Extrapulmonary TB

Andrew DiNardo, MD, PhD

July 16, 2024

TB Intensive
July 16 – 18, 2024
San Antonio, Texas

Andrew DiNardo, MD, PhD has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity

ExtraPulmonary TB:

September 2023

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Infectious Diseases

Objectives:

01

Diagnosis

02

Treatment

03

Additional Workup

04

Additional Monitoring

Case Study # 1

- 55 yr M w HTN develops new ESRD
  - 2019-2020: testicular abscess not improved s/p 2 courses Abxs
  - March 2021: mild fevers and weight loss
  - November 2021: further weight loss and new renal failure
    - Peri-renal abscess; CXR no disease
    - QFT: indeterminant
    - Urine Gene Xpert positive w Ct 18; Culture TTP 19 days
  - Started on RHZE
    - Symptoms first improve and then 2 months later:
      - Nausea, anuric→ found to have bilateral hydronephrosis
      - Urine Gene Xpert positive w Ct 17; Culture Negative
      - Improved on prednisone

Case Study # 1

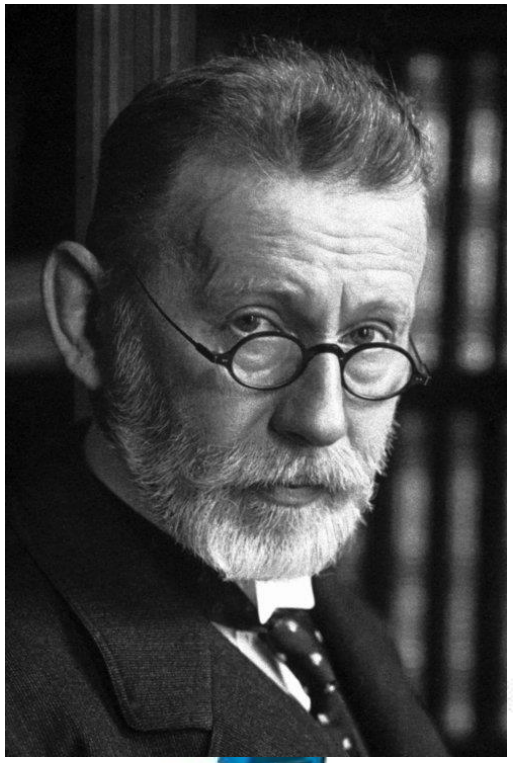
- 55 yr M w HTN develops new ESRD
  - 2019-2020: testicular abscess not improved s/p 2 courses Abxs
  - March 2021: mild fevers and weight loss
  - November 2021: Diagnosed w TB; started RHZE
    - Peri-renal abscess; CXR no disease; 2cm scrotal fluid collection; TB+
  - Jan 2022: Developed IRIS
  - *Jan 2023*
    - *Anorexia not resolved*
    - *Still with 2cm fluid collection in scrotum → Abxs won't treat an abscess*
    - *What is the right time to allow for Abx resolution before draining?*

3 Learning points

1. Sensitivity of diagnostics tests depends on specimen quality and the type of the specimen
2. Drainage matters
3. 3 headed monster:

Diagnosis, 1882 to 2006…

Test	Turn around time	LOD (organisms/ mL)	Sensitivity
AFB smear	< 2 hours	5,000	Low
Culture	14-42 days	1-10	Good Not perfect
PCR (Xpert ultra)	1h 42 min	18	Good Not perfect

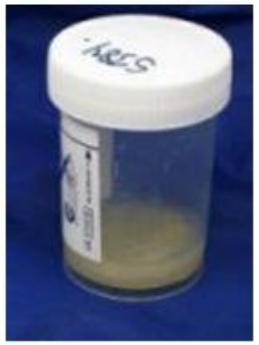


Gene Xpert work-station At Baylor-Eswatini TB Clinic

BAYLOR COLLEGE OF MEDICINE
Children's Foundation
SWAZILAND

Overview of the procedure

1
Mix



2
Add

3
Insert

4
Detect

Diagnostic accuracy depends on:

1. Specimen quality

2. Quantity of specimens evaluated

Cochrane Database of Systematic Reviews | Review - Diagnostic

Xpert Ultra versus Xpert MTB/RIF for pulmonary tuberculosis and rifampicin resistance in adults with presumptive pulmonary tuberculosis

Jerry S Zifodya, Jonah S Kreniske, Ian Schiller, Mikashmi Kohli, Nandini Dendukuri, Samuel G Schumacher, Eleanor A Ochodo, Frederick Haraka, Alice A Zwerling, Madhukar Pai, ✉ Karen R Steingart, David J Horne
Authors' declarations of interest

Version published: 22 February 2021 Version history

Gene Xpert (ULTRA) on Sputum

Specimen Type	Summary Sensitivity
Smear-positive	99%
Smear-negative	77%
All	91%
PLWHIV	87%

7 studies; 2834 patients

Original
Gene Xpert
LOD 112 CFU/mL

Ultra
LOD 15 CFU/mL

Xpert for Extra-pulm TB

Xpert MTB/RIF Ultra and Xpert MTB/RIF assays for extrapulmonary tuberculosis and rifampicin resistance in adults (Review)

Kohli M, Schiller I, Dendukuri N, Yao M, Dheda K, Denkinger CM, Schumacher SG, Steingart KR

Cochrane Database of Systematic Reviews

Specimen Type	# Studies	Number evaluated	Summary Sensitivity
CSF Xpert	33	3774	71%
CSF Ultra	6	475	89%
CSF 1 specimen*	4	496	63%
Pleural fluid Ultra	4	398	70%
Lymph node	14	1588	88%
Urine	9	943	85%
Bone	6	471	97%
Peritoneal fluid	13	580	59%
Pericardial fluid	5	181	61%

