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## **Pediatric Tuberculosis: Clinical Disease and Evaluation**

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**Levine  
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## **Disclosure**

- Dr. Ahmed's institution receives funding for CDC Tuberculosis Epidemiology Studies Consortium (TBESC) for research on latent tuberculosis infection.
- Dr. Ahmed's institution receives funding from the North Carolina DHHS for consultation on pediatric tuberculosis.

## Advanced Concepts in Pediatric Tuberculosis (TB)

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

## Objectives

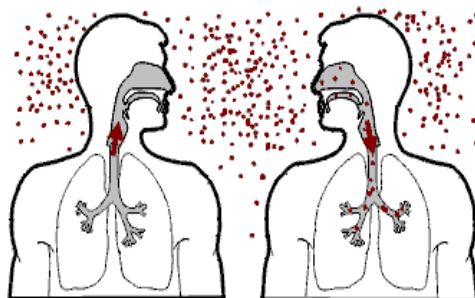
At the end of this session, participants will be able to:

- Recognize the clinical and radiographic manifestations of pulmonary TB.
- Recognize the clinical manifestations of extra-pulmonary TB, including
  - Tuberculous meningitis
  - Miliary tuberculosis
  - Tuberculosis lymphadenitis.
- Discuss the appropriate work up for the diagnosis of pediatric TB
  - Active case finding (screening, contact investigation)
  - Passive case finding (symptomatic disease)

## Terminology

- Exposure
- Latent tuberculosis infection (LTBI)
  - Tuberculin skin test (TST) reactive or interferon  $\gamma$  release assay (IGRA) positive
  - Asymptomatic, chest radiograph (CXR) normal
- Disease (TB)
  - Signs/symptoms and/or radiographic changes
  - TST / IGRA positive or negative

## Transmission and Pathogenesis



- Inhalation of droplet nuclei → alveolus
- Ingestion by alveolar macrophages
  - Multiplication → lymphohematogenous dissemination
- Macrophage and lymphocyte activation
- Development of DTH within 3-12 weeks of exposure

## Pathophysiology of Pediatric TB

- **Exposure → Infection → Disease**
  - Disease usually a rapidly evolving complication of primary infection in children
  
- **Incubation period for disease may be 6-8 weeks, before delayed type hypersensitivity develops**
  
- **Timely identification of children exposed to TB is critical in preventing disease**



## Risk of Disease Following Primary Infection

Age	Disseminated TB/ TB meningitis	Pulmonary TB	No Disease
< 1 year	10-20%	30-40%	50%
1-2 years	2-5 %	10-20%	75-80%
2-5 years	0-5%	5%	95%
5-10 years	< 0-5%	2%	98%
> 10 years	< 0-5%	10-20%	80-90%

## Pediatric TB Disease

- **Pulmonary (70-80%)**
  - Intrathoracic lymphadenopathy
  - Progressive primary disease
  - Pleural effusion
  
- **Extrapulmonary TB (20-30%)**
  - Lymphadenitis
  - Tuberculous meningitis/ tuberculoma
  - Miliary TB
  - Osteoarticular, abdominal, genitourinary TB
  - Congenital TB



## Characteristics of Pediatric TB Cases, United States, 1993-2001

	Total†		US-Born		Foreign-Born	
	n	%	n	%	n	%
Major site of disease	11 480	100.0	8603	100.0	2781	100.0
Pulmonary	8824	76.9	6639	77.2	2111	75.9
Pleural	132	1.1	92	1.1	36	1.3
Lymphatic	1778	15.5	1313	15.3	450	16.2
Bone or joint	156	1.4	96	1.1	59	2.1
Miliary	125	1.1	104	1.2	21	0.8
Meningeal	242	2.1	204	2.4	38	1.4
Other	217	1.9	149	1.7	66	2.4

Pediatrics 2004; 114: 333-341

### Clinical Syndromes Associated with Pediatric TB

		Group at Risk
Early disease		
2-6 mo	Uncomplicated lymph node disease	< 10 y
	Progressive Ghon focus	< 1 y or severely compromised
	Miliary TB, TB meningitis or both	< 3 y or severely compromised
4-12 mo	Complicated lymph node disease	> 1 y
	Pleural disease	> 3 y
	Peripheral lymphadenitis	1-10 Y
Late disease		
8-24 mo	Adult-type pulmonary disease	> 10 y
1-3 y	Osteoarticular disease	> 1 y
> 3 y	Urinary tract disease	> 5 y

N Engl J Med 2012; 367: 348-61

### Pulmonary TB

- **Lung parenchyma**
  - Ghon focus
    - Primary parenchymal process
  - Ghon complex
    - Ghon focus, local lymphangitis, regional lymph node involvement
  - Adult-type disease
- **Lymph node (LN) disease**
  - Uncomplicated
  - With hyperinflation, airway obstruction, bronchopneumonia
- **Progressive primary**
  - Primary focus develops caseous center
  - Resembles bacterial pneumonia

## Pulmonary TB: Clinical Presentation

- Most children have no or few signs or symptoms of disease
- Infants / adolescents more likely symptomatic
- Physical findings are limited
  - Most children will have a normal chest exam
  - Infants- wheezing, respiratory distress
  - Adolescents- rales/crackles, diminished breath sounds

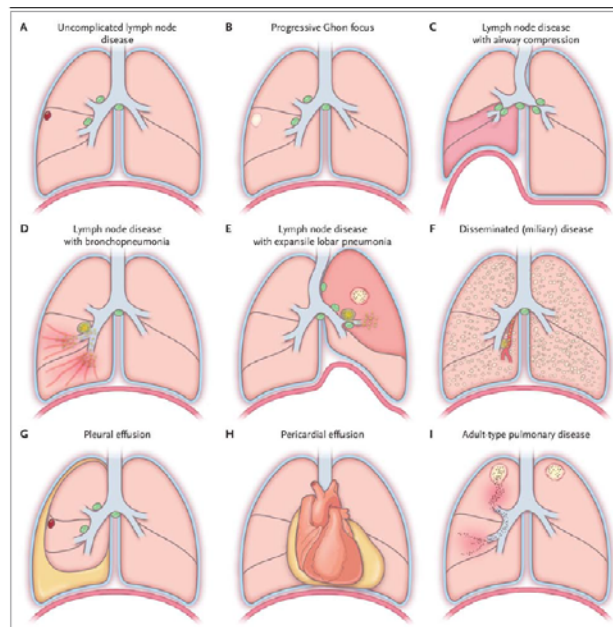
## Pulmonary TB: Clinical Presentation

- Signs and symptoms vary based on airway irritation and obstruction
  - Uncomplicated LN disease
    - Asymptomatic; physical examination unremarkable
  - LN disease with obstruction or hyperinflation (**e.g. infants**)
    - Fever, persistent cough, dyspnea
    - Respiratory distress, wheezing on examination
  - Adult-type cavitory disease (**e.g. adolescents**)
    - Fever, cough, weight loss, hemoptysis, night sweats
    - Diminished breath sounds, rales/crackles

