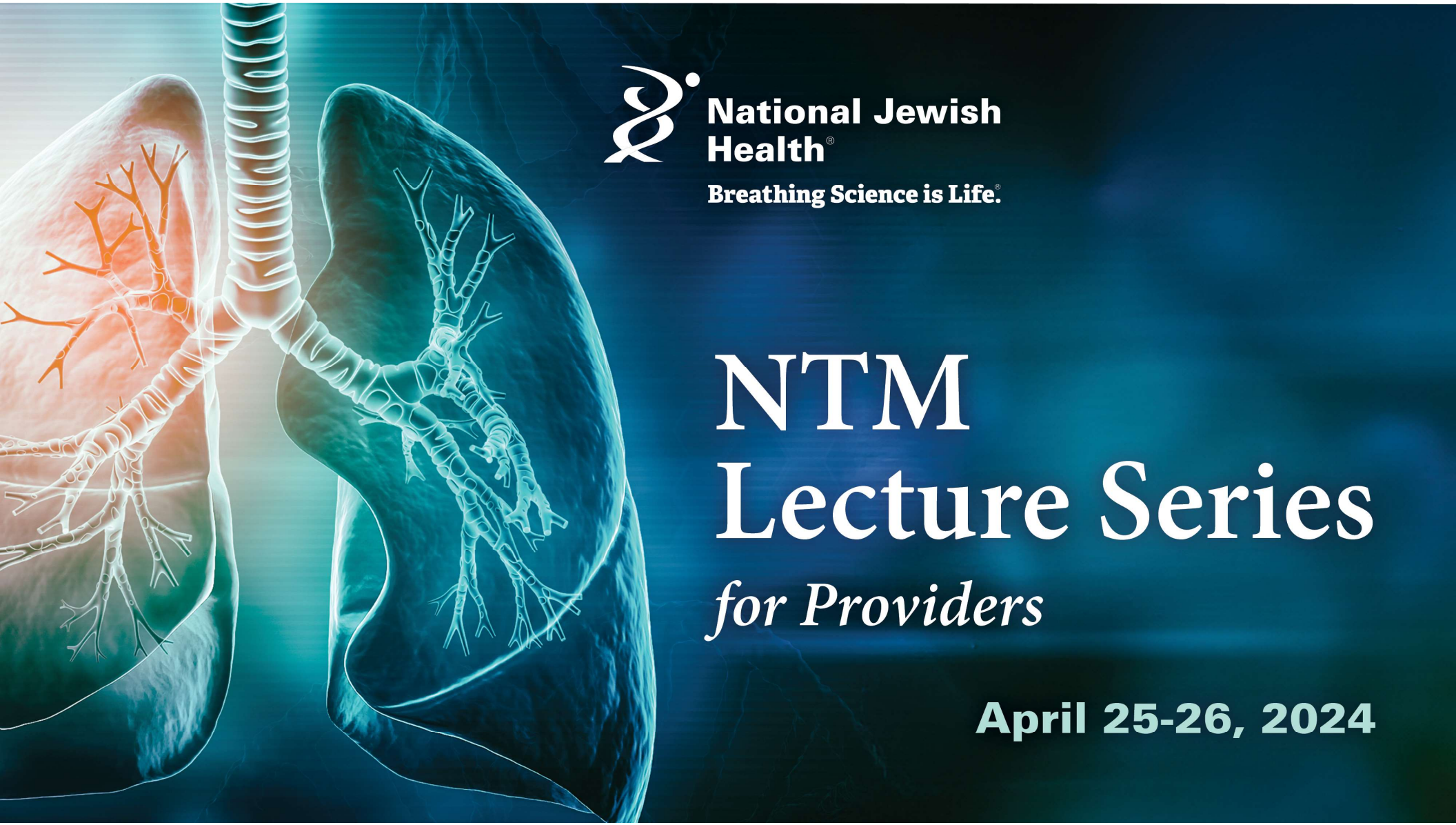
National Jewish Health®
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NTM
Lecture Series
for Providers
April 25-26, 2024

# Challenging Cases (Part 2)

*4/26/2024*

***Jared J. Eddy, MD MPhil MSc***

***Assistant Professor of Medicine***
***Division of Mycobacterial and Respiratory Infections***
***National Jewish Health***

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# Case (Macrolide-Resistant MAC)

- 71 year-old woman from California City, CA
- Past Medical History:
  - COPD (10 pack-yrs, albuterol only), Afib, Diastolic HF, Osteoarthritis, Anemia, Dysphagia, history of Obesity
- Social History:
  - Retired, worked in hospital laundry
  - No clear NTM exposures (hot tub, sauna, gardening)
- Family History:
  - Breast cancer (mother), CAD (father)
  - No known family history of bronchiectasis, NTM, or autoimmunity

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# Pre-NJH Treatment History (1 of 3)

- 2012-2013: develops cough, sputum MAC
  - azi/EMB/RIF 3x/week x 1 year
- 3/2018: recurrent MAC
  - azi/EMB/RIF 3x/week, paused for LFT elevations, then resumed
- 2/2019 CT with worsening cavitary changes
  - azi/EMB/RIF daily
- 3/2019 leukopenia and transaminitis
  - Rifampin stopped, side effects to moxifloxacin, tedizolid, inhaled amikacin
- 10/2020 persistently positive cultures
  - IV amikacin x8 weeks
  - Side effects to ethambutol (?dropped)

