

# Extrapulmonary Tuberculosis

**E. Ann Misch, MD**

**Assistant Professor**

Division of Infectious Diseases

Department of Medicine



School of Medicine  
and Public Health  
UNIVERSITY OF WISCONSIN-MADISON

# OBJECTIVES

## 1. Introduction

- pathogenesis of EPTB
- epidemiology of EP TB

## 2. Clinical features and diagnosis

- in-depth discussion of a case (*with audience questions*)
- other presentations of EP TB

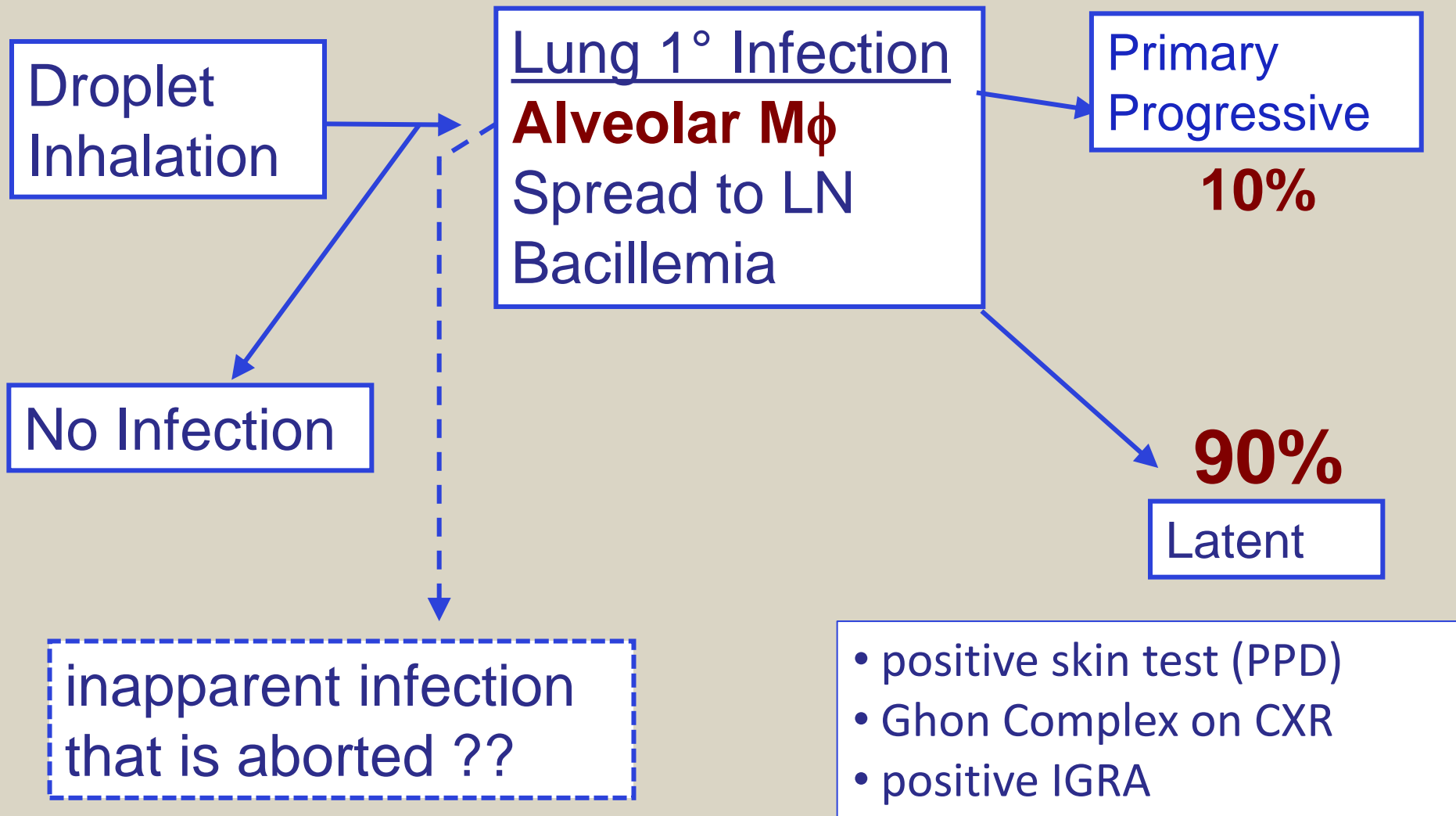
## 3. Summary

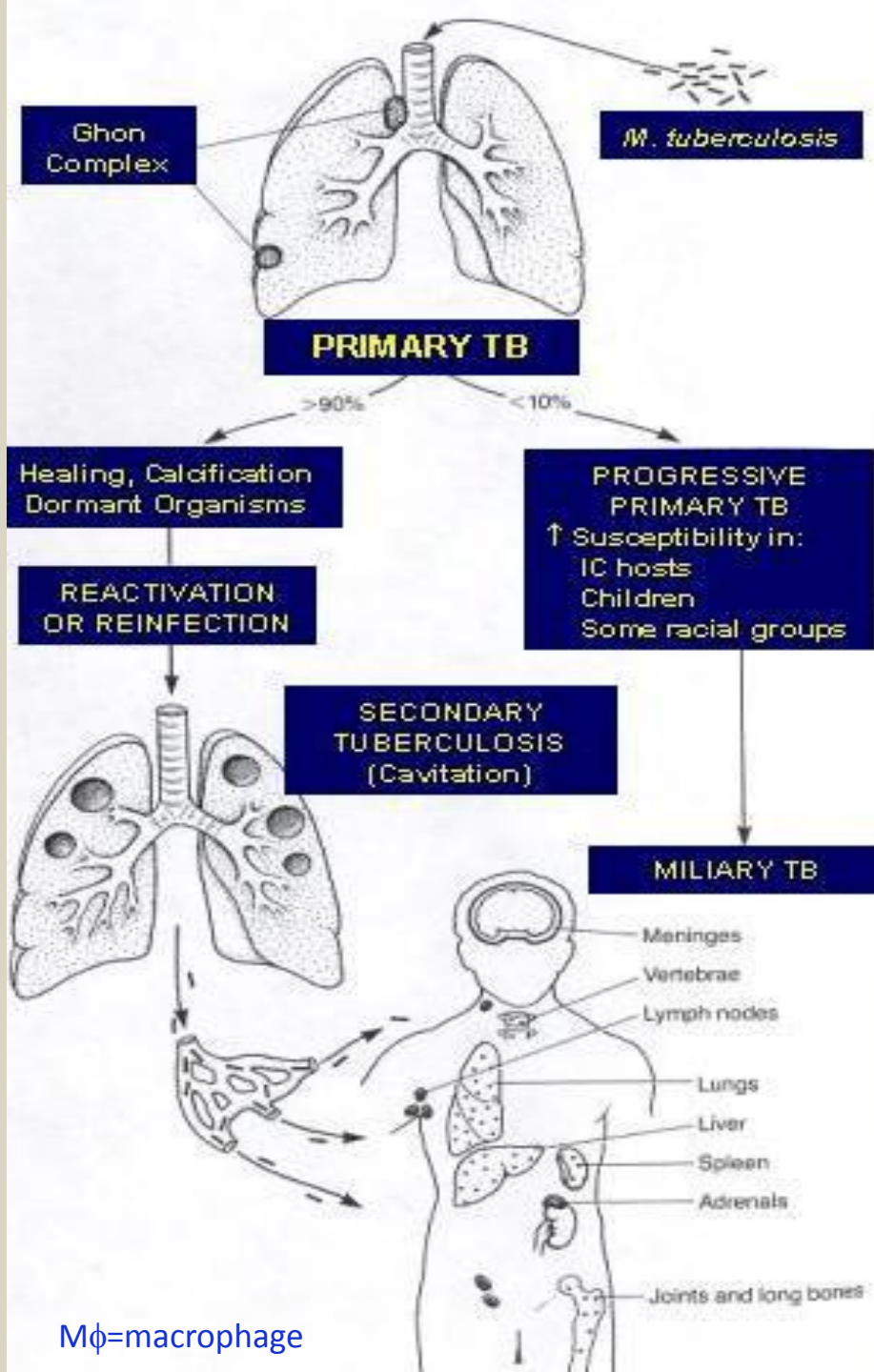


# TB pathogenesis

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# tuberculosis pathogenesis





## primary focus in lung:

- 85% within 1 cm of pleural surface
- 66% in lower half of lungs
- multiplication within Mφs in granuloma
- Mφ death → bacilli escape to local Lymph nodes → hilar focus

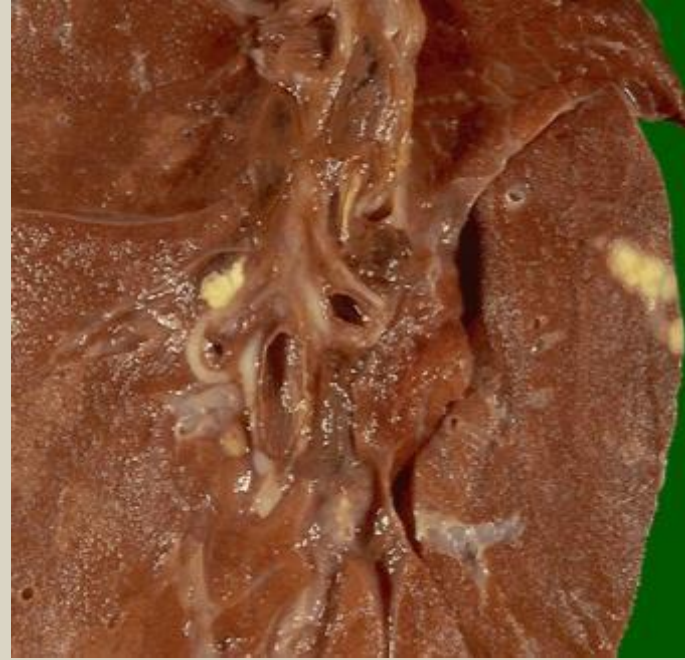
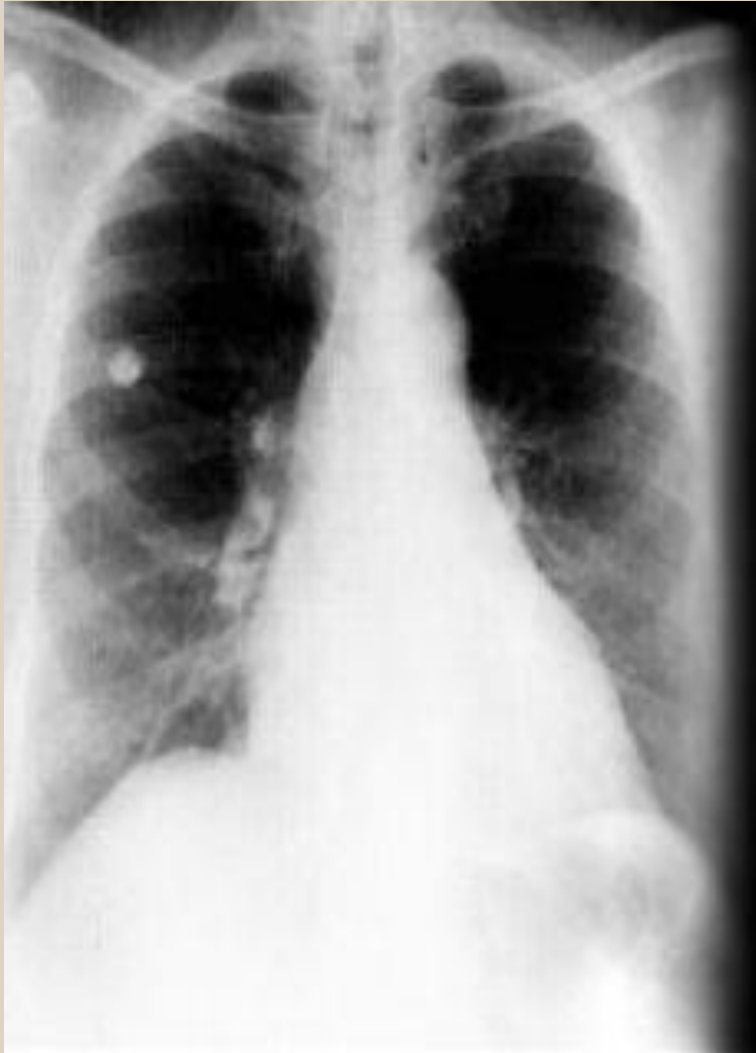
## 2-3 wks post infxn:

- hematogenous seeding from primary foci to sites in body:
  - brain
  - apical posterior lung
  - kidneys
  - vertebrae
  - epiphyses

