

WEST COAST ID Case Conference

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Date 2/7/24



LOMA LINDA UNIVERSITY
HEALTH SYSTEM



HPI/Timeline

- » █ y/o █ admitted for cardiogenic shock █ 2023
- » █ – █ inpatient on dobutamine with R axillary Impella, listed for transplant
 - ~ █ s/p OHT + R axillary Impella removal, induction with basiliximab
 - ~ █-█ s/p IVIG/PLEX
 - ~ █ s/p L VATS for hemothorax evacuation, likely due to prior thoracentesis
 - ~ █ Discharge with tacrolimus, mycophenolate, prednisone taper, fluconazole, valganciclovir, pentamidine
- » Jun – Aug
 - ~ Poor follow up, not answering phone calls, running out of medication, missing biopsy appointments and lab checks
- » Admitted 8/█/23 due to EF dropping to 50% on outpatient echo
 - ~ Strong suspicion for rejection (later confirmed) → Solumedrol 500mg x3
 - ~ **ID was consulted for right pulmonary mass found on initial chest imaging**
 - ~ ROS negative: No cough, fever



Histories

» Medications

- ~ Amlodipine 5mg
- ~ Aspirin 81mg
- ~ Atorvastatin 10mg
- ~ Colchicine 0.6mg
- ~ Empagliflozin 25mg
- ~ Gabapentin 100mg bid
- ~ Metformin 500mg bid
- ~ Magnesium oxide 400mg
- ~ Omeprazole 40mg

» Immunosuppression

- ~ Tacrolimus 5mg bid
- ~ Mycophenolate 1500mg bid
- ~ Prednisone 12.5mg PO daily

» Prophylaxis

- ~ Fluconazole 200mg PO daily
- ~ Valganciclovir 450mg PO daily
- ~ Pentamidine (last prior to d/c in May)

» Social History

- ~ Born in Mississippi, moved to CA in 19█, lives in █ county
- ~ Self-employed, works as landscaper/handyman
- ~ Imprisoned in █
- ~ █, has █ y/o daughter he takes care of █
- ~ Brief car trip to New Mexico the day prior to admission, no overnight stay



Initial Labs

» CBC

- ~ WBC 6.08
- ~ Hgb 9.2
- ~ MCV 83.7
- ~ PLT 333
- » FK 14.1
- » HLA PRA Class I/II negative
- » HbA1c 10.0
- » UDS negative

» CMP

- ~ Na 142
- ~ K 3.9
- ~ Cl 107
- ~ CO2 22
- ~ AG 13
- ~ BUN 16
- ~ Cr 1.1
- ~ Ca 2.3 mMol/L
- ~ Tot Protein 6.0
- ~ Albumin 3.9
- ~ AST 23
- ~ ALT 32
- ~ Alk Phos 181
- ~ Tbili 0.2



Pre-Transplant Labs

- » QuantiFERON Gold: Neg
 - ~ Nil 0.04
 - ~ Ag1 0.12
 - ~ Ag2 0.01
 - ~ Mitogen 9.85
- » Coccidioides ID/CF: Neg
- » Histo CF/ID: Neg
- » Toxoplasma IgG: Neg
- » Strongyloides IgG: Neg
- » T. Cruzi IgG: Neg
- » HIV Ab/Ab: Neg
- » Syphilis EIA: Neg
- » HBV
 - ~ sAb: Neg
 - ~ cAb: Neg
 - ~ sAb: Neg
- » HCV Ab: Neg
- » VZV IgG: +
- » HSV 1&2 IgG: +
- » CMV IgG: +
- » EBV IgG: +



