

# **Discussion of rare fungal infections observed in immunocompromised and immunocompetent patients.**

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Memorias en presentación de PowerPoint.



Discussion of rare fungal infections  
observed in immunocompromised and  
immunocompetent patients

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## CLINICAL CASE # 1

### Clinical History

- 51 y/o Caucasian female patient, immunosuppressed due to liver transplant on 10/9/2023 due to cirrhosis secondary to MASLD
- Past Medical History: DMT2 – HT - Upper back thoracic surgery – Liver Transplant
- Medications: Coreg-Procardia-Hydralazine Tacrolimus-Prednisone-MMF-Amphotericin-Itraconazole-Ertapenem-Pentamidine-Sofosbuvir-Velpatasvir

### Present Illness

- She consulted to the ED on 11/24/23 complaining of four days of fatigue, nausea, weakness, poor oral intake and fever (101)
- ED tests showed pancytopenia/anemia, CT abd./pelvis no fluid collections, Thorax CT showed bilateral basal ground glass opacities (atelectasis vs edema)
- She is admitted for evaluation and treatment

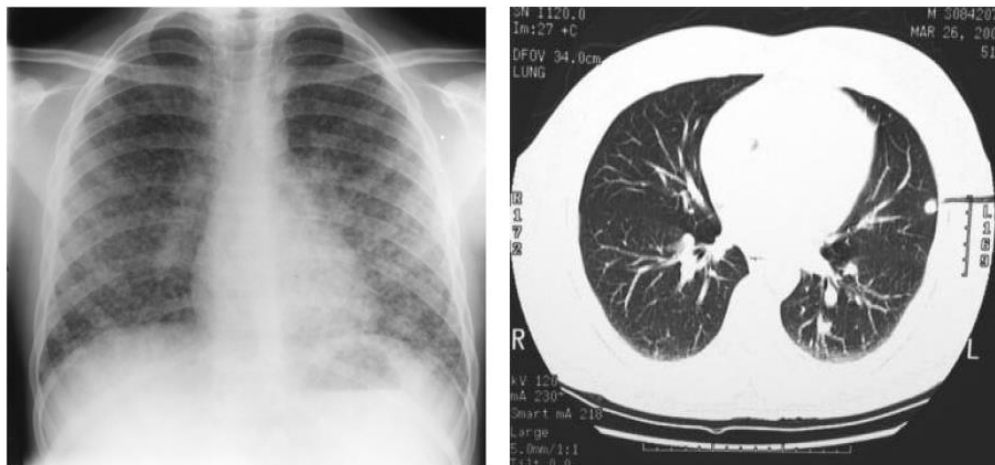
## Evolution

- 11-25-23: Patient continues with fever; the thorax CT is abnormal (pneumonia/pneumonitis vs Pulm. Edema) – Started on empiric antibiotics (Zosyn)
- 11-27-23: No improving, continues fever and leukopenia. Added Ertapenem
- 11-28-23: Bronchoscopy
- 11/30/23: Still with fever and leukopenia, Heme/Onc is consulted