## 3-4 wks post infxn:

- cell mediated immunity arrests 1<sup>o</sup>, 2<sup>nd</sup> foci

old, healed TB of lung  
→ Ghon /Ranke Complex

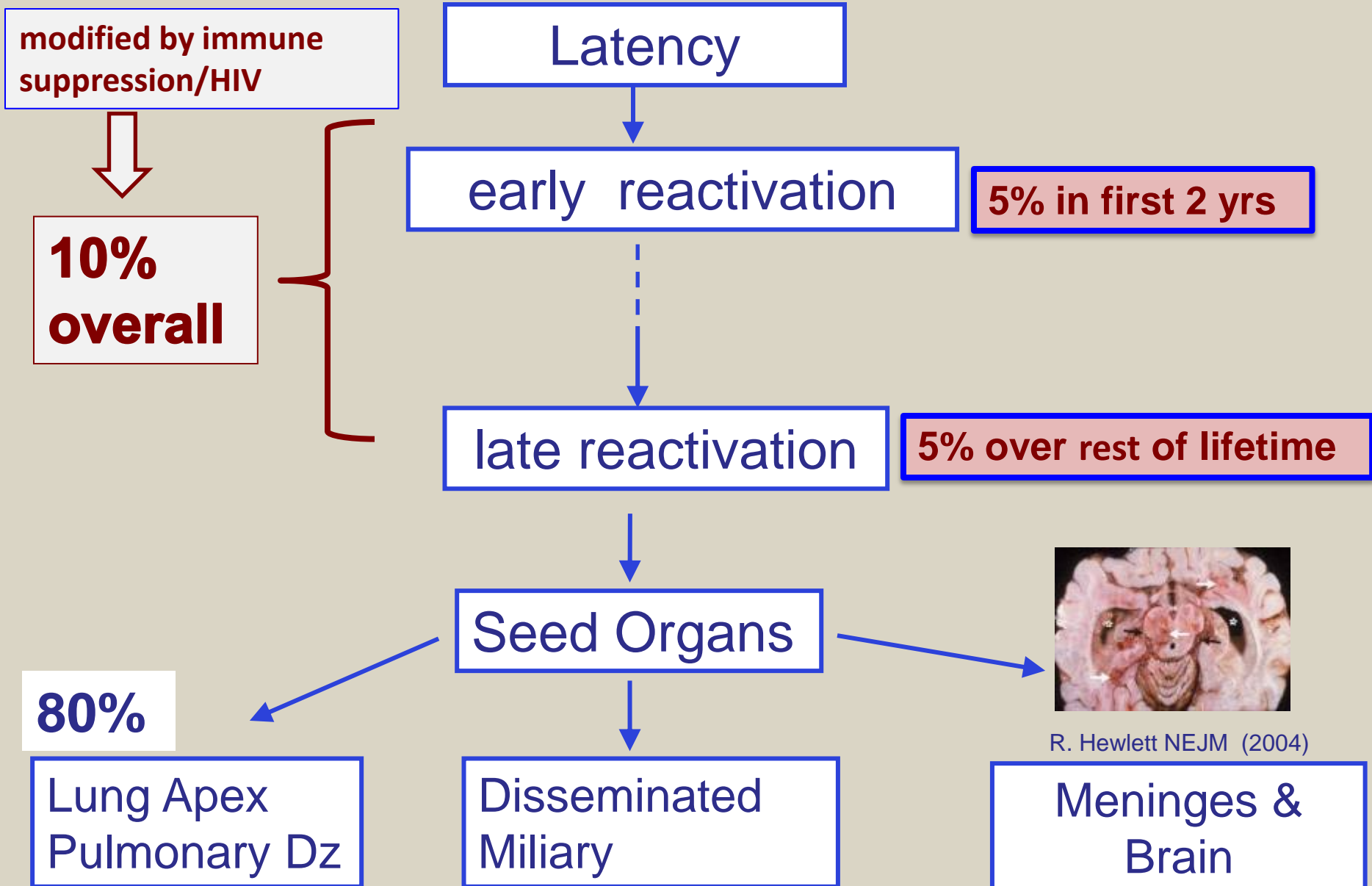


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**Q1:** what is the estimated rate of latent tuberculosis among foreign-born individuals in the United States?

1. 4%
2. 10%
3. 20%
4. 40%
5. 60%

# pathogenesis: reactivation

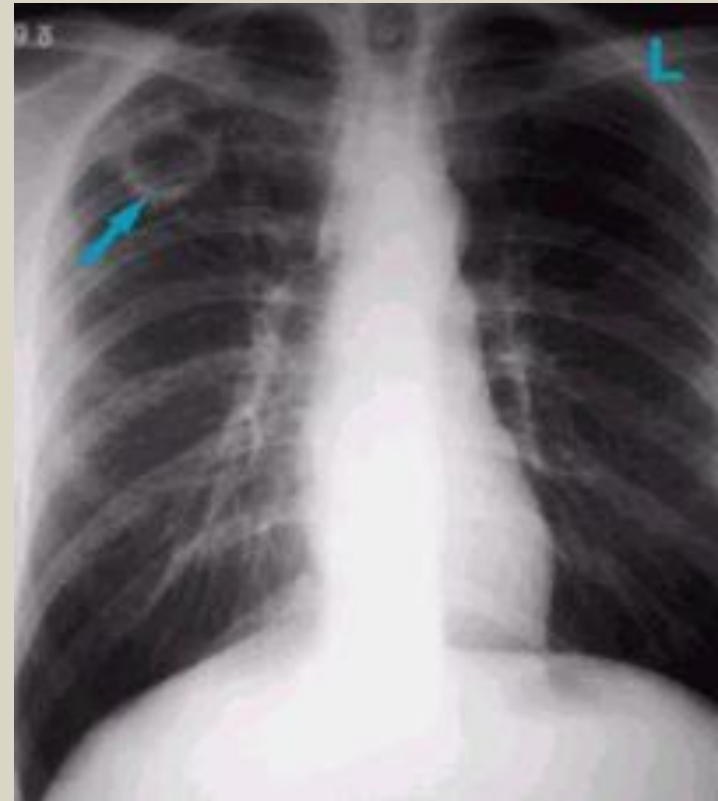




# reactivation of pulmonary tuberculosis

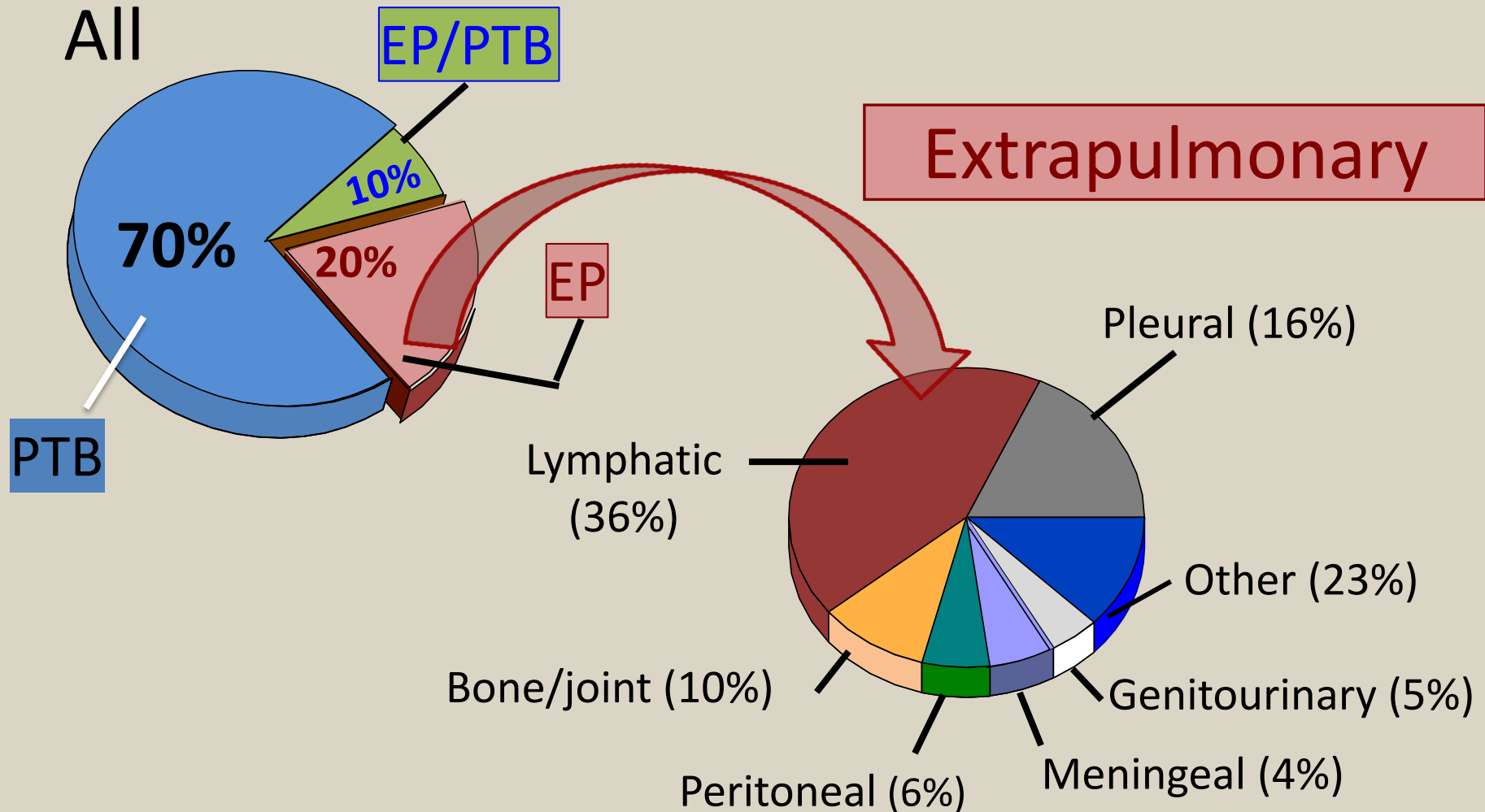
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classic reactivation  
tuberculosis with  
apical cavity  
("post primary  
tuberculosis")



# Extrapulmonary Sites of Disease

CDC Reported TB Cases, United States, 2016



# Extrapulmonary TB: effect of ethnicity

Dutch population subgroups	PTB (%)	EP TB (%)	Total (%)	<i>p</i>
<b>Total population</b>	8,216 (62.0)	5,042 (38.0)	13,258 (100)	
<b>Country of origin</b>				<0.01
Europe, central and eastern	395 (85)	70 (15)	465 (100)	
Turkey	449 (68)	212 (32)		
ethnic Dutch	3,800 (70)	1,882 (33)		
other	435 (67)	211 (33)	661 (100)	
Africa	789 (63)	456 (37)	1,267 (100)	
Morocco	758 (60)	509 (40)	1,692 (100)	
<b>Asia</b>	<b>895 (56)</b>	<b>705 (44)</b>	1,600 (100)	
<b>Somalia</b>	<b>695 (41)</b>	<b>997 (59)</b>	646 (100)	

# Extrapulmonary TB: effect of HIV

population subgroup, U.S.	OR, EPTB <sup>1</sup> vs PTB	<i>p</i>	OR, EPTB <sup>2</sup> vs PTB	<i>P</i>
<b>HIV-positive</b>	<b>1.1</b>	<0.001	<b>1.7</b>	<0.001
HIV-negative	ref	--	ref	--
<b>Foreign-born</b>	<b>1.5</b>	< 0.0001	--	--
U.S.-born	ref	--	ref	--

EPTB<sup>1</sup>, extrapulmonary TB, without concomitant pulmonary or disseminated TB. EPTB<sup>2</sup>, extrapulmonary TB with either concomitant pulmonary or disseminated TB

Adapted from Peto H (2009). Epidemiology of Extrapulmonary Tuberculosis in the United States, 1993–2006. *Clin Infect Dis* 49:1350–7

# Extrapulmonary TB: other risk factors

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- Tumor necrosis factor (TNF) blockers
- Corticosteroids
- Malignancy
- Female gender
- Nonsmoker
- Organ transplantation

# Case 1

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## MARCH 2016

- 53 year old Hmong male with hypertension, diabetes and renal failure. PPD negative: 10/29/2012
- Admitted to local hospital in March 2016 with dry cough x three months, shortness of breath and chest pain after dialysis earlier that day. No fever.
- Diagnosed with pulmonary emboli (blood clots in lung arteries)
- CT of chest: loculated, **moderate** pleural effusion on right
- Echocardiogram: severe diastolic dysfunction (stiff, noncompliant heart)
- Discharged home

# Case 1

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## Q2

- what percent of Wisconsin's non-US-born TB cases come from the Hmong community (ten year average: 1997-2006)
- what is the relative risk of TB in Hmong population compared to the white population in Wisconsin?

1. 10% | 17x higher
2. 18% | 143x higher
3. 40% | 17x higher
4. 65% | 143x higher
5. 85% | 17x higher

### Active TB rates per 100,000 population

<b>Hmong</b> in WI	<b>21.50</b>
Caucasian in WI	0.15
overall, WI	0.42
overall, U.S.	2.90

# Case 1

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**Q3:** In end-stage renal disease, what is sensitivity and specificity for tuberculin skin test for predicting progression to active disease?

