Invasive Fungal Infections
The Impact of
HOST-, ORGANISM-, & TREATMENT-
Related Factors on Outcomes

Friday, October 19, 2012
6:00 – 8:00 PM
San Diego, CA

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Educational Program
Understanding IFIs:
The Impact of Patient and Organism ............... 9
Clinical Updates on IFIs ....................... 11
Patient-Centered Approaches in Managing IFIs ...... 27
The management of invasive fungal infections (IFIs) has evolved immensely over the years, led by the development of a number of new antifungal agents and advanced diagnostic techniques that detect infections at early stages. The expanded use of antifungals (for prophylaxis, empiric or definitive treatment) has led to a global shift in etiology towards more infections caused by organisms less susceptible to commonly used antifungals. Despite advances in drug development, the incidence and mortality associated with IFIs have not changed substantially in the last 2 decades. This has led to a recent resurgence of updates to evidence-based practice guidelines for various types of fungal infections by the Infectious Diseases Society of America. Clinicians, including physicians, pharmacists, nurses, and other allied healthcare personnel, must understand and recognize these new developments in order to accurately diagnose, evaluate, prevent, and treat IFIs.

This activity is designed for Infectious Diseases physicians and other healthcare professionals on the frontline of managing patients with or at risk for invasive fungal infections.

Healthcare professionals participating in this educational activity will be able at its conclusion to:

- Recognize the changing epidemiology of invasive fungal infections
- Assess the latest diagnostic approaches for early detection of IFIs
- Identify at-risk patients to guide antifungal prophylaxis
- Select an appropriate antifungal agent based on evidence-based guideline recommendations and patient factors

Pranatharthi H. Chandrasekar, MD
Professor of Medicine/Infectious Diseases
Wayne State University School of Medicine
Chief, Section of Infectious Diseases
Karmanos Cancer Institute
Detroit, MI

Richard H. Drew, PharmD, MS, BCPS, FCCP
Professor
Campbell University College of Pharmacy and Health Sciences
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Duke University School of Medicine
Durham, NC

Kieren A. Marr, MD
Professor of Medicine
Johns Hopkins School of Medicine
Professor of Oncology
Sidney Kimmel Comprehensive Cancer Center
Director, Transplant and Oncology ID
Baltimore, MD
Educational Program

6:00 PM – 6:10 PM

Welcome and Introduction
Understanding IFIs: The Impact of Patient and Organism
Pranatharthi H. Chandrasekar, MD

6:10 PM – 6:50 PM

Clinical Updates on IFIs
Evolving Epidemiology of IFIs
Richard H. Drew, PharmD

Tools for Early Detection: Latest Diagnostic Approaches to Guide Antifungal Selection
Pranatharthi H. Chandrasekar, MD

6:50 PM – 7:50 PM

Patient-Centered Approaches in Managing IFIs
Series of Real-life Patient Cases with Evidence-based Support
Kieren A. Marr, MD

7:50 PM – 8:00 PM

Open Forum: Q&A
Invasive Fungal Infections: The Impact of Host-, Organism-, and Treatment Related Factors on Outcomes

Accreditation
Physicians
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Relevant relationships include roles such as speaker, author, consultant, independent contractor (including research), employee, investor, advisory committee member, board member, review panelist, and investigator. If a potential speaker or author indicates a possible conflict of interest, the conflict will be resolved by choosing another speaker or author for that topical area, or the slides, handouts, and/or monograph will be reviewed and approved by a qualified commercially-disinterested peer.

Planning Committee Members
Pranatharthi H. Chandrasekar, MD
Richard H. Drew, PharmD, MS, BCPS, FCCP
Kieren A. Marr, MD
Paul DeLisle
Marco Cicero, PhD
Maja Drenovac, PharmD

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Pranatharthi H. Chandrasekar, MD (Faculty/Planner) has relevant financial relationships with commercial interest as follows:
- Advisory Board: Optimer, Astellas
- Consultant: Pfizer, Astellas
- Research Support: Merck, Chimerix, Astellas

Dr. Chandrasekar does not intend to discuss the off-label use of a product.

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- Advisory Board: Astellas, Merck, Optimer, Pfizer
- Consultant: Astellas, Merck, Optimer, Pfizer
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Commercial Support
This activity is supported by an educational grant from Astellas Scientific and Medical Affairs, Inc.
FACULTY BIO

Pranatharthi H. Chandrasekar, MD
Professor of Medicine/Infectious Diseases
Wayne State University School of Medicine
Chief, Section of Infectious Diseases
Karmanos Cancer Institute
Detroit, MI

Dr. Pranatharthi Chandrasekar serves as Professor in the Department of Internal Medicine at Wayne State University School of Medicine in Detroit, Michigan. Dr. Chandrasekar is the Program Director for the Infectious Diseases Fellowship Program at Wayne State University and is the Section Chief of Infectious Diseases at the Karmanos Cancer Institute, Detroit, Michigan.

Dr. Chandrasekar’s research interests include epidemiology and management of infections in immunocompromised patients, including cancer patients and bone marrow transplant recipients. He serves as the Editor for the section on Fungal Infections for the British Journal of Antimicrobial Chemotherapy. He is a reviewer for several journals and has authored numerous peer-reviewed articles for such journals as Journal of Antimicrobial Chemotherapy, Clinical Infectious Diseases, European Journal of Clinical Infection, and Bone Marrow Transplantation.

Dr. Chandrasekar is a Fellow of the American College of Physicians and the Infectious Diseases Society of America. He is also a member of the International Immunocompromised Host Society and the American Society for Microbiology. He has been listed in Best Doctors in America several times and is the recipient of several teaching awards.
Dr. Richard Drew is Professor of Pharmacy at the Campbell University School of Pharmacy in Buies Creek, North Carolina. In addition, he is Associate Professor of Medicine, Infectious Diseases and Clinical Pharmacist, Infectious Diseases and Internal Medicine at Duke University Medical Center and School of Medicine in Durham, North Carolina.

