The Changing Epidemiology of Fungal Pathogens: Implications for Healthcare Associated Infections

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Lunch and Learn
September 23, 2020
Spouse works for Incyte. I will not be discussing any Incyte products
Estimated cost of fungal infections in the U.S.
Focus on *Candida auris (C. auris)* as a healthcare associated infection (HAI)
Brief update on emerging antifungal resistance of environmental Aspergillus spp., Mucormycetes
Updates on the changing epidemiology of endemic mycoses
- Histoplasmosis
- Blastomycosis
- Coccidioidomycosis
- Cryptococcus
Estimated Cost of Fungal Diseases

>$7.2 billion in 2017 in U.S. direct medical costs
  - $4.5 billion from 75,055 hospitalizations
  - $2.6 billion from 8,993,230 outpatient visits

- Likely an underestimation due to underdiagnosis and undercoding

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<tr>
<th>Disease</th>
<th>Inpatient</th>
<th>Outpatient</th>
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<tbody>
<tr>
<td>Aspergillus infections</td>
<td>1,221,559,161</td>
<td>33,274,501</td>
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<tr>
<td>Invasive/ABPA</td>
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<td>Candida infections</td>
<td>1,431,098,112</td>
<td>1,575,757,507</td>
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<tr>
<td>Invasive/ Non-invasive</td>
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<td>Coccidioidomycosis</td>
<td>186,323,486</td>
<td>12,132,656</td>
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<td>Cryptococcus</td>
<td>247,998,103</td>
<td>9,737,911</td>
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<td>Histoplasmosis</td>
<td>176,360,051</td>
<td>39,772,029</td>
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<tr>
<td>Mucormycosis</td>
<td>124,631,863</td>
<td>718,510</td>
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</tbody>
</table>

Candida Infections

- Genus Candida - more than 500 species, more than 20 species that can cause human infections
- Yeasts generally reside in the gut and on the skin of healthy people, as well as on mucous membranes

Colonization

Weakened Immune system
Diabetes
Use of antibiotics

Candida overgrowth (candidiasis or invasive infection)

Life threatening invasive disease

Overall mortality rate with invasive candidiasis is ~30%

[Image of Candida cells and diagram showing the progression from colonization to invasive infection]
Candida Infections

- **Background:**
  
  95% of Candida infections in the U.S. are caused by 5 species:
  
  - *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*
  
  - *C. albicans* is the most common cause of candidiasis
  
  - Can be a cause of HAIs
**Candida auris (C. auris)**

**Emerging yeast:**
- First described in 2009 when isolated from a patient with an ear infection in Japan
- Invasive disease in Korea in 2011
- Identified in U.S. in 2016
- Reasons for rapid emergence are unknown
- Nationally notifiable in 2019, 20 states by 2020
- Largest number of cases in NY and Illinois
  - As of June 2019- NY reported 801 patients with either colonization or infection
  - As of June 30, 2020- CDC confirmed 551 clinical cases in N.Y.
  - 3 patients reported in 2019 with pan-resistant C. auris
C. auris Epidemiology

Countries from which C. auris cases have been reported, June 30, 2020

Hatched marked countries represent U.S cases linked to healthcare stays in these countries.
Clinical cases of *Candida auris* reported by U.S. states, June 30, 2020

As of Aug 13, 2020:

- 1238 cases reported nationally
- 90% resistant to at least one antifungal
- 30% resistant to at least two antifungals
C. auris Health Alert

Issued jointly by PADOH and PDPH on Aug 18, 2020

C. auris identified in southeastern PA and Philadelphia

Three different healthcare setting types

https://hip.phila.gov/HealthAlerts/SignUp
HealthAlerts
https://han.pa.gov/
C. auris as an HAI

- Patients can be colonized or infected
- Colonization persists for long time
- High mortality - approx. 57%
- Delays in laboratory diagnosis - misidentification by detection systems
  - Requires MALDI-TOF
  - PCR
- Healthcare environment quickly becomes contaminated
- Contact transmission between patients, staff and environment
C. auris Colonization

