Diagnosis and Management of Childhood Tuberculosis Disease

Jeffrey R. Starke, M.D.
Professor of Pediatrics
Baylor College of Medicine

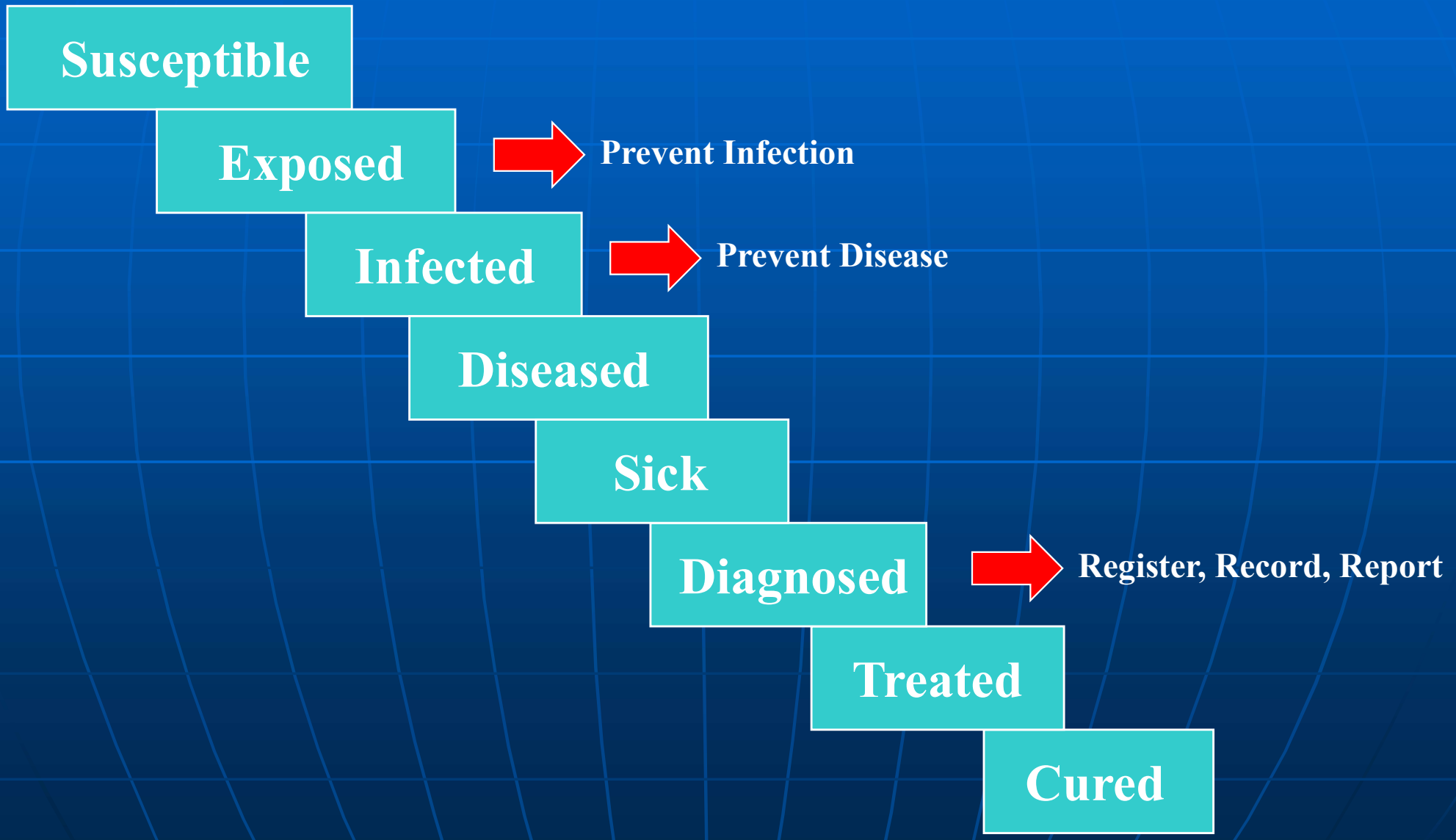
Disclosures

Dr. Starke has no conflicts to declare.

Objectives of This Talk

- To review the methods of diagnosis including epidemiology, clinical presentation, laboratory and radiologic studies
- To review the available drugs and drug regimens for childhood tuberculosis
- To consider the role of new drugs and diagnostic modalities in the management of children with tuberculosis

TRANSITIONS IN TUBERCULOSIS

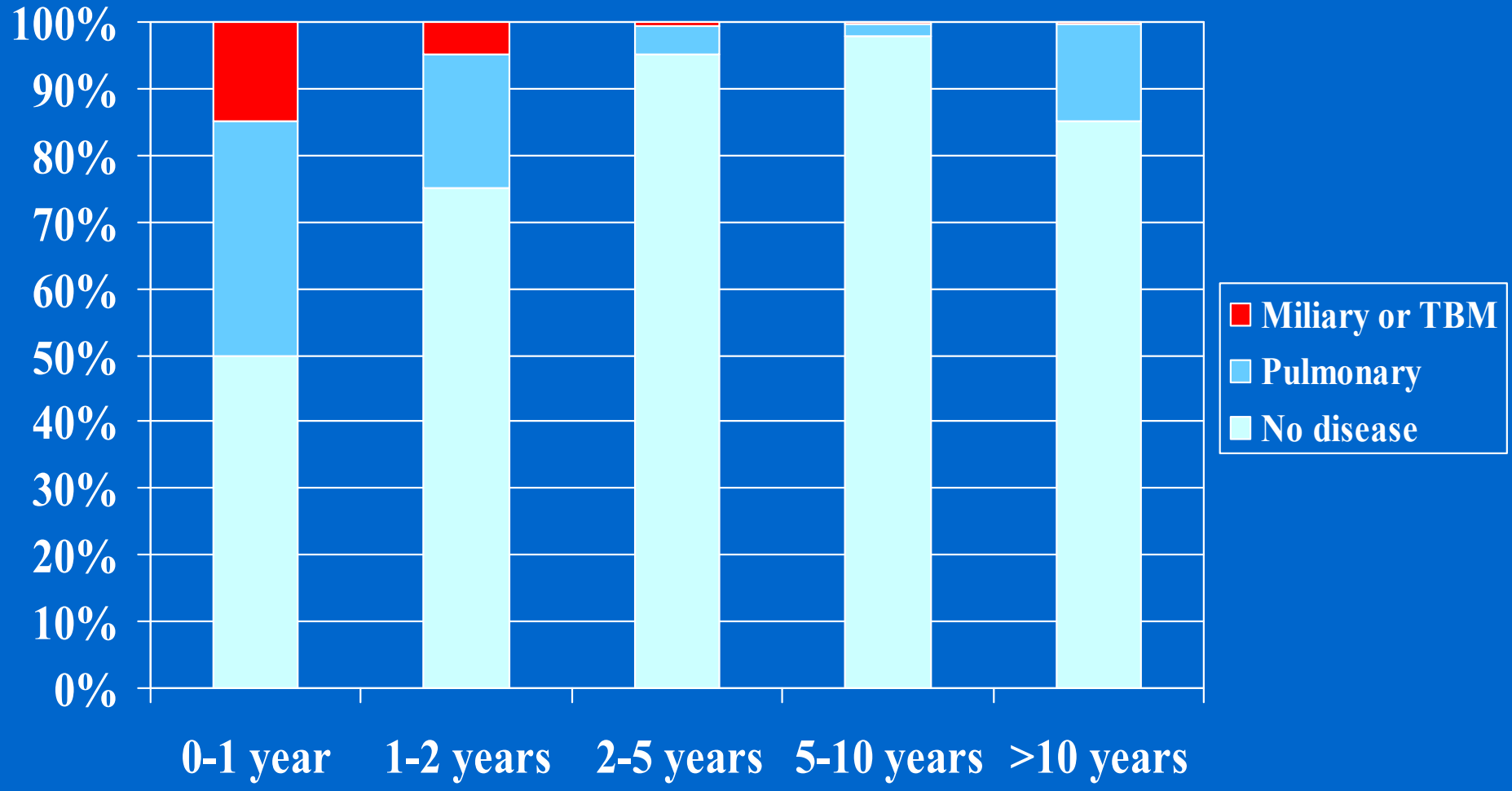


STAGES OF TUBERCULOSIS

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)**

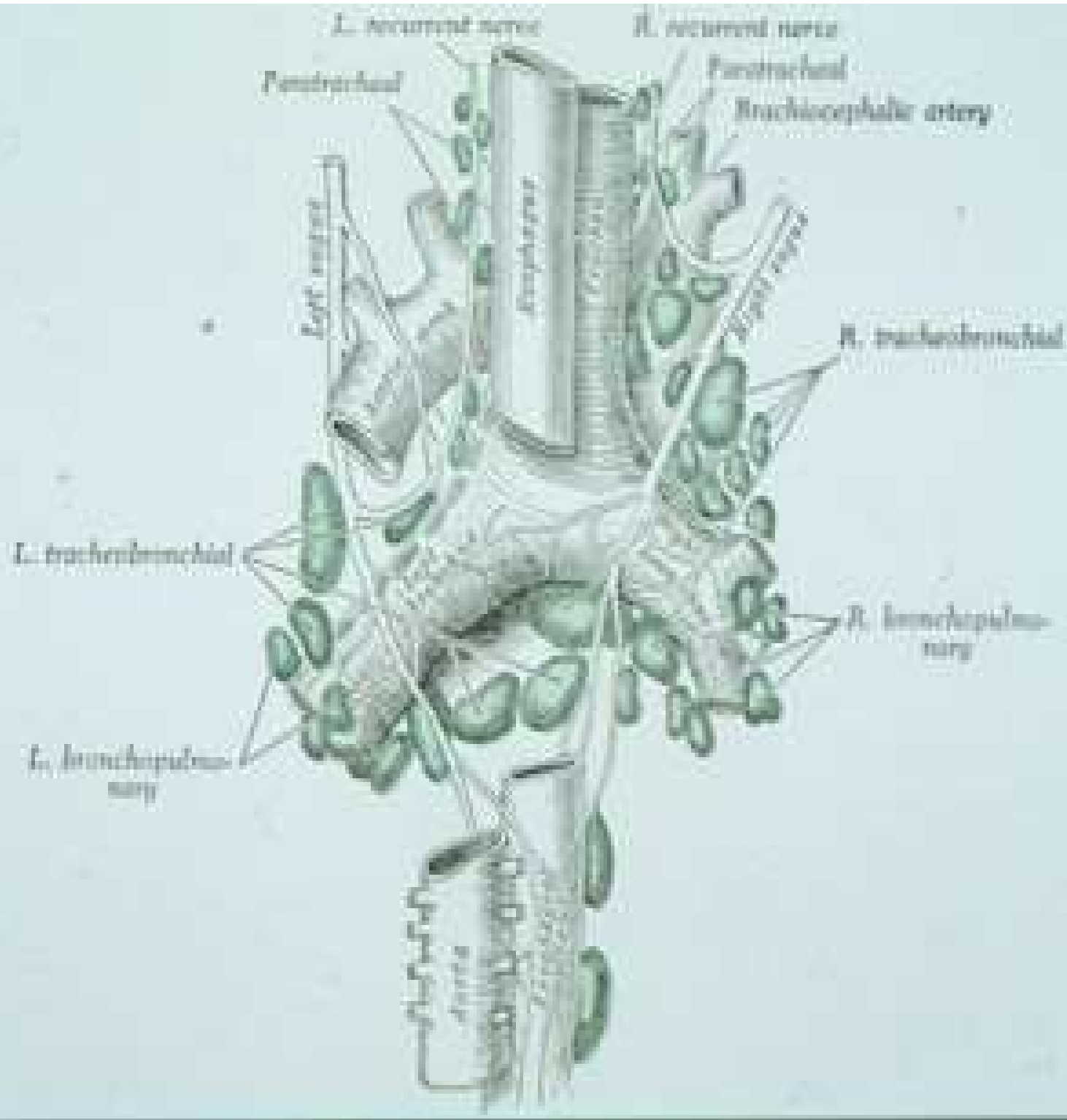
Average age specific risk for disease development following primary infection (pre-BCG)

