Extrapulmonary Tuberculosis XPTB

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National Jewish Health
Denver TB Course
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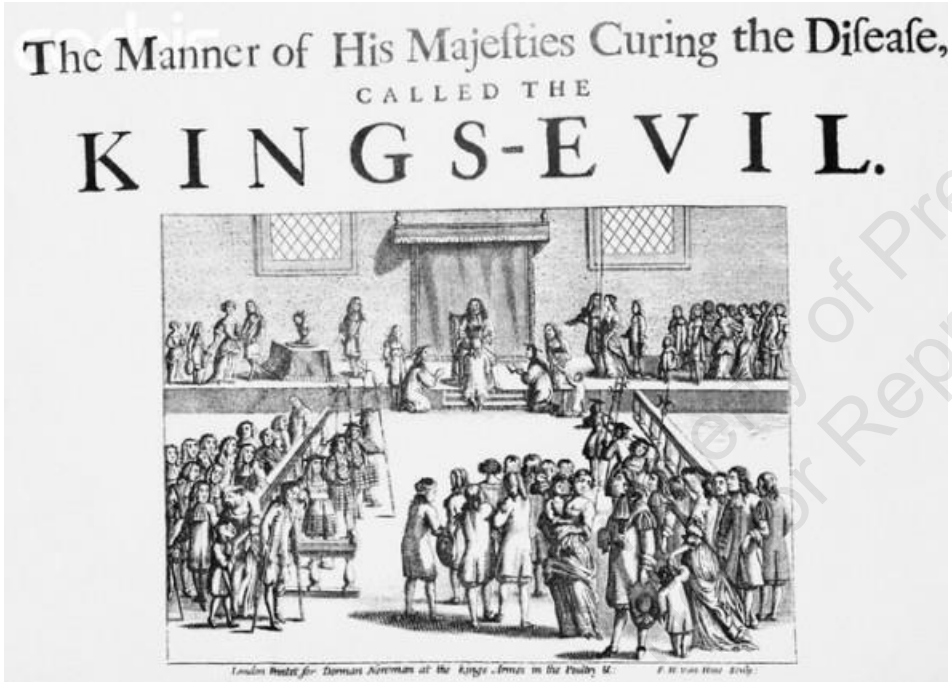
The Kings Evil



"…strangely visited people
all swol'n and ulcerous, pitiful to the eye,
the mere despair of surgery, he cures,
hanging a golden stamp about their necks,
put on with holy prayers; and 'tis spoken,
to the succeeding royalty he leaves
the healing benediction…"

-
Shakespeare, Macbeth

Burden of tuberculosis at post mortem in inpatients at a tertiary referral centre in sub-Saharan Africa: a prospective descriptive autopsy study

- Autopsy on adult inpatients: 4/12-5/13
- N: 125
- 64% male, 81% HIV +

  78 (62%) had TB

  20/78 (26%) undiagnosed TB

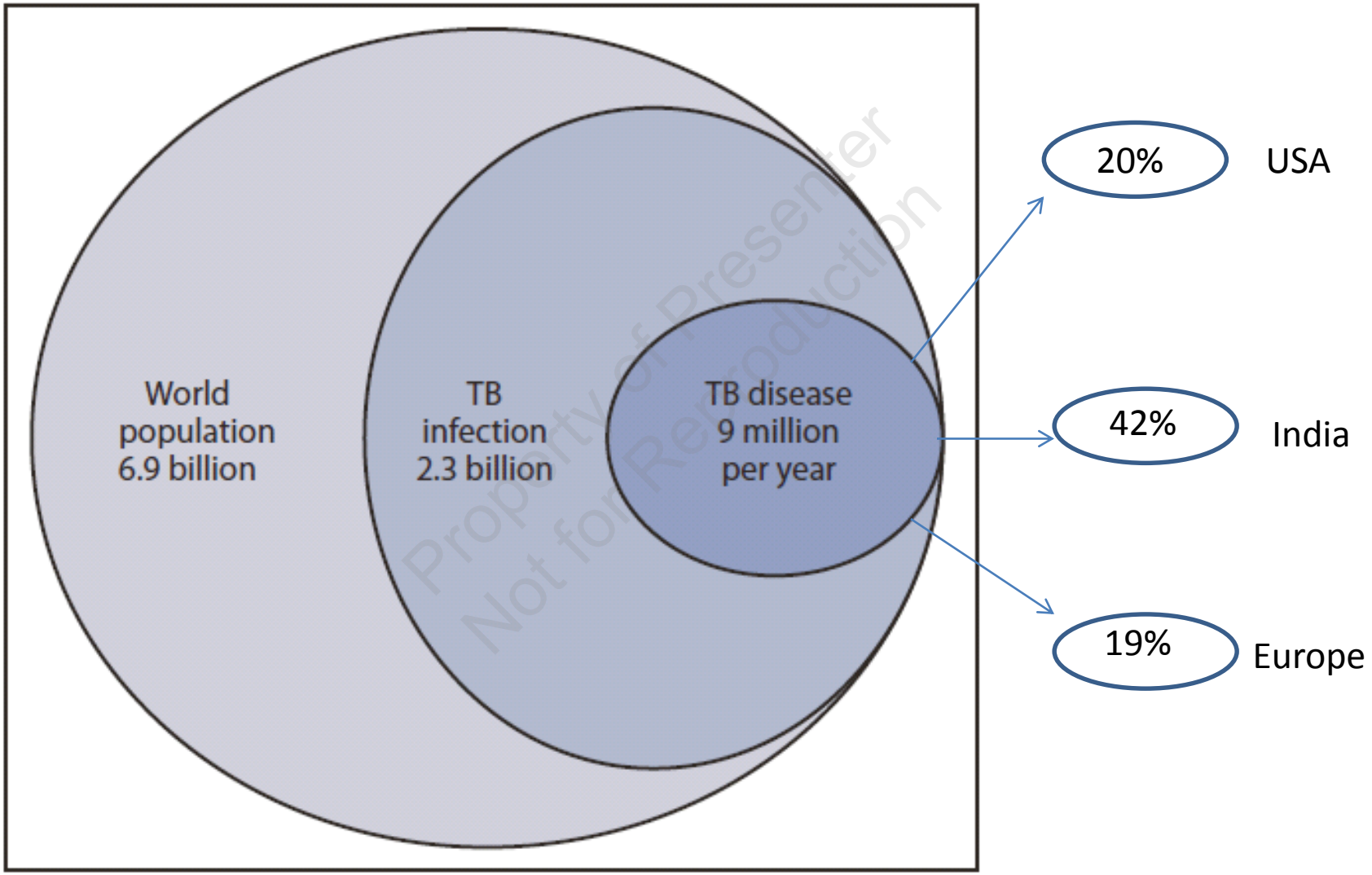
  13/78 (13%) undiagnosed MDR TB

  35/78 (45%) XPTB

  XPTB higher in HIV patients (OR 5.14)

Lancet Infect Dis 2015; 15: 544–51.

