Fungal Infections in the Immunocompromised Host

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No disclosures
Mortality due to invasive mycoses

United States, 1980-1997

Rate per 100,000 population

- Candida
- Aspergillus
- Other Mycoses


Comparative Epidemiology

**Candida**

- Usually acquired endogenously
- Some exogenous transmission
- Antifungal prophylaxis selects intrinsically resistant species

**Molds**

- Usually acquired through inhalation
- Limited host range for invasive infection
- Hospital engineering controls for prevention
- Antifungal prophylaxis selects intrinsically resistant species

80% of all healthcare-associated fungal infections
Healthcare-associated *Candida* infections

Risk factors for *Candida* infection

- Central venous catheter
- Prolonged antibiotics
- Hyperalimentation
- Surgery
  - especially if transects gut wall
- Prolonged ICU stay
- Renal failure
- *Candida* colonization of multiple nonsterile sites
Epidemiology of healthcare-associated candidemia

C. albicans 45%
C. glabrata 19%
C. parapsilosis 14%
C. tropicalis 12%
C. krusei 2%
Polyfungal 5%
Other 3%

N=1593


Courtesy of Jan Patterson, M.D.

Changing epidemiology of healthcare-associated Candida

Diekema D et al, Diagn Microbiol Infect Dis 2012
Temporal trends in antifungal resistance of *Candida glabrata* isolates

Pearls about healthcare-associated *Candida* species (non-*albicans*)

- **C. glabrata**
  - Some strains have decreased susceptibility to azoles and/or echinocandins (acquired)

- **C. parapsilosis**
  - Associated with intravenous catheters
  - Neonatal ICU

- **C. krusei**
  - Resistant to fluconazole (intrinsic)

- **C. lusitaniae**
  - Develops resistance easily to AmB
Candidemia in Neonates

Rate: 12.3 per 1000 discharges

Risk factors (MVA)

- Gestational age < 32 weeks
- 5 min Apgar < 5
- Shock
- Intralipids > 7 days; parenteral nutrition > 5 days
- Central venous catheters
- H2 blockers
- LOS > 7 days
- Intubation
- Invasive fungal dermatitis


Candidiasis by year and birth weight

Aliaga S et al. Pediatrics 2014;133:236-242
Healthcare-associated *Candida*

Changing epidemiology
Mostly endogenous transmission
Exogenous transmission can occur
Emergence of non-*albicans* species

Control and utilization measures
- Antisepsis
- Standard precautions
- Prudent use of antifungal agents

Healthcare-associated mold infections
Invasive aspergillosis

Ubiquitous mold: Soil, water, decaying vegetation

Aspergillosis in solid organ transplant

UTHSCSA Experience

1989-1997

Patterson JE et al. Transplant Infect Dis 2000
Case #1

- 64-year-old man with chronic myelomonocytic leukemia undergoing chemotherapy. He is on prophylactic fluconazole.
- On 12\textsuperscript{th} day of neutropenia, develops fever 38.3° C. Started on empiric antibiotics. Chest CT shows this:

![CT Scan Image]
September 9

November 4

BAL
Galactomannan index 0.7 (<0.5)

β-1,3-glucan 117 (<80)
How did he get it?

• The patient was in a protective isolation room, but…
  • Went to radiology and other areas wearing surgical mask
  • Went out on pass several times for several hours between cycles of chemotherapy, again on first day of neutropenia
• Prolonged neutropenia

Conidia (spores) are tiny and ubiquitous in air and dust

400x magnification
Palmore et al, JCM 2010
Patient populations at high risk

Prolonged neutropenia
Stem cell transplantation
Graft-versus-host disease
Organ transplantation (lung > heart > others)
Some primary immunodeficiencies
Advanced AIDS

Avoiding exposure to molds inside the hospital: Protective isolation

Hematologic malignancy, SCID, stem cell and organ transplantation
Engineering controls:
• Positive pressure room airflow; high rates of air exchange
• HEPA filtration
• Sealing of windows, outlets, walls
• No carpet
Avoiding areas and activities that aerosolize spores
• Leave room only for essential procedures
• Construction: N95 masks?
• Fresh flowers
• Water damage
Unsealed ceiling penetrations can introduce particulates from ‘dirty’ spaces and decrease the protective pressure differential.

Changing the light bulb breaks the seal around the fixture (ceiling penetration).

Particulates seep in from air infiltration around room fixtures.
Sweep on the entrance door allows entry of air and particles, and changes pressure differential

Clogged drains have been implicated in mosocomial outbreaks of waterborne infections, including mold infections
Air infiltration from the opening in a door jam in a pediatric oncology room

Aspergillus and construction

Association between aspergillosis outbreaks and construction

Environmental controls associated with decreased risk

- Maintain negative pressure
- Install appropriate barriers
- Control traffic in construction areas
- Monitoring of airborne spore count

Arnow 1991; Wald 1997; Comet 1999; Patterson 2000
Construction don’ts

Construction do’s
Avoiding exposures to molds outside the hospital

- Hand hygiene
- Construction/excavation sites
- Caves, chicken coops
- Mulching, mowing, leaf blowing and other gardening
- Water damage/damp basements
- Food safety

Pricked by the tip of a mini palm frond

*Fusarium proliferatum* grew from pus and from extracted plant spine

*Palmore et al, JCM 2010*
Avoid ingesting mold

Probiotics
   *Saccharomyces cervisiae* fungemia

Blue cheese

Naturopathic medications

Expired food and old leftovers

Mulch pneumonitis

Siddiqui et al, CID 2007
Floor sweeper

Floor Sweeper with dust guard
Aspergillus and hospital water

Aspergillus detected in water supply
- Water-related surfaces (7%)
- Water samples (24%)
  - Water tank lines, shower drains, shower heads, toilet bowls
- Higher concentrations in air from bathrooms