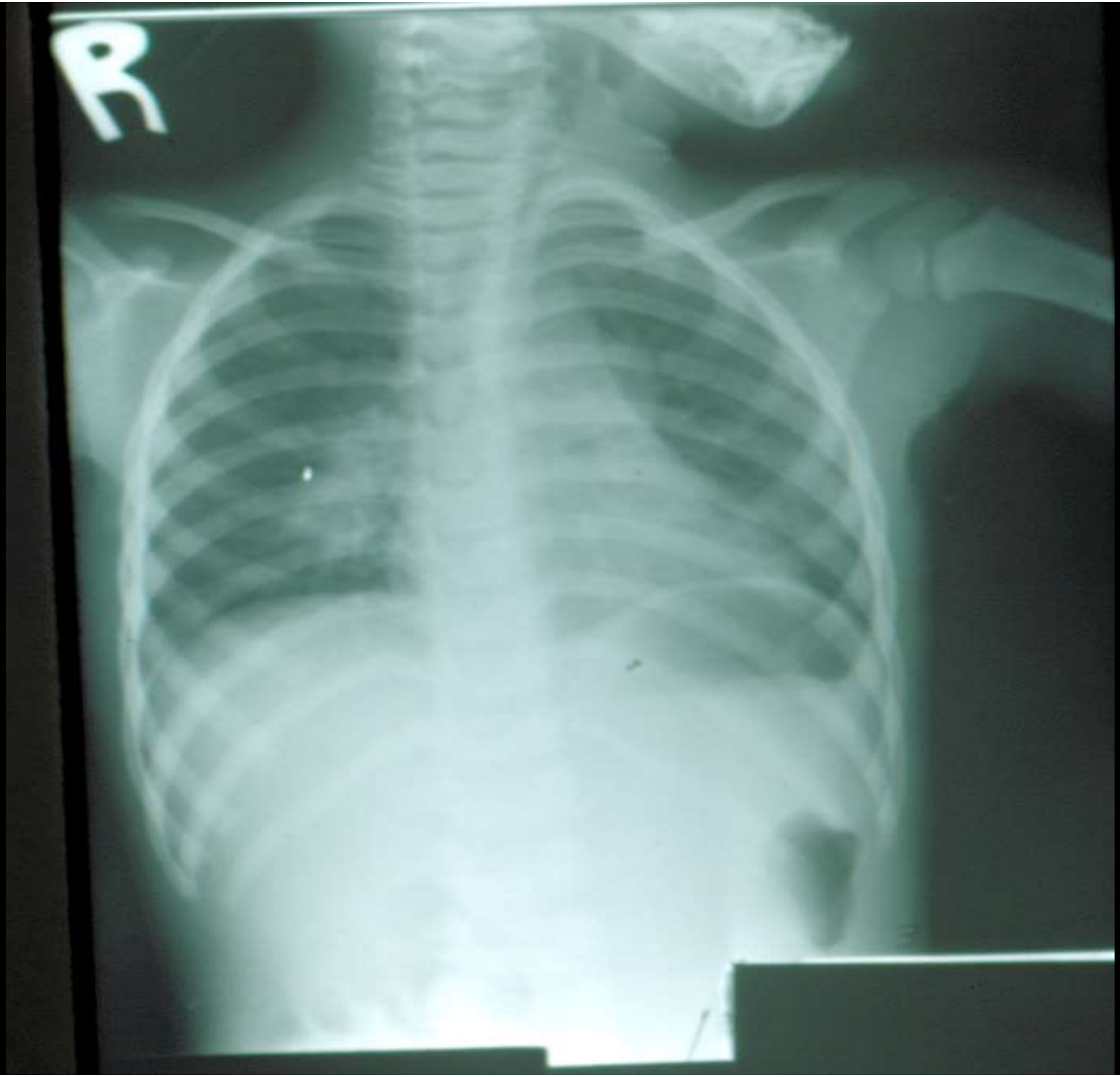


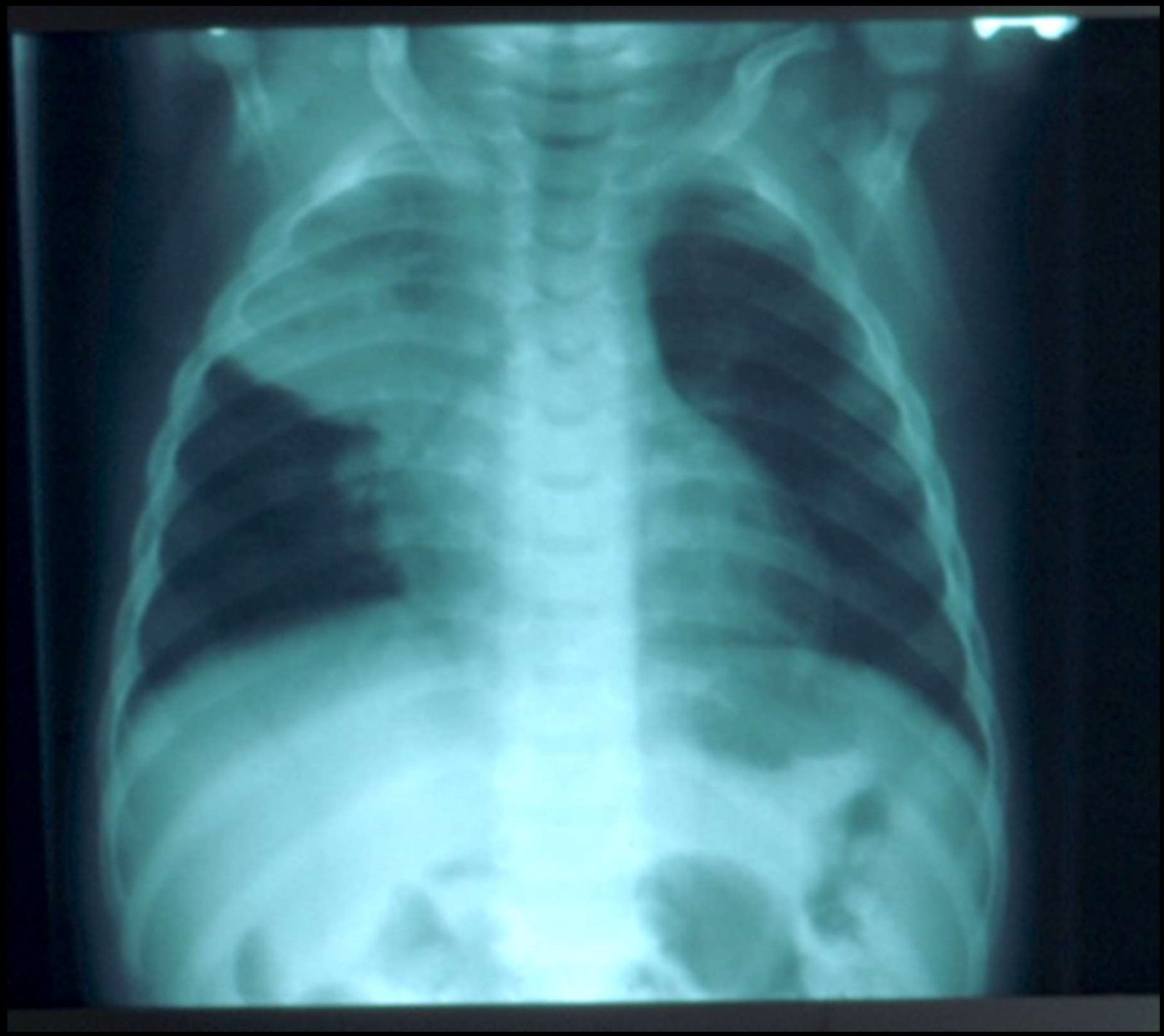
Adapted from Marais B, et al. Int J Tuberc Lung Dis 2004

PATHOGENESIS OF TUBERCULOSIS

- Organisms contained in droplet nuclei land in the alveoli
- Infectious dose probably < 10 organisms
- Organisms ingested by macrophages, transported to regional [hilar, mediastinal, cervical] lymph nodes
- Lymphohematogenous dissemination of organisms occurs early – meninges, apices of lungs, lymph nodes, other organs


L. recurrent nerve
R. recurrent nerve
Paratracheal
Paratracheal
Brachiocephalic artery
R. tracheobronchial
L. tracheobronchial
R. bronchopulmonary
L. bronchopulmonary


R



TIMETABLE OF PEDIATRIC TUBERCULOSIS

Miliary and Meningeal	2 – 6 months
Pulmonary	2 – 12 months
Lymph node	2 – 12 months
Pleural effusion	3 – 12 months
Skeletal	6 months – 2 years
Renal	1 – 5 years

ARE CHILDREN WITH TUBERCULOSIS EVER CONTAGIOUS?

- Difficult to answer in the community
- 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

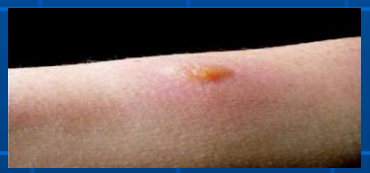
- Cavitary lung lesion
- Sputum production
- Positive acid-fast stain of sputum smear
- Bronchoscopy
- Draining lesions or surgical drainage of an abscess

Chest Radiographs on Family Members of Hospitalized Children with TB at Texas Children's Hospital

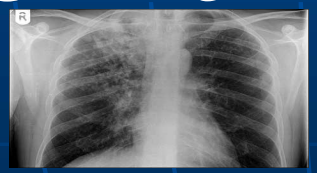
- 254 chest radiographs were obtained [mean 1.7 per child]
- Among 59 children ultimately diagnosed with TB, 10/59 families [16.9%] and 10/110 caregivers [9.1% or 9,100 per 100,000] had abnormal chest radiographs and each caregiver was confirmed to have pulmonary TB
- Of the 10 caregivers with TB, 4 were fathers, 3 were mothers, 2 were grandmothers and 1 was an aunt
- Two children who did not have TB had a caregiver with an abnormal chest radiograph, but neither had TB

DIAGNOSIS OF TUBERCULOSIS DISEASE IN CHILDREN

Even in the U.S., the "gold standard" for the diagnosis of tuberculosis in children is the triad of:



1. A positive TST or IGRA
2. An abnormal CXR and/or physical exam

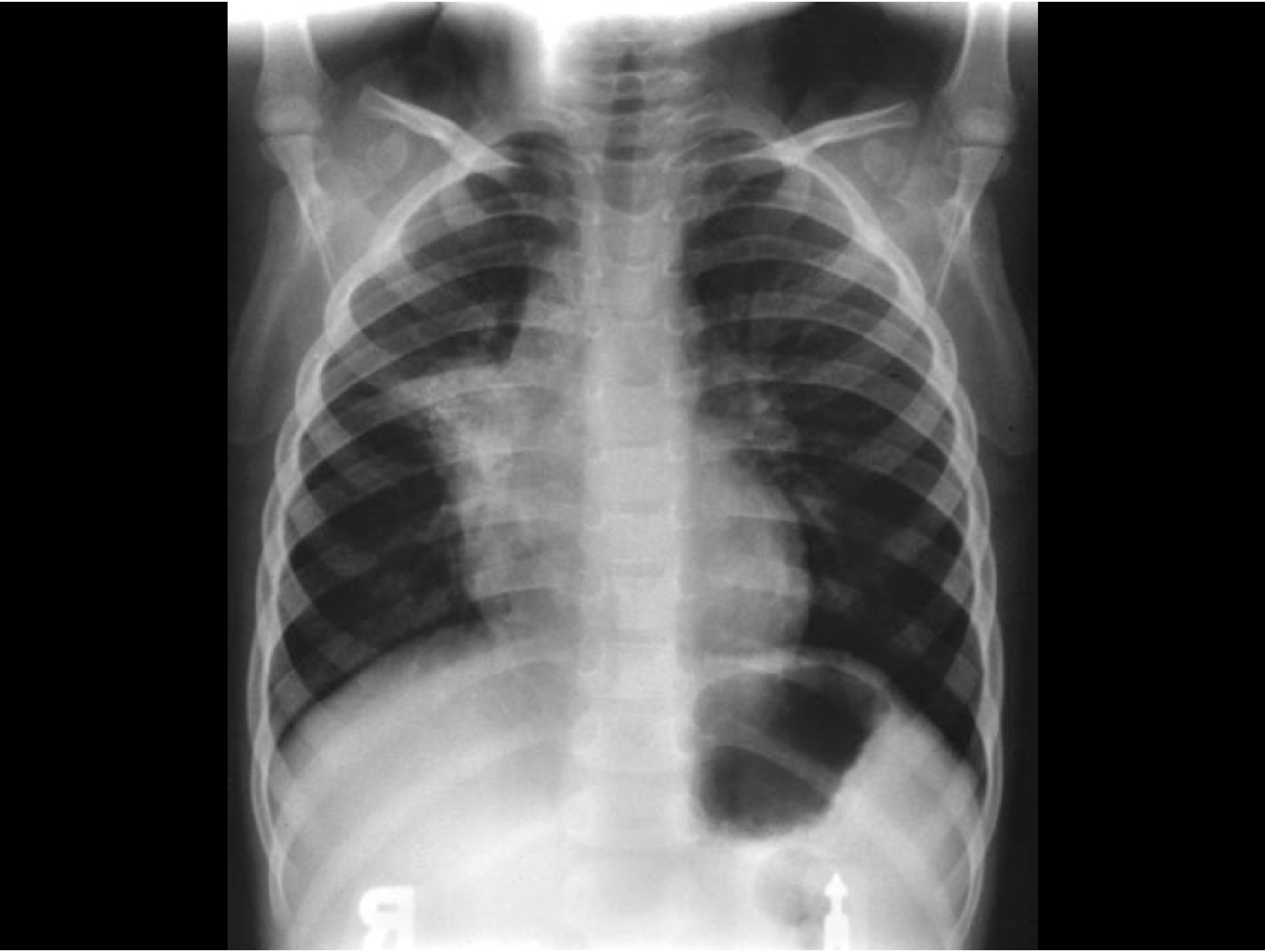


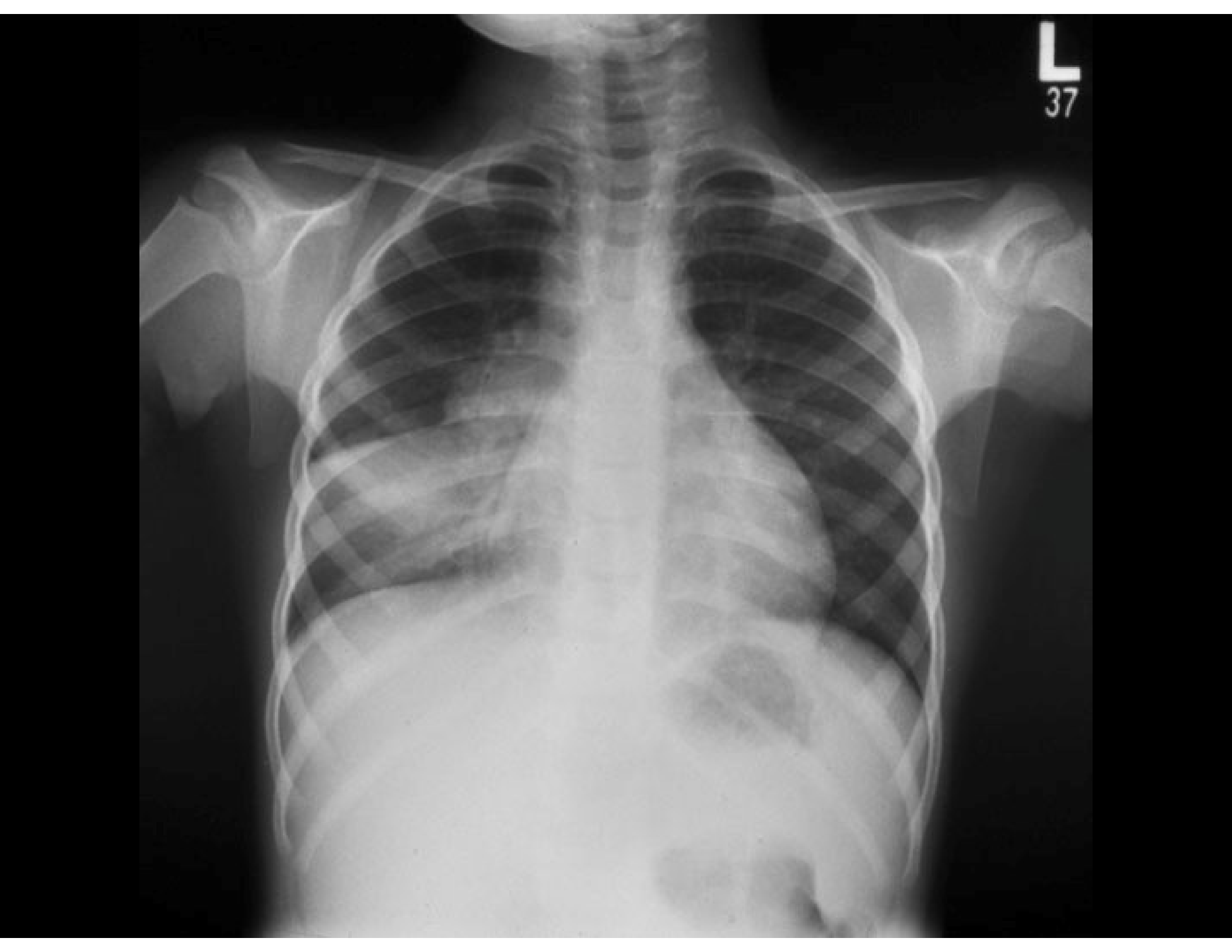
3. A history of recent contact to an infectious adult case of TB

