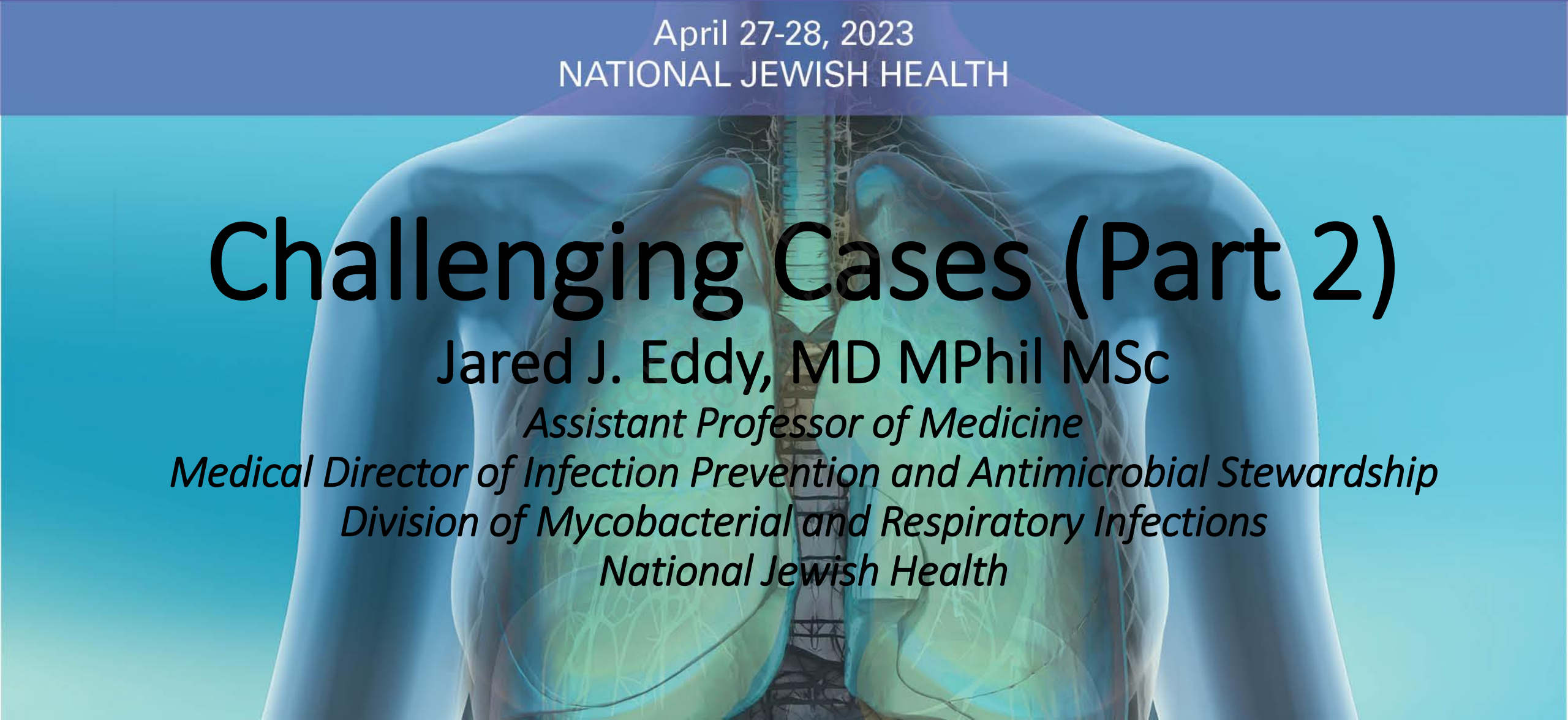
NTM Lecture Series for Providers

April 27-28, 2023
NATIONAL JEWISH HEALTH



Challenging Cases (Part 2)

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National Jewish Health

Disclosures

- No disclosures

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Case 1 (pulmonary): 50 year-old woman

- 53 year-old white woman from Kansas
- PMH:
  - Allergy, diverticulosis, GERD, gastroparesis, restless legs, fracture, migraine, depression
- Social:
  - Performs auto body estimates, limited smoking history
- Family History:
  - Asthma but no bronchiectasis, rheumatoid arthritis, CAD/CVA/HTN, diabetes mellitus, breast CA

Case 1 (50 yo F): History of Present Illness

- 9/2020: develops fever, cough worse when recumbent, dyspnea, fatigue, GI symptoms
- Diagnosed with pneumonia by CXR, 2 weeks PO *levofloxacin*
- Followed by 2 short courses of *IV antibiotics*
- 11/2020: CXR still abnormal, CT chest nodules, bronchiectasis
- Culture with ***MRSA*** and ***M. abscessus***, receives *doxycycline*, referred to infectious diseases
- 3/9/2021: bronchoscopy BAL cultures with ***M. abscessus***
- Referred to National Jewish Health

