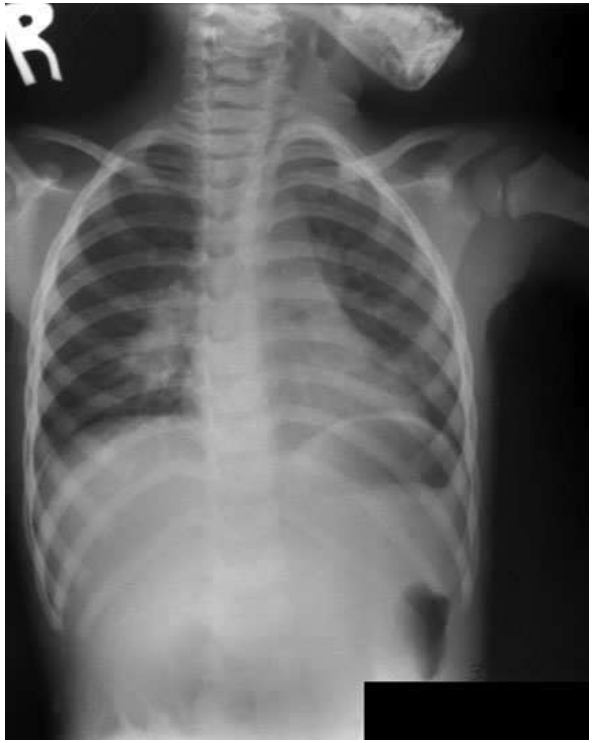
- The quick answer is : NO.
- Orphanages – caretaker with TB led to transmission; a child with TB did not
- Schools – only 2 reported “epidemics” caused by children <13 years old
- Children’s Hospitals – rare case reports of transmission, all with special circumstances, none has been patient -to - patient

FEATURES OF CONTAGIOUS PEDIATRIC TUBERCULOSIS

- Pulmonary:
  - Cavitary lung lesion
  - Sputum production
  - Positive acid-fast stain of sputum smear
  - Bronchoscopy
- Draining lesions or surgical drainage of an abscess
- This means Bone or Renal TB is not contagious as long as they not open.