## TB vs Histoplasmosis



## Radiographic Imaging XR and CT: Histoplasmosis in lungs



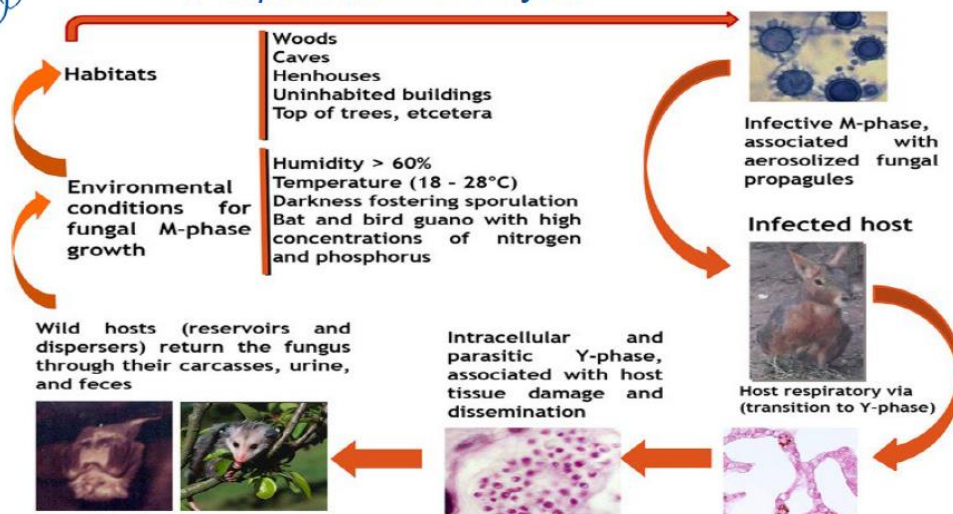
## Evolution

- 12/1/23: Positive Histoplasma PCR from BAL and positive for urinary antigen. Also, she underwent bone marrow biopsy to rule out malignancy vs Histoplasma involvement
- Started on Amphotericin (2 weeks induction followed by Itraconazole for 12 months). PCR from bone marrow is positive for Histoplasma showing disseminated Histoplasma infection
- PET-CT: Negative

## Evolution

- Patient shows notable improvement
- 12/15/23: Patient is considered medically stable for discharge with ambulatory controls

## *H. capsulatum* life cycle



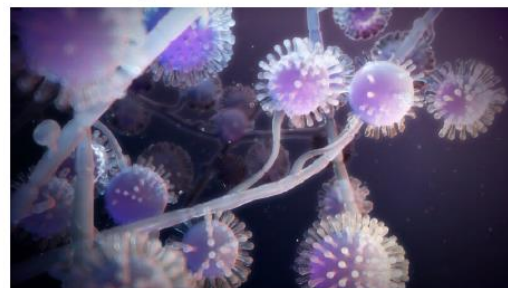


## Disseminated Histoplasmosis risk factors

- Age (infants)
- AIDS
- Hematologic malignancies
- Solid organ transplant
- Hematopoietic stem cell transplant
- Immunosuppressive agents
  - Corticosteroids
  - Tumor necrosis factor antagonists
- Congenital T-cell deficiencies
  - Gamma interferon receptor deficiency
  - Hyperimmunoglobulin M syndrome
  - Others

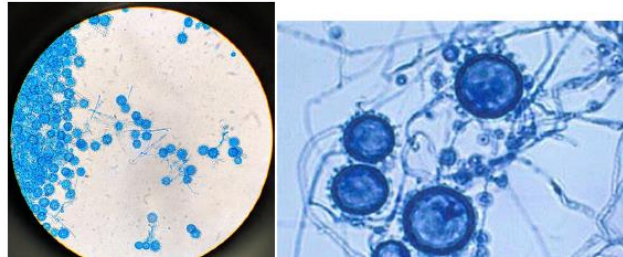
## Climate change and its impact on infectious diseases spreading

- “Climate change affects the occurrence and spread of diseases in marine and terrestrial microbiota, depending on diverse socioeconomic, environmental and host–pathogen-specific factors”
- “Climate change exacerbates the impact of pathogens. Anthropogenic climate change stresses native life, thereby enabling pathogens to increasingly cause disease”



## Diagnostic methods for identification of *H. capsulatum*

- **Serologic tests**
  - EIA – ID – CF
  - Detects antibodies in blood
    - Useful in subacute and chronic Histoplasmosis
- **Antigen testing**
  - Direct detection of the organism, used in urine, serum, BAL, CFS
    - Highest sensitivity for disseminated infection
- **Organism-specific PCR**
  - Specific ID of dimorphic fungi, rapid turnaround
- **Other**
  - MALDI-TOF MS, AccuProbe (DNA probes), Broad-range PCR and sequencing
  - Colony morphology, microscopic morphology based on sporulation and yeast phase conversion