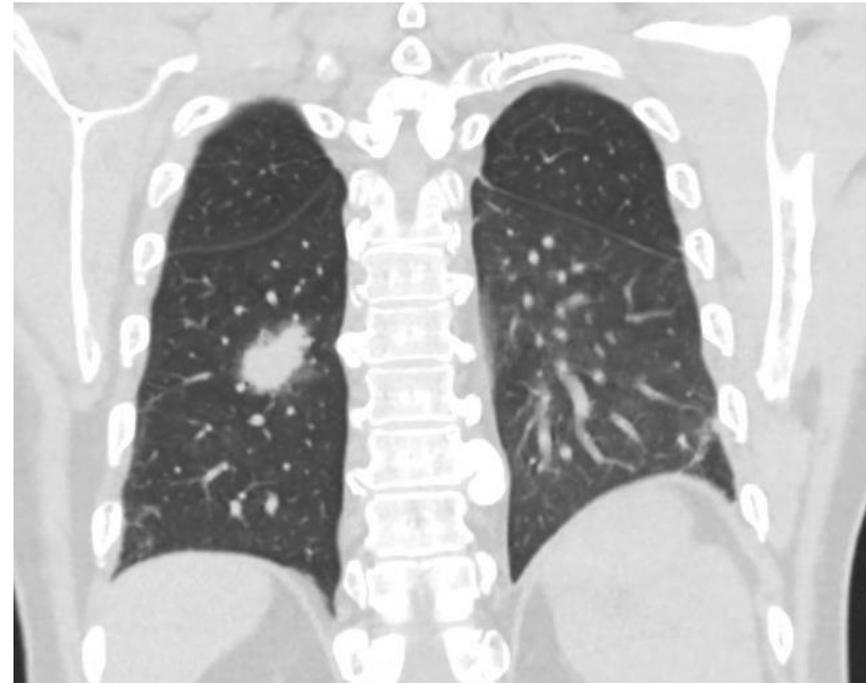
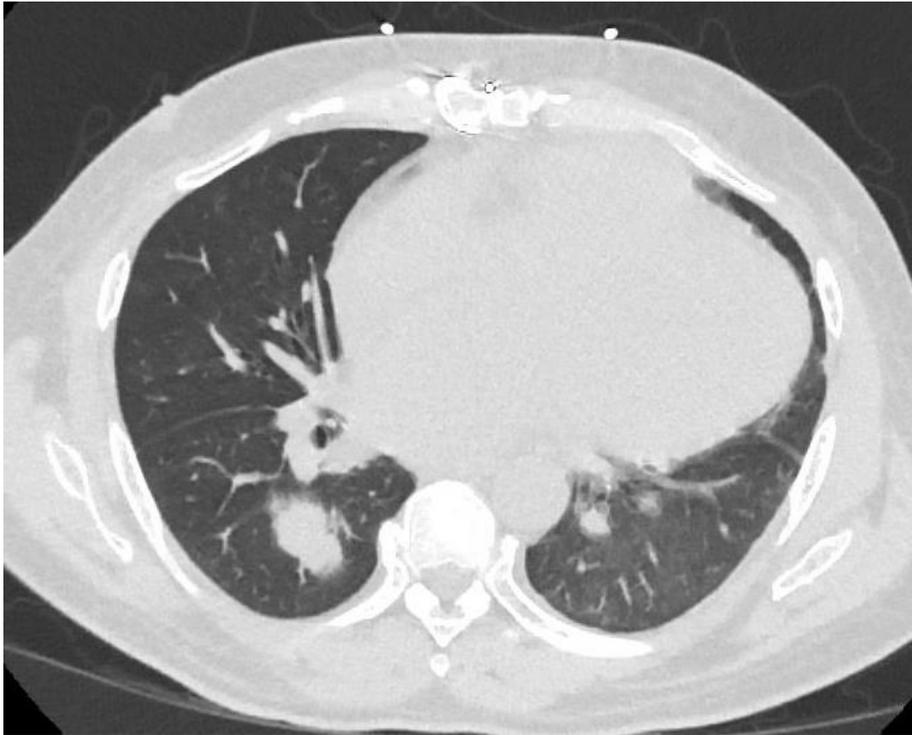
Imaging: Chest x-ray



Slightly worsened left basilar aeration when compared with prior, likely atelectasis



CT Thorax without contrast 8/26



Grouped right lower lobe non-calcified nodular densities measure up to 24 mm (8-327). There is adjacent groundglass surrounding these nodules. Additional small nodular opacity measuring 5 mm is seen inferior aspect of the right upper lobe adjacent to the minor fissure (8-287). Left apical calcified granuloma is noted.