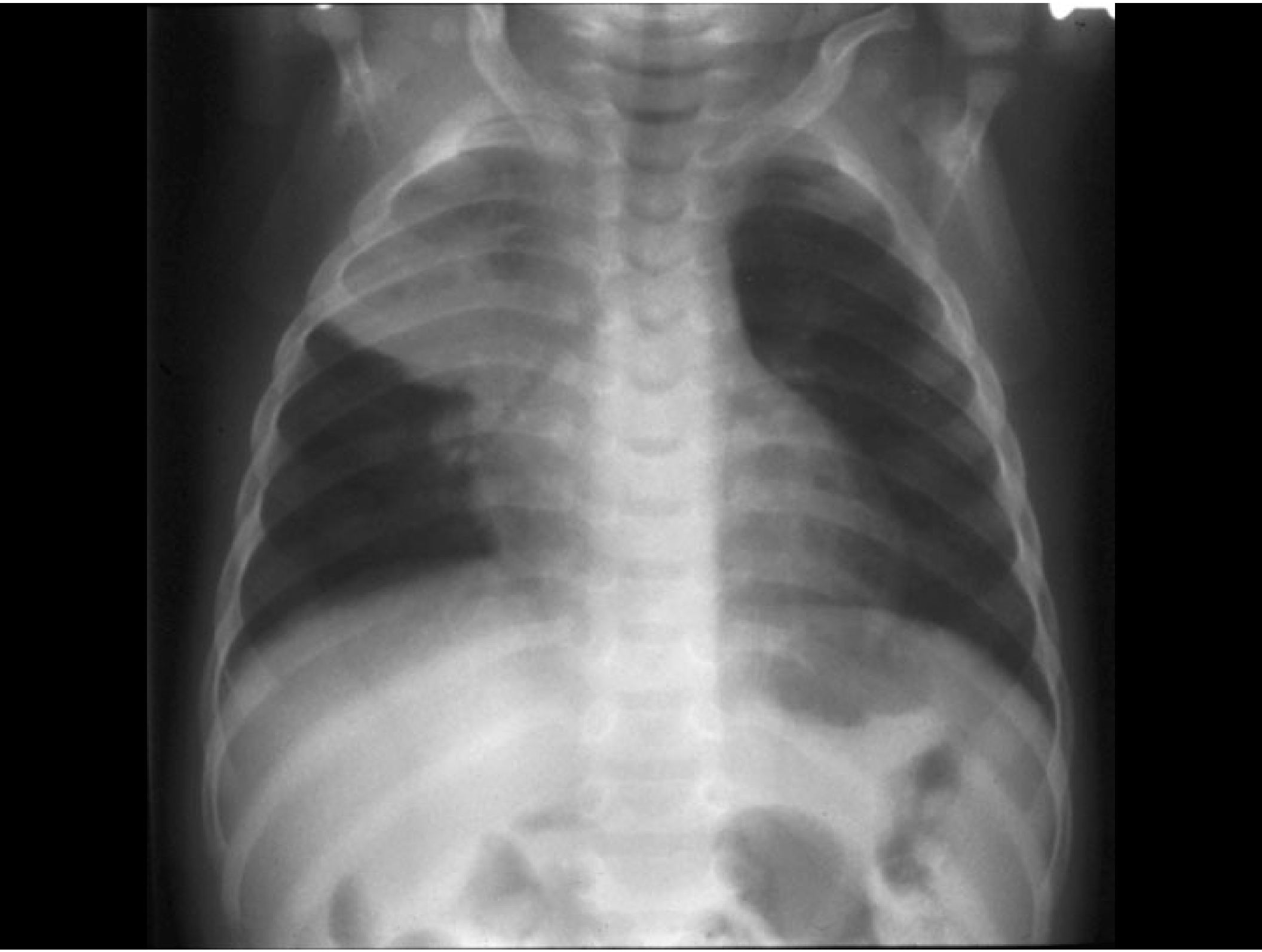
PTB in Adults and Children

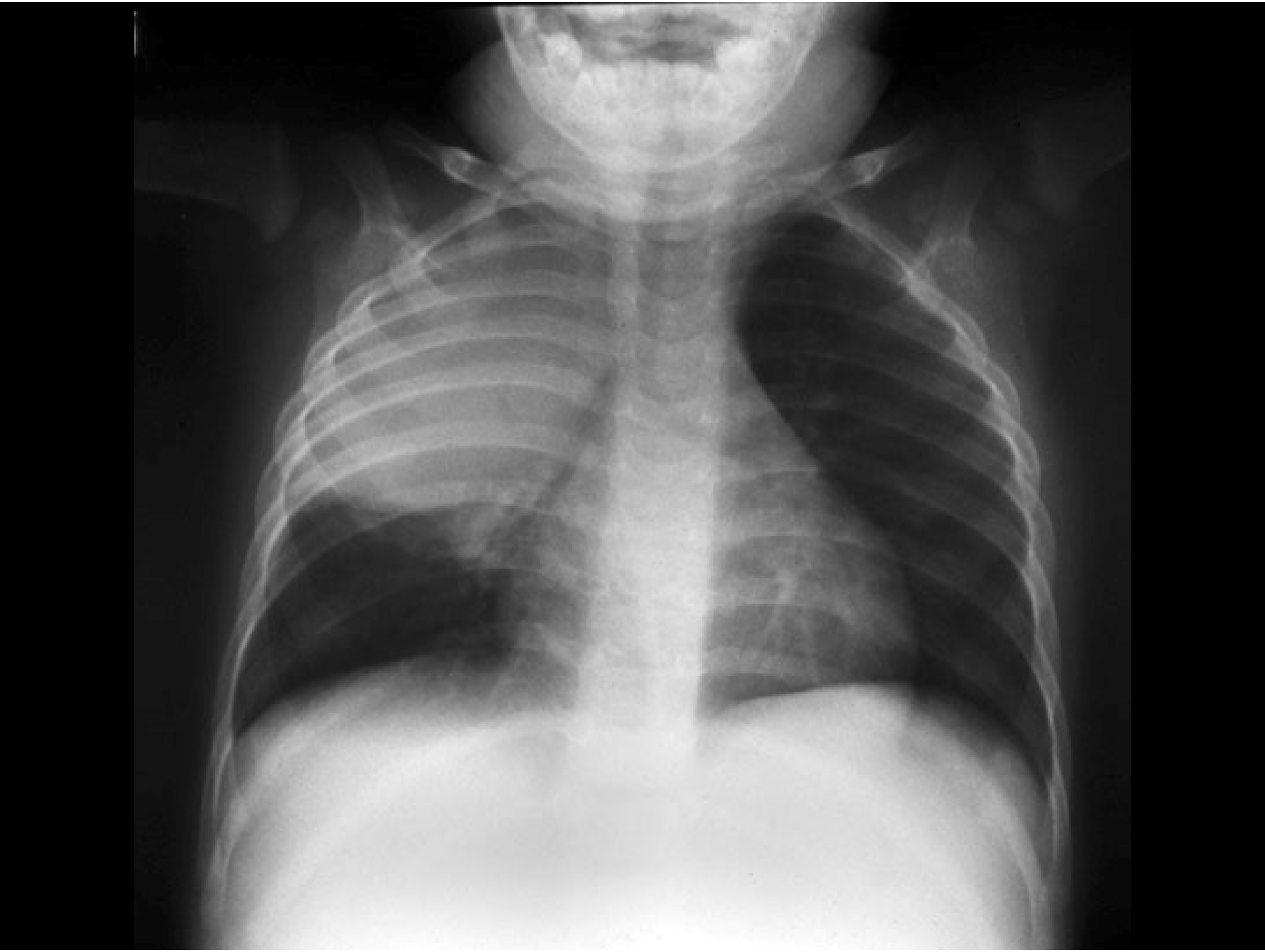
Adults	Children
Upper lobe apices	Any lobe, anywhere
Cough, fever, night sweats	Dry cough, ± fever
Sputum production common	Sputum production rare
Weight loss common	Weight loss uncommon
Long duration of symptoms	Short duration of symptoms
Cavities, infiltrate, nodules	Lymph nodes, atelectasis
Xray looks like the patient	Xray sicker than the patient
Presentation by symptoms	Contact investigation [1/2]

