Extrapulmonary Tuberculosis

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Disclosures

- No relevant disclosures for this talk

Objectives

-Review the epidemiology of extrapulmonary disease

-Describe host risk factors for extrapulmonary disease

-Review the presentation, diagnostic strategy and treatment of the different forms of extrapulmonary disease

-Explore the contribution of molecular techniques

-Summarize the guidelines for management

Extrapulmonary tuberculosis (EPTB)

-bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs

(i.e. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges).

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%) EPTB

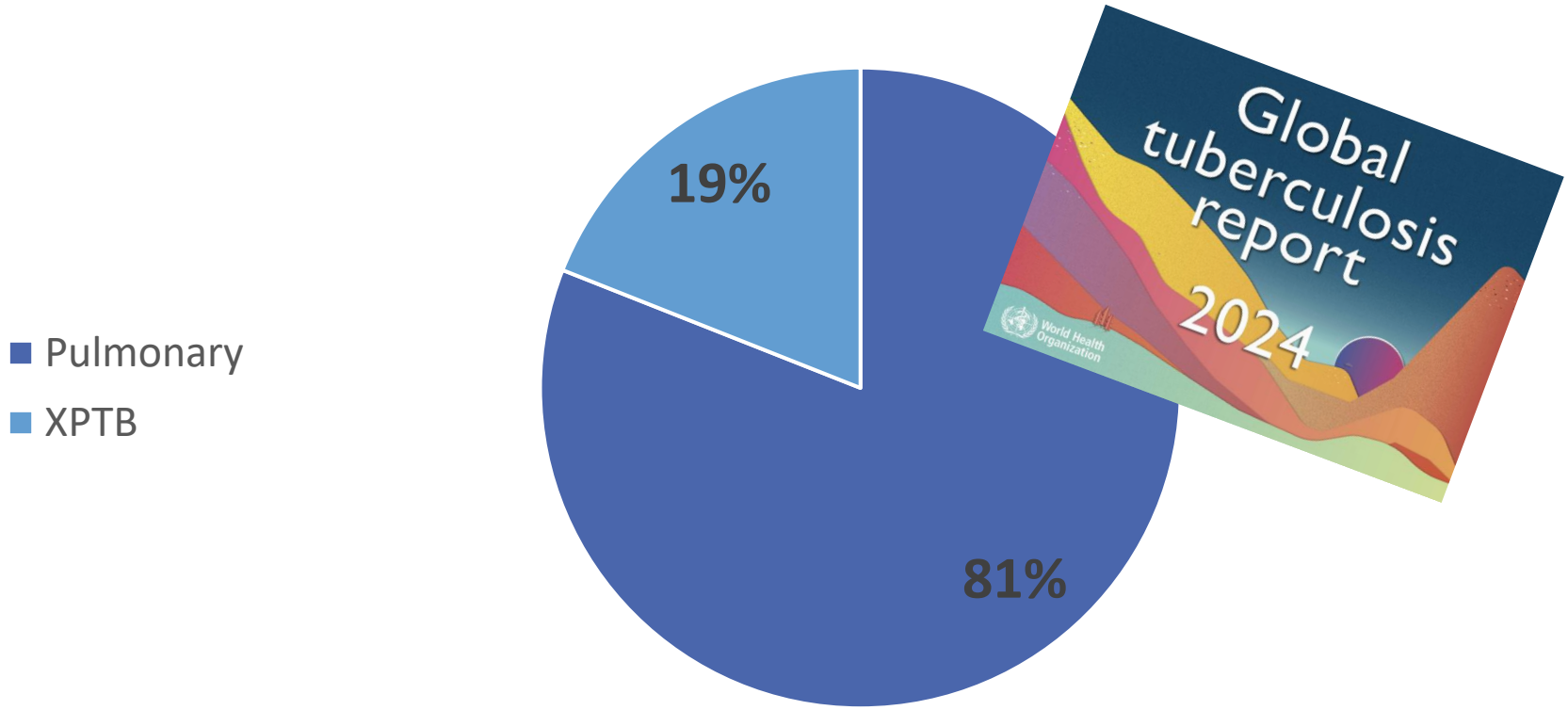
EPTB higher in HIV patients (OR 5.14)

KEY POINT:

In endemic regions there is a substantial burden of undiagnosed TB and MDR TB

Lancet Infect Dis 2015; 15: 544–51.

Extrapulmonary TB in 2023



www.who.int

WHO Global TB Report

TABLE 5.1

Notifications of TB, HIV-positive TB, MDR/RR-TB and XDR-TB cases, globally and for WHO regions, 2019

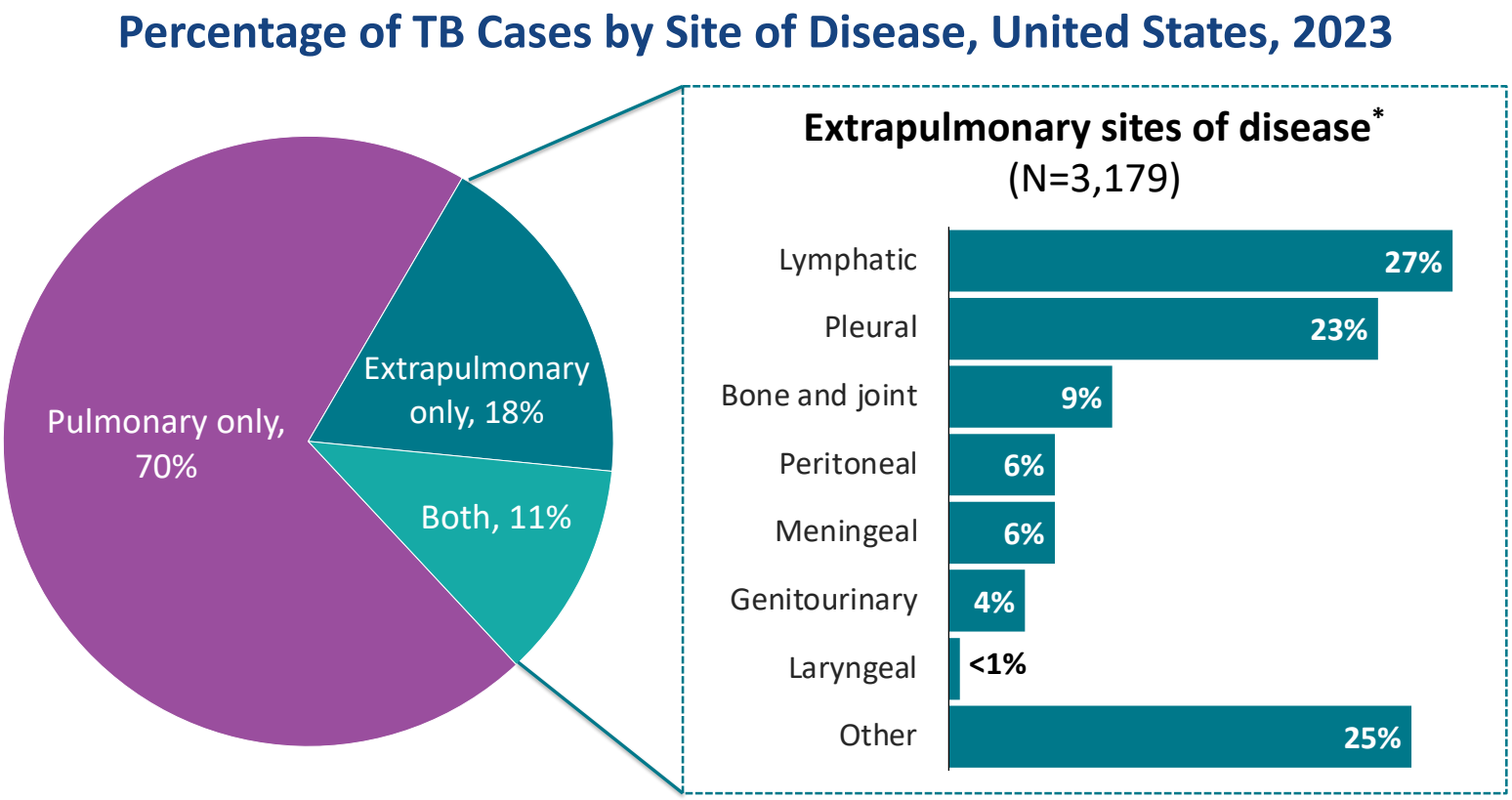
WHO REGION	TOTAL NOTIFIED	NEW AND RELAPSE[a]	PULMONARY NEW AND RELAPSE		EXTRA-PULMONARY NEW AND RELAPSE (%)	HIV-POSITIVE NEW AND RELAPSE	MDR/RR-TB	XDR-TB[b]
			NUMBER	OF WHICH BACTERIOLOGICALLY CONFIRMED (%)				
Africa	1 436 330	1 400 293	1 191 433	66%	15%	318 238	29 155	618
The Americas	250 341	235 600	199 417	78%	15%	20 122	4 979	138
Eastern Mediterranean	506 641	497 998	377 324	55%	24%	1 705	6 328	73
Europe	243 789	200 322	168 574	66%	16%	25 100	47 936	8 560
South-East Asia	3 641 245	3 378 887	2 728 541	57%	19%	75 366	86 623	2 444
Western Pacific	1 416 592	1 389 744	1 281 527	46%	8%	15 895	31 009	517
Global	**7 494 938**	**7 102 844**	**5 946 816**	**57%**	**16%**	**456 426**	**206 030**	**12 350**