## Pulmonary TB : Diagnosis

- **Diagnosis relies on:**
  - Epidemiology
  - Clinical findings
  - Immunologic tests - TST, IGRAs
  - Radiography
  - Microbiological/molecular confirmation
  - Identification of a source case
- **Definitive diagnosis requires detection of *Mycobacterium tuberculosis* (MTB) in respiratory specimen by culture or NAAT**
  - Microbiologic confirmation difficult due to paucibacillary nature of disease

## Pulmonary TB: Radiography





## Ghon Focus



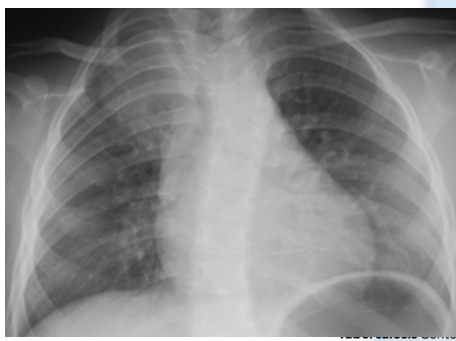
Pediatr Radiol 2004;  
34: 886-894

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## Uncomplicated LN Disease

- 2 y old male of Hmong descent
- Presents with cervical adenopathy
- CXR with hilar adenopathy
  - Hospitalized
  - MTB isolated from GA
- 3 y old "aunt" of Hmong male
- Evaluated as part of CI
  - TST reactive
  - CXR abnormal
- Treatment based on nephew's isolate

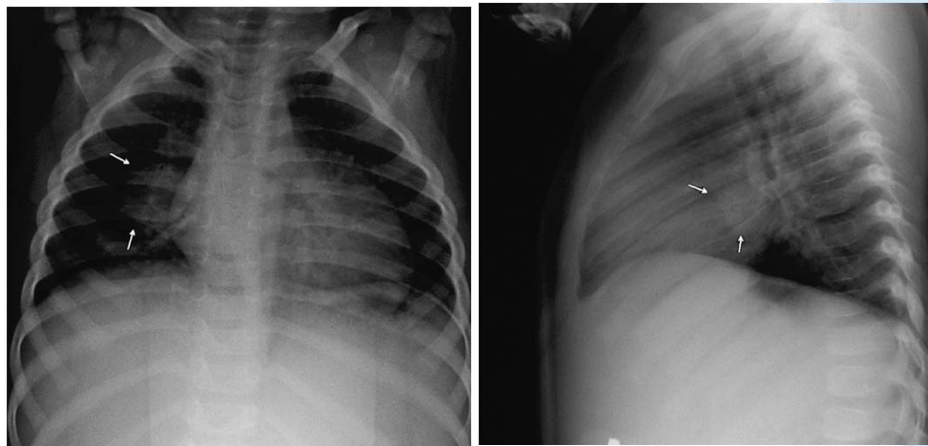


## Uncomplicated LN Disease: Hilar Lymphadenopathy

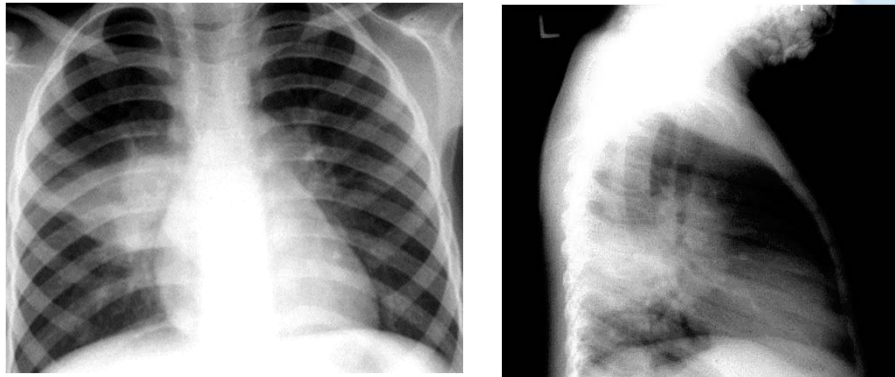
- 3 year old girl exposed to uncle with pulmonary TB
- Contact investigation (CI)
  - PE normal except for gastrostomy tube
  - TST nonreactive
  - CXR done prior to window prophylaxis
- Disease identified by CI



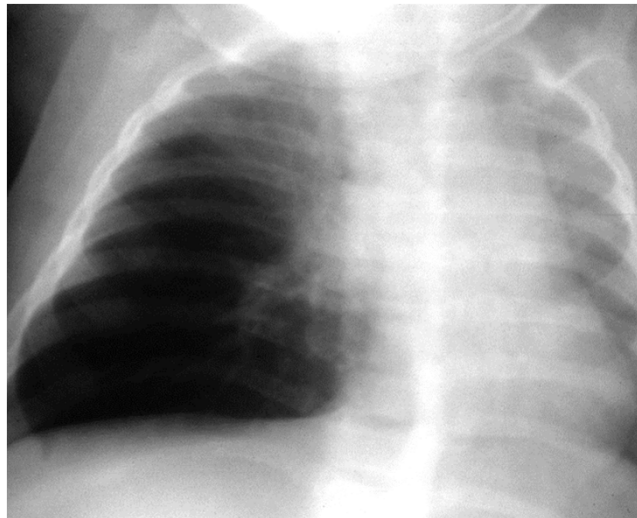
## Hilar Adenopathy : Value of Lateral CXR



### LN Disease with Airway Compression


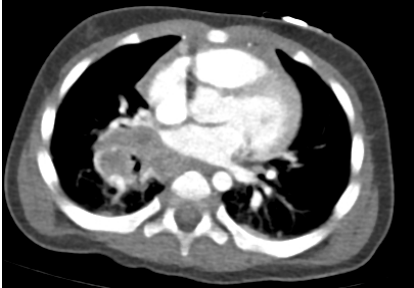


### LN Disease with Hyperinflation




## LN Disease with Bronchopneumonia

- 9 mo old Hispanic girl with FUO
- CXR demonstrates pneumonia
  - Fullness in hilar area
  - CT confirms adenopathy
- TST reactive at 12 mm
- Gastric aspirates, bronchoalveolar lavage
- Source case identified

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## Ghon Focus with Cavitation and Bronchopneumonia

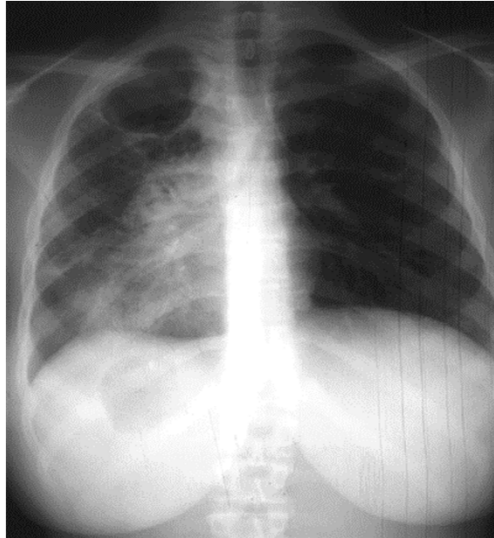


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## Adult-Type Cavitory Disease