After completing a Bachelor of Science in Pharmacy at the University of Rhode Island and a Residency in Hospital Pharmacy at Duke University Medical Center, Dr. Drew went on to earn a Master’s of Science in Hospital Pharmacy and a Doctor of Pharmacy at the University of North Carolina at Chapel Hill. He is a Board-certified Pharmacotherapy Specialist with added qualifications in Infectious Diseases.

Dr. Drew is the author of numerous articles and several book chapters. He serves as a reviewer for several journals including Clinical Infectious Diseases, Annals of Pharmacotherapy, American Journal of Health-System Pharmacy, and Antimicrobial Agents and Chemotherapy. His chief areas of research interest are gram-positive infections, respiratory tract infections, and information technology. Dr. Drew's research was acknowledged in 2008 when he received the Dean's Award for Research Excellence, Campbell University School of Pharmacy. An active member of several professional associations, Dr. Drew is past president of the Society of Infectious Diseases Pharmacists.
Invasive Fungal Infections: The Impact of Host-, Organism-, and Treatment Related Factors on Outcomes

Dr. Kieren A. Marr, MD is Professor of Medicine at the Johns Hopkins University School of Medicine, Department of Medicine and Professor of Oncology at the Sidney Kimmel Comprehensive Cancer Center in Baltimore, MD. Dr. Marr is also the Director of the Transplant and Oncology Infectious Diseases Program at the Johns Hopkins University School of Medicine and Professor of Business at the Johns Hopkins Carey Business School.

Upon completing her undergraduate degree at California State University, Dr. Marr earned her medical degree from Hahnemann University in Philadelphia, Pennsylvania. This was followed by an internship, residency, and assistant chief residency in Internal Medicine at Duke University in Durham, NC. Subsequently, Dr. Marr completed a fellowship in Infectious Diseases at the University of Washington and Fred Hutchinson Cancer Research Center in Seattle, WA.

Dr. Marr has authored over 100 articles in peer-reviewed journals, such as *New England Journal of Medicine, Blood* and *Clinical Infectious Diseases*. She has written many textbook chapters and is an editor for textbooks on Infectious Diseases. She is a frequent invited speaker at national and international meetings.

Dr. Marr is Chair of the Fungal Infection Working Group of the American Society for Blood and Marrow Transplantation and a member of the American Society of Clinical Oncology Guideline Panel for Outpatient Management of Fever During Neutropenia. She is also a member of several professional societies including Infectious Diseases Society of America, and American Transplant Society, and is the founding member of the The Transplantation Society: Women Leaders in Transplantation. The recipient of numerous federal and clinical grants, Dr. Marr’s areas of research and scholarly interest include host defense and pathogenesis of *Aspergillus* infections, diagnostics for fungal infections, and the epidemiology and outcomes of infections in transplant recipients.
Understanding IFIs:
The Impact of Patient and Organism

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Invasive Fungal Infections

**Pathogens**
- Candida
- Aspergillus
- Mucorales
- Fusarium
- Scedosporium
- Endemic fungi

**Increasing incidence secondary to**
- ↑ in use of IV catheters
- ↑ in intensive care units
- Development of novel immunosuppressive agents
- ↑ in solid organ transplants
- New modalities in stem cell transplantation

**Candidemia: Higher Mortality With Delayed Antifungal Therapy**

- 157 patients with Candidemia

<table>
<thead>
<tr>
<th>Time from when first blood sample was drawn to start of antifungal therapy</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 hr</td>
<td>11%</td>
</tr>
<tr>
<td>12-24 hr</td>
<td>30%</td>
</tr>
<tr>
<td>24-48 hr</td>
<td>31%</td>
</tr>
<tr>
<td>&gt;48 hr</td>
<td>34%</td>
</tr>
</tbody>
</table>

**Septic Shock (224 pts) with Candidiasis**

- Antifungal Therapy in <24 hrs & Source Control:
  - Yes – Mortality 52.8%  
  - No – Mortality 97.6%  
  - (p <0.001)

- Adjusted OR for mortality:
  - Delay in Rx: 33.7; No Source Control: 77.4


**Delayed Therapy and Mortality: Zygomyces**

![Graph showing survival rates with early and delayed treatment.

**Increasing IFI Mortality: WHY?**

- Compromised Host
  - Changing complex epidemiology

- Difficulties with Diagnosis
  - Evolving rapid diagnostics

- Suboptimal Drugs

- Patient-Centered Management
Clinical Updates on IFIs
Evolving Epidemiology of IFIs

Richard H. Drew, PharmD, MS, BCPS, FCCP
Professor
Campbell University College of Pharmacy and Health Sciences
Associate Professor of Medicine (Infectious Diseases)
Duke University School of Medicine
Durham, NC
IFI: Incidence and Impact

- **Incidence**
  - *Candida* spp. 4th leading cause of nosocomial bloodstream infections in the US (9%)\(^1\)

- **Impact**
  - Mortality
    - 5-fold increase (crude) in transplant recipients\(^4\)
    - Attributable mortality: 28.6%-56.9%\(^2\)
  - LOS
    - Longer for patients with IFI than uninfected (mean 25.8 vs. 18.4 days, respectively)\(^3\)
  - Cost of IFI
    - US: $32,196\(^3\) - $55,400\(^4\)


### Invasive Fungal Infections: Populations and Risk Factors

**Risk factors...**
- Immunosuppression
- Irradiation
- Neutropenia
- Graft-versus-host disease
- Environmental exposure
- Prior infection/colonization
- HLA mismatch
- Cytomegalovirus
- Damaged mucosa
- Antibacterials
- TPN
- Extremes of age (<1 and >70 yr)
- Surgery, catheters
- High APACHE II score
- Diabetes
- Prolonged ICU stay