[a] *New and relapse* includes cases for which the treatment history is unknown. It excludes cases that have been re-registered as *treatment after failure*, as *treatment after loss to follow-up* or as *other previously treated* (whose outcome after the most recent course of treatment is unknown or undocumented).

[b] XDR-TB is MDR-TB plus resistance to a fluoroquinolone and an injectable agent.

https://www.who.int/tb/publications/global_report/en/

CDC Data 2023



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

Incidence of EPTB 1964-1976

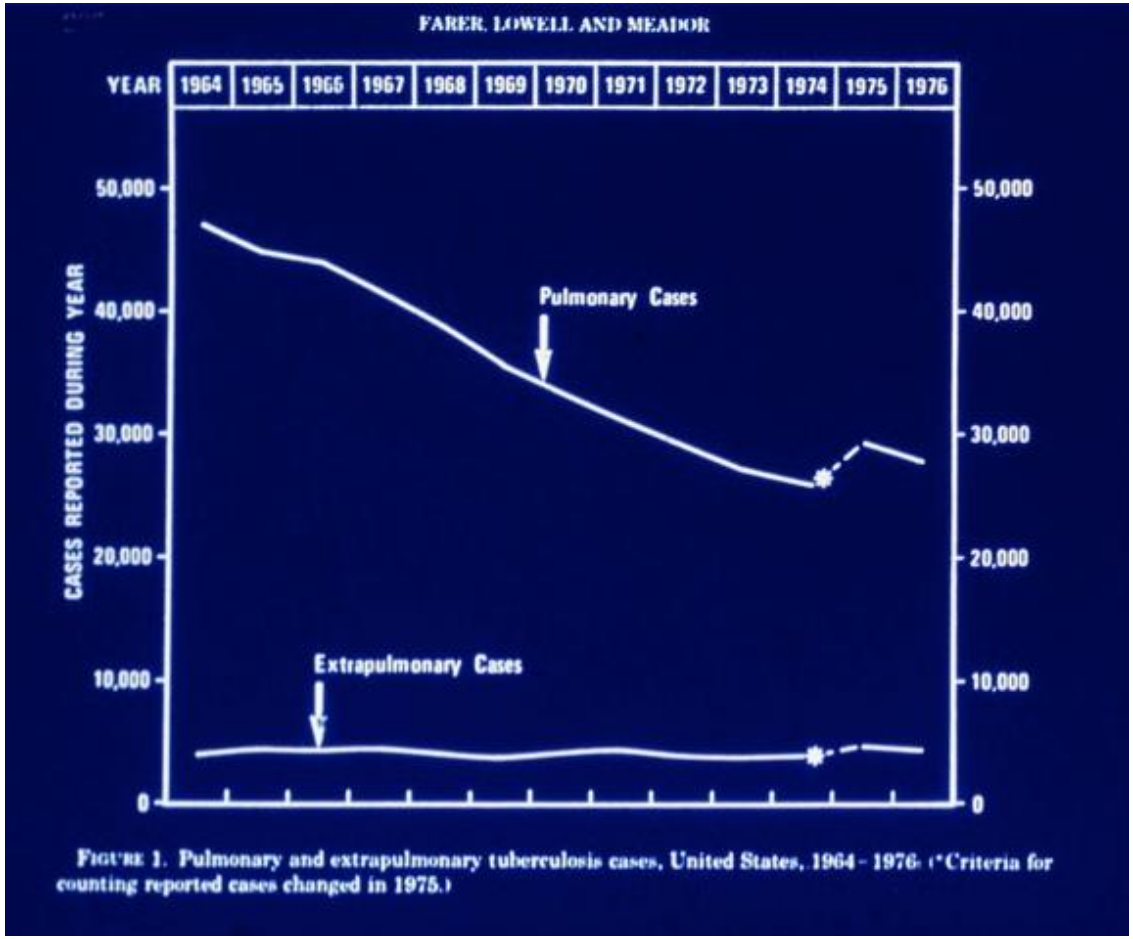


FIGURE 1. Pulmonary and extrapulmonary tuberculosis cases, United States, 1964–1976. (*Criteria for counting reported cases changed in 1975.)

Courtesy of the CDC, provided by Dr. M. Iseman

Risk factors for EPTB

- **Untreated Human immunodeficiency virus (HIV) infection**
- **Infancy**
- **Corticosteroids or other iatrogenic immunosuppression**
- **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