CLINICAL AND RADIOGRAPHIC MANIFESTATIONS OF CHILDHOOD PULMONARY TUBERCULOSIS

- The CXR is way worse than how the pt. looks.
- Infants more symptomatic: fever, cough, focal wheezing, respiratory distress
- Predominance of hilar and/or mediastinal adenopathy
- Any lobe of lung involved; 25% multilobar
- Local pleural reaction/effusion is common
- Collapse-consolidation or segmental pattern most common
- Obstructive signs/symptoms with endobronchial lesions
- Not contagious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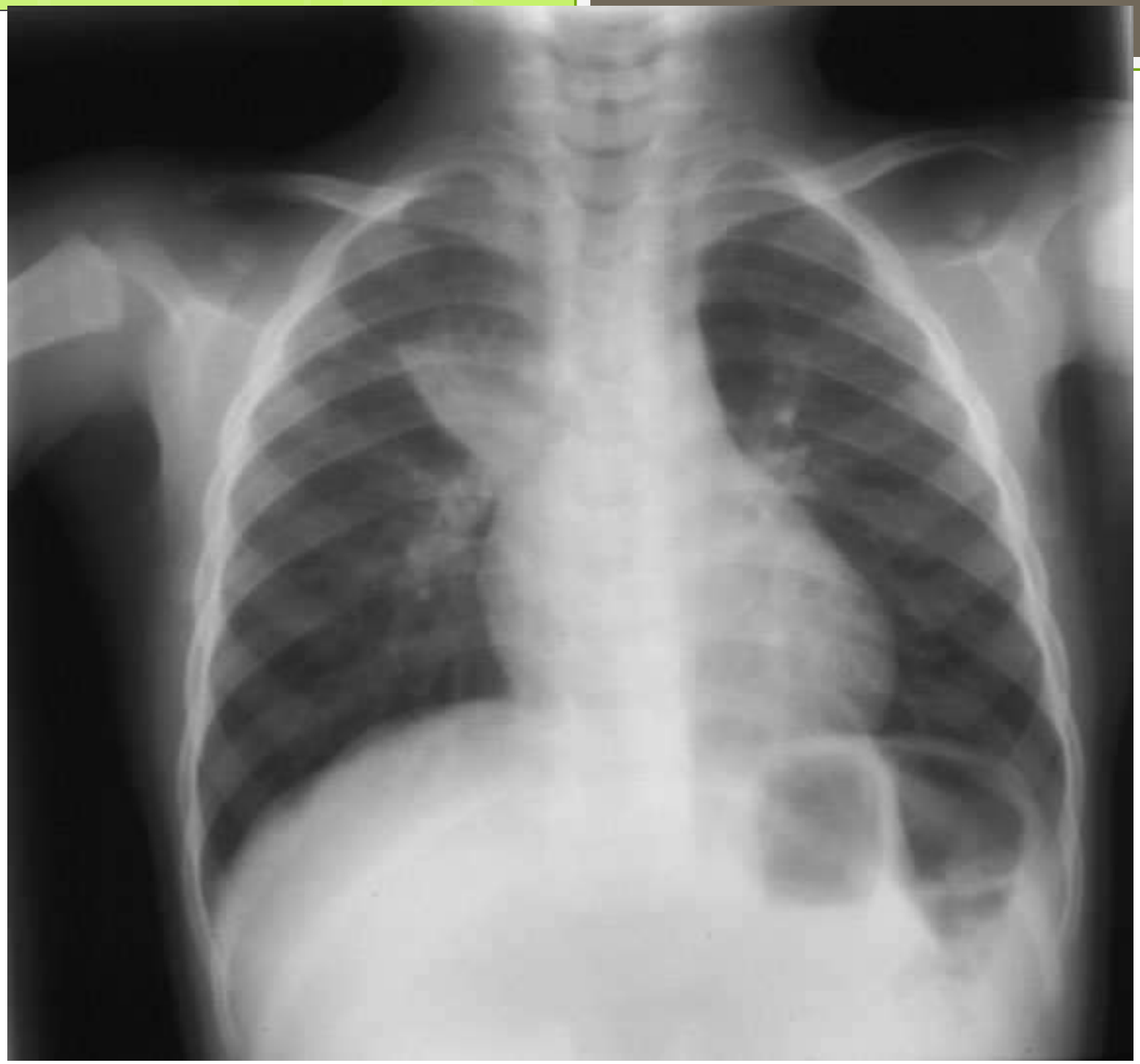
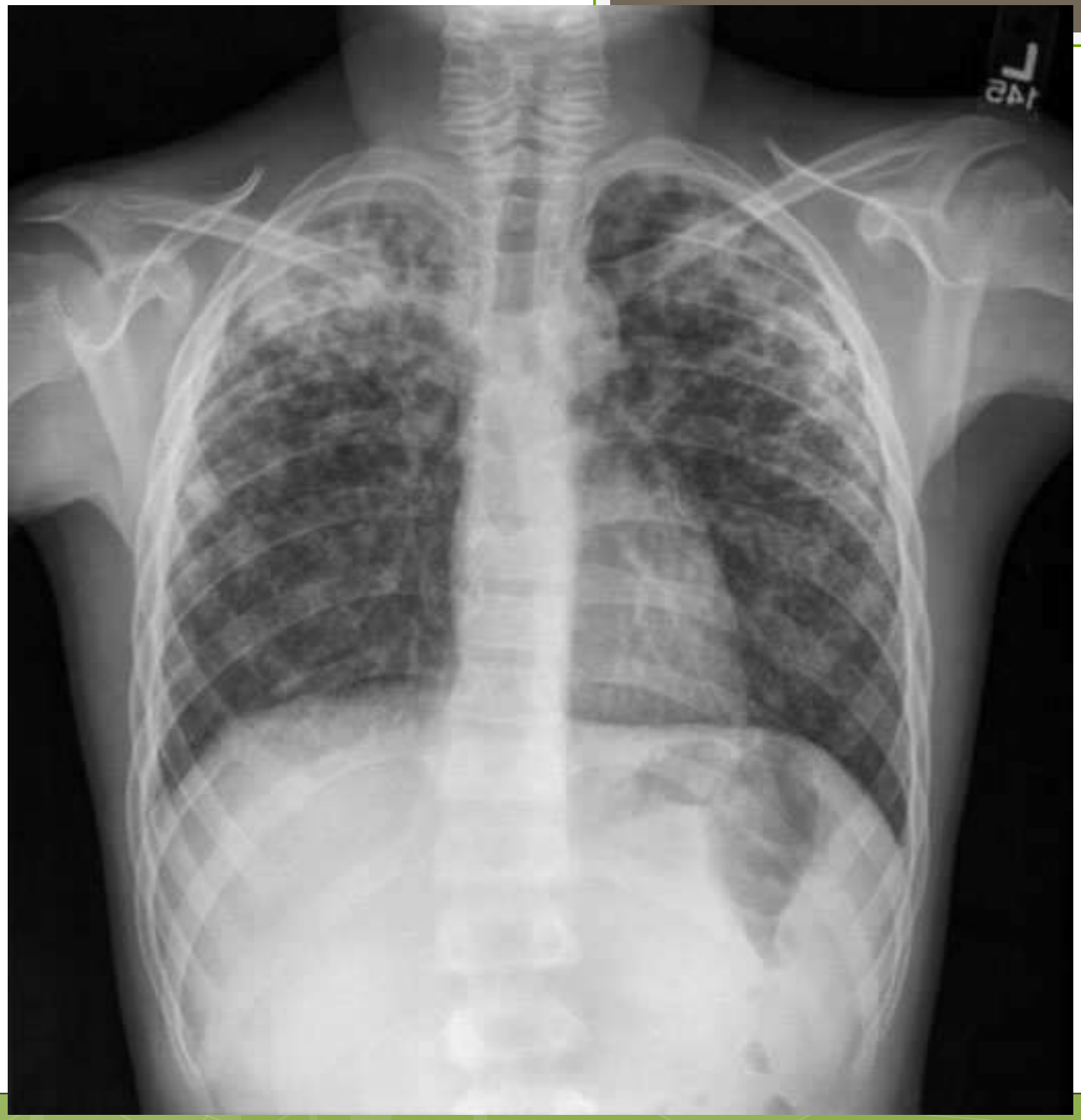


