Early Diagnosis and Therapy for Fungal Infections

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The Ohio State University Medical Center

- **James Cancer Center**
  - 165 beds
  - bone marrow transplants
- **Ross Heart Hospital**
  - 90 beds
  - Heart and lung transplants
- **The Ohio State University Hospital**
  - 850 beds
  - solid organ transplant
  - SICU, MICU, NICU, Burn unit
The Fungal World

- **FUNGI**
  - **YEASTS**
    - *Candida* spp.
    - *Cryptococcus* Trichosporon
  - **MOULDS**
    - *Zygomycetae*
      - *Rhizopus*
    - *Septate Fungi*
      - *Fusarium*
      - *Aspergillus* spp.
      - *Paecilomyces*
      - *Hyalohyphomycoses*
    - *Mucor*
    - *Absidia*
Significance of *Candida* Infections

- *Candida* species represent the most common cause of systemic fungal infections and a major cause of mortality among compromised hosts$^{1,2}$
- Sepsis due to fungi increased >200% in past 20 years$^{3}$
- Outcomes attributable to candidemia/candidiasis
  - Excess medical costs of $216-$281 million/year$^1$
  - Increased LOS (up to 34 days)$^1$
  - 38%-72% mortality$^{2,4}$
- However, the true incidence is still underestimated and frequently is a postmortem diagnosis$^3$

LOS, length of stay.

In a retrospective study in 100 adult MICU patients:

- 81% of antemortem diagnoses confirmed on autopsy
  - Most frequent diagnosis: bacterial pneumonia with MODS
- Major missed diagnoses (N = 36)
  - Class I errors (n = 22)
    - Autopsy findings revealed a diagnosis that if known might have led to a change in therapy
    - Invasive fungal infection (5 [22%])
    - Cardiac tamponade (5), abdominal bleeds (4), MI (3)
  - Class II errors (n = 14)
    - No effect on outcome
    - Cancer (6), small bowel infarction (3), acute hepatitis (2), pulmonary embolism (2)

MI, myocardial infarction; MICU, medical intensive care unit; MODS, multiple organ dysfunction syndrome.

Incidence and Severity of Invasive Fungal Infections (IFIs): BSIs

Most common pathogens and associated mortality rates in ICU patients with BSI (N=10,515)

Results from a nationwide surveillance study of patients who developed nosocomial BSI either in the ICU or on a non-ICU ward; the data shown here are for the 10,515 patients with ICU-onset of BSI.

BSI=bloodstream infections; CoNS=coagulase-negative staphylococci; ICU=intensive care unit.

Nosocomial Candidemia: Associated Mortality

Historical Perspective on Candidemia

Candidemia: LOS and Hospital Charges for Patients With and Without Candidemia

*Attributable increase (95% CI).
LOS=length of stay.

Additional Factors That Increase Risk of Invasive Candidiasis

- Prolonged antibiotic use
- Immunosuppression
- Neutropenia
- Broad-spectrum antibiotics
- More than 2 days of mechanical ventilation
- Total parenteral nutrition
- Prolonged ICU stay
- High APACHE II score
- Central venous catheter
- Candida colonization ≥2 sites

APACHE, Acute Physiology and Chronic Health Evaluation.

### Diagnostic Challenges: Aspergillosis and Candidiasis

<table>
<thead>
<tr>
<th>Aspergillosis</th>
<th>Candidiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Variable and nonspecific clinical presentation&lt;sup&gt;1&lt;/sup&gt;</td>
<td>• Lack of distinct clinical presentation&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Lack of availability of one universally applicable diagnostic test&lt;sup&gt;1&lt;/sup&gt;</td>
<td>• Tissue culture&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Delay in initiation of therapy&lt;sup&gt;1&lt;/sup&gt;</td>
<td>• A positive culture, considered definitive, may require invasive biopsy, which may not be feasible in critically ill patients</td>
</tr>
<tr>
<td>• Risk for potentially fatal progression of disease</td>
<td>• Blood culture&lt;sup&gt;4,5&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Diagnostic criteria exist for proven and probable IA&lt;sup&gt;2&lt;/sup&gt;</td>
<td>• Relatively insensitive</td>
</tr>
<tr>
<td>• Although useful in clinical trials, less valuable in practice</td>
<td>• Nonsterile site cultures may reflect colonization or contamination vs infection&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Catheter culture sensitivity varies with methodologies&lt;sup&gt;3,5&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Diagnostic Challenges of Candidiasis