**Caveat: anergy reported in 30-40% of dialysis patients**

Eleftheriadis T (2011). Hippokratia 15: 12-17

Woeltje KF (1998). Am J Kidney Dis. 31: 848-852

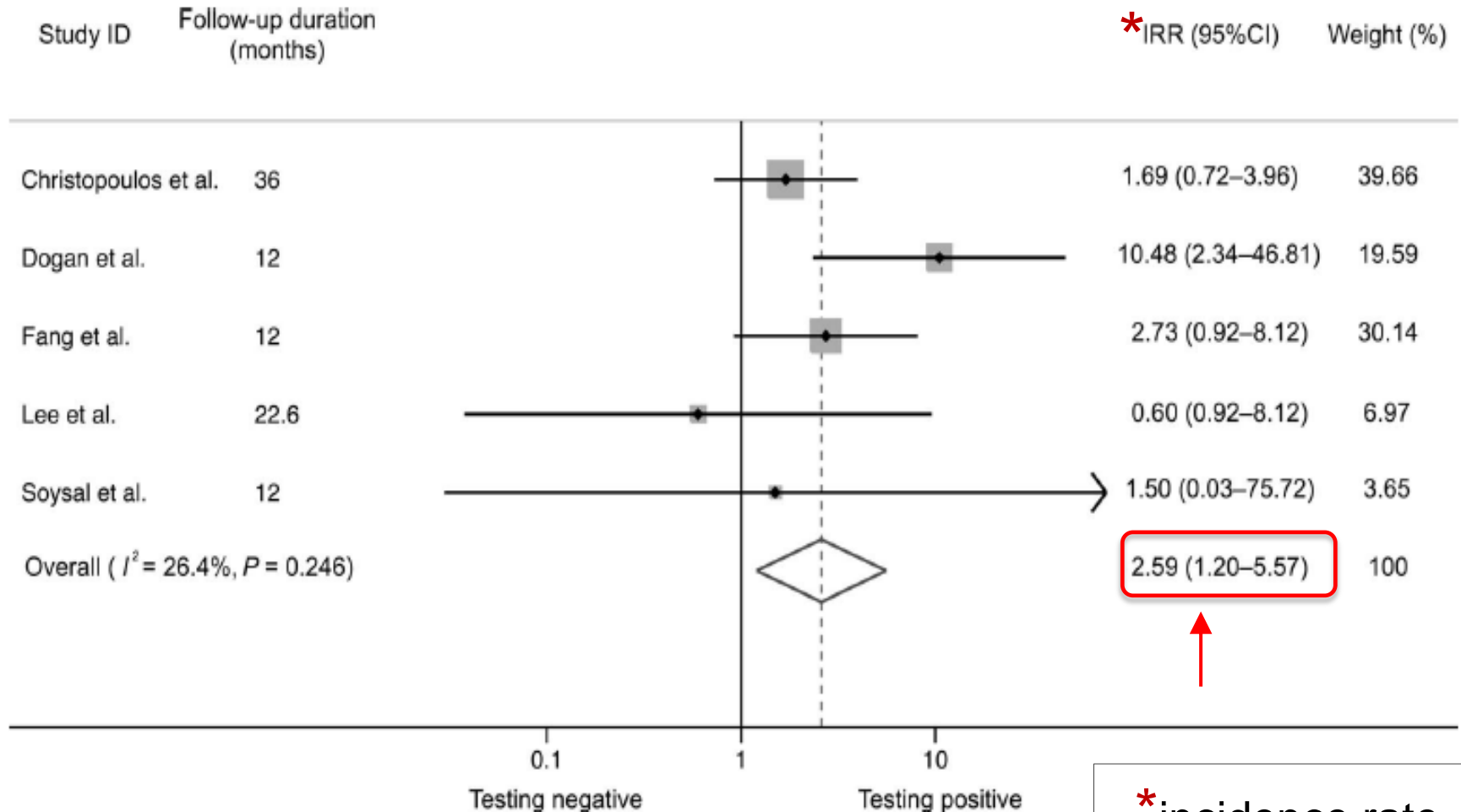
Fang HC (2002). Nephron. 91: 682-687

Poduval RD (2003). Clin Nephrol. 59: 436-40

Eleftheriadis T (2005). Am J Kidney Dis. 46: 706-712



# Does a positive TST predict future tuberculosis in dialysis patients?



\* incidence rate ratio of active TB

# Case 1, *cont'd*

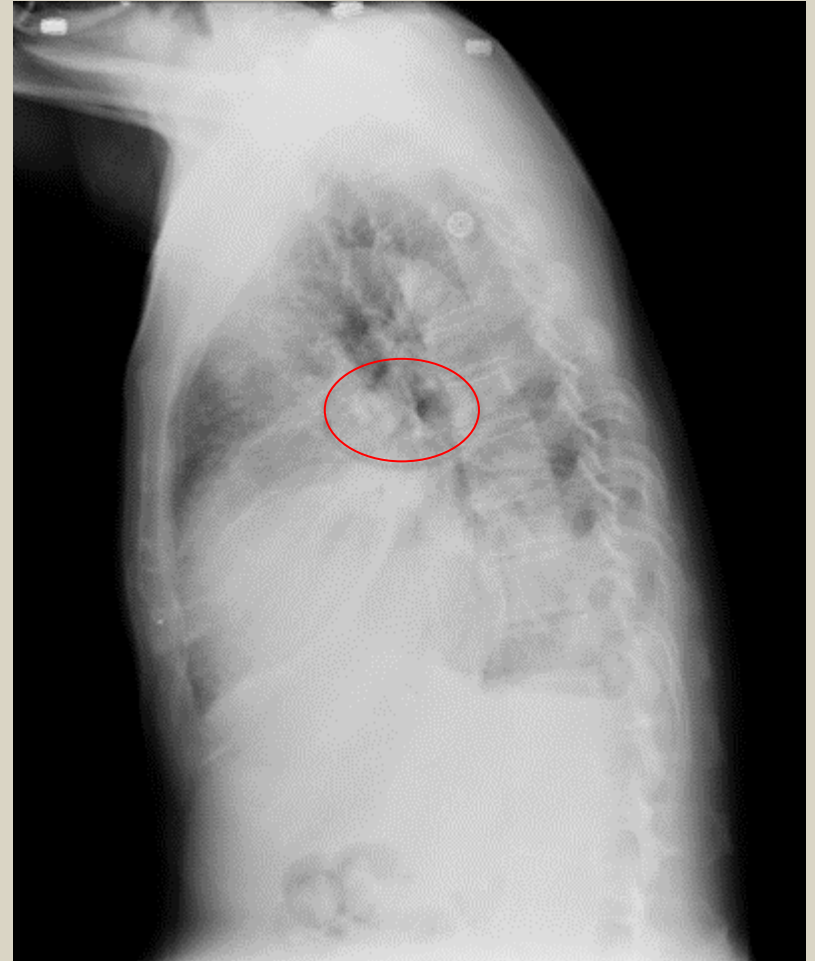
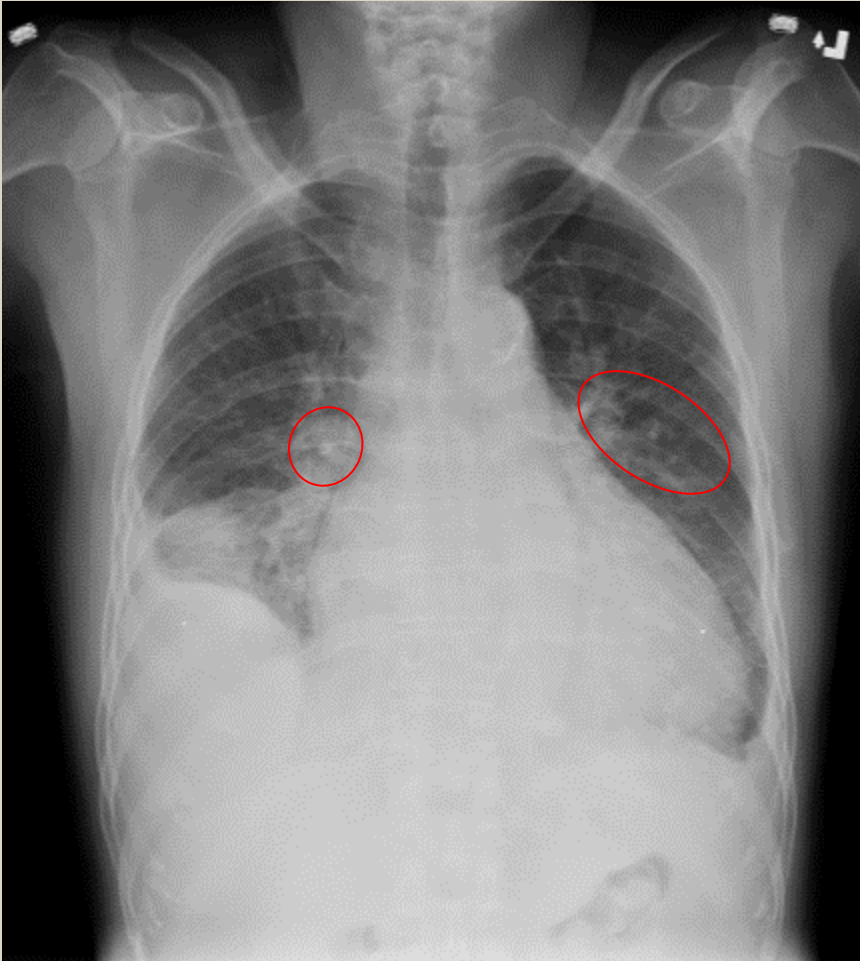
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## APRIL 2016

- 2 weeks later admitted with shortness of breath and
- hypoxia (87% on room air)
- CT shows
  - ❑ **large**, loculated pleural effusion involving right lung
  - ❑ patchy infiltrates in left lower lobe lobes. Enlarged heart.
  - ❑ **calcified granulomas within the mediastinum and hilum**
- 3 L of fluid removed at dialysis → breathing at baseline
- Discharged home (plans for outpatient thoracentesis)

# Case 1, *cont'd*

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# Case 1

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Q4: what TB risk factors does this patient have?

## Risk factor for Acquisition (latent TB infection)

1. Born in a TB-endemic country

## Risk Factor for Progression to Active Disease

2. Diabetes
3. End-stage renal disease
4. Signs of old TB on chest X ray, with no history of treatment

# Risk Factors for TB Progression, 1

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RISK FACTOR	RR
close contact with person with active TB	6.1
old, healed TB on imaging, not treated	5.2
≥ 15 mg prednisone per day	2.8
underweight (>10%)	1.6
smoking	1.5

# Risk Factors for TB Progression, 2

Risk Factor	Relative Risk*
Head and Neck Cancer	37.0
Silicosis	30.0
Jejunioileal bypass	27.0 – 63.0
pregnancy	26.0
Kidney Transplant	20.0 – 74.0
TNF- $\alpha$ blockade	2.0 (RR)- 41.7 [SIR]
Heart Transplant	16.0
<b>Chronic Renal Failure</b>	<b>2.3 - 10.0</b>
Cirrhosis	3.5 [HR]
HIV	3.1 – 26.0
Gastrectomy	2.0 – 5.0
<b>Diabetes Mellitus</b>	<b>1.7 – 4.1</b>

[Am Rev Respir Dis](#). 1991 Mar;143(3):501-4 (RR=26, pregnant females); [Int J Epidemiol](#). 1993 Dec;22(6):1159-65 (RR=8.3); [Barber et al. Medicine \(Baltimore\)](#). 1990 Nov;69(6):375-83 (9 patients and lit review: can present with mycobacteremia); [Tuber Lung Dis](#). 1994 Jun;75(3):220-6. (RR=3.1); [Tuber Lung Dis](#). 1995 Feb;76(1):11-6. (RR=11.5) Cote d'Ivoire; [AIDS](#). 1996 Mar;10(3):299-309. (RR=7.1; age and sex adjusted); [Trans R Soc Trop Med Hyg](#). 2000 Sep-Oct;94(5):500-3 (RR= 7.1); [Int J Epidemiol](#). 1998 Apr;27(2):289-95 (RR=9.1 for CD4 count <200 vs.  $\geq$  500) patients with HIV; [Med Pregl](#). 2004;57 Suppl 1:53-8.  $\rightarrow$  most estimates in slide (nonHIV) come from this abstract; cirrhosis risk: Lin YT [Am J Epidemiol](#). 2014 Jul 1;180(1):103-10. [hazard ratio reported]

# Case 1: pleural fluid analysis (4/28/2016)

component	Normal range	Patient value
Glucose	$\geq 60$ mg/dL	67
LDH	$\leq 120^a$	2,535
PROTEIN	$\leq 4.25^b$	5.4
CYTOLOGY	no atypical cells	No cancerous cells
pH	$> 7.30$	<b>Not done</b>
Adenosine deaminase	$< 40$ IU/L <sup>c</sup>	<b>Not done</b>

<sup>a</sup> 60% of upper limit of normal serum value [200])  
<sup>b</sup> 50% upper limit of normal serum value [8.5])  
<sup>c</sup> Aggarwal AN (2016). *Int J Tuberc Lung Dis.* 20(10):1386.

- Bacterial gram stain and culture: negative
- Fungal smear and culture: negative
- AFB smear and culture: negative

# Case 1

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**Q5:** which tissue has the lowest sensitivity for detection of AFB organisms on smear?

1. Pleural fluid
2. Pleural tissue
3. Cerebrospinal fluid
4. Pericardial fluid
5. Peritoneal fluid

1. Pleural fluid: 0-10%
2. Pleural tissue: 14-39%
3. CSF: 10-30%
4. Pericardial fluid: 0-42%
5. Peritoneal fluid: <5%

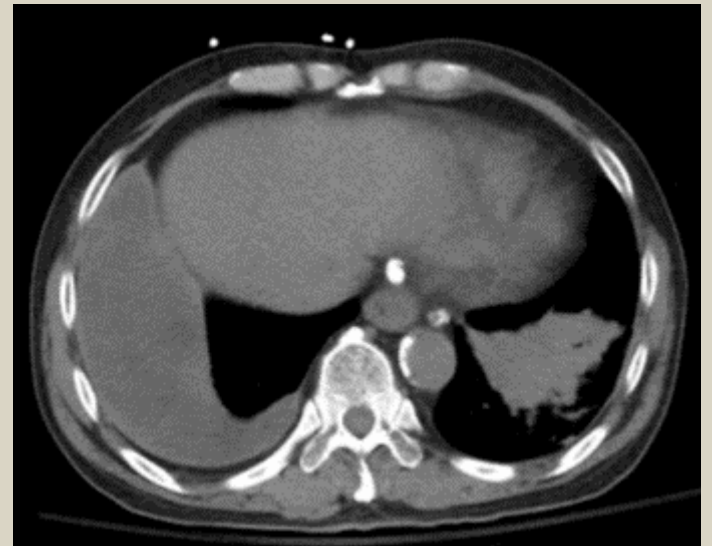
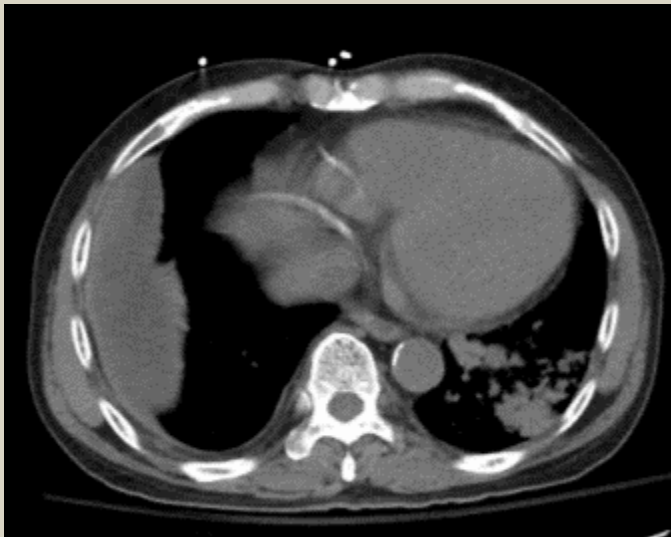