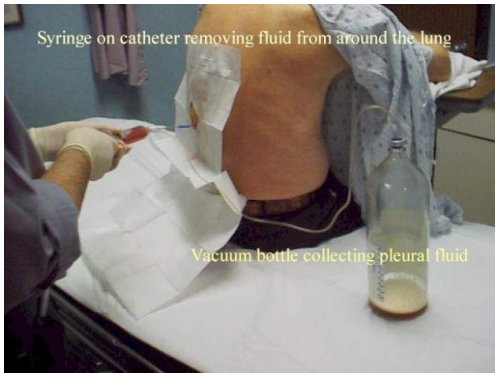
Diagnostic challenges

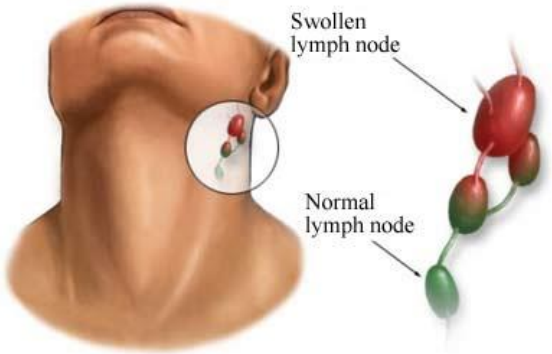
SIGNS AND SYMPTOMS ARE NONSPECIFIC

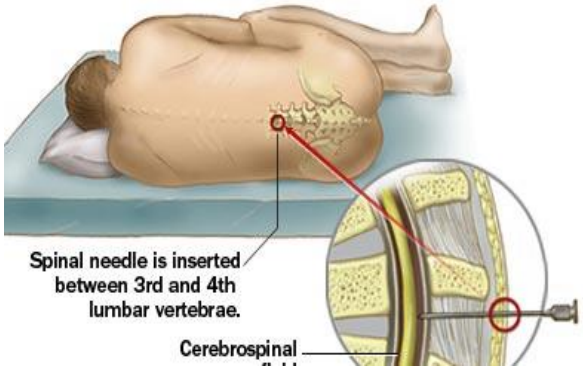
DIAGNOSTIC SAMPLING MAY BE DIFFICULT

SERIAL SAMPLING ON TREATMENT MAY NOT BE FEASIBLE

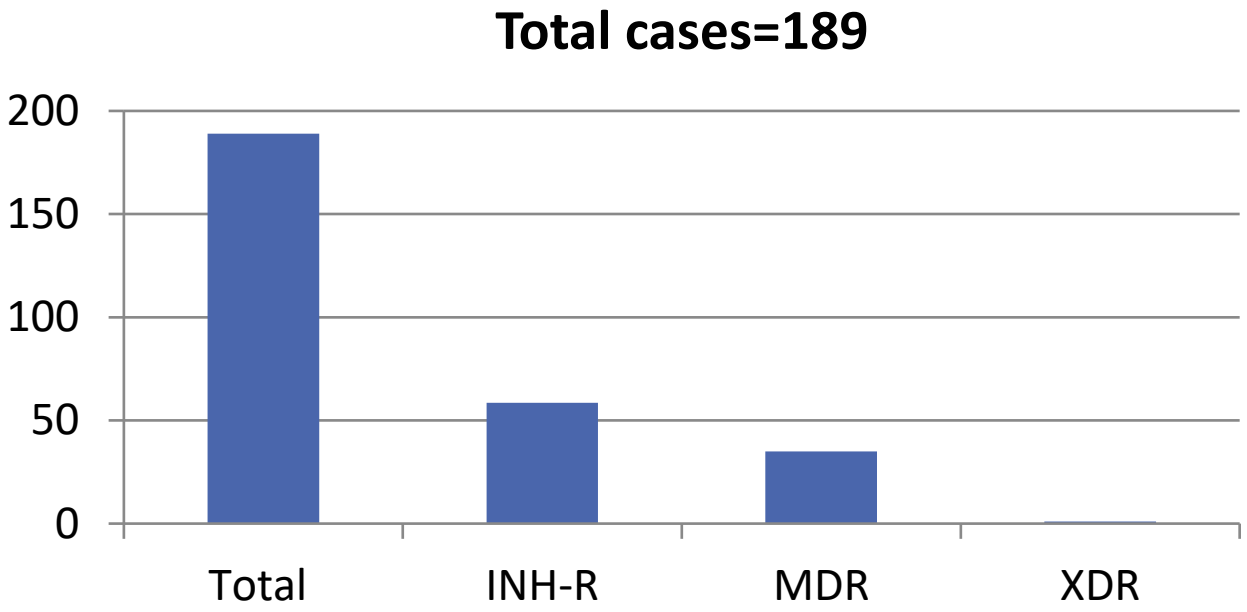
Diagnosis requires tissue/fluid sampling







EPTB in New Delhi
High rates of drug resistance



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.

EPTB + HIV

EPTB MORE COMMON IN AIDS

INCREASING RATE WITH DECREASING CD4

#1 LYMPHADENITIS
#2 DISSEMINATED

OBTAIN AS MANY CULTURES FROM AS MANY SITES AS POSSIBLE
USE MOLECULAR TOOLS
URINE LAM

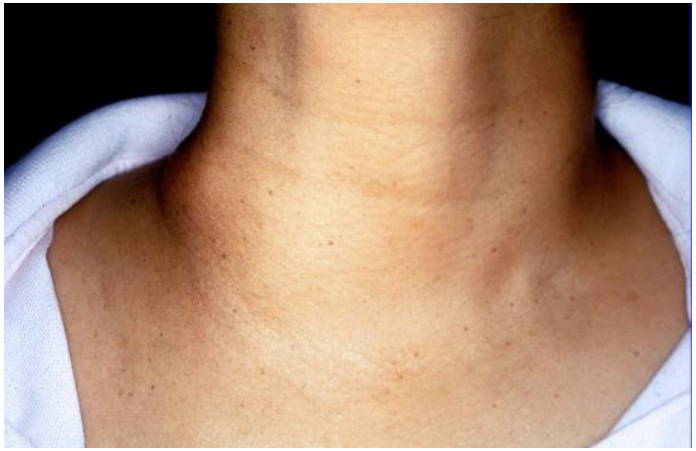
Gupta-Wright Lancet 2018

Lymphatic Tuberculosis

PRESENTATION
Painless, unilateral, cervical chain most common

DIAGNOSIS
Biopsy

TREATMENT
Chemotherapy (6 mo)
Be prepared for paradoxical reactions (up to 25%)



Pleural Tuberculosis

PRESENTATION
Fever, cough, pleurisy
Unilateral sm-mod effusion
Parenchymal disease 50%

DIAGNOSIS
Thoracentesis
Pleural Biopsy

TREATMENT
Chemotherapy
6 months

Diagnostic Thorn=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	Xpert MTB/RIF (%)	Xpert Ultra (%)	Culture (%)
Pleural fluid	49	75	26

Kohli Cochrane Review 2021

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

Zhou Scientific reports 2015

Genitourinary Tuberculosis

PRESENTATION
Pain, altered urination
Sterile pyuria, hematuria, proteinuria
Hydronephrosis, distortion of collecting system