### *H. capsulatum* blood smear with Giemsa dye

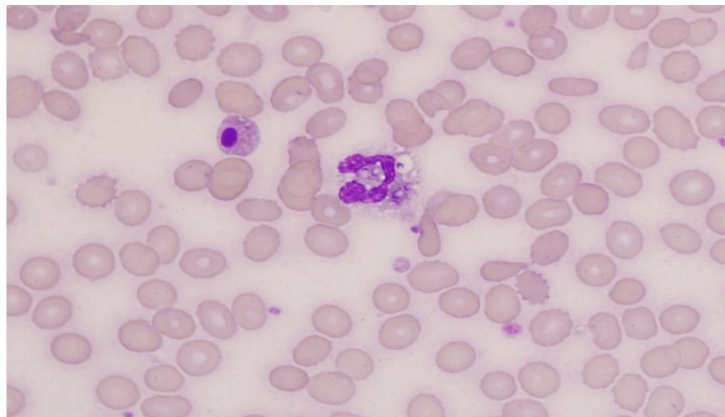
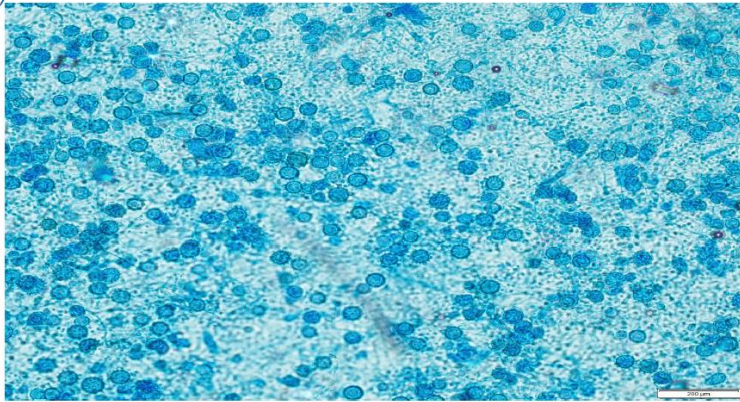


Image courtesy of the Microbiology Laboratory of the "Colegio Mayor de Antioquia," Medellin-Colombia

### *H. capsulatum* Culture in PDA (Potato Dextrose Agar)





Lactophenol Cotton Blue showing tuberculate macroconidia (40x)  
Image courtesy of the Microbiology Laboratory Mayo Clinic Florida



## Conclusions

- This patient has several risk factors:
  - Solid organ transplant patient
  - Taking immunosuppressive medications (corticosteroids + tacrolimus)
  - Pancytopenia/anemia
- Even we have no data confirming travel to endemic area, it is possible she had a prior infection, which remained latent and exacerbated with the use of immunosuppressive medications



## CLINICAL CASE # 2



## Clinical History

- 79-year-old female patient with history of right hip hemiarthroplasty in another facility due to right femoral neck fracture following a fall in July 2022 .
- In February 6, 2023, was admitted at MCF for worsening pain in the right hip pain secondary to a posterior dislocation, malaise, and confusion.
- Cultures revealed infection with *Lomentospora prolificans*, for which she was treated with a prolonged course of caspofungin. Then, was changed to voriconazole and terbinafine. Finalizing the treatment on 11/12/2023.
- She underwent a right hip revision procedure on January 19, 2024, with intraoperative repair, debridement and irrigation. The cultures of the right hip tissue showed growth of a filamentous fungus, which was compatible with *Lomentospora prolificans*.
- Medical History: Primary essential hypertension, Long-term use of opioids/analgesics, Chronic pain syndrome, Depressive disorder, Generalized anxiety disorder, Anemia due to iron deficiency.



## Clinical History (Cont.)

- Past surgeries: Bariatric surgery, Cholecystectomy, Colonoscopy, Hysterectomy, Spine surgery, the above-mentioned hip surgeries.
- Medications: Caspofungin 50 mg IV daily, Voriconazole 200 mg OP q12h, Terbinafine 250 mg PO daily for 3 to 6 months, Micafungin 150 mg IV q24h for 3 months, Vancomycin 15/kg/IV q12h, Ceftriaxone 1 g daily IV for 3 weeks.
- Denies side effects.
- Still non-weight bearing on her right hip.