* Culture vs composite reference standard; 1 vs multiple samples

Single PCR + 3 smears is for rule out, not if high suspicion

Send multiple specimens if high suspicion

1919 age 35:
Pleurisy

1962: age 78
fevers, night sweats, GI bleed, severe anemia

BmBx: grew Mtb weeks later

Beheading the first head: antibiotics

1. No missed doses!
2. At least 20mg/kg of rifampin
3. Therapeutic drug monitoring

5/7 = 71%

6/7 = 87%

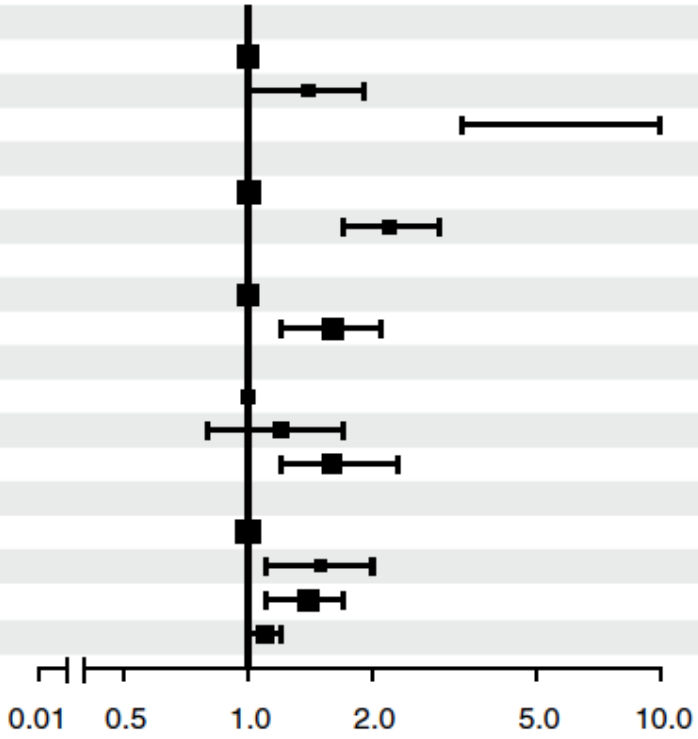
Nature Medicine | VOL 24 1708 | NOVEMBER 2

A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis

Marjorie Z. Imperial[1,11], Payam Nahid[1,11], Patrick P. J. Phillips[1], Geraint R. Davies[2], Katherine Fielding[3], Debra Hanna[4,5], David Hermann[5], Robert S. Wallis[6], John L. Johnson[7,8], Christian Lienhardt[9,10] and Rada M. Savic[1*]

Baseline characteristics, on-treatment culture status and adherence

Variable	Number of unfavorable outcomes/ number of study participants (%)	HR (95% CI)
Adherence		
100%	238/1,348 (18)	Reference
>90 and <100%	64/288 (22)	1.4 (1.0–1.9)
≤90%	15/32 (47)	5.7 (3.3–9.9)
Month 2 culture status		
Negative	212/1,357 (16)	Reference
Positive	105/311 (34)	2.2 (1.7–2.9)
Sex		
Female	64/492 (13)	Reference
Male	253/1,176 (22)	1.6 (1.2–2.1)
Smear grade		
Smear negative or 1+	53/388 (14)	Reference
Smear 2+	72/430 (17)	1.2 (0.8–1.7)
Smear 3+	192/850 (23)	1.6 (1.2–2.3)
HIV status		
Negative	270/1,463 (18)	Reference
Positive	47/205 (23)	1.5 (1.1–2.0)
BMI (per 5 kg m^{-2} decrease)	[b]	1.4 (1.1–1.7)
Age (per 10-year increase)	[b]	1.1 (1.0–1.2)



Beheading the first head: antibiotics

1. No missed doses!
2. At least 20mg/kg of rifampin
3. Therapeutic drug monitoring

No missed doses!

Table 2. Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

	Intensive Phase		Continuation Phase				
Regimen	Drug[a]	Interval and Dose[b] (Minimum Duration)	Drugs	Interval and Dose[b,c] (Minimum Duration)	Range of Total Doses	Comments[c,d]	Regimen Effectiveness
1	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	7 d/wk for 126 doses (18 wk), or 5 d/wk for 90 doses (18 wk)	182–130	This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.	Greater
2	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH	3 times weekly for 54 doses (18 wk)	110–94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 wk)	INH RIF	3 times weekly for doses (18 wk)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.	
4	INH RIF PZA EMB	7 d/wk for doses twice weekly for 12 doses[e]	INH RIF	Twice weekly for 36 doses (18 wk)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear-positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior.	Lesser

The first head: antibiotics

1. No missed doses!
2. At least 20mg/kg of rifampin
3. Therapeutic drug monitoring

Dose	% w CSF RIF MIC>1
10mg/kg (600mg)	11%
20 mg/kg (1200 mg)	93%
35 mg/kg (2400 mg)	95%

89% sub-therapeutic!