- No distinct manifestations\(^1\)
- Colonization vs infection\(^2\)
- Blood culture positivity rates ~40%-60\%\(^3\)
  - ↓ in patients on prior antifungals\(^4\)
  - ↓ if a non-\textit{albicans} \textit{Candida} species (~20%-40\%)\(^4\)
- High index of suspicion\(^3\)
- High-risk group\(^5\)

New Diagnostic Techniques

• Antibodies\(^1\)
  • Disappointing so far
• Metabolites\(^1\)
  • D-arabinitol: useful, but not practical
• Fungal cell wall components\(^2,3\)
  • New assays for β-D-glucan and galactomannan show promise
• Fungal PCR\(^4\)
  • Real-time PCR can contribute to rapid diagnosis
• PNA FISH\(^5\)
  • Potential for rapid identification of *C. albicans*

PCR, polymerase chain reaction; PNA FISH, peptic nucleic acid fluorescence in situ hybridization.

Nonculture Diagnostics: Benefits and Limitations

- **β-D-glucan from cell wall**\(^1\) (Fungitell BG)
  - Detects *Candida* spp. and Apergillus
  - Sensitivity for *Candida* pathogens 78%-90%, depending on cut-off values (>80 pg/ml is positive)
  - High false + in patients with bacterial infections (54-68%)
  - False + with hemodialysis, surgical gauze, albumin, immunoglobulin

- **Galactomannan from *Aspergillus* cell wall**\(^2,3\) Bio-Rad Platelia EIA
  - Sensitivity and specificity of BAL GM >90%
  - Positive and Negative predictive values are 76% and 96%
  - False + in pts receiving pip/tazo, amoxicillin or other beta-lactamase inhibitors

- **PCR for fungal DNA**\(^4\)
  - Able to distinguish among clinically significant *Candida* and *Aspergillus* spp.
  - Real-time PCR provides rapid results < 6 hours
  - Positive predictive value 100% Negative predictive value 99%

- **PNA FISH**\(^5\)
  - Probe for identifying *C. albicans*
  - Positive predictive value, 100%; negative predictive value, 99%

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Multiplex PCR detection enhancement of bacteremia and fungemia

**Objective**: test a multiplex RT-PCR method for simultaneous detection of multiple organisms in bloodstream infections.

**Methods**: Prospective observational study of 200 patients at risk of BSI with signs of SIRS.

Louie R. et al 2008 CCM :36(5);1487-1492.
Tsali E et al 2010 JCM 48(1); 26-33.
Organisms detected by multiplex PCR

<table>
<thead>
<tr>
<th>Gram-Positive</th>
<th>Gram-Negative</th>
<th>Fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONS</td>
<td>Acinetobacter baumannii</td>
<td>Aspergillus fumigatus</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>Enterobacter aerogenes/cloacae</td>
<td>Candida albicans</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>Escherichia coli</td>
<td>Candida glabrata</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Klebsiella pneumoniae/oxytocia</td>
<td>Candida krusei</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Proteus mirabilis</td>
<td>Candida parapsilosis</td>
</tr>
<tr>
<td>Streptococcus sp.</td>
<td>Pseudomonas aeruginosa</td>
<td>Candida tropicalis</td>
</tr>
<tr>
<td>MRSA (mecA gene)</td>
<td>Serratia marcescens</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stenotrophomonas maltophilia</td>
<td></td>
</tr>
</tbody>
</table>
Results

PCR detected bacteria/fungi in 45 cases vs 37 by blood culture.