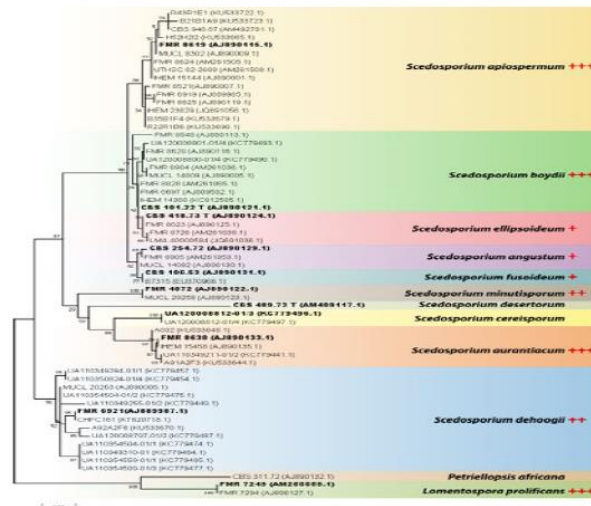
## Evolution

- July 2022: Right total hip arthroplasty due to femoral neck fracture, cultures reported infection by *Lomentospora prolificans*. She received long term treatment with antifungal medications.
- January 30, 2023: Repeated aspiration of her right hip tissue showed WBC 16,710; ANC 12,699, and cultures positive for *Lomentospora prolificans* again.
- February 6, 2023: Admitted due to fatigue, malaise, and confusion, on February 7, 2023, she underwent revision of arthroplasty in her right hip, bacterial cultures negative, fungal cultures positive (2/6) for *Lomentospora prolificans*.
- Treated with Micafungin through 11/11/2023 and Voriconazole and Terbinafine through 12/11/2023



- January 17, 2024: Right hip aspirate “No growth after 30 days of incubation ”
- January 19, 2024: Right hip prostatic exchange. Bacterial cultures negative. Fungal cultures (1/5) positive for *L. prolificans*

## Taxonomy *Scedosporium* sp. complex and *L. prolificans*



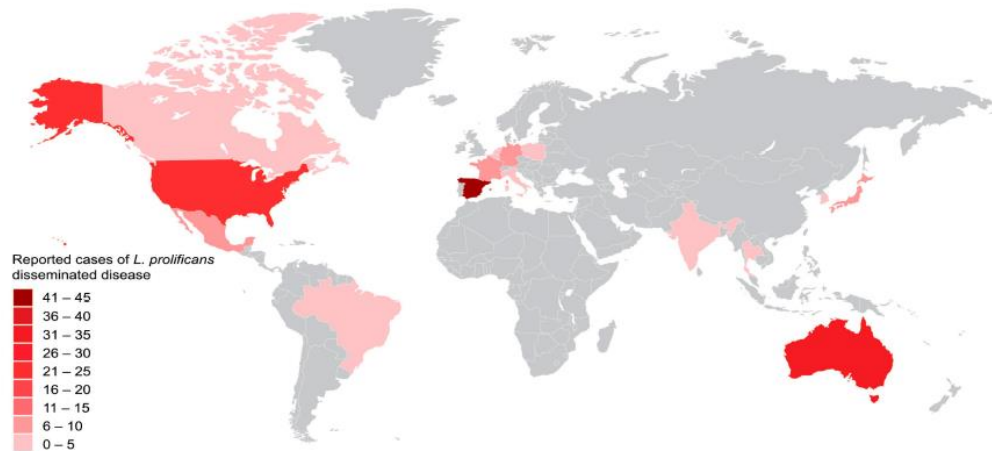
Atlas of Clinical Fungi, 4<sup>th</sup> ed.

## *Lomentospora prolificans* (formerly known as *Scedosporium prolificans*)

### Epidemiology

- The first report in humans was described in 1984, when was isolated from an immunocompetent patient with osteomyelitis.
- It is a highly virulent filamentous fungus and an emerging opportunistic pathogen. Mainly affecting immunocompromised people, but it also affects immunocompetent individuals. It is almost always fatal due to its intrinsic resistance to most of the available antifungal agents.
- Presents a wide spectrum of clinical manifestations from superficial to disseminated infections depending on the immune state of the affected individual.
- It has been isolated from a wide range of environmental sources such as oil-soaked soils, cattle dung, sewage, polluted waters, plants, chicken manure and other animals.
- It has been detected in Australia, Southern USA and European regions such as Spain, with a prominence in dry climates.