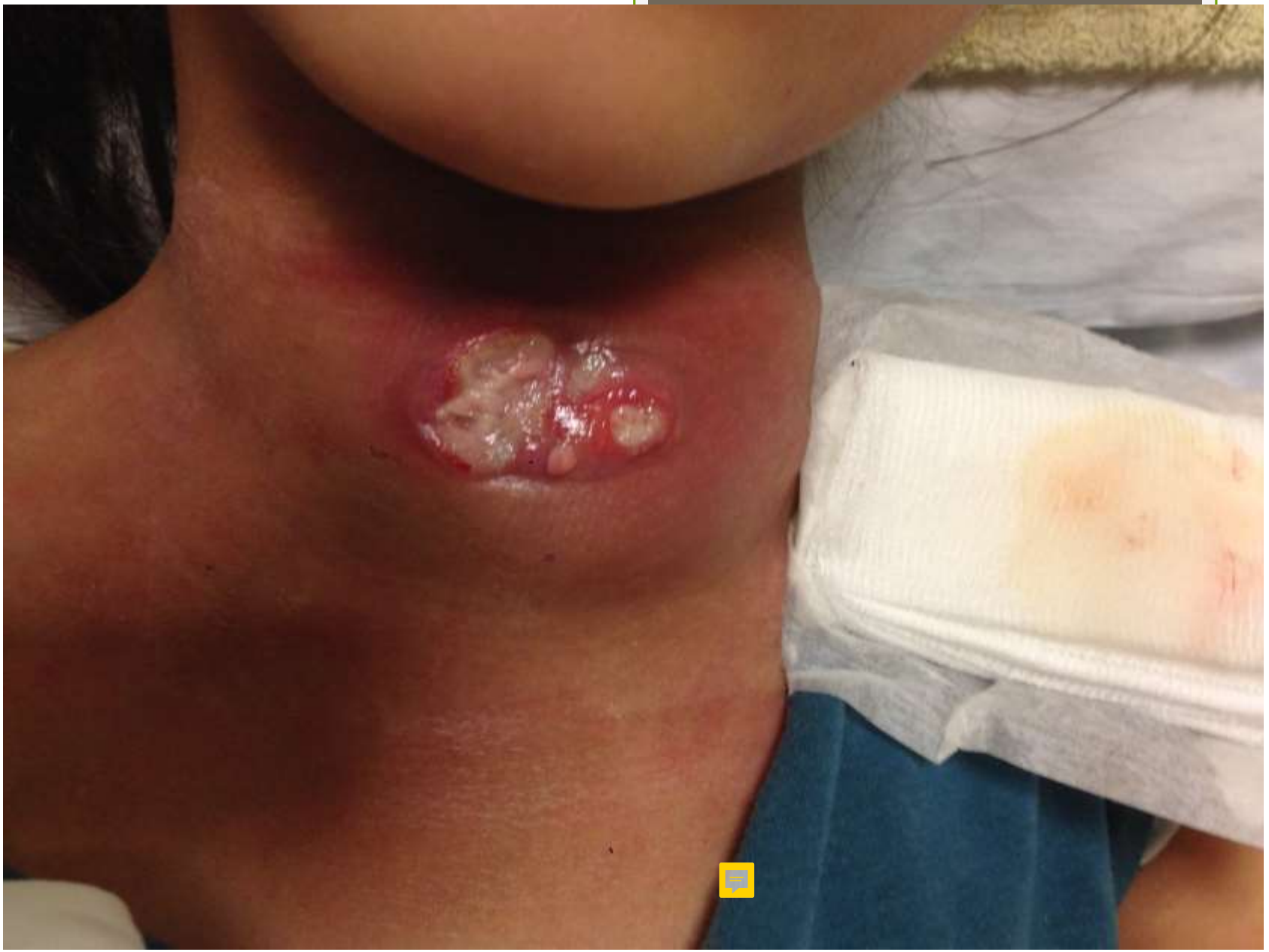
REACTIVATION TUBERCULOSIS IN PEDIATRICS

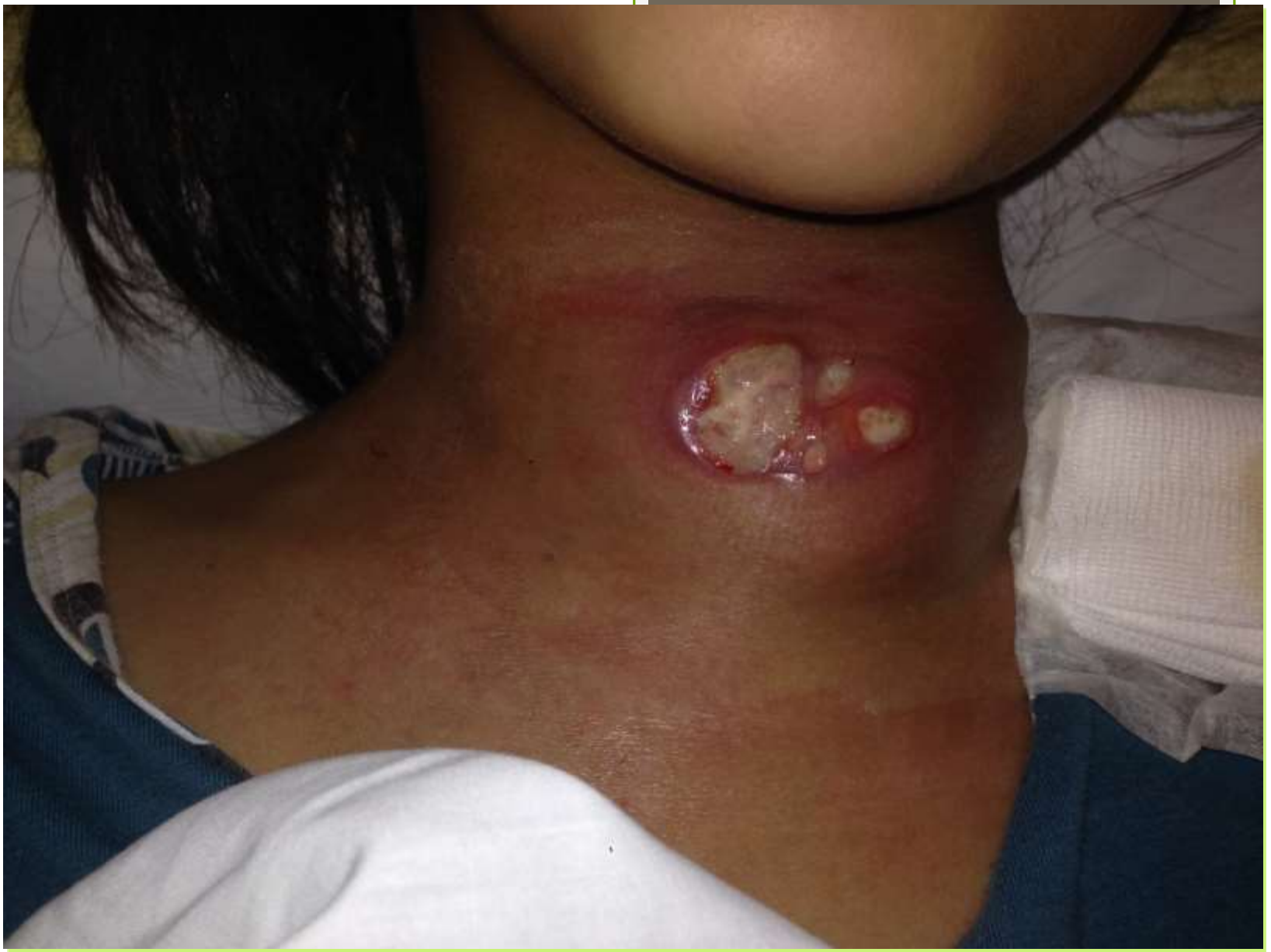
- **Adolescents primarily, but can occur in younger children**
- **Same as adult disease: cavity or upper lobe infiltrates; cough, fever, weight loss, hemoptysis**
- **Sputum or gastric aspirates to isolate organism; bronchoscopy occasionally necessary**