DIAGNOSIS
Urine smear is not performed
Urine AFB culture, early collection

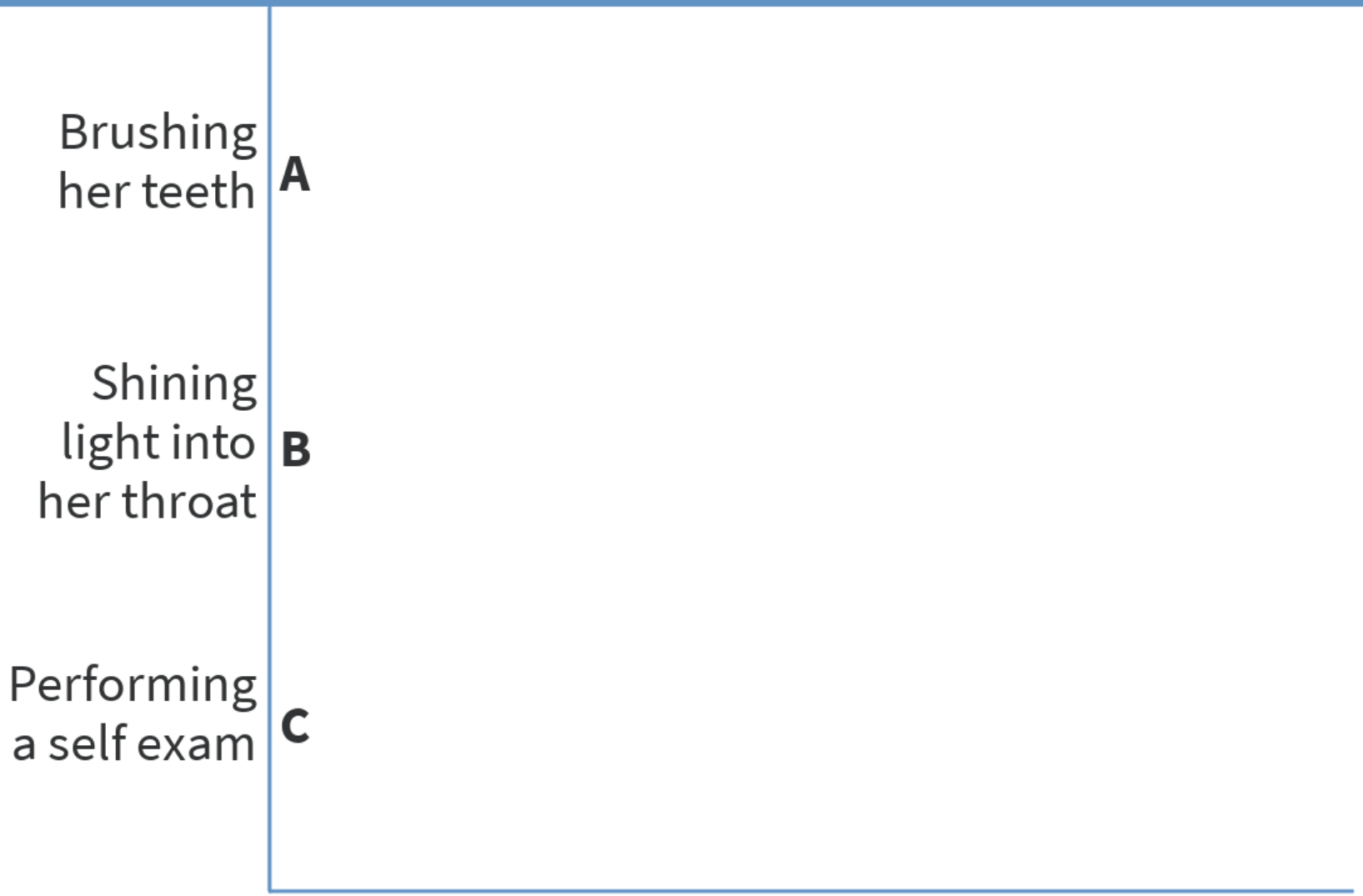
TREATMENT
Chemotherapy
6 months

Audience Response Question

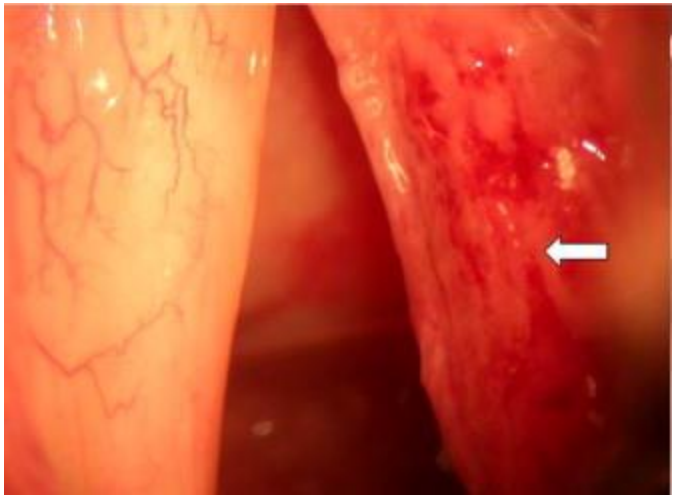
What is this woman doing?

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

What is this woman doing?



Laryngeal Tuberculosis



PRESENTATION
Hoarseness, odynophagia
Unilateral, true vocal cords

DIAGNOSIS
Laryngeal biopsy

TREATMENT
Chemotherapy 6 months
Surgery reserved for airway compromise
Prognosis usually good, immobility can be reversible

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

Gastrointestinal Tuberculosis

PRESENTATION
Hepatitis, enteritis, peritonitis
Abdominal pain, fever, ascites
70% symptoms > 4 months

DIAGNOSIS
Ascites: lymphocytic exudate
beware of dilution in cirrhosis
Ascites: Smear usually negative.
Culture + 45-69%
Peritoneal biopsy

TREATMENT
Chemotherapy
6 months

Lewinsohn CID 2017

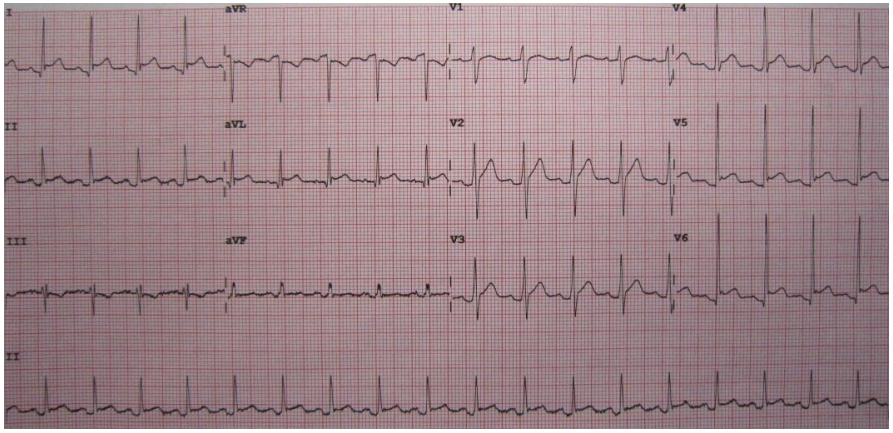
Audience Response Question

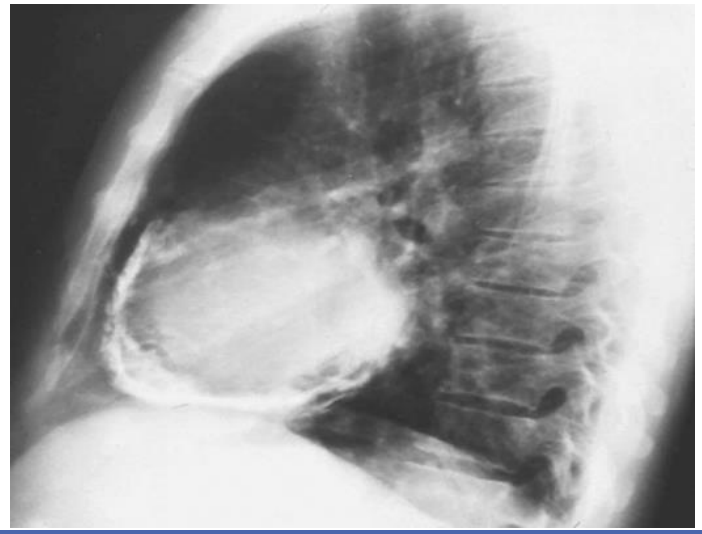
A 48-year-old male from South Africa complains of chest pain that worsens with leaning forward. ECG notes PR depression and diffuse ST elevation.

A. Begin Rifampin/INH/PZA/EMB

B. Begin Rifampin/NH/PZA/EMB and steroids after a pericardial biopsy for afb smear/culture and TB PCR.

C. Obtain a pericardiocentesis for afb smear and culture. A negative result excludes the diagnosis.





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.

Begin Rifampin/INH/PZA/EMB	**A**
Begin Rifampin/NH/PZA/EMB and steroids after a pericardial biopsy for afb smear/culture and TB PCR	**B**
Obtain a pericardiocentesis for afb smear and culture. A negative result excludes the diagnosis.	**C**

Pericardial Tuberculosis

PRESENTATION

Cough, wt loss, 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

DIAGNOSIS

Pericardial biopsy: Smear, culture, PCR

Negative biopsy does not exclude the diagnosis

TREATMENT

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
XPERT MTB/RIF	63.8	100

Pandie BMC Med 2014

Guidelines support selective use of steroids in pericarditis

Recent RCT (n=1400) NO difference in the combined primary endpoint of mortality, cardiac tamponade, or constrictive pericarditis

Subgroup analysis: Suggested a benefit in preventing constrictive pericarditis

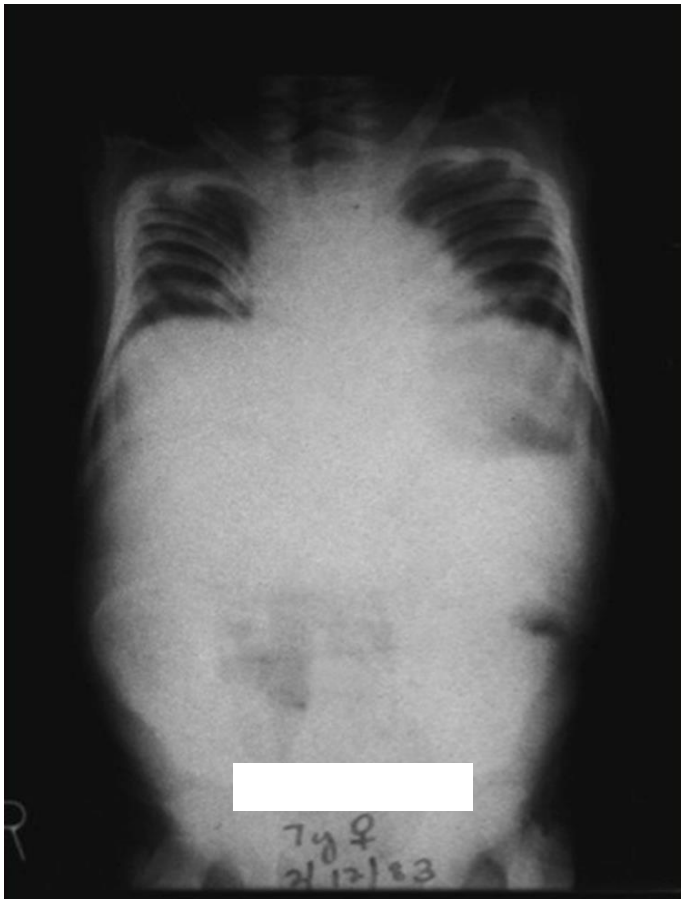
- large pericardial effusions, those with high levels of inflammatory cells or markers in pericardial fluid, or those with early signs of constriction