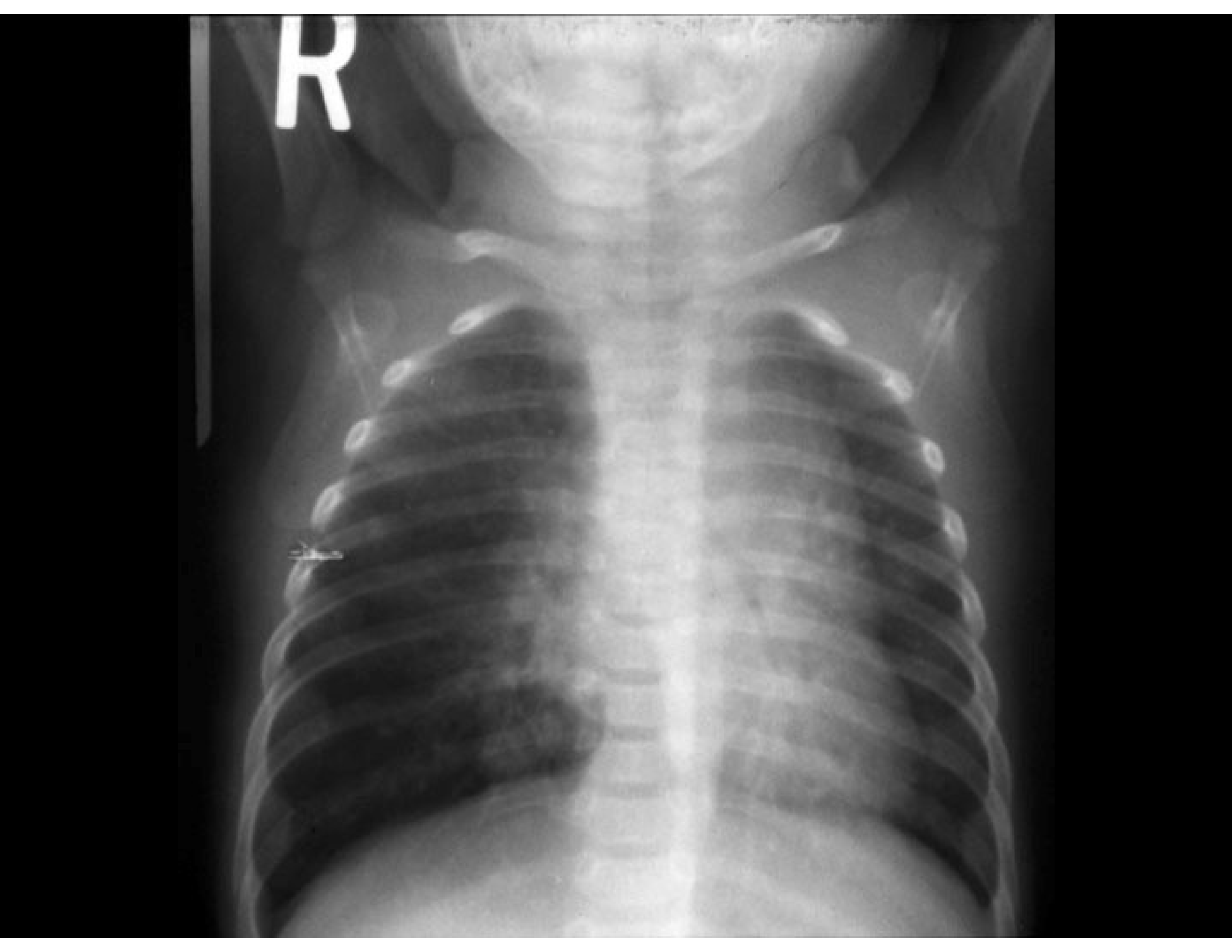
4 28-54 9386

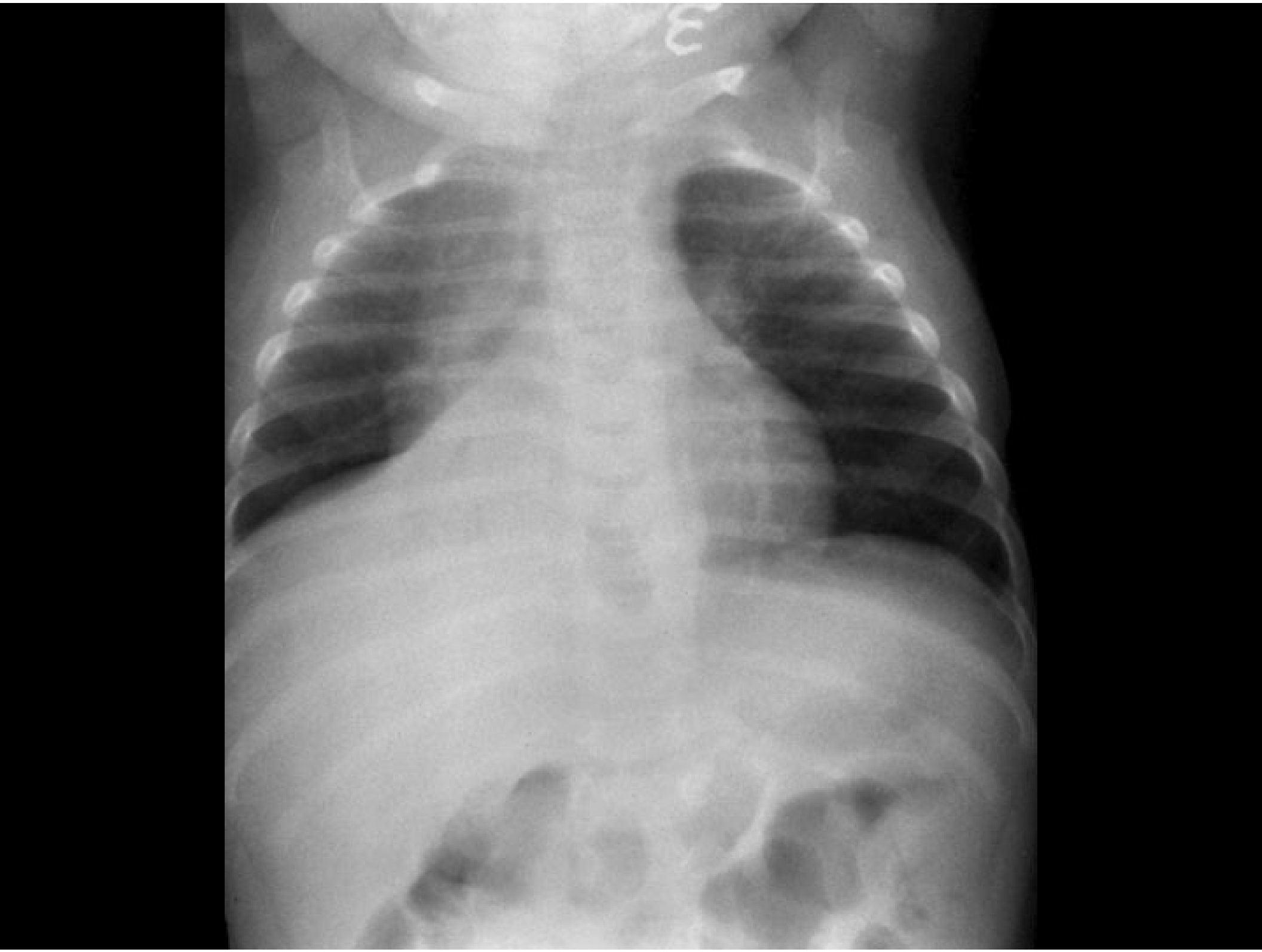



L
37



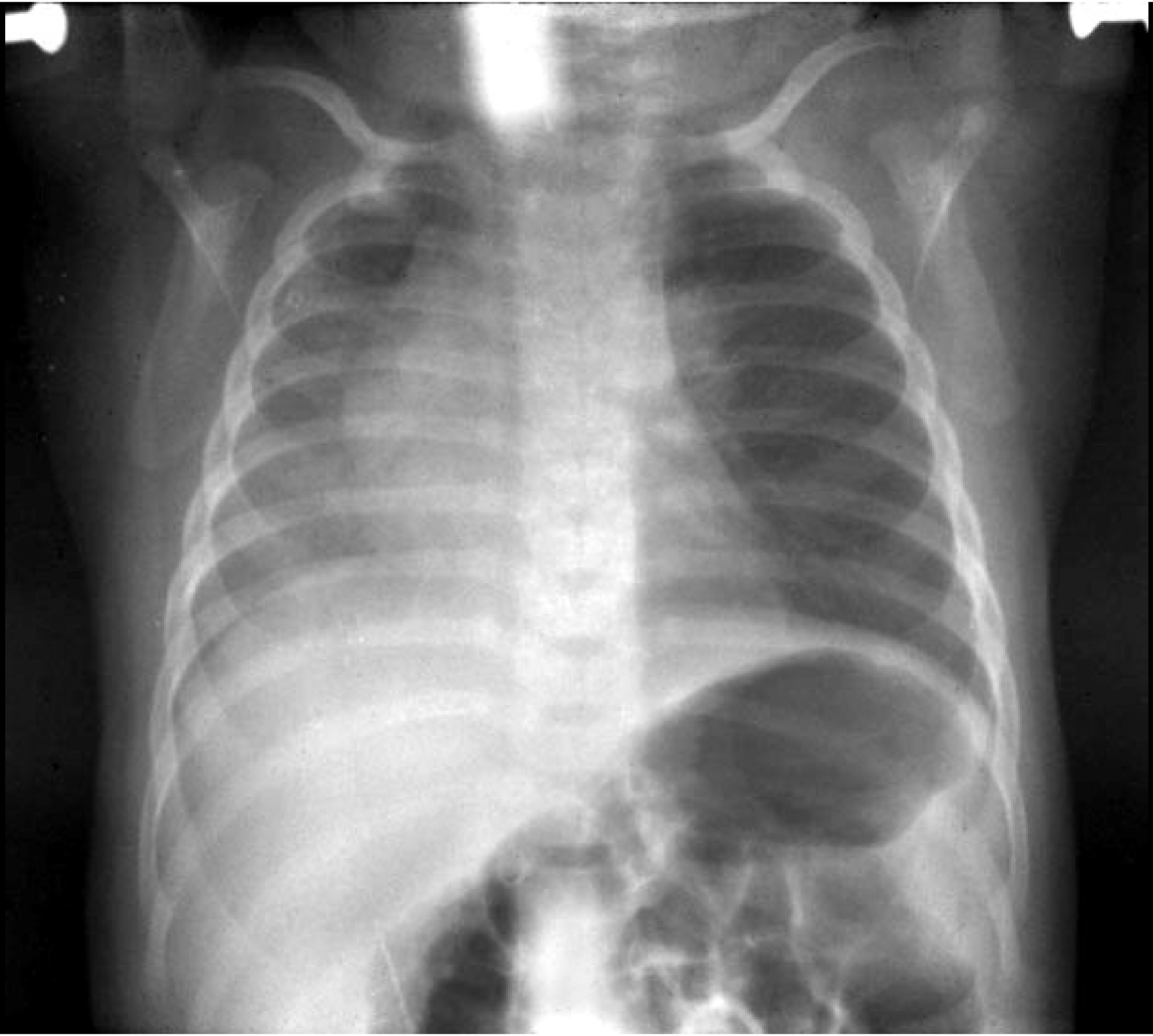


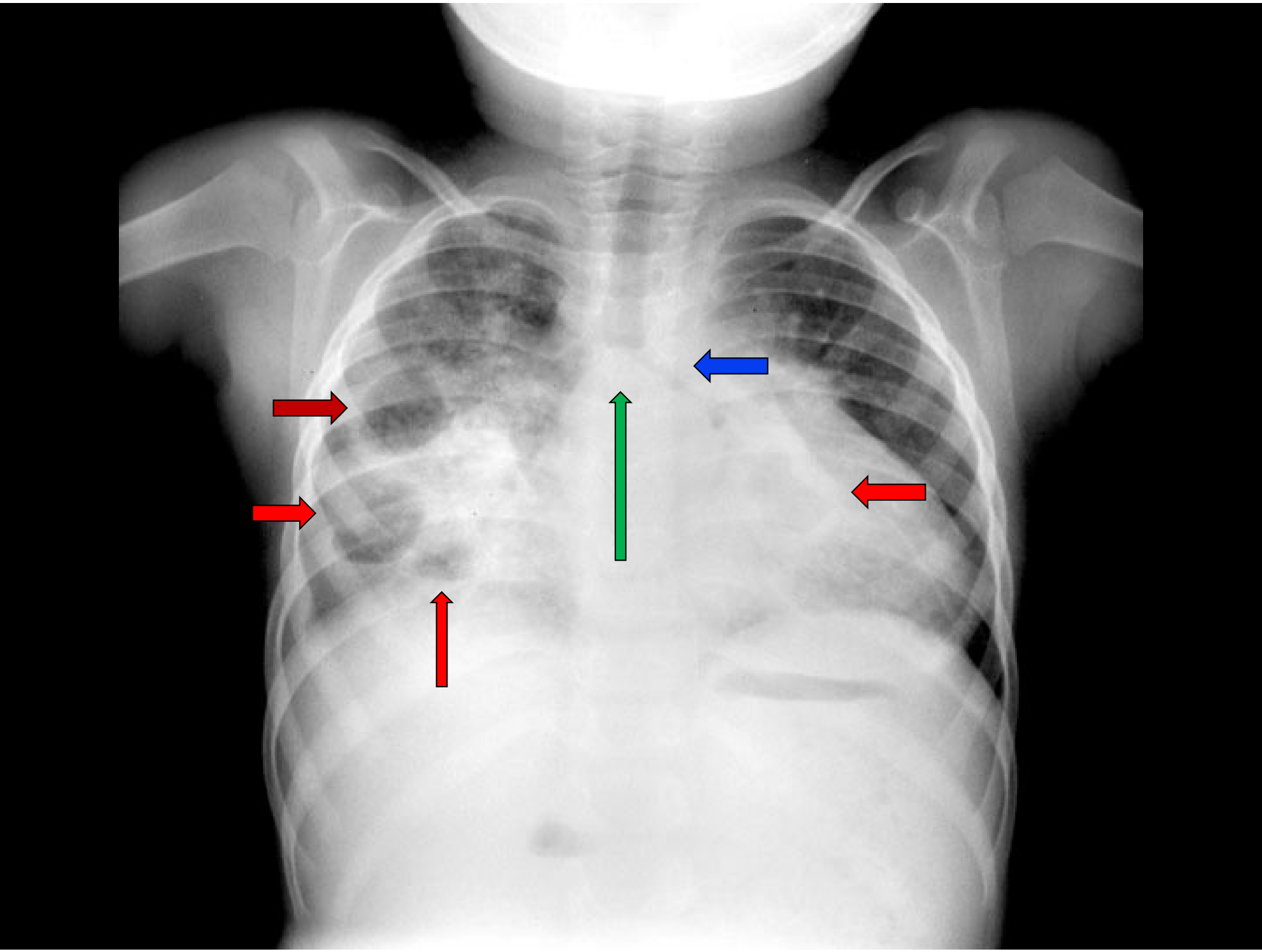

R

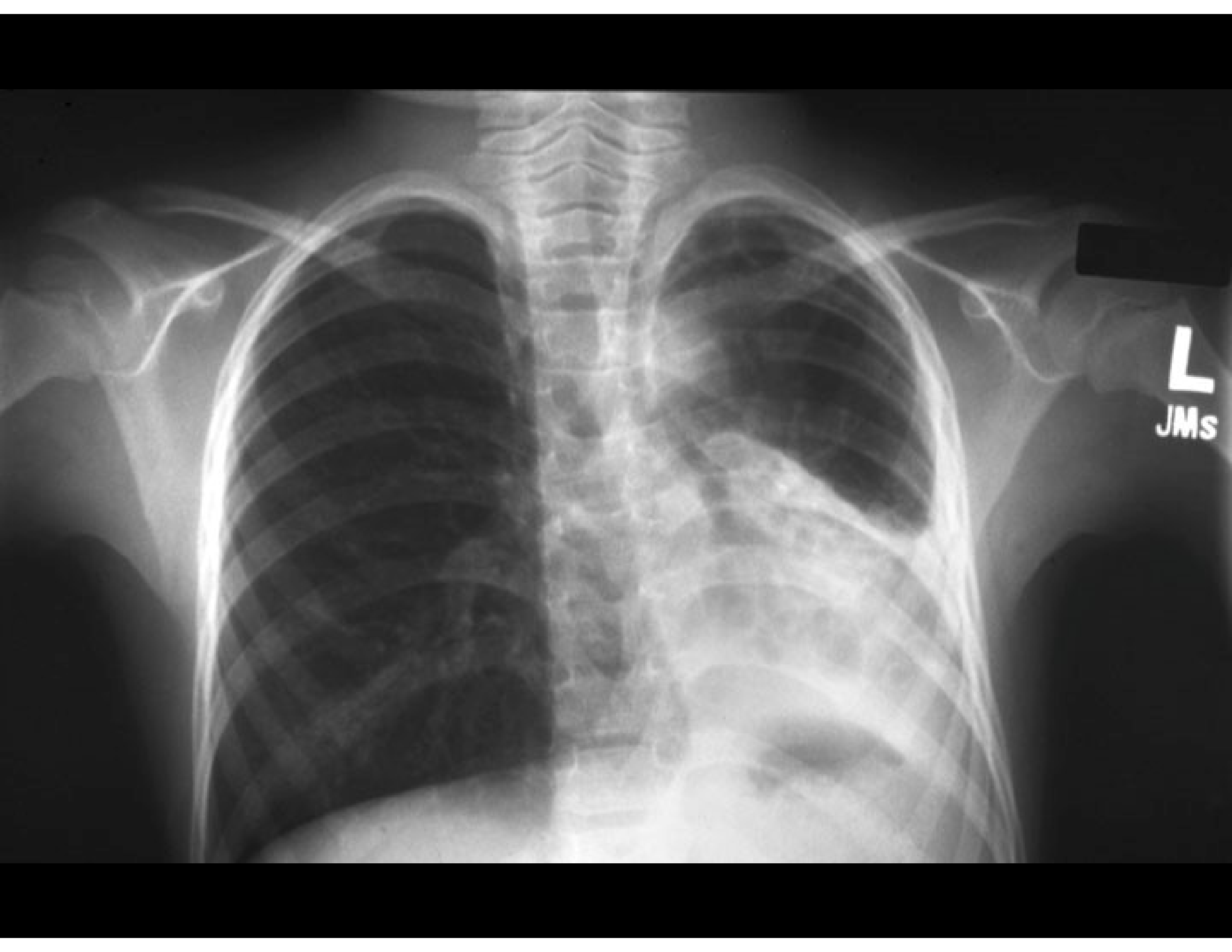


COMPLICATIONS OF PRIMARY CHILDHOOD PULMONARY TUBERCULOSIS

- Progressive local disease - cavitation
- Obstructive emphysema
- Pericardial or esophageal perforation or disease (subcarinal nodes)
- Sudden death - asphyxia, bleed
- Bronchiectasis - usually cylindrical
- Calcification - takes at least 6 months