**Leading to infections in...**
- HIV
- Chronic granulomatous disease
- Burns
- ICU (surgical)
- Solid organ transplant
- Bone marrow transplant
  - allogeneic > autologous
  - Neutropenics/cancer patients
  - Neonates
  - Elderly

### Risk Factors for IFI in Transplant Recipients

**HSCT**
- Allogeneic > auto
- Prolonged pre-engraftment
- History of IA before HSCT
- Haploidentical or T-cell-depleted
- GVHD on high-doses steroids w/ or w/o ATG or TNF blockade (infliximab)
- CMV or RSV (active)
- Leukemia (active)
- Retransplantation
- Secondary graft failure
- Fungal (mold) colonization
- Iron overload (for mucormycosis)
- Diabetes or chronic steroid-induced hyperglycemia
- Aspergillus-active antifungals (e.g. VOR, echinocandins) pre-exposure to

**SOT (All patients)**
- Immunosuppression
- Corticosteroids
- >1 organ transplant
- Rejection
- Advanced age
- CMV

**Liver transplant**
- Intraoperative blood >40u
- Choledochojejunostomy
- Retransplant
- Re-exploration
- Length of operation
- Fulminant hepatic failure

**Lung transplant**
- Delayed chest closure
- Bronchiolitis obliterans

**Heart transplant**
- Delayed chest closure

\*1 mg/kg prednisone equivalent
ATG, antithymocyte globulin; IA, invasive aspergillosis; CMV, cytomegalovirus; HSCT, hematologic stem cell transplant; TNF, tumor necrosis factor; VOR, voriconazole (modified) Kontoyiannis D. Bone Marrow Transplant. 2011;46:165-173.
Invasive Fungal Infections:
Population-Specific Etiologies

Prospective surveillance among hospitalized patients at 25 medical centers in North America, 2004-2008


IFI in HSCT Patients: Cumulative Incidence

Patients from 23 US transplant centers 3/01-3/06 (TRANSNET)


IFI in HSCT Patients: Time to Infection

Patients from 23 US transplant centers 3/01-3/06 (TRANSNET)

IFI in SOT Patients

Patients from 23 US transplant centers 3/01-3/06 (TRANSNET)

<table>
<thead>
<tr>
<th>IFI type</th>
<th>Kidney (n = 332)</th>
<th>Liver (n = 378)</th>
<th>Pancreas (n = 128)</th>
<th>Lung (n = 246)</th>
<th>Heart (n = 99)</th>
<th>Small bowel (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidaemia</td>
<td>184 (40%)</td>
<td>196 (41%)</td>
<td>97 (77%)</td>
<td>96 (73%)</td>
<td>45 (45%)</td>
<td>19 (90%)</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>47 (14%)</td>
<td>42 (11%)</td>
<td>6 (5%)</td>
<td>109 (44%)</td>
<td>23 (23%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Zygomycosis</td>
<td>8 (3%)</td>
<td>9 (2%)</td>
<td>0 (0%)</td>
<td>8 (3%)</td>
<td>3 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other mold</td>
<td>10 (3%)</td>
<td>9 (2%)</td>
<td>4 (3%)</td>
<td>49 (19.8%)</td>
<td>7 (7.1%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Unspecified mold</td>
<td>7 (2.1%)</td>
<td>6 (1.7%)</td>
<td>0 (0.0%)</td>
<td>7 (2.8%)</td>
<td>2 (2.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>49 (15%)</td>
<td>24 (6%)</td>
<td>6 (5%)</td>
<td>6 (2%)</td>
<td>10 (10%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Endemic mycoses</td>
<td>33 (10%)</td>
<td>17 (5%)</td>
<td>8 (6%)</td>
<td>3 (1.1%)</td>
<td>3 (3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Pneumocystis</td>
<td>5 (1%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>4 (2%)</td>
<td>3 (3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Other yeast</td>
<td>6 (1.8%)</td>
<td>9 (2.4%)</td>
<td>6 (5.1%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Unspecified yeast</td>
<td>3 (0.9%)</td>
<td>5 (1.3%)</td>
<td>1 (0.8%)</td>
<td>6 (2.4%)</td>
<td>0 (0.0%)</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>


IFI: Fungal Pathogens

Prospective surveillance among hospitalized patients at 25 medical centers in North America 2004-2008

- C. albicans
- C. dubliniensis
- C. glabrata
- C. guilliermondii
- C. krusei
- C. parapsilosis
- C. tropicalis
- C. tropicalis

N=5,526 isolates


N=6807

New and Emerging Risk Factors

- Iron overload (mucormycosis)\(^2\)
- Renal replacement therapy
  - ECMO (Aspergillus)\(^3\)
- TNF-alpha blockers (Alemtuzumab-Campath\(^6\)):
  - disseminated IFI: OR 4.76 (95% CI 1.58-14.28)\(^1\)
- Prior antifungal therapy
  - non-albicans Candida

ECMO, extracorporeal membrane oxygenation
Risk Factors for non-albicans Candidemia

Case control study of patients with candidemia due to C. albicans (n=79) and non-albicans Candida (n=67)

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>ODDS RATIO (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole exposure</td>
<td>11.6 (2.28-58.8)</td>
</tr>
<tr>
<td>CV catheter</td>
<td>1.95 (1.10-3.47)</td>
</tr>
<tr>
<td>No. of antibiotics (mean)</td>
<td>2.31 (0.71-7.54)</td>
</tr>
<tr>
<td>TPN</td>
<td>0.16 (0.05-0.47)</td>
</tr>
</tbody>
</table>


Prior Antifungal Exposure and Risk of Resistance

Prospective multicenter study of yeast bloodstream infections (2618 isolates in 2441 patients)