## Adult-Type Cavitory Disease



## Pleural TB

- **Occurs within 6-9 months of initial infection**
  - Uncommon in < 5 y of age
- **Hypersensitivity response bacilli discharged from subpleural focus into pleural space**
  - Unilateral, not associated with segmental pulmonary lesions
- **Clinical presentation**
  - Fever, pleuritic chest pain
  - Diminished breath sounds on affected side

## Pleural Effusion



Pediatr Radiol 2004;  
34: 886-894

## Pleural TB: Diagnosis

- **Pleural fluid**
  - Yellow, blood-tinged
  - Protein 2-4 g/dL; glucose 20-40 mg/dL
  - WBC 100-1000 cells/mm<sup>3</sup>
- **Definitive diagnosis requires detection of MTB by culture or NAAT in pleural fluid sample or pleural tissue**
  - AFB stain usually negative
  - MTB isolated in 30-50% of cases
  - Biopsy- granuloma in 90% of cases
    - MTB isolated in up to 70% of cases

## Tuberculous Lymphadenitis

- **Most common form of extrapulmonary disease**
  - “Scrofula”
- **Epidemiology differs from pulmonary TB**
  - Predilection for immigrants from Southeast Asia
  - Women > men; peak age 30-40 y
  - May be associated with ingestion of unpasteurized dairy products (*Mycobacterium bovis* disease)

## TB Lymphadenitis: Clinical Presentation

- Typically occurs 6-9 months after infection
- Typically unilateral, involving 1-3 nodes
  - Cervical, submandibular, supraclavicular LN
  - Firm, painless; slightly discolored
  - Slow progression over 1-2 months
  - Draining sinus in < 10% cases
- Pulmonary disease may be absent

## TB Lymphadenitis: Diagnosis

- Diagnostic tests
  - TST typically reactive
  - CXR abnormal in 10-40% of cases
- Definitive diagnosis by detection of MTB by culture or NAAT
  - Excisional biopsy offers highest yield
  - Fine needle aspiration (FNA) lower yield
- Histology
  - Granulomas, Langerhans giant cells, caseous necrosis



## Diagnostic Tests in TB Lymphadenitis

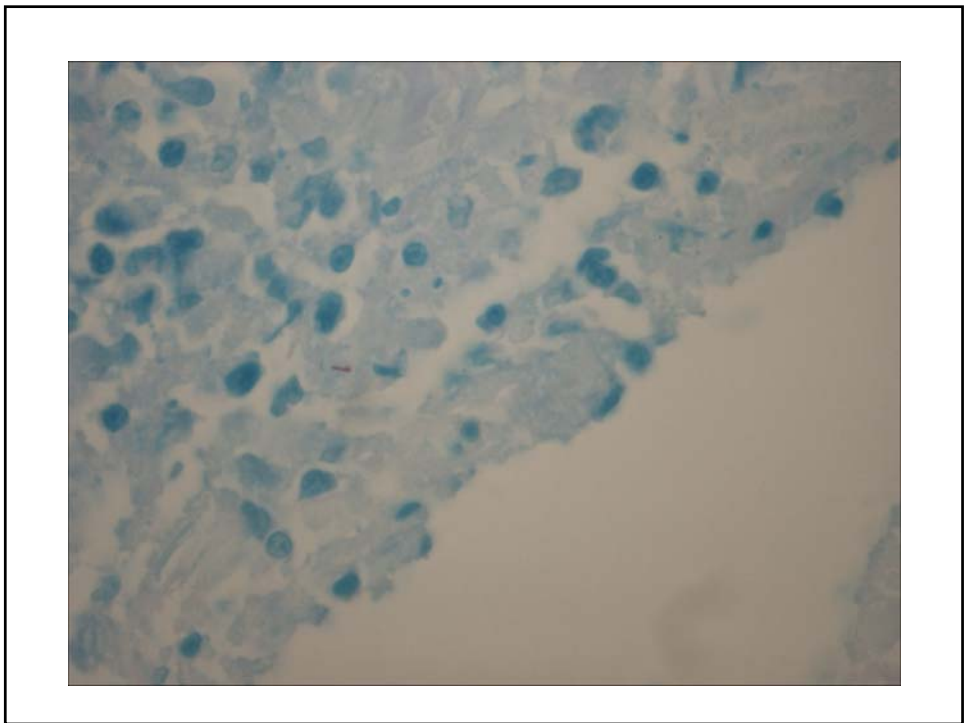
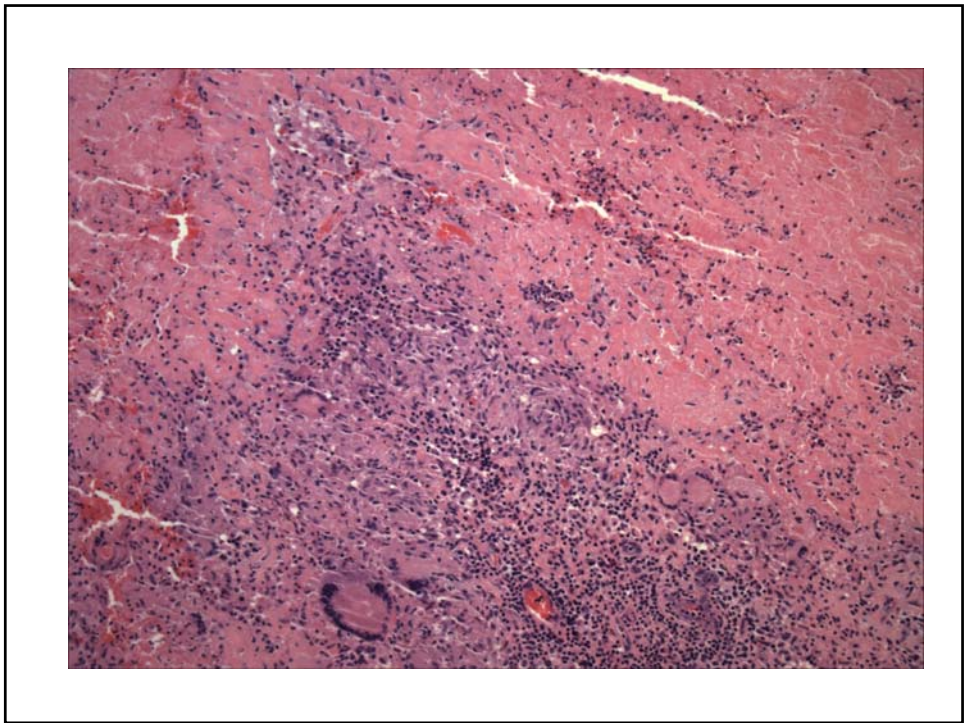
Location (Year)	Culture (+)	AFB (+)	GI (+)	Culture + GI (+)	NAAT (+)
California (1992) [28]					
Excisional Biopsy	28/30 (93%)	11/30 (37%)	23/30 (77%)	N/A	N/A
FNA	18/29 (62%)	10/29 (35%)	16/29 (55%)	N/A	N/A
France (1999) [9]					
Excisional Biopsy	12/39 (31%)	2/39 (5%)	32/39 (82%)	N/A	N/A
FNA	8/26 (31%)	2/26 (8%)	N/A	N/A	N/A
California (1999) [29]					
FNA	44/238 (18%)	58/238 (24%)	84/238 (35%)	N/A	N/A
India (2000) [30]					
Excisional Biopsy	4/22 (18%)	5/22 (23%)	13/22 (59%)	17/22 (77%)	15/22 (68%)
FNA	2/22 (10%)	4/22 (18%)	7/22 (32%)	9/22 (41%)	12/22 (55%)
California (2005) [5]					
Excisional Biopsy	24/34 (71%)	15/39 (38%)	36/31 (88%)	N/A	N/A
FNA	48/77 (62%)	5/19 (26%)	47/76 (62%)	N/A	N/A
UK (2010) [12]					
FNA	65/97 (67%)	22/97 (23%)	77/97 (79%)	88/97 (91%)	N/A