## *Lomentospora prolificans* Geographical distribution



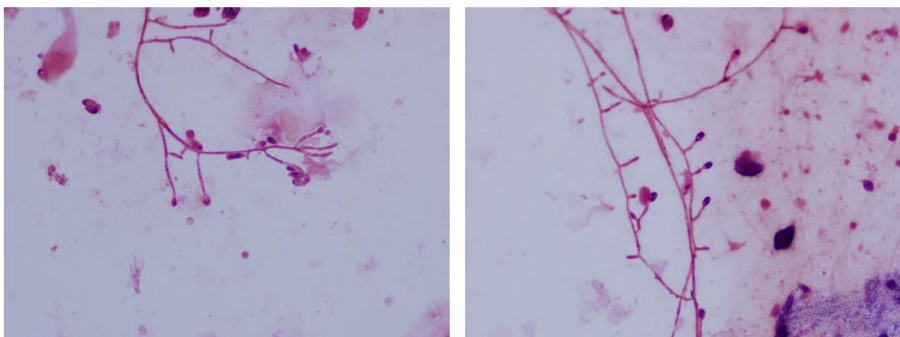
JCM , June 2024

## *Lomentospora prolificans*

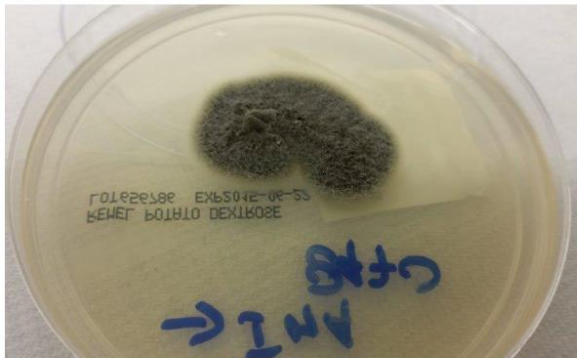
### Epidemiology (Cont.)

- *Lomentospora prolificans* is increasing as a cause of invasive fungal infection in Australia, the United States, and parts of Europe. Additionally, its high rates of intrinsic resistance to several antifungals decrease the possibility of successful recovery.
- Immunocompromised patients, such as those from solid organ transplant and especially hematopoietic stem cell transplant patients, are at elevated risk for invasive *Lomentospora prolificans* infections.
- Predictors for development of invasive disease include acute leukemia (with mortality rates up to 77%) and neutropenia in patients with hematologic malignancies.
- It is rarely observed in HIV-positive patients and in patients with primary immunodeficiency.

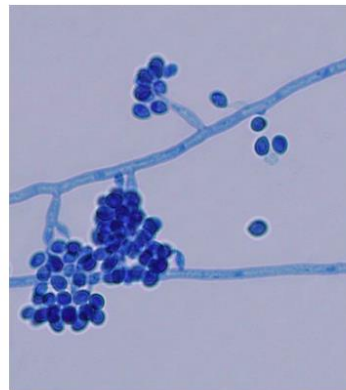
## Diagnostic methods for identification *Lomentospora prolificans*



## Lomentospora prolificans Culture and microscopic exam



PDA, Mayo Clinic Florida

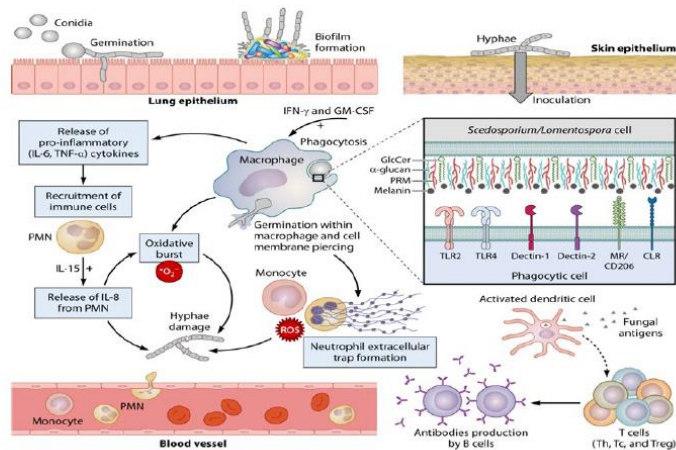


LPCB, Mayo Clinic Florida

## Lomentospora prolificans Culture in PDA (Potato Dextrose Agar)



## Pathogenesis



## *Lomentospora prolificans*

### • Diagnosis

- Imaging techniques
- Histopathological examination of clinical specimens
- Culture from clinical specimens, using standard mycology media as Saboreaud Dextrose Agar (SDA), Inhibitory Mold Agar (IMA)
- Macroscopic and microscopic morphology
- MALDI-TOF-MS Identification
- Molecular identification
- Broad-range PCR
- Serology
- Next –generation sequencing approaches

