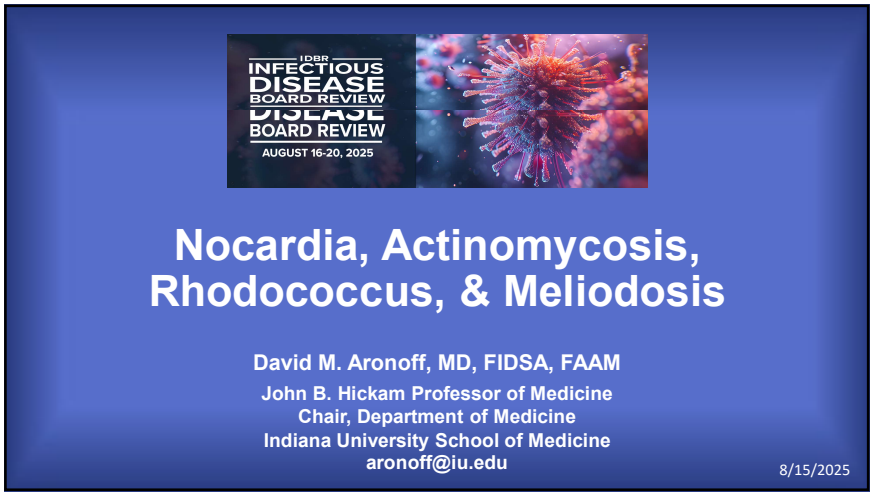
24 Nocardiosis, Actinomycosis, Rhodococcus and Actinomycosis

Speaker: David Aronoff, MD, FIDSA, FAAM



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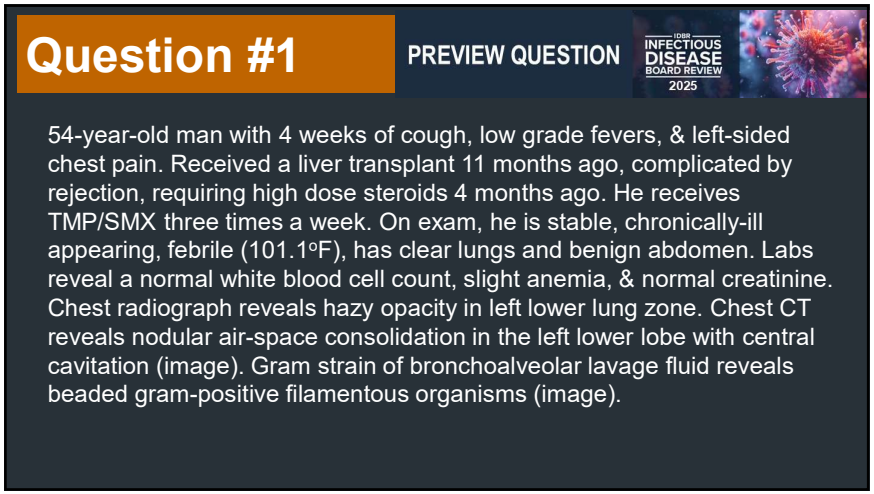

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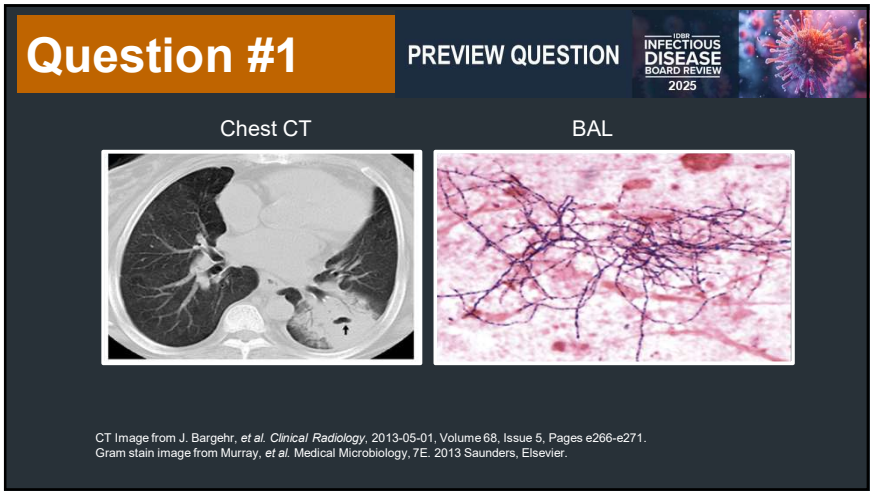

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Question #1

PREVIEW QUESTION

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

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

5

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C. *Actinomyces israellii*
D. ***Nocardia farcinica****
E. *Aspergillus fumigatus*

6

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

7

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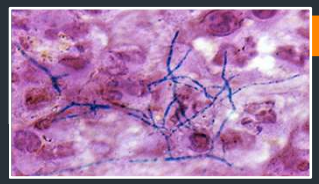
8

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.