Clinical Infectious Diseases, Volume 73, Issue 5, 1 September 2021, Pages 876–884, https://doi.org/10.1093/cid/ciab162

Beheading the first head: antibiotics

1. No missed doses!
2. At least 20mg/kg of rifampin
3. Therapeutic drug monitoring

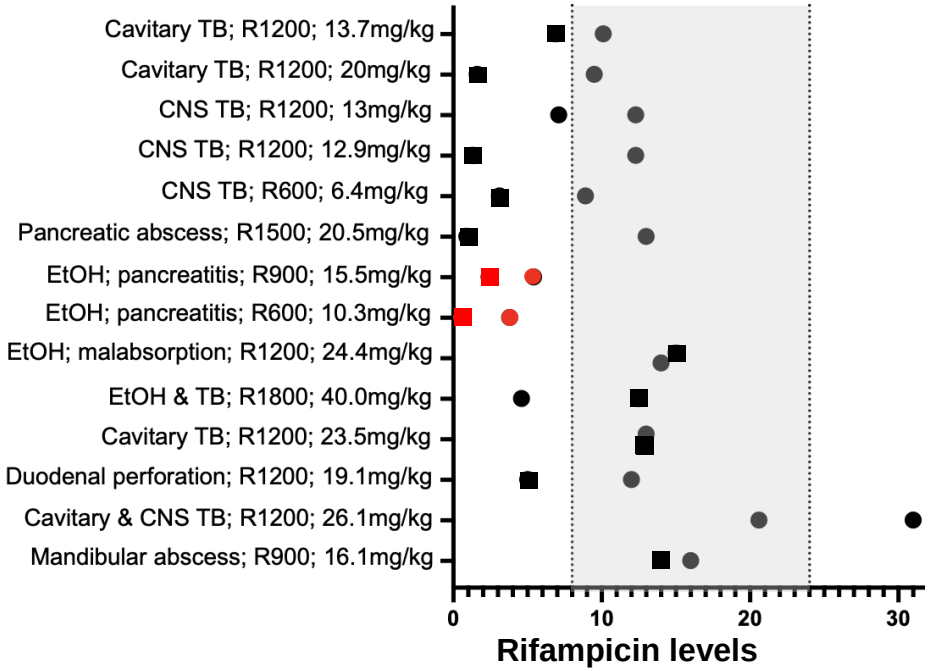
TEXAS Health and Human Services
Texas Department of State Health Services

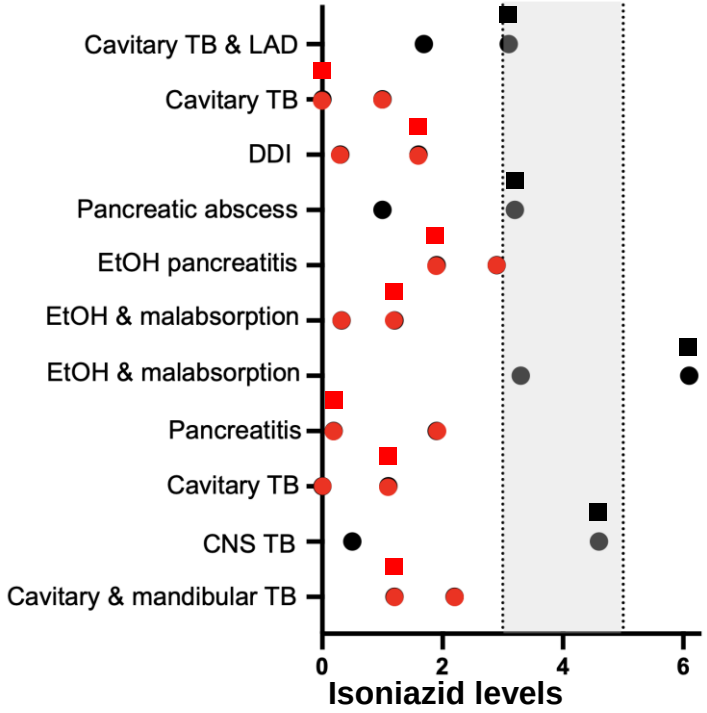
THERAPEUTIC DRUG MONITORING PROCESS

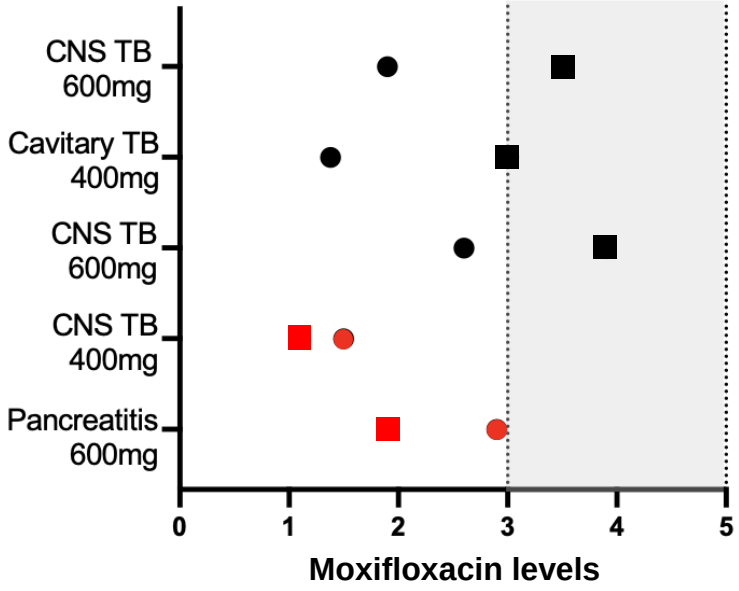
Considerations for Using Therapeutic Drug Monitoring