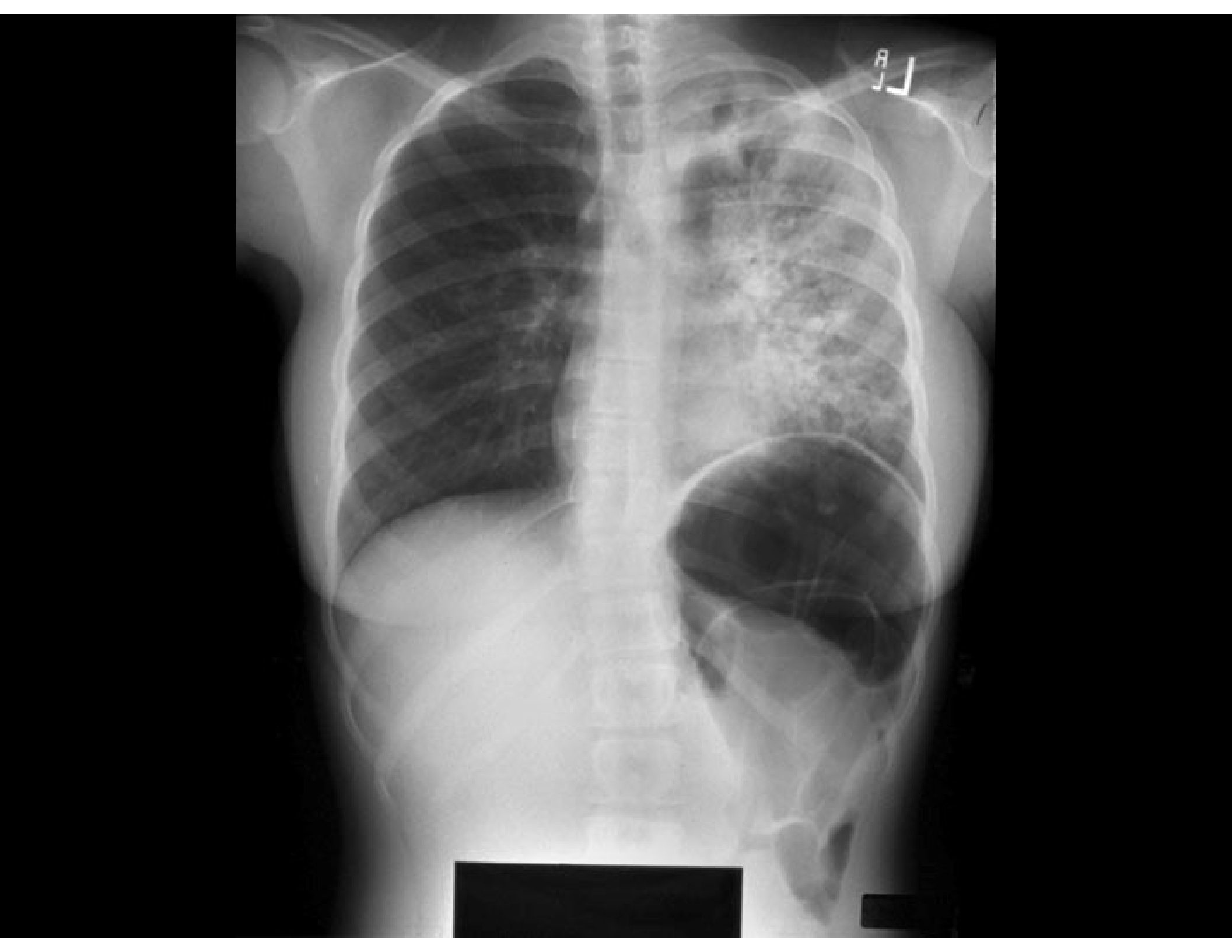


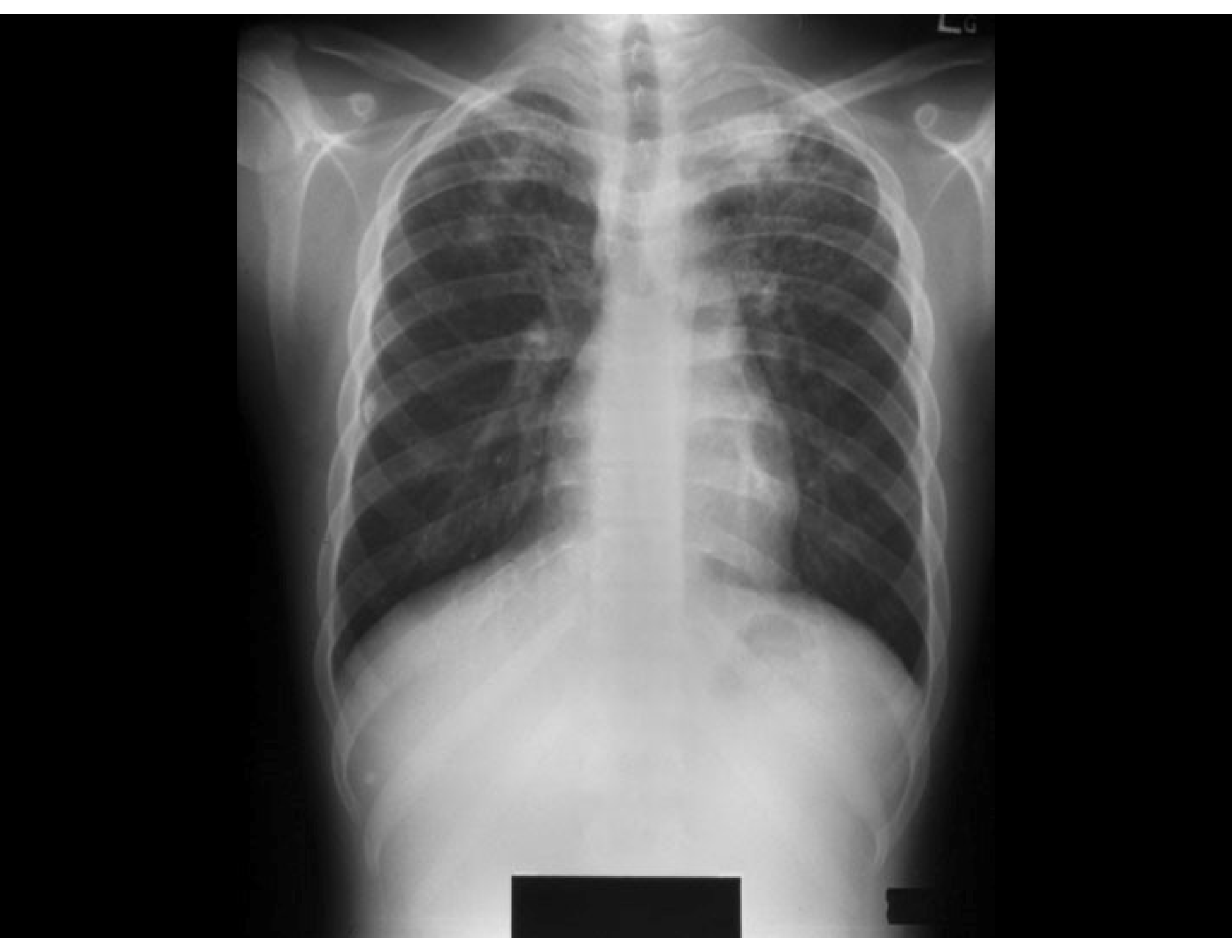


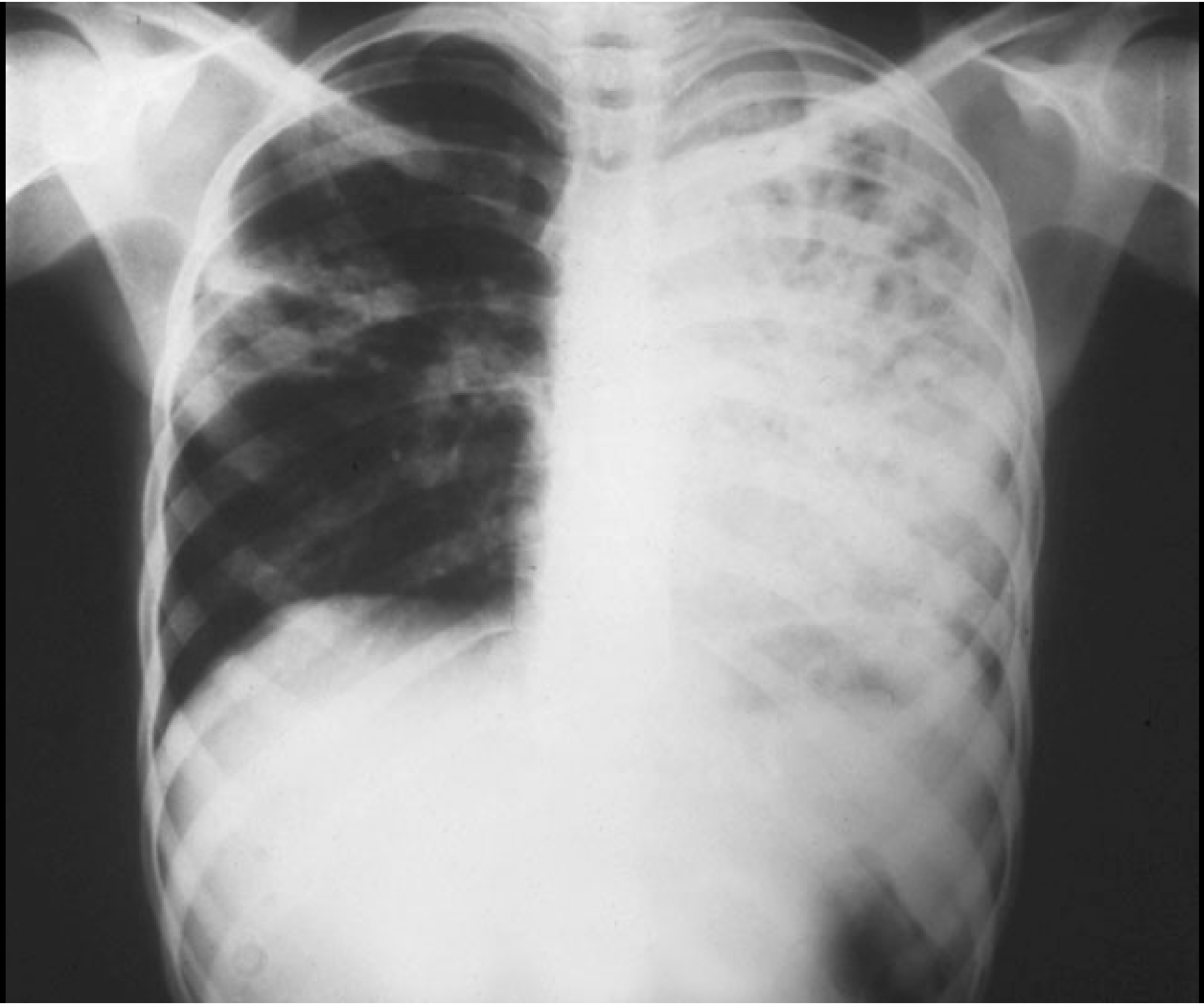

L
JMs

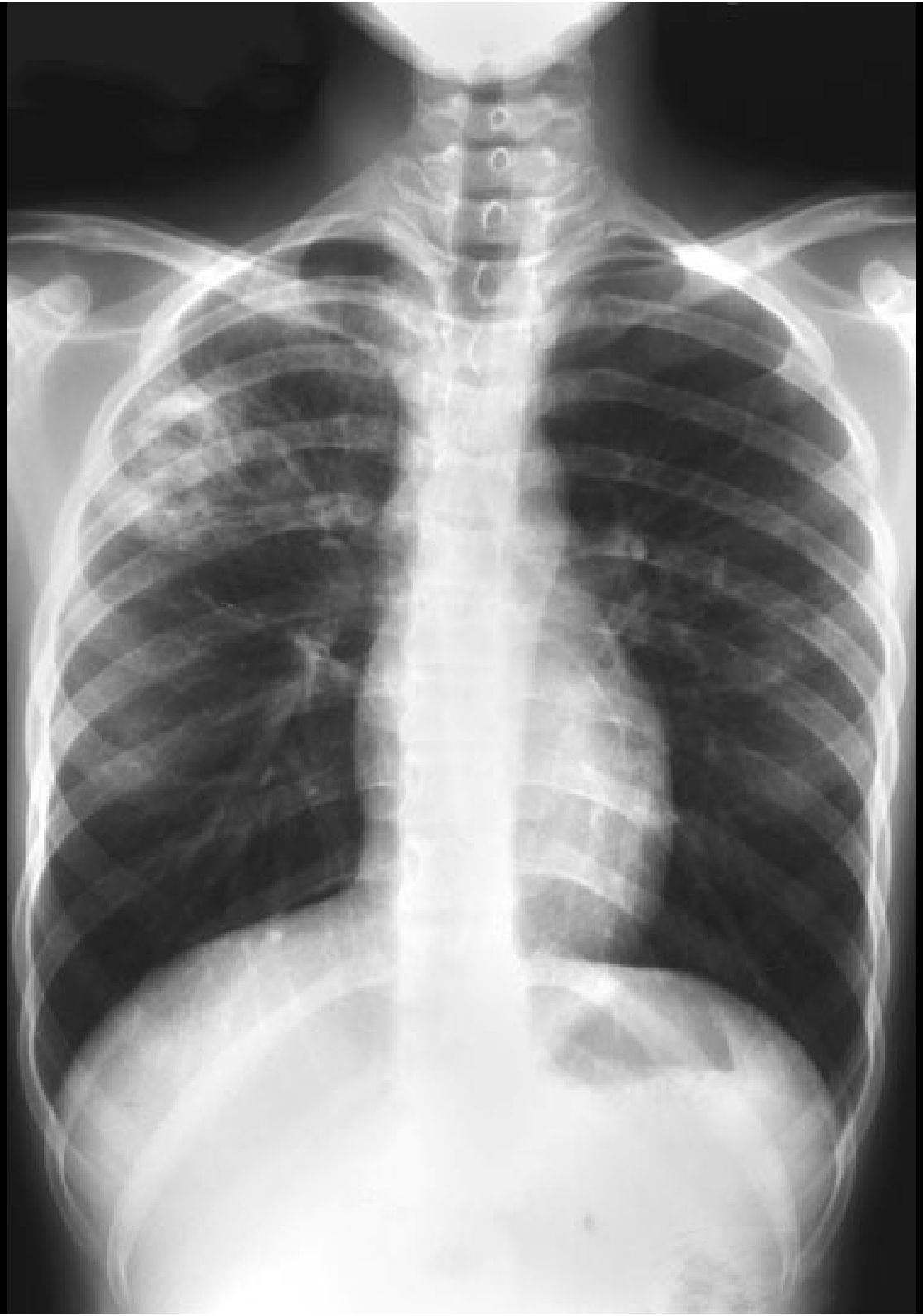
REACTIVATION TUBERCULOSIS IN PEDIATRICS

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


R



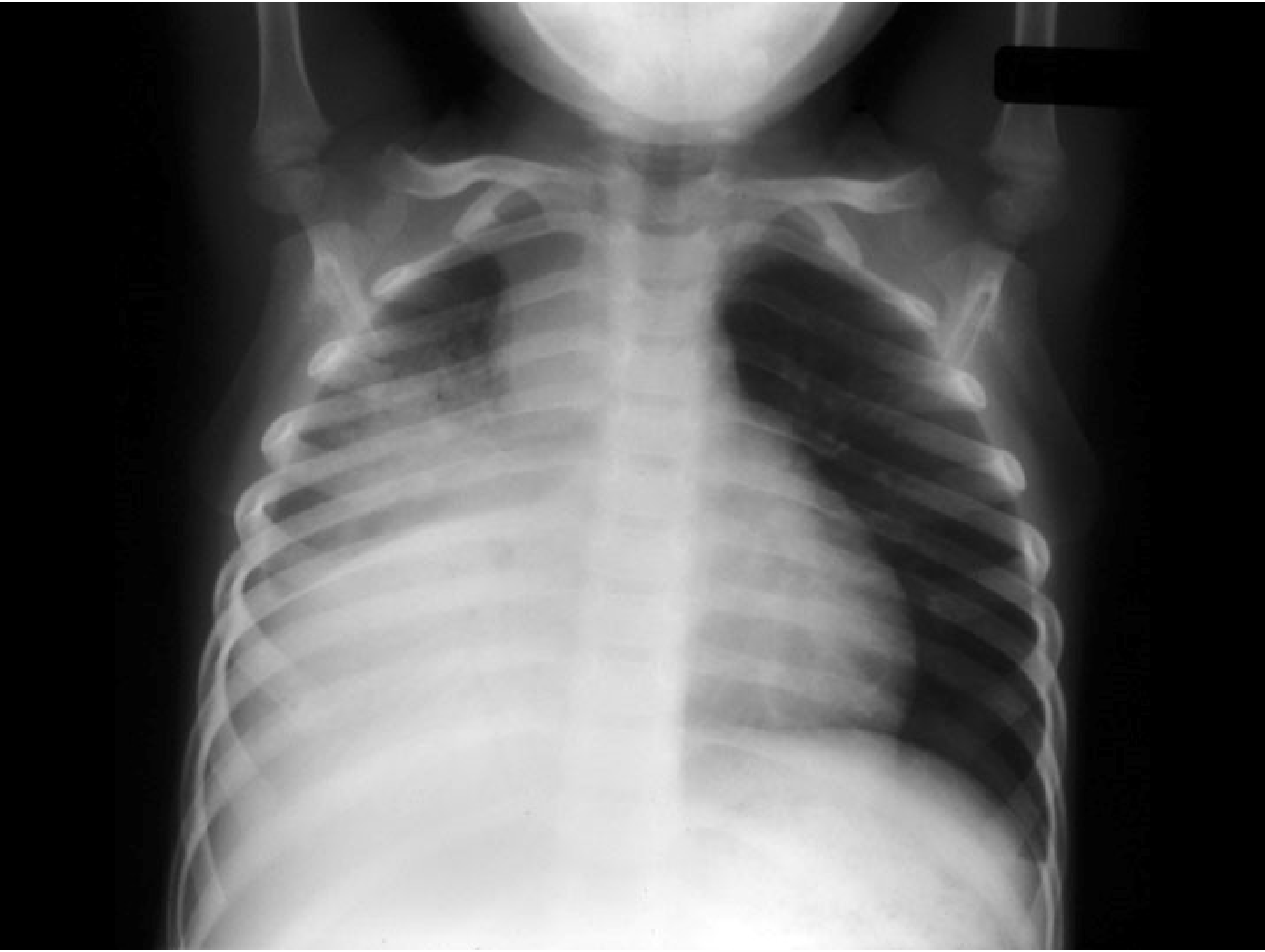




TUBERCULOUS PLEURAL EFFUSION IN PEDIATRICS

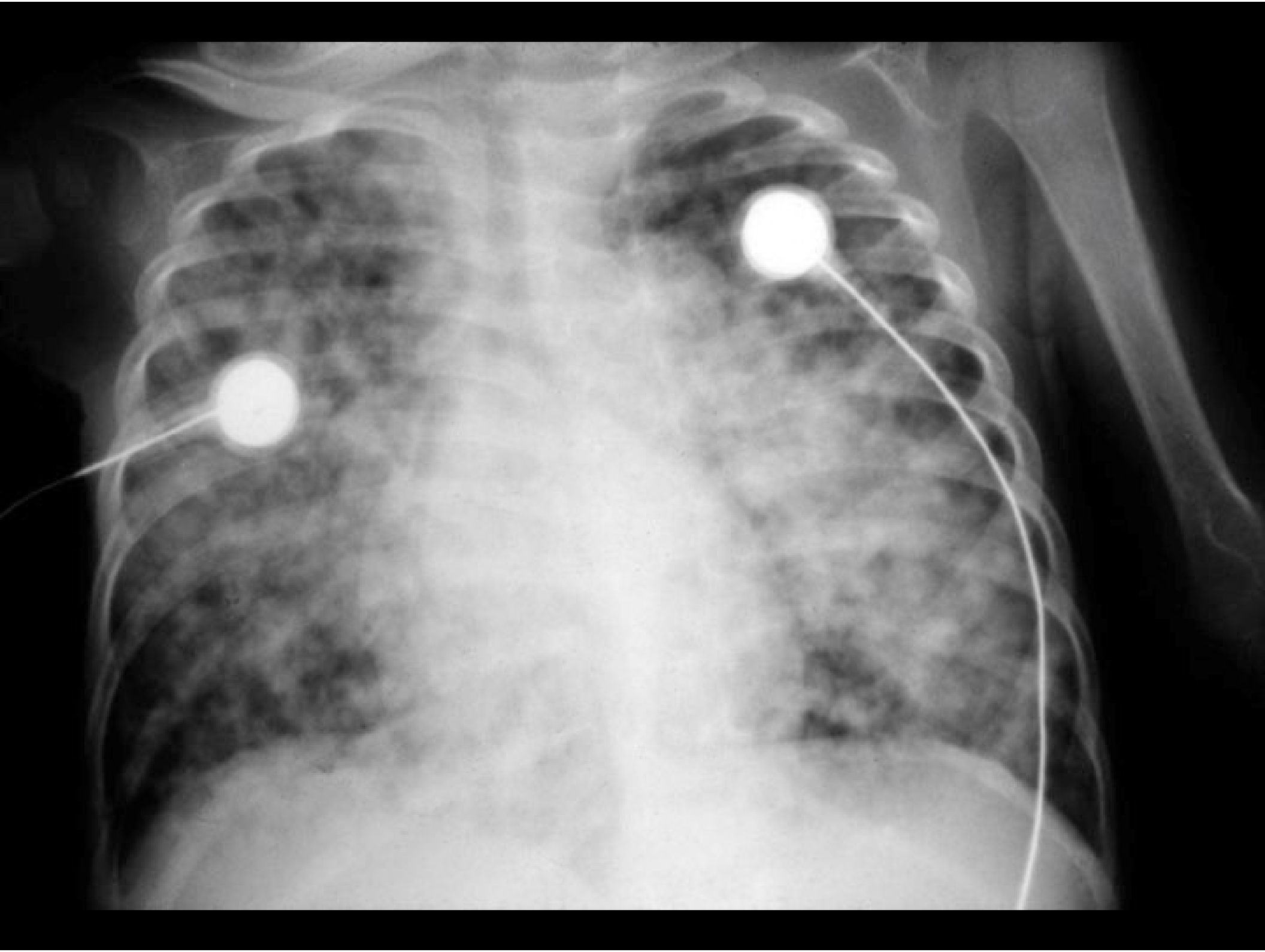
- Primarily in adolescents; uncommon before age 5, rare before age 2
- Usually unilateral, but can be bilateral