Polling Question

- » What type of empiric therapy would you start in this scenario?
 - ~ No therapy at this point
 - ~ Vancomycin + Cefepime
 - ~ Linezolid + Meropenem + Isavuconazole
 - ~ Liposomal Amphotericin B
 - ~ High-dose TMP-SMX + Meropenem + Azithromycin + L-AMB + Isavuconazole + RIPE



Initial Hospital Course

- » ID Recs 8/█
 - ~ Requested for pulmonary consult for bronchoscopy with BAL
 - Send for bacterial, fungal, AFB cultures, BAL galactomannan, Aspergillus PCR, Cocci PCR
 - ~ Discuss with IR and Pulmonary if transthoracic vs transbronchial biopsy is feasible
 - ~ Obtain serum Aspergillus Ag, Cocci CF/ID, Crypto screen, beta-D-glucan
 - ~ Liposomal-amphotericin 5mg/kg was started
- » IR → Biopsy performed with EMB 8/█
 - ~ Cultures sent

Right lung lesion (core biopsy):

Extensive fibrinopurulent exudate with intra-alveolar fibrin plugs, favor bacterial infectious etiology (see COMMENT)

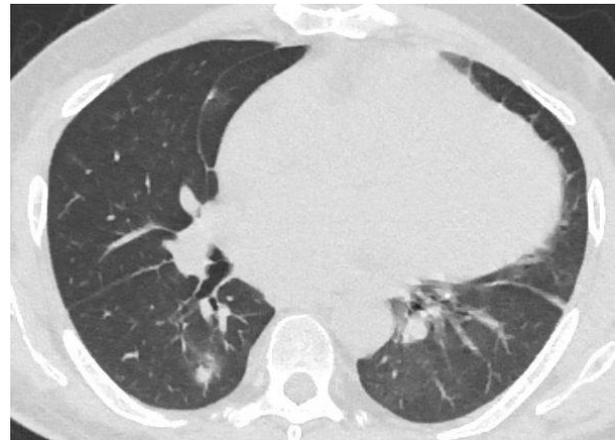
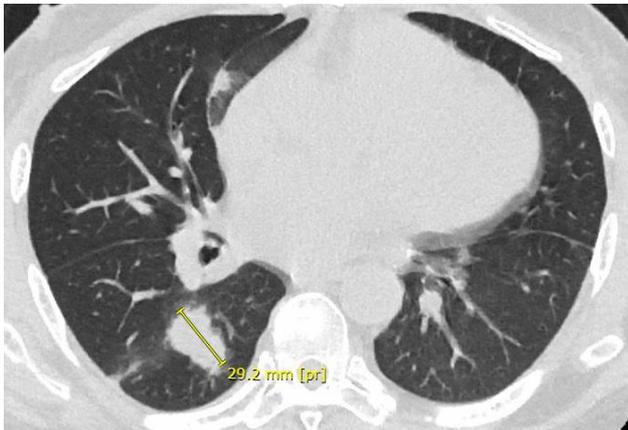
Special stains negative for fungal organisms (GMS and PAS; adequate controls)

CMV immunostain is negative (adequate control)

Negative for malignancy



Worsening despite L-AMB Day 8



» 9/2

8/26



Initial Microbiology by 9/1

- » CMV PCR: neg
- » EBV PCR: neg
- » Respiratory PCR Panel: neg
- » Serum Beta-D-glucan: neg <31
- » Serum Aspergillus Ag: neg
- » Serum Cocci CF/ID: neg
- » Histo CF/ID: neg
- » Crypto screen: neg
- » Induced Sputum
 - ~ Bacterial ctx → normal flora
 - ~ Fungal ctx → NGTD
- » IR Biopsy
 - ~ Tissue ctx → No organisms, NGTD
 - ~ Fungal ctx → No organisms, NGTD
 - ~ AFB ctx → No organisms, NGTD
 - ~ Anaerobic ctx → Very light growth
Staph epidermidis

*Called regarding adding AFB stain to pathology slide however lab was out of reagents and unable to perform



Clinical Summary

- » ■ y/o ■ s/p OHT on 5/■/2023, induction with basiliximab, maintenance with 3-drug regimen, admitted for rejection, given solumedrol x3, incidentally found to have RLL pulmonary mass
- » Asymptomatic, afebrile, off oxygen
- » CT Thorax with RLL nodular mass growing despite 1 week of L-AMB
- » IR biopsy → Extensive fibrinopurulent exudate with intra-alveolar fibrin plugs, negative for malignancy, GMS/PAS stains are negative, no AFB stain, cultures all negative but pending



Polling Question

- » What is your top differential diagnoses?
~ Free text



Differential Diagnosis

» Invasive fungal infection

- ~ Aspergillus
- ~ Mucormycosis
- ~ Phaeohyphomycosis
- ~ Endemic fungi
- ~ Cryptococcus
- ~ Scedosporium
- ~ Fusariosis

» MTB

» Nocardiosis

» Thoracic Actinomycosis

» PTLD

» Organizing Pneumonia

» Legionella

» Rhodococcus

» PCP?