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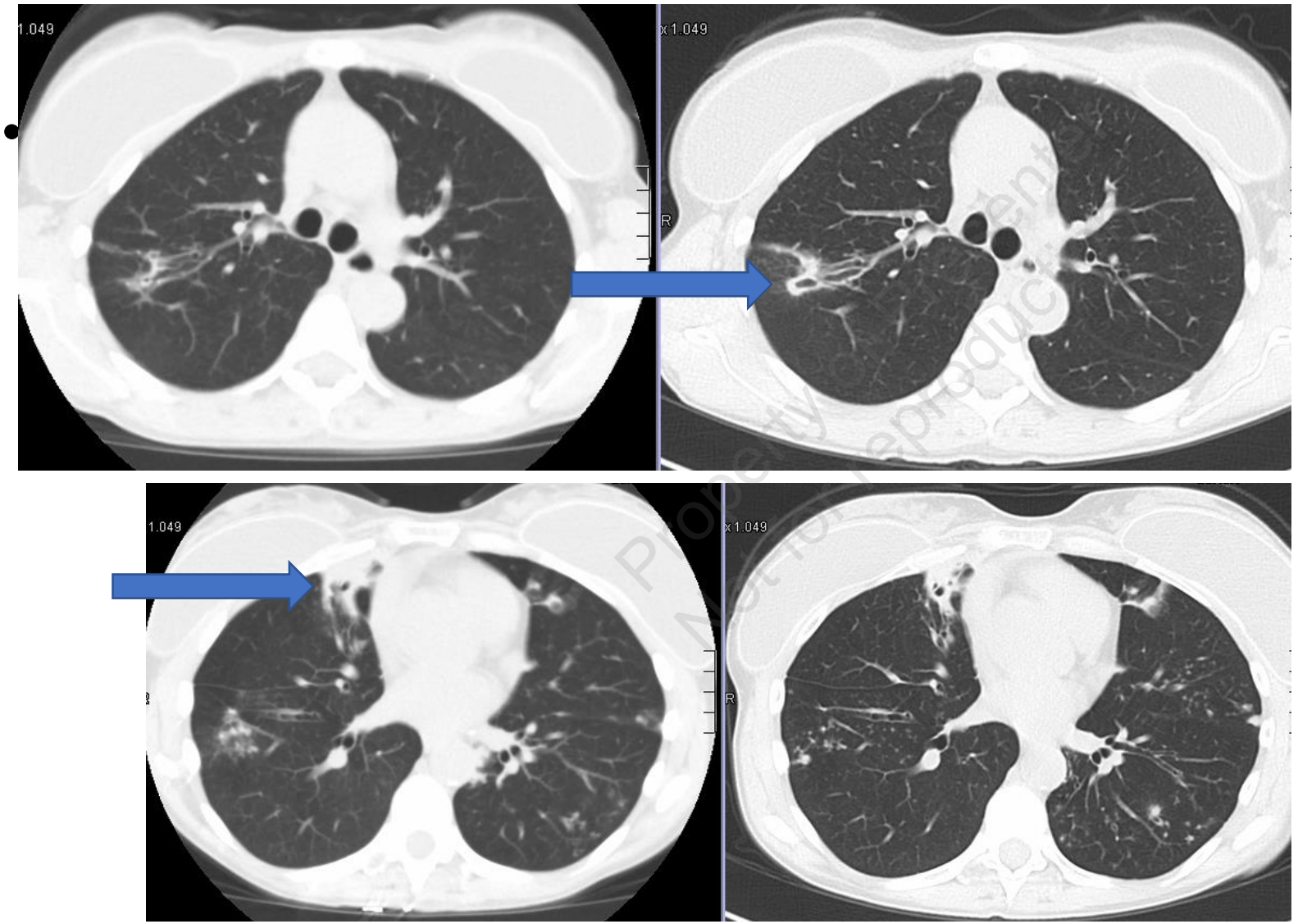
Case 1 (50 yo F): History of Present Illness (2)

- GI work-up in parallel with respiratory work-up…
- Ca. 9/2020: increasing intolerance to food and liquids with odynophagia, sensation of food stuck in chest, regurgitation (including fish dinner in the middle of the night)
- EGD and gastric emptying study performed locally
- Diagnosed with gastroparesis, intolerant of metoclopramide
- Weight loss 115 pounds to nadir of 84 pounds
- 3/2021: GJ tube placed, nightly feeds, very little by mouth

Case 1 (50 yo F): NJH adult day unit (ADU)

- Arrives ADU 12/2021, 100 pounds, productive cough, fatigue
- PFTs: FEV1 94%, FVC 94%, ratio 99%, RV 120%, DLCOcor 88%, no significant response to bronchodilator
- Bronchiectasis lab work-up:
  - Sweat chloride 37 (intermediate)
  - ANA elevation (1:2560 homogenous), other autoimmune serologies negative
- Introduced to Aerobika flutter valve and hypertonic saline
- Esophagram: moderate GERD to the level of the clavicles
- Tailored barium swallow: mild-to-moderate pharyngeal dysphagia, silent aspiration with mixed consistency

Case 1 (50 yo F): Imaging



6/2021 (left) vs. 12/2021 (right)

Worsening bronchiectasis vs. cavitation in right upper lobe (top)

Bronchiectasis most prominent in inferior right upper lobe and right middle lobe (bottom)