LYMPHADENITIS CAUSED BY MYCOBACTERIUM TUBERCULOSIS

- Most often unilateral; may be bilateral
- Chest x-ray usually normal
- Usually indolent onset of enlarged, fixed, matted nodes in anterior chains, submandibular
- Sub mental, occipital, axillary, supraclavicular nodes less common
- Absence of systemic findings; minimal tenderness
- Often progress and “break down” - suppuration, sinus tracts
- Major differential dx: Non-Tubeculosis Mycobacterium (NTM), Bartonella, malignancy





TUBERCULOUS AND NONTUBERCULOUS MYCOBACTERIAL LYMPHADENITIS

	NTM	TB
Age (years)	1-5	any
Residence	rural	suburban urban
Risk factors for TB	no	yes
TST on family	negative	often positive
Chest x-ray	usually neg.	positive in 10-20%
TST (mm) 0-15	usual >10;	many >15
Response to anti-TB drugs:	no	yes but slow

CERVICAL LYMPHADENITIS DUE TONONTUBERCULOUS MYCOBACTERIA

- paucity of systemic signs and symptoms
- anterior cervical chain and submandibular most common
- also preauricular, postauricular, submental
- firm, non-tender, fixed to underlying structures or skin
- Usually multiple nodes: “tip of the iceberg”
- Mycobacterium Avium Complex (MAC) > M. kansasii >M. fortuitum >
- others