## JUNE 2016

renal transplant June 4 → immune suppression  
(basilixumab, belatacept, mycophenolate, tacrolimus)

## SEPTEMBER 2016

- Admitted for trauma after motor vehicle accident  
9/15/2016

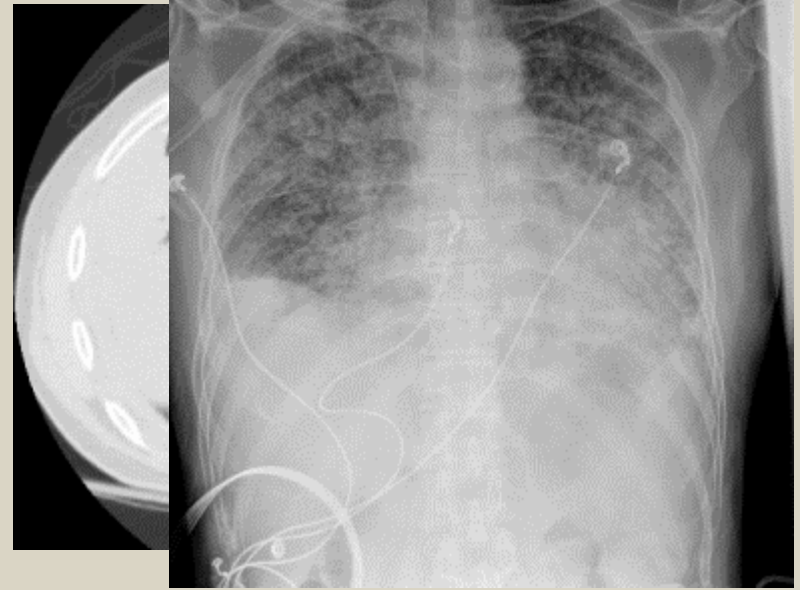
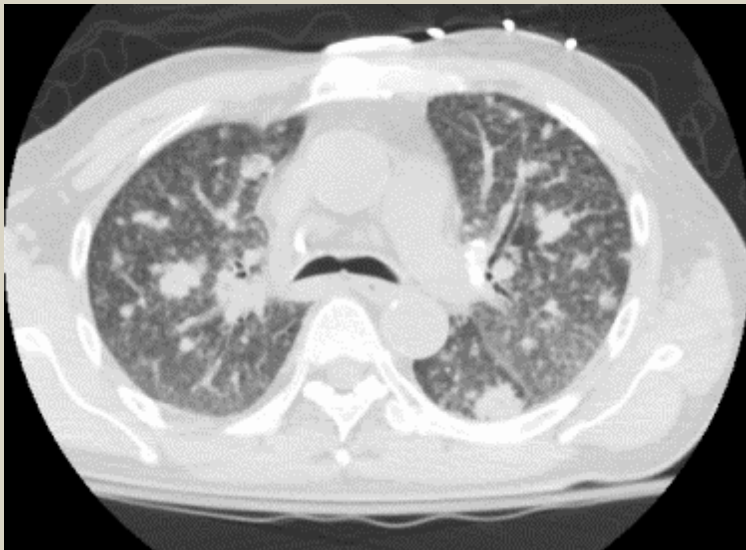


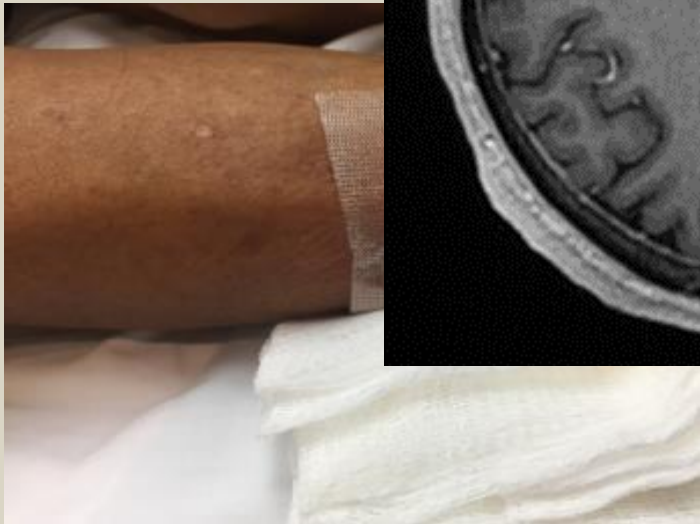
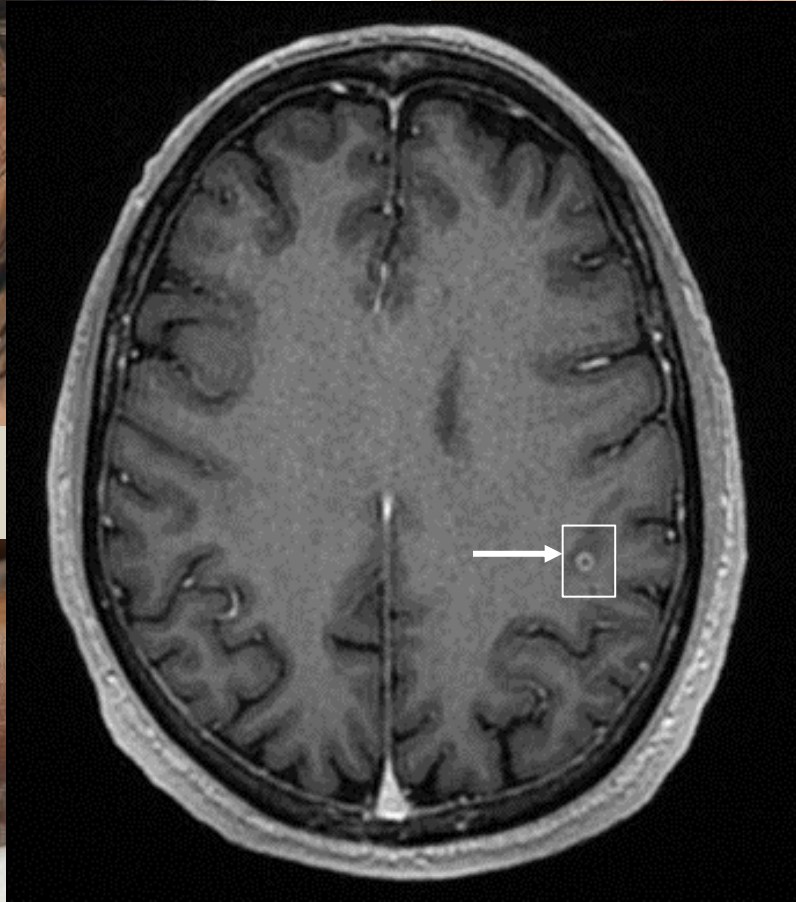
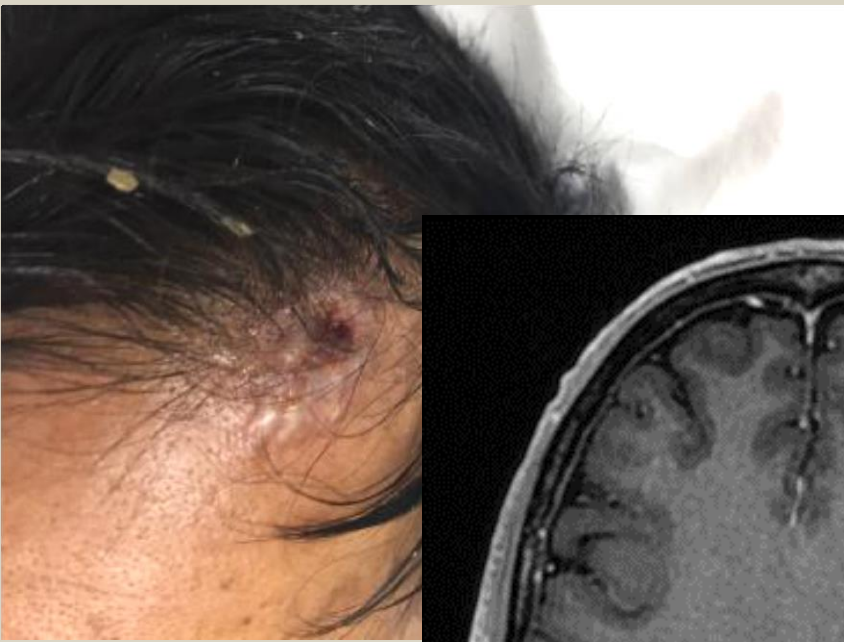
# Case 1

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## OCTOBER 2016

- Re-admitted with fever and diagnosed with ...pulmonary and disseminated blastomycosis
- Involvement of skin, CNS, knee (infected joint)
- Placed on amphotericin → voriconazole





# Case 1

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## Interferon gamma release assay

10/14/2016

test component	normal range	patient values
TB minus NIL	$\leq 0.34$ IU/mL	0.01
MITOGEN minus NIL	--	1.44
NIL	$\leq 8.00$ IU/mL	0.05

Interpretation: ***NEGATIVE***

## Case 1

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**Q6:** Does a very high interferon-gamma level on the IGRA predict greater likelihood of progression to active disease?

1. Yes
2. No
3. Maybe

At the individual level, not very well. However, two recent studies suggest that higher IFN-gamma levels *might be* associated with greater risk of progression to active tuberculosis

# Do interferon-gamma levels predict future active disease?

	N	Cases	Incidence (95% CI)	IRR (95% CI)	p value
<b>Revised case definition 1</b>					
<0.35 IU/mL	2232	16	0.7 (0.4-1.1)	Ref	Ref
0.35-4.00 IU/mL	79	2	2.5 (0.4-9.4)	3.7 (0.4-15.8)	0.23
>4.00 IU/mL	63	10	28.0 (14.9-45.7)	42.5* (17.2-99.7)	<0.0001
<b>Culture or Xpert positive</b>					
<0.35 IU/mL	2232	11	0.5 (0.2-0.8)	Ref	Ref
0.35-4.00 IU/mL	79	2	2.5 (0.4-9.4)	5.4 (0.6-24.8)	0.13
>4.00 IU/mL	63	7	19.6 (8.9-36.8)	43.3† (14.2-122.3)	<0.0001

Incidence reported in cases per 100 person-years. IRR=incidence rate ratio. Ref=reference. \*IRR of higher than 4.00 vs 0.35-4.00 for revised case definition 1: 11.4 (95% CI 2.4-107.2),  $p<0.000047$ . †IRR of higher than 4.00 vs 0.35-4.00 for culture or Xpert positive: 8.0 (95% CI 1.5-78.8);  $p=0.0094$ .

**Table 1: Incidence of tuberculosis (cases per 100 person-years) according to day 336 QuantiFERON interferon- $\gamma$  value by case definition**

ORIGINAL ARTICLE

## Stratification by interferon- $\gamma$ release assay level predicts risk of incident TB

Brita Askeland Winje,<sup>1</sup> Richard White,<sup>2</sup> Heidi Syre,<sup>3</sup> Dag Harald Skutlaberg,<sup>4,5</sup> Fredrik Oftung,<sup>6</sup> Anne Torunn Mengshoel,<sup>7</sup> Hege Salvesen Blix,<sup>8</sup> Arne Broch Brantsæter,<sup>9,10</sup> Ellen Kristine Holter,<sup>11</sup> Nina Handal,<sup>12</sup> Gunnar Skov Simonsen,<sup>13,14</sup> Jan Egil Afset,<sup>15,16</sup> Anne Marte Bakken Kran<sup>11,17</sup>

### LOW INCIDENCE SETTING

- population-based, prospective cohort of 44, 875 Norwegians
- QFT results linked with diagnosis and LTBI prescription data from national registries
- outcome: TB diagnosis >3 months after QFT testing
- Only tests with IFN- $\gamma$  levels <10.0 IU/mL were included (levels >10 IU not quantified by lab)

# Do interferon-gamma levels predict active disease?

**Table 2** Univariate and multivariable time-dependent Cox regression results for incident TB (n=252) by interferon- $\gamma$  (IFN- $\gamma$ ) level, age group, country of origin and medical risk factors (n=48 121) QuantiFERON TB Gold (QFT) results for 44 006 individuals

Covariate	Tests (n)	TB events <sup>a</sup> *	Years <sup>b</sup> †	c HR	a HR	P values	95% CI
IFN- $\gamma$ level (IU/mL) <sup>c</sup> ‡						<0.001§	
Negative (<0.35)	37 253	29	1 33 647	1 (ref)	1 (ref)		
Low positive (0.35 to<1.0)	2488	16	6995	10.7	8.8	<0.001	4.66 to 16.50
Medium positive (1.0 to<4.0)	2971	50	9087	25.1	19.2	<0.001	11.62 to 31.60
High positive ( $\geq$ 4.0)	5373	157	16 233	43.0	31.3	<0.001	19.82 to 49.53

- 90% of individuals had only a single test
- no data on whether positive test represented conversions
- 25% of Norwegian-born were receiving immune suppression
- very low levels of HIV (1-3%)
- foreign-born: 43%



# Summary: Do interferon- $\gamma$ levels predict active disease?

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1. At the population level, maybe
2. at the individual level, magnitude of the IFN- $\gamma$  response has poor positive predictive value for active TB
  - meta-analysis: PPV 2.7%
  - TB contacts: PPV 2.4% – 28.6%
  - immunocompromised: PPV 7%–8%
3. None of this applies to patients with end-stage renal disease

