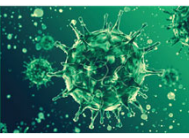


7 – Nocardia, Actinomycosis, Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD

IDBR
INFECTIOUS DISEASE BOARD REVIEW
AUGUST 17-21, 2024

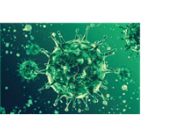


Nocardia, Actinomycosis, Rhodococcus, & Melioidosis

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7/17/2024

IDBR
INFECTIOUS DISEASE BOARD REVIEW
AUGUST 17-21, 2024



• Disclosures of Financial Relationships with Relevant Commercial Interests

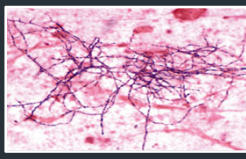

- None

Case

INFECTIOUS DISEASE BOARD REVIEW **PREVIEW QUESTION**

54 year old man with 4 weeks of cough, low grade fevers, & left-sided chest pain. Received a liver transplant 11 months ago, complicated by rejection, requiring high dose steroids 4 months ago. He receives TMP/SMX three times a week. On exam, he is stable, chronically-ill appearing, febrile (101.1°F), has clear lungs and benign abdomen. Labs reveal a normal white blood cell count, slight anemia, & normal creatinine. Chest radiograph reveals hazy opacity in left lower lung zone. Chest CT reveals nodular air-space consolidation in the left lower lobe with central cavitation (image). Gram stain of bronchoalveolar lavage fluid reveals beaded gram positive filamentous organisms (image).

INFECTIOUS DISEASE BOARD REVIEW **PREVIEW QUESTION**



CT image from J. Bargheer, et al. *Clinical Radiology*, 2013;68:01, Volume 68, Issue 5, Pages e266-e271.
Gram stain image from Murray, et al. *Medical Microbiology*, 7E, 2013 Saunders, Elsevier.

INFECTIOUS DISEASE BOARD REVIEW **PREVIEW QUESTION**

What is the most likely cause of this patient's pneumonia?

- A. *Cryptococcus neoformans*
- B. *Histoplasma capsulatum*
- C. *Actinomyces israelii*
- D. *Nocardia farcinica*
- E. *Aspergillus fumigatus*

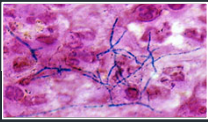
What are the most appropriate next steps in this patient's care?

- A. Initiate therapy with intravenous TMP/SMX
- B. Obtain a needle biopsy of the lung nodule to confirm the diagnosis
- C. Obtain a brain MRI & start amikacin & TMP/SMX
- D. Defer therapy until antimicrobial susceptibilities return

7 – Nocardia, Actinomycosis, Rhodococcus, and Melioidosis

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Nocardia Infections

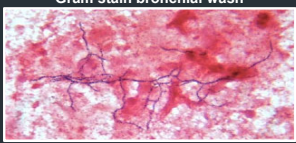
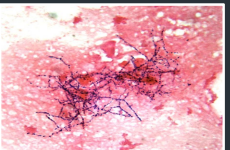



- Microbiology:**
 - Beaded & branching gram-positive rods
 - Partially acid-fast
 - Aerobic (unlike anaerobic *Actinomyces*)
 - More than 80 species & >40 cause disease in humans
 - New phylogeny based on DNA sequence (formerly, *N. asteroides* complex); species names are **lookups**.
- Pathogenesis:**
 - Inhalation (most common)
 - Direct inoculation through the skin

Photo: <http://path.uconn.edu/cases/case226/dx.html>. Good reference: Restrepo A & Clark NM. *Clinical Transplantation*. 2016:e13509

Images of Nocardia

- Beaded
- Branching
- Gram positive
- Partially acid-fast

Images from <http://www.who.int/mediacentre/diseases/nocardiosis/nocardiosis.html>