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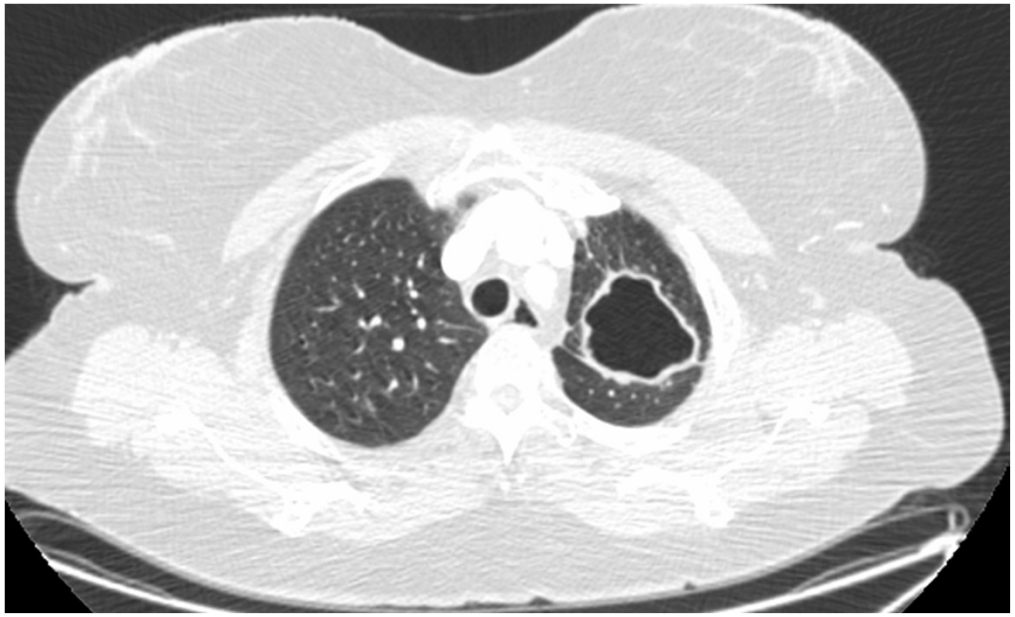
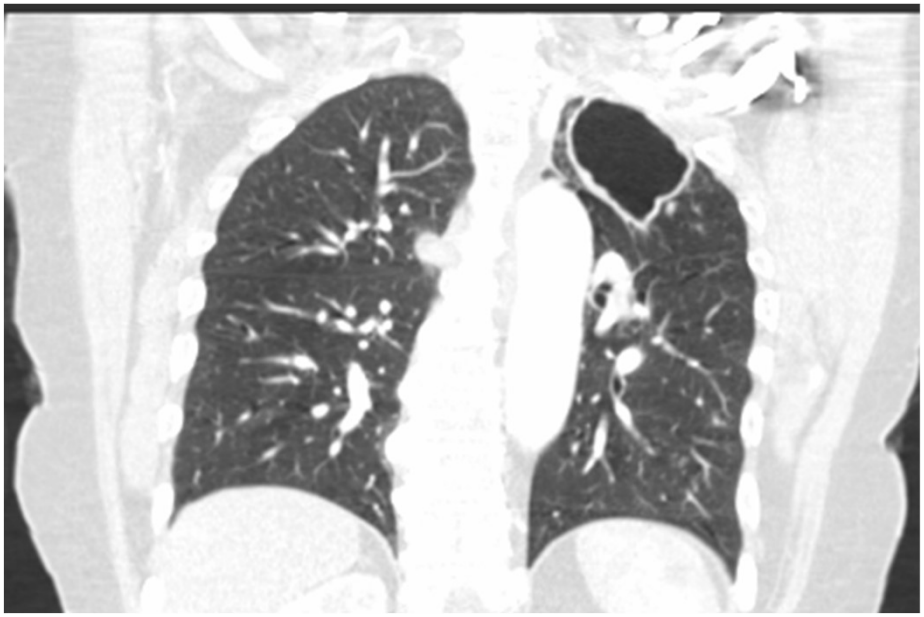
# January 2021

- ca. 5cm x 5cm





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# Pre-NJH Treatment History (2 of 3)

- 2/2021 Pneumonia admit
  - ***1.7cm cavity lingula, 5cm thin L apical cavity***
- 7/2021 CT with new density superior segment L lower lobe (spillage?)
- 11/2021 Bronchoscopy 1+ smear, MAC (***clari >64***)

- 1/2022 Sputum MAC (clari >64)
  - Restarted azi/EMB/RIF, ***inhaled liposomal amikacin*** added soon after
  - ***?Ethambutol stopped*** for visual side effects
- 3-4/2022 LUL cavity now 7.1cm (from 6.3cm), sputum smear+ MAC
  - Azithromycin, tedizolid, inhaled liposomal amikacin
- 6/2022
  - Add ethambutol and rifabutin but both stopped 7/2022 (side effects)