- Almost never associated with a segmental lesion; rare in miliary disease
- Usually abrupt onset: fever, chest pain, SOB
- Thoracentesis: several hundred WBC's (M), high protein, glucose < 30, AFB stain negative, culture positive in 30% to 60%

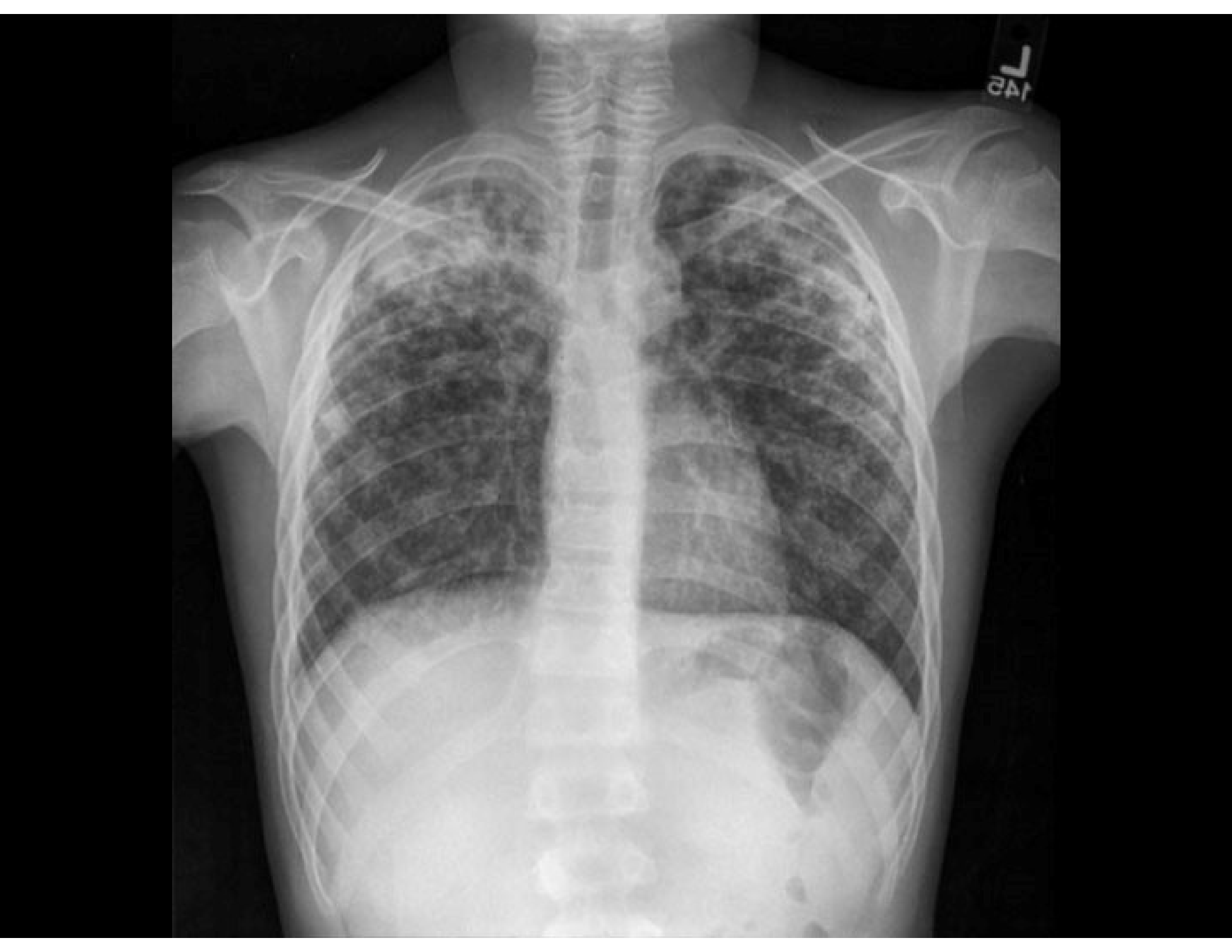
AP

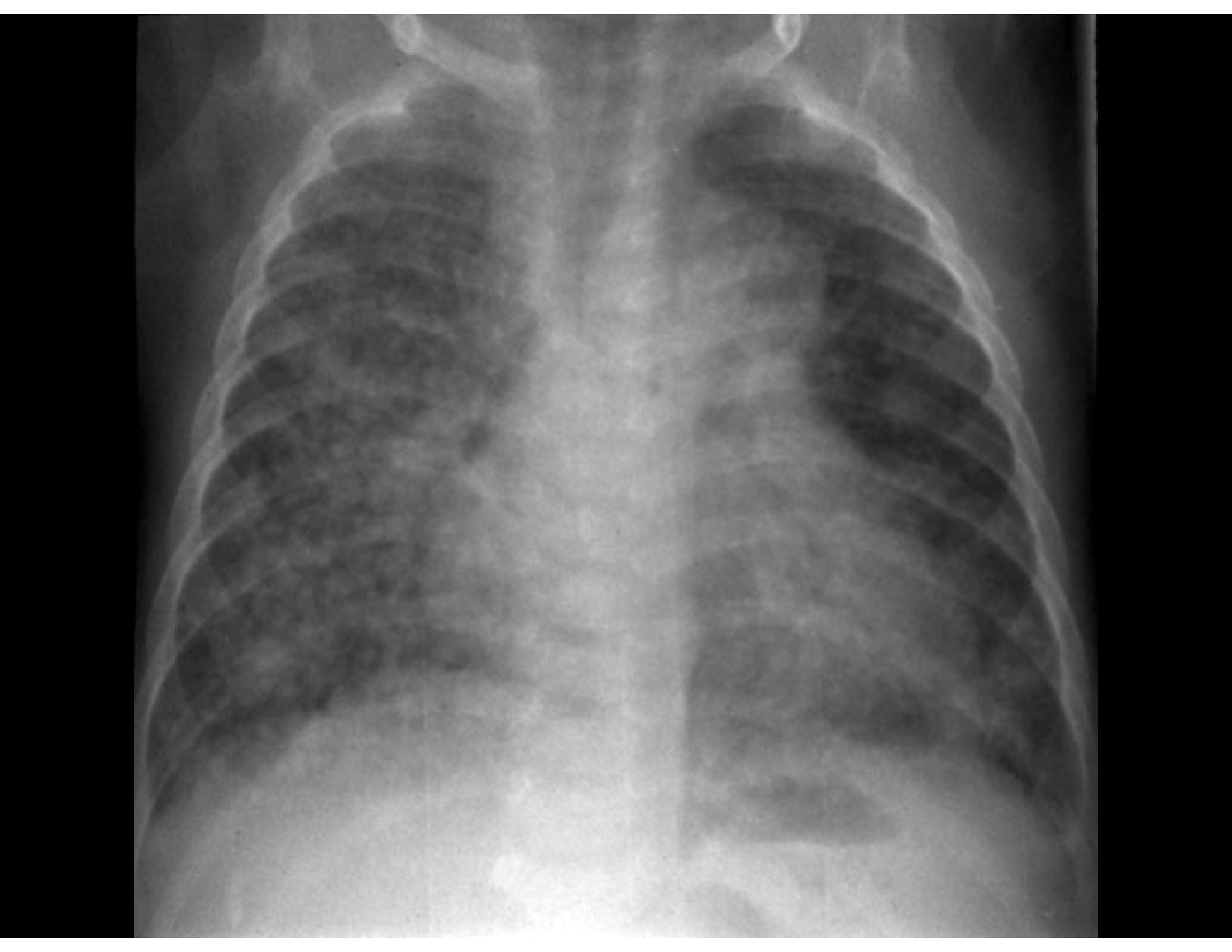


DISSEMINATED (MILIARY) TUBERCULOSIS IN CHILDHOOD

- most common in infants, recent after infection
- protean manifestations at first - 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