Clinical Features of Nocardia

- Immunocompromised**
 - Glucocorticoid use, solid organ transplant, hematopoietic transplant, alcoholism, diabetes, CGD, CF, autoantibodies against GM-CSF (seen in autoimmune pulmonary alveolar proteinosis), anti-TNF therapy, ectopic ACTH syndrome, AIDS (less common)
 - PJP prophylaxis may not prevent nocardiosis (& does not predict TMP/SMX resistance)*
 - Months to years after transplantation
- 90%: slowly progressive pneumonia** with cough, dyspnea, & fever
 - Aspergillus* similar; co-infections occur
 - Similar to cryptococcal disease & actinomycosis
 - Can disseminate to any organ (brain in particular: **get MRI**; can be asymptomatic!)

Margalit I, et al. *Clinical Microbiology and Infection* (2021).

Clinical Features of Nocardia

- 10%: Skin infections from direct inoculation:**
 - Immunocompetent host in tropical region (*N. brasiliensis*)
 - Immunocompromised patient who gardens or walks barefoot
 - Sporotrichoid lesions**
 - Mycetomas:** chronic, progressive, lower limbs, draining sinuses (similar to *Actinomycetes* & *eumycetoma*). "Madura foot"

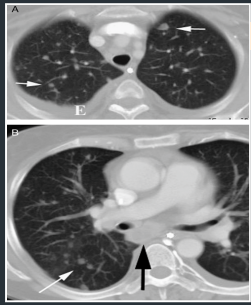



Baradkar V P, et al. *Indian J Pathol Microbiol* 2008;51:432-4. Sharma NI, et al. *Indian J Dermatol Venereol Leprol* 2008;74:635-40.

Nocardia Diagnosis

- Diagnosis:**
 - Suggestive radiology
 - Chest imaging: **nodules**, cavities, infiltrates with consolidation, effusions, ground-glass opacities
 - MRI brain: single or multiple **abscesses**
 - Blood culture, BAL, biopsy
 - Gram stain, **modified acid-fast stain**, culture
 - Species identification with nucleic acid sequencing or MALDI: **predictive of drug susceptibility**

- 56-year-old woman post kidney-pancreas transplant & *N. brasiliensis*
- Small lung nodules (white arrows), small right pleural effusion & subcarinal lymphadenopathy (black arrow)

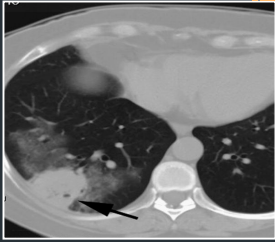


Pulmonary Nocardiosis: Computed Tomography Features at Diagnosis. Slackton, Kevin, Ravelli, James, Gomez, Juan, Cialini, Jody, Wilay, Danish. *Journal of Thoracic Imaging*. 26(3):224-226, August 2011. DOI: 10.1097/R11.0b013e31819456d5

7 – Nocardia, Actinomycosis, Rhodococcus, and Melioidosis

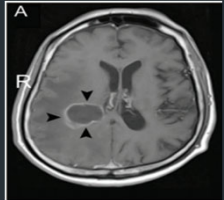
Speaker: David M. Aronoff, MD

- 55-year-old woman with acute myelogenous leukemia & *N. nova*
- Axial CT image without contrast = solitary RLL mass with single focus of cavitation (arrow) & surrounding ground-glass opacity



Pulmonary Nocardiosis: Computed Tomography Features at Diagnosis. Blackmon, Kevin; Ravneh, James; Gomez, Juan; Ciolino, Jody; Wray, Danaah. Journal of Thoracic Imaging. 2003;18(4):228-230. August 2011. DOI: 10.1097/RIT.0b013e3181f49d55

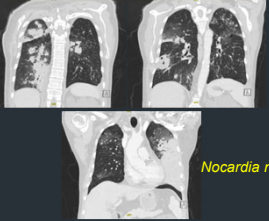
- Right frontoparietal subcortical ring lesion with a central dark signal & bright ring enhancement (black arrowheads) in postcontrast T1-weighted image.