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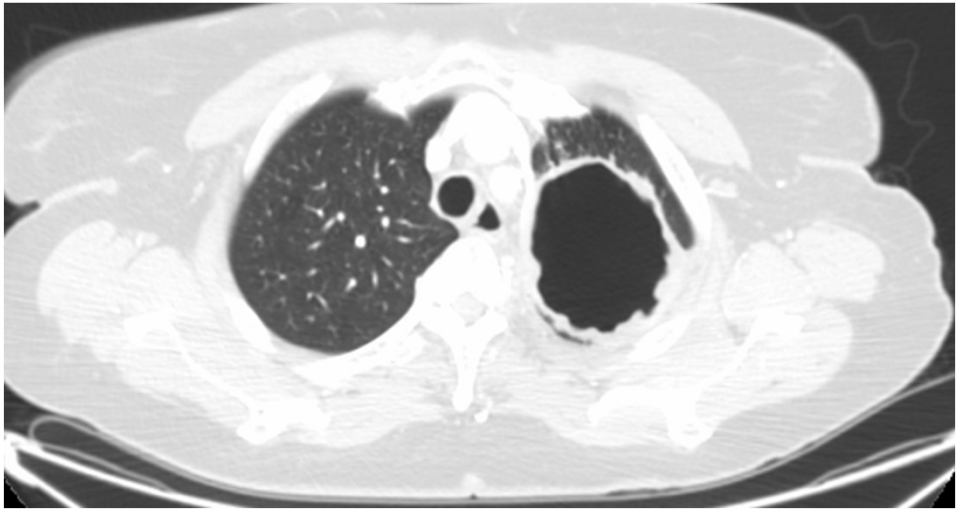
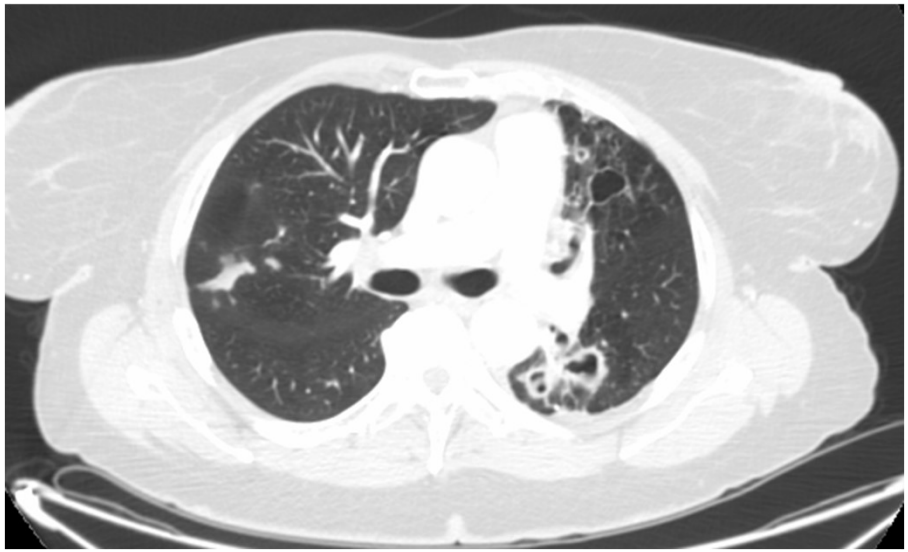
# 6/2022

7 x 6.5 cm L apical cavity and smaller lower L-sided cavities





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# Pre-NJH Treatment History (3 of 3)

- 8/2022-11/2022
  - ***IV amikacin*** replaces inhaled liposomal amikacin
  - Drug holiday following (unclear duration)
- 1-2/2023 More cavities L lung, new patchy R lung findings, 4+ smear
- 4/2023 Sputum 3+ smear MAC (clari >64 S, amik 32 I, linez 16 I)

- 6/2023 Hospitalized for tachycardia
  - More ***IV amikacin*** through 7/2023
- 8/2023 Hospitalized for Pseudomonas pneumonia
  - 3 weeks of carbapenem
- Ca. 9/2023 MAC regimen changes
  - Azithromycin, tedizolid, clofazimine
- 11/2023 presents to NJH (purulent cough, 50 lb drop in 3 mo)

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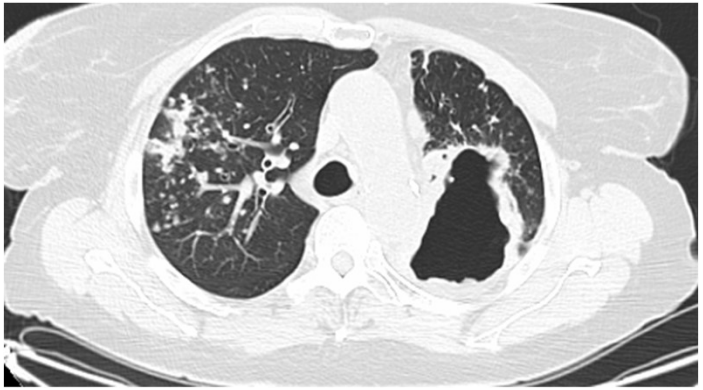
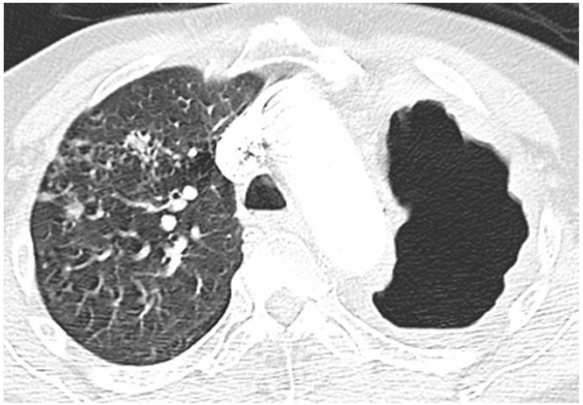
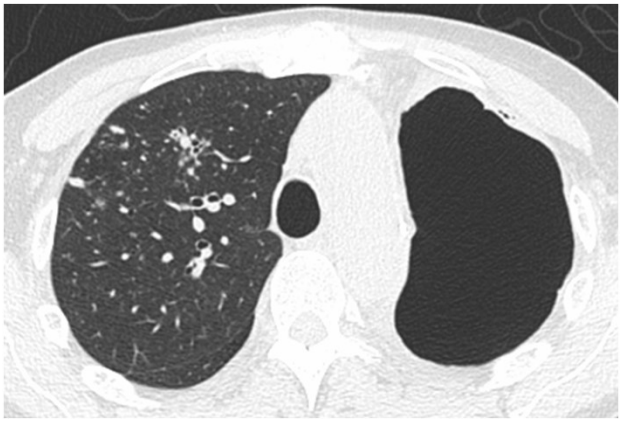
| 2/2023 | 7/2023 | 11/2023 |
| --- | --- | --- |