Clin Infect Dis 2011; 53: 555-564

## Case: Like mother, like daughter

- 16 year old Vietnamese girl with cervical adenitis
- Referred to pulmonologist → TST placed → referred to surgeon
  - TST 21 mm
- CXR normal





## Case : TB or not TB?

- **2 year with subacute cervical lymphadenitis**
  - Afebrile
  - After 10 days of amoxicillin-clavulanate, the lymphadenitis is unchanged
  
- **TST is reactive at 8 mm**
  - CXR normal.
  
- **Mother has a history of LTBI, untreated**



## MTB versus NTM Lymphadenitis

	TB	NTM
Age range (years)	20-40	1-6
Sex distribution	F>M	F≥M
Birth country	TB-endemic	Non-TB-endemic
HIV infection	Common in HIV-endemic countries Uncommon in developed countries	Rare
Clinical features	Indolent painless swelling Systemic symptoms: uncommon in HIV-negative, common in HIV-positive	Indolent painless swelling Systemic symptoms: uncommon
Location	Cervical	Cervicofacial
Pulmonary disease	Common	Absent
Tuberculin skin test	Positive	Occasionally positive
IGRA	Positive	Negative
Histology	Reactive adenitis	Caseating granuloma
Treatment	Antibiotics +/- excision	Excision +/- antibiotics
Paradoxical reactions	Common	Absent

## TB versus NTM Lymphadenitis

- ***Mycobacterium tuberculosis* complex**
  - *M. tuberculosis* (scrofula), *M. bovis*
- **Nontuberculous mycobacteria (NTM)**
  - Most commonly due to *M. avium* complex
  - NTM lymphadenitis more common than TB lymphadenitis
- **NTM versus *M. tuberculosis***
  - Not distinguishable clinically or histologically
  - TST may be reactive in either; CXR may be normal in TB
  - Differentiation requires isolation of pathogen in tissue

## Tuberculous Meningitis

- Occurs within 2-6 months after initial infection
- **Reactivation of caseous lesion in meninges or cerebral cortex from early occult lymphohematogenous dissemination or from direct invasion during uncontrolled dissemination**
  - Exudative discharge of bacilli into subarachnoid space
  - Infiltration of cortical and meningeal blood vessels
  - Inflammation, obstruction and infarction of cerebral cortex
  - Exudate interferes with flow of CSF at basilar cisterns, leading to communicating hydrocephalus

## TB Meningitis: Clinical Presentation

- **Stage I (1-2 weeks)**
  - Nonspecific symptoms- fever, HA, irritability
  - No focal neurologic signs (GCS 15)
- **Stage II (2-4 weeks)**
  - Lethargy, nuchal rigidity
  - Seizures, CN palsies (GCS 11-14)
- **Stage III**
  - Coma, hemiplegia or paraplegia
  - Decerebrate or decorticate posturing (GCS < 11)



## Presenting Symptoms and Signs in > 500 Children with Central Nervous System TB, South Africa, 1985-2005

Symptoms / Signs	Number of patients (%)
Decreased consciousness	356 (70)
Fever	339 (67)
Vomiting	269 (53)
Malaise	263 (52)
Seizures	240 (47)
Weight loss	236 (46)
Cough	164 (32)
Weakness	157 (31)
Headache	128 (25)
Meningeal irritation	445 (98)
Cranial nerve palsies	145 (27)

Pediatrics 2009; 123: e1

## TB Meningitis : Diagnosis

- **Ancillary criteria**
  - TST nonreactive in up to 40% of cases
  - CXR normal in up to 50% of cases
- **CSF**
  - Pleocytosis (10-500 WBC/mm<sup>3</sup>)
  - Glucose low/normal (20-40 mg/dL)
  - Protein elevated (up to > 400 mg/dL)
  - MTB isolation in 20-50% of cases
    - With 10 ml CSF, AFB smear positive in up to 30%,  
MTB culture positive in up to 70%

## TB Meningitis: CNS Imaging

- **Computed tomography (CT)**
  - Hydrocephalus (90%)
  - Basal meningeal enhancement
  - Infarcts, tuberculoma
- **MRI- more sensitive than CT**
  - Hydrocephalus
  - Basal meningeal enhancement
  - Infarcts, tuberculoma (especially of brainstem)

### Diagnostic Findings in > 500 Children with Central Nervous System TB, South Africa, 1985-2005

Symptoms / Signs	Number of patients (%)
TST, reactive	304 (61)
Chest radiograph, abnormal	249 (46)
Chest radiograph, miliary	66 (12)
CT, abnormal	165 (70)
CT, basal meningeal enhancement	387 (75)
CT, infarction	164 (32)
CT, tuberculoma	66 (13)
Culture positive, CSF	64 (12)
Culture positive, other specimen	104 (19)

Pediatrics 2009; 123: e1

## TB Meningitis: Diagnosis

- **Definitive diagnosis**
  - Identification of MTB in CSF by culture or by NAAT
- **Presumptive diagnosis**
  - Identification of MTB from specimen other than CSF
  - Clinical findings consistent with TB meningitis
- **Consensus statement on diagnostic criteria for meningitis**
  - Lancet ID 2010; 10: 803-812



## Case: Missed Opportunity

- 16 mo old Vietnamese girl, obtunded
  - CSF: 56 WBC/mm<sup>3</sup>, glucose 11 g/dL, protein 129 mg/dL
- MRI: basilar meningitis, infarcts
  - TST nonreactive
  - CXR with RUL infiltrate
  - CSF AFB smear negative
  - Sputum smear negative
    - MTB isolated by culture
- Source investigation
  - Mother with pulmonary TB



## TB Meningitis: Diagnosis

- Aseptic meningitis in the setting of hydrocephalus or basilar meningitis should be suspected to be TB.
- Antituberculosis treatment should be instituted empirically in any child with basilar meningitis, hydrocephalus, infarction or CN involvement that has no other apparent cause
- Source case identification is often the key to diagnosis