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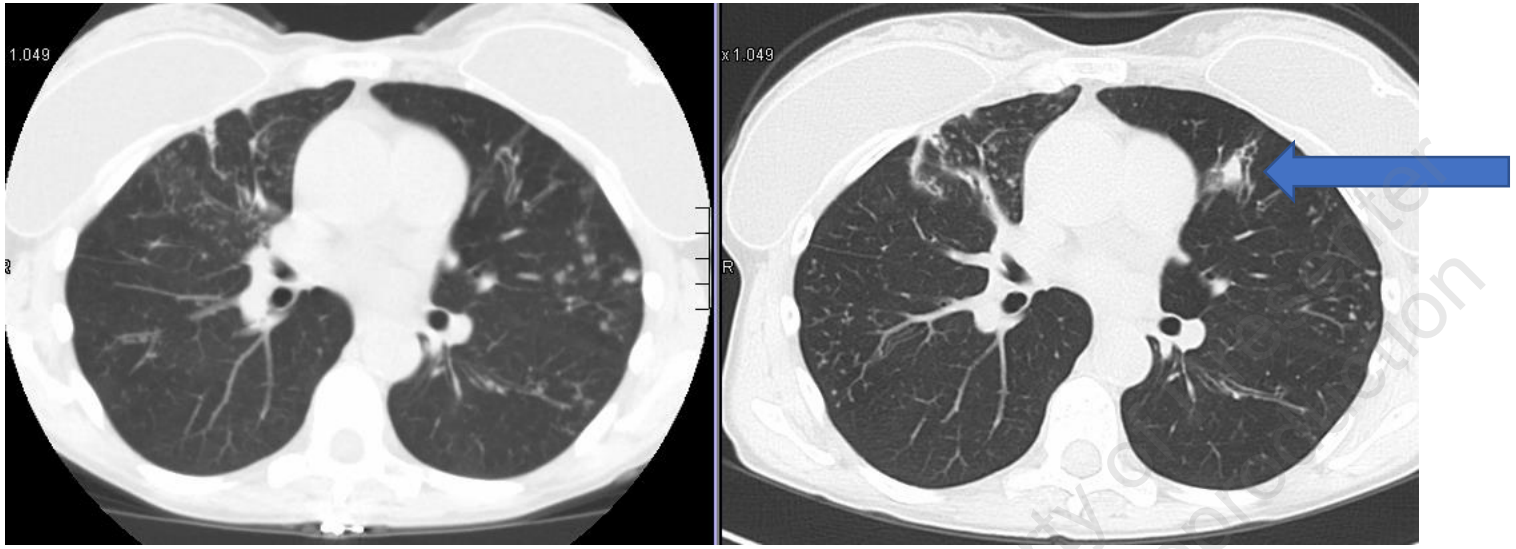
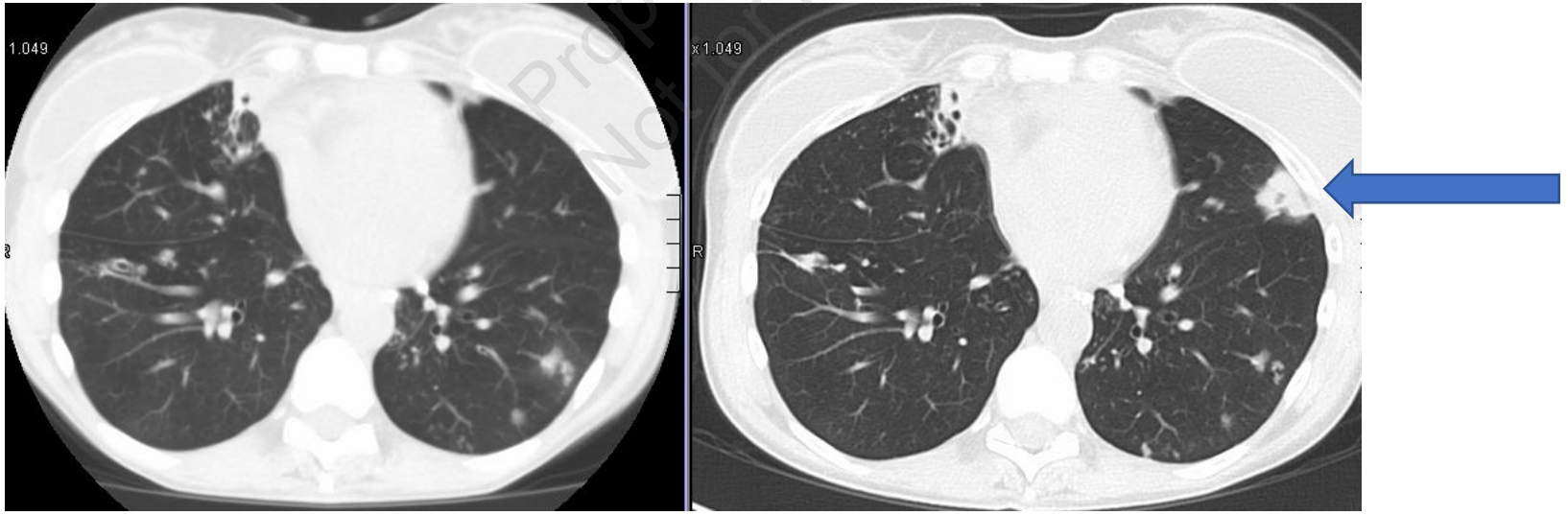
Case 1 (50 yo F): Imaging (2)



6/2021 (left) vs.
12/2021 (right)

Worsening nodularity in left upper lobe including lingula



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Case 1 (50 yo F): Microbiology (ca. 12/2021)

(Prior bronch/sputa data: ***MRSA***, ***M. abscessus*** in several cultures)

Preadmission sputum (11/9/2021, AFB smear negative):

- Moderate ***Proteus mirabilis***, few ***Candida albicans***
- ***M. abscessus subsp abscessus***, from broth
- ***M. intracellulare***, >400 colonies

Sputum, induced (11/30/2021, AFB smear negative):

- No respiratory pathogens, ***rare yeast***
- ***M. intracellulare***, 6 colonies

Sputum, induced (12/2/2021), 1+ AFB smear):

- ***M. abscessus subsp abscessus***, 400 colonies
- ***M. intracellulare***, 400 colonies

Sputum, induced (12/3/2021, AFB smear negative):