XPTB



Incidence of Extrapulmonary Tuberculosis

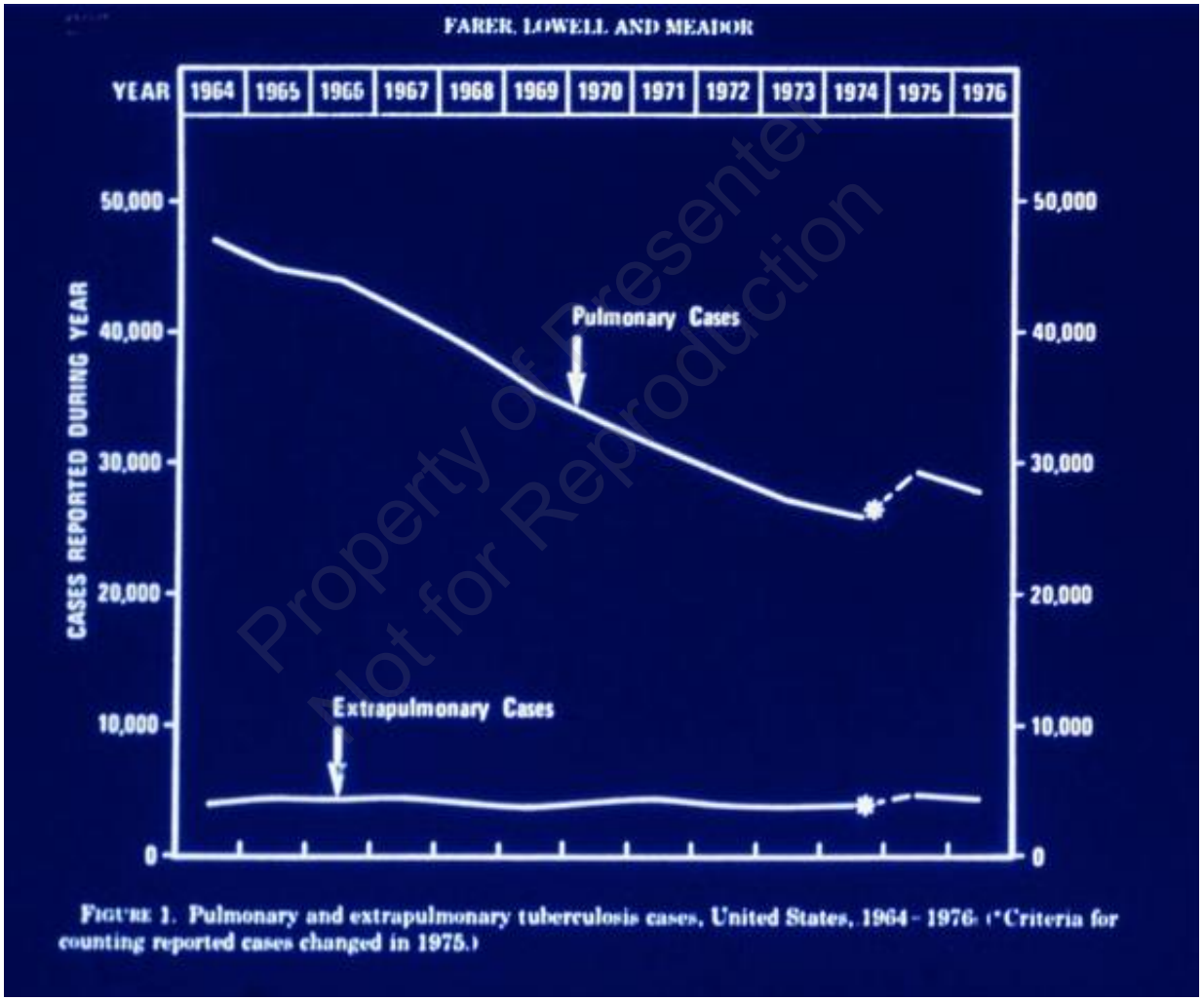
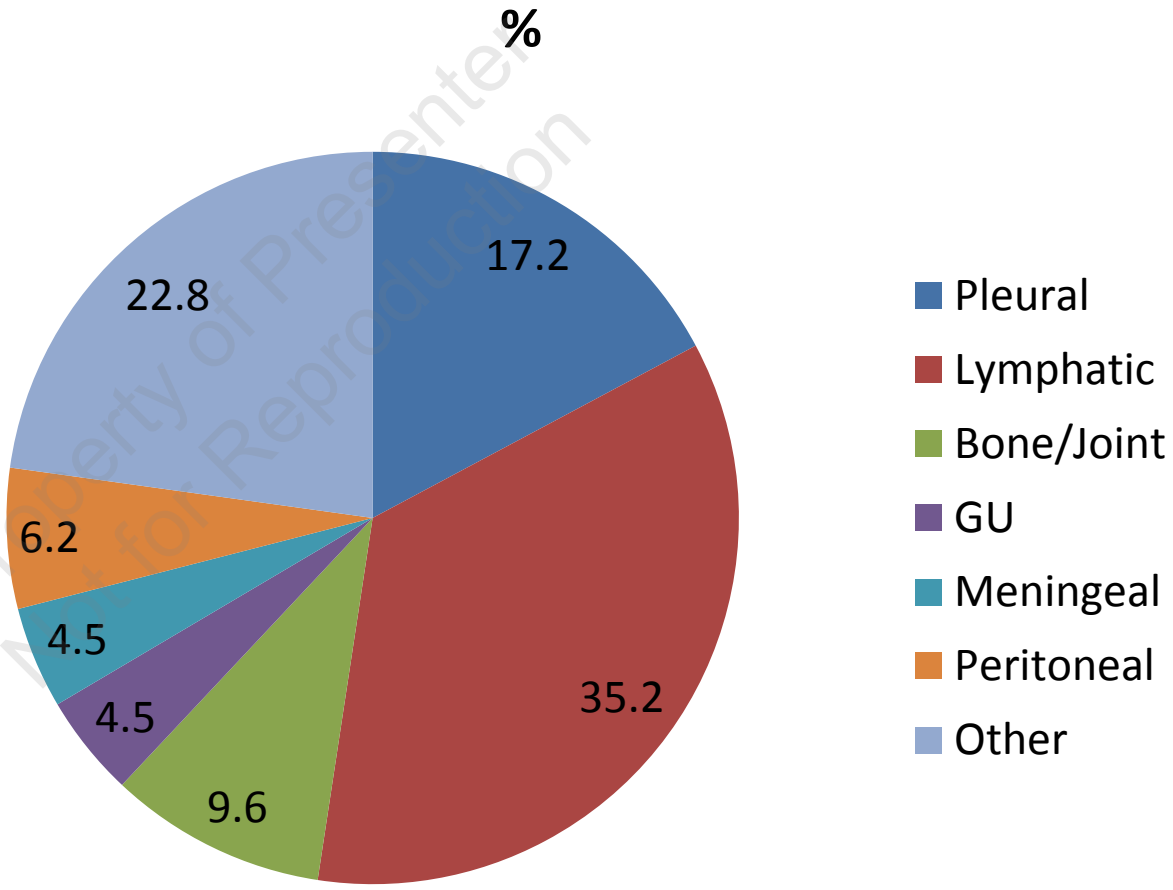


FIGURE 1. Pulmonary and extrapulmonary tuberculosis cases, United States, 1964–1976 (*Criteria for counting reported cases changed in 1975.)