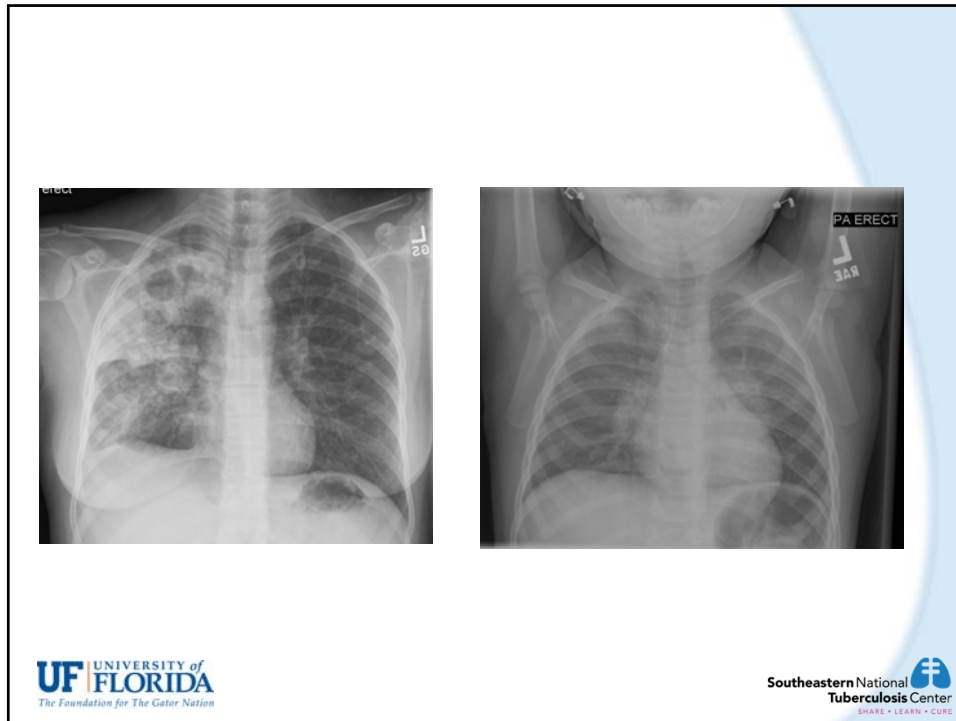


## Tuberculoma

- Another manifestation of CNS TB disease
  - May not be distinct from TB meningitis
  - Most often occurs in children < 10 y of age
- Lesion that is typically singular and infratentorial
- Symptoms
  - Headache, fever
  - Seizures

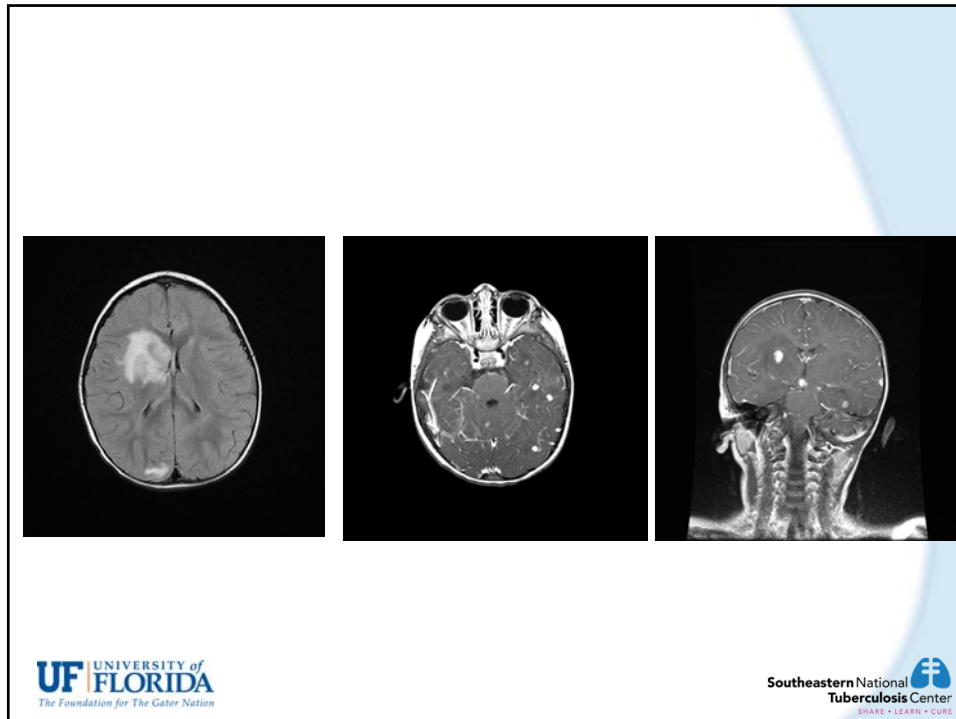
## Case : If at first you don't succeed...

- 19 month old with a mother hospitalized with suspected TB
- Contact investigation (Health Department)
  - Physical examination notable for irritability
  - TST reactive
  - CXR abnormal
- Physical examination normal per PCP



## Case : If at first you don't succeed...

- Patient to ED for repeat CXR and lumbar puncture (LP)
  - CXR done but not reviewed
  - LP required sedation but patient ate Tootsie Pop
- Return to ED the next day for LP
- LP done- CSF reported normal; patient discharged
  - WBC 30 cells/mm<sup>3</sup>, RBC 113,000 cells/mm<sup>3</sup>
  - Glucose 52 mg/dL, protein 466 mg/dL



## Miliary TB

- **Occult hematogenous spread with primary infection**
  - Bacilli enter bloodstream via pulmonary lymphatic drainage
  - Form tubercles in capillaries- typical (< 2mm) miliary lesions
  - Insidious presentation with fever, lymphadenopathy and hepatosplenomegaly before radiographic abnormalities
  - Disseminated disease in very young or immunocompromised
- **Second type (rare)**
  - Caseous focus eroding into blood or lymph vessel
  - Frequently progresses to disseminated disease irrespective of age or immune status

## Symptoms and Signs of Miliary TB

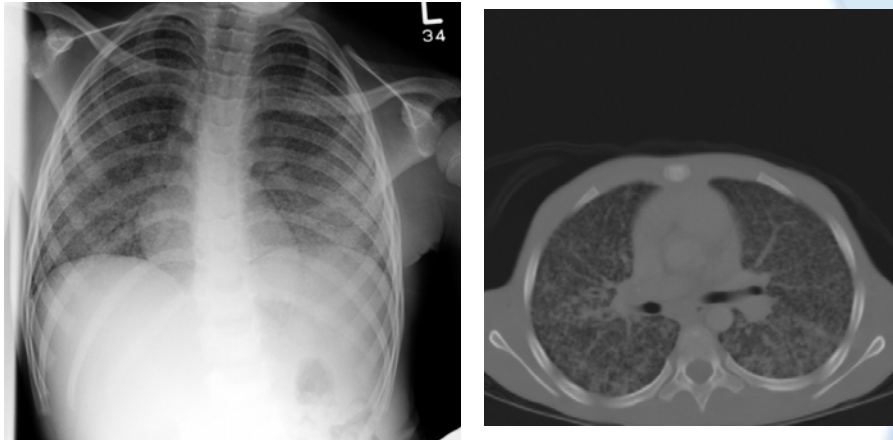
Symptoms / Signs	Percent (%) Children
Hepatomegaly	82
Splenomegaly	54
Lymphadenopathy	46
Fever	39
Respiratory distress	34
Meningitis	19

Ped Infect Dis J 1991; 10:832-6

## Miliary TB in Young Infant



## Miliary TB in Immunocompromised Host



## Miliary TB : Diagnosis

- Definitive diagnosis requires detection of MTB by culture or NAAT in respiratory or other appropriate specimen
- Presumptive diagnosis based on clinical and radiographic findings and/or evidence of dissemination
- Further evaluation
  - LP and/or CNS imaging to exclude dissemination to CNS
  - US or CT to evaluate for HSM