- ***M. abscessus subsp abscessus***, ?400 colonies
- ***M. intracellulare***, ?400 colonies

Case 1 (50 yo F): Susceptibilities

Organism / Antibiotic	M. abscessus MIC	INT
Amikacin (IV)	32	I
Amikacin (Liposomal, Inhaled)		
Augmentin	>32/16	NI
Azithromycin	<=16	NI
Azithromycin (14 Day)	128	NI
Cefepime	>32	NI
Cefotaxime	>64	NI
Cefoxitin	<=16	S
Ceftriaxone	>64	NI
Ciprofloxacin	>8	R
Clarithromycin	<=0.25	S
Clarithromycin (14 Day)	4	I
Clofazimine	<=0.5	NI
Clofazimine/Amikacin	<=0.5/2	NI
Doxycycline	>16	R
Gentamicin	16	NI
Imipenem	4	S
Kanamycin	<=8	NI
Linezolid	>16	R
Minocycline	>8	NI
Moxifloxacin	>4	R
Rifabutin		
Rifampin		
Streptomycin		
Tigecycline	0.5	NI
Tobramycin	16	R
Trimethoprim/Sulfamethoxazole	>4/76	R

A cytosine has been detected at position 28 (T28C) of the erm(41) gene.
THIS SUGGESTS SUSCEPTIBILITY TO MACROLIDES.

No mutations are present at rrl.
ACQUIRED (HIGH LEVEL) MACROLIDE RESISTANCE IS NOT PREDICTED.

No mutations are present at rrs.
THIS SUGGESTS SUSCEPTIBILITY TO AMINOGLYCOSIDES.

Organism / Antibiotic	M. intracellulare MIC	INT	
Amikacin (IV)	16	S	
Amikacin (Liposomal, Inhaled)	16	S	
Ciprofloxacin	>8	NI	
Clarithromycin	4	S	D1
Clofazimine	0.12	NI	
Doxycycline	>8	NI	
Linezolid	>32	R	D2
Minocycline	>8	NI	
Moxifloxacin	>4	R	D2
Rifabutin	0.5	NI	D3
Rifampin	>4	NI	D3
Streptomycin	32	NI	
Trimethoprim/Sulfamethoxazole	>4/76	NI	

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Case 1 (50 yo F): Audience Question #1

Given growth of both M. abscessus and MAC what is the next step?

1) Start treatment of *M. abscessus* only

2) Start treatment of *MAC* only

3) Start treatment for both *M. abscessus* and *MAC* at the same time

4) Treat neither organism, collect more data and rely on airway clearance measures, GERD behavioral changes, and dysphagia management to manage infections for the time being

Case 1 (50 yo F): functionality of erm gene

- The *erm(41)* gene (erythromycin resistance methylase)
- Confers inducible macrolide resistance if functional
- Some organisms have non-functional *erm*(41) genes and hence no *inducible* macrolide resistance, but may still *acquire* resistance
- 3 ways to determine *erm*(41) gene functionality:
  - Species/subspecies identification (somewhat imperfect, *M. abscessus* group only)
  - Direct molecular sequencing (C or T at position 28?)
  - Prolonged 14-day incubation of clarithromycin
    - If S becomes R then inducible resistance is detected

Case 1 (50 yo F): Susceptibilities again

Organism Antibiotic	M. abscessus MIC	 INT
Amikacin (IV)	32	I
Amikacin (Liposomal, Inhaled)		
Augmentin	>32/16	NI
Azithromycin	<=16	NI
Azithromycin (14 Day)	128	NI
Cefepime	>32	NI
Cefotaxime	>64	NI
Cefoxitin	<=16	S
Ceftriaxone	>64	NI
Ciprofloxacin	>8	R
Clarithromycin	<=0.25	S
Clarithromycin (14 Day)	4	I
Clofazimine	<=0.5	NI
Clofazimine/Amikacin	<=0.5/2	NI
Doxycycline	>16	R
Gentamicin	16	NI
Imipenem	4	S
Kanamycin	<=8	NI
Linezolid	>16	R
Minocycline	>8	NI
Moxifloxacin	>4	R
Rifabutin		
Rifampin		
Streptomycin		
Tigecycline	0.5	NI
Tobramycin	16	R
Trimethoprim/Sulfamethoxazole	>4/76	R

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Organism Antibiotic	M. intracellulare MIC	 INT	
Amikacin (IV)	16	S	
Amikacin (Liposomal, Inhaled)	16	S	
Ciprofloxacin	>8	NI	
Clarithromycin	4	S	D1
Clofazimine	0.12	NI	
Doxycycline	>8	NI	
Linezolid	>32	R	D2
Minocycline	>8	NI	
Moxifloxacin	>4	R	D2
Rifabutin	0.5	NI	D3
Rifampin	>4	NI	D3
Streptomycin	32	NI	
Trimethoprim/Sulfamethoxazole	>4/76	NI	

No mutations are present at rrl.
ACQUIRED (HIGH LEVEL) MACROLIDE RESISTANCE IS NOT PREDICTED.

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THIS SUGGESTS SUSCEPTIBILITY TO AMINOGLYCOSIDES.