Nardhagopal, Ramachandran, Zakariya Al-Muhammi, and Abdullahi Balkhair. "Nocardia brain abscess." QJM 107.12 (2014): 1041-1042.

Case

- 60 YO s/p kidney transplant on immunosuppression with 3 week of cough, fevers, dyspnea & malaise
- SARSCoV2 negative
- MRI head negative

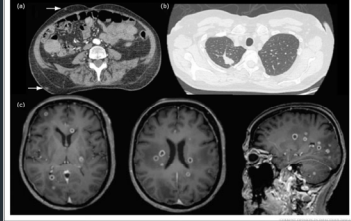


Nocardia nova

- Severe bilateral pneumonia with scattered areas of ground glass attenuation, consolidation, soft tissue nodules & tree-in-bud micronodules throughout
- L>R pleural effusions & small pericardial effusion

Case

Nocardia cerraodoensis



Total body CT & brain MRI of a solid organ transplant recipient with disseminated nocardiosis. (A) Sub-cutaneous nodules (white arrow) on CT-scan. (B) Nodule in the R upper lung seen on CT-scan. (C) Multiple round-shaped, contrast-enhanced lesions on gadolinium-enhanced T1-weighted brain MRI.

Lebeaux D, et al. Current Opinion in Infectious Diseases 34(6):611-618, December 2021.

Nocardia Treatment

- Susceptibility testing is a must**
 - Important because of drug resistance
- TMP/SMX is mainstay** (skin = monotherapy; LZD/TZD alternatives)
- Empiric 2-drug combination therapy:**
 - TMP/SMX + one of these:
 - Amikacin, imipenem/meropenem >> ceftriaxone/cefotaxime
 - Linezolid/tedizolid ± imipenem/ceftriaxone/cefotaxime as alternate agents
- Empiric 3-drug combination therapy for CNS (TMP/SMX + IMI + Ami)**
- Desensitize for sulfa allergy
- 2-6 weeks induction followed by 6+ months of oral TMP/SMX monotherapy

Restrepo A & Clark NM. Clinical Transplantation. 2019;e13519. Margalit L, et al. "How do I manage nocardiosis?" Clinical Microbiology and Infection (2021). Traxler RM, et al. CMAJ. 2022.

Nocardia Treatment

Antibiotics 2022, 11, 612

Table 3. Therapeutic management of nocardiosis according to clinical presentation.

Localization	Empiric Induction Treatment *±	Maintenance Oral Therapy ±	Duration
Primary skin	TMP/SMX orally	TMP/SMXM	6-12 months
Pulmonary stable	Linezolid orally	Minocycline Amoxicillin/clavulanate	
Pulmonary moderate/severe	TMP/SMX iv + imipenem OR amikacin TMP/SMX iv + ceftriaxone ± linezolid Linezolid + ceftriaxone OR imipenem	TMP/SMX Minocycline Amoxicillin/clavulanate	6-12 months
CNS involvement	TMP/SMX iv + imipenem ± amikacin Linezolid + imipenem	TMP/SMX	9-12 months
Disseminated (>two organs without CNS involvement)	TMP/SMX iv + imipenem OR amikacin TMP/SMX iv + linezolid + imipenem OR amikacin Imipenem + amikacin	TMP/SMX Minocycline Amoxicillin/clavulanate	6-12 months

TMP/SMX: trimethoprim/sulfamethoxazole; CNS: central nervous system. * Continue multi-drug parenteral therapy for two to six weeks and adjust based on susceptibility test. ± Antibiotic dosing: TMP/SMX 15 mg/kg (divided in three to four doses), linezolid 600 mg q12h, imipenem 500 mg q6h, minocycline 100-300 q12h, amikacin 20-30 mg/kg/day, ceftriaxone 2 g q24h.

