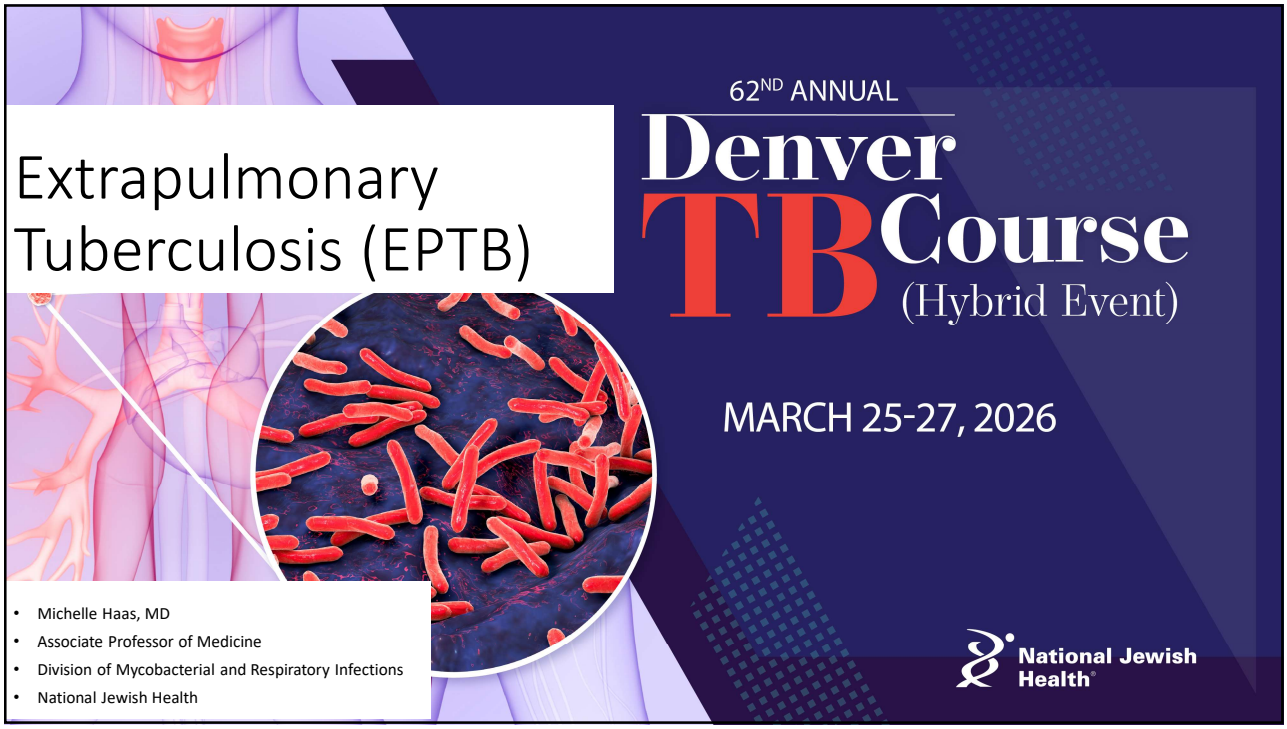

- Michelle Haas, MD
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DISCLOSURES

- I have no disclosures or conflicts of interest to report
- Off-label uses: NAAT on extrapulmonary specimens

Objectives

- Review the epidemiology of extrapulmonary disease
- Review the presentation, diagnostic strategy and management of the different forms of extrapulmonary disease
  - Focus on lymphatic, bone/joint, pleural, CNS
- Explore the contribution of molecular techniques
- Summarize the guidelines for management