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Case 1 (50 yo F): Treatment Considerations

Scenario 1: (macrolide-susceptible M. abscessus)

Option 1: Treat MAC only…. Mabs acquired macrolide resistance

Antibiotic	MAC	M. Abscessus (macrolide-S)
Azithromycin	Yes	Yes
Ethambutol	Yes	No
Rifampin (RIF)	Yes	No
Clofazimine	Yes (e.g., substitute for RIF)	Yes
Amikacin	Yes (serious disease)	Yes
Imipenem (or Cefoxitin)	No	Yes
Linezolid/tedizolid	Maybe (susceptible?)	Maybe (susceptible?)
[Other drugs, e.g. omadacycline, bedaquiline]	Maybe/Yes	Yes

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Case 1 (50 yo F): Treatment Considerations

Scenario 1: (macrolide-susceptible M. abscessus)

Option 2: Treat Mabs only…. MAC acquired macrolide resistance? MAC acquired amikacin resistance?

(importance of ethambutol for preventing acquired macrolide resistance in MAC)

Antibiotic	MAC	M. Abscessus (macrolide-S)
Azithromycin →	Yes	Yes ←
Ethambutol	Yes	No
Rifampin (RIF)	Yes	No
Clofazimine →	Yes (e.g., substitute for RIF)	Yes ←
Amikacin →	Yes (serious disease)	Yes ←
Imipenem (or Cefoxitin)	No	Yes ←
Linezolid/tedizolid	Maybe (susceptible?)	Maybe (susceptible?)
[Other drugs, e.g. omadacycline, bedaquiline]	Maybe/Yes	Yes

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Case 1 (50 yo F): Treatment Considerations

Scenario 2: (macrolide-resistant M. abscessus)

Option 1: Treat MAC only…. Safe from a drug resistance standpoint

Antibiotic	MAC	M. Abscessus (macrolide-R)
Azithromycin	Yes	No
Ethambutol	Yes	No
Rifampin (RIF)	Yes	No
Clofazimine	Yes (e.g., substitute for RIF)	Yes
Amikacin	Yes (serious disease)	Yes
Imipenem (or Cefoxitin)	No	Yes
Linezolid/tedizolid	Maybe (susceptible?)	Maybe (susceptible?)
[Other drugs, e.g. omadacycline, bedaquiline]	Maybe/Yes	Yes

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Case 1 (50 yo F): Treatment Considerations

Scenario 2: (macrolide-resistant M. abscessus)

Option 2: Treat Mabs only…. MAC acquired amikacin resistance?

Antibiotic	MAC	M. Abscessus (macrolide-R)
Azithromycin	Yes	No
Ethambutol	Yes	No
Rifampin (RIF)	Yes	No
Clofazimine ⇨	Yes (e.g., substitute for RIF)	Yes ⇦
Amikacin ⇨	Yes (serious disease)	Yes ⇦
Imipenem (or Cefoxitin)	No	Yes ⇦
Linezolid/tedizolid	Maybe (susceptible?)	Maybe (susceptible?)
[Other drugs, e.g. omadacycline, bedaquiline] ⇨	Maybe/Yes	Yes ⇦

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Case 1 (50 yo F): Treatment Regimen

Induction Regimen:
- Azithromycin PO
- Ethambutol PO
- Clofazimine PO
- Amikacin IV
- Imipenem IV

Maintenance Regimen:
- Azithromycin PO
- Ethambutol PO
- Clofazimine PO
- Amikacin inhaled

Induction Regimen:

MAC therapy:
- Azithromycin PO
- Ethambutol PO
- Clofazimine PO
- Amikacin IV PO

Maintenance Regimen:

MAC therapy:
- Azithromycin PO
- Ethambutol PO
- Clofazimine PO
- Amikacin inhaled

Induction Regimen:

M. abscessus therapy:
- Azithromycin PO
- Clofazimine PO
- Amikacin IV
- Imipenem IV

Maintenance Regimen:

M. abscessus therapy:
- Azithromycin PO
- Clofazimine PO
- Amikacin inhaled

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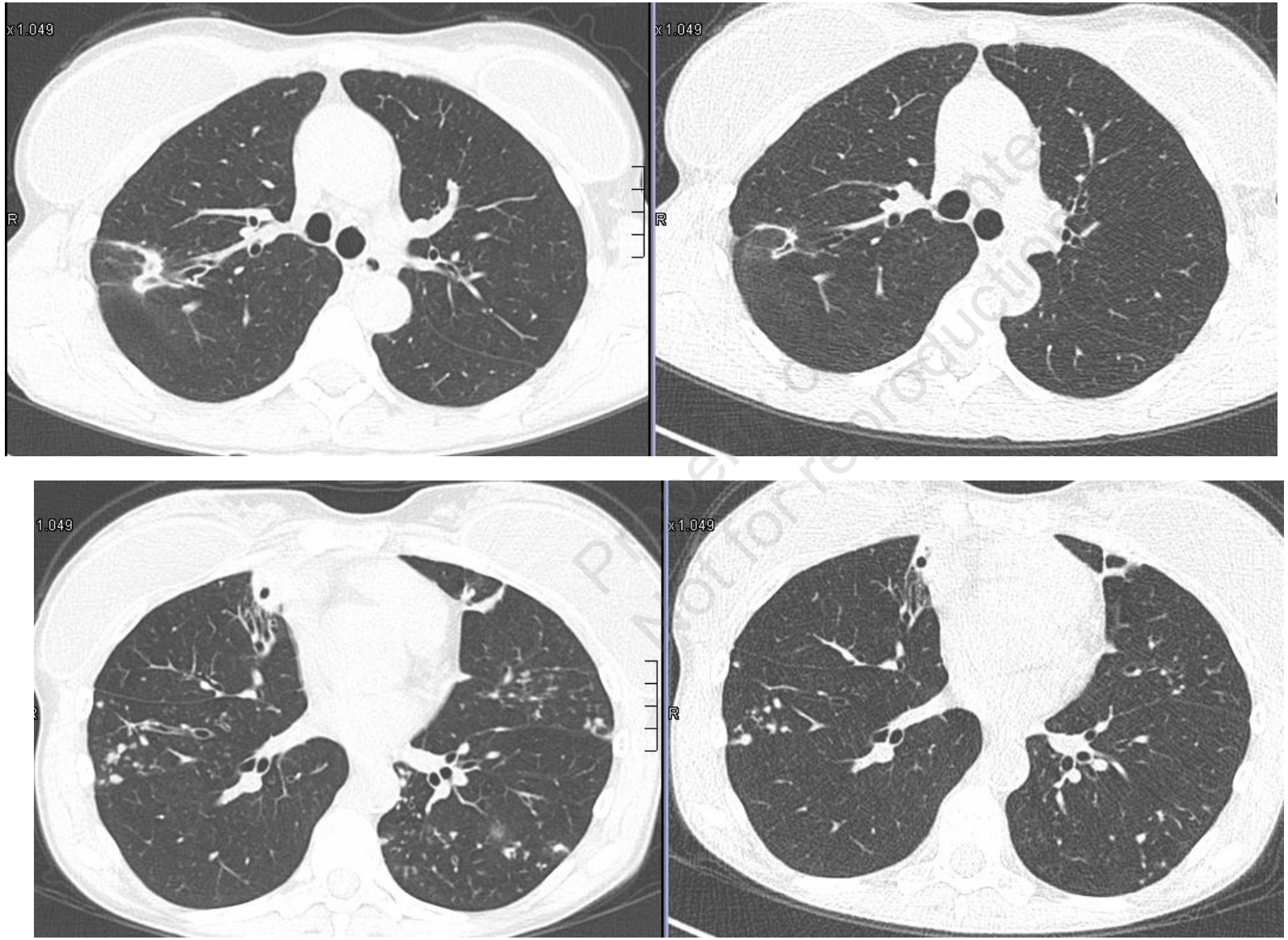
Case 1 (50 yo F): Treatment Response