<table>
<thead>
<tr>
<th>Risk of Resistance</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced FLU susceptibility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥15 yrs</td>
<td>2.45</td>
<td>1.39-4.31</td>
<td>0.002</td>
</tr>
<tr>
<td>Recent FLU exposure</td>
<td>2.17</td>
<td>1.51-3.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reduced CASPO susceptibility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;15 yrs</td>
<td>2.53</td>
<td>1.43-4.48</td>
<td>0.001</td>
</tr>
<tr>
<td>Recent CASPO exposure</td>
<td>4.79</td>
<td>2.47-9.28</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

FLU, fluconazole; CASPO, caspofungin

Echinocandin and Voriconazole Susceptibility Among Fluconazole-Resistant C. glabrata

Bloodstream isolates from SENTRY Global Surveillance Program (847 isolates worldwide in 2006-2010) and the CDC population-based surveillance program (822 isolates from metropolitan Atlanta and Baltimore in 2008-2010)

(2001–2004): all susceptible to echinocandins
(2006–2010, n=1669)

Of FLU-R isolates:
- voriconazole-NS: 98.8% (MIC >0.5 µg/mL)
- echinocandin-R: 8.0%–9.3%
  (all R isolates with acquired fks1 or fks2 mutation)

Emerging Pathogens: Mucormycosis

22 (7.9%) proven/probable IFIs among 280 allogeneic HSCT recipients at DUH 1/09-4/12

- Aspergillus
- Candida
- Mucormycosis
- Rhodotorula spp

KNOW YOUR LOCAL EPIDEMIOLOGY !!!

DUH, Duke University Hospital.
Data (unpublished) courtesy of Dr. Jennifer Horan.

New Treatment Strategies / Adjuncts?

- New diagnostics / biomarkers
  - PNA FISH\textsuperscript{a}, galactomannan, PCR, β-D-Glucan
- New drugs (investigational)\textsuperscript{a}
  - triazoles (isavuconazole, ravuconazole), echinocandins (amiconidin)
- New formulations of existing agents
  - posaconazole (IV\textsuperscript{b}, new oral formulation\textsuperscript{c})
- New use of existing agents
  - combinations (azoles + echinocandins, LFAmB + echinocandins)
  - dose escalation (echinocandins, LFAmB)
  - continuous infusions (LFAmB)
  - TDM (ITRA, POS, VORI)
  - PO absorption enhancement
    - ex. POS fatty meals, no PPIs, ginger ale
- Adjuncts (limited success to date)
  - calcineurin inhibitors\textsuperscript{d}
  - immunostimulants / adjuvants – growth factors, interferon, Mycograb\textsuperscript{e}
  - iron chelators (mucormycosis) – deferasirox\textsuperscript{f}


LFAmB, lipid-based formulations of amphotericin B; POS, posaconazole; PNA, paraconfocal PNA; TRA, triazoles; VORI, voriconazole

Clinical Updates on IFIs
Tools for Early Detection: Latest Diagnostic Approaches to Guide Antifungal Selection

Pranatharthi H. Chandrasekar, MD
Professor of Medicine/Infectious Diseases
Wayne State University School of Medicine
Chief, Section of Infectious Diseases
Karmanos Cancer Institute
Detroit, MI
Diagnostic Methods

- **Clinical presentation - Etiology indistinguishable**
- **Isolation and identification in lab**
  - Fungi grow slowly; histologic similarities; frequently negative cultures
- **Serology**
  - Antibody Production (Not reliable in immunosuppressed patients)
  - Antigen Assays
    - Histoplasmosis, Cryptococcosis (excellent reliability)
    - Recent: Candidiasis, Aspergillosis (Glucan, Galactomannan)
- **Radiology**
  - X-ray – poor sensitivity/specificity
  - High-resolution CT scan
  - CT-angiography – invasive molds
  - Positron Emission Tomography (PET) – ?
- **Molecular Assay**
  - Peptide Nucleic Acid/Fluorescent in situ Hybridization (PNA FISH™)
  - Polymerase Chain Reaction (PCR) – ?

Candidiasis

- Rapid identification: PNA-FISH
- Serum Beta-D-Glucan (BDG)
- Polymerase chain reaction (PCR)

Rapid Identification of *C. albicans*

**PNA FISH™**

PNA FISH™: Identifying Multiple *Candida* spp.

- Positive Blood Culture
- Gram stain
- Yeast Traffic Light™ PNA FISH™
- C. albicans and/or C. parapsilosis
- C. tropicalis
- C. glabrata and/or C. krusei
- Mixed
- Negative


(1→3)β-D-Glucan Assay: Candidiasis

- Measures β-D-glucan in serum
- Presumptive diagnosis of IFI
- “Pan-fungal”: *Candida, Aspergillus, others*
  - Does NOT detect *Cryptococcus* or Mucorales
- False-positives: dialysis filters, gauze, sponges, IVIG, and albumin
- Most data: hematologic malignancy/stem cell transplant patients
- Limited data: solid organ transplant patients

IVIG, Intravenous immunoglobulin.


β-D-Glucan (BDG): Prognostic Marker/Candidiasis

- 257 pts with proven invasive candidiasis (203 with ≥2 BDG levels)
- Initial BDG: <416 pg/mL predicts Rx success (PPV 89%)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Initial BDG (pg/mL)</th>
<th>Final BDG (pg/mL)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>573 ± 681</td>
<td>499 ± 635</td>
<td>0.03</td>
</tr>
<tr>
<td>Failure</td>
<td>1224 ± 1583</td>
<td>1293 ± 1283</td>
<td>0.29</td>
</tr>
</tbody>
</table>

- Declining BDG Slope (predicts success): 90%
- Increasing BDG Slope (predicts failure): 90%

Invasive Candidiasis: BDG, PCR & Blood Culture

- Invasive candidiasis: 55 cases [candidemia (17), deep-seated candidiasis (33), both (5)]
- Controls: 73 cases [colonization (48), mucosal candidiasis (5), no known Candida colonization (20)]

- Invasive Candidiasis
  Sensitivity:  PCR + Blood Culture: 98%
  BDG + Blood Culture: 79%