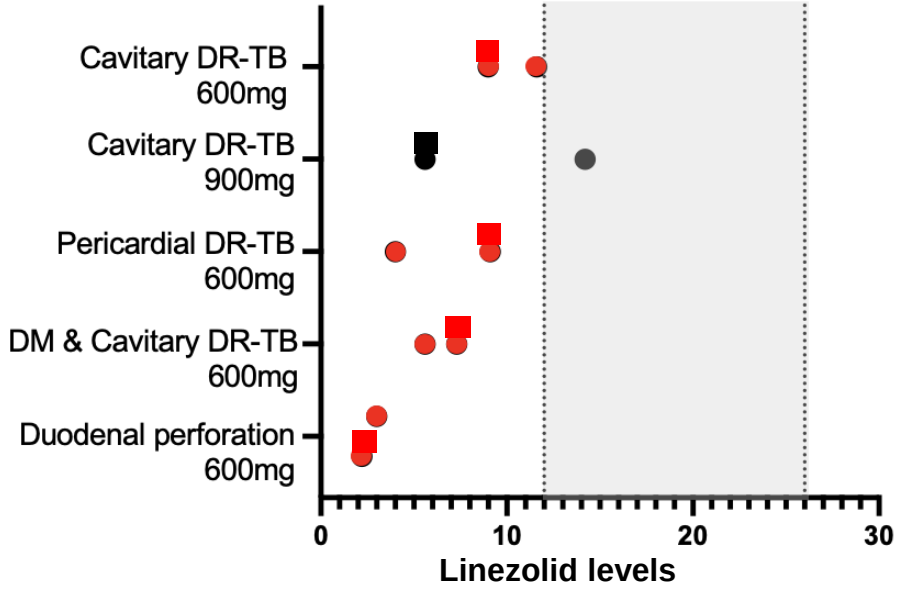
Bacteriological Criteria (consider at 8 weeks of therapy)	**Medical Criteria** (consider at 2-4 weeks of therapy)	**Clinical Criteria** (consider at 8 weeks of therapy)	**Criteria based on TB Diagnosis****
Slow response to adequate therapy at **8 weeks** of treatment, evidenced by the following: • Patient remains AFB sputum smear positive 2+ or greater (unless easily explained) And/or • Sputum smear results not decreasing as expected (4+ to 3+, 2+, etc.)	• TB/poorly controlled diabetes comorbidity • Mal-absorption due to chronic or acute co-morbidity • Chronic or excessive vomiting or diarrhea • HIV infection and CD-4 count <100** • Low or high body mass index (>10% above or below ideal body weight)	• No improvement of TB symptoms (i.e. no weight gain, no reduction in cough, etc.) at 8 weeks • Worsening CXR anytime during course of adequate therapy • New clinical deterioration, likely related to TB (i.e. new evaluation for TB relapse or concern for drug resistance**)	• Patient Relapse: When signs and symptoms of TB return within two years of a prior episode of disease and there was a good possibility that relapse was due to low drug levels (exclude previous poor adherence, missed doses, or N/V) • When second line drugs need monitoring, as per consult recommendations • TB meningitis

https://www.dshs.texas.gov/sites/default/files/IDCU/disease/tb/forms/PDFS/TherapeuticDrugMonitoringProcess.pdf


Cavitary TB; R1200; 13.7mg/kg
Cavitary TB; R1200; 20mg/kg
CNS TB; R1200; 13mg/kg
CNS TB; R1200; 12.9mg/kg
CNS TB; R600; 6.4mg/kg
Pancreatic abscess; R1500; 20.5mg/kg
EtOH; pancreatitis; R900; 15.5mg/kg
EtOH; pancreatitis; R600; 10.3mg/kg
EtOH; malabsorption; R1200; 24.4mg/kg
EtOH & TB; R1800; 40.0mg/kg
Cavitary TB; R1200; 23.5mg/kg
Duodenal perforation; R1200; 19.1mg/kg
Cavitary & CNS TB; R1200; 26.1mg/kg
Mandibular abscess; R900; 16.1mg/kg
0
10
20
30
Rifampicin levels


Cavitary TB & LAD
Cavitary TB
DDI
Pancreatic abscess
EtOH pancreatitis
EtOH & malabsorption
EtOH & malabsorption
Pancreatitis
Cavitary TB
CNS TB
Cavitary & mandibular TB
0
2
4
6
Isoniazid levels


CNS TB 600mg
Cavitary TB 400mg
CNS TB 600mg
CNS TB 400mg
Pancreatitis 600mg
0
1
2
3
4
5
Moxifloxacin levels


Cavitary DR-TB 600mg
Cavitary DR-TB 900mg
Pericardial DR-TB 600mg
DM & Cavitary DR-TB 600mg
Duodenal perforation 600mg
0
10
20
30
Linezolid levels

