



Nocardia, Actinomycosis, Rhodococcus, & Melioidosis

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Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Question #1

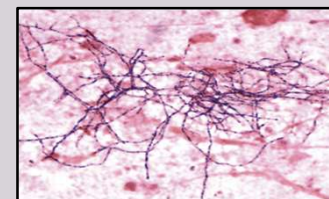
54-year-old man with 4 weeks of cough, low grade fevers, & left-sided chest pain. Received a liver transplant 11 months ago, complicated by rejection, requiring high dose steroids 4 months ago. He receives TMP/SMX three times a week. On exam, he is stable, chronically-ill appearing, febrile (101.1oF), 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).

Question #1

Chest CT



BAL



CT Image from J. Bargehr, et al. Clinical Radiology, 2013-05-01, Volume 68, Issue 5, Pages e266-e271.
Gram stain image from Murray, et al. Medical Microbiology, 7E, 2013 Saunders, Elsevier.

Question #1

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*

Question #2

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

Nocardia Infections

- 500-1000 cases in US/year
- 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

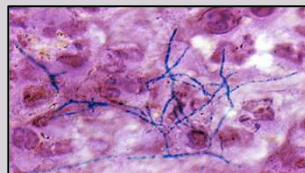


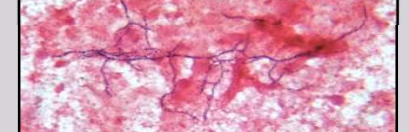
Photo: <http://path.upmc.edu/cases/case226/dx.html>; Good reference: Restrepo A & Clark NM. *Clinical Transplantation*. 2019;e13509.

Images of Nocardia

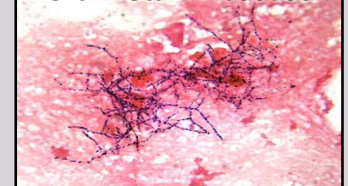
- Beaded
- Branching
- Gram positive
- Partially acid-fast



Gram Stain Bronchial Wash



Gram Stain Abscess



Images from <http://thunderhouse4-yuri.blogspot.com/2010/06/nocardia-species.html>

Clinical Features of *Nocardia*

- **Immunocompromised (~60-70% of cases)**
 - **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); Liu Y, et al. *BMC Microbio*. (2024)

Clinical Features of *Nocardia*

- 10%: Skin infections from direct inoculation:
 - Immunocompetent host in tropical region (*N. brasiliensis*; ~80%)
 - Immunocompromised patient who gardens or walks barefoot
 - Sporotrichoid lesions
 - Mycetomas: chronic, progressive, lower limbs, draining sinuses (similar to Actinomycetes & eumycetoma).



Baradkar V P, et al. *Indian J Pathol Microbiol* 2008;51:432-4



Sharma NL, et al. *Indian J Dermatol Venereol Leprol* 2008;74:635-40

Clinical Features of *Nocardia*

- A 75-year-old woman
- 10-day history of painful lesions on the R. hand & forearm
- Nodules appeared on back of hand at site of a thorn puncture sustained while gardening
- **Reminder: tetanus booster needed**



Pipito L, et al. *N Engl J Med* 2023;388:1701

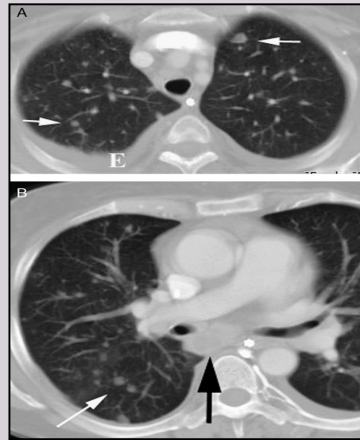
Nocardia Diagnosis

- **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-TOF MS: **predictive of drug susceptibility**