## Evaluation and Diagnosis of Pediatric TB

- **Evaluation and diagnosis relies on:**
  - Epidemiologic factors
  - Immunologic findings
  - Clinical presentation
  - Radiographic findings
  - Microbiologic /molecular confirmation
  
- **Source investigation is often the key to diagnosis**

## Approach to Diagnosis of Pediatric TB

- **Active case finding**
  - More common in industrialized countries
    - Most children asymptomatic/mildly symptomatic
  - Identified by contact investigation or screening
  
- **Passive case finding**
  - Children present with symptoms- need to confirm disease
    - In low and middle-income countries, limited resources for microbiological confirmation
    - In industrialized countries, microbiological confirmation not always attempted

### Primary Reason Evaluated Among Children and Adolescents with TB, United States, 2009-2010

	US-born With Linked TB Case, 188 (100), <i>N</i> (%)	All US-born, 1162 (100), <i>N</i> (%)	Foreign-born With Linked TB Case, 13 (100), <i>N</i> (%)	All Foreign-born, 518 (100), <i>N</i> (%)
Contact investigation	131 (70)	367 (32)	13 (100)	39 (8)
TB symptoms	31 (16)	334 (29)	—	169 (33)
Abnormal radiograph	17 (9)	170 (15)	—	112 (22)
Targeted testing	5 (3)	40 (3)	—	32 (6)
Immigration examination	Not applicable	Not applicable	—	43 (8)
Other	2 (1)	36 (3)	—	18 (3)
Unknown	2 (1)	215 (19)	—	105 (20)

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Pediatrics 2012; 130: e1425

### Diagnostic Tools

- **Clinical**
  - Diagnostic scores
- **Immunologic**
  - TST, IGRAs
- **Radiological**
  - CXR
  - US, CT, MRI
- **Microbiological / molecular**
  - Microscopy, culture
  - NAAT, Xpert MTB/RIF
- **Source investigation**

## Immunological Tests

- TST
  - Delayed hypersensitivity to PPD
  - Limitations of sensitivity and specificity
- IGRAs
  - Immune-based tests that measure ex-vivo IFN- $\gamma$  production by lymphocytes incubated with highly specific antigens

## TST and IGRA in Diagnosis of TB

- Neither distinguishes between infection and TB disease
- Variable sensitivity in TB disease
  - Young age
  - Overwhelming infection
  - Immunocompromised state (e.g. HIV+)
- Neither test excludes TB disease if negative
  - Consider dual testing to increase sensitivity



## Immunologic Tests in TB Disease

	All patients (n=113)	Culture-confirmed tuberculosis (n=18)	Highly probable tuberculosis (n=8)	Probable tuberculosis (n=12)	Not tuberculosis (n=63)	Indeterminate (n=12)
Age (years)	6.1 (2.1-10.3)	4.6 (1.5-12.7)	8.1 (5.2-11.9)	6 (1.8-10.5)	6.1 (2.0-9.8)	5.4 (2.2-10.5)
Female sex	52 (46%)	8 (44%)	5 (63%)	6 (50%)	27 (43%)	6 (50%)
Symptoms at enrolment						
Cough	108 (96%)	16 (89%)	6 (75%)	12 (100%)	62 (98%)	12 (100%)
Fatigue or lethargy	28 (25%)	8 (44%)	2 (25%)	2 (17%)	16 (25%)	0
Wheezing	16 (14%)	1 (6%)	1 (13%)	3 (25%)	9 (14%)	2 (17%)
Breathing difficulties	47 (42%)	10 (56%)	4 (50%)	8 (67%)	22 (35%)	3 (25%)
Fever	82 (73%)	16 (89%)	6 (75%)	9 (75%)	45 (71%)	6 (50%)
Chest pain	23 (20%)	1 (6%)	0	1 (8%)	18 (29%)	3 (25%)
Haemoptysis	4 (4%)	1 (6%)	0	1 (8%)	1 (2%)	1 (8%)
Enlarged lymph nodes	12 (11%)	5 (28%)	1 (13%)	1 (8%)	5 (8%)	0
Weight loss	55 (49%)	13 (72%)	3 (38%)	5 (42%)	32 (51%)	2 (17%)
Abdominal pains	20 (18%)	5 (28%)	2 (25%)	3 (25%)	9 (14%)	1 (8%)
Malnutrition	60 (53%)	12 (67%)	4 (50%)	5 (42%)	24 (38%)	5 (42%)
HIV infection	33 (29%)	4 (22%)	3 (38%)	7 (58%)*	15 (24%)	4 (33%)
WHO immunological staging						
Not clinically significant	7/33 (21%)	0/4 (0%)	0/3 (0%)	2/7 (29%)	4/15 (27%)	1/4 (25%)
Mild	6/33 (18%)	1/4 (25%)	1/3 (33%)	2/7 (29%)	2/15 (13%)	0/4 (0%)
Advanced	1/33 (3%)	1/4 (25%)	0/3 (0%)	0/7 (0%)	0/15 (0%)	0/4 (0%)
Severe	19/33 (58%)	2/4 (50%)	2/3 (67%)	3/7 (43%)	9/15 (60%)	3/4 (75%)
Disseminated therapy-naïve	12/33 (36%)	3/4 (75%)	1/3 (33%)	2/7 (29%)	7/15 (47%)	1/4 (25%)
Positive tuberculin skin test	31/103 (30%)	13/17 (76%)	3/8 (38%)	2/11 (18%)	9/57 (16%)	4/10 (40%)
Positive interferon-γ release assay	27/110 (25%)	13/18 (72%)	1/7 (14%)	3/12 (25%)	8/61 (13%)	4/12 (33%)
Positive tuberculin skin test or interferon-γ release assay	47/112 (42%)	17/18 (94%)	3/8 (38%)	4/12 (33%)	15/63 (24%)	4/11 (36%)

Data are median (IQR), number (%), or n/N (%). \*p=0.033 compared with not tuberculosis distribution (Fisher's exact test).