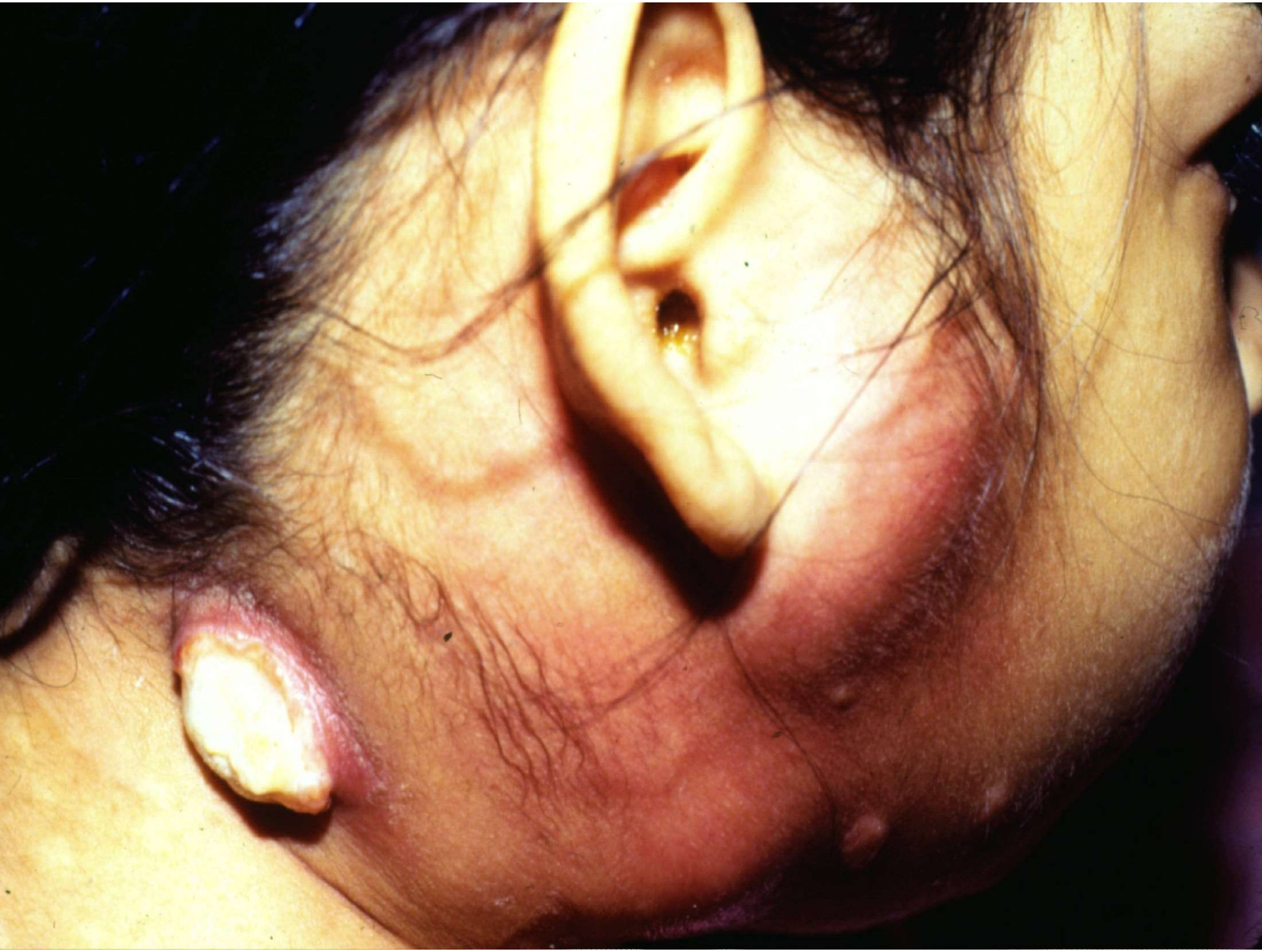


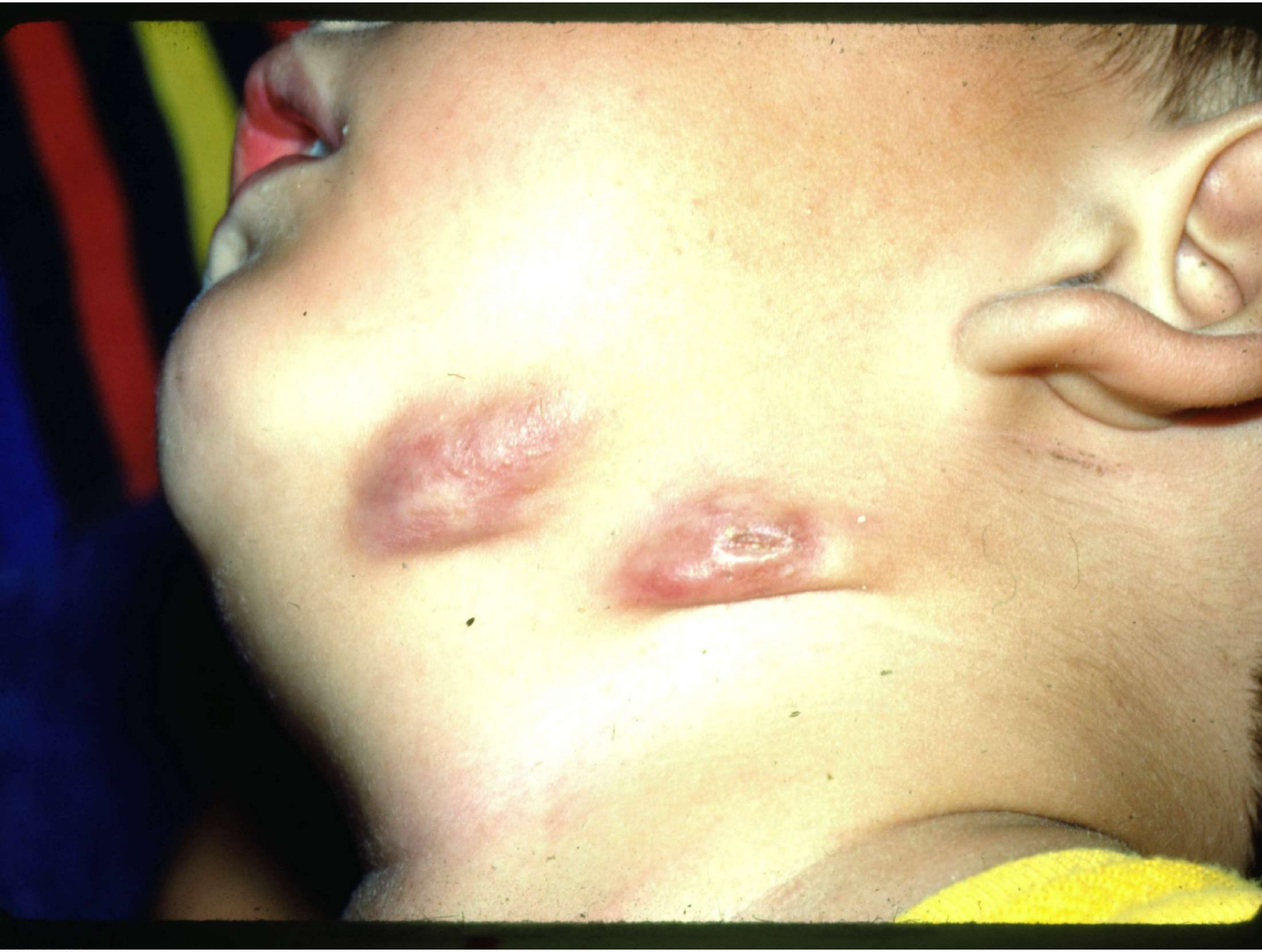

L



LYMPHADENITIS CAUSED BY MYCOBACTERIUM TUBERCULOSIS

- most often unilateral; may be bilateral
- chest xray usually normal
- usually indolent onset of enlarged, fixed, matted nodes in anterior chains, submandibular
- submental, occipital, axilliary, supraclavicular nodes less common
- absence of systemic findings; minimal tenderness
- often progress and "break down" - suppuration, sinus tracts
- major differential dx: NTM, *Bartonella*, malignancy





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
- 3 clinical stages: correlate with sequelae

  I - non-specific signs and symptoms

  II -focal neurologic findings, increased ICP

  III -profound findings - coma, paralysis, death

CLASSIC FINDINGS IN CEREBROSPINAL FLUID

	Viral	Bacterial	TB
Cells	0-500	5-10,000	10-500
Differential	polys → mono	polys	polys → monos
Protein (mg/dl)	20-60	20-400	50-5,000
Glucose (mg/dl)	30-80	<20	20-50

CT SCAN/MRI FINDINGS IN TUBERCULOUS MENINGITIS

- Basilar enhancement
- Hydrocephalus (communicating)
- Vasculitis
- Infarct
- "Paradoxical" tuberculomas - while on ultimately successful chemotherapy

TUBERCULOSIS IN HIV-INFECTED CHILDREN
Clinical and Radiographic Presentation

- in children with preserved immunocompetence, presentation is indistinguishable from HIV-uninfected children
- most common symptoms remain malnutrition, fever, night sweats, lymphadenopathy and cough
- extrapulmonary disease (meningitis and tuberculoma, abdominal) is more common
- TB meningitis has the same clinical and CSF findings as in HIV-uninfected children except that intracerebral mass lesions are more common
- chest radiograph findings are typical, but more extensive and a broader differential diagnosis

Impact of HIV on Diagnosis of PTB

Diagnostic feature	Impact of HIV
chronic symptoms	less specific
positive TB contact (if parent)	less specific
malnutrition	less specific
positive tuberculin test	less sensitive
"typical"CXR findings	less specific
satisfactory response to TB treatment	less sensitive

Diagnosis of Tuberculosis Disease in Children

- A cheap, easy and noninvasive, and accurate [especially sensitive] test for the diagnosis of TB disease is the “Holy Grail” of childhood tuberculosis

Rates of positive results in strongly positive clinical cases of child pulmonary TB:

- AFB stain: < 10%
- PCR/Xpert: 10% - 40%
- Culture: 20% to 50%
- Extrapulmonary TB, all tests: ~ 25%

Texas Children’s Hospital

BCM
Baylor College of Medicine

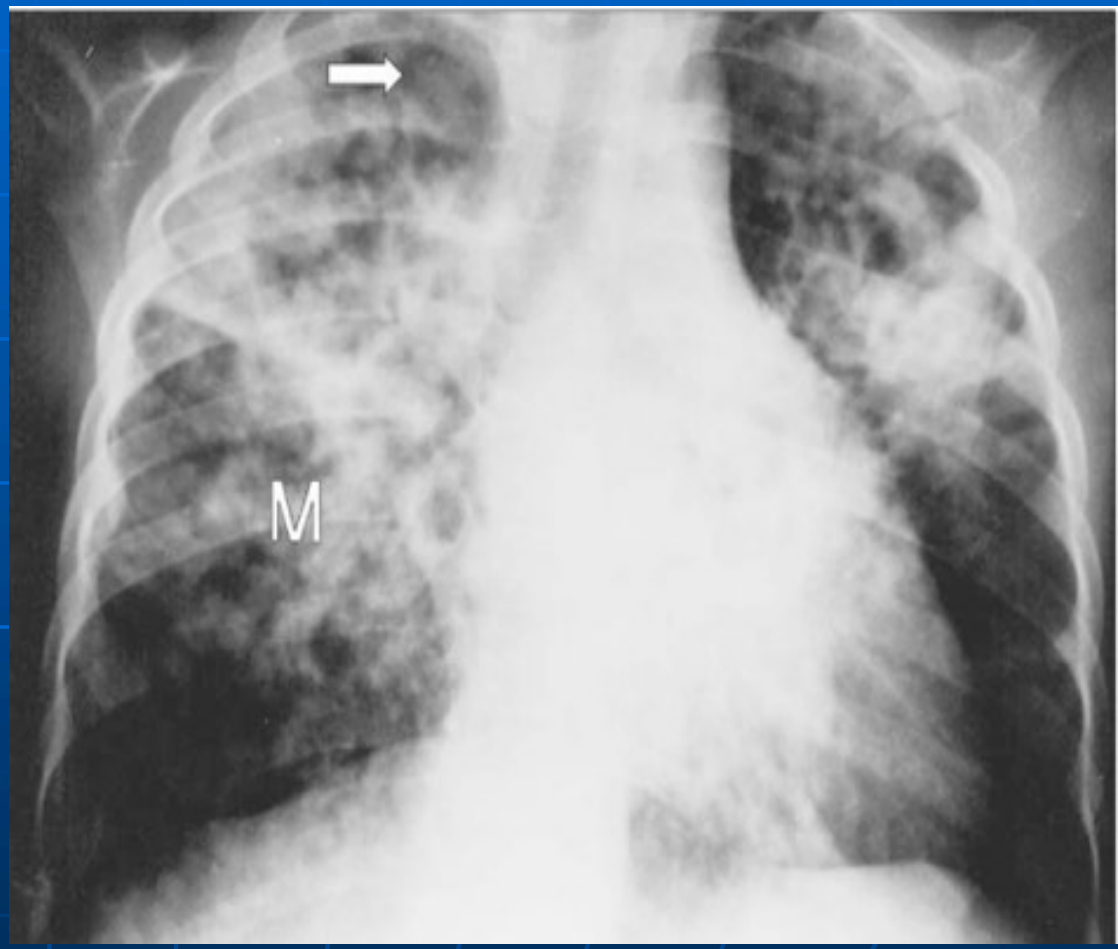
EVALUATION OF A CHILD WITH SUSPECTED TUBERCULOSIS DISEASE

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

Gastric Aspirates

- Inpatient procedure
- Overnight fasting
- Lavage with NS if volume < 20cc

- Generally done qAM x3
- Inpatient costs substantial
- AFB smear yield: minimal
- AFB Culture yield: 20-30%



Induced Sputum

- Outpatient procedure
- 2-3h fasting period
- Pretreated with salmeterol; nebulized saline, then CPT given
- Nasopharynx suctioned

- One specimen sufficient
- Minimal costs

Lancet. 2005;365:130

Gene Xpert MTB/RIF

- Cartridge-based NAAT & closed sample preparation = minimal biosafety requirements

WHO-endorsed
December, 2010
http://www.who.int/tb/features_archive/new_rapid_test/en/index.html

Accuracy of the Xpert MTB/RIF test for the diagnosis of pulmonary tuberculosis in children admitted to hospital in Cape Town, South Africa: a descriptive study

Mark P Nicol, Lesley Workman, Washiefa Isaacs, Jacinta Munro, Faye Black, Brian Eley, Catharina C Boehme, Widaad Zemanay, Heather J Zar

- 452 children (median: 19m) with ≥ 1 induced sputa
- 108 (24%) HIV+
- 6% smear-positive; 16% culture-positive
  - Gold standard: liquid culture
- Xpert detected twice as many cases as smear
  - Detected all smear-positive and 61% of smear-negative
- Sensitivity: HIV+ > HIV -
- Results in 1d for Xpert, versus 12d for liquid culture

Lancet 2011; e-published 7/18/11

Anderson et al. Diagnosis of childhood tuberculosis and host RNA expression in Africa. NEJM 2014; 370:1712.

- Evaluation of 2,955 children in South Africa, Malawi [discovery cohorts] and Kenya [validation cohort] undergoing evaluation for clinically-suspected TB
- 4 categories: culture-confirmed TB, clinical TB, diseases other than TB, and TB infection
- Genomic analysis of RNA expression in host blood
- Identified 409 transcripts differentially expressed between TB disease and other diseases
- Identified 3,434 transcripts differentially expressed between TB disease and infection
- **51 transcripts was the smallest number that differentiated TB disease from other diseases**

Texas Children's Hospital

BCM
Baylor College of Medicine

Togun et al. Biomarkers for diagnosis of childhood tuberculosis: A systematic review. PLoS One 13(9):e0204029.