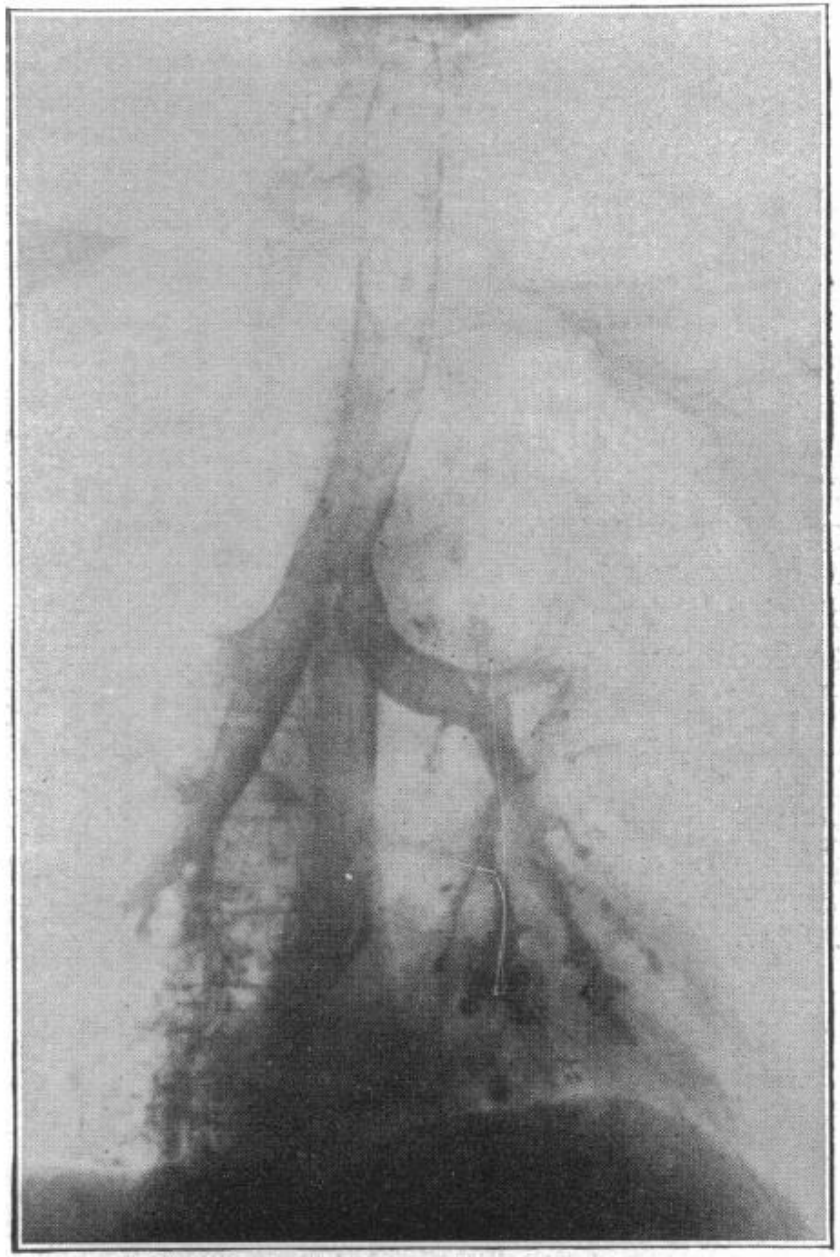
Case Study # 2: AD

- 21 yr M from India
  - 4 weeks of malaise, weight loss, anorexia
  - 2 weeks progressive headache and blurry vision
  - Admitted for meningitis
    - Xpert CSF negative x 1
    - CSF 220 WBCs, 70% lymphocytes, gluc 33, protein 87
    - QFT Nil 0.2, TB1 1.3, Mitogen 4.4

Extra Pulm Diagnostic take home points

- Smear is antiquated w low sensitivity
- Culture is slow
- PCR is an improvement
  - Send multiple samples
- Commercial RNA (MBLA) is coming

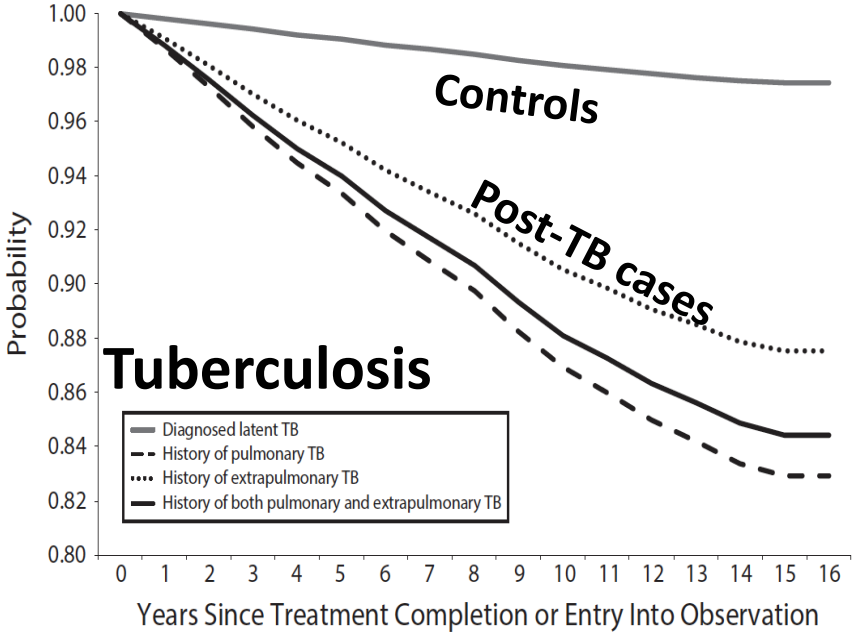
- No diagnostic test works if you can't get a specimen; never stop being a clinician; it's ok to empirically start RHZE