12/2021 (left)

5/2022 (right)

Received ca. 4 months of IV amikacin and imipenem with orals (and airway clearance)

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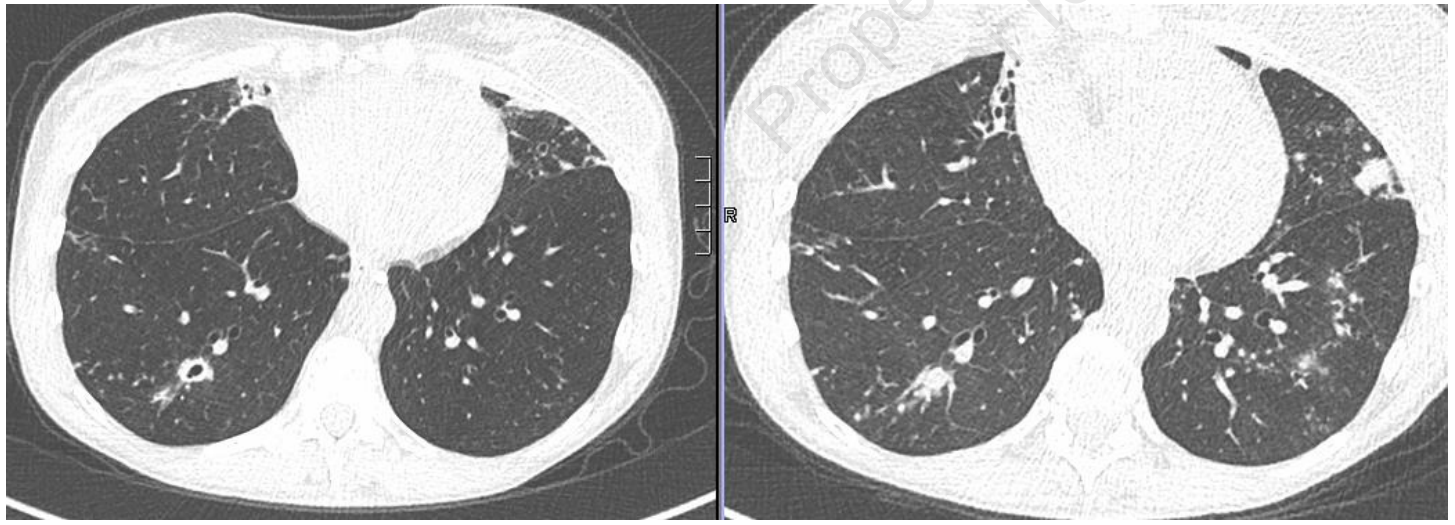
Case 1 (50 yo F): Follow-up developments

- CFTR disease-modifying mutation (TG)11-5T on genetic testing, repeat sweat chloride 48 (high intermediate), cystic fibrosis team diagnoses a ***CFTR-related disorder***
- Not tolerating domperidone, continuing to regurgitate regularly
- Rheumatology: history & symptoms not consistent with rheumatologic disease
- Patient declined further IV therapy at this time: next steps optimize airway clearance, return to GI and speech language pathology



12/2022 (left)
Received 2 weeks of piperacillin/tazobactam for MSSA and Pseudomonas aeruginosa locally (midline clot) (+ NTM antibiotics), added vest therapy

3/2023 (right)

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Case 1 (50 yo F): Principles

If MAC and Mabs both growing:

- Determine a dominant organism and treat that only
- Treat neither? (if mild disease)
- Treat both
- Ongoing sputum surveillance is critical!