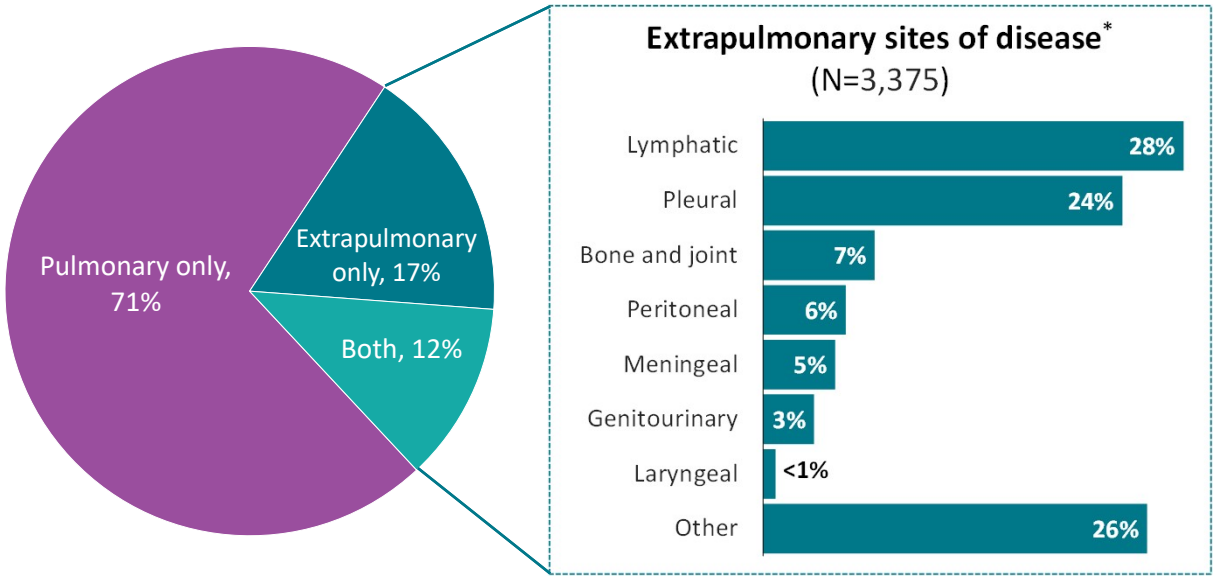
Tuberculosis can manifest in nearly any body site

- 65 y/o man who presented with a 6-month history of a draining right upper back/scapular abscess
  - No response to doxycycline and drainage.
  - Repeat cultures a month later included an AFB culture: grew *M.tuberculosis*
  - Started on IREZ and has had complete resolution of findings

WHO Global TB report-estimates of extrapulmonary TB

WHO region	Total notified	New and recurrent[a]	Pulmonary new and recurrent number	Pulmonary new and recurrent bacteriologically confirmed (%)	Extrapulmonary new and recurrent (%)
African Region	1 971 436	1 931 363	1 709 832	70%	11%
Region of the Americas	284 484	259 194	224 356	81%	13%
South-East Asia Region	3 264 399	3 134 998	2 366 649	64%	25%
European Region	160 679	139 608	115 704	70%	17%
Eastern Mediterranean Region	672 749	664 741	512 006	55%	23%
Western Pacific Region	2 223 054	2 174 780	2 008 045	59%	8%
Global	**8 576 801**	**8 304 684**	**6 936 592**	**64%**	**16%**

Percentage of TB Cases by Site of Disease, United States, 2024



*Persons might have more than one extrapulmonary site of disease.

Extrapulmonary TB among US Veterans

- Risk factors:
  - Renal disease
  - Diabetes
  - HIV
- Health disparities—highest risk seen among veterans who identify as Black

Table 1. Patients With Extrapulmonary Tuberculosis by Infection Site, Stratified by Age Group and All-Cause Mortality at 90 Days (n = 1397)

	OR (95% CI)[b]			
EPTB Site[a]	Age 20–44 y (n = 331)	Age 45–54 y (n = 388)	Age 55–69 y (n = 363)	All-Cause Mortality at 90 d (n = 277)
Pleural (n = 441 [31.6%])	0.36 (.26–.51)[c]	0.46 (.33–.63)[c]	0.67 (.49–.91)[c]	0.95 (.71–1.26)
Lymphadenitis (n = 207 [14.8%])	1.78 (1.17–2.71)[c]	1.10 (.71–1.70)	0.76 (.48–1.21)	0.32 (.18–.52)[c]
Urogenital (n = 181 [13.0%])	1.15 (.72–1.85)	1.14 (.73–1.80)	1.17 (.74–1.86)	0.68 (.43–1.03)
Gastrointestinal (n = 176 [12.6%])	2.32 (1.37–4.05)[c]	2.02 (1.20–3.52)[c]	2.72 (1.64–4.68)[c]	1.62 (1.12–2.32)[c]
Blood or bone marrow (n = 129 [9.2%])	5.77 (2.91–12.76)[c]	5.15 (2.61–11.34)[c]	2.09 (.97–4.86)	2.90 (1.97–4.24)[c]
Musculoskeletal (n = 95 [6.8%])	0.39 (.19–.75)[c]	0.68 (.38–1.20)	1.00 (.56–1.64)	0.40 (.19–.77)[c]
Meningitis (n = 55 [3.9%])	0.65 (.26–1.53)	1.13 (.55–2.39)	1.00 (.46–2.17)	4.55 (2.63–7.90)[c]
Spinal abscess (n = 39 [2.8%])	1.60 (.59–4.76)	1.36 (.50–4.04)	1.91(.75–5.50)	0.10 (.01–.48)[c]
Cutaneous (n = 32 [2.3%])	1.28 (.44–3.91)	1.79 (.70–5.13)	0.72 (.21–2.41)	0.26 (.04–.88)
Pericardial (n = 24 [1.7%])	0.52 (.16–1.53)	0.53 (.18–1.50)	0.38 (.10–1.18)	1.68 (.64–3.94)
Head/neck[d] (n = 18 [1.3%])	0.57 (.12–2.33)	1.14 (.36–3.88)	0.52 (1.11–2.12)	0.81 (.19–2.47)