» CMV?



Hospital Course 9/█ – 9/█

- » ID Recs 9/█
 - ~ Start Posaconazole, Linezolid, Imipenem, L-AMB stopped due to AKI
 - ~ Karius sent
- » Pulmonary 9/█ → Bronch w/ BAL, TBNA of RUL and RLL nodules

A

TBNA, RLL nodule with ROSE:

Abundant necrotic debris and mixed inflammatory cells

Structures suggestive of filamentous bacteria seen on GMS stain (see comment)

No evidence of Mucormycosis seen on PAS and GMS stains

No acid fast organisms identified on AFB stain

No malignant cells identified

Comment

Although structures resembling rare fungal hyphae are seen on the smears, convincing evidence of fungal organisms are not noted on the PAS and GMS stains (blocks A1 and B1 with adequate controls). Clinical correlation is suggested. The GMS stain (block A1) shows multiple clusters of filamentous structures suggesting the possibility of nocardia species. A Gram stain is pending and will be reported in an Addendum. Correlation with the microbiologic culture results is recommended.

Comment, Addendum

The bacteria are gram positive and filamentous (controls adequate)



Initial Discharge and Readmission

- » 9/█ Patient leaves AMA
 - ~ Discharged with posaconazole, amoxicillin-clavulanate, linezolid empirically
- » 9/█ Nocardia was confirmed, patient called for readmission
 - ~ Patient initially refuses, eventually agrees
- » 9/█ -9/█
 - ~ Started on IV imipenem
 - ~ Linezolid switched to minocycline due to thrombocytopenia
 - ~ Posaconazole switched to fluconazole prophylaxis
 - ~ MRI Brain → No enhancing lesions
 - ~ PICC line placed for imipenem x6 weeks + minocycline 200mg PO bid



Updated Microbiology

- » Induced Sputum 9/█
 - ~ Fungal ctx →

Final Report ? (P)
Filamentous fungi (Ascomycete)
Test performed by Mayo Medical
Laboratories
200 First Street SW
Rochester, Minnesota 55905

- » IR Biopsy 8/█
 - ~ Tissue ctx → Final NGTD
 - ~ Fungal ctx → Final NGTD
 - ~ AFB ctx → Final NGTD
 - ~ Anaerobic ctx → Staph epi

- » Bronchoscopy 9/█
 - ~ BAL Galactomannan <0.500
 - ~ RLL BAL/TBNA →

Final Report ? (P)
Very light growth Nocardia species
(Nocardia wallacei) - refer to Misc SO
collected 9/5/2023 11:20 for
susceptibilities
Test performed by Mayo Medical
Laboratories
200 First Street SW
Rochester, Minnesota 55905

- ~ RUL BAL/TBNA →

Final Report ? (P)
Nocardia kruczakiea
Test performed by Mayo Medical
Laboratories
200 First Street SW
Rochester, Minnesota 55905
No acid fast bacillus isolated at 6
weeks



Updated Microbiology

SUSC, AEROBIC ACTINOMYCETES FINAL

NOCARDIA KRUCZAKIAE

Organism	NOCARDIA KRUCZAKIAE	
Antibiotic	MIC (mcg/mL)	Interpretation
Amox/Clav	128/64	R
Ceftriaxone	8	S
Imipenem	1	S
Ciprofloxacin	16	R
Moxifloxacin	4	R
Clarithromycin	0.06	S
Amikacin	2	S
Tobramycin	>64	R
Doxycycline	4	I
Minocycline	1	S
TMP/SMX	1/19	S
Linezolid	8	S

Ciprofloxacin: Ciprofloxacin and levofloxacin are interchangeable, but both are less active in vitro than moxifloxacin.

Clarithromycin: Class representative for newer macrolides.