XPTB: 2015 US Cases (n= 1933)

Leading cities
1. CA 21.5%
2. TX 10.9%
3. NY 7.8%



www.cdc.gov/tb/statistics

Risk factors for XPTB

- **Untreated Human immunodeficiency virus (HIV) infection***
- **Corticosteroids or other iatrogenic immunosuppression**
  - **(i.e, TNF-α blocking agents)***
- **Infancy***
- **Female sex (OR 1.7**)
- Alcohol abuse
- Malignancy
- Connective tissue disease
  - (with or without iatrogenic immunosuppression)
- Renal failure
- Diabetes
- Pregnancy
- Vitamin D deficiency*

*Pareek M, et al. Thorax 2015;70:1171–1180

Question

- 23 year old male with HIV/AIDS presents with unilateral painless cervical lymphadenopathy:

A. Obtain a biopsy for afb smear/culture as well as routine and fungal cultures.

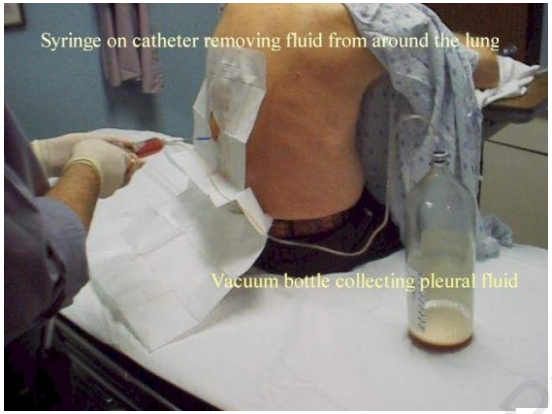
B. This is an unusual presentation for TB therefore a biopsy for pathology is warranted.

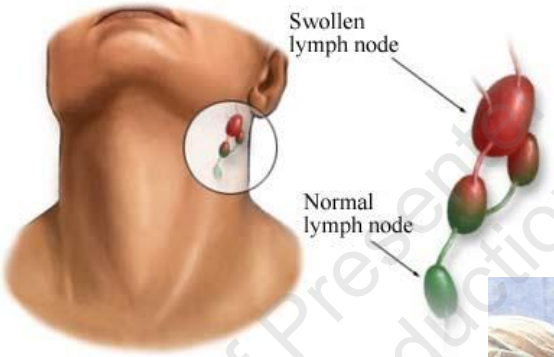
C. Begin empiric TB therapy as this is most likely TB.

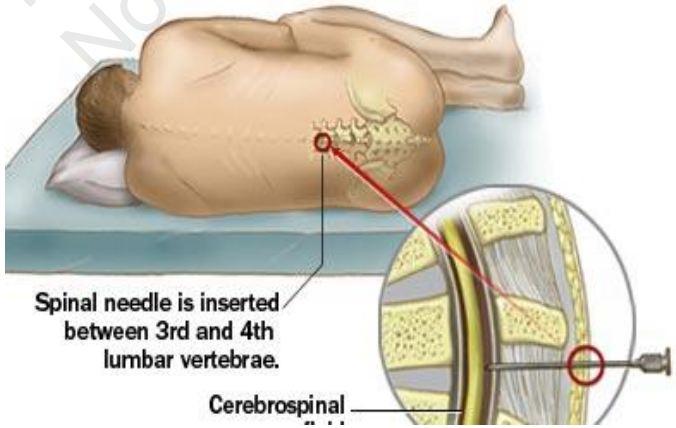
Challenges in the diagnosis of XPTB

- Signs and symptoms are nonspecific
- Appropriate specimens must be obtained for microscopy/culture and histology
- Serial cultures may not be readily available/feasible on treatment

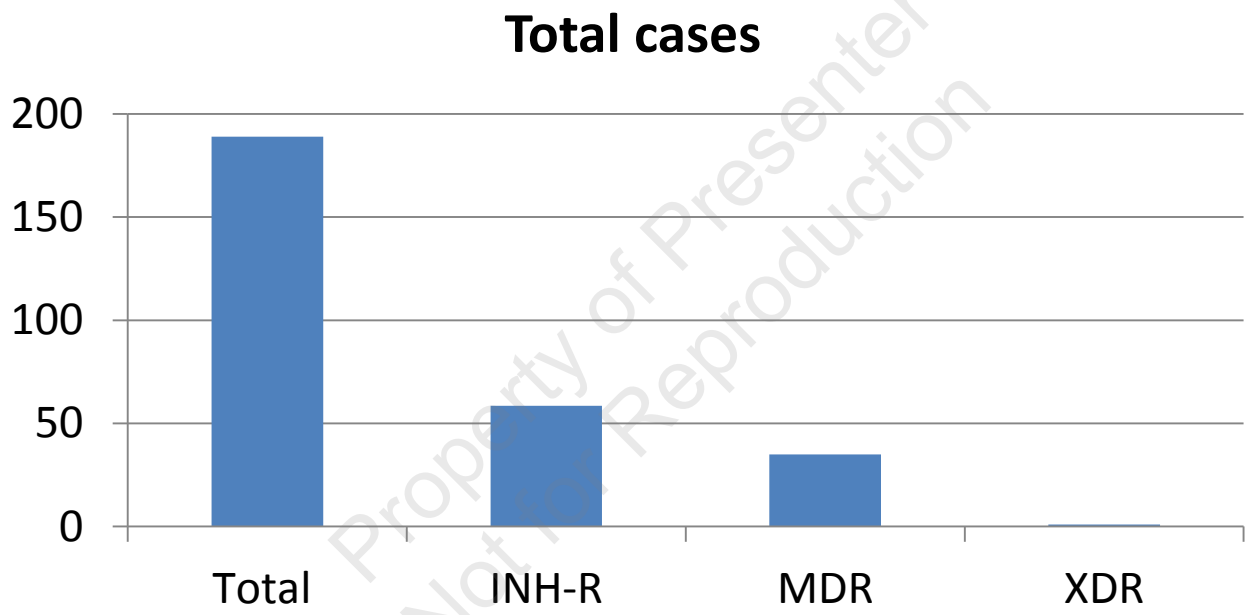
Diagnosis







XPTB in New Delhi
Six years experience in a reference lab



KEY POINT

- In some areas of the world, resistance is seen in over 30% of cases, therefore CULTURE AND DRUG SUSCEPTIILITY are of critical importance

Indian J Med Res. 2015 Nov;142(5):568-74.