PCR detected mecA in all 3 culture confirmed MRSA

PCR did not detect *E. faecalis* in 5 BC confirmed cases

7 samples could be tested simultaneously in 6.54 hours

Louie R. et al CCM 2008:36(5);1487-1492.
Conclusion

• Despite limitations of both blood culture and RT multiplex PCR methods
  1. PCR could be an adjunct to BC
  2. PCR can facilitate early detection
  3. Early detection can facilitate evidence-based treatment decisions

Louie R. et al 2008 CCM 36(5);1487-1492.
Tsakik E et al 2010 JCM 48(1); 26-33.
Overview of Antifungal Management Strategies

- Highest-risk patient (eg, HSCT for *Candida*)
- No infection

- High-risk patient with persistent fever despite antibiotics
- Possible infection

- High index of suspicion (based on signs and symptoms) but without definitive diagnostic proof
- Probable infection

- Full-blown disease
- Proven infection

- For patients refractory to or intolerant of primary therapy

Increasing certainty of fungal infection

A Multi-Institutional Study of Antifungal Use in Surgical Intensive Care Units

Indication for Antifungal Therapy*

- Empiric 44%
- Preemptive 43%
- Definitive 12%

*Evaluated on the start date of antifungal therapy.
Infections Caused by Non-\textit{albicans} \textit{Candida} Are Increasing

Neither \textit{C. glabrata} nor \textit{C. krusei} showed a consistent increase or decrease in isolation rates overall. Increased rates of isolation of \textit{C. tropicalis} (4.2\% to 7.5\% increase) and \textit{C. parapsilosis} (4.6\% to 7.3\% increase) were observed between 1997 and 2003.

Why Should *Candida* Spp. Be Identified?

- *C. albicans*¹
- *C. glabrata*—less susceptible to all antifungals¹,²
- *C. parapsilosis*—catheter related¹
  - Reduced echinocandin susceptibility
- *C. tropicalis*¹
- *C. krusei*—“neutropenics”¹
  - Intrinsic azole resistance, less susceptible
  - Decreased susceptibility to AMB
- *C. guillermondii*
- *C. lusitaniae* \(\text{AMB resistance}^1\)

AMB, amphotericin B.

Importance of *C. glabrata*?

- **US incidence:** 20%-24% of all BSIs\(^1\)
- **Susceptibility\(^2\)**
  - 10%-15% resistant to fluconazole
  - 46%-63% resistant to itraconazole
  - Also less susceptible to all antifungals, including AmB
- **IDSA recommended antifungal therapy\(^3\):**
  - Echinocandins—drug of choice
  - Voriconazole or AmB
    OR
  - Echinocandin followed by azole

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Prediction of Non-\textit{Albicans} Candidemia

- Retrospective case series of 245 patients (60% in the ICU) in 2 academic, tertiary care centers
- \textit{C albicans} in 52% of infections and \textit{C glabrata} in 20%
- No variable, including both previous fluconazole exposure and severity of illness, correlated with the fungemia due to a non-albicans species

- Conclusion: Simple clinical factors do not allow the clinician to effectively identify patients likely infected with non-albicans pathogens or with possible fluconazole-resistant fungi

Challenges in the Management of Candidiasis

- The longer the wait, the higher the mortality rate\(^1\)
- Nonspecific clinical presentation\(^2\)
- No single, sensitive, universally applicable test available for establishing diagnosis\(^1,3\)
- Timing of therapy\(^1\)
  - Waiting for definitive proof increases the risk for potentially fatal progression of disease

Mortality Related to Untreated Candidemia

- Times between admission and onset of candidemia
  - Median: 13 days
  - Mean: 20.8 days

- Deaths in 12/15 who never received antifungal therapy
  - 11/12 deaths within 72 hours after the first Candida-positive blood cultures were obtained (and before positive culture results were available)

Delaying Empirical Treatment of Positive *Candida* Bloodstream Infections Until Positive Cultures Are Available