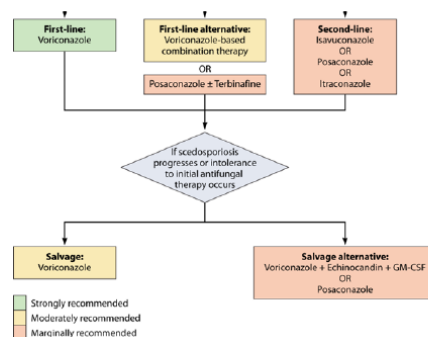
## *Lomentospora prolificans*

### Treatment options

- Treatment of infections by *L. prolificans* is a challenge due to the fungus resistance to most of the antifungal regimens currently in use.
- The lack of new and effective antifungal agents makes the treatment of such infections even harder.
- *L. prolificans* is described as a pan-antifungal resistant species, with innate resistance to commonly used antifungals.
- The recommendation is that the first line of antifungal treatment should include a combined therapy with voriconazole and terbinafine plus surgical resection of the infected tissue when possible.
- The recommended duration of treatment is at least 4 to 6 months, and it is highly recommended frequent assessment of the treatment.

Konsoula A, Tsioutis C, Markaki I, Papadakis M, Agouridis AP, Spernovasilis N. *Lomentospora prolificans*: An Emerging Opportunistic Fungal Pathogen. *Microorganisms*. 2022 Jun 29;10(7):1317. doi: 10.3390/microorganisms10071317. PMID: 35889036; PMCID: PMC9316904.

## *Lomentospora prolificans*

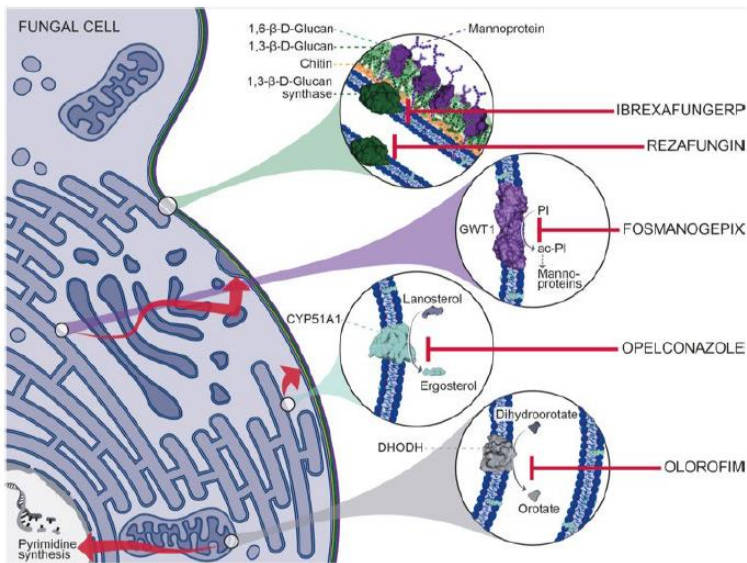




## *Lomentospora prolificans*

New Antifungals currently in development :

- Fosmanogepix
- Olorofim



Europe PMC 2021

## Conclusions

- The most important problems regarding *L. prolificans* infections are the inexperience of healthcare professionals with its clinical manifestations and epidemiology, the lack of or difficulties to access rapid species-specific diagnostic methods, and its intrinsic resistance to most available antifungal treatments.
- *L. prolificans* is now considered a truly emerging, life-threatening pathogen, particularly in immunocompromised patients.
- Commitment to good hygiene and wound care, especially after trauma or injury that may introduce the fungus into the body.
- Use of safety gear (gloves and masks), when handling potentially contaminated materials or specimens.
- Screening for the fungus in transplant donors and recipients, and in those with cystic fibrosis or a chronic lung condition.
- Administering prophylactic antifungal therapy to high-risk patients (patients undergoing hematopoietic stem cell transplantation or solid organ transplantation).
- The most effective antifungal agents against *L. prolificans* are voriconazole and terbinafine, which have synergistic activity.
- Other medications that may be useful are posaconazole, miltefosine, and albaconazole.



Thank you to the Mayo Clinic Florida mycology team and Alexandra for contributions to this presentation