XPTB + HIV

- XPTB more common in HIV/AIDS
- Increasing rate with decreasing CD4
- #1 Lymphadenitis
- #2 Disseminated
  - Similar to GNR bacteremia, sepsis, death
- Obtain directed bx, sputum, blood, urine afb cultures

Lymphatic Tuberculosis

- Spread from local infection
- Painless
- Unilateral
- Cervical chain most common
- Biopsy
- Chemotherapy (6 mo)
- Be prepared for paradoxical reactions
  - (up to 23%)

Pleural Tuberculosis

- Delayed hypersensitivity vs. TB infection
- Unilateral, sm-moderate sized
- Parenchymal disease 50%
- Fever, np cough, pleurisy
- Thoracentesis (Cx + < 30%)
- Exudate, high protein, high LDH, low pH, low glucose
- lymphocytic pleocytosis
- Pleural biopsy Cx + ~ 90%
- Chemotherapy (6 mo)

Diagnosis of Pleural TB

	AFB smear (%)	AFB culture (%)	Histology (%)
Pleural fluid	0-10	23-58	
Pleural tissue	14-39	40-85	69-97

Lewinsohn CID 2017

Sensitivity	Gene Xpert	Culture
Pleural TB	46	21

Denkinger Eur Resp J 2014

Meta-analysis in pleural TB (n= 1626)		
	Sensitivity	Specificity
ADA	92	90
INF-**γ**	89	97

Zhou Scientific reports 2015

Genitourinary Tuberculosis

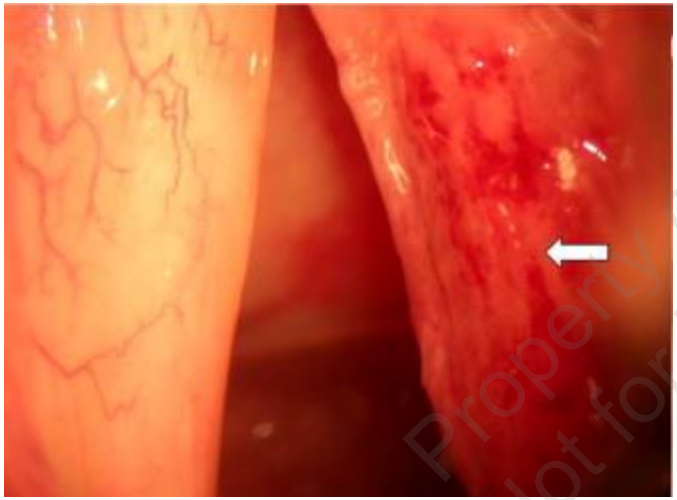
- Pain, altered urination
- Sterile pyuria, hematuria, proteinuria
- Imaging: hydronephrosis, distortion of the collecting system
- Urine: Smear not performed
- Urine Culture AFB + (80-94%)
- Chemotherapy (6mo)

Question

- What is this woman doing?

A. Brushing her teeth
B. Shining light into her throat
C. Performing a self exam

Laryngeal Tuberculosis



- Hoarseness, odynophagia
- True vocal cords
- Unilateral
- Variable pathology
- Historically a complication of pulmonary TB
- Prognosis usually good, immobility can be reversible
- Chemotherapy (6mo)
- Surgery reserved for airway compromise

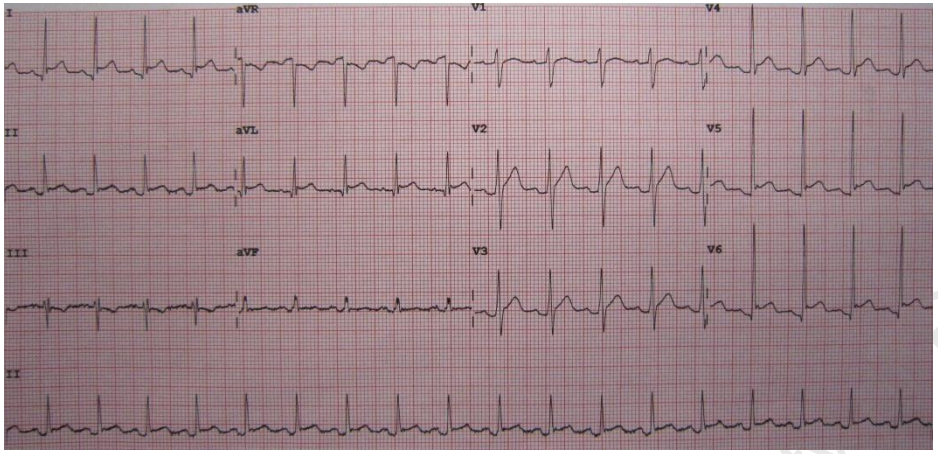
http://www.sciencedirect.com/science/journal/01945998

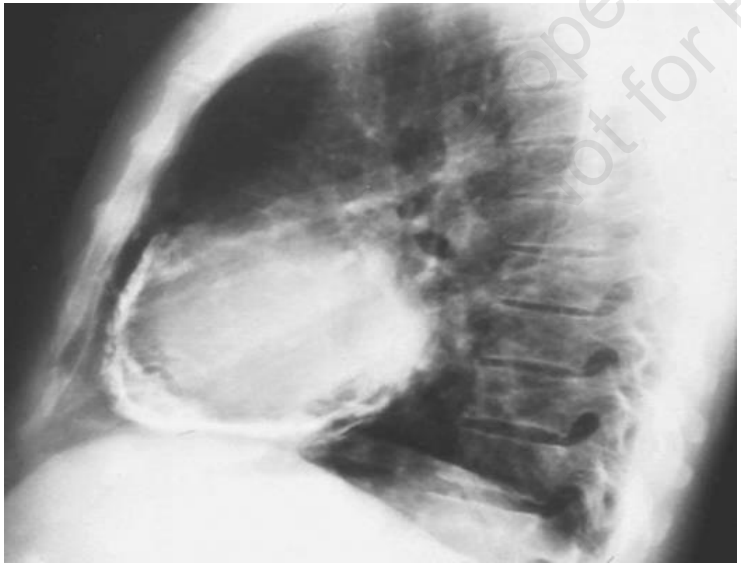
Gastrointestinal Tuberculosis

- Hepatic, enteritis, peritonitis
- Abdominal pain, fever, ascites
- 70% have sx for > 4 months
- Ascites: lymphocytic exudate
  - beware of dilution in cirrhosis
- Ascites:
  - Smear usually negative.
  - Culture + 45-69%
- Peritoneal biopsy
- Chemotherapy (6mo)

Lewinsohn CID 2017

Audience Response Question





A 48 year old male from South Africa complains of chest pain that worsens with leaning forward. ECG notes PR depression and diffuse ST elevation.

A. Begin Rifampin/INH/PZA/EMB as TB pericarditis is the most likely diagnosis.
B. Begin Rifampin/NH/PZA/EMB and steroids after a pericardial biopsy for afb smear/cutlure and TB PCR.
C. Request a pericardiocentesis for afb smear and culture. A negative result excludes the diagnosis.