1. Diel R. Chest 2012;142:63–75 (meta-analysis)
2. Zellweger JP. Am J Respir Crit Care Med 2015; 191:1176–84 (low-incidence)
3. Hermansen TS. Thorax 2016;71:652–8 (low-incidence)
4. Diel R. Am J Respir Crit Care Med 2011;183:88–95 (TB contacts)
5. Sloot R. Am J Respir Crit Care Med 2014;190:1044–52 (TB contacts)
6. Aichelburg MC. Clinical Infectious Diseases 2009;48:954–62 (IC host)

# Case 1

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DECEMBER 2016-JUNE 2017: IMPROVED

AUGUST 2017

- Skin lesions healed; still on voriconazole
- Temperature noted

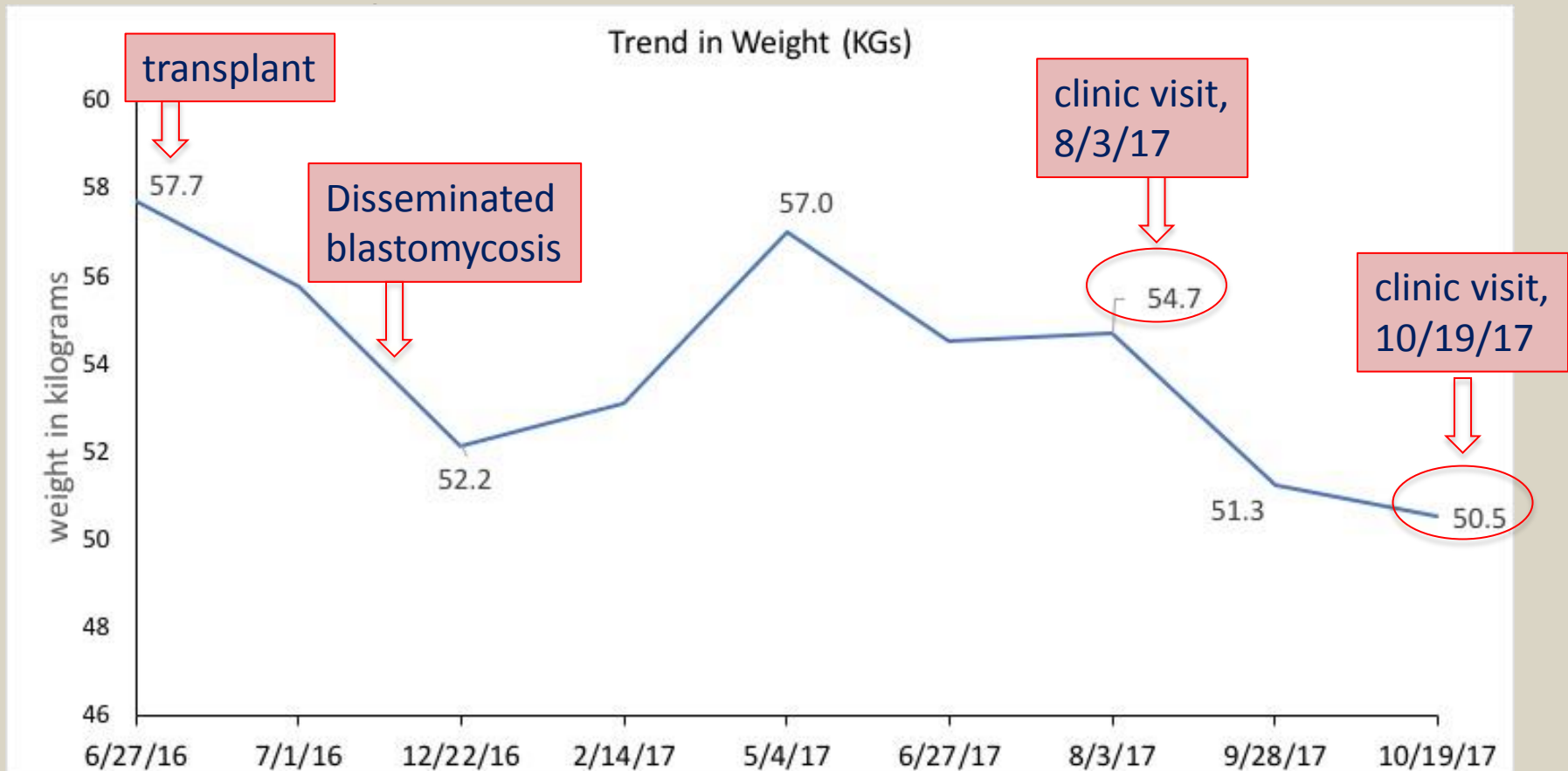


ng well.”

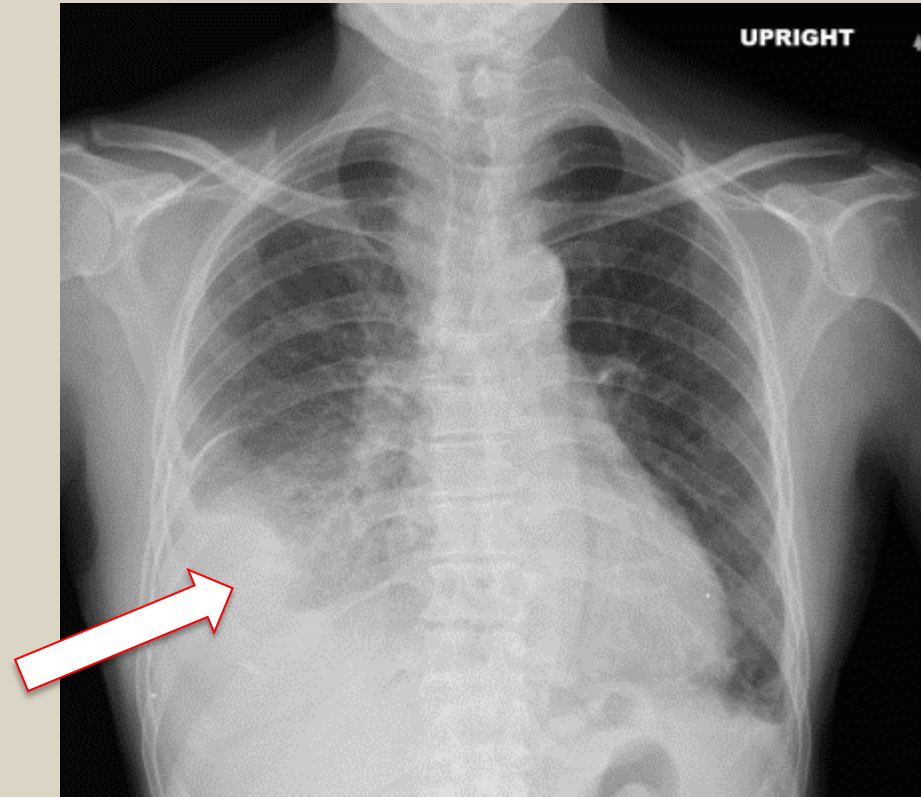


# OCTOBER 2017

- Followed up again in ID clinic on
- Temperature noted again to be **99.4 °F**.



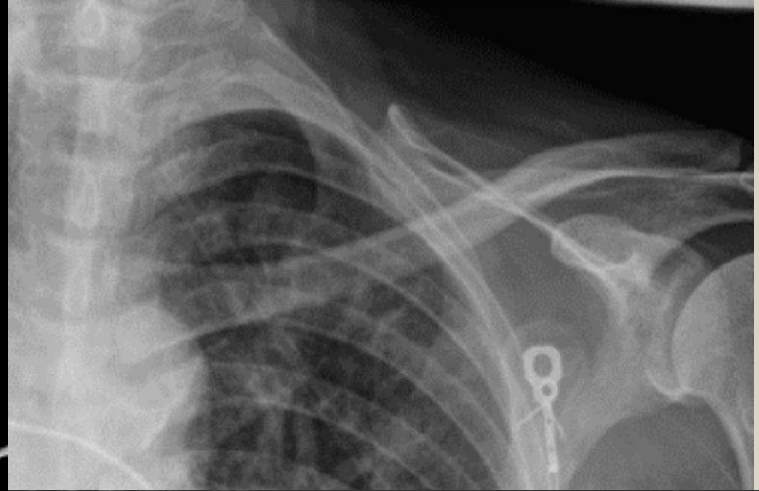
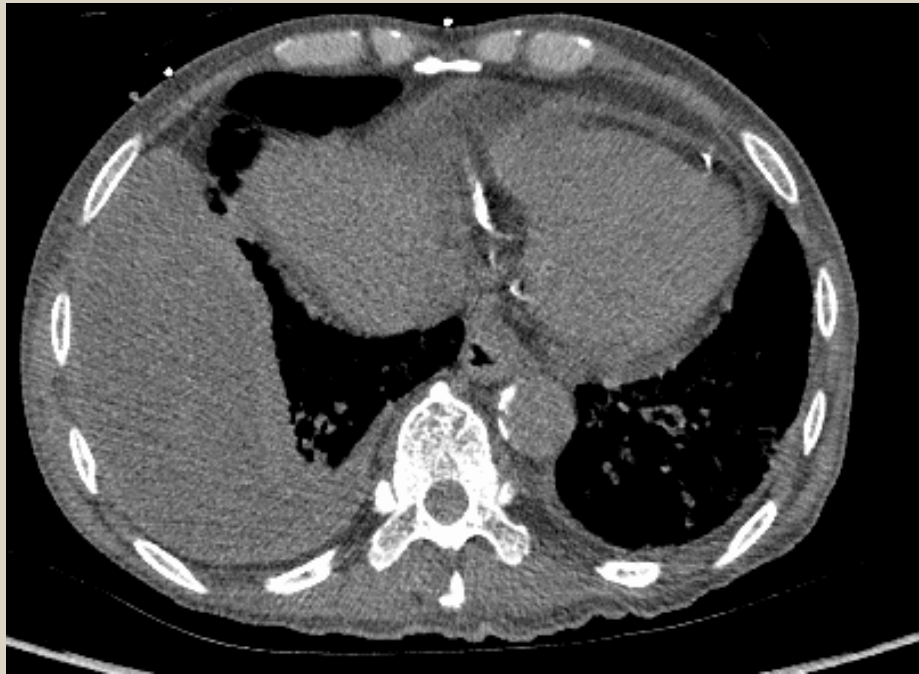
- Absence of breath sounds right lower lung fields.
- ID clinician noted prior **history of effusion, since March 2016**. Became concerned about reactivation of latent TB.
- Patient refused CT and went home.



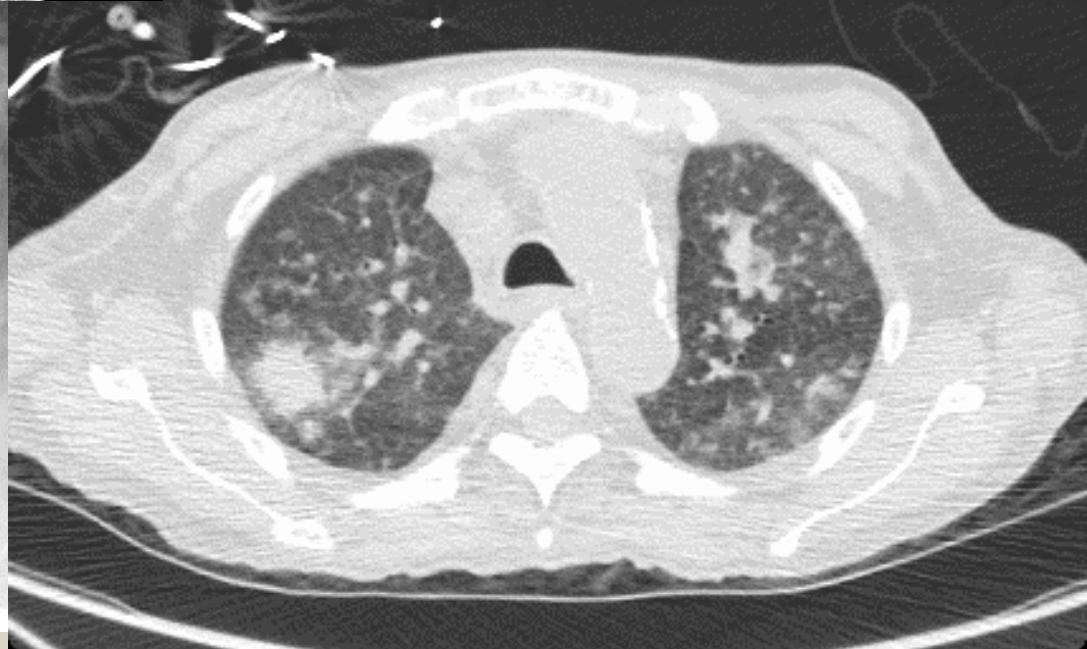
- 7 days later, admitted to outside (local) hospital
- Felt unwell, burning sensation all over body. Temp 97.8°F. Glucose in 600s. Insulin increased and discharged.
- ID clinician spoke to inpatient hospitalist to request chest CT and thoracentesis. This was not done.

## NOVEMBER 2017

- Admitted again to local hospital, with complaint of increasing weakness, intermittent diarrhea, intermittent fevers, dehydration, body aches. Temp 96.5°F. Hydrated and discharged.



to



# Case 1

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**Q7:** what TB diagnostic studies can be sent on bodily fluids, incl pleural fluid?