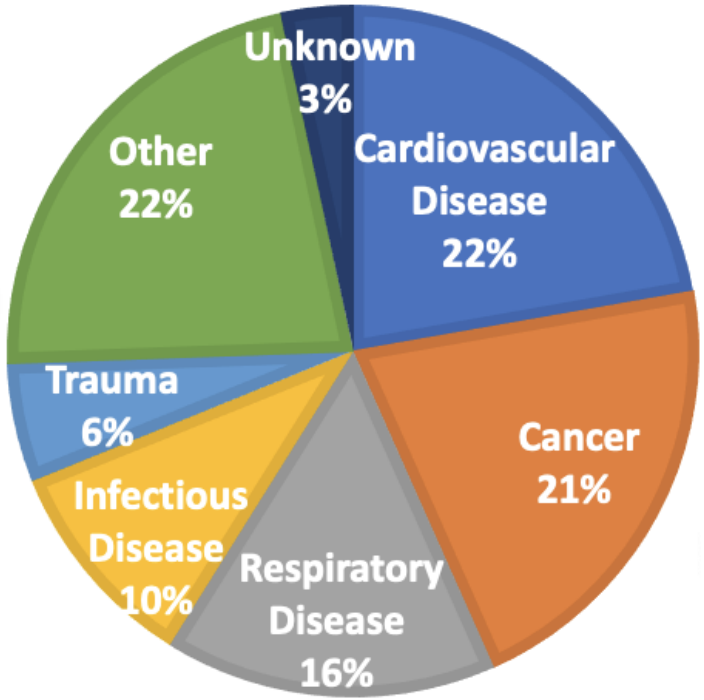


Iodized poppy-seed oil was injected into the trachea by means of a catheter passed between the vocal cords. This shows the iodized oil in both the tracheobronchial tree and the esophagus. There is an actual spilling over of the iodized oil from the trachea into the esophagus. The patient did not cough at any time.

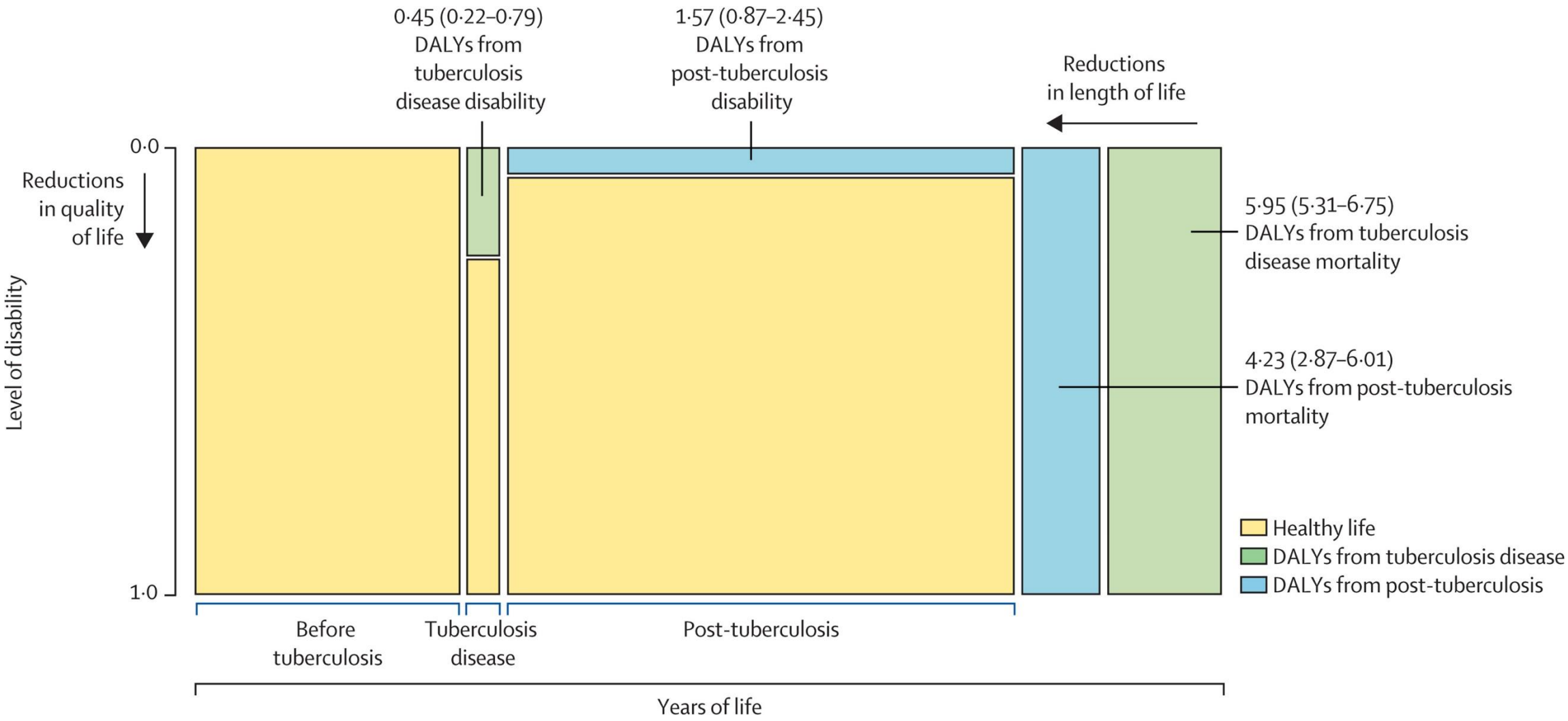
3 headed beast

- Some patients need anti-inflammatory drugs
- Pathologic inflammation acutely:
  - Prednisone, Infliximab, Anikinra,
- Pathologic inflammation chronically:
  - Increased risk CVD disease
- Pathologic anergy chronically:
  - Increased risk cancer & recurrent infections