SURGICAL APPROACH TO MYCOBACTERIAL ADENITIS

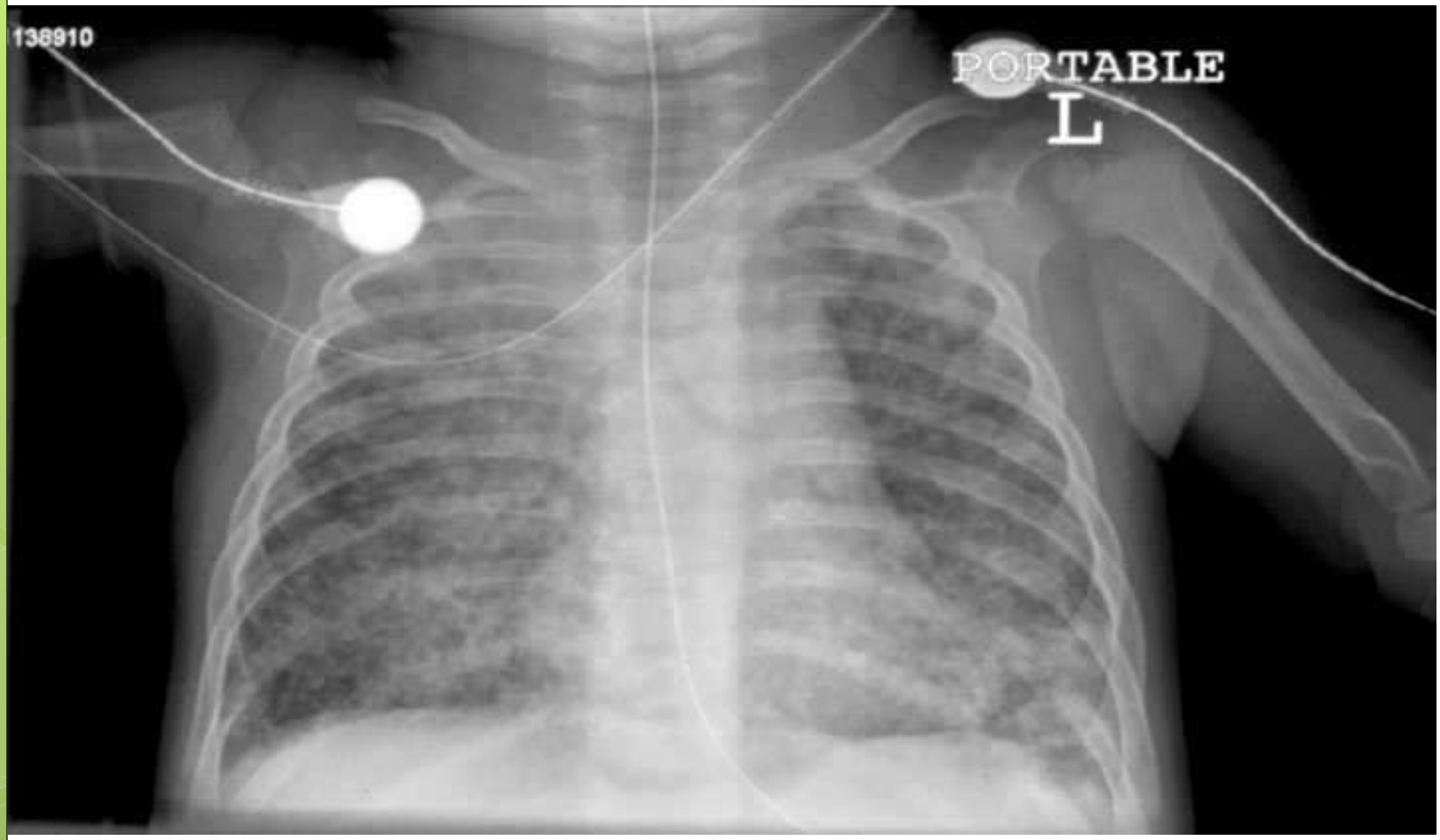
- Fine needle aspirate can define histology, less helpful for culture (low volume of tissue)
- Surgical excision both diagnostic and curative of NTM(if complete)
- NEVER do an incision and drainage.
- Antibiotics may be effective to prevent or treat recurrence clarithromycin + rifamycin + ethambutol

TUBERCULOUS MENINGITIS IN CHILDREN

- Most common in infants, young children
- Occurs soon after infection; source case often not yet identified (negative family history)
- Pathogenesis: basilar infiltrate, hydrocephalus, vasculitis,
- infarct, tuberculoma