**Upper lung**

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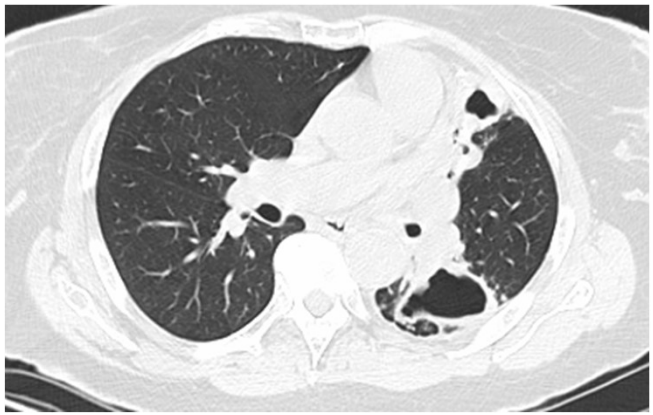
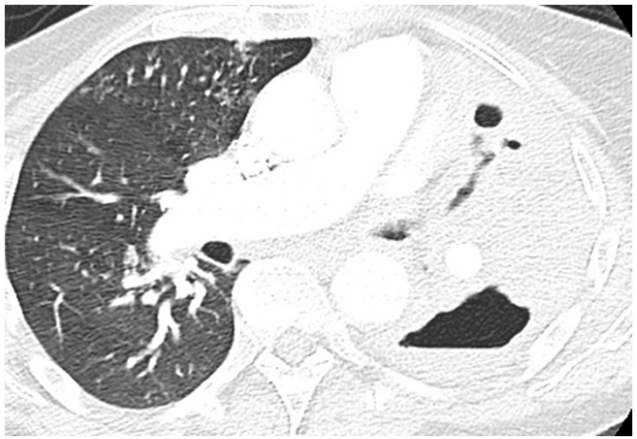
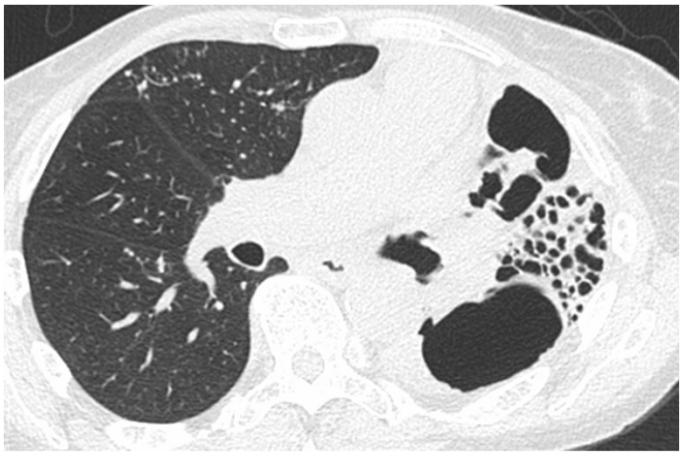
| 2/2023 | 7/2023 | 11/2023 |
| --- | --- | --- |
|  |  |  |

**Mid lung**

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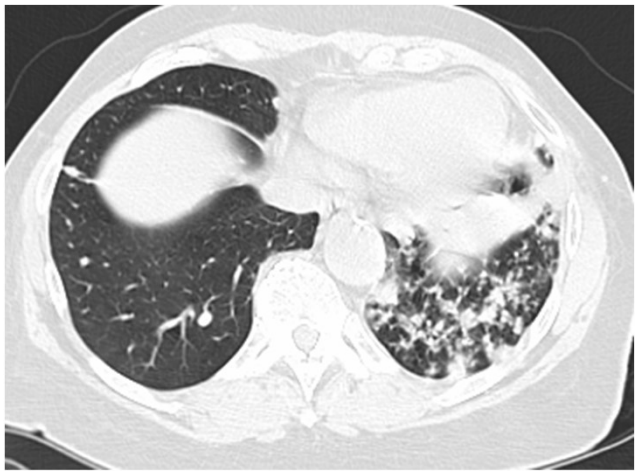
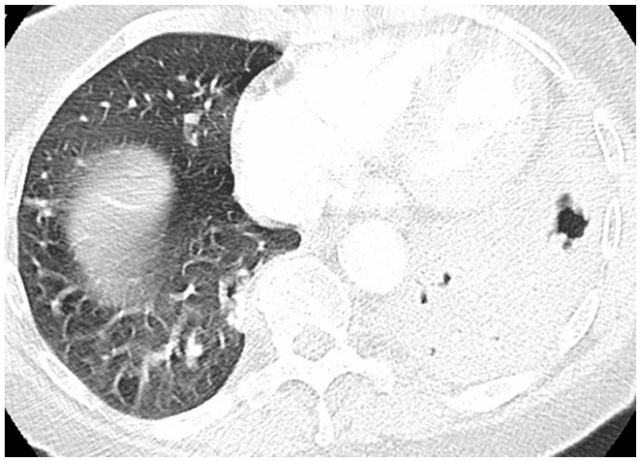
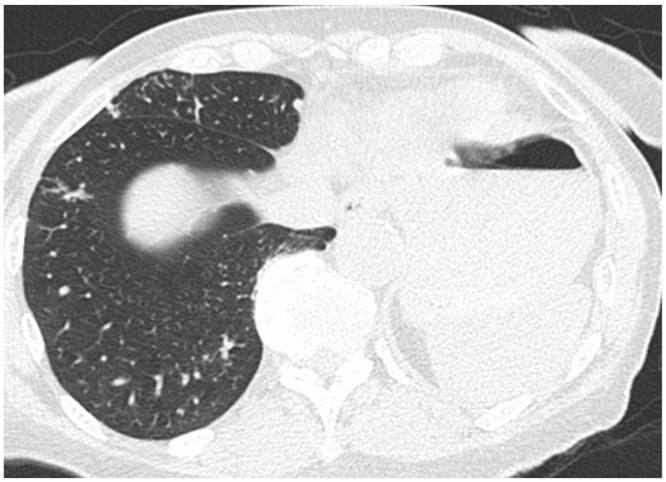
| 2/2023 | 7/2023 | 11/2023 |
| --- | --- | --- |