- Retrospective cohort analysis of 157 patients with candidemia
  - Deaths in 50 (31.8%) of patients
- Definition of “inappropriate treatment” in this study:
  - “The absence of antifungal agents at the time that fungus-positive blood samples for culture were drawn”
  - “Fluconazole treatment with the subsequent isolation of either *Candida krusei* or *Candida glabrata*”
- Timing of the administration of antifungal therapy:
  - Within 12 hours in 9 (5.7%) patients
  - Between 12 and 24 hours in 10 (6.4%) patients
  - Between 24 and 48 hours in 86 (54.8%) patients
  - Greater than 48 hours in 52 (33.1%) patients

Delaying Antifungal Treatment Has Been Associated With Increased Mortality

Hospital mortality based on timing of antifungal therapy

- **Independent determinants (by multivariate analysis) of hospital mortality**
  - APACHE II score (1-point increments) (P < .001)
  - Prior antibiotic treatment (P = .028)
  - Administration of antifungal treatment 12 hours after having the first positive blood sample for cultures (P = .018)

**APACHE** = acute physiology and chronic health evaluation.
Impact on Mortality of Candidemia Based on Time to Initiation of Antifungal Therapy

- Retrospective cohort study of 230 patients from 4 medical centers
- 162 patients (70%) with nonsurgical hospital admission
- C albicans most commonly isolated (56% of patients)
- 192 patients with no previous fluconazole treatment
- Mortality rates based on time of initiation of fluconazole (P = .0009 for trend)

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>14/92 patients (15%)</td>
<td>9/38 patients (24%)</td>
<td>12/33 patients (37%)</td>
<td>12/29 patients (41%)</td>
</tr>
</tbody>
</table>

Effect of Antifungal Therapy **Timing** on Mortality in Patients with Candidemia

106 episodes analyzed

**Incubation**: time from BC collection to positivity

**Provider notification**: time from positivity to provider notification

**Antifungal initiation**: time from provider notification to 1st dose

Delay in Therapy Increases Mortality

Impact of Inadequate Antifungal Therapy on Crude Mortality in Candidemia

Region 1
(Connecticut)

- Controls: 23% (182/789)
- All Candidemia: 42% (90/214)
- Candidemia: 34% (37/108)
- + Adequate Treatment: 54% (38/70)

Region 2
(Baltimore/Baltimore County)

- Controls: 15% (309/2065)
- All Candidemia: 39% (206/529)
- Candidemia: 31% (56/179)
- + Adequate Treatment: 56% (44/78)

*Adequate treatment was defined as any systemic antifungal medication administered for a minimum of 7 days after the first Candida-positive blood culture.


- “Clinicians should also consider whether candidemia is a likely pathogen when choosing initial therapy.”

- “When deemed warranted, the selection of empirical antifungal therapy will be tailored to the local pattern of the most prevalent Candida species and any prior administration of azoles drugs.”

- “Risk factors for candidemia should also be considered when choosing initial therapy.”

<table>
<thead>
<tr>
<th>Condition</th>
<th>Primary</th>
<th>Alternative†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidemia</td>
<td><strong>Fluconazole</strong></td>
<td>LFAmB 3-5 mg/kg daily; or AmB-d 0.5-1 mg/kg daily; or voriconazole 400 mg (6 mg/kg) bid for 2 doses, then 200 mg (3 mg/kg) bid (A-I)</td>
</tr>
<tr>
<td>Nonneutropenic adults</td>
<td>800-mg (12-mg/kg) loading dose, then 400 mg (6 mg/kg) daily or an echinocandin* (A-I)</td>
<td></td>
</tr>
<tr>
<td>Neutropenic adults</td>
<td><strong>An echinocandin</strong>* (A-II)</td>
<td>Fluconazole 800-mg (12-mg/kg) loading dose, then 400 mg (6 mg/kg) daily; or voriconazole 400 mg (6 mg/kg) bid for 2 doses, then 200 mg (3 mg/kg) bid (B-III)</td>
</tr>
</tbody>
</table>

* Echinocandin dosing in adults is as follows: anidulafungin, 200-mg loading dose, then 100 mg/day; caspofungin, 70-mg loading dose, then 50 mg/day; and micafungin, 100 mg/day.

† AmB-d (0.5-1.0 mg/kg daily) or LFAmB (3-5 mg/kg daily) are alternatives if there is intolerance to or limited availability of other antifungal agents (A-I).