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Lancet ID 2014 [http://dx.doi.org/10.1016/S1473-3099\(14\)70884-9](http://dx.doi.org/10.1016/S1473-3099(14)70884-9)

## Radiography

- **Pulmonary TB**
  - Chest radiograph (CXR)
  - Computed tomography (CT)
  
- **Extrapulmonary TB**
  - Lymphadenitis- US, CT
  - Meningitis- CT, MRI
  - Osteoarticular disease- MRI

## Proposed Radiological Classification of Pediatric TB

- **Lymph node disease**
  - Uncomplicated
  - With airway compression
  - With hyperinflation
  - With infiltration
- **Lung parenchymal disease**
  - Ghon complex
  - Adult-type cavitary disease
- **Disseminated (miliary)**
- **Pleural effusion**
- **Pericardial effusion**

## Chest Radiograph

- Diagnostic value limited by lack of radiologist or inexperienced radiologist
- Features suggestive of childhood TB
  - Hilar adenopathy- most common manifestation
    - Frontal and lateral films recommended

## Microbiological Confirmation

- Definitive diagnosis of pediatric TB is difficult
  - Specimens difficult to obtain
  - Microbiology limited by paucibacillary disease
  
- Most pediatric TB is not culture-confirmed
  - AFB smear positive in <10-15% of children
    - Negative AFB smear does not exclude TB
  - MTB isolated in < 30-60% of children
    - Negative culture does not exclude TB

## Characteristics of Pediatric and Adult TB Cases, United States, 1993-2001

	Total†		Pediatric*				Adult	
			US-Born		Foreign-Born		Total	
	n	%	n	%	n	%	n	%
Major site of disease	11 480	100.0	8603	100.0	2781	100.0	169 587	100.0
Pulmonary	8824	76.9	6639	77.2	2111	75.9	135 508	79.9
Pleural	132	1.1	92	1.1	36	1.3	7013	4.1
Lymphatic	1778	15.5	1313	15.3	450	16.2	11 512	6.8
Bone or joint	156	1.4	96	1.1	59	2.1	3692	2.2
Miliary	125	1.1	104	1.2	21	0.8	2355	1.4
Meningeal	242	2.1	204	2.4	38	1.4	1602	0.9
Other	217	1.9	149	1.7	66	2.4	7852	4.6
Unknown	6	0.05	6	0.1	0	0.0	53	0.03
TB case criteria‡	11 480	100.0	8603	100.0	2781	100.0	169 587	100.0
Culture positive	2712	23.6	2136	24.8	553	19.9	143 044	84.3
Smear positive	92	0.8	76	0.9	16	0.6	1364	0.8
Clinical diagnosis	6040	52.6	4370	50.8	1625	58.4	15 812	9.3
Provider diagnosis	2636	23.0	2021	23.5	587	21.1	9367	5.5
Sputum smear for acid fast bacilli	11480	100.0	8603	100.0	2781	100.0	169 587	100.0
Positive	362	3.2	244	2.8	116	4.2	65 044	38.4
Negative	2584	22.5	1638	19.0	925	33.3	67 510	39.8
Not done	8353	72.8	6571	76.4	1712	61.6	33 897	20.0

## When is Confirmation of TB Important?

- Bacteriologic confirmation often not attempted in children
  - Specimens difficult to obtain
  - Low yield from culture (30-60%)
- Attempt at microbiologic isolation especially important if:
  - Source case unknown or > 1 source case
  - Isolate not available
  - Resistance suspected in source case
  - Patient has extrapulmonary disease

## Specimens for Diagnosis of Pediatric TB

- Sputum
  - Expecterated sputum (ES)
  - Induced sputum (IS)
- Gastric aspirates/ lavages (GA)
- Bronchoalveolar lavage (BAL)
- Nasopharyngeal aspirates (NPA)
- Stool

## Gastric Aspirates/Lavage

- For children < 10 y of age who cannot produce sputum
  - Requires hospitalization
  - Requires overnight fast
  - Generally unpleasant for patient and HCW
- Yield depends on *reproducibility* and *number* of specimens
  - Yield is 40-70% depending on age and presentation
  - 3 consecutive GAs optimal
  - Yield with protocol higher than if no protocol

## Bronchoscopy and BAL

- Not available in resource-limited areas
- Yield traditionally lower than GA
  - 1 specimen versus 3
  - Bronchoscopy may induce cough and increase yield of GA collected after BAL
- Increased yield of culture using both specimens

## Gastric Aspirate and BAL

- Turkey, 2008-2012
- 157 children with suspected TB
  - BAL and 3 GAs
    - MTB isolated in 54 (33%) GAs
    - MTB isolated in 48 (29%) BAL
- Overall yield in 70 (42%) from both BAL and GAs

## Induced Sputum (IS)

- Can be used in young infants and children
  - Yield higher than GAs if done correctly
- Requires training, equipment, consumables, staffing and infection control
  - Pretreatment with  $\beta$ -agonist to prevent bronchospasm
  - Nebulized hypertonic saline
  - Chest physiotherapy
  - Expectoration or catheter suctioning

## Induced Sputum versus GA

- 250 children with suspected TB (South Africa)
  - 1 month- 5 years of age
- IS (3 samples) compared with GA (3 samples)
  - 58 (23%) with MTB isolated
    - IS 54/58 (87%) versus GA 40/58 (64%)
    - Yield from 1 IS equal to that from 3 GA
- IS safe and useful for microbiologic confirmation; preferable to GA for diagnosis of pulmonary TB in HIV infected and noninfected children



## Induced Sputum versus Gastric Aspirate

Specimens	GA Smear Positive	IS Smear Positive	GA Culture Positive	IS Culture Positive	GA Cumulative Yield	IS Cumulative Yield
First	3%	8%	7%	15%	32%	66%
Second	5%	5%	9%	11%	56%	79%
Third	4%	5%	8%	13%	64%	87%
Total	7%	10%	15%	20%	64%	87%

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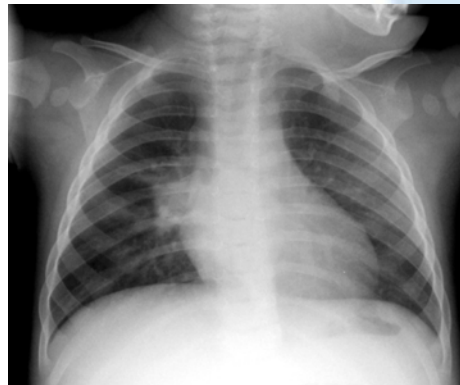
Lancet 2005; 365:130-34

## Approach to Evaluation of Pediatric TB

- **Active case finding**
  - Screening for LTBI or TB
  - Contact investigation
    - Microbiologic confirmation not necessary if isolate available from source case
- **Passive case finding**
  - Children present with symptoms or with radiological findings suggestive of TB
    - Attempt at microbiologic confirmation is important
    - Source case investigation important

## Screening : Source Case Unknown

- **9 month old adopted from Guatemala**
- **TST reactive at 14 mm**
  - CXR abnormal
- **Hospitalized for evaluation**
  - GA X 3
  - Lumbar puncture





## Evaluation of the Child with Pulmonary TB Identified by Screening with Source Case Unknown

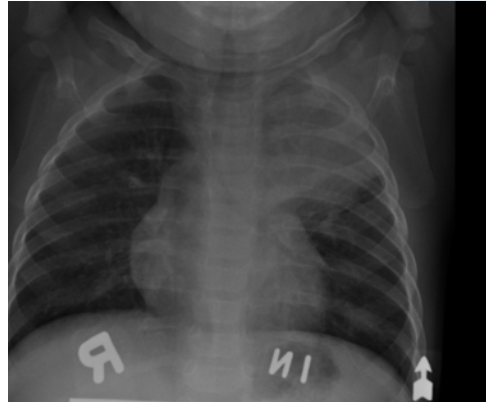
- **Microbiologic confirmation important- no known source case**
  - MTB isolated from GA
  - Treatment tailored based on susceptibility
- **Further evaluation**
  - PE to evaluate for dissemination
  - LP to evaluated for dissemination to CNS
    - Patient's CSF normal
  - Testing for HIV
    - Patient HIV negative