**Lower lung**

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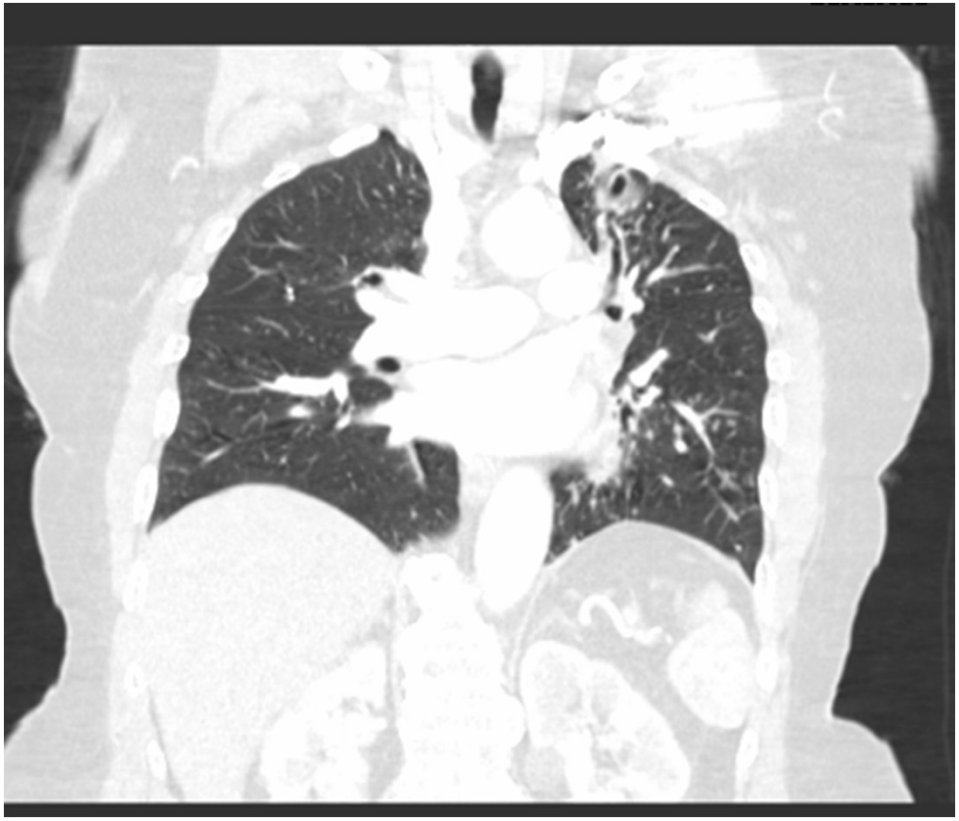
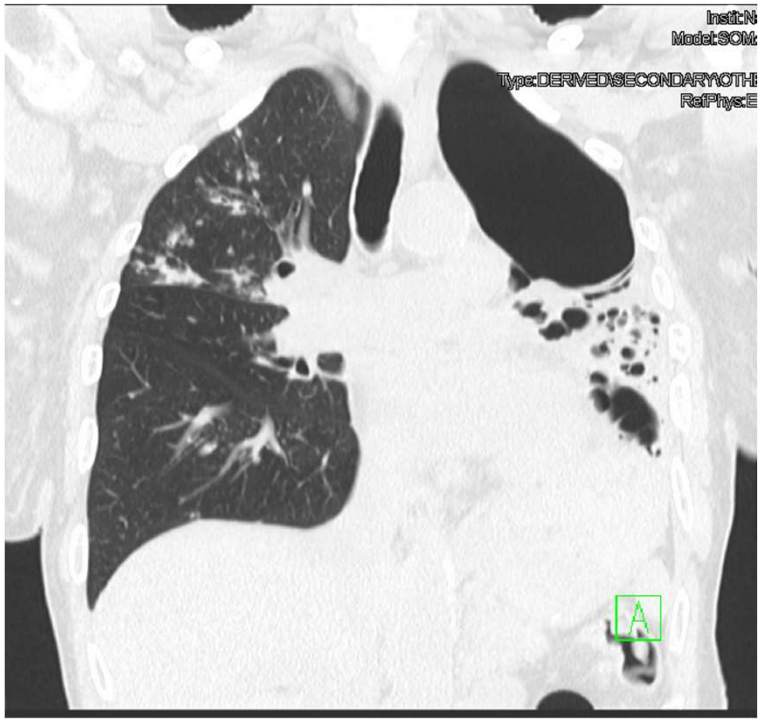
# January 2021 to November 2023



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# Audience Question

- What regimen changes do you make?

