



## Nocardia, Actinomycosis, Rhodococcus, & Melioidosis

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### Disclosures of Financial Relationships with Relevant Commercial Interests

- None

### Question #1

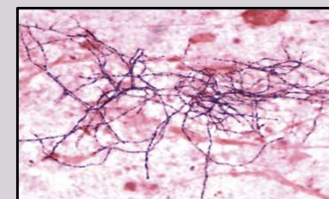
54-year-old man with 4 weeks of cough, low grade fevers, & left-sided chest pain. Received a liver transplant 11 months ago, complicated by rejection, requiring high dose steroids 4 months ago. He receives TMP/SMX three times a week. On exam, he is stable, chronically-ill appearing, febrile (101.1oF),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

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### 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

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## 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

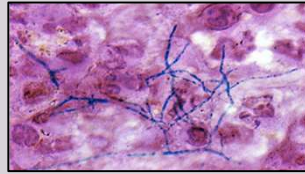
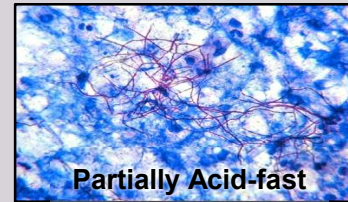
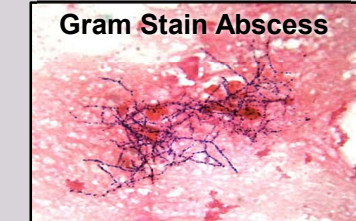


Photo: <http://path.upmc.edu/cases/case226/dx.html>. Good reference: Restrepo A & Clark NM. *Clinical Transplantation*. 2019:e13509.

## Images of Nocardia

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



Partially Acid-fast

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 Microbiol.* (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 Actinomyces & 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

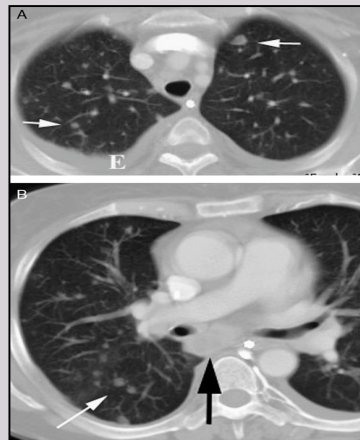
### • Diagnosis:

- 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 Microbiol.* (2024)

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



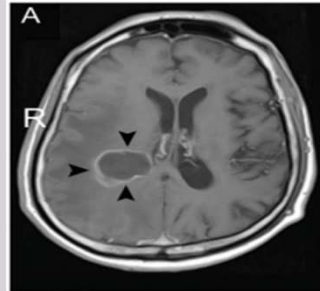
Pulmonary Nocardiosis: Computed Tomography Features at Diagnosis. Blackmon, Kevin; Ravenel, James; Gomez, Juan; Ciolino, Jody; Wray, Dannah. *Journal of Thoracic Imaging*. 26(3):224-229, August 2011. DOI: 10.1097/RTI.0b013e3181f45dd5

- 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 <sup>*,‡</sup>                                                                           | Maintenance Oral Therapy <sup>‡</sup>              | Duration    |
|-------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|-------------|
| Primary skin<br>Pulmonary stable                      | TMP/SMX orally<br>Linezolid orally                                                                                   | TMP/SMXM<br>minocycline<br>Amoxicillin/clavulanate | 6–12 months |
| Pulmonary moderate/severe                             | TMP/SMX iv + imipenem OR amikacin<br>TMP/SMX iv + ceftriaxone ± linezolid<br>Linezolid + ceftriaxone OR imipenem     | TMP/SMX<br>Minocycline<br>Amoxicillin/clavulanate  | 6–12 months |
| CNS involvement                                       | TMP/SMX iv + imipenem ± amikacin<br>TMP/SMX iv + imipenem + linezolid<br>Linezolid + imipenem<br>Imipenem + amikacin | TMP/SMX                                            | 9–12 months |
| Disseminated (>two organs<br>without CNS involvement) | TMP/SMX iv + imipenem OR amikacin<br>TMP/SMX iv + linezolid + imipenem OR amikacin<br>Imipenem + amikacin            | TMP/SMX<br>Minocycline<br>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. <sup>‡</sup> Antibiotic dosing: TMP/SMX 15 mg/kg (divided in three to four doses), linezolid 600 mg q12h, imipenem 500 mg q6h, minocycline 100–300 mg 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