1. Xpert MTB/RIF and culture
2. Culture only
3. Free interferon-gamma level
4. IL-1 $\beta$
5. Lipoarabinomannan ←urine/blood only
6. Adenosine de-aminase

# Case 1

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- Thoracentesis: Pleural fluid culture: AFB smear+, MTD probe positive, culture positive (drug susceptible)
- Blood cultures: MTB culture-positive (drug susceptible)
- Sputum cultures: > 9 AFB stain , MTB probe-positive, MTB culture-positive (drug susceptible)



# Case 1

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## Interferon gamma release assay

12/16/2017

test component	normal range	patient values
TB minus NIL	$\leq 0.34$ IU/mL	0.73
MITOGEN minus NIL	--	0.65
NIL	$\leq 8.00$ IU/mL	0.59

Interpretation: ***POSITIVE***

# Case 1

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- Taken to OR 12/18/2017 for decortication of right lung, bronchoscopy, and mediastinal lymph node biopsy
  - **Pathology of right pleura:** suppurative inflammation, fibrosis and **non-necrotizing granulomas**. AFB and GMS stain negative
  - **Stain/culture of pleural tissue:** **>9 AFB, MTB culture-positive**
  - **Pathology of mediastinal lymph node:** **necrotizing and non-necrotizing granulomas**.
  - Stain/culture of Lymph node: Stain **positive for acid-fast bacilli**. **AFB culture positive**
  - **Bronchoalveolar lavage:** Multiple black submucosal endobronchial lesions noted. +broad-based yeast. **1-9 AFB, MTB culture-positive**

# Case 1

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- Presumed CSF involvement

<b>CSF</b>	<b>Normal Range</b>	<b>Patient Data</b>
nucleated cells	0 - 5 /uL	73
differential		97% lymphocytes
red blood cells	0 - 0 /uL	3
GLUCOSE	40 - 80 mg/dL	97
PROTEIN	15 - 40 mg/dL	266

- CSF AFB smear negative, culture negative
- **diagnosis: disseminated TB with pulmonary and extrapulmonary involvement**

# Notable features of case

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1. overlooked risk factor for infection: birth in Laos
  2. multiple risk factors for progression also overlooked: diabetes, renal failure, radiographic evidence of old, untreated TB and immune suppression
  3. neither active TB nor LTBI was aggressively investigated prior to transplant
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4. **Diagnostic delay**
  5. **Atypical presentation** (fever was intermittent; weight loss, anorexia, body pain, persistent loculated effusion were prominent)
  6. **extrapulmonary and disseminated disease**

# Extrapulmonary tuberculosis: clinical spectrum

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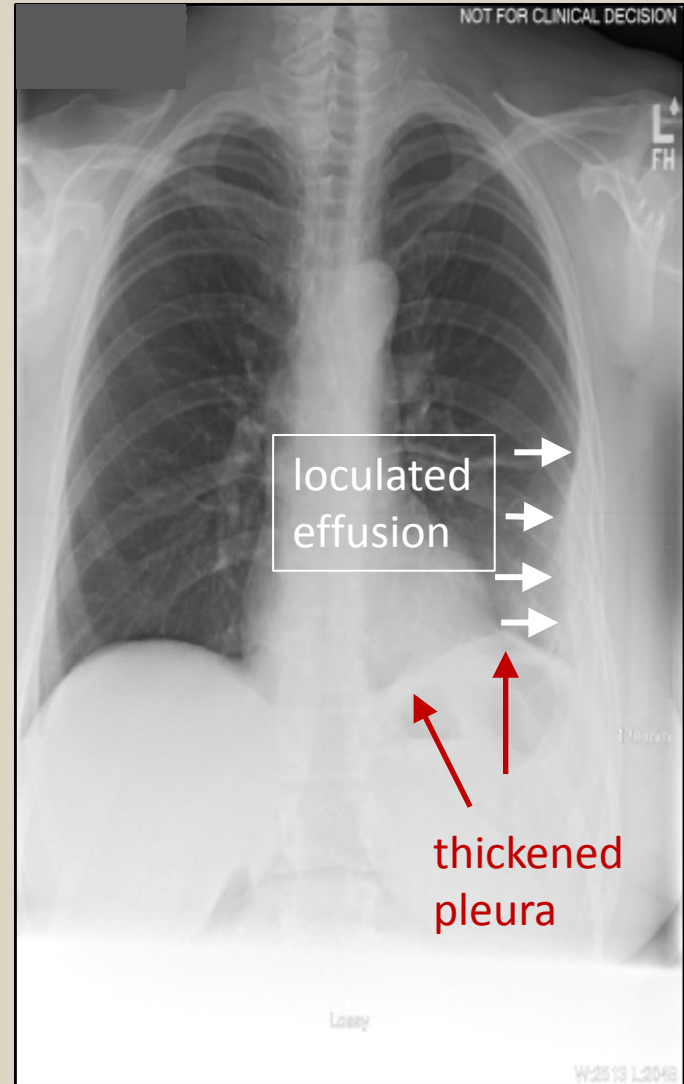
# pleural tuberculosis

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# pleural TB

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# lymphadenitis

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43 yo male with cervical LN swelling x 4 wks. No fever, cough.

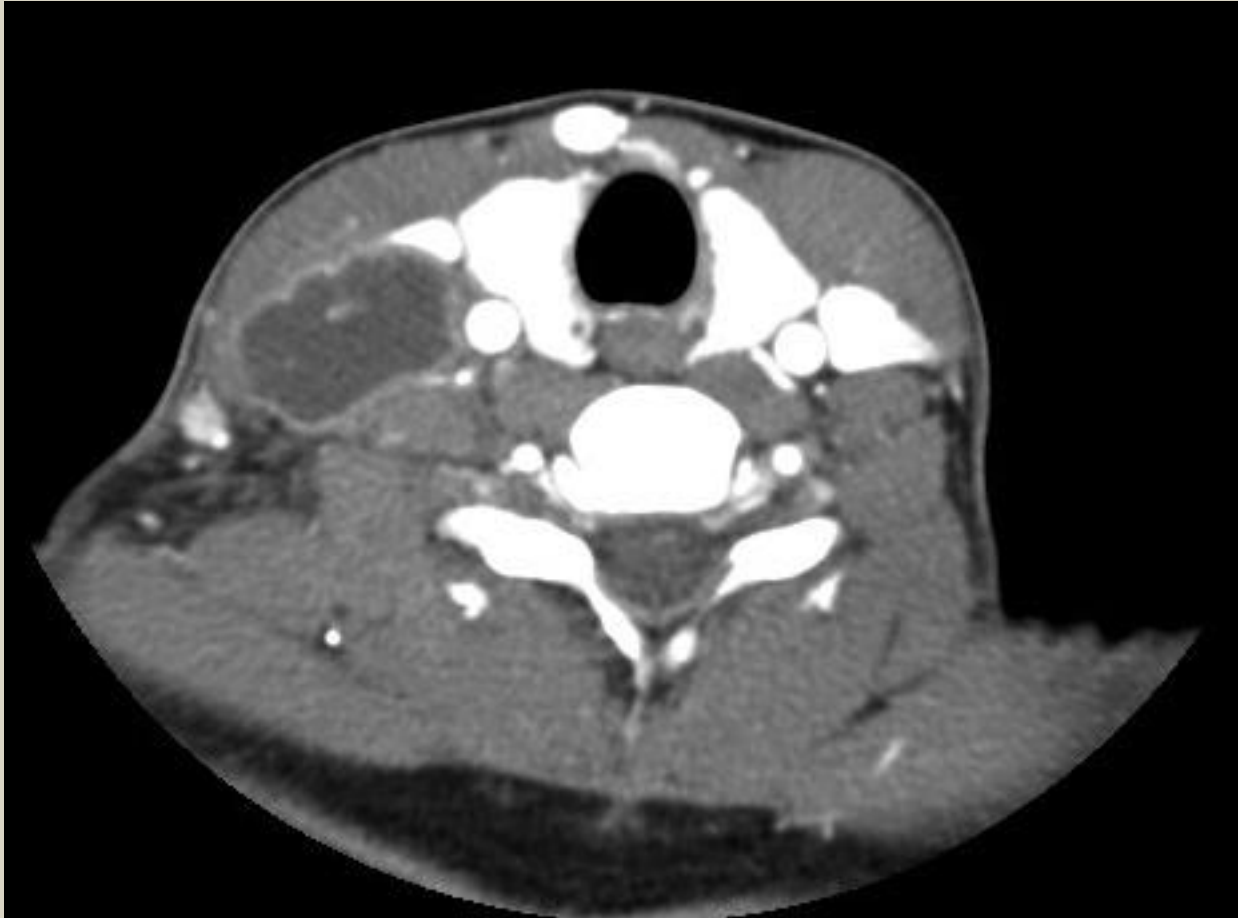
Exposure: No TB contacts. Born in Afghanistan

exam: Unilateral enlarged, non-tender, sub-  
mandibular LN.

PPD 10 mm. CXR: NL

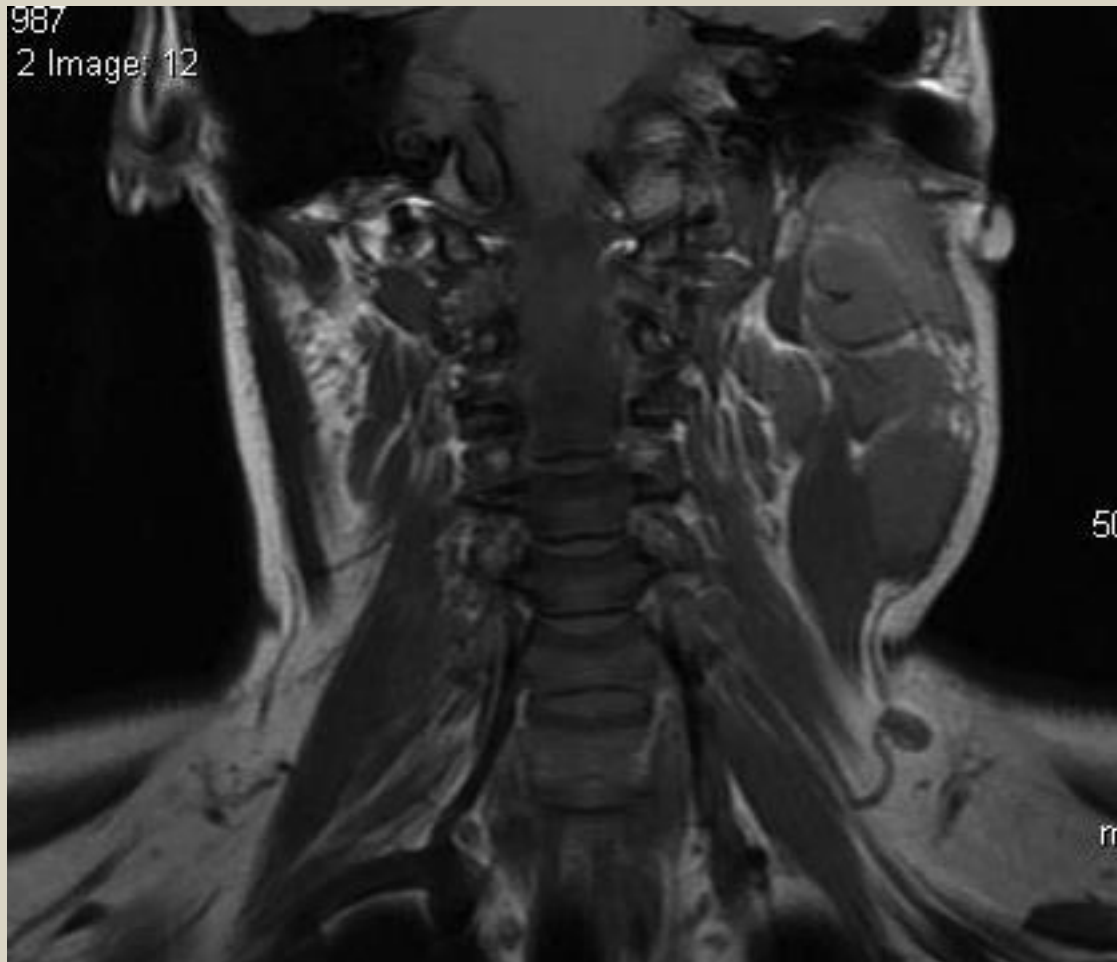






# scrofula

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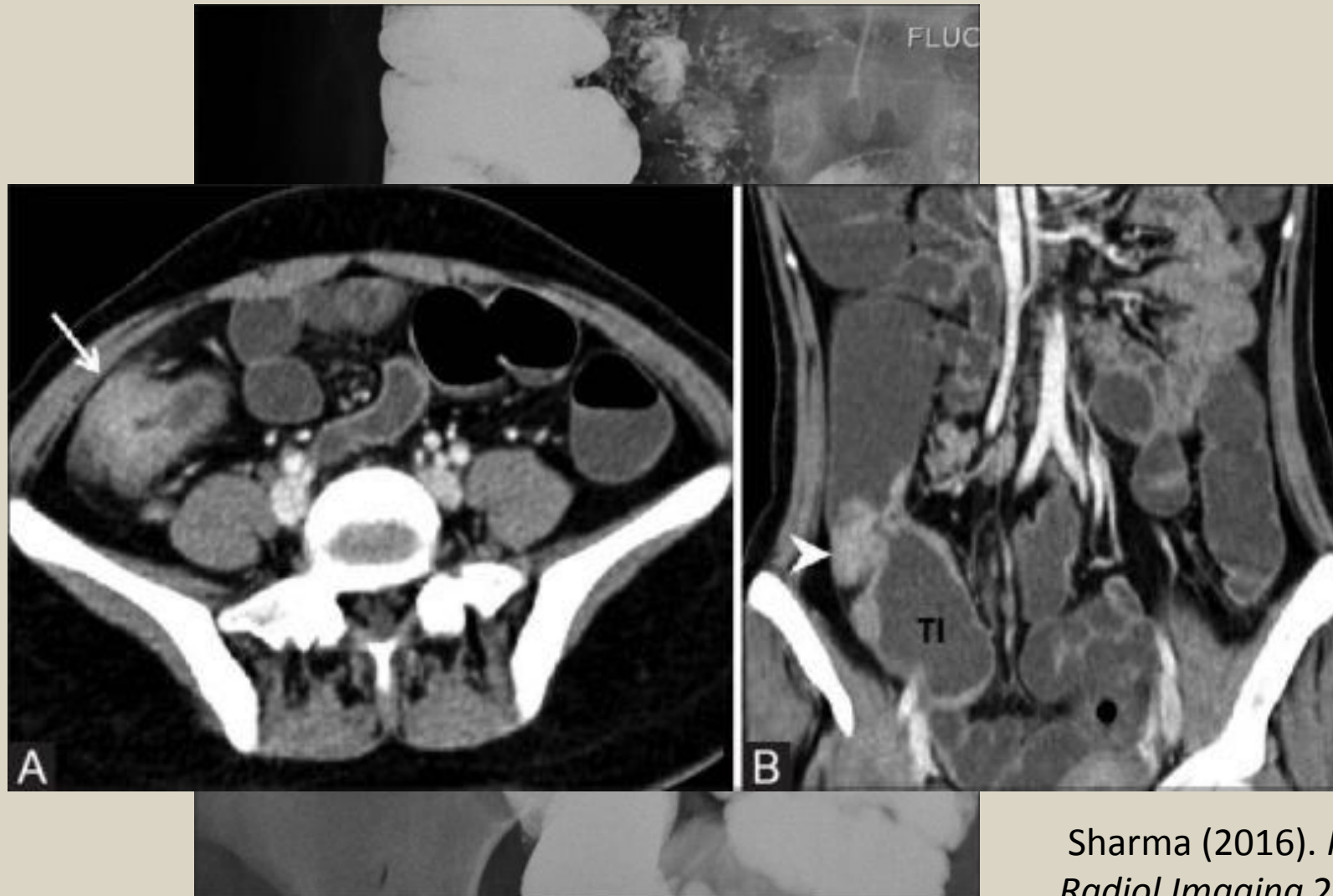