1) Azithromycin, clofazimine, linezolid/tedizolid + inhaled amikacin
2) Azithromycin, ethambutol, rifampin/rifabutin + IV amikacin
3) Ethambutol, clofazimine or bedaquiline + IV amikacin
4) Ethambutol, clofazimine, bedaquiline + inhaled amikacin
5) Rifabutin, clofazimine, bedaquiline + IV amikacin
6) Ethambutol, clofazimine, bedaquiline, + IV amikacin + IV imipenem with IV ceftazidime

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# Drug Considerations

- ***Azithromycin***: immunomodulatory, but QT-prolonging, another antibiotic to confound side effects
- ***Tedizolid***: tedizolid on shortage, linezolid MIC rising to 32 (R)
- ***Rifabutin/Rifampin***: Most likely to cause liver dysfunction and side effects in general, drug interactions
- ***Imipenem + Ceftazidime***: good overlap with pseudomonas/GN treatment but evidence for effectiveness in *M. abscessus* vs. *MAC*
- ***Ethambutol***: protects macrolide from drug resistance, does it do the same for the aminoglycoside? "Liver-sparing", optic neuritis and neuropathy concerns
- ***Bedaquiline*** and ***Clofazimine***: supportive but QT-prolonging, potential contributors to liver dysfunction

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# Bedaquiline (Sirturo)

- A diarylquinoline, bactericidal, inhibits the proton transfer chain for mycobacterial ATP synthase (required for energy generation)
- A paradigm-shifting drug in *M. tuberculosis*, but sadly not in NTM
- Ordered from MMS Solutions specialty pharmacy (CareFusion, formerly Cardinal Health), must be delivered to a physician's practice
- Johnson&Johnson financial assistance only for those without insurance (targeting TB patients)
- Off patent now for tuberculosis

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# Bedaquiline considerations

- Shares a mechanism of resistance with clofazimine
- Requires QT monitoring
  - ATS/CDC/ERS/IDSA 2019 Drug-Resistant-TB guideline:
    - baseline, 2 weeks, thereafter monthly
  - Baseline calcium, potassium, magnesium with correction as needed
  - More frequent EKGs if the QT is prolonged or increasing
- Nausea, joint pains, headache, chest pain
- Liver dysfunction

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# NJH Adult Day Unit Course (Data)

- Labs: CRP 2.84 mg/dL, AST 69/ALT 75, WBC 4.7, Hg 11.4, IgE 517
- Sputa:
  - ***Pseudomonas aeruginosa*** (penem-R, otherwise S with low MICs)
  - ***M. intracellulare*** (amik 64 R, clari >64 R, linez 32 R)
    - rrl mutation for acquired macrolide resistance
    - **No rrs mutation for acquired aminoglycodside resistance**

Testing:

- EKG: incomplete RBBB, S1-Q3 pattern, QTc 464ms
- PFTs: FEV1 64%, FEV1/FVC 112%, DLCOcor 46%, DL/VA 83%
- Esophagram: mild dysmotility, no reflux
- Tailored barium swallow: mild oropharyngeal dysphagia

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# NJH Adult Day Unit Course (Management)

Antibiotics:

- Stop azithromycin and tedizolid but continue clofazimine
- Recs: add IV amikacin, add bedaquiline, eventually add ethambutol
- Add ceftazidime for pseudomonas with the aim of keeping it and adding imipenem for dual Beta-lactam therapy for NTM
- Contacted local epetraborole trial site (trial currently paused)

Airway clearance, Other:

- Flutter valve (OPEP) with in-line use of nebulized 7% hypertonic saline
- Apply for percussion vest and other oscillation & lung expansion device
- Swallow exercises for oropharyngeal dysphagia
- Gastroesophageal reflux lifestyle/behavioral changes
- Plan ***lung surgery (pneumonectomy)***

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# Subsequent Events

- 11/27/2023: Full-body itching attributed to imipenem while also on ceftazidime, stop imipenem before starting IV amikacin and bedaquiline

- 12/4/2023 Echo: EF 53%, calcific AV and MV leaflets, mild pulmonary hypertension (RVSP 39mmHg), cleared by cardiologist for lung surgery

- 12/17/2023: rash and hives attributed to bedaquiline; able to continue with hydroxyzine (delay: insurance approval)

- Told (falsely) she could only have one audiogram a year (Medicare)
- Difficult to obtain home lab draws in her remote area
- Asked to stop trazodone and zolpidem for sleep
- Oscillation/lung expansion device approved, delivered 1/4/2024

- 12/26/2023: amikacin peak 43, increase dose; LFTs uptrending

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# IV Amikacin

- Generally 15mg/kg ABW to start
- Aim for Cmax or peak to be 2-3x the MIC of the organism to amikacin
- Adjust up for significant disease
- Adjust down for hearing loss

- 1/10/2024: amikacin MIC 16 S, no rrs mutations
- 1/8/2024: amikacin MIC 32 I, no rrs mutations
- 12/6/2023: amikacin MIC 32 I, no rrs mutations
- 12/5/2023: amikacin MIC 16 S, no rrs mutations
- 11/14/2023: amikacin MIC **64 R**, (but) no rrs mutations
- 11/13/2023: amikacin MIC 32 I, no rrs mutations
- 11/3/2023: amikacin MIC 32 I, no rrs mutations
- 11/2/2023: amikacin MIC 32 I, no rrs mutations
- 11/1/2023: amikacin MIC 32 I, no rrs mutations
- 4/13/2023: amikacin MIC 32