- Deep-seated candidiasis
  Sensitivity:  PCR: 88%
  BDG: 62%
  Blood culture: 17%


Biomarkers

Cryptococcosis
- Antigen - Latex agglutination
  Lateral Flow

Histoplasmosis
- Antigen

Coccidioidomycosis
- Antibody
- Antigen

Cryptococcosis – Antigen Detection

- Polysaccharide capsular antigen: CSF, serum
  - Sensitive/specific for diagnosis
  - Serial measurements: better correlation in CSF
  - Useful in relapses/IRIS
- Detection
  - EIA/latex agglutination – high cost, refrigeration
  - Lateral flow immunoassay (serum, urine)
    - Simpler, rapid, inexpensive
    - High sensitivity (vs. EIA)

<table>
<thead>
<tr>
<th>Cryptococcal Meningitis (n=62)</th>
<th>Serum</th>
<th>Plasma</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRAG LFA +</td>
<td>61</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>LFA +/-</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>LFA -</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

CRAG, cryptococcal antigen.
Histoplasmosis – Antigen
• AIDS: high sensitivity in disseminated cases
  – Serum/urine
  – Useful for monitoring response
  – Non-HIV infected: limited sensitivity
• Cross Reactions
  – Blastomyces, Penicillium, Paracocci, Cocci
  – Aspergillus, Sporothrix

Coccidioidomycosis - Antibody
• Diagnosis: Histopathology
  – Serology: Antibody by ID/CF
  – Antigen (Urine, serum) > serology (in compromised host)
  
  PCR
  BDG
  Adenosine deaminase


Invasive Molds

Aspergillosis
• Radiology
  – High-resolution computed tomography (HRCT)
  – CT Angiography
• Galactomannan
• PCR

CXR, chest X-ray; HRCT, high-resolution computed tomography; PMN, polymorphonuclear neutrophils.

Radiologic Diagnosis of IA
CXR: Unreliable; HRCT: Excellent

Halo Sign
Occurs early
Highly sensitive (100% of cases)
Persists <5 days

Air-crescent Sign
Occurs late
Correlates with PMN ↑
Not useful for early diagnosis

CXR, chest X-ray; HRCT, high-resolution computed tomography; PMN, polymorphonuclear neutrophils.
High-Resolution CT: Specificity for IFI

111 consecutive HSCT patients with proven pneumonia
CT within 24 h of symptoms
Viruses: 57; Bacteria: 26; Fungi: 21; Protozoa: 1

<table>
<thead>
<tr>
<th></th>
<th>Fungus</th>
<th>Bacteria</th>
<th>Respiratory Syncytial Virus</th>
<th>CMV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodules (≥1 cm)</td>
<td>62%</td>
<td>19%</td>
<td>10%</td>
<td>14%</td>
</tr>
<tr>
<td>Halo</td>
<td>48%</td>
<td>8%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Smaller Nodules</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ground Glass Opacities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consolidation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No significant difference


Pulmonary Aspergillosis

Pulmonary TB

Invasive Fungal Infections: The Impact of Host-, Organism-, and Treatment Related Factors on Outcomes
High Resolution CT Angiography: Invasive Fungal Infection (IFI)

Neutropenia, on antibiotics – refractory fevers (10 pts)
14 lesions in 8 patients

<table>
<thead>
<tr>
<th>CT Angiography</th>
<th>Final Diagnosis (IFI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>Positive</td>
<td>4</td>
</tr>
<tr>
<td>Negative</td>
<td>1*</td>
</tr>
</tbody>
</table>

* 1 of 3 lesions – mucormycosis in a heart transplant patient


CT Pulmonary Angiography: Invasive Mold Disease (IMD) Patients with Heme Malignancy

Single Center, Prospective Study: 36 pts with ? Pulmonary IFI

<table>
<thead>
<tr>
<th>EORTC Criteria</th>
<th>CTPA-positive</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven IMD</td>
<td>5/5 pts</td>
<td>CTPA(+) [Art. Vessel cut off]</td>
</tr>
<tr>
<td>Probable IMD</td>
<td>5/7 pts</td>
<td>CTPA(+)</td>
</tr>
<tr>
<td>Possible IMD</td>
<td>10/24 pts</td>
<td>14 CTPA(-) [Bact/Viral pneumonia; lymphoma]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 CTPA(+) [S. aureus with septic emboli]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 CTPA(+)</td>
</tr>
</tbody>
</table>


Clues Favoring Mucormycosis Over Aspergillosis

<table>
<thead>
<tr>
<th>Epidemiology/Host</th>
<th>Clinical/Lab/Radiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institutions with ↑ rates of Mucor</td>
<td>Community-acquired sinusitis (pansinusitis/ethmoid inv.)</td>
</tr>
<tr>
<td>Iron overload</td>
<td>Necrotic lesions – hard palate</td>
</tr>
<tr>
<td>Hyperglycemia ± diabetes mellitus</td>
<td>Chest wall cellulitis adjacent to pulmonary infarct</td>
</tr>
<tr>
<td>Prior voriconazole/ echinocandin use</td>
<td>Acute vascular event (e.g., GI bleed)</td>
</tr>
<tr>
<td></td>
<td>CT: Multiple nodules (&gt;10); pl. eff</td>
</tr>
<tr>
<td></td>
<td>Reversed halo sign</td>
</tr>
<tr>
<td></td>
<td>CT: ‘Fungal pneumonia’ despite good voriconazole levels</td>
</tr>
<tr>
<td></td>
<td>CT: ‘Fungal pneumonia’ – multiple (-) GM/Glucan levels</td>
</tr>
</tbody>
</table>