Odd fact: *Nocardia* can cause a false positive galactomannan test

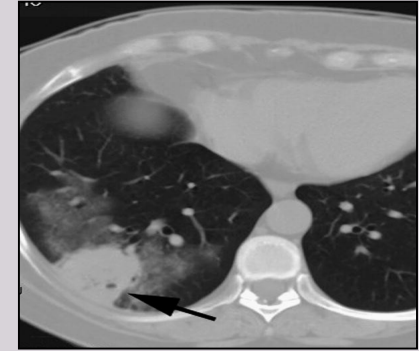
MALDI-TOF: Liu Y, et al. *BMC Microbio*. (2024)

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



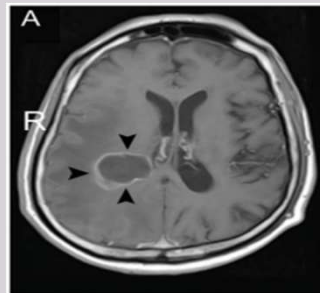
Pulmonary Nocardiosis: Computed Tomography Features at Diagnosis. Blackmon, Kevin; Ravenel, James; Gomez, Juan; Ciolino, Jody; Wray, Dannah. *Journal of Thoracic Imaging*. 26(3):224-229, August 2011. DOI: 10.1097/RTI.0b013e3181f45dd5

- 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; Ravenel, James; Gomez, Juan; Ciolino, Jody; Wray, Dannah. *Journal of Thoracic Imaging*. 26(3):224-229, August 2011. DOI: 10.1097/RTI.0b013e3181f45dd5

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



Nandhagopal, Ramachandiran, Zakariya Al-Muhammi, and Abdullah Balkhair. "Nocardia brain abscess." *QJM* 107.12 (2014): 1041-1042.

Case Study

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



Nocardia nova

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

Case Study

Nocardia cerraadoensis



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:e13509
Margalit I, et al. "How do I manage nocardiosis?" *Clinical Microbiology and Infection* (2021).
Traxler RM, et al. *CMR*. 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 Pulmonary stable	TMP/SMX orally Linezolid orally	TMP/SMX minocycline Amoxicillin/clavulanate	6–12 months
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 TMP/SMX iv + imipenem + linezolid Linezolid + imipenem Imipenem + amikacin	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).

Nocardia Buzzwords

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

Rhodococcus



Photo: Microbe canvas

- Clinical findings:
 - **Indolent pneumonia** (80%) in **immunocompromised** host
 - **Fever, cough, hemoptysis**, fatigue, subacute, pleuritic CP
 - Nodules, thick-walled **cavities**, infiltrates, effusions possible
 - Extrapulmonary dissemination possible (**blood, skin & brain**)
 - Mimic of TB, NTM, *Aspergillus*, *Nocardia*

Rhodococcus

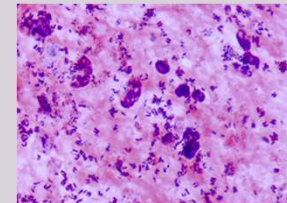


Image from W.V. Lin et al. / Clinical Microbiology and Infection (2019)

- 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, aerobe, coccobacillary
 - Colonies can be **salmon pink**
 - **Weakly acid fast**: can be mistaken for *Nocardia* but **no branching**

Rhodococcus



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

- 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

Rhodococcus

- **Diagnosis:**
 - **Culture** followed by 16S rRNA, MALDI-TOF
 - Tissue: gram stain, **necrotizing granulomatous** reaction; microabscess
 - Blood cultures may be positive (>25%)
- **Treatment:**
 - Combination therapy is recommended
 - **Macrolide or fluoroquinolone** in combination with **rifampin** 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)

Zhu H, et al. Infect Drug Res (2025), Lin WV, et al. Clin Micro Infect (2019), Stewart A., et al. IDCases. (2019), Kotton CN. Update (2023)

***Rhodococcus* Buzzwords**

- **Short** Gram-positive rod (coccobacillus)
- **Cavitary** pneumonia (hemoptysis)
- **Salmon pink** colonies
- Advanced **HIV/AIDS**
- **Horse** / manure exposure

Odd fact: *Rhodococcus* can cause a false positive galactomannan test

Question #3

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 #3

Which of the following would have been a likely source of this infection?