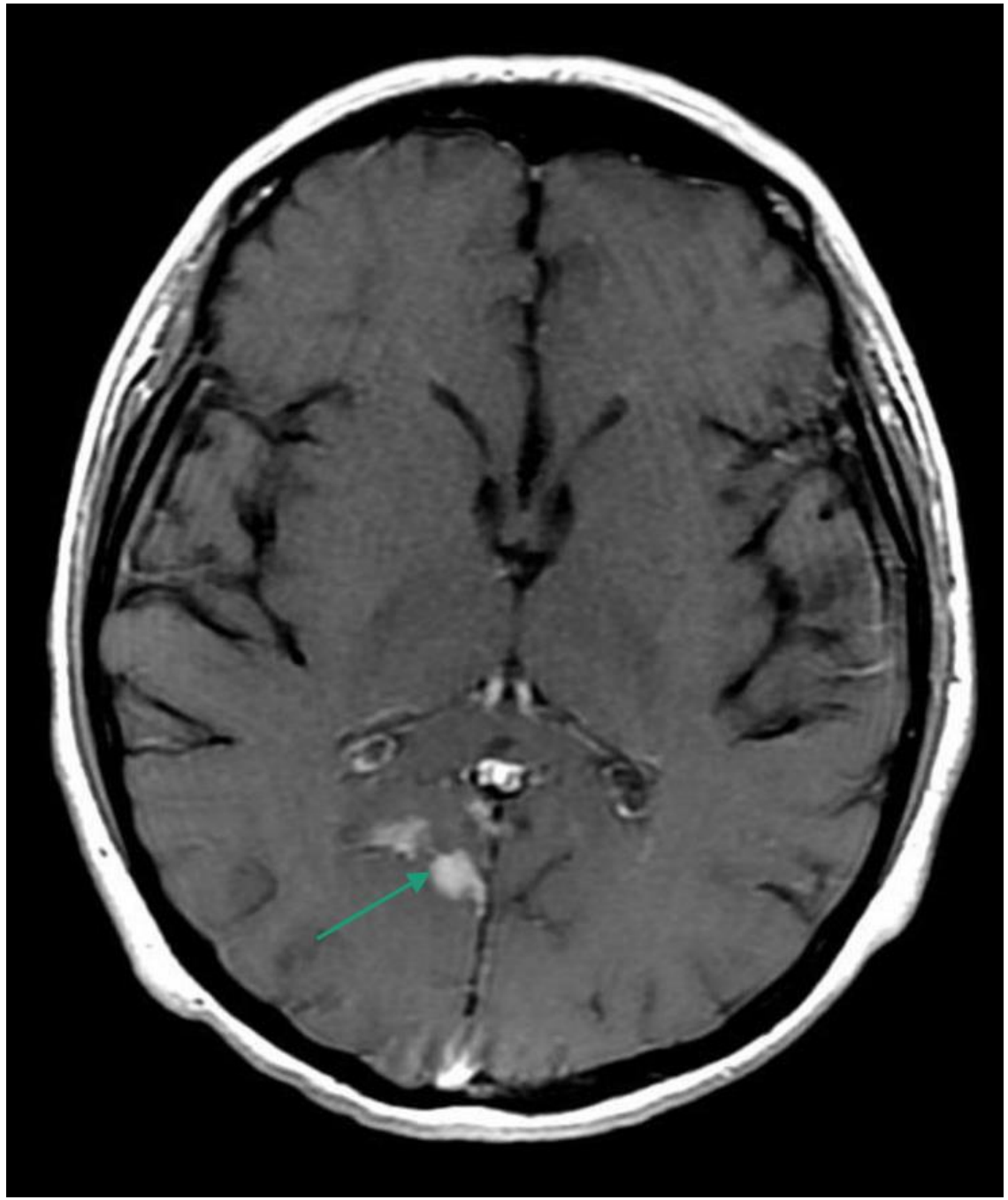


When does our care of the patient end?