Serum Galactomannan Assay: IA

<table>
<thead>
<tr>
<th>False-positives</th>
<th>False-negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other fungi</td>
<td>Antifungal use</td>
</tr>
<tr>
<td>(Histoplasma, Cryptococcus, Fusarium, Paecilomyces)</td>
<td>Focal infection</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td></td>
</tr>
<tr>
<td>Solid organ transplantation</td>
<td></td>
</tr>
<tr>
<td>GI flora (Bifidobacterium)</td>
<td></td>
</tr>
</tbody>
</table>


Voriconazole vs. Pre-emptive

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Aspergillus Infections</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plazamolast (N=245)</td>
<td>9 vs. 17</td>
<td>0.09</td>
</tr>
<tr>
<td>Voriconazole (N=305)</td>
<td>7.3 vs. 11.2%</td>
<td>0.012</td>
</tr>
</tbody>
</table>

FFS at Day + 180 = VOR 75% vs. FLU 78%, P=0.49

FFS, fungal-free survival


Galactomannan (GM) in Bronchoalveolar Lavage (BAL)

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk patients with suspected IA</td>
<td>110</td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td>33%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22%</td>
</tr>
<tr>
<td>Deaths</td>
<td>73/110</td>
</tr>
<tr>
<td>Autopsy</td>
<td>69/73 (95%)</td>
</tr>
<tr>
<td>Proven IA</td>
<td>26</td>
</tr>
<tr>
<td>Probable IA</td>
<td>8</td>
</tr>
<tr>
<td>GM in BAL: Sensitivity</td>
<td>88%</td>
</tr>
<tr>
<td>GM in BAL: Specificity</td>
<td>87%</td>
</tr>
<tr>
<td>GM in Serum: Sensitivity</td>
<td>42%</td>
</tr>
<tr>
<td>(+) GM-BAL with (+) GM-serum and (-) BAL culture</td>
<td>11/26 (40%)</td>
</tr>
</tbody>
</table>

Utility of BAL: PCR/GM (Invasive Aspergillosis)

- Diagnosis: BAL → nested PCR, GM (EIA)
- 76 evaluable patients (hematological malignancies)
  - 29 with proven/probable disease

<table>
<thead>
<tr>
<th></th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR</td>
<td>74</td>
<td>77</td>
<td>9.7</td>
</tr>
<tr>
<td>GM (≥0.5)</td>
<td>92</td>
<td>88</td>
<td>86.3</td>
</tr>
<tr>
<td>Either +</td>
<td>75</td>
<td>89</td>
<td>23.4</td>
</tr>
<tr>
<td>Both +</td>
<td>100</td>
<td>79</td>
<td></td>
</tr>
</tbody>
</table>

- GM + PCR: Positivity → Diagnosis highly likely

PPV, positive predictive value; NPV, negative predictive value; OR, odds ratio.

Lateral Flow Device (LFD) Immunoadsay Invasive Aspergillosis

- Immunochromatographic assay/ Murine monoclonal Ab
  - Detection of extracellular *Aspergillus* glycoprotein Ag during growth; point of care assay
  - Differentiates hyphae and conidia

<table>
<thead>
<tr>
<th>Time</th>
<th>LFD</th>
<th>BDG</th>
<th>GM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hr</td>
<td>0/5</td>
<td>0/5</td>
<td>1/5</td>
</tr>
<tr>
<td>D + 3</td>
<td>12/25</td>
<td>0/25</td>
<td>1/25</td>
</tr>
<tr>
<td>D + 5</td>
<td>14/17</td>
<td>4/17</td>
<td>10/17</td>
</tr>
<tr>
<td>D + 7</td>
<td>6/6</td>
<td>6/6</td>
<td>6/6</td>
</tr>
<tr>
<td>Uninfected</td>
<td>0/10</td>
<td>2/10</td>
<td>0/10</td>
</tr>
</tbody>
</table>

- LFD: Detection of GM-like antigens in urine (guinea pig models, humans)

LFD, lateral-flow device; BDG, beta-D-glucan; GM, galactomannan.

PCR: IFI

- Fungal DNA Extraction
  - Varied sensitivity/specificity
  - False +/-
  - No standardization
  - No external validation
  - Home-brewed
  - Not Ready for Primetime

Diagnosis of Invasive Fungal Infection: Summary

- Early Diagnosis Remains Key for Good Outcome
- Non-Invasive Tools: Radiology – Radiation exposure

<table>
<thead>
<tr>
<th>Infection</th>
<th>Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis</td>
<td>β-D-Glucan; PCR</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>Galactomannan; β-D-Glucan; PCR</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>Antigen (LA; EIA; Lat Flow) (Serum, CSF)</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>Antigen (Urine, Serum)</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td>Antigen</td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td>Antibody (? Antigen)</td>
</tr>
<tr>
<td>Paracoccidioides</td>
<td>Antibody (? Antigen)</td>
</tr>
<tr>
<td>Mucormycosis</td>
<td>? Investigational</td>
</tr>
<tr>
<td>Pneumocystosis</td>
<td>β-D-Glucan; PCR</td>
</tr>
</tbody>
</table>

**Ideal Test:** Rapid, non-invasive; high sensitivity/specificity; help early targeted treatment; help predict/monitor response; inexpensive
Patient-Centered Approaches in Managing IFIs
Series of Real-life Patient Cases with Evidence-based Support

Kieren A. Marr, MD
Professor of Medicine
Johns Hopkins School of Medicine
Professor of Oncology
Sidney Kimmel Comprehensive Cancer Center
Director, Transplant and Oncology ID
Baltimore, MD
Why “Patient-Centered”?