S=SUSCEPTIBLE I=INTERMEDIATE R=RESISTANT
NS=NONSUSCEPTIBLE SDD=SUSCEPTIBLE DOSE DEPENDENT

KARIUS TEST REPORT
Karius ID: KA-228712

INTERVAL	DNA MOLECULS PER	REFERENCE
MICROORGANISM DETECTED	MICROLITER (MPM) *	(MPM) **
Nocardia kruczakiae	283	<10

SUSC, AEROBIC ACTINOMYCETES FINAL

NOCARDIA WALLACEI

Organism	NOCARDIA WALLACEI	
Antibiotic	MIC (mcg/mL)	Interpretation
Amox/Clav	8/4	S
Ceftriaxone	8	S
Imipenem	>32	R
Ciprofloxacin	2	I
Moxifloxacin	0.5	S
Clarithromycin	>16	R
Amikacin	32	R
Tobramycin	>64	R
Doxycycline	8	R
Minocycline	4	I
TMP/SMX	0.5/9.5	S
Linezolid	2	S

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Outpatient Course Oct – Nov

» With susceptibilities, ID Recs:

- ~ Stop minocycline and start Bactrim 5 mg/kg ... never picks up
- ~ Switch imipenem to IV ceftriaxone 2gm q12h ... never switched

» October

- ~ Repeat CT thorax 10/10

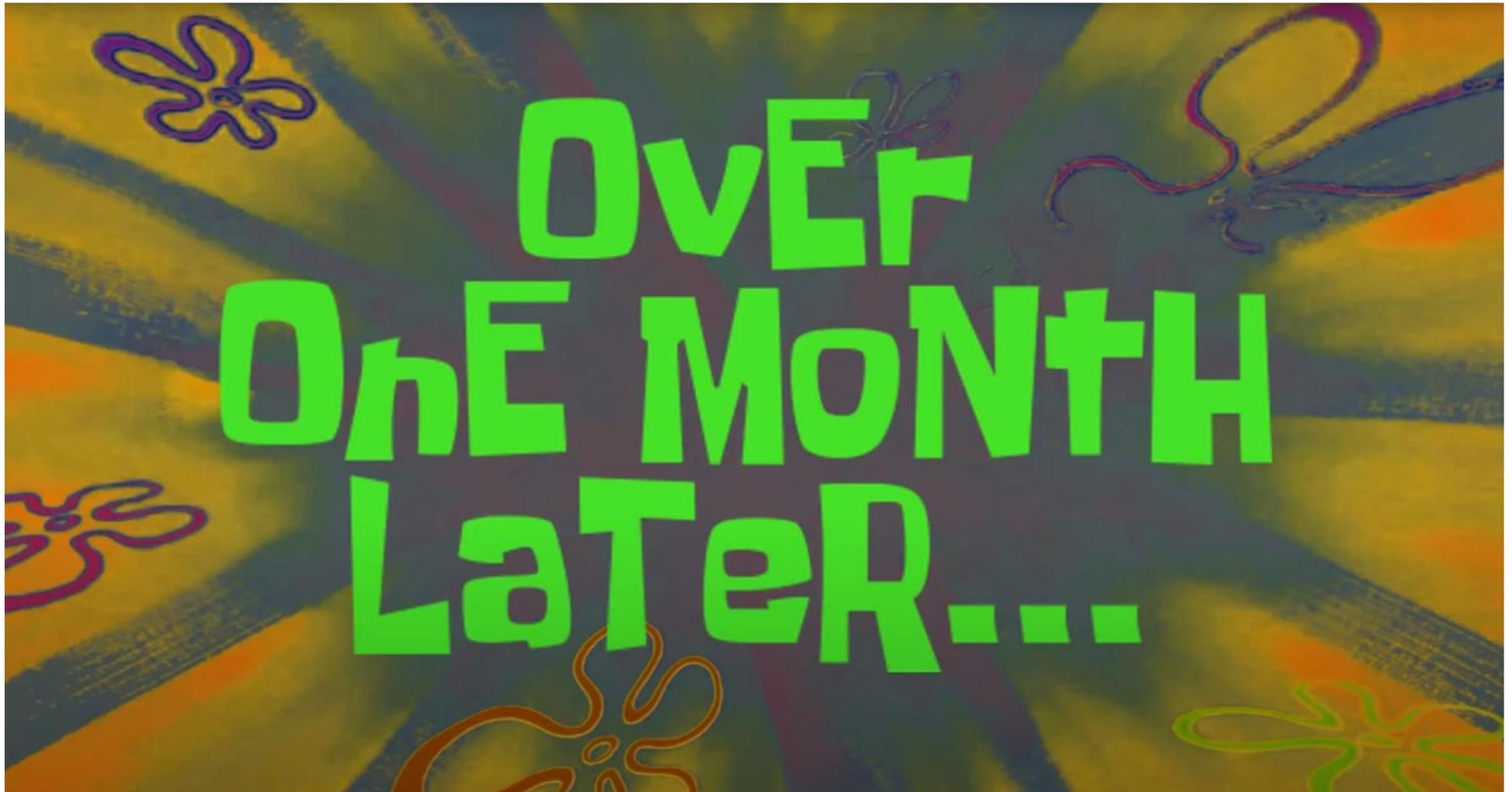
IMPRESSION:

Redemonstration of findings consistent with nocardia infection with decreased size of the right upper lobe consolidation, and slight increase in size of the right lower lobe lesion with new adjacent nodule measuring 0.5 cm.

- ~ Was presumably taking the original minocycline and imipenem
- ~ Intermittent telephone encounters
- ~ ID Recs: Stop IV and remove PICC, Start PO linezolid, augmentin, azithromycin, obtain labs and repeat CT in 2 weeks



Outpatient Course Oct – Nov





Second Admission

» 12/█ Admitted for draining RUE wound of old PICC site

~ Transplant pharmacy reviewed with patient → never picked up abx

~ ID Recs:

- CT thorax → significantly worse
- IV ceftriaxone 2gm q12h + Linezolid
- MRI brain w/w/o → No enhancing lesions
- CT RUE w/o → Soft tissue defect lateral arm with 1.5cm fluid collection
- Obtain wound ctx →



Component 12/11/23 1620
Final Report

! (P)
Light growth *Nocardia wallacei*
Test performed by Mayo Medical
Laboratories
200 First Street SW
Rochester, Minnesota 55905 See Misc
sendout for MICs collected on 12/11/23
1620

» 12/█ Discharge on Linezolid, Augmentin, Azithromycin

~ Pharmacy hand delivered 3 months to bedside before leaving



Final Susceptibilities

SUSC, AEROBIC ACTINOMYCETES NOCARDIA KRUCZAKIAE		
Organism	NOCARDIA KRUCZAKIAE	
Antibiotic	MIC (mcg/mL)	Interpretation
Amox/Clav	128/64	R
Ceftriaxone	8	S
Imipenem	1	S
Ciprofloxacin	16	R
Moxifloxacin	4	R
Clarithromycin	0.06	S
Amikacin	2	S
Tobramycin	>64	R
Doxycycline	4	I
Minocycline	1	S
TMP/SMX	1/19	S
Linezolid	8	S

Ciprofloxacin: Ciprofloxacin and levofloxacin are interchangeable, but both are less active in vitro than moxifloxacin.
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SUSC, AEROBIC ACTINOMYCETES NOCARDIA WALLACEI		
Organism	NOCARDIA WALLACEI	
Antibiotic	MIC (mcg/mL)	Interpretation
Amox/Clav	8/4	S
Ceftriaxone	8	S
Imipenem	>32	R
Ciprofloxacin	2	I
Moxifloxacin	0.5	S
Clarithromycin	>16	R
Amikacin	32	R
Tobramycin	>64	R
Doxycycline	8	R
Minocycline	4	I
TMP/SMX	0.5/9.5	S
Linezolid	2	S

Ciprofloxacin: Ciprofloxacin and levofloxacin are interchangeable, but both are less active in vitro than moxifloxacin.
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SUSC, AEROBIC ACTINOMYCETES NOCARDIA WALLACEI		
Organism identified by client.		
Organism	NOCARDIA WALLACEI	
Antibiotic	MIC (mcg/mL)	Interpretation
Amox/Clav	8/4	S
Ceftriaxone	16	I
Imipenem	>32	R
Ciprofloxacin	2	I
Moxifloxacin	0.5	S
Clarithromycin	>16	R
Amikacin	>32	R
Tobramycin	>64	R
Doxycycline	8	R
Minocycline	4	I
TMP/SMX	4/76	R
Linezolid	2	S

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Clarithromycin: Class representative for newer macrolides.