* van den Bogaart L & Manuel O. Antibiotics (2022)

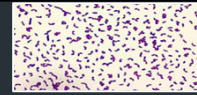
7 – Nocardia, Actinomycosis, Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD

Nocardia Buzzwords

- **B**eaded
- **B**ranching
- **B**rain (+ lung)
- **B**actrim

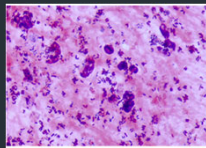
Rhodococcus



- **Clinical findings:**
 - **I**ndolent **p**neumonia (80%) in **i**mmunocompromised host
 - **F**ever, **c**ough, **h**emoptysis, fatigue, subacute, pleuritic CP
 - Nodules, thick-walled **c**avities, infiltrates, effusions possible
 - Extrapulmonary dissemination possible (**s**kin & **b**rain)
 - Mimic of TB, NTM, *Aspergillus*, *Nocardia*

Photo: microbe canvas

Rhodococcus



- **Typical patient:**
 - T cell immunosuppressed
 - PLWHA & CD4<100; organ transplant
 - Inhalation or ingestion
 - Farm, soil, manure or horse exposure in some patients
- **Microbiology:** *R. equi* is the most common
 - Gram positive, **a**erobe, **c**occobacillary
 - Colonies can be **s**almon **p**ink
 - **W**eakly **a**cid **f**ast: can be mistaken for *Nocardia* but **n**o **b**ranching

Image from W.V. Lin et al. / Clinical Microbiology and Infection (2019)

Rhodococcus

33 year-old male PLWHA (CD4 = 20) who lived on a cattle & horse farm

Presented to hospital with 1 month of fever, dry cough, 13# weight loss, sweats & anorexia

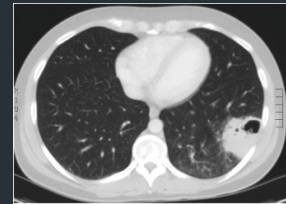


Image from Stewart A., et al. IDCases. (2019)

Rhodococcus

- **Diagnosis:**
 - **C**ulture followed by 16S rRNA, MALDI-TOF
 - Tissue: gram stain, **n**ecrotizing **g**ranulomatous reaction; microabscess
 - Blood cultures may be positive (>25%)
- **Treatment:**
 - Combination therapy is recommended
 - **M**acrolide or **f**luoroquinolone in combination with **r**ifampin or in combination with 2 of the following: vancomycin, imipenem, linezolid, or an aminoglycoside x 2-3 wks then 2 drugs until clinical response complete (macrolide or FQ + a second agent)

Lin WV, et al. Clin Micro Infect (2019), Stewart A., et al. IDCases. (2019), Kottan CN, Update (2023)

Rhodococcus Buzzwords

- **S**hort Gram positive rod (coccobacillus)
- **C**avitary pneumonia (hemoptysis)
- **S**almon **p**ink colonies
- **A**dvanced **H**IV/**A**IDS
- **H**orse / manure exposure

7 – Nocardia, Actinomycosis, Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD

Case PREVIEW QUESTION

A 62 yr old sheep rancher from Northern Australia referred hospitalized for refractory pneumonia that failed to respond completely to multiple, prolonged courses of antibiotics over 3 months, leaving him with continued low-grade fever, productive cough & asthenia.

Gram negative rods noted in moderate abundance on sputum Gram stain & in sputum culture. Identification by automated system failed & isolate sent to referral lab.