Pericardial Tuberculosis

- Rupture of a mediastinal lymph node
- Cough, wt loss, dyspnea, orthopnea, chest pain, edema, fever
- Tachycardia, cardiomegaly, JVD, muffled sounds, 1/2 with friction rub
- ECG: ST/TW depression, CXR enlarged heart, echo: effusion, constrictive pericarditis
- Pericardial biopsy:
  - send for smear/culture and PCR
- Negative biopsy does not exclude the diagnosis
- Chemotherapy (6 mo) + steroids

Diagnosis of Pericardial TB

Sensitivity	AFB smear (%)	AFB culture (%)	Histology (%)
Pericardial Fluid	0-42	50-65	73-100

Lewinsohn CID 2017

Suspected Pericardial TB (151 suspect/74 definite/50 probable)		
	Sensitivity	Specificity
ADA (>35 IU/L)	95.7	84
IFN-γ (>44 µg/ml)	95.7	96.3
Gene Xpert	63.8	100

Pandie BMC Med 2014

Adjunctive steroids in pericarditis?

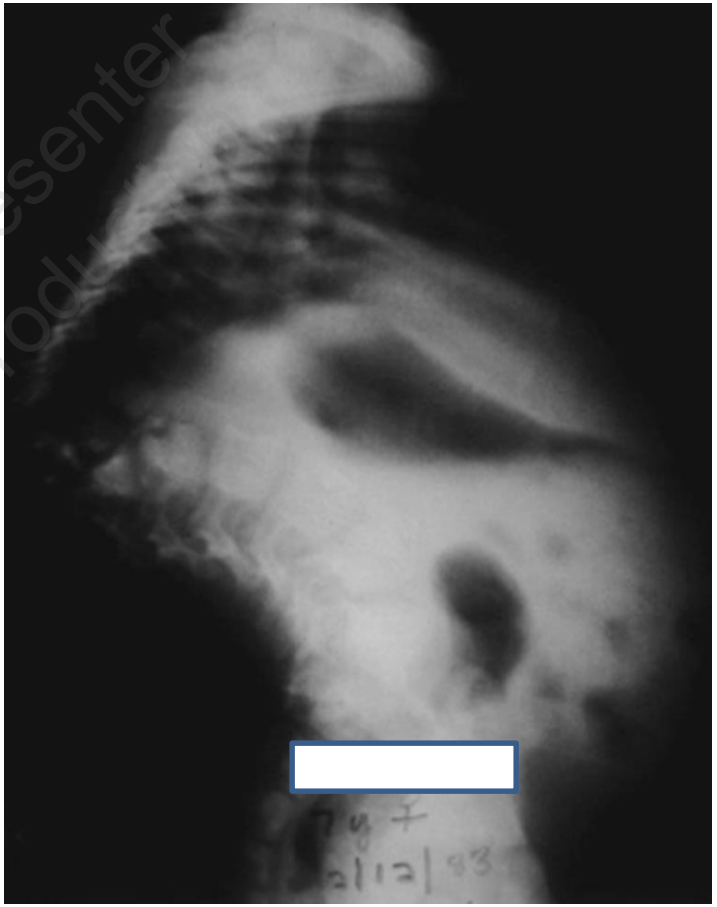
- Small studies had shown a mortality benefit in patients who received corticosteroids.
- Recent RCT (n=1400) did not find a difference in the combined primary endpoint of mortality, cardiac tamponade, or constrictive pericarditis
- In a subgroup analysis: It did suggest a benefit in preventing constrictive pericarditis
  - large pericardial effusions, those with high levels of inflammatory cells or markers in pericardial fluid, or those with early signs of constriction

2016 Guidelines:

- Adjunctive corticosteroids should not be used routinely in the treatment of patients with pericardial tuberculosis
- However, selective use of corticosteroids in patients who are at the highest risk for inflammatory complications might be appropriate

Mayosi N Engl J Med 2014; 371:2534
Nahid CID 2016;63(7):e147–95

CXR

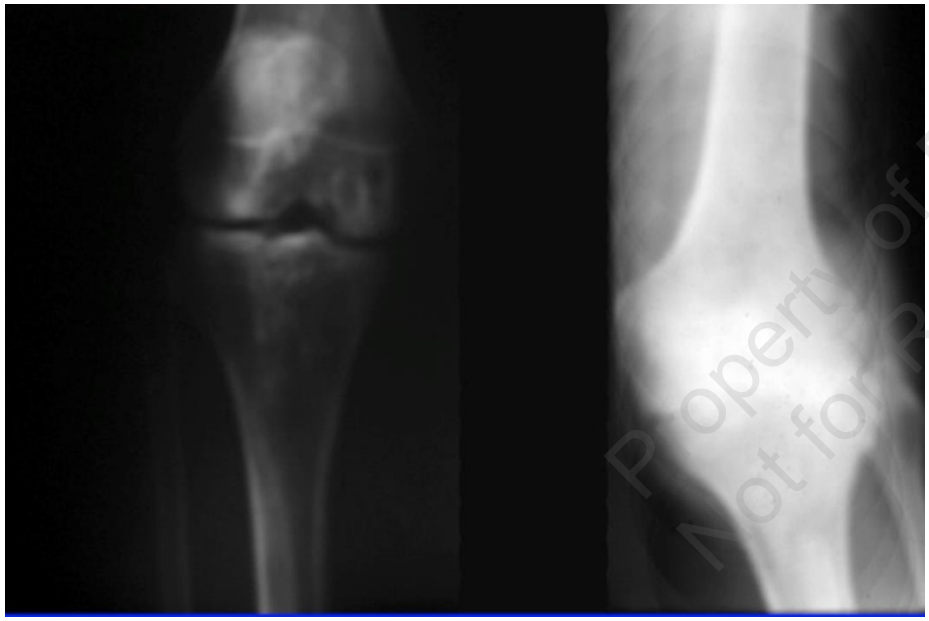


Spinal Tuberculosis- Pott's disease

- Lower thoracic and lumbar vertebrae
- Back pain, cold abscess, nerve root compression, *scoliosis, limp
- Bone destruction, anterior wedging, paraspinous abscess
- Biopsy for smear and culture
- Chemotherapy 6 (IIB) months +/- surgery
- Extend 9-12 months for advanced disease


LESTER
DAIRY
FARM

Extra-spinal bone/joint tuberculosis



- Osteomyelitis < arthritis
- hip and knee
- Cold abscess, pain, swelling, loss of joint function
- Constitutional symptoms <30%
- X-ray findings may be nonspecific, destruction is a late finding
- Bone/synovial biopsy for smear and culture
- Chemotherapy for 6 months
- 9-12 months for advanced disease