S=SUSCEPTIBLE I=INTERMEDIATE R=RESISTANT
NS=NONSUSCEPTIBLE SDD=SUSCEPTIBLE DOSE DEPENDENT

Mayo Clinic Laboratories Rochester main campus

» New susceptibilities 12/



Final Diagnosis

- » **Disseminated Nocardiosis due to *N. wallecei* and *N. kruczakiae* with Pulmonary and Soft Tissue involvement without CNS involvement in a recent Heart Transplant Recipient**
 - ~ Poorly adherent to therapy
 - ~ Hopefully taking and responding to linezolid, azithromycin, amoxicillin-clavulanate



Polling Question

- » Aside from trimethoprim-sulfamethoxazole, which agent is most likely to be effective therapy for nocardiosis?
- ~ Imipenem
 - ~ Amikacin
 - ~ Linezolid
 - ~ Ceftriaxone
 - ~ Moxifloxacin



Nocardiosis in SOT: Epidemiology

- » Etiologic Agent
 - ~ Aerobic actinomycete, gram + branching filamentous bacilli
 - ~ Ubiquitous environmental saprophyte found in soil, >100 species
- » Incidence in heart recipients in Southwestern US = 4.57% (Majeed A., et al. 2018. TID)

RISK FACTORS IN SOT

- » Peleg et al., 2007, CID
 - ~ Frequency in heart recipients = 2.5%
 - ~ **Receipt of high-dose steroids in preceding 6 months** (OR 27, CI 3.2-235)
 - ~ **CMV disease in preceding 6 months** (OR 6.9, CI 1.02 – 46)
 - ~ **High median calcineurin inhibitor level in previous 1 month** (OR 5.8, CI 1.5 – 22)
- » Coussement et al., 2016, CID
 - ~ **Use of tacrolimus** (OR 2.65, CI 1.02 – 1.07)
 - ~ **Not associated with CMV disease in preceding 6 months but associated with high-risk serostatus D+/R-** (OR 2.65, CI 1.32 – 5.31)



Nocardia: Classification

Nocardia asteroides Complex: Major Changes in Taxonomic Categories ^a

FORMER SPECIES OR SPECIES GROUP ASSIGNMENT	CURRENT SPECIES GROUP DESIGNATION	CURRENT SPECIES DESIGNATION
<i>N. asteroides</i> drug pattern I	—	<i>N. abscessus</i>
<i>N. asteroides</i> drug pattern II	<i>N. paucivorans</i> / <i>N. brevicatena</i> complex	<i>N. paucivorans</i> ^b <i>N. brevicatena</i> ^b
<i>N. asteroides</i> drug pattern III	<i>N. nova</i> complex ^c	<i>N. nova</i> sensu stricto, <i>N. africana</i> <i>N. aobensis</i> <i>N. elegans</i> , <i>N. kruczakiae</i> , <i>N. veterana</i>
<i>N. asteroides</i> drug pattern IV ^d	<i>N. transvalensis</i> complex	<i>N. wallacei</i> , <i>N. transvalensis</i> sensu stricto, <i>N. blacklockiae</i>
<i>N. asteroides</i> drug pattern V		<i>N. farcinica</i>
<i>N. asteroides</i> drug pattern VI		<i>N. cyriacigeorgica</i>



Nocardiosis in SOT: Manifestations

- » Primary cutaneous nocardiosis \approx 10%

- » Invasive nocardiosis \approx 80-90%
 - ~ Pulmonary
 - Evolution usually subacute or chronic
 - Lungs are primary site of infection \approx 90%
 - Nodular lesions are most frequent, halo sign may be present
 - ~ Dissemination occurs in about 1/3 of cases
 - Most frequently CNS or skin/soft tissue
 - Other reported sites include eyes, liver, bone, endocarditis, muscle, joint, and testis

- » Co-infections may occur
 - ~ Several reports with *Aspergillus*, *Mucor*, MTB, MAC, *Histoplasma* etc.
 - ~ No reports of co-infection with different nocardia species