Patients are often colonized indefinitely

- Persistent, for many months
- No currently known decolonization strategies
- Patients can be intermittently positive on colonization screening
- CDC updating recommendations to not repeat testing to establish clearance of C. auris

The percentage of those patients who are colonized with C. auris that will go on to develop invasive infection is not known
C. auris Screening

Recommendations for screening

Healthcare contacts

Healthcare abroad in past year

On site Infection Control Assessments
• *C. auris* persists in the environment
  - Can survive over a month
  - Some common disinfectants (quaternary ammonia compounds) do not work
  - Few products have EPA claims for efficacy against *C. auris*
  - If not available should use products effective against *C. difficile* (List K)
### Antimicrobial Products Registered with EPA for Claims Against C. auris

<table>
<thead>
<tr>
<th>Registration</th>
<th>Product Brand Name</th>
<th>Company</th>
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<tr>
<td>70627-72</td>
<td>Avert Sporicidal Disinfectant Cleaner</td>
<td>Diversey Inc.</td>
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<tr>
<td>67619-24</td>
<td>Blondie</td>
<td>Clorox Professional Products Company</td>
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<tr>
<td>67619-25</td>
<td>Dagwood</td>
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<td>37549-1</td>
<td>Micro-Kill Bleach Germicidal Bleach Wipes</td>
<td>Medline Industries Inc.</td>
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<td>70627-74</td>
<td>Oxivir 1</td>
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<td>70627-77</td>
<td>Oxivir 1 Wipes</td>
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<td>70627-60</td>
<td>Oxivir Wipes</td>
<td>Diversey Inc.</td>
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<tr>
<td>1677-237</td>
<td>Oxycide™ Daily Disinfectant Cleaner</td>
<td>Ecolab Inc.</td>
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<tr>
<td>1677-226</td>
<td>Virasept</td>
<td>Ecolab Inc.</td>
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<tr>
<td>9480-12</td>
<td>Wonder Woman Formula B Germicidal Wipes</td>
<td>Professional Disposables International</td>
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<tr>
<td>9480-10</td>
<td>Wonder Woman Formula B Spray</td>
<td>Professional Disposables International</td>
</tr>
</tbody>
</table>

**As of February 2020**
Colonized and/or infected patients should be put in contact precautions!
C. auris Infection Prevention

C. auris prevention

- Updated guidance on precautions in nursing homes
  - Enhanced Barrier Precautions

Candida auris: Learn how you can stop it from spreading.

This drug-resistant fungus causes serious infections and spreads in healthcare facilities.

https://www.cdc.gov/haa containment/PPE-Nursing-Homes.html
C. auris Infection Prevention

- Maintain excellent communication regarding C. auris colonization/infection status with referring facilities
  - Utilize a transfer form
  - Note status in electronic medical record
  - Verbal communication upon transfer

- See Philadelphia Department for Public Health (PDPH) Health Information Portal C. auris page (hip.phila.gov)
  - Transfer form
  - Reporting form
  - C. auris resources
The Philadelphia Department of Public Health (PDPH) and the Centers for Disease Control and Prevention (CDC) recommend that:

This patient should immediately be placed on contact precautions

This patient has been colonized or infected with Candida auris. Candida auris is difficult to detect yeast that can cause life-threatening infections and has caused long-lasting outbreaks in healthcare facilities (HCFs). It is easily spread, hard to remove from the environment, and often very resistant to antifungal medications. Implementation of transmission-based precautions is necessary to prevent outbreaks. Contact precautions should be implemented by all HCFs, including long-term care facilities (LTCFs), as the primary option. LTCFs may be able to utilize Enhanced Barrier Precautions\(^ \star \) for long-term management of these patients per CDC guidance and in consultation with the PDPH.