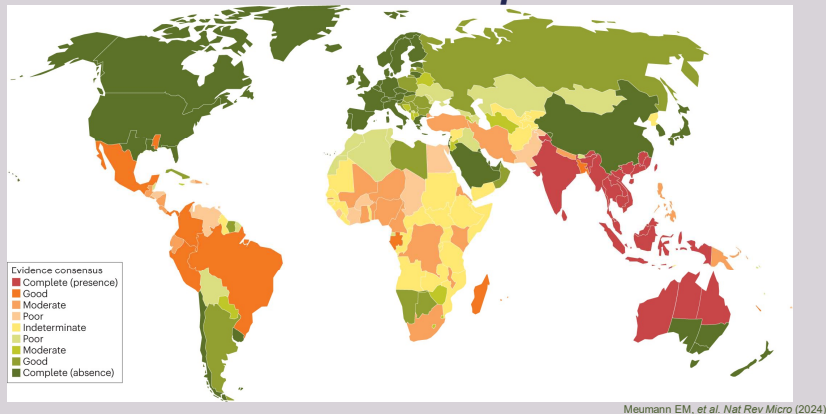
- A. Hospital nebulizer while hospitalized in Australia (nosocomial superinfection)
- B. Water or soil from his ranch
- C. Coughing worker on his ranch
- D. Sick sheep on his ranch

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)

Global Distribution of *B. pseudomallei*



AN ASIDE:

If I Say **Non-Fermenting GNR** You Think of

- *Pseudomonas aeruginosa*
- *Acinetobacter baumannii*
- *Burkholderia cepacia*, *B. pseudomallei*
- *Stenotrophomonas maltophilia*
- *Sphingomonas paucimobilis*
- *Ralstonia pickettii*

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)

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



Gee 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/p0727-Melioidosis.html>

Bacteria with “Safety Pin” Appearance

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



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**

For the most up-to-date recommendations by the International Melioidosis Society:
<http://www.melioidosis.info>

Wiersinga WJ, et al. Nat Rev Dis Primers (2018); Hemarajata P, et al. JCM (2016)
Peacock SJ, et al. EID (2008); Neumann EM, et al. Nat Rev Micro (2024)

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)

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)



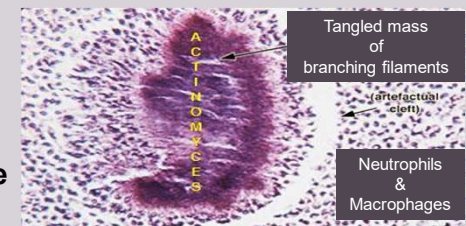
Photos: <http://intranet.tdmu.edu.ua/> & webpathology.com

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
 - Doxycycline can be used in PCN-allergic people

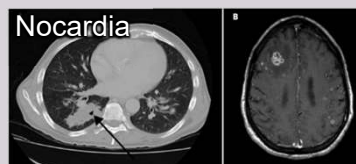
Actinomyces: Buzzwords

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

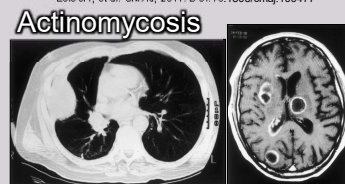


Lesions in the Lungs & Brain

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



Leis JA, et al. *CMAJ*, 2011. DOI:10.1503/cmaj.100477



Colmegna I, et al. *Am J Med Sci*, 2003. DOI: 10.1097/0000441-200309000-00010

Causes of Sporotrichoid Lesions

Nodular lymphangitis



Organism	Exposure
<i>Sporothrix schenckii</i>	Gardening, soil, splinters, animal bites/scratches
<i>Nocardia brasiliensis</i>	Gardening, soil, splinters
<i>Mycobacterium marinum</i>	Aquarium, fish handling, water exposure
Cutaneous leishmaniasis	Living/traveling in endemic regions
Several others	Blasto/Cocci/Histo, Crypto, tularemia, <i>Erysipelothrix</i> , etc.

Tirado-Sanchez, et al. *J Fungi*, 2018,4,56;doi:10.3390/jof4020056. Photo: eScholarship

Thank You

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