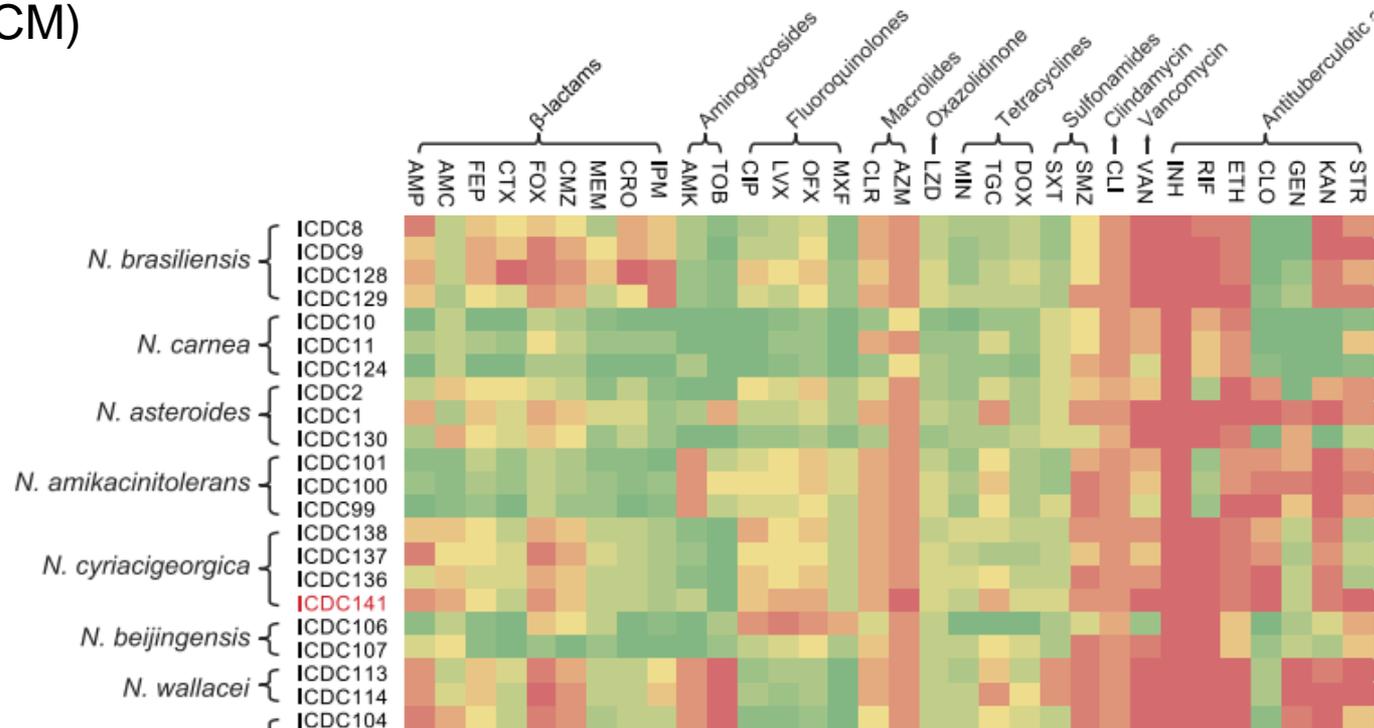
Nocardiosis in SOT: Treatment

- » Combination therapy generally recommended initially
 - ~ Particularly with CNS disease, disseminated disease, or seriously ill
 - ~ 3-drug regimens recommended for life threatening disease
 - ~ Several reasons:
 - Early studies with sulfonamide monotherapy had high mortality in immunosuppressed
 - Concern for resistance or development of resistance
 - Synergy
 - High mortality
 - Using alternative agents
- » TMP-SMX high-dose 15mg/kg/d in 2-4 divided doses is first line
 - ~ Combination agents → imipenem and amikacin (most literature)



Nocardiosis: TMP-SMX Resistance

» Historically very low in clinical isolates from US \approx 2% (Brown-Elliott et al., 2011, JCM)



- » 98% susceptible to SXT (TMP-SMX), only *N. wallacei* resistant
- » Next most active agent is Linezolid (near 100% susceptibility)



Polling Question

- » By routine, for SOT recipients with non-life threatening pulmonary, non-CNS nocardiosis, do you begin combination therapy pending ID and sensitivities or are you comfortable with TMP-SMX monotherapy?
 - ~ Free text reply

The image features a central graphic consisting of several concentric circles. The innermost circle is a dark blue color. Surrounding it are several rings of varying shades of red, from a deep, dark red to a lighter, more vibrant red. The outermost ring is a solid black color. Overlaid on this circular pattern is the text "That's all Folks!" written in a white, elegant cursive script. The text is positioned diagonally across the center of the graphic, starting from the left side and ending on the right side. The overall composition is balanced and visually striking due to the high contrast between the white text and the dark background elements.

That's all Folks!