- Medicine evolved towards treatment of “problems” or diseases
  - Genesis of the very word “patient”: a person defined by disease

- Modern movement towards applying health care with a “patient center”
  - “Seeks to focus medical attention on the individual patient’s needs and concerns, rather than the doctor’s”

A Medical Paradigm-Shift

- History of “Patient-centered”
  - Enid Balint (1969): psychotherapy technique for illnesses that are psychosomatic
  - Taken on many new meanings
    - Biopsychosocial model that accounts for patient “in the social context in which he lives” (Engel 1977)
    - Patient-doctor relationship (Cassell, 1985)
    - Definition of ‘disease’ and ‘illness’ – mechanics vs. sickness (Kleinman 1989)
    - A metaphor – not “Doctor centered”

Our Intent

- Not truly “patient-centered” given historical, paradigm-changing meaning
- Discuss therapeutic decision-making in specific people (cases) to illustrate individual considerations
  - Differs from the way we have coined treatment paradigms for antifungal therapy
    - “empiric” therapy- treating fever
What is your institutional practice for preventing invasive fungal infections in neutropenic people with AML?

How do you prevent invasive fungal infections in people with graft-versus-host disease s/p BMT?

How do you treat fever for >4 days in a neutropenic patient?
Invasive Fungal Infections: The Impact of Host-, Organism-, and Treatment Related Factors on Outcomes

Do you use antifungal prophylaxis in high-risk ICU patients?

What is your preferred first-line therapy for candidiasis caused by germ-tube positive organism?

What is your preferred first-line therapy for a new infiltrate appearing concerning for “aspergillosis” in a neutropenic patient?
PATIENT #1

Patient #1

70-year-old M with follicular lymphoma diagnosed in 2004. s/p fludarabine, rituximab, with minimal response. Progressive adenopathy in 2008, s/p cytoxan + rituximab. 2012 - being evaluated for a MUD transplant

PMHx: “pneumonia” 1960s; herpes zoster 5/12
  PPD positive, age 12, not treated

From Illinois; lived on a farm (cattle, produce); hunter

Radiography

Studies

• CBC: ANC 110; alkaline phosphatase 69; AST 22; ALT 13; Serum Creatinine 1.5
• Sputum AFBs negative; culture no growth
• Galactomannan Ag negative
• Histoplasma Ab negative (ID + CF)
• Histoplasma Ag not detected in urine / serum
• Quantiferon negative
Recommendations

Proceed with non-ablative conditioning regimen with:
1. No antifungal prophylaxis
2. Fluconazole
3. Voriconazole
4. Posaconazole
5. Ambisome

3 days later...

Received valacyclovir, moxifloxacin, voriconazole

Acute right eye pain, photophobia, proptosis
MRI – infiltration of superior rectus, no discreet mass
Optho – proptosis with normal retinal exam

2 days later...

• Fever, chills
• Blood culture: “yeasts” (1 / 3 cultures)
• Recommend
  1. Fluconazole
  2. Check voriconazole level, continue
  3. Lipid formulation amphotericin B
  4. Echinocandin
  5. Pull central venous catheter, no change in antifungals
Course

- Voriconazole changed to lipid formulation amphotericin B
- Creatinine 1.5–3; micafungin began
  - Received 2 weeks, no repeat cultures positive
  - Back to voriconazole
- Clinical symptoms improved until 6 days later
  - 1 month after candidemia
  - Cough; CT – bilateral pleural effusions

Course

- Serum Platelia GM negative (0.08)
- Histoplasma Ag positive
  - Urine 0.59 ng/mL (MiraVista, cut-off 0.4)
  - Blood >100 EIA units (Quest, cut-off 4)

This patient

- Institutional practice for antifungal prophylaxis is to use fluconazole followed by either vori / posaconazole with GVHD
  - Voriconazole chosen pre-transplant
  - Prior history consistent with possible latent histoplasma / TB / mould infection
    - Nothing active by diagnostic testing
  - Long history of T cell suppression, receipt of non-ablative conditioning
    - Breakthrough *C. tropicalis*
    - Progression of histoplasmosis
Considerations for Antifungal Prophylaxis

- Clinical trials: what works with consideration of risk-benefits?
- In this patient
  - What are you trying to prevent?
  - Who is the patient?
    - Renal disease
    - Liver disease
    - Mucositis (IV / oral)

Treatment of Fever

- This patient
  - ANC = 0
  - Receiving voriconazole as maintenance after candidemia (lung nodules)
  - Acute renal insufficiency on lipid amphotericin B previously
  - ID: Changed to lipid formulation again, despite renal function
    - Explanation: suspected histoplasmosis
    - Use of antifungals here not data driven
      - “Fever” has different meanings in different people

Genesis of Empirical Antifungal Therapy

Patients with persistent febrile neutropenia for 7 days:

- Discontinue abx 16 patients
- Continue abx 16 patients
- Add amphotericin B 18 patients

- 9 patients with infection and/or shock
- 6 patients with infection (5 fungal infections)
- 2 patients with infection (*P. boydii*, CMV)

Data: Empirical Therapy

- Studied in randomized trials
  - Fluconazole
  - Itraconazole
  - Amphotericin B
  - Liposomal amphotericin B
  - Caspofungin
  - Voriconazole

Treatment of Fever During Neutropenia

- Clinical trials: what works with consideration of risk-benefits?
- In this patient
  - What are you trying to prevent / treat?
  - Who is the patient?
    - Renal disease
    - Liver disease
    - Mucositis (IV / oral)

Diagnostics

- Antigen assays useful
  - Galactomannan
    - Histoplasmosis
    - Aspergillosis

Take-home Practice Points
PATIENT #2

Patient #2

• Taken to the operating room (OR) for debridement; stents inserted
• Pancreatic tissue cultures reveal *Klebsiella* spp.
  – Started on piperacillin-tazobactam
• 10 days post-admission
  – Fever, WBC 22,000
  – Blood cultures negative
  – CT repeat – no change in fluid collection

How do you treat this patient?
Risk Factors for Invasive Fungal Disease (IFD)

Host Factors
- Extremes of age
- Neutropenia
- Renal failure
- High APACHE II score
- Trauma or burns
- Bowel perforation
- Candida colonization

Medical Interventions
- Chemotherapy
- Dialysis
- Central venous catheters or nasogastric tubes
- Prior antibiotic use
- Prior surgery (especially abdominal)
- Parenteral nutrition
- ICU stay >7 days