Osteomyelitis of the wrist and forearm

Shoulder septic arthritis

Distal clavicular osteolysis

Outbreak of XPTB associated with acupuncture, China

- 33 XPTB cases
  - all confirmed MTB, Beijing strain

Clin Microbiol Infect. 2014 Nov 14

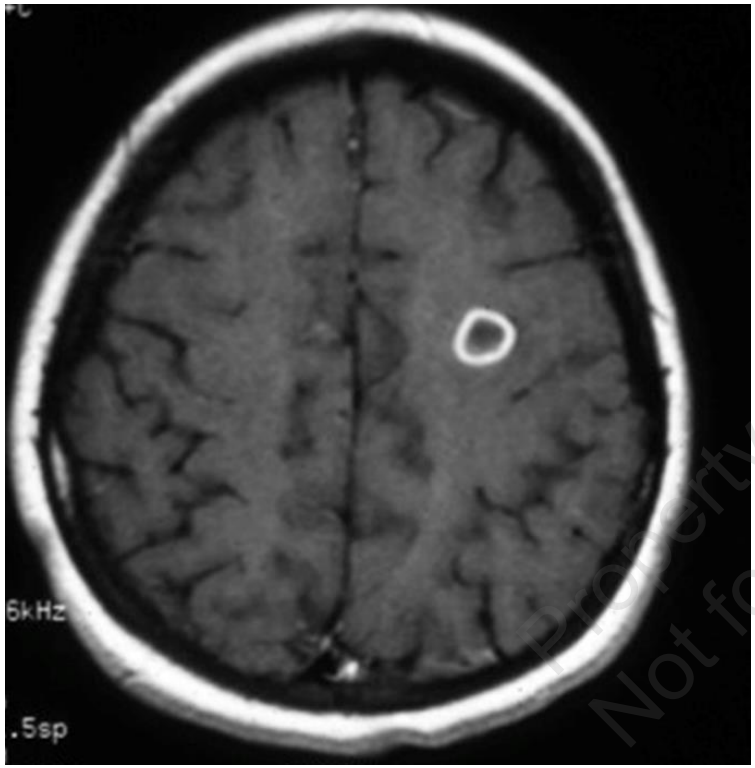
Case Question

- 9 month old with subacute altered mental status, facial droop
- Evidence of lymphocytic pleocytosis on CSF, low glucose and high protein

- While waiting for the diagnostic studies:
  1. Begin ceftriaxone and vancomycin
  2. Begin dexamethasone, ceftriaxone and vancomycin
  3. Begin dexamethasone, ceftriaxone, vancomycin, INH, RIF, ETH, PZA

Img.wikinut.com

CNS Tuberculosis



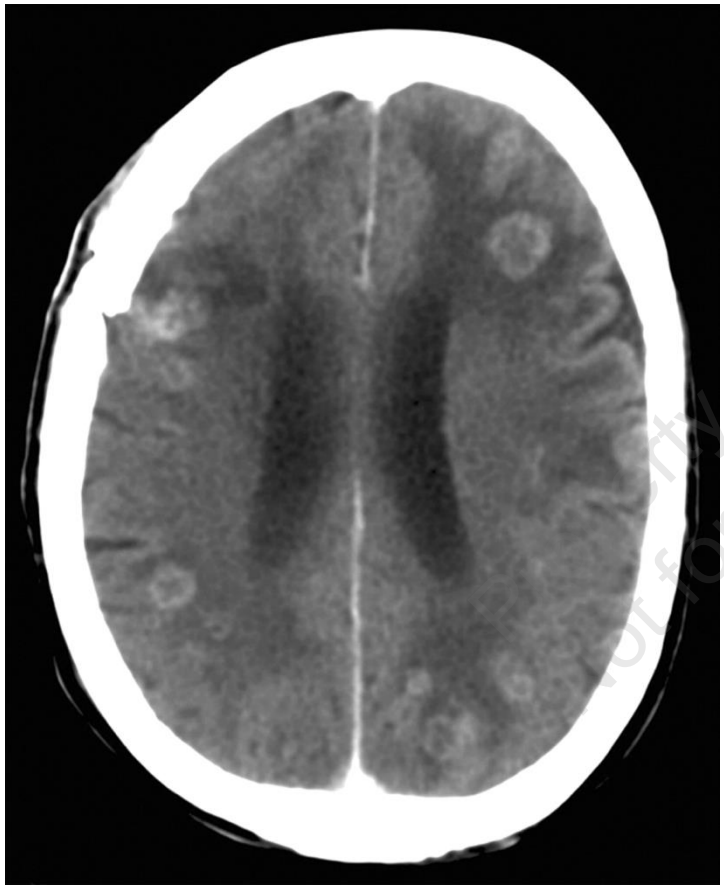
DO NOT DELAY TREATMENT FOR + DIAGNOSITICS

- Hematogenous or direct
- 3 Stages
- OP on LP normal or high
- CSF analysis:
  - Lymphocytic pleocytosis
  - elevated protein
  - low glucose
  - Send off the 4th tube
  - minimum of three serial lumbar punctures should be performed at daily intervals

Phases of TB meningitis

Prodromal phase (2-3 weeks)	Malaise, headache, low grade fever, personality change
Meningitic phase	Neurologic features: meningismus, protracted headache, emesis, lethargy, confusion, CN signs
Paralytic phase	Confusion, stupor, coma, seizures, hemiparesis and death

CNS Tuberculosis



- Look elsewhere for dissemination
- 1/3 have miliary TB
  - check eyes
- Smear/culture
- PCR of CSF
  - WHO recommends XPERT MTB/RIF

J Clin Microbiol. 2004;42(1):378.
Eur Respir J 2014; 44:435.
RadioGraphics 2007:;27: 1255-1273.

Diagnosis of TB in the CSF

	AFB smear (%)	AFB culture (%)	Histology (%)
CSF	10-30	45-70	

Lewinsohn CID 2017

Sensitivity	Gene Xpert	Culture
CSF	81	63

Denkinger Eur Resp J 2014

Suspected TB Meningitis (1490 suspect/92 diagnosed)		
	Sensitivity	Specificity
ADA (>2U/L)	85.9	77

Ekermans BMC 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis

	Treatment 1st 3 mo	Daily Dose (max dose)	Treatment Last 6 mo	
Standard Treatment Arm	INH RIF PZA EMB +/- SM	5mg/kg (300mg) 10mg/kg 25 mg/kg (2gm) 20mg/kg (1200mg) 20mg/kg (2gm)	INH RIF	5mg/kg (300mg) 10mg/kg
Intensified Treatment Arm	INH RIF PZA EMB LEVO +/- SM	 15mg/kg 20mg/kg	INH RIF	5mg/kg (300mg) 15mg/kg

N Engl J Med 2016;374:124-34.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis

	Standard	Intensified	Hazard Ratio	P value
Primary Outcome No. of death/N	114/409	113/408	0.94 (0.73–1.22)	0.66
HIV infected	68/174	68/175	0.91 (0.65–1.27)	0.57
Isoniazid resistance	16/41	11/45	0.45 (0.20–1.02)	0.06

Summary:

- Well designed RCT in Vietnamese Adults with TB meningitis
- No advantage associated with the use of this intensified treatment regimen, with regard to overall mortality (28%)

N Engl J Med 2016;374:124-34.

Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial

	Oral rifampicin 450 mg	Intravenous rifampicin 600 mg	Total
Ethambutol 750 mg	7/12 (58%)	3/10 (30%)	10/22 (45%)
Moxifloxacin 400 mg	6/10 (60%)	2/9 (22%)	8/19 (42%)
Moxifloxacin 800 mg	7/9 (78%)	5/10 (50%)	12/19 (63%)
Total	20/31 (65%)	10/29 (34%)	30/60 (50%)

Data are n/N (%). All patients received standard dose isoniazid, pyrazinamide, and adjunctive corticosteroids.