Oda G, et al. OFID 2024

Additional reported risk factors for EPTB

- **Living with HIV and not on ART**
- **Infancy**
- **Corticosteroids/iatrogenic immunosuppression**
- **Female sex (OR 1.7**)
- pregnancy
- Alcohol use
- Malignancy
- Connective tissue disease (with or without iatrogenic immunosuppression)
- Renal failure
- Diabetes

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

Pulmonary Involvement in EPTB is common/expected

- Retrospective analysis of 19,279 hospitalized patients in China:
  - 6.1% (1,255) had concurrent extrapulmonary TB and pulmonary TB
- US review of 72 EPTB cases, 2003-2004
  - CXR abnormal: n=35 (49%)
  - Sputum collected (spontaneous-or-induced): n=57 (79%)
    - ***(n=12) 21% identified to have concomitant pulmonary TB***
      - AFB smear positive: 5 (9%)
- Sputum examinations in EPTB patients…may identify potentially infectious cases of TB

Parimon, et al. Chest 2008;134:589-594
Pang Y, et al. EID 2019

Patient #2

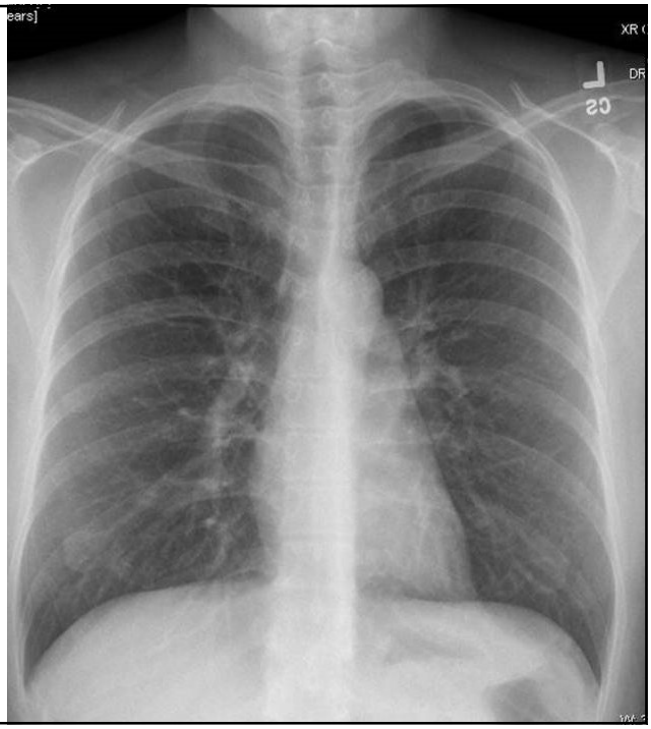
33-year-old woman, prior residence in the Philippines presented with right sided neck swelling. Some subjective fevers, no other symptoms

Partial improvement with amoxicillin-clavulanate

QFT+, HIV negative

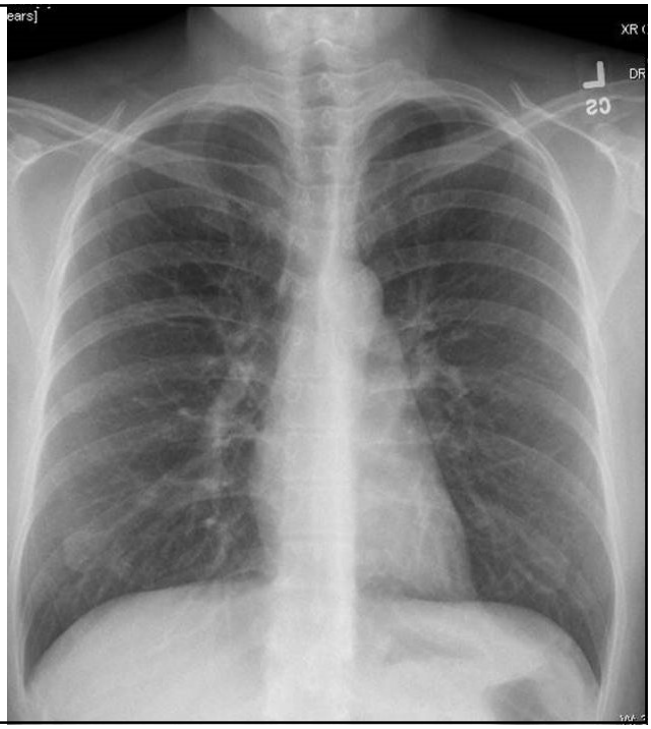
Excisional Biopsy of right supraclavicular node: caseating granulomas