- The underlying issues are reflux and aspiration and abnormal CFTR function, address underlying causes as much as possible
- Multiple organisms in the sputum (not just NTM), difficult to discern when and what to treat

Case 2 (Extrapulmonary): 38 year-old woman

- 38 year-old white woman from South-West US
- PMH: partial thyroidectomy/parathyroidectomy, endometriosis, gastric ulcers, migraines, meningioma, anxiety/depression
- **Liposuction** 5/18/2021 (halted for pneumothorax)
- **Liposuction** again 8/18/2021
  - ***Thighs, abdomen, gluteal region, back, back of arms***
- Bruising receding, persistent erythematous lesions on legs (no clot)
- Surgeon provides **steroid injections** (8/2021-9/2021)
- "Pimples" opening, hospitalized, seen by infectious diseases

Liposuction (general pictures)

Case 2 (38 yo F): Early Lesions

- One week after liposuction (left), lesions a few weeks afterwards (center), and opening (right)

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Case 2 (38 yo F): September 2021 Events

- Punch biopsies by dermatology:
  - Skin, left thigh (9/8/2021): "skin with ***deep fat necrosis and foamy histiocytes***; Comments: these findings are consistent with prior procedural-related changes. No features to suggest an underlying cellulitis."
  - Skin, right thigh (9/21/2021): "***mixed inflammation*** involving the deep dermis subcutaneous tissue, and focally the superficial dermis. There are ***large collections of neutrophils***. PAS, Gram, GMS, and Fite [AFB] stains are negative for organisms; however, the findings are highly suspicious for an infectious process. Correlation with tissue cultures is recommended. The changes of erythema nodosum are not identified."
- Cultures are negative for bacteria
- Suspicion for pyoderma gangrenosum, receives **oral steroids**, IV antibiotics
- Leaves hospital, outpatient rheumatology evaluation is negative

Case 2 (38 yo F): October-December 2021 Events

- "Septic" at the end of 10/2021, admitted to a different hospital
- CT scans: abscesses throughout legs, abdomen, chest
- Taken quickly to **surgery 10/29/2021** (right thigh excisional biopsy and left groin wound debridement with partial closure)
  - Histology: granulomas, foreign body reaction, no organisms seen
  - Deeper cultures grow ***M. abscessus group***
- ID starts ***azithromycin PO, amikacin IV, cefoxitin IV, tigecycline IV*** after consultation with National Jewish
- 30-pound weight loss, IV tigecycline changed to eravacycline
- Admissions for weight loss, minor surgeries (11/2021-12/2021) to drain fluid collections (ca. 2-3cm) in thighs
- Referred to plastic surgeon specializing in wounds

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Case 2 (38 yo F): isolated excisions

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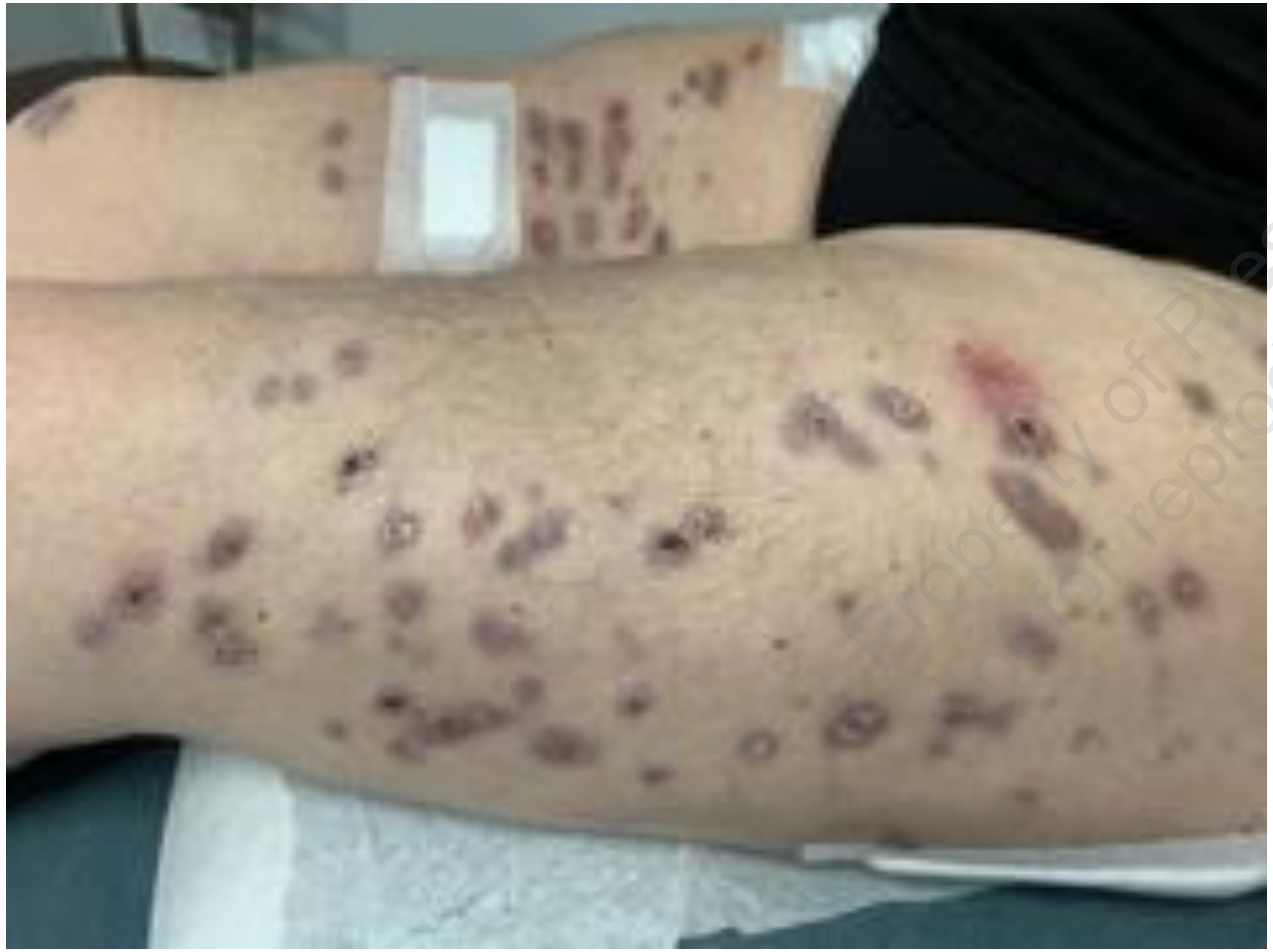
Case 2 (38 yo F): New Lesions