Table 5: **6 month mortality by rifampicin regimen**

Summary:

- 6-month mortality in moxifloxacin arms (42% and 63%) did NOT differ significantly from that associated with the regimen without moxifloxacin (45%)
- Mortality was lower in the higher IV rifampin vs. standard oral rifampin dose of 10 mg per kilogram (34% vs. 65%)

Lancet Infect Dis 2013; 13: 27–35

2016 Guidelines
Treatment of TB meningitis

1. INH, RIF, PZA, and EMB in an initial 2-month phase.
2. After 2 months of 4-drug therapy, for meningitis known or presumed to be caused by susceptible strains, PZA and EMB may be discontinued, and INH and RIF continued for an additional 7–10 months.
3. Adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks
4. Repeated lumbar punctures early in the disease should be considered to document response to therapy.

Nahid CID 2016;63(7):e147–95

Short Intensified Treatment in Children with Drug-susceptible Tuberculous Meningitis

- 184 Children
- 80% having stage 2-3 (BRMC classification)
- 6 months /4 drug treatment
  - isoniazid (15 to 20 mg/kg)
  - rifampin (20 mg/kg)
  - pyrazinamide (40 mg/kg)
  - ethionamide (20 mg/kg)
- **Overall mortality 3.8%**

Outcome after end of treatment	
Normal	79 (42.9%)
Mild sequelae	68 (36.9%)
Severe sequelae	30 (16.3%)
Death	7 (3.8%)
Relapse rate of treatment survivors*	
Home-based treatment (n = 90)	
No relapses (cured)	88
Death	2
Lost to follow up	0
In-hospital treatment (n = 87)	
No relapses (cured)	52
Death	6
Lost to follow up	29

Pediatr Infect Dis J 2014;33:248–252

TB meningitis in Children

American Academy of Pediatrics recommends an initial 4-drug regimen of INH, RIF, PZA, and an aminoglycoside or ethionamide for 2 months, followed by 7–10 months of INH and RIF

Dexamethasone in CNS TB

Table 3. Outcomes of 545 Patients Nine Months after Randomization.

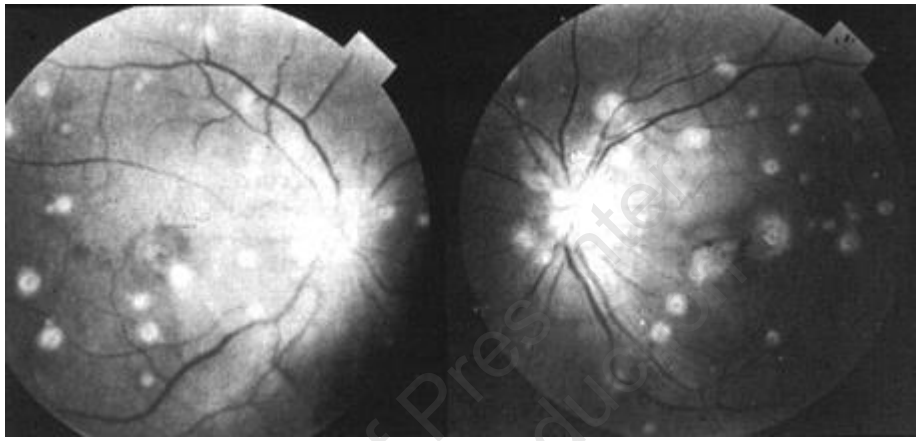
Group	No. of Patients	Outcome			
		Good	Inter-mediate	Severe Disability	Death
		number (percent)			
Dexamethasone*	274	104 (38.0)	49 (17.9)	34 (12.4)	87 (31.8)
Placebo	271	95 (35.1)	42 (15.5)	22 (8.1)	112 (41.3)

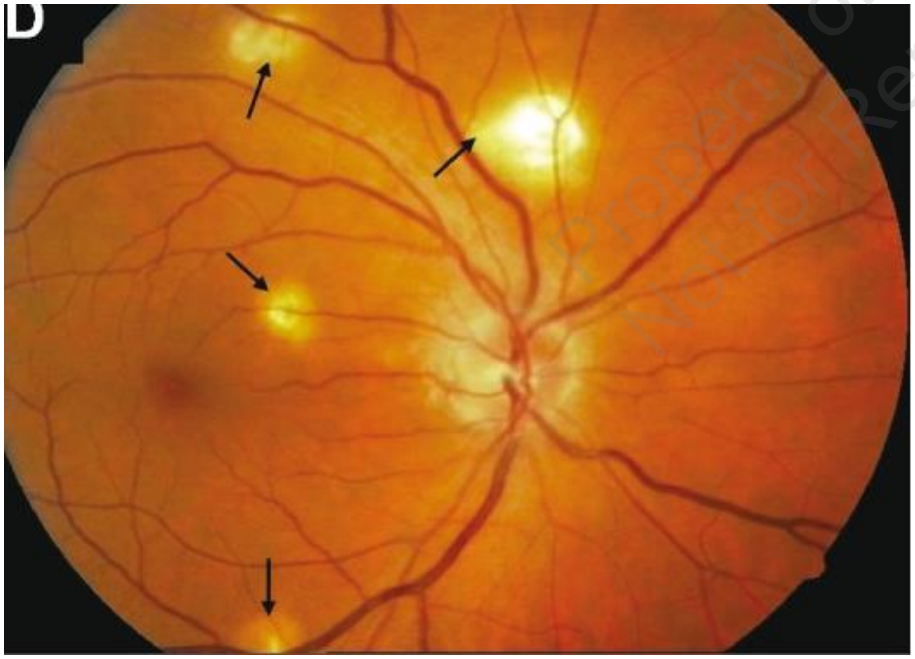
Dexamethasone was associated with a reduced risk of death (relative risk, 0.69; 95 percent confidence interval, 0.52 to 0.92; P=0.01)

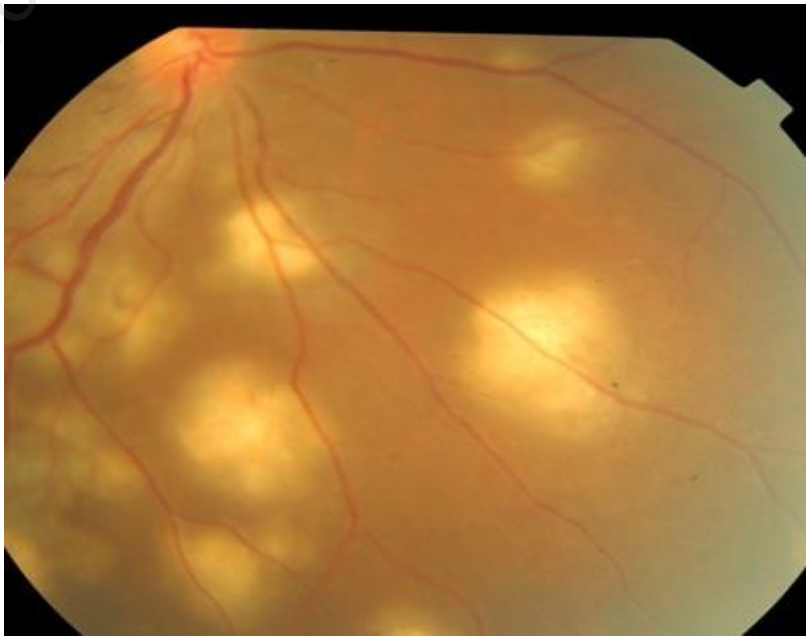
2016 TB Treatment Guidelines: recommend adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks with tuberculous meningitis