# scrofula

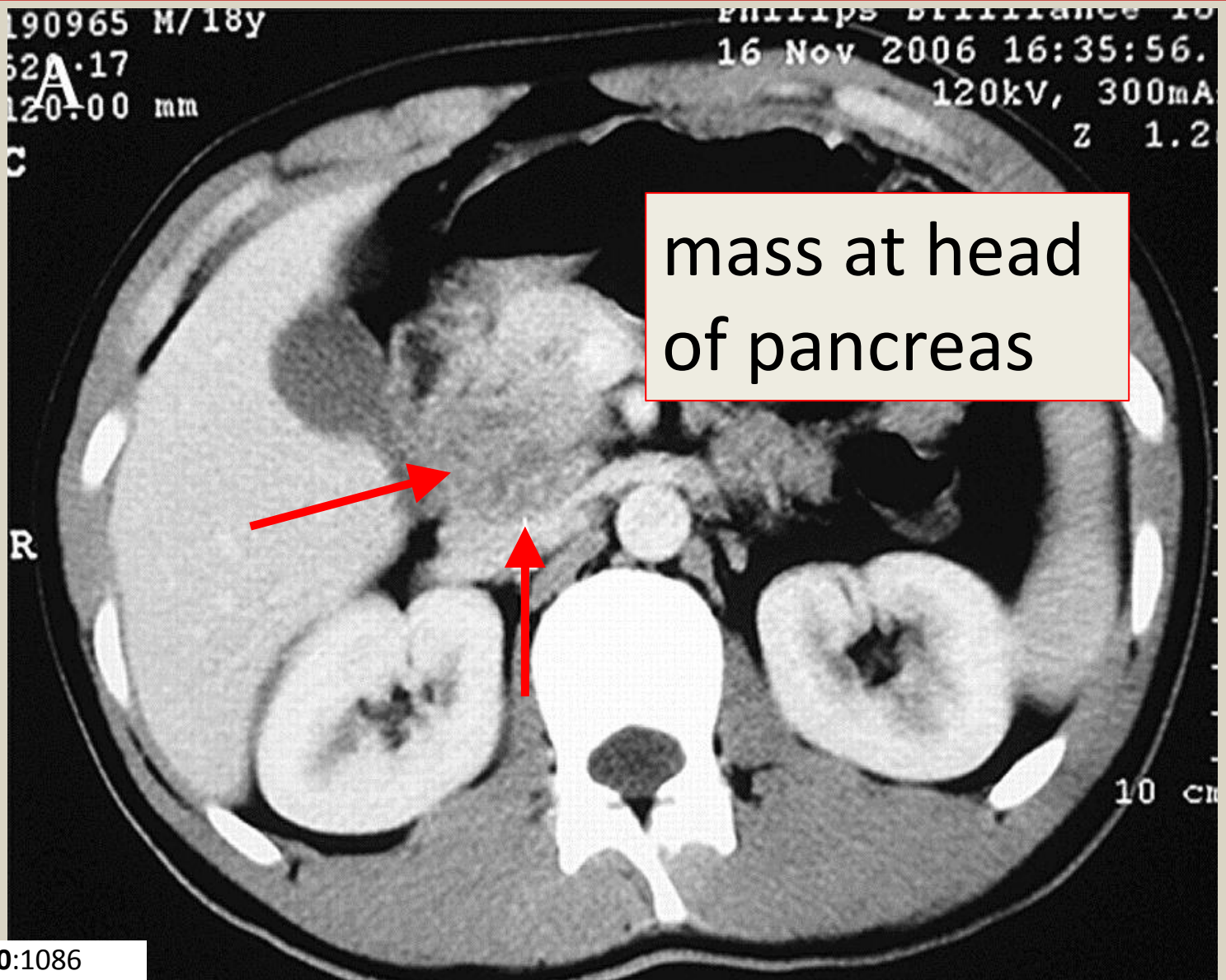
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# GI TB: often involves ileo-cecal junction, mimicking inflammatory bowel disease

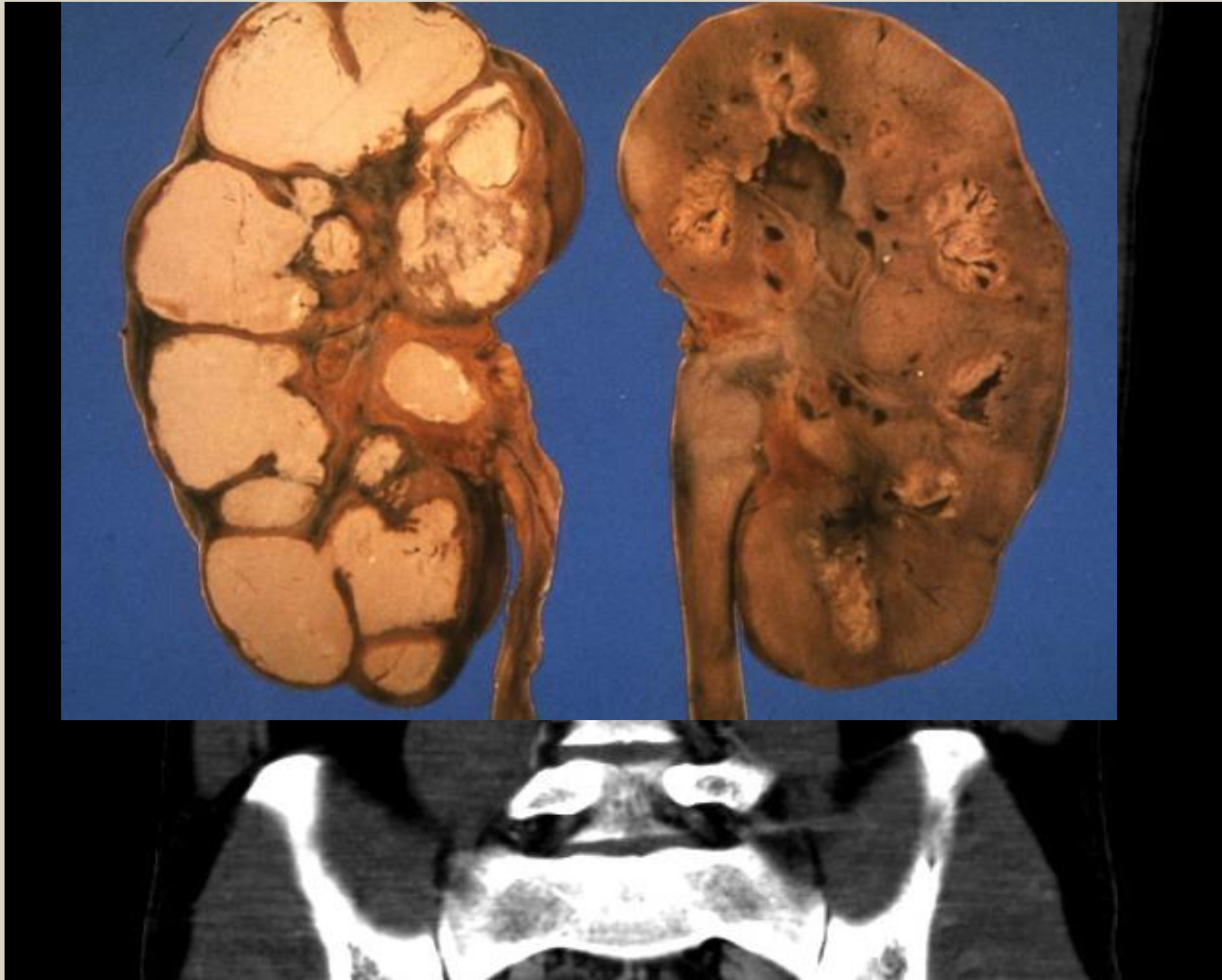


# pancreatic tuberculosis



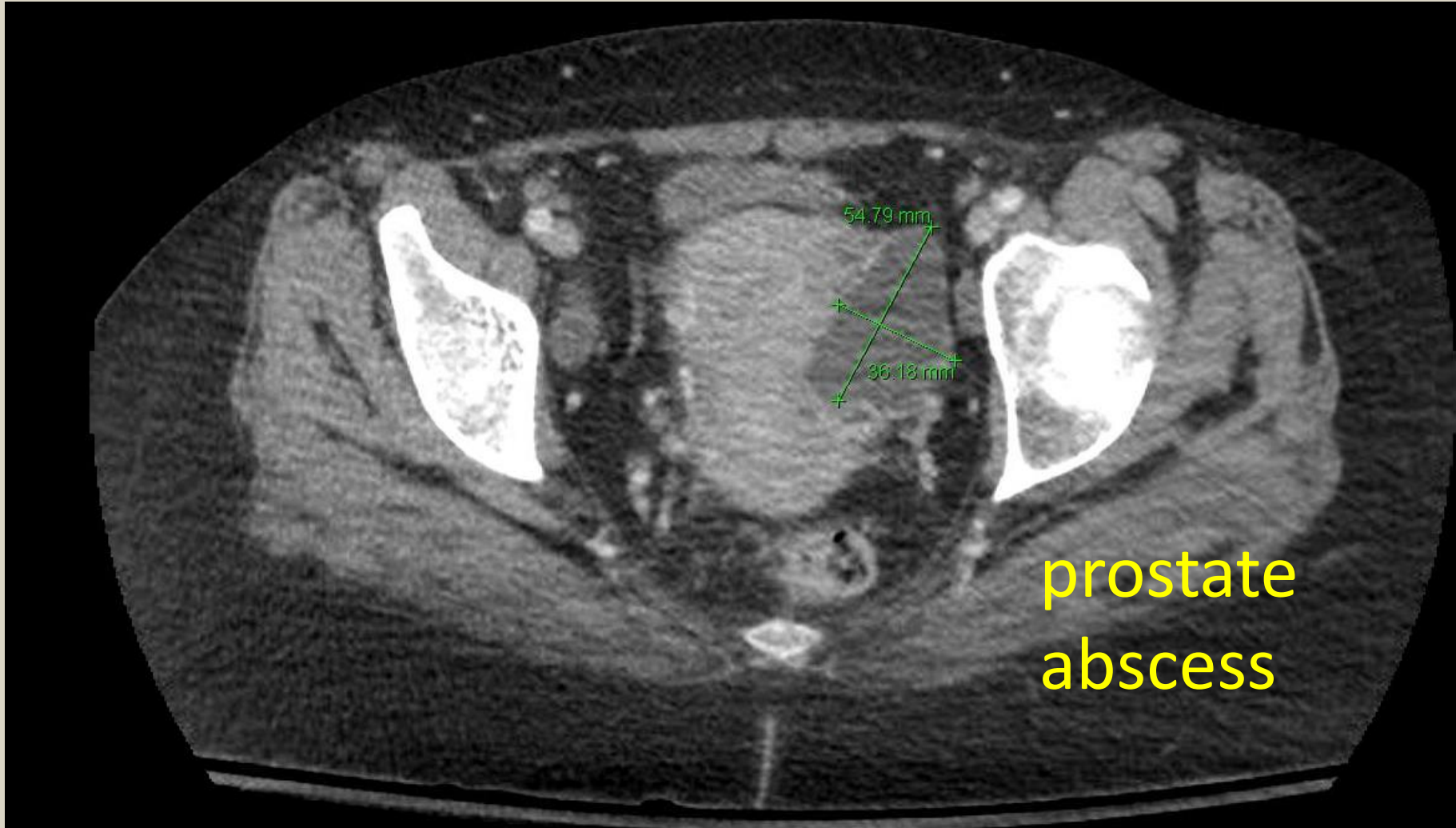
# Genitourinary tuberculosis

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# Genitourinary tuberculosis