Contact Precautions and Recommendation Checklist:
- This patient should be placed in a private room, if possible.**
- Healthcare personnel interacting with patients on Contact Precautions, or their environment, are required to wear a gown and gloves, donning their PPE upon room entry and properly discarding before exiting
- Healthcare personnel should conduct diligent hand hygiene during and after contact with a C. auris patient or their environment; ensure alcohol-based hand rub is readily available
- Disposable or dedicated patient-care equipment should be used whenever possible
- All disinfection should be completed with an Environmental Protection Agency (EPA) registered disinfectant effective against Candida auris or other resistant fungi. Disinfection should be performed according to the manufacturer's instructions for use. Examples include:
  - Shared equipment should be thoroughly cleaned/disinfected after contact with this patient (e.g., stethoscopes, x-ray machines, respiratory therapy equipment)
  - The patient's room should be cleaned/decontaminated daily and terminally upon discharge
  - Transport vehicles/equipment should be terminally cleaned/disinfected after use
- Ensure written and verbal communication of isolation status for intra and inter-facility transfers

* More information on enhanced barrier precautions can be found on CDC's website: [https://www.cdc.gov/HAI/infectioncontrol/HandHygieneHandwash.html](https://www.cdc.gov/HAI/infectioncontrol/HandHygieneHandwash.html). Enhanced barrier precautions should only be used in the place of contact precautions under consultation with PDPH.

** If a patient cannot be placed in a private room, ensure roommates are at low risk of developing Candida infections (e.g., no immunocompromising conditions or antifungal therapies, no indwelling devices or open wounds), maintain separation of at least 6 feet, use privacy curtains to limit direct contact, clean/disinfect surfaces on a more frequent schedule, and have healthcare workers change PPE and perform hand hygiene when moving between roommates. Patients with C. auris who have uncontrolled infections, excretions, acute diarrhea, or draining wounds should only be roomed with other C. auris patients.

Resources:
- CDC Health Information Portal: [https://gis.cdc.gov/HAI/infectioncontrol/HandHygieneHandwash.html](https://gis.cdc.gov/HAI/infectioncontrol/HandHygieneHandwash.html)
- PPE in Nursing Homes to Prevent MDR: [https://www.cdc.gov/nhsn/containment/PPE-nursing-homes.html](https://www.cdc.gov/nhsn/containment/PPE-nursing-homes.html)
• Report all positive cultures of Candida auris and Candida haemulonii (Candida auris is frequently misidentified as Candida haemulonii)

• Report cultures from all body sites (including but not limited to blood, wound, skin, ear, urine, rectum, and respiratory secretions) that were collected for diagnostic purposes as well as surveillance or screening purposes

• All positive test results should be reported to PDPH within 24 hours. Please call PDPH at (215) 685-6748 [after-hours (215) 686-4514] to report a case of Candida auris

• A Candida auris case report form should also be filled out and faxed to PDPH at (215) 238-6947 after reporting the case via phone

• Isolates should be retained for one month. PDPH will follow up to coordinate further testing as needed.
Genus *Aspergillus* includes several hundred mold species - found indoors and outdoors

*A. fumigatus* is the major species associated with human disease
- *A. niger, A. flavus, A. terreus*
- People become ill from Aspergillus when they have a weak immune system, damaged lungs, or major allergies
- Aspergillus spp. can cause infections in animals, birds, and plants and produce toxins that lead to food spoilage or are carcinogenic

Aspergillosis refers to the group of diseases caused by Aspergillus
- Invasive aspergillosis - high mortality rate, 25% to 90%
- Chronic pulmonary aspergillosis - long term infection in patients with underlying lung disease
Aspergillus as a cause of HAIs

- HAIs may be sporadic or may be associated with dust exposure during building renovation or construction
- Occasional outbreaks of cutaneous infection have been traced to contaminated biomedical devices

Multistate Outbreak of Fungal Infection Associated with Injection of Methylprednisolone Acetate Solution from a Single Compounding Pharmacy — United States, 2012

753 cases
64 deaths
Current antifungal therapies for invasive and chronic aspergillosis syndromes may be unsuccessful

Recent emergence of triazole-resistant A. fumigatus
  - Environmental usage of triazole fungicides
  - Not previous patient exposure to antifungals

Four out of seven reported cases were from PA (years 2010, 2014, 2016, 2017)
Two of these four patients died of their infections, one died of hydropneumothorax not related to her infection
Mucormycetes
(Zygomycosis)