Sputum AFB smear+



Patient #2 Follow up

- Started on IREZ
- Converted sputum cultures at one month
- LN swelling slowly improved
- Completed a 6-month course of treatment



XPERT MTB RIF in EPTB 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

Issue	Pulmonary	Extrapulmonary
Bacillary load	Often high	Usually low
Imaging	Plain radiography Chest CT	CT MRI
Diagnostic specimens	Sputum Induce sputum BAL Post bronchoscopy Gastric aspirate	FNA Bx: core/needle, excisional/surgical Serous cavity fluids Joint fluids CSF
Sampling	Usually multiple	Usually single
Tests	AFB smear/culture Nucleic acid amplification	AFB smear/culture **NAAT** Cytology/histopathology Cell count & diff Protein (+/- LDH), glucose ADA, gamma-interferon
Smear/culture positive	Smear+: 50-70% Culture+:90%	Smear+: 25-50%; Culture+:60-70%

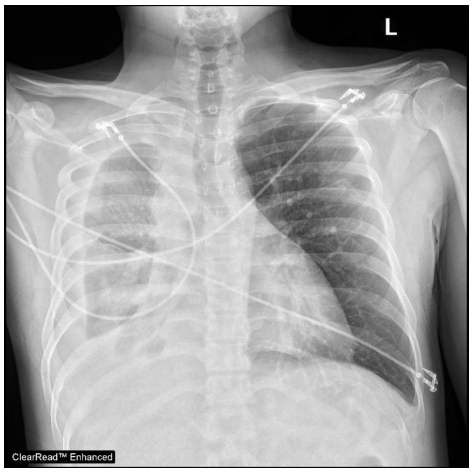
Typical Findings Extrapulmonary Specimens

- Tissue specimens:
  - Necrotizing or non-necrotizing granulomas
- Body fluid specimens:
  - Protein elevated
    - Pleural/peritoneal (>4-5gm/dL)
    - CSF (>100-500mg/dL)
  - Moderately decreased glucose (~40-50mg/dL)
  - Pleocytosis
    - Pleural (1,000-5,000 WBC/uL)
    - CSF (100-500/uL)
    - Lymphocyte predominant differential

Radiographic Findings in EPTB

- Lympadenopathy with central attenuation, septation (neck, chest, abdomen, pelvis)
- Effusions
- Discitis, osteomyelitis +/- paraspinous abscess
- Enhancement of meninges, peritoneum, pericardium
- Ring enhancing CNS lesions
- Omental stranding, mesenteric adenopathy
- Bowel wall thickening +/- abscess
- Urinary collecting system obstruction +/- renal parenchymal destruction
- Adnexal mass

Pleural disease evaluation



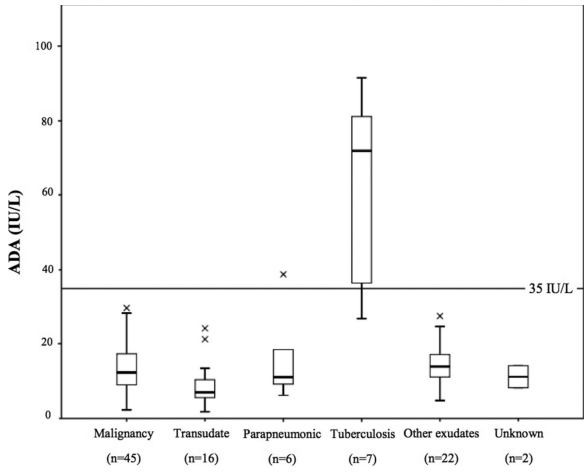
Specimen Cultured	AFB Culture Sensitivity
Sputum only	48%
Fluid only	63%
Sputum + Fluid	79%

- Pleural Biopsy
  - Closed
    - Up to 40% of specimens contain no pleural tissue
    - Image guided gaining favor
    - Sensitivity (pathology + culture): 80-90%
- Thoracoscopy/VATS: sensitivity approaches 100%

Koegelenberg CF, et al. Respirology 2011;16(5):738-46.
Kirsch CM, et al. Chest 1997;112(3):702-6.
Vorster, MJ, et al. J Thorac Dis 2015;7(6):981-991
Ruan SY, et al. Thorax 2012;67:822-7

Pleural Fluid ADA Low Incidence Setting

- N=338 patients
- Lymphocytic exudate
- 7 pleural TB cases
- Typical cut-off: >40
- Sensitivity: 85%
- Specificity: 90%
- PPV: 85%
- NPV: 99%