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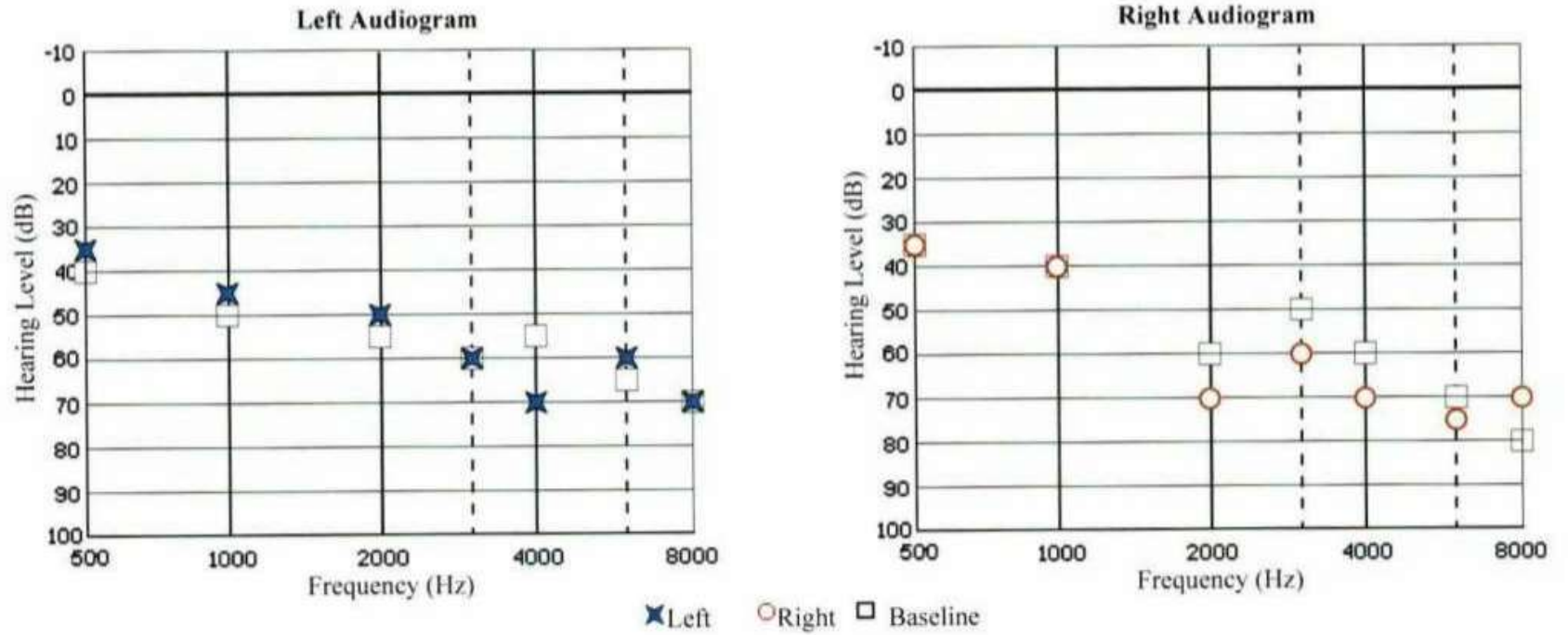
# Audiometry on IV Amikacin

- 10/31/2023 (baseline, boxes) vs. 1/8/2024 (cross and circle)

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# Events around the time of surgery (1/10/2024)

- 1/11/2024: Atrial fibrillation: diltiazem augmented with amiodarone
- 1/19/2024: AST 146, ALT 142, Aphos 142
  - IV amikacin continued
  - Bedaquiline held (half-life, terminal: ~5.5 months)
  - Clofazimine held (half-life: ~25 days, range 6.5-160)
- 1/29/2024: AST 282, ALT 197, Aphos 213
  - Added back ethambutol 1000mg PO daily
  - Liver work-up recommended
- 1/31/2024: AST 289, ALT 260, Aphos 219
  - Added back clofazimine 100mg PO daily ca. 2/15/2024
  - Cardiology stops amiodarone late 2/2024
- 3/7/2024: LFTs “improved”, no sputum production
  - Added back bedaquiline 200mg PO 3x/week
  - Cr 1.2, amikacin dose decreased (recent peak ca. 50)
- 4/15/2024: weight increasing but hearing issues, Cr 1.6
  - IV amikacin held, IVF ordered