LFAmB, lipid formulation of amphotericin B.

Non-neutropenic Initial Therapy for Adult Patients

**Must consider Local pathogen prevalence data**

- **Moderate to Severe illness or recent azole exposure**
  - **NO**
    - fluconazole 800mg LD 400mg daily A1
    - culture result
      - C. albicas
        - fluconazole
      - C. tropicalis
  - **Yes**
    - echinocandin A1
    - culture result
      - C. parapsilosis
        - fluconazole B-III
        - for pt who initially received echinocandin and follow up cultures are neg continue echinocandin
      - C. glabrata
        - echinocandin B-III

**Key piece of data**

<table>
<thead>
<tr>
<th>Species</th>
<th>Frequency</th>
<th>Ampho B</th>
<th>Flu or Itra</th>
<th>Vori or Posa</th>
<th>Echinocandins</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>40-60%</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>20-30%</td>
<td>S-I</td>
<td>S-DD to R</td>
<td>S to S-DD</td>
<td>S</td>
</tr>
<tr>
<td>C. parapsolosis</td>
<td>10-20%</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S to I</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>20-30%</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>C. lusitania</td>
<td>0-5%</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>C. krusei</td>
<td>5-10%</td>
<td>S-I</td>
<td>R</td>
<td>S to S-DD</td>
<td>S</td>
</tr>
</tbody>
</table>

Ref: Ostrosky-Zeichner et al. CCM 2006 34:3
The Ohio State University Medical Center

- 1000 bed tertiary care academic medical center
- Antimicrobial Stewardship Program (ASP)
- Multi-disciplinary team
Candidemia Management Algorithm

Blood Culture Drawn

Confirmed Candidemia*
Detect yeast consistent with *Candida* on Gram Stain
Inoculate positive blood culture on media

Microbiology calls RN/MD & pages ID PharmD

2-5 days

10 minutes

24-48 hours

- Intravenous catheter removal is recommended
- Rule out disseminated candidiasis & endocarditis
- Consider Infectious Diseases & Ophthalmology Consultation

- Empiric Caspofungin IV (loading dose 70 mg, then 50 mg daily)
- Severe hepatic dysfunction (Child-Pugh Score 7-9): Caspofungin IV (loading dose 70 mg, then 35 mg daily)

Growth of yeast on media
Candidemia Management Algorithm

2-4 hours

Growth of yeast on media

Germ Tube Positive
(i.e. *Candida albicans* or *dubliniensis*)

- Change to fluconazole IV/PO\(^\text{#}\) (loading dose 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily)
- ESRD or HD: Fluconazole IV/PO\(^\text{#}\) (dose adjustment may be considered)\(^^\text{^}\)
- CVVHD: Fluconazole IV/PO\(^\text{#}\) (loading dose 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily)
- Clinically Unstable: continue caspofungin

Germ Tube Negative
(i.e. other non-albicans species)

Continue caspofungin
Germ Tube Test for *C. albicans*

Early forms of hyphae are referred to as germ tubes.

*C. albicans* when placed in a nutrient environment, is able to form germ tubes in less than 3 hours.

This is a quick and inexpensive method to differentiate *albicans* from non-*albicans* species of Candida.

The downside of this method is:

- It is very time sensitive.
- Requires experienced lab personnel.
- Samples incubated too long can cause false positives.
- Heavy inoculum may produce false negatives.
So How Do I Choose?
Treatment of Invasive Candidiasis

• Consider **alternatives** to fluconazole when:
  • recent **exposure** to fluconazole or other azole
  • **broader spectrum** is desirable
    (e.g., persistently neutropenic patient)
  • **non-albicans** species isolated during or immediately following azole therapy
  • unstable or severely **immunocompromised** patient
  • Hospital has high rate of non-albicans
Conclusion

• Timing is everything!
• Select the most effective antifungal agent based on local pathogen prevalence data
• Review the ordering process at your hospital
• You can select effective therapy but if it isn’t given in a timely fashion the outcome may not be optimal