Arnold, et al. Thorax 2014;69:A62 doi:10.1136/thoraxjnl-2014-206260.121

ADA Limitations

False negatives

- Early disease
- Advanced age
- Smokers

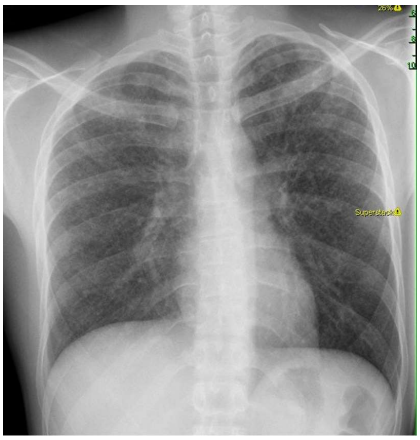
False positives

- Non-TB empyema, parapneumonic effusions
- Mesothelioma, lung and hematologic malignancies
- Rheumatologic conditions

Vorster MJ, et al. J Thorac Dis. 2015 Jun; 7(6): 981–991.

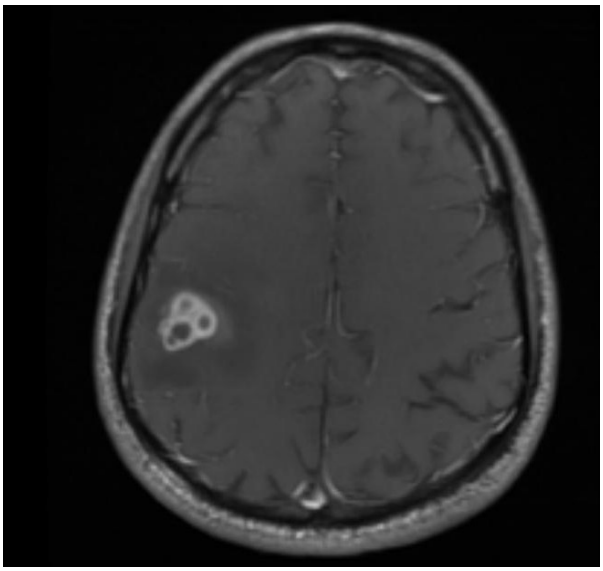
Patient # 3

- 24 year old graduate student from India
- Hospitalized with several weeks of cough, night sweats and fevers
- HIV negative
- Sputum AFB smear+, initiated on I/R/E/Z daily
  - Cultures eventually grew drug-susceptible *M. tuberculosis*
- Urine culture positive for *M. tuberculosis*
- Converted sputum culture at one month with excellent clinical response
- After 8 weeks of I/R/E/Z daily, changed to I/R



Patient #3

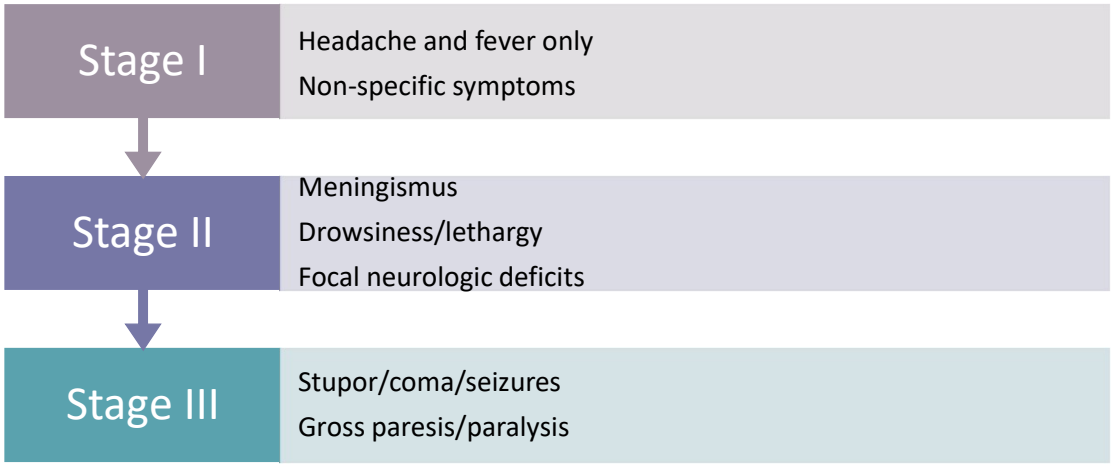
- One month later (3 months into therapy) he presented with new onset seizures
- LP results:
  - WBC 0
  - RBC 2
  - glucose 52 mg/dL (ref 50-75)
  - protein 78 mg/dL (ref-12-60)
  - MTB PCR NAAT neg
  - AFB smear/culture negative at 6 weeks
- Toxo IgG/IgM neg
- Started steroids, slowly tapered and then he developed some mild difficulties in word finding