## Why the lumbar puncture?

- **Meningitis is an early complication of infection**
  - May occur before DTH develops
  - Children  $\leq 4$  y of age primarily affected
  - Insidious process occurring over 3-6 weeks
- **Management of disease affected by meningitis**
  - Duration of therapy, adjunctive use of corticosteroids
- **LP recommended in children  $\leq 1- 2$  y diagnosed with TB disease even in the absence of symptoms**

## Contact Investigation: Source Case Known

- 7 month old exposed to aunt with TB
- Contact investigation
  - PE normal
  - TST 20 mm
  - CXR abnormal

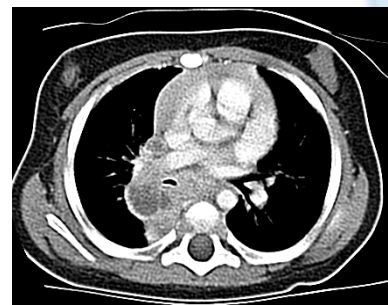


## Evaluation of the Child with Pulmonary TB Identified by Contact Investigation with Source Case Known

- Microbiologic confirmation not necessary if source case known and clinical and radiological findings consistent with TB
  - Patient was afebrile, asymptomatic
  - CXR consistent with TB
- Further evaluation
  - CSF normal
  - HIV- negative
- Treatment initiated based on source case's isolate

## Symptomatic Presentation: Source Case Unknown

- 5 month old Hispanic female evaluated in ED with a cough
- CXR - hilar adenopathy
- Admitted for evaluation
  - GA X 3
  - LP
  - Source investigation



## Evaluation of the Symptomatic Child with Suspected Pulmonary TB with Source Case Unknown

- Bacteriologic confirmation if source case unknown
  - GA, sputum, BAL, CSF, tissue, etc
  - Negative culture does not exclude TB
- Source case investigation
  - Identification of adult source of infection
  - Critical to diagnostic evaluation
  - Likelihood of identifying source case (and isolating MTB) is often higher than isolating MTB from the patient
- Further evaluation
  - HIV testing, LP if indicated

### Symptomatic Presentation: Source Case Unknown

- GA X 3, induced sputum X 1
  - MTB ultimately isolated from GA
- CSF normal, HIV negative
- Source case investigation
  - Parents with LTBI
  - Uncle with abnormal CXR
- Isolation of MTB from GA specimen- matched source's



### Symptomatic Presentation : Source Case Known

- 9 month old exposed to MDR TB
  - Initial TST nonreactive
    - CXR normal
    - No window prophylaxis
- Repeat TST nonreactive but patient symptomatic
  - CXR- ? Abnormal
  - CT confirmed adenopathy
- Hospitalized for PICC
  - 3 GAs, BAL
  - MDR MTB isolated from GA

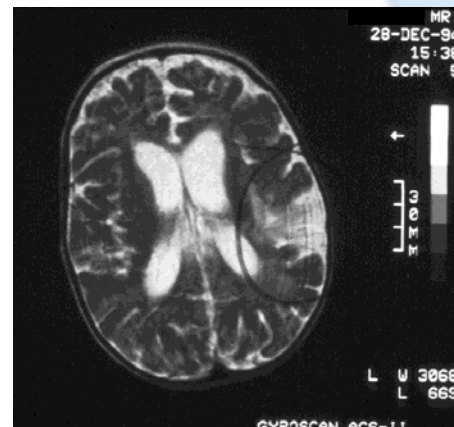


### Evaluation of the Symptomatic Child with Suspected Pulmonary TB with Source Case Known

- Microbiologic confirmation important if:
  - Source case unknown or > 1 source case
  - Isolate not available
  - Resistance suspected in source case
  - Patient has extrapulmonary disease
- Further evaluation
  - Lumbar puncture- CSF normal
  - Testing for HIV- negative
- Treatment initiated based on source case's isolate but important to verify in child given toxicity of therapy

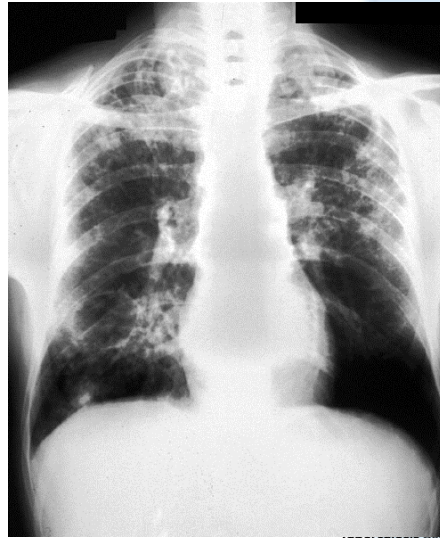
### Symptomatic Presentation: Meningitis

- 7 month old male with lethargy
  - Afebrile, 4 days of URI
  - Receiving amoxicillin
- Apneic and hypoperfused in ED
  - Intubated
- CSF- 143 WBC/mm<sup>3</sup>, glucose 21 mg/dL, protein 424 mg/dL



## Symptomatic Presentation: Meningitis

- Antibiotics initiated for partially treated meningitis
- CT demonstrated infarcts
- Infectious disease consultation
  - TST nonreactive
  - CXR with infiltrate
  - Sputum and CSF -AFB culture
  - Source investigation
- MTB isolated from GA
  - Isolated from source first



## Evaluation of the Symptomatic Child with Suspected CNS TB with Source Case Unknown

- Bacteriologic confirmation if source case unknown
  - GA, sputum, BAL, CSF, tissue, etc.
  - Negative culture does not exclude TB
- Source case investigation
  - Identification of adult source of infection
  - Critical to diagnostic evaluation
  - Likelihood of identifying source case (and isolating MTB) is often higher than isolating MTB from the patient
- Further evaluation
  - HIV testing, LP if indicated (already done in this case)

## Symptomatic Presentation: Lymphadenitis

- 2 year old Hispanic female with subacute adenitis
  - Amoxicillin for 2 weeks without improvement
- Enlargement noted
  - Referred to a surgeon
- TST reactive at 12 mm
  - CXR normal



## Symptomatic Presentation: Lymphadenitis

- Excisional biopsy recommended
  - Granulomata, necrosis
  - AFB smear positive
  - MTB complex isolated
- Empiric treatment initiated
  - PZA resistance
  - *M. bovis* confirmed
- Father sells Mexican cheese in store, and patient eats it



## Evaluation of the Symptomatic Child with Suspected TB Lymphadenitis with Source Case Unknown

- **Bacteriologic confirmation if source case unknown**
  - GA, sputum, BAL, CSF, tissue, etc.
  - Negative culture does not exclude TB
- **Source case investigation**
  - Sometimes the source is cheese
- **Further evaluation**
  - HIV testing, LP if indicated (not done in this case)

## Summary

- **Epidemiology**
  - Young children at highest risk for TB disease
- **Pathogenesis**
  - Young children at higher risk of progressing to primary disease
- **Clinical manifestations**
  - Most disease in children is pulmonary
  - EP disease plays more significant role in children
- **Evaluation of disease**
  - Approach to evaluation depends on whether identified through screening, contact investigation, or symptomatic presentation
  - Microbiologic confirmation is important in pediatric TB and should always be attempted unless an isolate is available from the source





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