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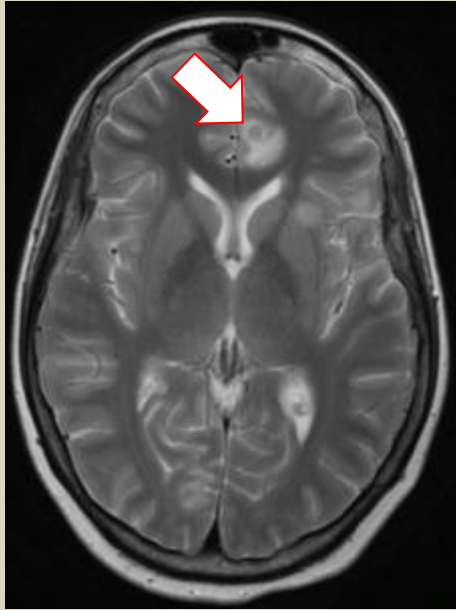
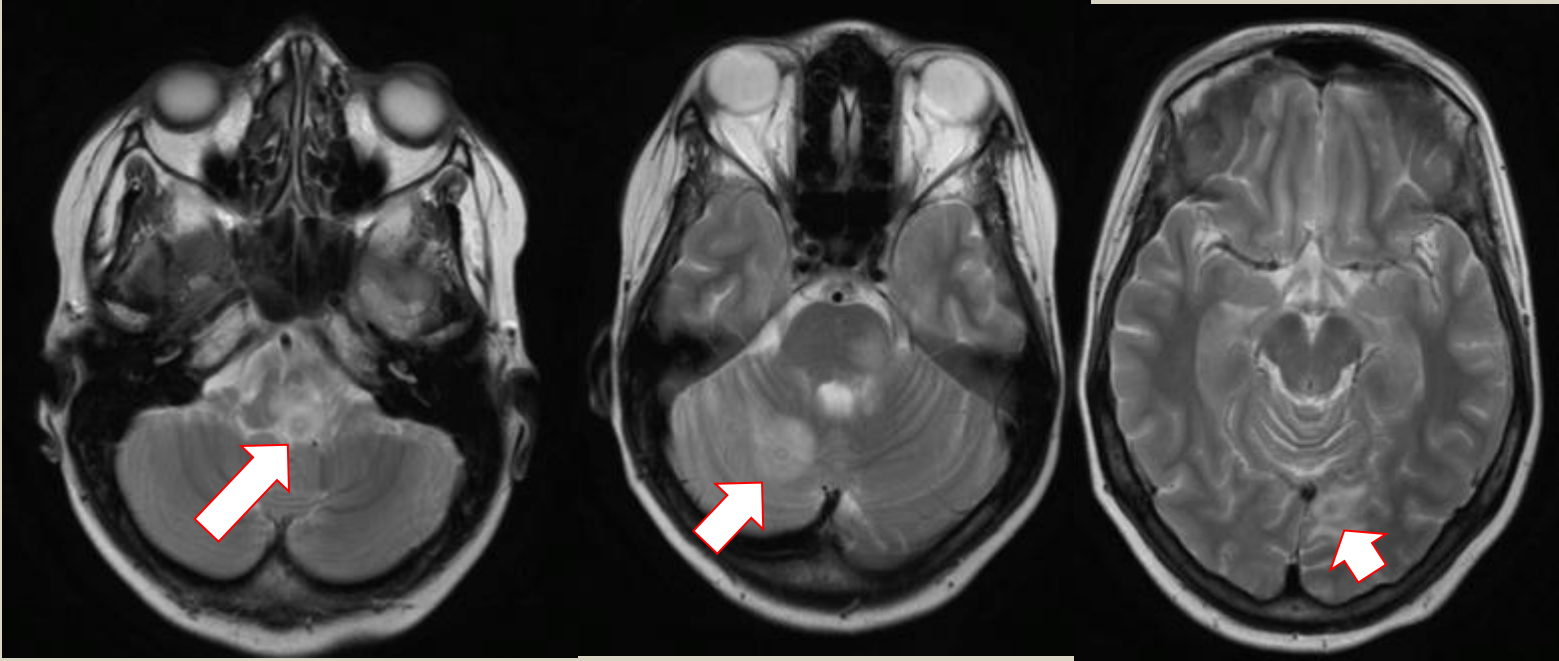


# spinal tuberculosis



Diskitis,  
osteomyelitis +/-  
paraspinous  
abscess





# Extrapulmonary tuberculosis: diagnosis

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symptoms

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# A Population-Based Survey of Tuberculosis Symptoms: How Atypical Are Atypical Presentations?

Loren G. Miller,<sup>1,4</sup> Steven M. Asch,<sup>2</sup> Emily I. Yu,<sup>2</sup>  
Laura Knowles,<sup>5</sup> Lillian Gelberg,<sup>3</sup> and Paul Davidson<sup>5</sup>

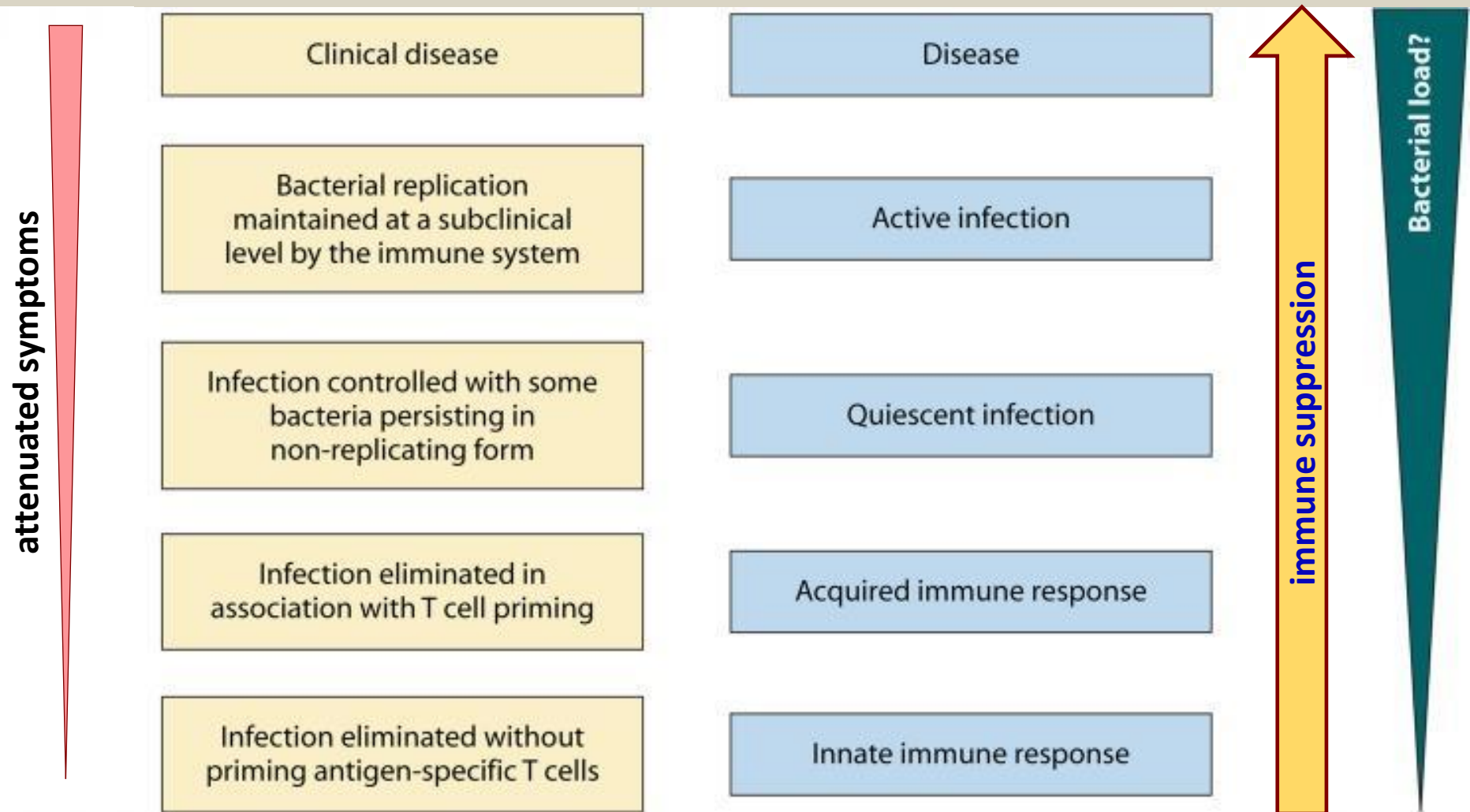
*From the Divisions of <sup>1</sup>Infectious Diseases and <sup>2</sup>General Internal Medicine, Veterans Affairs Greater Los Angeles Healthcare System; <sup>3</sup>Department of Family Medicine, and <sup>4</sup>Division of Infectious Diseases, UCLA Medical Center; and <sup>5</sup>Los Angeles County Tuberculosis Control, Los Angeles County Department of Health, California*

- Los Angeles county, California: April-Sept 1993
- 735 consecutive cases of confirmed tuberculosis identified prospectively
- 526 sent questionnaires → 313 completed
- predominantly male (64%), non-white (90%), foreign-born (71.4%), few HIV + (12%) , pulmonary TB (80%)
- “significant symptoms” within past 2 years:
  - cough for >2 weeks– weight loss
  - fever for >2 weeks           – hemoptysis

**Table 2.** Percentage of tuberculosis patients with specific symptoms.

	All patients ( <i>n</i> = 313)	Pulmonary disease ( <i>n</i> = 254) <sup>a</sup>	Extrapulmonary disease ( <i>n</i> = 54)
Significant symptoms	218 (70.6)	176 (70.4)	37 (68.5)
Cough	226 (72.7)	191 (75.8)	30 (55.6)
Present for >2 w	150 (48.2)	132 (52.4)	15 (27.8)
Fever	162 (52.3)	127 (50.6)	32 (59.3)
Present for >2 w	91 (29.4)	66 (29.3)	23 (42.6)
Fatigue	185 (59.7)	147 (58.6)	35 (64.8)
Present for >2 w	127 (41.0)	105 (41.8)	20 (37.0)
Weight loss	138 (44.5)	108 (43.0)	27 (50.0)
Sweats	148 (47.9)	116 (46.0)	28 (53.9)
Present for >2 w	91 (29.4)	72 (28.6)	19 (36.5)
Anorexia	127 (40.6)	102 (40.2)	22 (40.7)
Present for >2 w	81 (25.9)	66 (26.0)	15 (27.8)
Chest pain	128 (41.0)	105 (41.5)	22 (40.7)
Present for >2 w	87 (27.9)	71 (28.1)	15 (27.8)
Diarrhea	69 (22.0)	54 (21.3)	15 (27.8)
Present for >2 w	38 (12.1)	27 (10.6)	11 (20.4)
Hemoptysis	65 (20.9)	80 (23.8)	3 (5.6)

Trait	overall No. (%)	No. (%) with significant sxs	Multivariate Analysis	
			OR	<i>P</i>
Ethnicity				
Asian	74 (23.9)	30 (42.2)	0.17	<0.0001
Black	38 (12.3)	28 (73.7)		0.43
White	32 (10.4)	25 (78.1)		0.84
Hispanic	153 (49.5)	124 (81.0)		0.96
No Insurance	147 (51.2)	120 (82.8)	3.60 (1.65–7.83)	0.001
Homeless	26 (8.6)	23 (88.5)		0.71
Incarceration	83 (27.3 )	65 (78.3)		0.74
TB diagnosed because of				
Symptoms	216 (70.1)	177 (81.9)	5.89 (2.69–12.89)	<0.0001
Screening	92 (29.9)	37 (42.0)		
Skin Test				
Positive	218 (83.5)	144 (67.0)	6.40 (1.36–30.01)	0.02
Negative	43 (16.5)	39 (92.9)		



Adapted from Pai M (2014). *Clinical Microbiology Reviews* 27: 3-20.

# Diagnosis of Extra Pulmonary TB: tissue sampling

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- Send respiratory samples even if chest imaging is negative.
- Bronchoscopy if cannot obtain sputum biopsy
- biopsy enlarged lymph nodes
- use CT or MRI to find extrapulmonary lesions that can serve as biopsy targets
- for pleural TB, pleural biopsy is often required
- tissue should be sent for AFB stain and culture, as well as PCR/probe testing (may need to be a reference lab)



# Non-culture-based methods

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## Bacteria or bacterial product is detected

- *In-situ* hybridization (probe)
- DNA/RNA amplification = NAAT
  - PCR
  - rtPCR
- MALDI-TOF
- urine Lipoarabinomannan

## Host response is measured

- in principle, gene expression signature

# Nucleic Acid Amplification Tests (NAAT)

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- **Versions**

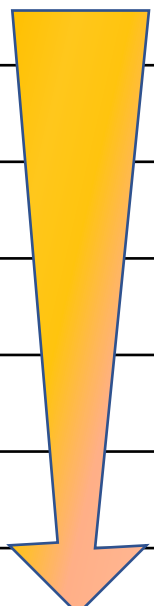
- Amplified MTD (GenProbe)
- GeneXpert Mtb/RIF (Cepheid)
- Non FDA-Approved
  - MTBDR Plus (Hain)
  - Others

- **When to Use**

- Directly on processed (unfixed) specimen
- No current TB rx >7 days
- No prior TB rx within past 12 months

# Sensitivity and speed of various methods of TB identification

<b>Method</b>	<b>Sensitivity (# bugs required)</b>	<b>Speed</b>
<b>AFB Smear</b>	$10^4$	Hours
<b>Conventional Culture</b>	$10^3$	Weeks
<b>Radiometric/MGIT</b>	$10^{2-3}$	Days
<b>DNA Probe</b>	$10^{3-4}$	Days (min?)
<b>RNA Probe</b>	$10^{1-2}$	Days (min?)
<b>PCR (MTD) + Probe</b>	$10^{0(?)}$	Days (hours)
<b>PCR + DNA sequencing</b>	$10^{0(?)}$	Days



# Summary: clinical features and diagnosis

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1. the key to making the diagnosis is understanding the host
2. classic symptoms (fever, cough, night sweats, weight loss, hemoptysis) may be absent or attenuate
3. diagnostic delay is common
4. certain ethnic groups may be more likely to present with extrapulmonary disease

# Summary: clinical features and diagnosis

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5. PPD and IGRAs have relatively poor positive predictive value for active disease
6. EPTB is typically a “paucibacillary” disease. Thus, smear and culture are less sensitive than for pulmonary TB.
7. Molecular methods are critical to making a microbiologic diagnosis. PCR is currently the most reliable non-culture-based diagnostic tool