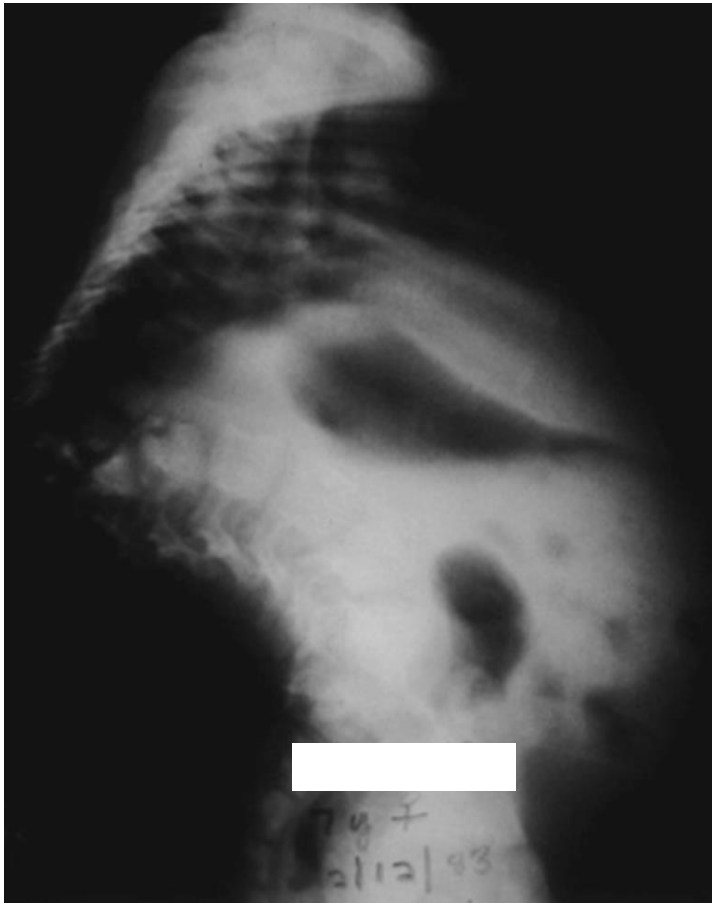
2016 Guidelines:

- 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

What is unusual about this CXR in a 7-year-old male?






LESTER
DAIRY
FARM

Spinal Tuberculosis

PRESENTATION

Lower thoracic and lumbar vertebrae

Back pain, cold abscess, nerve root compression *scoliosis, limp

Bone destruction, anterior wedging, para-spinous abscess

DIAGNOSIS

Biopsy for smear and culture

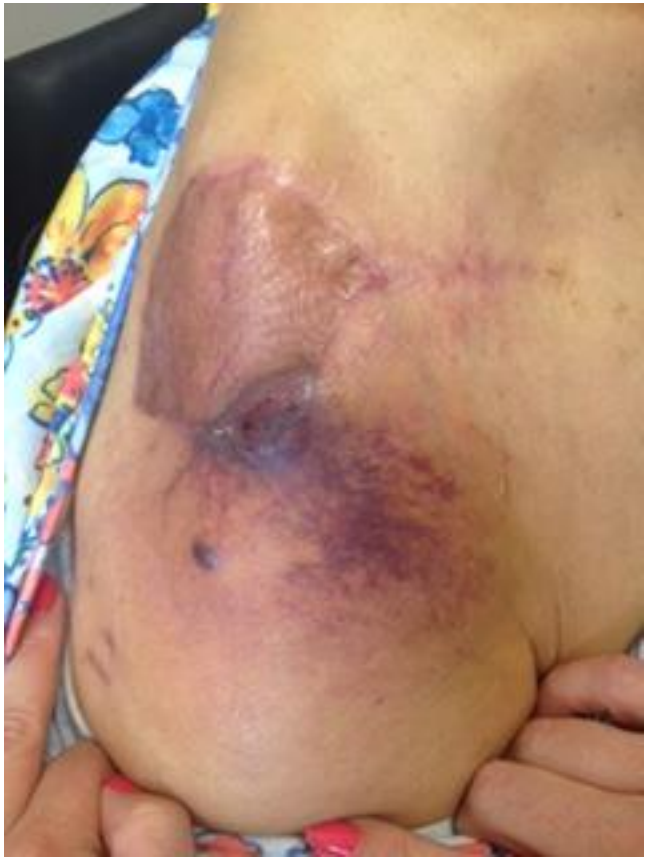
TREATMENT

Chemotherapy 6 months +/- surgery

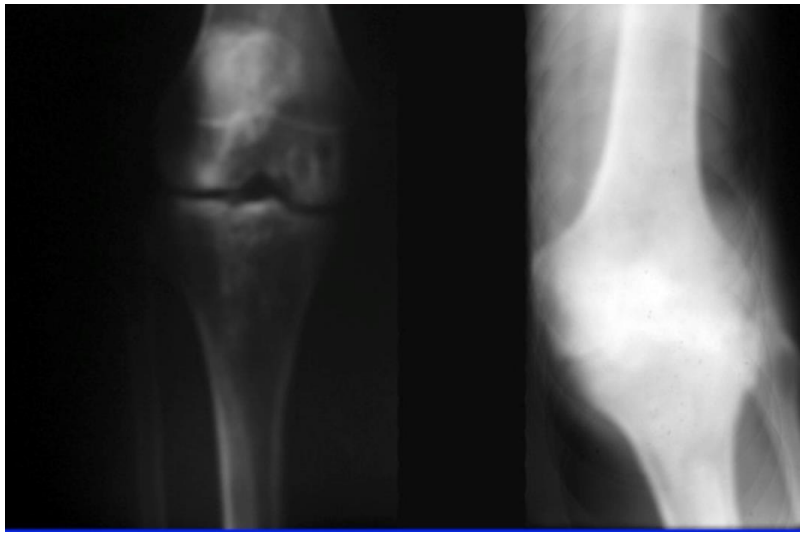
Extend 9-12 months for advanced disease

Osteomyelitis of the wrist and forearm

Tuberculous septic arthritis with associated clavicular osteomyelitis



Extra-spinal bone/joint tuberculosis



PRESENTATION

Osteomyelitis < arthritis :hip and knee

Cold abscess, pain, swelling, loss of joint function

Constitutional symptoms <30%

DIAGNOSIS

X-ray findings may be nonspecific, destruction is a late finding

Bone/synovial biopsy for smear and culture

TREATMENT

Chemotherapy for 6 months

9-12 months for advanced disease

Outbreak of EPTB associated with acupuncture, China

33 EPTB cases

- all confirmed MTB, Beijing strain

Clin Microbiol Infect. 2014 Nov 14

Audience Response Question

9-month-old girl 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, AMK, PZA

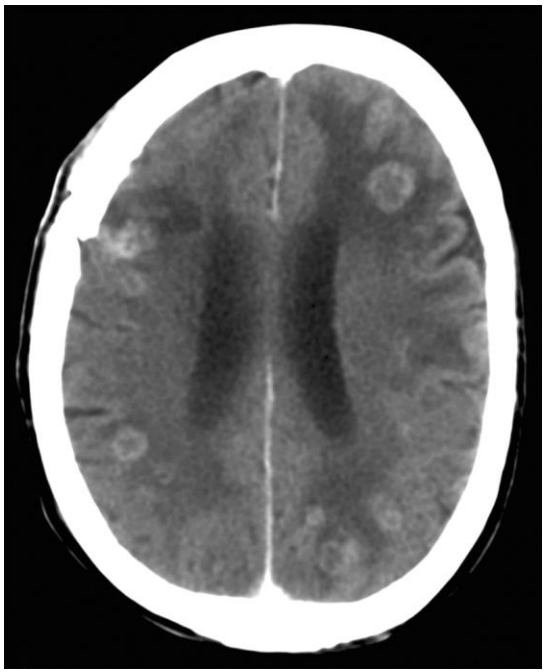
Img.wikinut.com

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:

Begin ceftriaxone and vancomycin	**A**
Begin dexamethasone, ceftriaxone and vancomycin	**B**
Begin dexamethasone, ceftriaxone, vancomycin, INH, RIF, ETH, PZA	**C**

CNS Tuberculosis:

meningitis, tuberculoma, spinal arachnoiditis, and transverse myelitis



DO NOT DELAY TREATMENT FOR + DIAGNOSITICS

PRESENTATION
Three stages of meningitis: Prodromal, Meningitic, Paralytic

DIAGNOSIS
Lumbar puncture: OP normal or high
CSF: Lymphocytic pleocytosis, elevated protein, low glucose
Send off the 4th tube, 6ml+
Smear, Culture (70%)
NAAT*

TREATMENT
Chemotherapy 9-12 months
Steroids

Phase	Key identifier	BMRC	Signs and symptoms
Prodromal phase (2-3 weeks)	**ALERT**	**BRMC STAGE I GCS score >15**	Malaise, headache, low grade fever, personality change
Meningitic phase	**LETHARGIC**	**BRMC STAGE II GCS score 11-14**	Neurologic features: meningismus, protracted headache, emesis, lethargy, confusion, CN signs
Paralytic phase	**COMA**	**BRMC STAGE III GCS score <11**	Confusion, stupor, coma, seizures, hemiparesis and death

Overall mortality in TBM (meta-analysis) 42%.

-J Neurol. 2022;269(7):3482. Epub 2022 Mar 15.

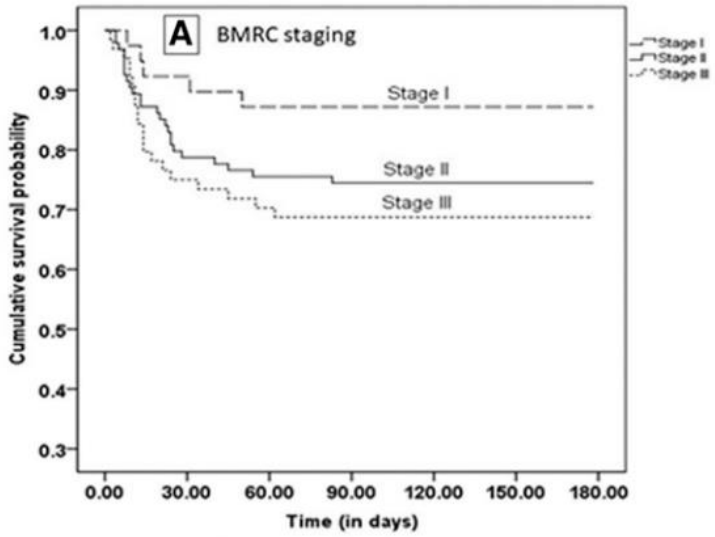
Paradoxical worsening can be seen on treatment in 1/3 of patients

-BMC Infect Dis. 2016;16:306. Epub 2016 Jun 21

Over half of survivors have neurologic disability.

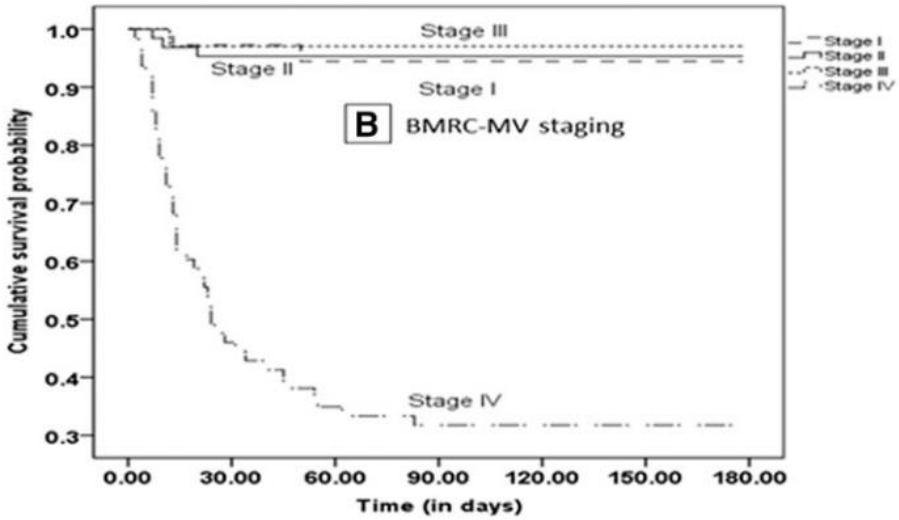
*BRMC: British research medical council

Survival probability best predicted by need for mechanical ventilation



Number of individuals at risk

Stage I	39	36	34	34	34	34	34
Stage II	94	74	71	70	70	70	70
Stage III	64	48	45	44	44	44	44



No. of individual at risk

Stage I	36	35	34	34	34	34	34
Stage II	64	61	61	61	61	61	61
Stage III	34	33	33	33	33	33	33
Stage IV	63	29	22	20	20	20	20

Am. J. Trop. Med. Hyg., 103(2), 2020, pp. 689–69.

Diagnosis of TB in the CSF

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

Lewinsohn CID 2017

Sensitivity	Gene Xpert	Xpert Ultra
CSF	71	89

Cochrane Review 2021

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

Ekermans BMC ID 2017

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

Rovina Ruslami, A Rizal Ganiem*, Sofiati Dian, Lika Apriani, Tri Hanggono Achmad, Andre J van der Ven, George Borm, Rob E Aarnoutse, Reinout van Crevel*

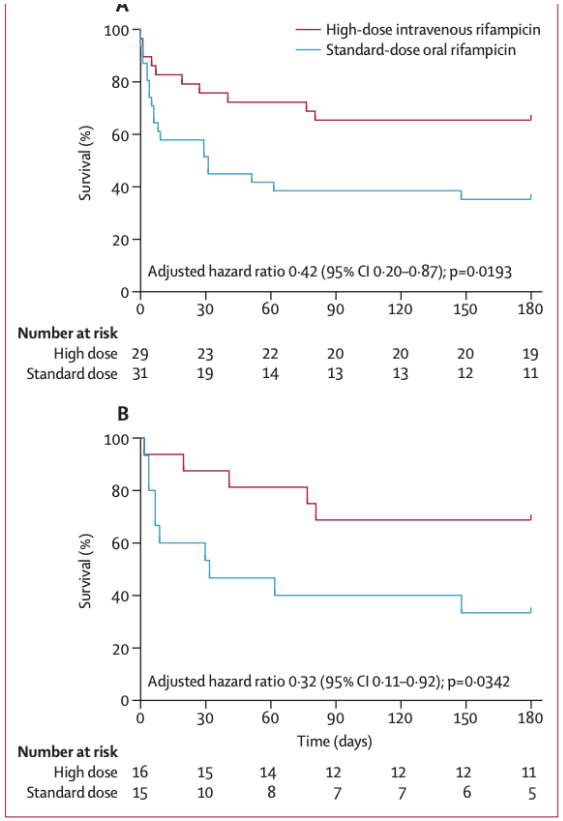


Figure 2: Survival according to rifampicin treatment in all 60 patients (A) and in 31 bacteriologically proven cases of tuberculous meningitis (B)

- Patients randomized to 450 mg oral rifampin daily vs. 600 mg IV rifampin daily for the first 2 weeks of treatment
- 50% reduction in mortality seen in the higher dose rifampin group

Lancet Infect Dis. 2013 Jan;13(1):27-35.