- Thermotolerant molds found in soil and decaying organic matter, most often *Rhizopus*
- Can cause life-threatening infection called mucormycosis or zygomycosis in people with weakened immune systems
- Climatic events, such as tornadoes and tsunamis, can lead to outbreaks as debris can become embedded in skin or eyes or lead to pulmonary infections
- Fungus can spread through the bloodstream leading to infections of brain, spleen, heart, and skin
Mucormycetes (Zygomycosis)

- Can cause HAIs
  - often associated with healthcare facility construction or water damage
- Can cause outbreaks
- Prevention is vital
  - Avoid areas with dust ex. construction sites, excavation sites
    - N95 masking if unable to avoid
  - Avoid direct contact with water-damaged buildings and flood water
  - Avoid gardening, yard work if possible- wear gloves if can’t avoid, wash hands, clothes if exposed
- Antifungal prophylaxis
Mucormycetes (Zygomycosis)

- Early recognition of disease improves clinical outcome histopathology and cultures
- Aggressive treatment: overall mortality is approximately 50%
  - Debridement
  - Antifungal therapy
  - Reduction of immunosuppression if possible
- Organism is typically drug resistant
  - Amphotericin B, posaconazole, isavuconazole are active
  - Fluconazole and voriconazole are not active
Dimorphic Fungi

- Dimorphic fungi
  - *Histoplasma capsulatum*
  - *Blastomyces dermatitidis*
  - *Coccidioides immitis/posadasii*
- Characterized by having two morphotypes or shapes
  - Exist as filamentous molds in the environment
  - At mammalian body temperature, they transition to a spherical yeast form
- Capable of causing disease in otherwise healthy humans
- Inhalation of spores initiates infection
- Organisms are prevented from leaving the lung by the patient’s immune response → granulomas around the fungi
Updates on Endemic Mycoses

- Expansion of endemic geographic locations
  - Global climate change

- Histoplasmosis: 12 states reportable
  - Estimated U.S. direct medical cost- $216 million in 2017
  - 82% from hospitalization- 5,000 hospitalizations
  - Number of death certificates-44

- Burden of coccidioidomycosis: 27 states reportable
  - At least 10% of the 15,000 U.S. residents infected with annually seek medical treatment for pneumonia
  - 1% of these patients requiring life-long antifungal therapy to avoid a fatal outcome, at a cost exceeding $30,000/year

Benedict K, *Clin Infect Dis*, 2018
Histoplasmosis

- Histoplasmosis is found worldwide
- In North America, it is endemic to the Mississippi and Ohio River Valleys
- Sporulates in bat and bird guano
- Disturbance of bat and bird roosts can lead to inhalation of spores and infection
- Most hosts are unaware of their infection because their immune systems control the infection with granuloma formation
  - Significant percentage seek treatment for pneumonia or flu-like symptoms
  - Small percentage require life-long antifungal therapy
- Higher incidence in immunocompromised humans and in areas where antiretroviral therapy is not available
  - Mortality in patients infected with HIV reaches 30%
Histoplasmosis outbreak at Louisiana campsite: CDC partners with state health department to respond

"Fungal diseases [like histoplasmosis] have taken a back seat to bacterial and viral infections, to the point where many doctors don’t think about fungi as a cause of illness. But statewide tracking of fungal diseases and outbreak findings show that we should be concerned about fungal diseases." — Jose Serrano, MPH, epidemiologist at the Louisiana Department of Health and lead investigator of the histoplasmosis outbreak

https://www.cdc.gov/ncezid/dfe/wed/stories/louisiana-histoplasmosis-outbreak.html

Histoplasmosis: Be Safe Around Bird or Bat Poop!

Histoplasmosis is a fungal infection that can affect anyone. Learning about histoplasmosis can help you stay healthy and recognize symptoms early if you do get the infection.