Typical Findings CSF in TB Meningitis

Protein elevated: 100-500mg/dL (may be higher in spinal block)
Moderately decreased glucose (~25-50mg/dL)
Pleocytosis: 100-500/uL
Lymphocyte predominant, but can be mixed or neutrophilic early in presentation
TB PCR sensitivity: ~50% (range 40-75%)
AFB smear sensitivity: ~10% (higher for tissue biopsy and CSF pellicle)
AFB culture sensitivity: ~50%

TBM Clinical Presentation



Typical Complications TB Meningitis

- Pressure of exudate→ cranial nerve palsies (e.g., IV, VI, VII), deafness, visual disturbances, other paresis/paralysis
- Hydrocephalus
- Occlusive vasculitis
- SIADH
- Mass effect
- Paradoxical worsening/IRIS

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

Slide courtesy of Shannon Kasperbauer

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:

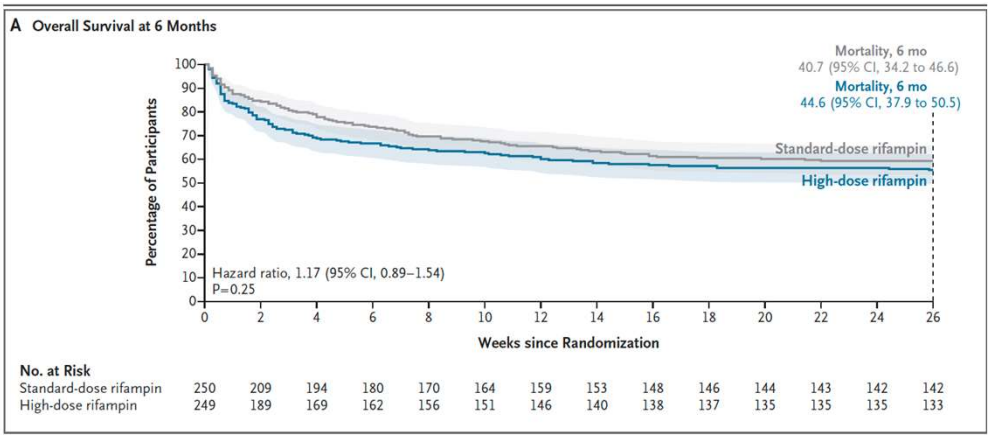
- Well designed RCT in Vietnamese Adults with TB meningitis
- No advantage associated with the use of this intensified treatment regimen with regard to overall mortality (28%)

Slide courtesy of Shannon Kasperbauer

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

High Dose rifampin (35mg/kg) did not improve outcomes in TB meningitis (TBM)

- N=499 in ITT –South Africa, Uganda, Indonesia
  - 60.9% with HIV, 85% with probable/proven TBM
  - Standard rifampin 10mg/kg; high dose-35mg/kg



Meya DB, et al. N Engl J Med 2025;393:2434-46.

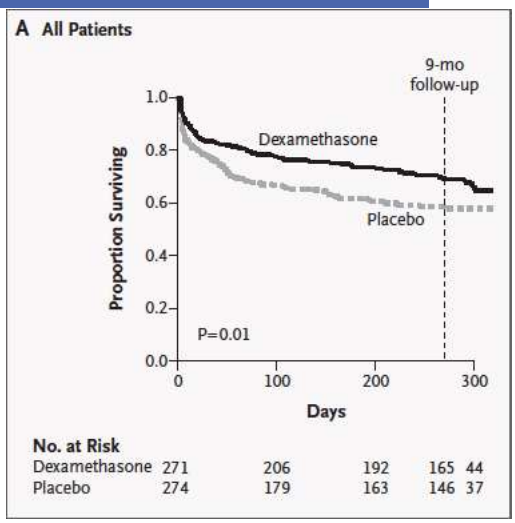
Treatment considerations for adults with TB meningitis (TBM)

- Levofloxacin: good CNS penetration; use/higher doses not clearly associated with benefit over standard therapy
- Linezolid: good CNS penetration; limited data
  - One study in RR/MDR-TB showed inclusion of linezolid for TBM associated with reduced mortality
- Rifampin
  - Modeling has suggested higher doses could be better but recent clinical trials indicate otherwise
  - Maintain current dosing; some increase to 15mg/kg
- Ethionamide—most of the data are in pediatric populations

Mohzari Y, et al. Abstract # 1281, ID Week 2022
Cerrone, M et al. JAC 2019
Mpofu R et al. Abstract # 0646 CROI 2026

Corticosteroids in TB Meningitis

- RCT, double-blinded, age>14, N=542
- Dexamethasone vs placebo
- RR death 0.69 (0.52-0.92), p=0.01
- Severe disability: 18% vs 13% (NS; p=0.27)
- Adverse effects: 9% vs 20% (p=0.02)