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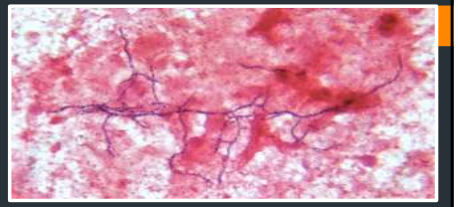
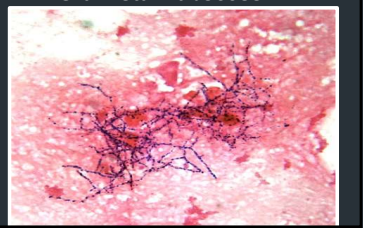
Images of *Nocardia*

- **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

10

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)

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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). "Madura foot"

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

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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

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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**

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

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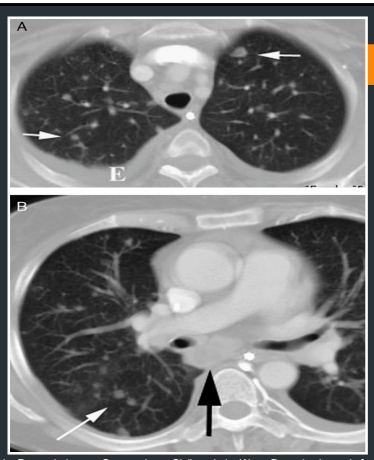
- 56-year-old woman post kidney-pancreas transplant & *N. brasilienses*
- Small lung nodules (white arrows), small right pleural effusion & subcarinal lymphadenopathy (black arrow)



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

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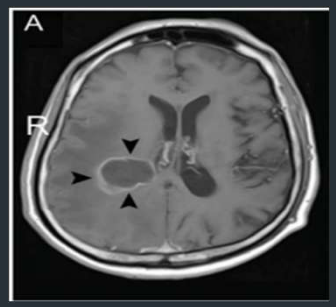
- 55-year-old woman with acute myelogenous leukemia & *N. nova*
- Axial CT image without contrast = solitary RLL **mass** with single focus of **cavitation** (arrow) & surrounding **ground-glass opacity**

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

16

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

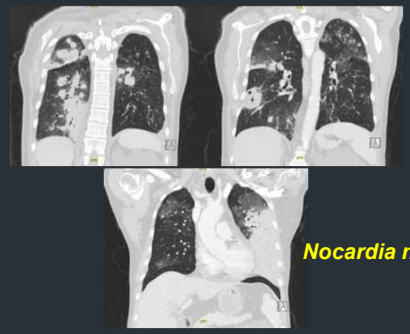


Nandhagopal, Ramachandiran, Zakariya Al-Muharrmi, and Abdullah Balkhair. "Nocardia brain abscess." *QJM* 107.12 (2014): 1041-1042.

17

Case

- 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

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Case

Nocardia cerradoensis

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.

19

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

20

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/SMXM 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)

21

Nocardia Buzzwords

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

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Rhodococcus

- **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*

Photo: microbe canvas

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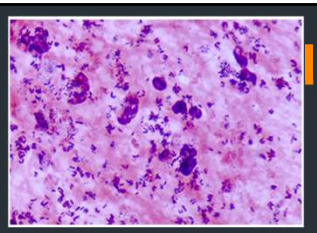
Rhodococcus



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

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

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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

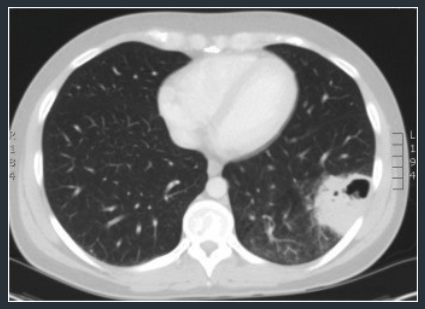

Image from Stewart A., *et al. IDCases*. (2019)

25

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)

Lin WV, *et al. Clin Micro Infect* (2019), Stewart A., *et al. IDCases*. (2019)
Kotton CN, *Uptodate* (2023)

26

Rhodococcus Buzzwords

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

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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.

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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.

29

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C. Coughing worker on his ranch
D. Sick sheep on his ranch.