Histoplasmosis is caused by Histoplasma, a fungus that lives in the soil, particularly where there’s a large amount of bird or bat poop. The infection ranges from mild to life-threatening. It can be misdiagnosed because its symptoms are similar to those of other illnesses. Here are some important things to know about histoplasmosis.

https://www.cdc.gov/fungal/features/histoplasmosis.html
Blastomycosis

- Caused by the dimorphic fungus *Blastomyces dermatitidis*
- Found in moist soil and decomposing organic matter such as wood and leaves
- Endemic areas in the U.S.:
  - Mid-western, south-central, and south-eastern states
  - Particularly areas surrounding the Ohio and Mississippi River valleys, Great Lakes, and St. Lawrence River
- Wisconsin has one of the highest incidences of any state, with yearly rates ranging from 10 to 40 cases per 100,000 persons in some northern counties
- Blastomycosis is typically acquired via inhalation of airborne fungal spores
  - Primary cutaneous blastomycosis is uncommon, but can result from traumatic inoculation
- Outbreaks often involve activities that disrupt soil:
  - Construction/excavation
  - Recreational activities near lakes or rivers such as hunting, fishing, or camping
Blastomycosis

- Influenza-like symptoms (50% asymptomatic)
- Acute pulmonary blastomycosis can progress to acute respiratory distress syndrome (ARDS)
- 25 to 40% of symptomatic cases will develop extrapulmonary infection
  - Cutaneous, osteoarticular, genitourinary, central nervous system disease
- Laboratory tests
  - Culture
  - Histopathology
  - Cytopathology
  - Antigen testing
  - Molecular assays
- Amphotericin B is drug of choice
  - Itraconazole is recommended for mild to moderate disease and step-down therapy
Coccidioidomycosis

- Coccidioides is endemic in arid zones of the Americas
- Most common in highly populated areas of Arizona and California
- Fungus has evolved to use soil rich in small desert rodent excrement as a substrate and has jumped hosts to humans, domesticated dogs and horses
- Soil disturbance, by natural causes or human activity, aerosolizes the spores and leads to infection
- Global climate change is certain to alter the distribution of this arid zone fungus
  - *C. immitis* has already been identified in eastern Washington State and Missouri, far outside of the traditionally defined area where it is endemic
Coccidioidomycosis

U.S. Volunteers Get Sick from Soil Fungus After Building Houses

Volunteers dug trenches at multiple worksites in Tijuana during a community house-building service trip.

Prevention Tips for Service Groups

CDC recommends that service groups consider the following prevention measures to help avoid exposure to the fungus that carries Valley fever.

- Allow trained construction workers to perform activities that generate a lot of dust, such as building foundations and digging trenches.
- Wet the soil before digging, to reduce the amount of dust in the air.
- Stay upwind of digging, when possible.
- NIOSH approved or FDA cleared N95 or greater respirators when performing activities that generate dust.

Endemic mycoses: Cryptococcus

- **Cryptococcosis**
  - *Cryptococcus neoformans*
  - *Cryptococcus gattii*

- Usually affects the lungs or central nervous system

- Globally 220,000 new cases each year of cryptococcal meningitis and 180,000 deaths

- *C. neoformans* thrives in the environment and gains entry into humans when spores or desiccated yeast cells are inhaled

- *C. gattii* resides in soil and with some trees in tropical and subtropical environments

- *C. gattii* has caused infections of humans and other animals in British Columbia and the U.S. Pacific Northwest

- Most infections occur in people with impaired immune systems, especially those with AIDS
Conclusions

• Fungal diseases in the U.S are costly
• *C. auris* has emerged as a multi-drug resistant fungal pathogen causing HAIs, is now present in southeastern PA and is a reportable condition in Philadelphia
• Newly emerging azole resistant aspergillus is linked with environmental use of antifungals and is also present in PA including Philadelphia
• Epidemiology of endemic mycoses in the U.S. is evolving
• Ongoing fungal pathogen surveillance will be crucial to reducing transmission
References

- One health: fungal pathogens of humans, animals and plants. 2019; American Society for Microbiology, [www.asmscience.org](http://www.asmscience.org)
- CDC, Mucormycosis. [www.cdc.gov/fungal/diseases/mucormycosis](http://www.cdc.gov/fungal/diseases/mucormycosis)
- Jackson B, Chow N, Forsberg K et al. On the origins of a species: what might explain the risk of *Candida auris*?. *J of Fungi* 2019; 5(58),:1-17
Thank you

- PDPH HAI/AR program
  - 215-685-4501
  - Signup to receive HAI/AR newsletter, “Healthcare Happenings” at http://eepurl.com/gLX6GV

Questions?