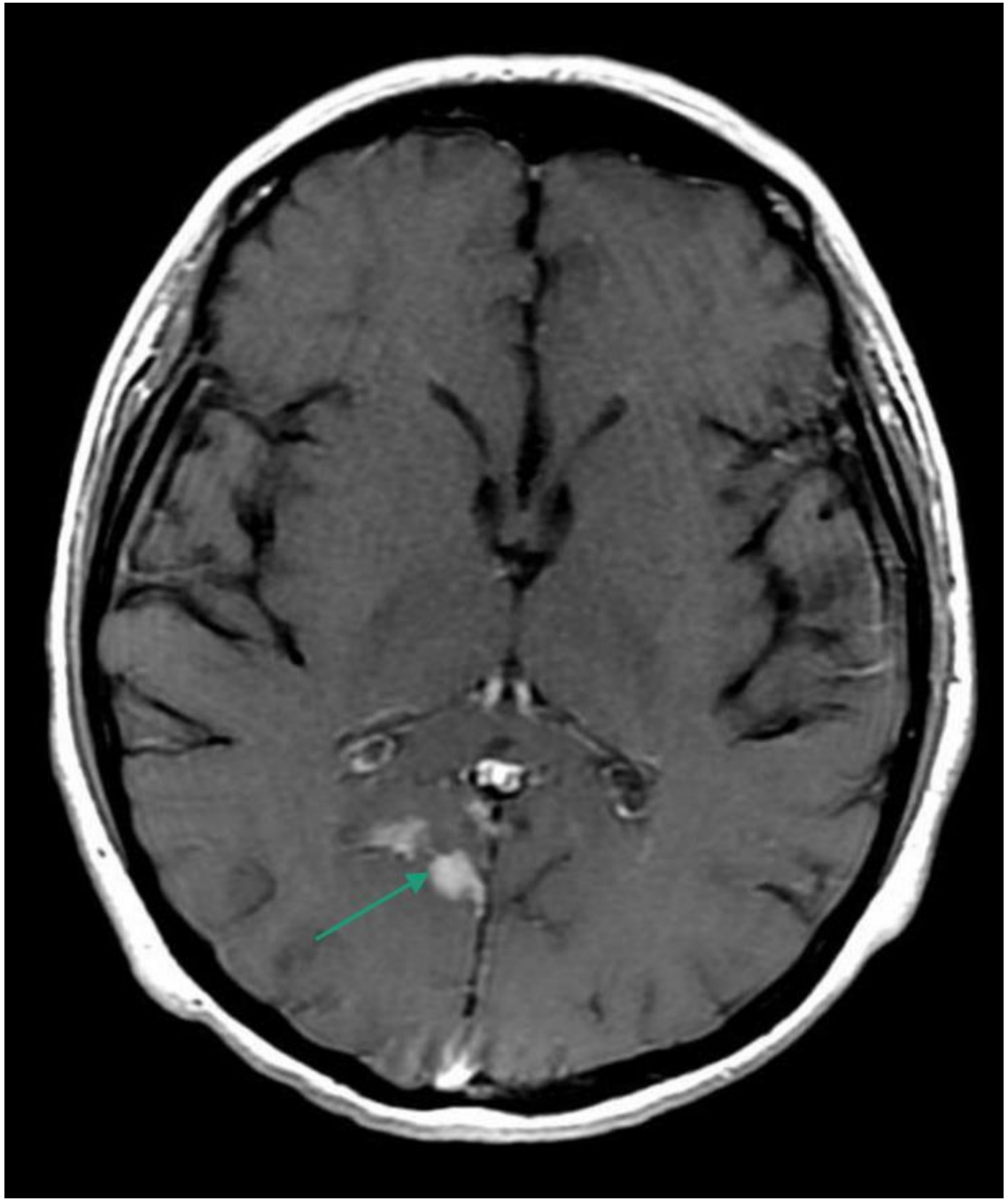
Case Study # 3: JC

- 22 yr M w developmental delay, from Ecuador
  - 3 yrs of knee pain, arthrocentesis negative x 3
  - 6 weeks of cough, fevers, weight loss, BMI 11 (temporal wasting), seizure
  - CXR: multiple cavities, sputum Xpert+
  - CT head: focal mass; CNS w low glucose, lymphocytic pleocytosis, Culture and Xpert negative;



Case Study # 3: JC

- 22 yr M w developmental delay, from Ecuador
  - Micro-confirmed pulm TB
  - Clinically probable CNS TB
  - Clinical probable TB osteomyelitis
  - Started on RHZE
  - QFT: Nil 4.3, TB1 2.5, Mitogen >10
  - Urine histo Ag+
  - What the heck???



Case Study # 3: JC

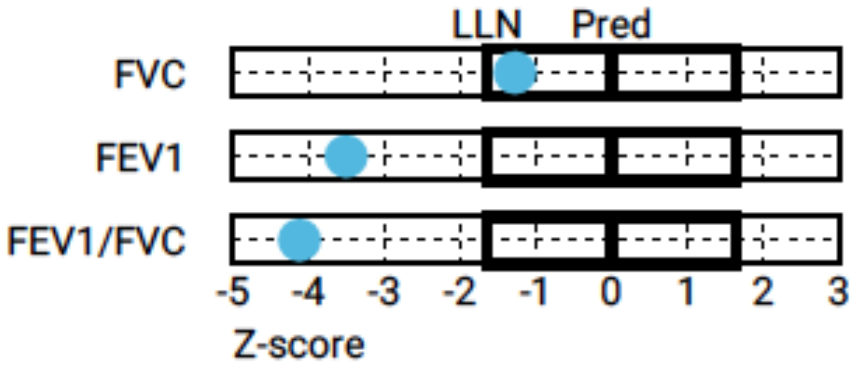
- 22 yr M w developmental delay, from Ecuador
- Mom states he has had intermittent ear infections annually and pneumonia >5 times since birth
- Problem #1: does he have an immune deficiency?
  - Yes, whole genome sequencing found a new metabolic-immune deficiency
- Problem #2: How to dose the ATT with an azole
  - TDM
  - Linezolid & Quinolone and no RIF

Case: CAGM

- TBD later
- PTLD w Severe obstructive Lung Disease

Test1 27.12.2023 02:47 PM

Parameter	Best	LLN	Z-sc.	%Pred	Pred	Trial4	Trial3	Trial2
FVC[L]	4.65	4.45	-1.27	87.0	5.35	4.65	4.65	4.55
FEV1[L]	▼LLN 2.80	3.66	-3.50	63.3	4.43	▼LLN 2.80	▼LLN 1.72	▼LLN 2.59
FEV1/FVC	▼LLN 0.60	0.74	-4.12		0.83	▼LLN 0.60	▼LLN 0.37	▼LLN 0.57
FEF2575[L/s]	▼LLN 2.53	2.97		54.1	4.68	▼LLN 2.53	▼LLN 1.13	▼LLN 2.24
PEF[L/s]	▼LLN 2.87	7.81		27.5	10.44	▼LLN 2.84	▼LLN 2.07	▼LLN 2.87
FET[s]	10.52					9.91	10.52	8.56
FIVC[L]	4.84	4.45		90.5	5.35	4.84	4.84	4.65
PIF[L/s]	2.88	–		–	–	2.88	2.59	4.76



When to work up immune deficiencies?

- No clear answer; ask for help
- Always check for:
  - Ask an in-depth history, including recurrent infections
- Co-infections are atypical unless HIV
- If no history of EtOh, granite cutting, tobacco use, diabetes or other pre-disposing risk factor
- QFT screening
- Auto-antibodies for IFNg or GM-CSF

Summary

1. Drainage is important
2. >25% extra-pulm pts are anergic; beware ⊖ tests of infection
3. Extra-pulm TB presentations have atypical presentations
4. 3 headed beast
    1. Abxs (every day!) for the pathogen
    2. Inflammation; some pts need anti-inflammatory meds
    3. Immune responsiveness: many remain anergic
5. Send extra samples (for PCR and culture) to increase yield
6. Work up weird cases for immune deficiencies
7. Stool is cool and helps confirm the diagnosis