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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)

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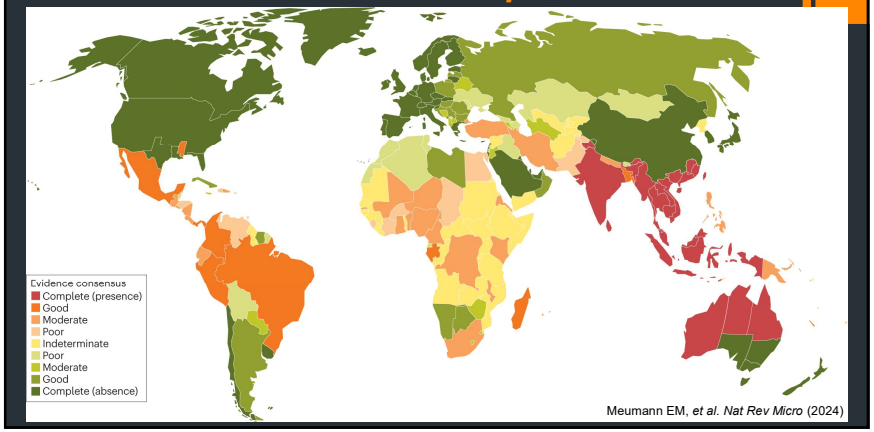
Global distribution of *B. pseudomallei*



Meumann EM, *et al. Nat Rev Micro* (2024)

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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*

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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)

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Melioidosis Clinical Syndromes

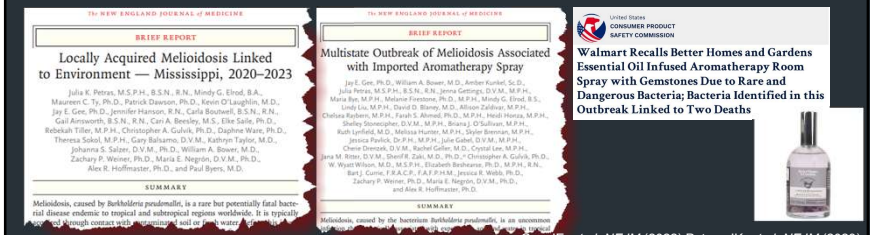
- **Risk Factors:**
  - Infection occurs from exposure to contaminated soil or water by percutaneous inoculation, **inhalation**, or ingestion
  - Risk factors = **diabetes**, **alcohol use disorder**, chronic renal & lung disease, corticosteroid therapy, malignancy, & thalassemia
  - Acute infection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

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

35

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)

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Melioidosis in the US


CDC Newsroom

Bacteria that Causes Rare Disease Melioidosis Discovered in U.S. Environmental Samples

Press Release

For Immediate Release: Wednesday, July 27, 2022
Contact: Media Relations
(404) 639-3286

The Centers for Disease Control and Prevention (CDC) has identified for the first time in domestic environmental samples the bacteria that causes a rare and serious disease called melioidosis. The bacteria, *Burkholderia pseudomallei* or *B. pseudomallei*, was identified through sampling of soil and water in the Gulf Coast region of

- 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

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Bacteria with "Safety Pin" Appearance

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


Y. pestis

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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**

Wiersinga WJ, *et al. Nat Rev Dis Primers* (2018); Hemarajata 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

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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)

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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

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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

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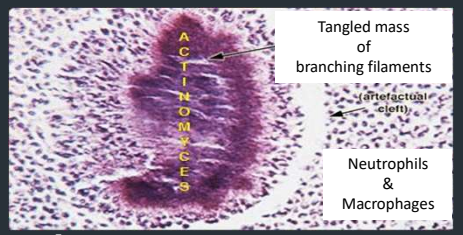
Actinomyces: Buzzwords

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



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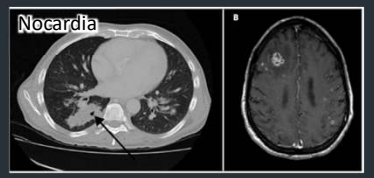
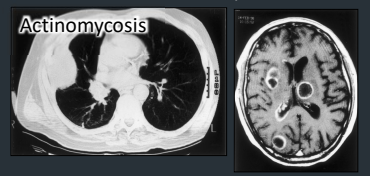
Lesions in the Lungs & Brain

- 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: 10.1097/00000441-200309000-00010

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Causes of Sporotrichoid Lesions

Nodular lymphangitis

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

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

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THANK YOU

aronoff@iu.edu
@DMAronoff (Bluesky)
david.aronoff (Insta, Threads)

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