DISSEMINATED (MILIARY) TUBERCULOSIS IN CHILDHOOD

- most common in infants, recent after infection
- FUO common
- usually insidious but may be explosive
- chest radiograph usually normal early, then classic
- other common features: hepatosplenomegaly, lymphadenopathy, cutaneous lesions, choroid tubercles
- TST negative in up to 50% of cases
- Dx: gastric aspirate, bronchoscopy, lung biopsy, liver biopsy, bone marrow, urine culture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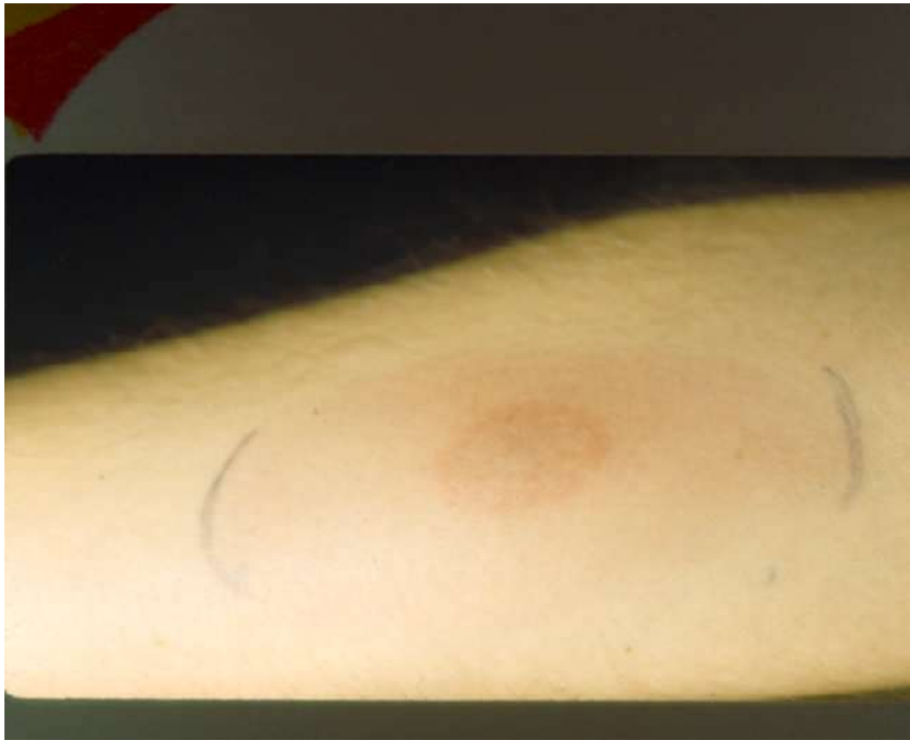
TST I Tuberculin Skin Test (Or PPD)

Measure Induration not redness



INDURATION SIZE – POSITIVE TUBERCULIN SKIN TEST

- > 5 mm
  - HIV co-infection
  - Immune compromise
  - Recent contact to TB
  - Suspected disease

- > 10 mm
  - Foreign-born from a HR country (applicable to Jordan)
  - Drug users
  - Living in HR congregate setting
  - Children < 4 yrs old

- >15 mm
  - No risk factors

Does BCG VACCINES has an effect on positive TUBERCULIN SKIN TEST ?

- The quick answer: no or very limited effect.
- 50% of vaccinated infants do not react to a TST; most of the rest stop reacting within 5 years
- most non-infants who get one or more BCG vaccinations will react to a TST (usually < 15 mm), but effect wanes over 5 – 10 years
- outside infancy, “positive” TST more likely to indicate infection with M. tuberculosis than be residual from BCG

INTERFERON TESTS (IGRA)

- Identifies Latent TB Infection (LTBI) &/or disease
- Does not cross react with BGC vaccine or most other mycobacteria
- Requires:
  - single medical visit
  - blood collection
  - laboratory equipment and personnel
- Results in 24-48 hrs
- Alternative test for TST (PPD)

Comparison of Tuberculin Skin Test and Interferon- gamma Release Assays

	TST	IGRA
Patient visits required	Two	One
Distinguish between TB infection and TB disease	No	No
Specificity in adults	70-95%	90-100%
Sensitivity in adults	75-90%	75-95%
Cross-reactivity with NTM	Yes	Less Likely
Cross-reactivity with BCG	Yes	Unlikely
Antigens studied Many	-PPD	ESAT-6, CFP-10, TB7.7

INTERFERON-GAMMA RELEASE ASSAYS (IGRA) Vs TST

1. No preference for one test over the other
2. Should replace the TST except for immune compromised, children < 5 years
3. Can be used in contact investigations (just like TST)