APACHE = Acute Physiology and Chronic Health Evaluation


Relationship Between Time to IC Treatment and Hospital Mortality

IC, invasive candidiasis
Relationship Between Time to Treatment for IC and Hospital Mortality

![Graph showing the relationship between time to treatment and hospital mortality.](image)


**Empiric Antifungal Treatment in Non-Neutropenic Patients with Suspected IC**

**2009 IDSA Recommendations**

- Fluconazole for patients less critically ill with no recent azole exposure
- Echinocandins for patients with moderate to severe illness or recent azole exposure
  - Caspofungin
  - Micafungin
  - Anidulafungin
- Amphotericin B deoxycholate or lipid formulation (AmB-d or LFAmb) when other antifungals are not tolerated


**Empiric Antifungal Treatment in Non-Neutropenic Patients with Suspected IC (cont’d)**

- Transition from fluconazole to echinocandin for patients whose isolates are likely to be azole-susceptible, once patient is clinically stable
- Intravenous catheter removal as applicable

For confirmed candidiasis, do you routinely test for susceptibility?
### General Pattern of Susceptibility of Candida Species

<table>
<thead>
<tr>
<th>Species</th>
<th>Fluconazole</th>
<th>Voriconazole</th>
<th>Anidulafungin</th>
<th>Micafungin</th>
<th>Echinocandin</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>S-DD to R</td>
<td>S-DD to R</td>
<td>S-DD to R</td>
<td>S-DD to R</td>
<td>S to I</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S to R*</td>
</tr>
<tr>
<td>C. krusei</td>
<td>R</td>
<td>S-DD to R</td>
<td>S</td>
<td>S to I</td>
<td>S</td>
</tr>
</tbody>
</table>

*S = susceptible; S-DD = susceptibility dose-dependent; R = resistant; I = intermediately susceptible

*Echinocandin resistance to C. parapsilosis isolates is uncommon


### Patient #2 (cont’d)

- 2-day positive cultures
- Lines changed
- Micafungin: 5 days, afebrile
- Fluconazole: 14 days plus continued surgical drainage
- Infection resolved

### This patient...

- Controversy in management of complicated abdominal infections with consideration of population-based data
- Patient specific management
  - Should he have been treated with fluconazole earlier?

### Take-home Practice Points
What tests would you perform on the BAL?

Antimicrobial therapy would include broad spectrum coverage for bacteria and which other antifungal agents?
Polyene Therapy vs. Voriconazole for Invasive Aspergillosis (IA)


Polyene Therapy for Invasive Aspergillosis (IA)


Efficacy of Liposomal AmB (L-AmB) in Invasive Mycoses: AmBiLoad Trial

L-AmB = liposomal amphotericin B; CR+PR = complete and partial responses; EOT = End of Therapy; IPA = invasive pulmonary aspergillosis; Allo-SCT = allogeneic stem cell transplant
**Combination Therapy: Randomized Trial**

- Different design of study
  - Primary endpoint, patients
- 459 patients randomized in 93 centers, 24 countries (2008–2011)
  - Data review committee adjudicated cases
  - Presented at ECCMID, London
- 228 combination voriconazole + anidulafungin vs. 226 monotherapy
  - Matched well

**Primary Endpoint**

MITT = 277 patients with proven / probable IA

Probable 272 pt (98%)  
Proven 5 pt (2%)

6-wk mortality 26/135 (19.3%) for combination treatment and 39/142 (27.5%) for monotherapy (two-sided \( P=0.09 \); 95% CI -19.0 to 1.5).

**Probable IA with GM**

Probable IA = Radiography + Microbiology (culture and/or GM)

Culture/cytology/histopath - 54 pts (20%); GM (BAL or serum) - 218 pts (80%)

6-wk mortality 17/108 (15.7%) for combination treatment and 30/110 (27.3%) for monotherapy (\( P=0.05 \); 95% CI -22.7 to -0.4)
Patient #3 (cont’d)

• Voriconazole at 4 mg/kg bid is started
• BAL: no growth
• 7 days later, AST, ALT slight elevation: 200, 155, Alkaline phosphatase 80
• Repeat CT scan: worse pulmonary disease

Questions That This Brings Up

• Diagnostic certainty
  – Is this failure?
  – Are there other tests that can be helpful?
• If this is failure, what options do we have?
  – Increase voriconazole dose?
  – Add another drug?
  – Change drug?
• How do you interpret the liver enzyme abnormalities?
  – Drug?
  – GVHD?

Dosing Voriconazole

• No activity against Zygomycetes
• Metabolized by unusual cytochrome P450 subunit (CYP 2C19, 3A4, 2C9)
  – Poor metabolizers: high concentrations associated with an increase in hepatic toxicity
• Are we giving enough?
  – Role of therapeutic drug monitoring
Therapeutic Drug Monitoring

- Randomized, non-blinded trial (n=110)
  - Voriconazole standard dosing vs. voriconazole with TDM
    - Target 1 – 5.5 mg/L
    - Outcomes driven by AE and withdrawal

Alternatives

- Go to an AMB formulation
- Give combination therapy
- Look for something else

When to Start Polyene Instead – Patient-Driven Decision

- Abnormalities develop despite long / prior exposure to voriconazole
- Host appears to be at higher risk for Zygomycetes infection
  - Vague – late with GVHD, steroid exposure, diabetes, iron overload
- Cannot tolerate azole drugs
  - Particularly common in older people on concomitant calcineurin inhibitors
    - Hallucinations, hepatic abnormalities

Antifungal Therapy

- There are some clear 'right' and 'wrong' answers to treatment
  - Many more patients and questions fall into gray zone
  - Decisions need to be made with consideration of many patient-specific issues
    - What are we targeting?
    - Organ function, drug interactions
    - Risk-benefits to many therapeutic questions

Take-home Practice Points