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Case 2 (38 yo F): Audience Question #2

- Most lesions becoming crusted but some newer erythematous lesions

<u>What would you recommend?:</u>

1) Change/increase antibiotic therapy, given concern for antibiotic failure

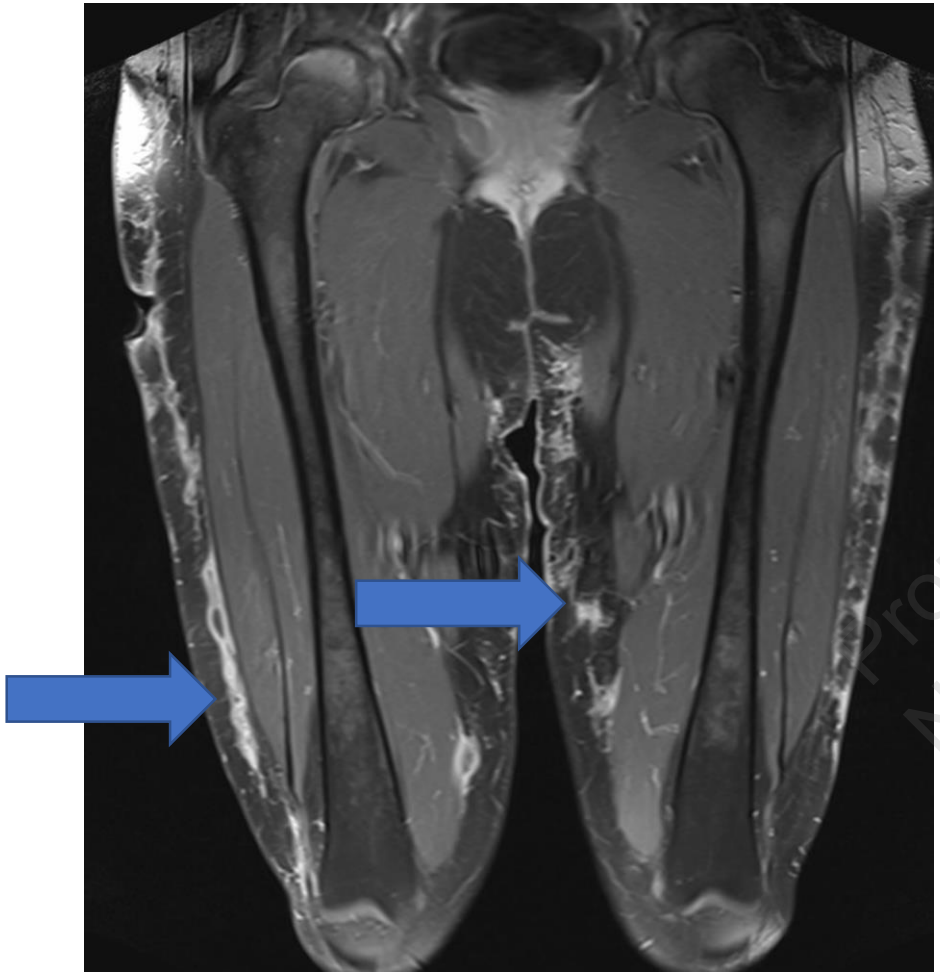
2) Further surgery for culture/removal newer lesions (+ antibiotics)

3) Removal of all affected skin/SQ tissue (+ antibiotics)

4) Maintain current antibiotic plan, as new lesions are expected as part of the natural history of the infection

5) Add prednisone for paradoxical-type reaction (akin to steroids for IRIS in HIV)

Case 2 (38 yo F): MRIs reveal extensive infection



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Case 2 (38 yo F): Dermatofasciectomies

Abdomen (2/26/2022)

Right hip (3/3/2022) [NJH cultures negative]

Right thigh (3/11/2022)

Left thigh & hip (3/24/2022)

Case 2 (38 yo F): Skin Grafting 5/2022

All areas: Integra regenerative matrix covered with split thickness skin graft, healing properly

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Case 2 (38 yo F): Healed by 1/20/2023

Further surgeries for peripheral lesions & to release contractures (7/2022-12/2022)
Current treatment: ***azithromycin***, ***clofazimine***, ***omadacycline***

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Case 2 (38 yo F): Takeaways

- Beware steroids in lesions that are potentially NTM
- Imaging (especially MRI) helps determine the (deep) extent of infection
- Aggressive early debridement, beware “cherry-picking”
- Culture/debride new lesions
- Periodic imaging for new/residual infection, followed by debridement