- Found 29 studies that met criteria: 20 case-control, 6 cohort, 3 cross-sectional
- 27/29 studies did not meet the criteria in at least 1 of the 4 domains of the QUADAS-2 reporting framework
- However, the performance in 22 studies met the WHO-recommended minimal targets of 66% sensitivity and 98% specificity for diagnosis and/or 90% sensitivity and 70% specificity for a triage test
- Types of markers: cytokines, mRNA signatures, specific lymphocytes, cell-wall antigens, antibodies

Texas Children's Hospital

BCM
Baylor College of Medicine

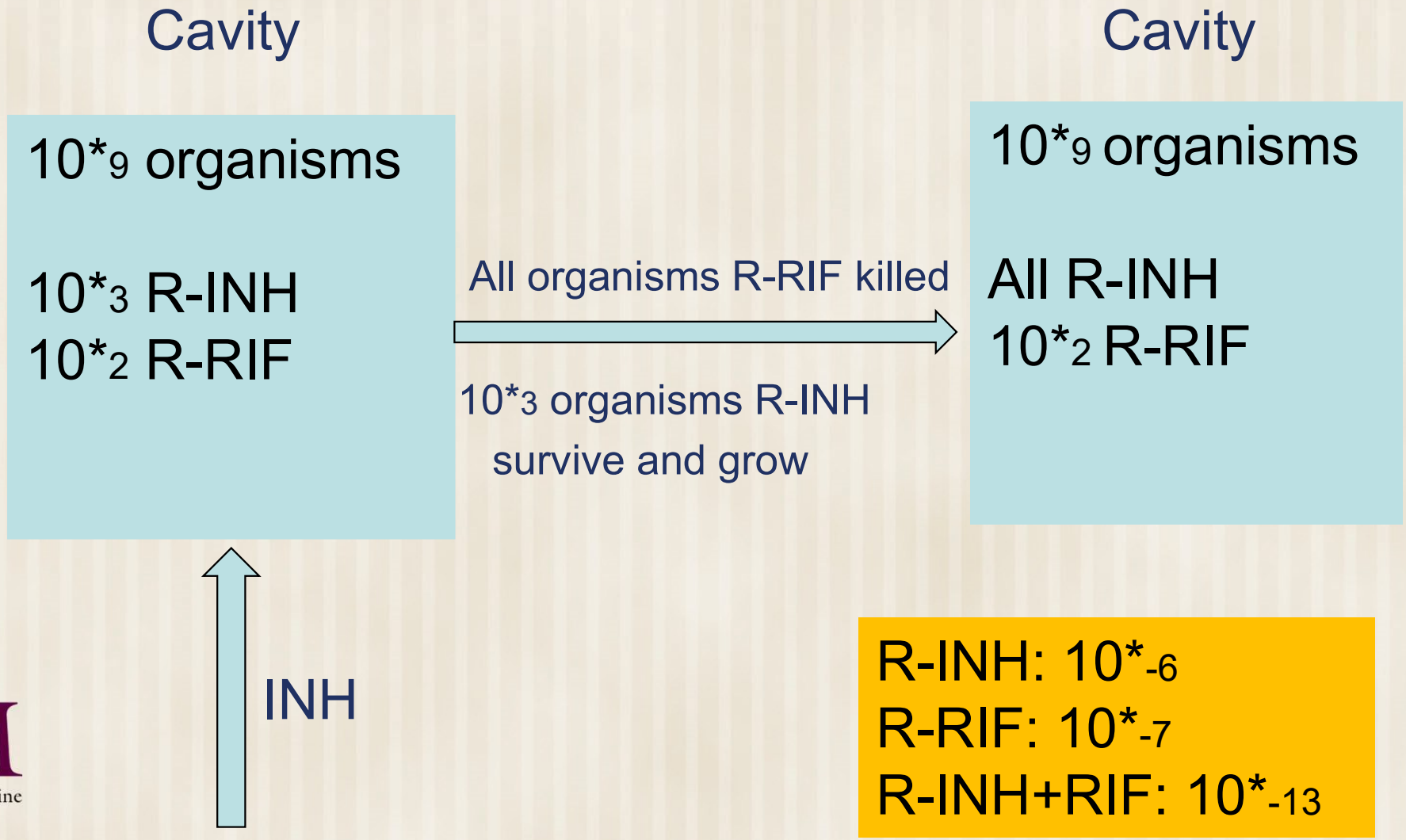
DRUG RESISTANCE IN TUBERCULOSIS

The development of drug resistance in *M. tuberculosis* is the result of a conspiracy among the organism, the patient, the doctor and the healthcare system!

DRUG RESISTANCE IN *MYCOBACTERIUM TUBERCULOSIS*

- genetic loci for resistance on chromosome, unlinked
- resistance of drugs independent
- frequency of mutations at loci is known
- more likely to have mutations when mycobacterial population is larger : infection vs. disease
- primary - resistance present when infection acquired
- secondary - resistance develops while on therapy

Preventing Drug Resistance in TB



R-INH: 10^{*-6}
R-RIF: 10^{*-7}
R-INH+RIF: 10^{*-13}

Texas Children's Hospital

BCM
Baylor College of Medicine

Preventing Drug Resistance in TB

Cavity

10^{*9} organisms

10^{*3} R-INH
10^{*2} R-RIF

RIF kills R-INH organisms

INH kills R-RIF organisms

CURE!

INH + RIF

R-INH: 10^{*-6}
R-RIF: 10^{*-7}
R-INH+RIF: 10^{*-13}

Texas Children's Hospital

BCM
Baylor College of Medicine

Preventing Drug Resistance in TB

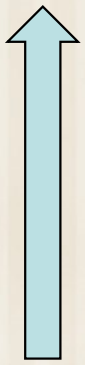
Granulomas

$10^{*}_{4\text{-}5}$ organisms

? any R-INH
? any R-RIF

Granulomas

? Cure



INH

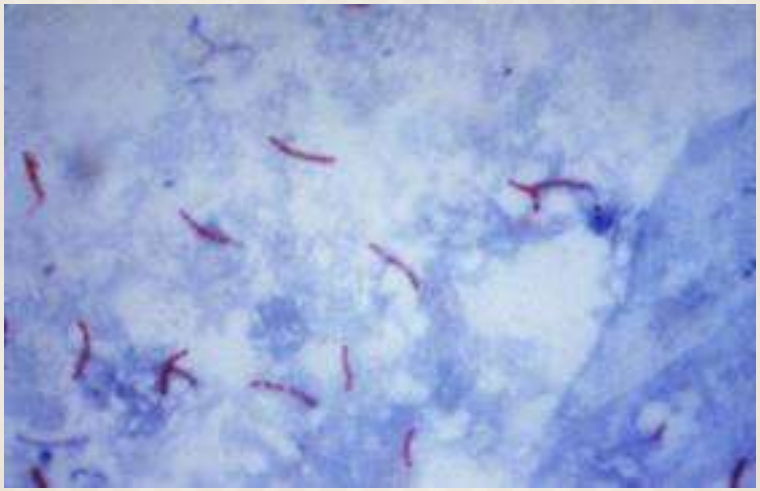
R-INH: 10^{*}_{-6}
R-RIF: 10^{*}_{-7}
R-INH+RIF: 10^{*}_{-13}

Texas Children's Hospital

BCM
Baylor College of Medicine

Treatment of Tuberculosis

"More bugs More drugs!"



Texas Children's Hospital

BCM
Baylor College of Medicine

Roles of Specific TB Drugs in Regimens

Isoniazid

- Bactericidal
- Prevents emergence of resistance to other drugs

Rifampin

- Bactericidal
- Prevents emergence of resistance to other drugs

Ethambutol

- Bacteriostatic at lower doses
- Prevents emergence of resistance to other drugs

Pyrazinamide

- Allows for shorter durations of therapy

Texas Children's Hospital

BCM Baylor College of Medicine

Treatment of Tuberculosis Infection in Children: 2021 Red Book: Rifampin Dosing

Standard Treatment

2015: 10-20 mg/kg/day

2018: 15-20 mg/kg/day

Infants, Toddlers and TBM [any age]

2015: 10-20 mg/kg/day

2018: 20-30 mg/kg/day

Texas Children's Hospital

BCM Baylor College of Medicine

Therapy for TB Disease

- Start 4-drug therapy - RIPE
  - INH, rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB); INH/RIF are the backbone of therapy
- Use PZA only during 1st 2 months for susceptible TB
  - This is your 'shortening agent': consolidate from 9 to 6 months of therapy
- Stop EMB once culture results known, if have pan-susceptible TB
  - This is your insurance in case you have drug-resistant TB
- Anticipate minimum 6 month therapy, and we often extend it to longer periods, especially for extrapulmonary disease
- ***Always*** administered by directly observed therapy (DOT)

Texas Children's Hospital

BCM Baylor College of Medicine

Ethambutol

- Metabolized faster by children than adults
  - Same mg/kg dose results in lower serum levels in children
- Consequently, risk of optic neuritis is very low
- You can feel very comfortable using ethambutol even in the pre-verbal child in whom visual acuity screening is challenging!
- Remember, however, that it crosses the blood-brain barrier poorly and should not be used for meningitis

Texas Children's Hospital

BCM
Baylor College of Medicine

Medication Tolerance

- Pediatrics:
  - 5% risk of side effects in children
    - Most minor – abdominal pain without elevation in LFTs
    - 3.3% incidence of elevated LFTs with INH and Rifampin (usually asymptomatic)
  - Peripheral neuropathy quite rare before adolescence
- Adults:
  - Hepatotoxicity:
    - 3-4% with INH alone
    - Up to 5% with INH and Rifampin
  - Peripheral neuropathy: 4%
  - Bone marrow suppression: 2%

Texas Children's Hospital

BCM Baylor College of Medicine

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

Texas Children's Hospital

BCM Baylor College of Medicine

TUBERCULOSIS IN CHILDREN
IMPACT OF DRUG-RESISTANCE

- **Usually must link the child with an adult case to identify it**
- **Adults with drug-resistant TB are as contagious as those with susceptible disease**
- **Disease expression in children the same as with susceptible strains**
- **Children tolerate and respond well to second-line drugs**

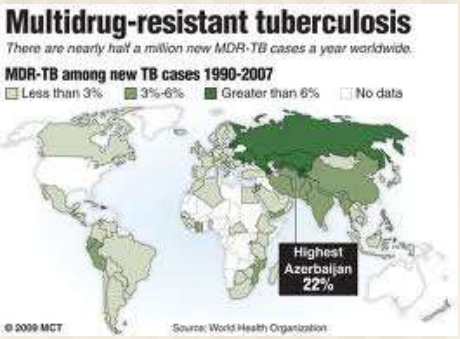
Some Issues in the Management of MDR-TB in Children

- Clinical trial data are extremely limited
- Optimal drug combinations are unknown
- Optimal durations of therapy are unknown
- Pharmacokinetic data are lacking
- Child-friendly dosing forms nonexistent
- Adverse drug effects often more difficult to assess, but children tend to tolerate drugs better
- Children have more intercurrent illnesses

Texas Children's Hospital

BCM
Baylor College of Medicine

Treatment of Drug Resistant TB in Children



INH mono-resistance: well-treated with 6-9 months of rifampin, pyrazinamide and ethambutol

MDR- TB: treatment must be individualized depending on

- Exact drug susceptibility profile
- Anatomic location of disease
- Extent of disease
- Tolerance of medications
- Requires 4-6 drugs to which the organism is susceptible, at least 2 being bactericidal

Texas Children's Hospital

BCM
Baylor College of Medicine

Harausz et al. Treatment and Outcomes in Children with MDR-TB: A Systematic Review and Individual Patient Data Meta-analysis. PLoS Medicine 2018; 15:e1002591.

- Based on published an unpublished data including children for whom specific drug use data could be obtained
- Cohort eligible if ≥ 3 children
- 975 children from 18 countries
- 39% co-infected with HIV [mainly South Africa]
- Included culture-confirmed [75%] and clinically diagnosed [25%] cases
- Culture-confirmed were more likely to be older, infected with HIV, malnourished and have more severe TB on chest radiograph

Texas Children's Hospital

BCM
Baylor College of Medicine

Harausz et al. Treatment and Outcomes in Children with MDR-TB: A Systematic Review and Individual Patient Data Meta-analysis. PLoS Medicine 2018; 15:e1002591.

- 78% had a successful treatment outcome [75% of confirmed and 89% of clinical cases]
- Treatment was successful in only 56% of children with HIV infection who did not also receive ART [compared with 82% who received ART]
- Use of high dose isoniazid and second-line injectible drugs was associated with treatment success

Texas Children's Hospital

BCM
Baylor College of Medicine

Schaaf et al. Challenges of Using New and Repurposed Drugs for the Treatment of Multidrug-Resistant Tuberculosis in Children. Exp Rev Clin Pharm 2018; 11;233.

- Efficacy trials almost non-existent
- pK, safety and tolerability studies needed; should start as soon as Phase 2b studies in adults have established pK targets, dosing and safety
- Pediatric dosing forms expense to study and produce
- Small market and limited R&D funding
- Regulatory challenges – no orphan status

Texas Children's Hospital

BCM
Baylor College of Medicine

Repurposed Drugs To Consider

Linezolid

- No pK data for long-term use; optimal pediatric dosing not yet
- Only case reports and very small series
- Linezolid suspension is expensive
- Bone marrow suppression, peripheral and optic neuritis fairly common at usual doses

Clofazimine

- No pK data for children
- No pediatric formulation
- Good safety profile in children
- Effective in regimens for adults but almost no data for children

Texas Children's Hospital

BCM Baylor College of Medicine

Repurposed Drugs To Consider

Fluoroquinolones

- Lots of experience with levofloxacin, much less with moxifloxacin
- Young children tolerate these medications well
- Adolescents frequently have joint pain; Achilles tendon injury is rare
- Early concern about growing cartilage no longer a concern
- Children < 5 years get BID dosing
- Good CNS penetration; role in childhood TB meningitis not clear
- Treatment of MDR TB infection: fluoroquinolone with or without a second drug

Texas Children's Hospital

BCM Baylor College of Medicine

New Drugs to Consider

Bedaquiline

- Important drug for patients with MDR-TB who are not eligible for the shorter regimens
- No pediatric pK data yet available; 2 trials underway [age de-escalation trial - SLOW]
- pK in adolescents similar to adults, so bedaquiline recommended by the Sentinel Project [but not by WHO] for children ages ≥ 12 years
- Pediatric formulation developed but available only in trials
- Bioavailability similar for crushed and whole tablets, so younger children could receive the adult tablet

Texas Children's Hospital

BCM Baylor College of Medicine

New Drugs to Consider

Delamanid

- Pediatric Phase 1 and 2 age de-escalation trials started in 2013 [The Philippines and South Africa]
- pK data showed that for children ages 6 to 17 years, the delamanid exposures were within the range seen in adults
- WHO has adapted guidance to include delamanid for children ages 6 to 17 years
- Similar results were found for children ages 3 to 6 years***, but not for children 0 to 2 years of age***
- Two strengths of dispersible tablets available
- Uptake for children has been slow despite guidance

Texas Children's Hospital

BCM
Baylor College of Medicine

FOLLOW-UP EVALUATIONS FOR CHILDREN WITH TUBERCULOSIS

- skin test stays positive "forever"
- frequent chest x-rays unnecessary - at diagnosis, 1-2 months, end of therapy
- 30% to 50% of children still have an abnormal but improved CXR at end of therapy
- follow growth & development closely
- adequate nutrition
- routine liver enzyme monitoring not necessary
- routine vitamin B_6 not necessary except breast-feeding, pregnant adolescents, poor diet