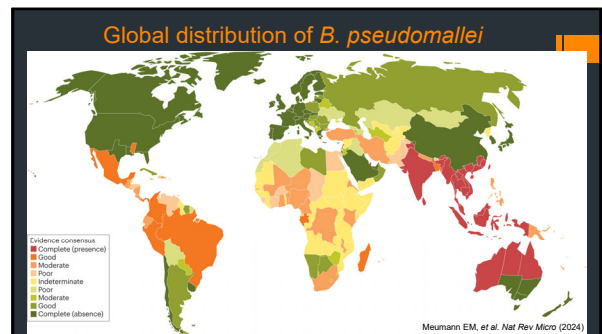
Question PREVIEW QUESTION

- Which of the following would have been a likely source of this infection?
- A. Hospital nebulizer while hospitalized in Australia (nosocomial superinfection)
- B. Water or soil from his ranch
- C. Coughing worker on his ranch
- D. Sick sheep on his ranch.

Melioidosis Microbiology & Epidemiology

- Microbiology lab:
 - Facultative intracellular GNR, *Burkholderia pseudomallei*
 - Oxidase positive, **non-fermenting** GNR
 - Characteristic **bipolar staining** with a "safety pin" appearance
- Melioidosis is highly endemic in Southeast Asia & northern Australia
 - **Esp. Northeastern Thailand & northern Australia**

Chakravorty A, Heath CH. Australian Journal of General Practice (2019)
Meumann EM, et al. Nat Rev Micro (2024)



AN ASIDE:

If I Say Non-Fermenting GNR You Think of

- *M. tuberculosis*
- *M. fortuitum*
- *M. chelonae*
- *M. neoaurum*
- *M. goodii*

Melioidosis Clinical Syndromes

- **Clinical findings:**
 - Acute infection can present with **pneumonia, bacteremia & septic shock**
 - Metastatic abscesses: skin ulcers or abscesses more common than bone, spleen, brain, prostate
 - Chronic infection presents like TB (cough, hemoptysis, night sweats)
 - Can become latent & reactivate like TB (rare)

Wiersinga WJ, et al. Nat Rev Dis Primers (2018); Kottarathil M, et al. Indian J Tuberculosis (2024)

7 – Nocardia, Actinomycosis, Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD

Melioidosis Clinical Syndromes

- Risk Factors:**
 - Infection occurs from exposure to contaminated soil or water by percutaneous inoculation, **inhalation**, or ingestion
 - Risk factors = **diabetes**, **alcohol use disorder**, chronic renal & lung disease, corticosteroid therapy, malignancy, & thalassemia
 - Acute infection more common than chronic infection

Chakravorty A, Heath CH. *Australian Journal of General Practice* (2019)
<https://www.cdc.gov/melioidosis/health-care-workers/>

Melioidosis in the US

- In the United States**
 - Rare: about 10-15 cases a year & usually from exposure elsewhere
 - 4 recent cases in the US linked to imported aromatherapy products & also 3 recent autochthonous cases with exposure in the southern US

Geer JE, et al. *NEJM* (2022) Petras JK, et al. *NEJM* (2023)

Melioidosis in the US

- 2 unrelated people living in the **Gulf Coast region** of the southern US became sick with melioidosis two years apart—in 2020 & 2022
- Three samples from soil & puddle water in 2022 tested positive at CDC for *B. pseudomallei*

<https://www.cdc.gov/media/releases/2022/s0727-Melioidosis.html>

Bacteria with "safety pin" appearance

- Yersinia pestis*
- Vibrio parahaemolyticus*
- Burkholderia mallei* & *pseudomallei*
- Haemophilus ducreyi*
- Klebsiella granulomatis* (granuloma inguinale)
- Pasteurella multocida*

Y. pestis

Melioidosis Diagnosis & Rx

- Diagnosis: Culture on Ashdown Medium**
 - Alert the lab you are concerned about this pathogen!**
 - Indirect immunofluorescence, lateral flow immunoassays & nucleic acid amplification tests have been developed; none have sufficient sensitivity to replace culture assays
- Treatment: Treat all cases**
 - Mild disease: initial intensive IV therapy for two weeks followed by eradication therapy orally for 3-6 months
 - B. pseudomallei* resistant to penicillin, ampicillin, 1st/2nd generation cephalosporins, polymyxin, aminoglycosides
 - TMP/SMX for postexposure prophylaxis
 - Meropenem or ceftazidime then tmp/smx for 3-6 months**