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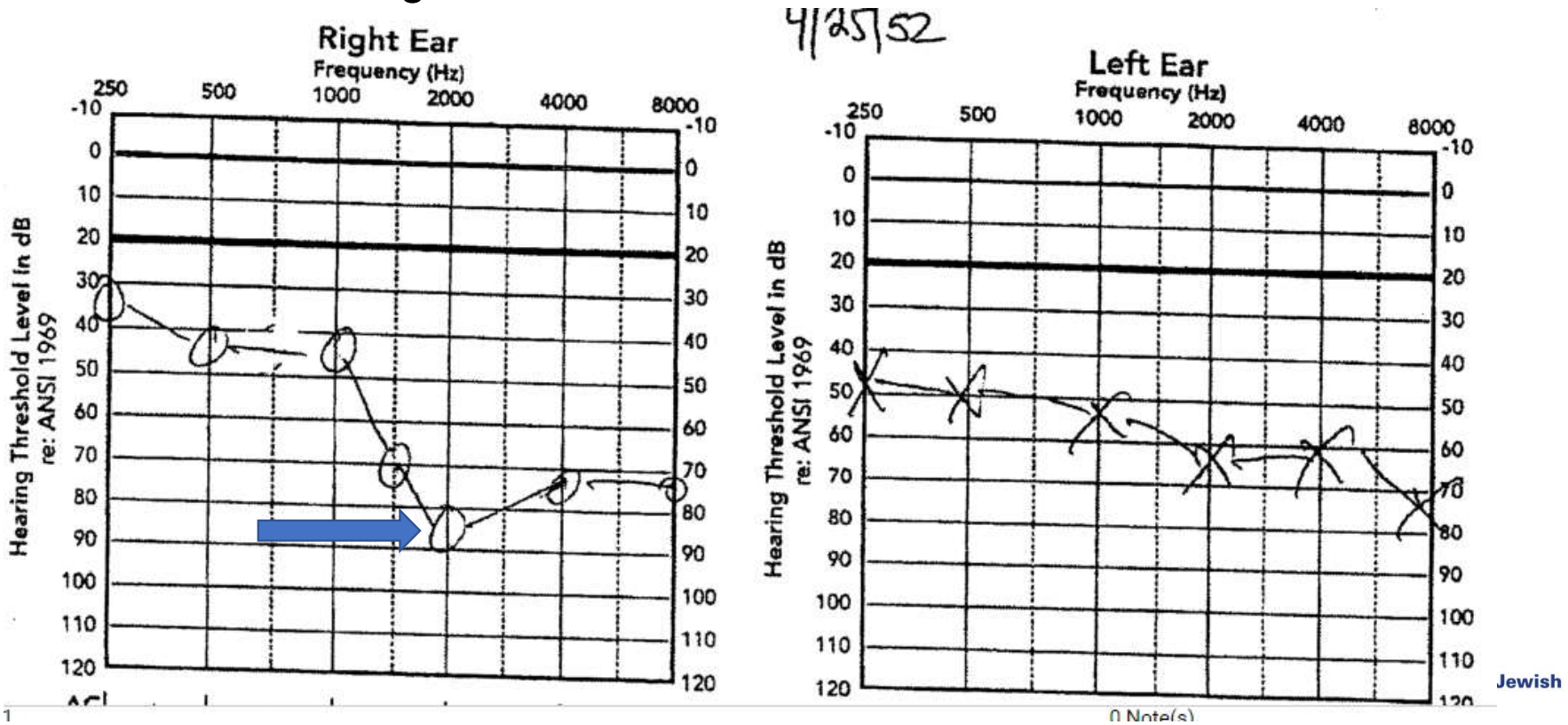
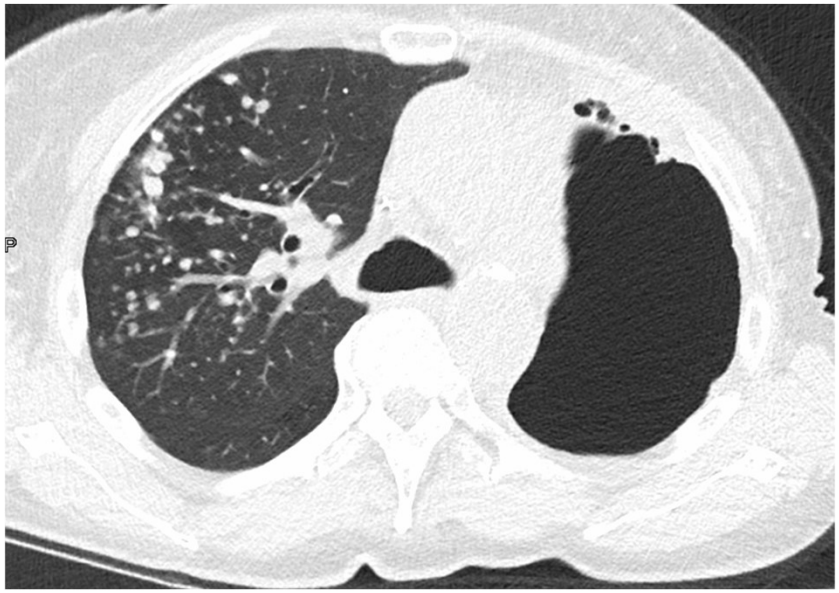
# Latest Audiometry

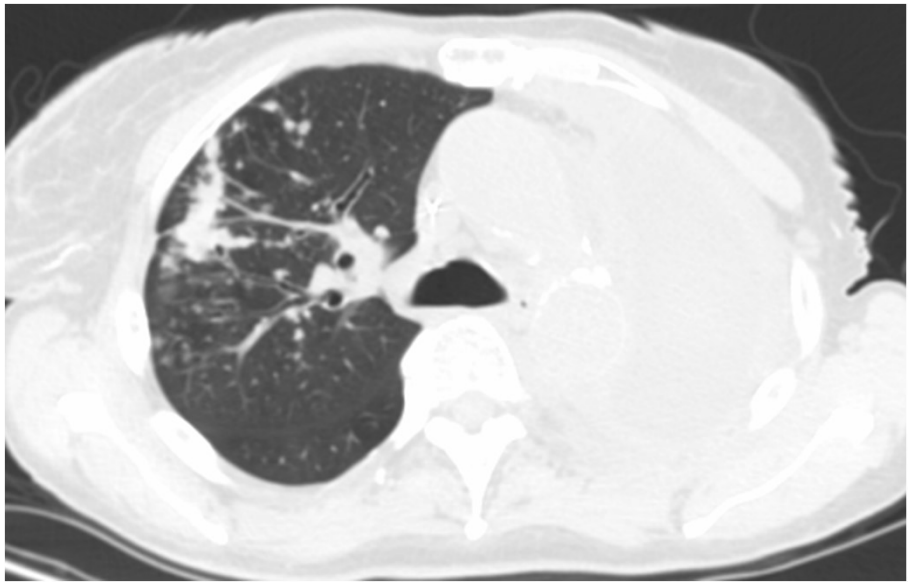
- 2/15/2024 Audiogram



# Follow-up Chest CT

- 1/8/2024 (left) vs. 3/5/2024 (right)





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# Potential Contributors to Macrolide Resistance

- Poor adherence
- Poor drug absorption (consider therapeutic drug monitoring)
- Weak regimens (especially lacking ethambutol)
- Insufficient strengthening of the regimen without ethambutol
- Large burden of infection (especially cavitary disease)

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# Take-Away Points

- IV amikacin early in cavitary MAC
- Consider lung surgery in difficult-to-treat cavitary infection
- Beware bacterial superinfection in cavitary lung disease (and fungal infection)
- Don’t forget about predispositions (e.g., oropharyngeal dysphagia, GERD)
- Repeat MICs and molecular markers of drug resistance are helpful
- Close follow-up:
  - EKGs
  - Audiograms
  - Bloodwork
  - Drug reaction management
  - Airway clearance adherence
  - Aspiration management

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