Thwaites G, et al. NEJM 2004;351:1741-51

Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

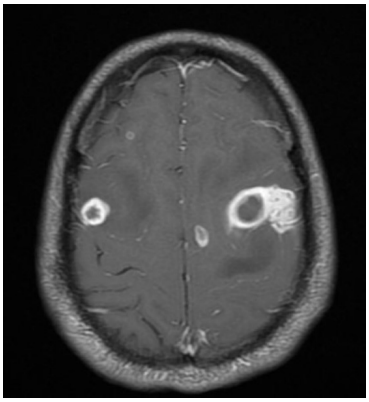
Corticosteroids in TB Meningitis

- Dexamethasone 0.4mg/kg/d split 4 times per day or prednisone 1mg/kg/d
  - Tapered over 6-8 weeks
    - Most experts would say you need much longer tapers
- Less clear role in tuberculoma

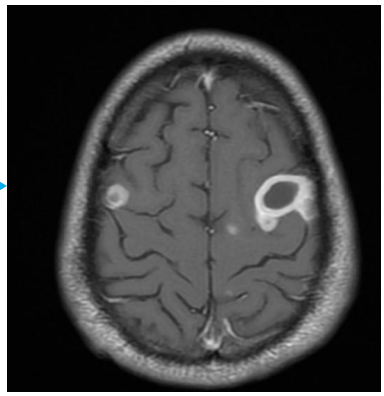
Back to our patient:

Waxing and waning lesions, prednisone dosing also waxing and waning, continued TB treatment for 18 months until finally stabilized

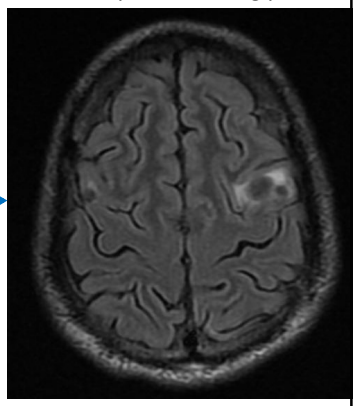
January



February



January the following year



Is there anything else other than prednisone to offer?

Infliximab to treat severe CNS TB related inflammation

- Retrospective review N=18; at least one dose 5mg/kg infliximab
  - additional doses at 2-week intervals during the first month, and then monthly infusions for up to 3 months
  - 82% with grade II or III severity of symptoms; 44% with ICU admission; all worsening pre-infliximab on standard of care
  - Modified Rankin scores (measure of disability) remained in the moderate to moderately severe range (3-4)

Outcome	n (%)
At 1 mo	
mRS evolution	
Improvement	6/16 (38)
Stability	9/16 (56)
Worsening	1/16 (6)
Radiological evolution	
Improvement	10/14 (71)
Stability	2/14 (14)
Worsening	2/14 (14)
Survival	18/18 (100)
Continuation of anti-TNF after 1 m[a]	13/18 (72)
At 1 y	
mRS evolution	
Improvement	14/18 (78)
Stability	3/18 (16)
Worsening	1/18 (6)
Radiological evolution	
Complete response	2/17 (12)
Partial improvement	14/17 (82)
No improvement	1/17 (6)
Survival	17/18 (94)
Death attributed to PR	0/18 (0)

Benhard, J et al. OFID 2025

Patient # 4

- 49 year old man with newly diagnosed type II diabetes who presented to an outside hospital with back pain and numbness/tingling in his legs bilaterally
  - No fever/chills
  - No weight loss
  - Vitals stable, afebrile
  - Exam without neurologic deficits

MRI report:
- "likely metastatic disease"
- Pathologic 80% vertebral body fracture at T3, mass-like lesion with epidural extension of presumed tumor and retropulsion →severe canal stenosis

Patient # 4

- TST reportedly negative; HIV negative
- Underwent biopsy of T3:
  - Fibroadipose tissue and fragments of bone with prominent granulomatous inflammation
  - No evidence of malignancy, no AFB or fungal organisms
- Discharged home on the following:
  - Dexamethasone
  - Metformin

Patient #4

- Presents again 3 weeks later with:
  - Continued numbness and tingling of the entire bilateral LE's as well as unsteady gait
  - Worsening right sided upper back pain
  - IGRA positive
  - PSA 4.76 (>4 abnormal)

Patient # 4

Transferred to a referral center and admitted to neurosurgery

- Underwent debulking with T3 corpectomy, T1-T5 spinal fusion, T2-4 decompression

Concern for malignancy, PET scan ordered

Patient #4

- Intense FDG activity in the following:
  - Soft tissues around the site of the T3 corpectomy
  - left lateral sixth rib lesion with likely pathologic fracture
  - Prostate
  - Right scrotum