Wieringa WJ, et al. *Nat Rev Dis Primers* (2019); Hemrajita P, et al. *JCM* (2016)
 Peacock SJ, et al. *EID* (2008); Meumann EM, et al. *Nat Rev Micro* (2024)
 For the most up-to-date recommendations by the International Melioidosis Society: <http://www.melioidosis.info>

Melioidosis: Buzzwords

- SE Asia** (Thailand)/Australia
- Soil/water exposure** (inhalation/inoculation/rainy season; post-tsunami injury)
- Pneumonia + **severe sepsis**/shock or multiple abscesses
- Can be **years after exposure** (not usually)
- Safety pins** on methylene blue or Wright's stain; Gram negative rods
- Ashdown media**

Le Tohic, s., et al. *European Journal of Clinical Microbiology & Infectious Diseases* (2019)

7 – Nocardia, Actinomycosis, Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD

Glanders

- Caused by *Burkholderia mallei* & is rare in humans
- Requires close contact w/ infected animals (horses, donkeys, mules)
- Bacteria enter through the eyes, nose, mouth, or skin wounds
- B. mallei* is an obligate mammalian pathogen & must cause the disease to be transmitted between hosts
- Africa, Asia, Middle East, Central America, South America
- Similar presentation to melioidosis

Smith ME, Gossman WG. Glanders And Melioidosis. [Updated 2017 Oct 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan.

Actinomyces Take-Aways

- Microbiology lab:
 - Gram-positive, **anaerobic**, non-spore-forming bacteria
 - Part of the normal mucosal flora of the oral, gastrointestinal, respiratory, & genital tracts
 - Actinomyces israelii* most common species
 - Produce **sulfur granules**
- Typical patient:
 - Recent **dental procedures**
 - Aspiration** (thoracic)
 - IUD** (pelvic)

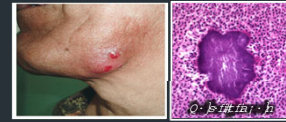


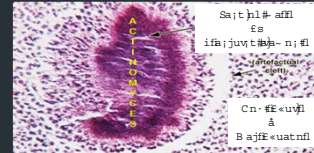
Photo credit: [unreadable] biology.com

Actinomyces Take-Aways

- Clinical findings:
 - Oral-cervicofacial more common > abdominal & thoracic infection
 - Lumpy jaw**
 - Slow growing mass, **ignores tissue planes**, can pus-out (necessitate), form sinuses, fistulas
 - DDx: Cancer, TB, *Nocardia*
- Diagnosis:
 - Culture, histopathology (sulfur granules)
- Treatment:
 - Penicillins** (PCN, ampicillin) x weeks to months

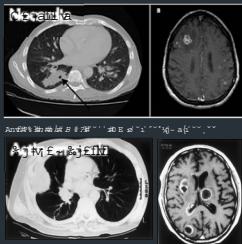
Actinomyces: Buzzwords

- Sulfur granules**
- Dental work**
- IUD**
- Erosive mass**
- Filamentous anaerobe**



Lesions in the Lungs & Brain

- Actinomycosis
- Aspergillus*, *Zygomycetes*
- Blastomyces*, *Coccidioides*, *Cryptococcus*, *Histoplasma*
- Mycobacterium tuberculosis*
- Nocardia*
- Infectious emboli (SBE)
- Lemierre syndrome (*Fusobacterium*)
- Toxoplasma*
- Tumors



Causes of Sporotrichoid Lesions

Nodular lymphangitis



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Traido-Sanchez, et al. J Fungi. 2018;4:56.doi:10.3390/jf4020056. Photo: eScholarship

7 – Nocardia, Actinomyces, Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD

THANK YOU

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