N Engl J Med. 2004;351(17):1741
Cochrane Database Syst Rev. 2008

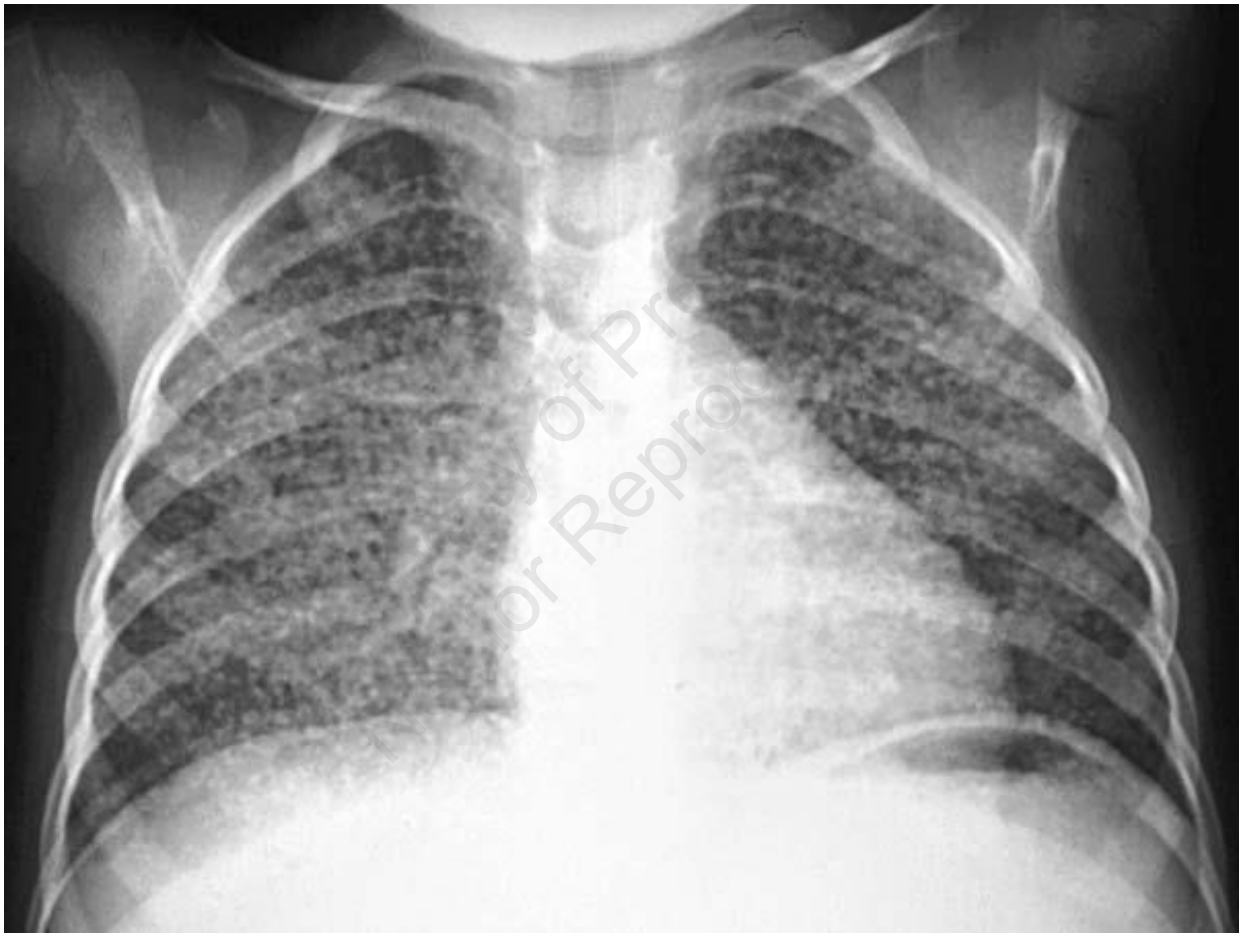
Early Clues in disseminated TB







Miliary TB in a newborn



http://www.mevis-research.de

Disseminated Tuberculosis

- Primary or secondary hematogenous infection
- Insidious, cryptic fever, weight loss
- Rare: ARDS, DIC, pancytopenia
- CXR often atypical or normal
- PPD and sputum negative in up to 50%
- Investigate involved organs
- Chemotherapy 6+ months

XPERT MTB RIF in XPTB diagnosis Meta-analysis

	XPERT MTB/RIF Sensitivity	XPERT MTB/RIF Specificity
Pleural fluid	0.34 (95% CI, 0.24–0.44)	0.98 (0.96 – 0.99)
Non pleural serous fluid	0.67 (IQR, 0.00-1.00)	1.00 (1.00 – 1.00)
Gastric aspirate	0.78 (IQR, 0.68 – 0.85)	1.00 (0.99 – 1.00)
CNS fluid	0.85 (IQR, 0.75-1.00	1.00 (0.98 – 1.00)
Lymphatic TB	0.96 (95% CI, 0.72-0.99)	1.00 (0.94 – 1.00)
Smear + specimen	0.95	
Smear – specimen	0.69	

BMC Infect Dis. 2014;14:709

Diagnosing XPTB

- Culture and drug susceptibility testing remain critical in the diagnosis and should be pursued in all suspects
- WHO: recommends Xpert as the initial test for XPTB
- CDC/ATS/IDSA recommends NAAT testing on XPTB specimens (off label use)
- Guidelines recommend measuring ADA and INF-γ levels in fluid when pleural, peritoneal, meningeal or pericardial TB is suspected
- Rationale: if senstivity is >70% and specificity is >80% then it may be beneficial

Lewinsohn CID 2017

XPTB Treatment

- 6 Months of standard TB chemotherapy
  - Bone/Joint: consider extending treatment to 9 months
  - CNS disease 9-12 months
- The preferred frequency of dosing for extrapulmonary tuberculosis is once daily for both the intensive and continuation phases

Nahid CID 2016;63(7):e147–95

Adjunctive corticosteroids

- Steroids recommended with CNS disease (+/- pericardial disease)
  - Dexamethasone for CNS: 0.3 to 0.4 mg/kg/day for two weeks, then 0.2 mg/kg/day week three, then 0.1 mg/kg/day week four, then 4 mg per day and taper 1 mg off the daily dose each week; total duration approximately eight weeks.
  - prednisone or prednisolone for pericardial disease (60 g/day and taper 10 mg per week; total duration of 6 weeks)

http://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/325/tb