Patient # 4

- Excisional biopsy of left rib mass, and fluid sampling for culture
  - Blood and fibroadipose tissue
- **2nd Rib biopsy**:
  - Bone and bone marrow with extensive infiltration by **non-caseating granulomas**
    - No mycobacterial or fungal elements noted by AFB and GMS staining
- **Prostate**, right medial, right lateral, left medial and left lateral core biopsies:
  - Benign prostatic tissue with acute and chronic inflammation, foreign body giant cell reaction and abundant **non-caseating granulomas**

Patient # 4

- Initiated on isoniazid, rifampin, pyrazinamide and ethambutol
- PCR for *Mycobacterium tuberculosis (Mtb)* was positive from spinal mass/abscess fluid a few days later.
  - Culture positive, pan-susceptible
- Rib biopsy, urine and sputum cultures all negative for *Mtb*
- ***Completed 12 month course—extended due to hardware***

Corticosteroids in TB Pericarditis

- ***Routine administration NOT endorsed by IDSA/ATS guidelines***
  - RCT showed a small benefit in reducing constrictive pericarditis
    - N=1400, 67% people with HIV
    - Constrictive pericarditis reduced: 4.4% vs 7.8%; HR 0.56 (0.36-0.87; p=0.04)
  - Follow up systematic review no benefit to reduce risk of constrictive pericarditis
  - Selective use in patients at high risk for inflammatory complications *might* be appropriate:
    - Large pericardial effusion, high levels of inflammatory cells/markers in pericardial fluid; early signs of constriction

Mayosi, et al. NEJM 2014;371:1121-30
ATS/CDC/IDSA 2016 Rx Guidelines

Clinical course: paradoxical worsening can be common

Most commonly seen with lymphatic TB

- 20-25% of HIV-negative LN cases

Also common in CNS TB

Very rarely, other disease sites

Median onset: 46 days (IQ: 34-111 days)

Can be prolonged→ Median duration: 69 days

NSAIDs, corticosteroids, aspiration (very limited data in patients without HIV)

Fontanilla, et al. CID 2011:53(6):555-62.

Other Sites of EPTB

Site	Diagnostics	Treatment	Comment
Urinary tract	Urine AFB culture Urine PCR Biopsy specimens	Standard	Flank pain+fever Hematuria Sterile pyuria
Genital tract	Biopsy specimens	Standard	Female>male Tubes, ovaries Epididymis
Liver/spleen	LFTs: mild cholestatic profile Biopsy (rare)	Standard	Not uncommon in disseminated* TB, especially miliary
Ocular	Exam Positive TST/IGRA Exclusion of other causes Aqueous/vitreous fluid (rare)	"Standard" +/- ophthalmic corticosteroids	Anterior uveitis Pan uveitis/choroiditis TB bacilli or hypersensitivity Choroidal nodules
Erythema induratum	Biopsy: panniculitis	??	Hypersensitivity (not disease) Some PCR+ No organisms
*disseminated = involvement of two anatomically non-contiguous sites			

What about 4-month rifapentine-moxifloxacin in EPTB?

- When the extrapulmonary TB is…
  - likely to be paucibacillary,
  - not pose a substantial risk of death or disability,
  - and not require prolonged treatment (i.e., pleural or lymph node TB)

Intensive Phase			Continuation Phase				
Drugs	Duration[a]	Frequency[b]	Drugs	Duration[c]	Frequency[b]	Total Doses	Comments[d,e]
RPT MOX INH PZA	8 weeks	7 days/week for 56 doses	RPT MOX INH	9 weeks	7 days/week for 63 doses	119	Recommended for people ages 12 and older with body weight at or above 40 kg, with pulmonary TB caused by organisms that are not known or suspected to be drug-resistant, and who have no contraindications to this regimen.

Slide courtesy of Shannon Kasperbauer

https://www.cdc.gov/tb/topic/treatment/tbdisease.htm

EPTB Key Aspects of Management

- Diagnosis of pulmonary vs EPTB
- Extension of therapy for certain sites of disease
- Paradoxical worsening & IRIS
- Adjuvant treatment with corticosteroids for some conditions
- Monitoring response to therapy

Treatment: when to extend treatment in drug-susceptible extrapulmonary TB?

CNS disease

- 9-12 months recommended
- optimal duration of chemotherapy is not defined

Bone/Joint/Spinal disease

- some experts recommend 9 months
- Many favor extending duration of treatment to 12 months if hardware is present
  - "suppressive therapy" not recommended

Extra pulmonary TB summary

- Lymph node, pleura most common; any site can be affected
- Look for concurrent pulmonary TB
- Dx: imaging→sampling→ cultures
- Rx: most 6 months: exceptions CNS and bone/joint/spine disease
- Corticosteroids indicated: TB Meningitis
  Consider in selected patients with pericardial disease
- Monitor closely for paradoxical worsening, particularly in lymphatic disease


Questions?