DIAGNOSIS OF TUBERCULOSIS IN CHILDREN

- **Clinical/epidemiology : gold standard**
- **Acid-Fast Bacilli Stain (AFB) stains positive in < 10% of cases**
- **ABF culture 3 early a.m. gastric aspirates is best:**
  - **all children : sensetive 20% to 40% of cases**
  - **infants : up to 75% of cases**
  - **CSF, pleural fluid, other : average 25% of cases**
- **PCR:**
  - **compared with clinical:**
    - **sensitivity is 40% to 60%**
    - **specificity is 80% to 90%**

EVALUATION OF A CHILD WITH SUSPECTED TUBERCULOSIS DISEASE

- **Evaluate family members, other contacts**
- **Tuberculin skin test**
- **Appropriate radiographs**
- **Sputum (if available) for AFB stain, culture**
- **3 early a.m. gastric aspirates (pulmonary)**
- **Lumbar Puncture (LP) if < 1 year old**
- **Bronchoscopy - if anatomy needs to be defined or diagnosis is in doubt**
- **Report suspicion of disease to Ministry of Health.**

TREATMENT OF LTBI (Latent TB Infection) IN CHILDREN

- **9 months of isoniazid (daily or twice weekly under DOT) is only accepted regimen.**

- **Use isoniazid unless there is documented exposure to a specific case of drug-resistant TB.**

TREATMENT OF TUBERCULOSIS DISEASE IN CHILDREN

- **Pulmonary (and extra pulmonary except meningitis):**
  - **Start with RIPE: Rifampin RIF , Isoniazid INH, Pyrazinamide PZA and Ethambutol EMB for 2 months**
  - **followed by INH, RIF for another 4 months**
  - **Usual length 6 months**
  - **Can be once aday or twice weekly Direct Observed Therapy (DOT)**

- **Meningitis:**
  - **Start with RIP: Rifampin RIF , Isoniazid INH, Pyrazinamide PZA PLUS aminoglycoside or ethionamide for 2 months**
  - **followed by 7–10 mo of isoniazid and rifampin**
  - **usual length: 9-12 months**

Infection or Disease Category	Regimen	Remarks
Latent *M tuberculosis* infection (positive TST or IGRA result, no disease)[a]		
• Isoniazid susceptible	9 mo of isoniazid, once a day	If daily therapy is not possible, DOT twice a week can be used for 9 mo.
• Isoniazid resistant	4 mo of rifampin, once a day	If daily therapy is not possible, DOT twice a week can be used for 4 mo.
• Isoniazid-rifampin resistant	Consult a tuberculosis specialist	
Pulmonary and extrapulmonary (except meningitis)[b]	2 mo of isoniazid, rifampin, pyrazinamide, and ethambutol daily or twice weekly, followed by 4 mo of isoniazid and rifampin[c] by DOT[d] for drug-susceptible *Mycobacterium tuberculosis* 9 to 12 mo of isoniazid and rifampin for drug-susceptible *Mycobacterium bovis*	Some experts recommend a 3-drug initial regimen (isoniazid, rifampin, and pyrazinamide) if the risk of drug resistance is low. DOT is highly desirable. If hilar adenopathy only and the risk of drug resistance is low, a 6-mo course of isoniazid and rifampin is sufficient. Drugs can be given 2 or 3 times/wk under DOT.
Meningitis	2 mo of isoniazid, rifampin, pyrazinamide, and an aminoglycoside or ethionamide, once a day, followed by 7–10 mo of isoniazid and rifampin, once a day or twice a week (9–12 mo total) for drug-susceptible *M tuberculosis*	For patients who may have acquired tuberculosis in geographic areas where resistance to streptomycin is common, kanamycin, amikacin, or capreomycin can be used instead of streptomycin.

CORTICOSTEROIDS IN PEDIATRIC TUBERCULOSIS

- Useful when host inflammatory response is contributing to tissue damage or dysfunction
  - Meningitis
  - Endobronchial
  - miliary with alveolar block
  - pericardial with constriction
  - vertebral with spinal root irritation
- Can use prednisone or dexamethasone

BCG VACCINES

- Used in all but 2 countries: USA and Notherland
- Given in first month of life in Jordan.
- Negligible effection on TB epidemiology (Weak Vaccne)
- do not prevent infection (LTBI)
- little effect on reactivation disease
- not instruments of TB control
- **Major use is preventing life-threatening forms of tuberculosis in infants and children (60% - 90%)**