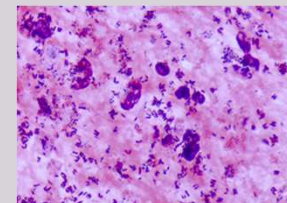


Image from W.V. Lin et al. / Clinical Microbiology and Infection (2019)

- 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

- 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:

- **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

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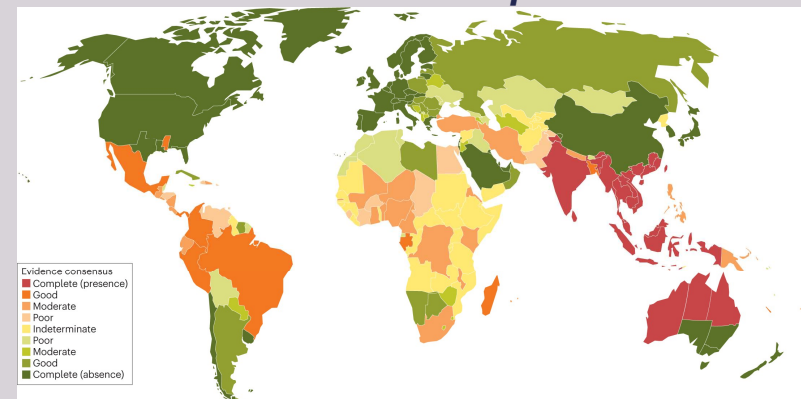
- A. Hospital nebulizer while hospitalized in Australia (nosocomial superinfection)
- B. Water or soil from his ranch\*
- C. Coughing worker on his ranch
- D. Sick sheep on his ranch

### 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*



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

### 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

The image displays three news snippets. The first, titled 'Locally Acquired Melioidosis Linked to Environment — Mississippi, 2020–2023', is a brief report from the New England Journal of Medicine. The second, titled 'Multistate Outbreak of Melioidosis Associated with Imported Aromatherapy Spray', is also a brief report from the same journal. The third is a Walmart recall notice from the United States Consumer Product Safety Commission, stating 'Walmart Recalls Better Homes and Gardens Essential Oil Infused Aromatherapy Room Spray with Gemstones Due to Rare and Dangerous Bacteria; Bacteria Identified in this Outbreak Linked to Two Deaths'. A small image of a bottle of the recalled product is shown next to the recall notice.

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 parahaemolyticus*
- *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); Meumann 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)



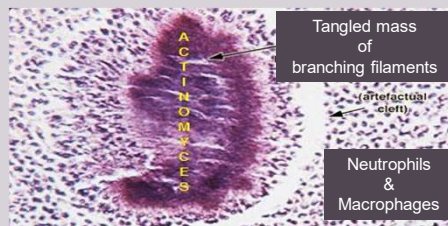
Photos: <http://intranet.tdmu.edu.ua/> & [webpathology.com](http://webpathology.com)

## 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

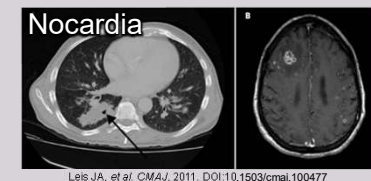
## Actinomyces: Buzzwords

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

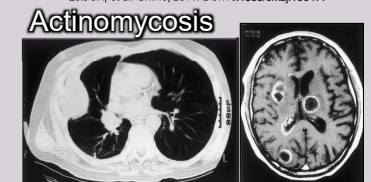


## Lesions in the Lungs & Brain

- 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: 10.1097/00000441-200309000-00010

## 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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