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

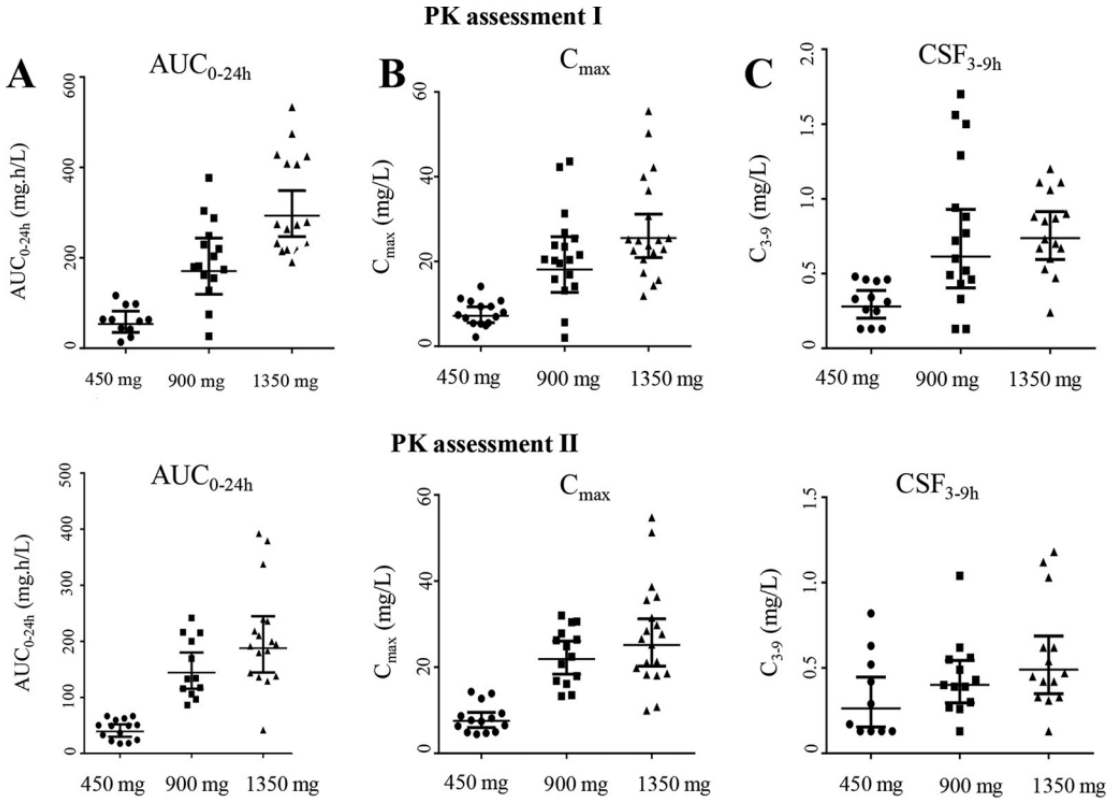
Summary:

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

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

Double-Blind, Randomized, Placebo-Controlled Phase II Dose-Finding Study To Evaluate High-Dose Rifampin for Tuberculous Meningitis

S. Dian,[a,c,g] V. Yunivita,[d,g] A. R. Ganiem,[c,g] T. Pramaesya,[g] L. Chaidir,[e,g] K. Wahyudi,[f] T. H. Achmad,[e] A. Colbers,[b] L. te Brake,[b] R. van Crevel,[a] R. Ruslami,[d,g] and R. Aarnoutse[b]



Rifampin 30mg/kg

Increased exposure in CSF

No association with an increase in grade 3-4 AE

Antimicrob Agents Chemother. 2018 Dec; 62(12): e01014-18.

Additional trial in the pipeline

Intensified tuberculosis treatment to reduce the mortality of HIV-infected and uninfected patients with tuberculosis meningitis (INTENSE-TBM): study protocol for a phase III randomized controlled trial

Thomas Maitre [1], Maryline Bonnet [2], Alexandra Calmy [3], Mihaja Raberahona [4 5 6], Rivonirina Andry Rakotoarivelo [4 7 8], Niaina Rakotosamimanana [9], Juan Ambrosioni [10 11], José M Miró [10 11], Pierre Debeaudrap [12], Conrad Muzoora [13 14], Angharad Davis [15 16 17], Graeme Meintjes [17 18], Sean Wasserman [17 19], Robert Wilkinson [15 17 20], Serge Eholié [21], Frédéric Ello Nogbou [22], Maria-Camilla Calvo-Cortes [23], Corine Chazallon [24], Vanessa Machault [24], Xavier Anglaret [24], Fabrice Bonnet [25 26]

https://clinicaltrials.gov/study/NCT04145258

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)

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

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

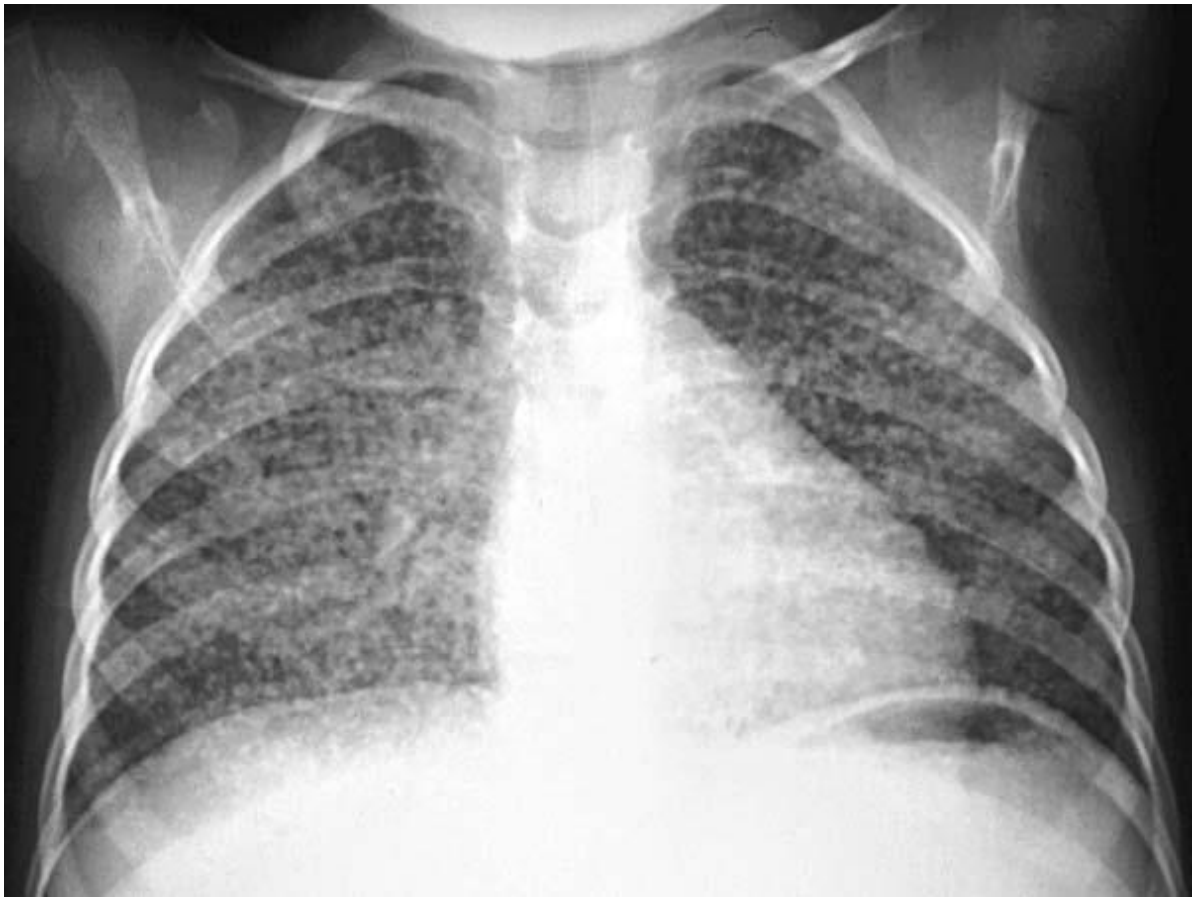
TB meningitis in Children

American Academy of Pediatrics:

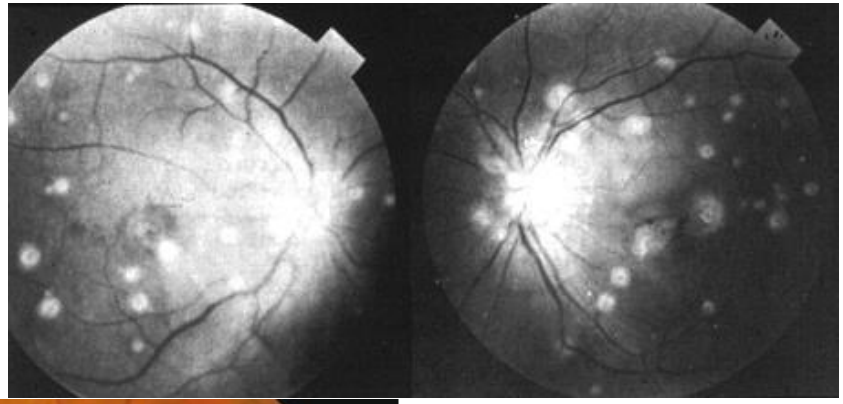
1. An initial 4-drug regimen of INH, RIF (20-30 mg/kg/day), PZA, and an aminoglycoside or ethionamide for 2 months
2. If/when susceptibility to first-line drugs is established, the ethionamide or aminoglycoside may be discontinued
3. Followed by 7–10 months of INH and RIF

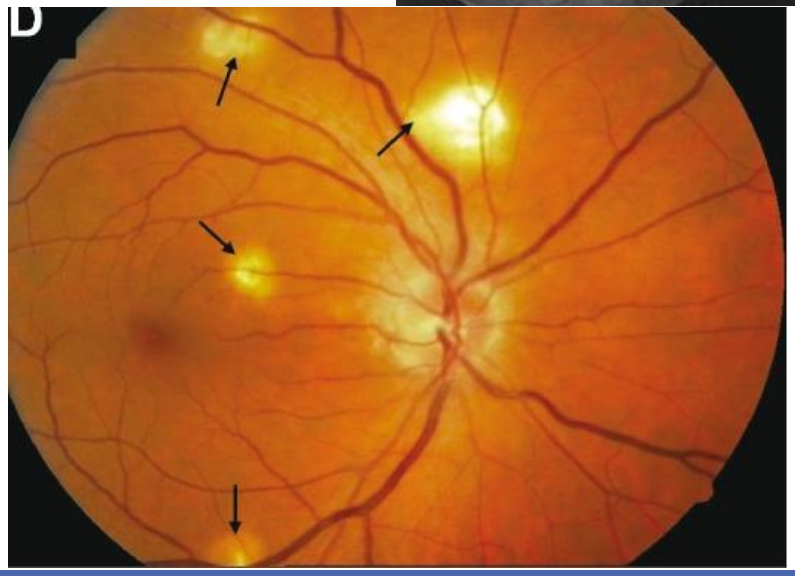
American Academy of Pediatrics. Red Book: 2021-2024 Report of the Committee on Infectious Diseases, 32 ed

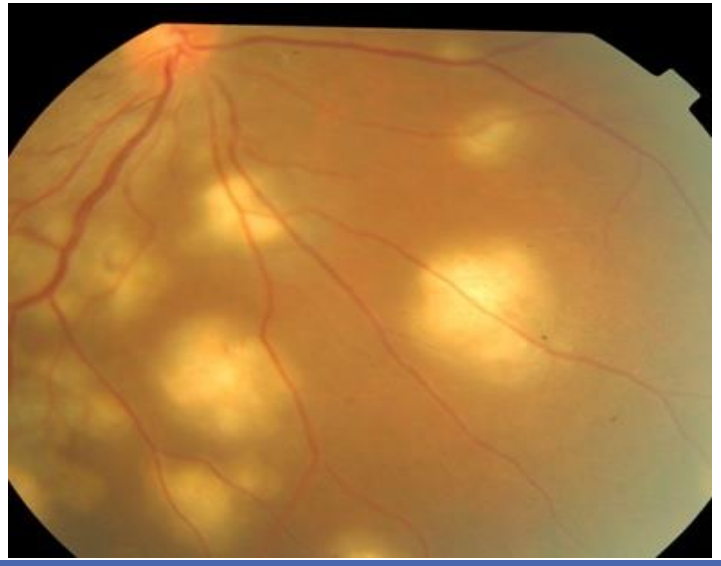
Miliary TB in a newborn



Early Clues in disseminated TB







Disseminated Tuberculosis

PRESENTATION
Primary or secondary hematogenous infection
Insidious, cryptic fever, weight loss
Rare: ARDS, DIC, pancytopenia

DIAGNOSIS
CXR often atypical or normal
PPD and sputum negative in up to 50%
PCR

TREATMENT
Chemotherapy 6 months
Extend therapy for CNS/bone joint disease

XPERT MTB RIF & XPERT ULTRA in XPTB

Site	XPERT MTB/RIF Sensitivity (95% CrI)	XPERT MTB/RIF Specificity (95%CrI)	XPERT ULTRA Sensitivity (95% CrI)	XPERT ULTRA Specificity (95% CrI)
Pleural fluid	49.5% (39.8 to 59.9)	98.9% (97.6 to 99.7)	75.0% (58.0 to 86.4)	87.0% (63.1 to 97.9)
Bone/Joint aspirate	97.9%(93.1 to 99.6)	97.4% (80.2 to 100.0)		
Gastric aspirate	78% (0.68 – 0.85)	100% (0.99 – 1.00)		
CNS fluid	71.1% (62.8 to 79.1)	96.9% (95.4 to 98.0)	89.4% (79.1 to 95.6)	91.2% (83.2 to 95.7)
Lymphatic node aspirate	88.9% (82.7 to 93.6)	86.2% (78.0 to 92.3)		
Urine	85.9% (71.4 to 94.3)	98.1% (93.1 to 99.7)		
Pericardial fluid	61.4% (32.4 to 82.4)	89.7% (74.9 to 99.0)		

Kohli M et al. Cochrane Database of Systematic Reviews 2021

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.

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

Drug resistant XPTB

	6 mo BPaLM/BPaL	9 Mo Oral regimen	18 mo regimen
XPTB	Yes	Yes	Yes
Exception:	TB involving CNS, miliary TB and osteoarticular TB	TB meningitis, miliary TB, pericardial TB and osteoarticular TB	

Vanino E et al. Int J Infect Dis. 2023 May:130 Suppl 1:S12-S15.

Summary: Diagnosing EPTB

Culture and drug susceptibility testing remain critical in the diagnosis and should be pursued in all suspects

WHO: recommends Xpert (Ultra*) as the initial test for XPTB
CDC/ATS/IDSA recommends NAAT testing on XPTB specimens

Guidelines recommend measuring ADA and INF-γ levels in fluid when pleural, pericardial, peritoneal, or meningeal TB is suspected

Lewinsohn CID 2017

Summary: EPTB Treatment

6 MONTHS OF STANDARD TB TREATMENT IN MOST CASES

Bone/Joint: consider extending treatment to 9 months
CNS disease: 9-12 months

Dosing is once daily for both the intensive and continuation phases

Nahid CID 2016;63(7):e147–95

Summary: 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 mg/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