Genetic similarity of one environmental isolate with a patient isolate

Anaisse. CID 2002;34:780-9

Fusariosis and hospital water

Fusarium infections in an oncology center
- Investigation
  - Fusarium isolated from 57% cultures
    - Sink drains, faucet aerators, shower heads, water tank
  - Molecular typing
    - Some patient isolates matched environmental isolates

Anaisse. CID 2001;33:1871-8
Prophylaxis: Vori vs. Flu

- P for Aspergillus spp. = 0.05
- P for total = 0.11

Voriconazole therapy: Breakthrough infections

‘Usual Suspects’
- Candida spp. (esp. glabrata)
- Aspergillus spp
- Scedosporium prolificans
- Trichosporon asahii
- Mucorales
- Other non-Aspergillus molds

Common Factors
- Late complication: median day 196 (range, 9-837)
- Severe acute or chronic GvHD: 90%
- All received azole prophylaxis

Trifilio, Bone Marrow Transplant 2007
Non-Aspergillus invasive mold infections in transplant recipients, 2001-06

- Scedosporium
- Fusarium
- Mucorales

Park B, Emerg Infect Dis 2011

Emerging Resistant Mycoses: Mucorales

- Emergence on suppressive therapy (voriconazole, echinocandin):
  - Severely immunosuppressed (allo BMT)
  - Pulmonary/disseminated infections
- Other clinical presentations: trauma; burns
  - Tsunami/tornado victims
  - May not grow in culture (homogenized tissue)
- Echinocandins & voriconazole: no activity
- In vivo activity: posaconazole
  - Clinical trials (Greenberg, AAC 2006)
    - 71% response in 55 patients
- Primary therapy with high dose lipid formulation of amphotericin B

Saksenaea vasiformis: traumatic wound infection & Apophysomyces elegans light microscopy (420X, cotton-blue stain)

Courtesy of Jan Patterson, M.D.

Anderson D, Lancet 2005
Case #2

- 45 yo man with AML diagnosed in 2004, underwent induction with 7+3 and second induction with etoposide, mitoxantrone and HIDAC → CR.
- Consolidation with high dose Ara-C and gemtuzumab. Lost to follow-up.
- First relapse in 2009. Treated with a cycle of Ara-C, idarubicin and gemtuzumab.
- Nodular lung infiltrates – positive for Aspergillus. Rx – voriconazole + ambisome for “a few weeks.” Lost to follow-up.

Case 2

July 2011 – fever, chills, fatigue, pleuritic right lower chest pain and nodular violaceous swellings on left posterior ear & right leg.

CXR – No acute pulmonary process.
Case 2

Peripheral blood – 91% blasts, ANC 0.0
Biopsy of skin nodules – leukemic infiltrate
Started on FLANG (fludarabine/Ara C/mitoxantrone)
Antimicrobials:
  Ceftazidime + vancomycin started on admission
  Caspofungin added for secondary prophylaxis of invasive aspergillosis

Given the history of invasive aspergillosis, a chest CT was obtained:
PET CT a week later showed a different, new nodule that was hypermetabolic.

Voriconazole was started. Here is the evolution of the nodule:
Liposomal amphotericin B was started, and a BAL was performed

The BAL grew a colony of an unidentified mold
The patient developed hemoptysis the next day

What is the next appropriate step?

A. Increase dose of liposomal amphotericin
B. Add caspofungin
C. Get a needle biopsy
D. Call the surgeon
E. Call the interventional radiologist
Phaeohyphomycoses

Etiologic agents


Mycotic infections caused by dematiaceous fungi (melanin in cell walls)

Fontana Masson stain

Tropical, subtropical and temperate climates
Hyalohyphomycoses

Etiologic agents

- *Fusarium* spp., *Paecilomyces* spp., *Trichoderma* spp., *Scedosporium apiospermum/Pseudallescheria boydii*

Mycotic infections caused by colorless, sepatate molds

Inhalation or direct inoculation into skin/soft tissue/eye

Clusters of mold infection

How to prove that a ubiquitous organism is a cause of nosocomial infection?

- High index of suspicion
- Air samples and swabs from relevant sites
  - Typing methods – multilocus sequence typing, ITS sequencing, whole-genome sequencing, others to compare environmental isolates to patient isolates

CDC PHIL  
Palmore et al, JCM 2010
Hospital source of invasive fungal infection is suspected far more often than proven

- Usually sporadic cases
- Incubation periods vary
- Sampling error
- Community exposure is a confounder
- Colonization vs. infection
- Investigation is resource intensive
- Some notable exceptions

Outbreak of fungal meningitis due to contaminated injectable steroids

- September 2012-present
- 765 patients, 85 deaths
- Contamination of methylprednisolone produced by New England Compounding Center
- Meningitis >> epidural abscess, vertebral osteo >> peripheral joint infections
- Only 9% of patients immunocompromised
- Attack rate 4.4/100

Exserohilum spp. CDC
Marion Kainer
April Pettit
Healthcare-associated fungal infections

- *Candida* in the ICU
  - Non-*albicans* emerging
  - Exogenous transmission
- Mold infections
  - *Aspergillus*, Mucorales
  - Phaeohyphomycoses, *Fusarium*
- Immunocompromised pts
  - BMT, chemo-induced neutropenia
  - Solid organ transplant
  - Neonates
  - ICU, trauma, burns, surgery