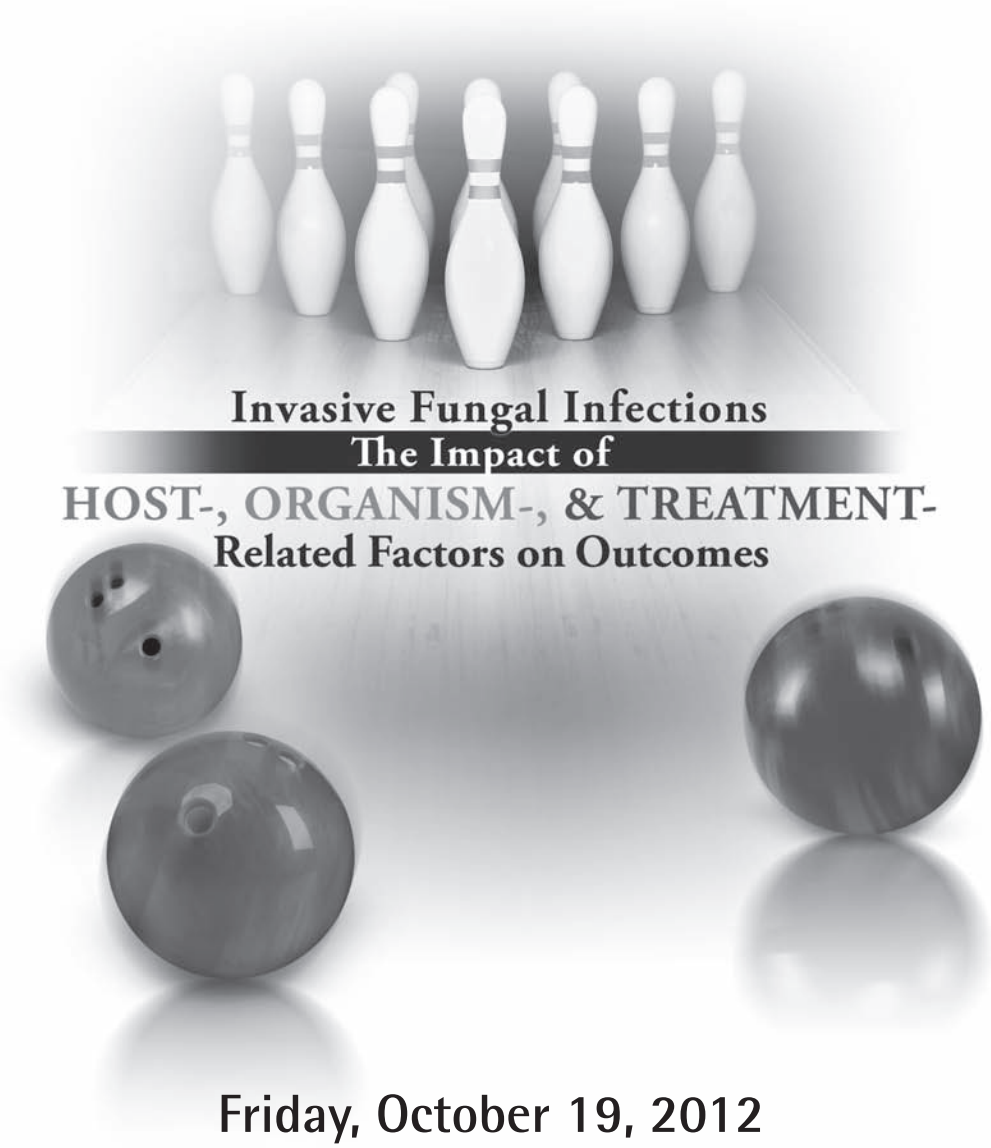

Friday, October 19, 2012
6:00 – 8:00 PM
San Diego, CA

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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

Educational Overview

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.

Target Audience

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.

Learning Objectives

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

Faculty

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
Associate Professor of Medicine (Infectious Diseases)
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

Accreditation

Physicians

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the Center for Independent Healthcare Education and Vemco MedEd, LLC. Center for Independent Healthcare Education is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Center for Independent Healthcare Education designates this live activity for a maximum of 2.0 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

For questions regarding the accreditation of this activity, please contact us at *info@jointsponsor.com*

Instructions for Credit

To receive a CME Certificate of Credit, participants must register for the symposium, document attendance, and complete and return the evaluation form. A Certificate of Credit will be mailed to you 4 weeks after the symposium.

Disclosure of Conflicts of Interest

In accordance with policies set forth by the Accreditation Council for Continuing Medical Education (ACCME), Center for Independent Healthcare Education requires all faculty members and spouses/significant others with an opportunity to affect the content of a continuing education activity to disclose any relevant financial relationships during the past 12 months with commercial interests. A commercial interest is any entity producing, marketing, reselling or distributing health care goods or services consumed by or used on patients. Relationships with commercial interests and conflicts of interest resulting from those relationships must be revealed to the audience and resolved prior to the activity

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

Disclosure of Financial Interest Summary

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.

Richard H. Drew, PharmD, MS, BCPS, FCCP (Faculty/Planner) has relevant financial relationships with commercial interests as follows:

- Consultant: Merck
- Speaker's Bureau: Merck
- Research Support: Merck
- Development Team: CustomID

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

Kieren A. Marr, MD (Faculty/Planner) has relevant financial relationships with commercial interests as follows:

- Advisory Board: Astellas, Merck, Optimer, Pfizer
- Consultant: Astellas, Merck, Optimer, Pfizer
- Grant Recipient/Research Support: Funds to JHMI, Astellas, Merck, Pfizer, Sigma Tau

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

No other speakers, authors, planners or content reviewers have any relevant financial relationships to disclose. No other speakers or authors will discuss off-label use of a product.

Content review confirmed that the content was developed in a fair, balanced manner free from commercial bias. Disclosure of a relationship is not intended to suggest or condone commercial bias in any presentation, but it is made to provide participants with information that might be of potential importance to their evaluation of a presentation.

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.

FACULTY BIO

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

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.

FACULTY BIO

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

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

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

Invasive Fungal Infections (IFI)

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[1]

Timing of Antifungals & Mortality

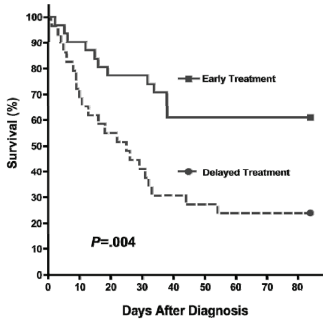
Time from when first blood sample was drawn to start of antifungal therapy	Mortality Rate
<12 hr	11%
12–24 hr	30%
24–48 hr	31%
>48 hr	34%

Septic Shock (224 pts) with Candidiasis[2]

- 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

1. Morrell M ,et al. *Antimicrob Agents Chemother.* 2005;49:3640-3645.
2. Kollef M, et al. *Clin Infect Dis.* 2012;54:1739-1746.

Delayed Therapy and Mortality: Zygomycosis



Chamilos G, et al. *Clin Infect Dis.* 2008;47:503-509.

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]

1. Wisplinghoff H, et al. *Clin Infect Dis*. 2004;39:309-317. 2. Hahn-Ast C, et al. *J Antimicrob Chemother*. 2010;65:761-768.
3. Dodds-Ashley L, et al. *Pharmacother*. 2012 (in press). 4. Menzin J, et al. *Am J Infect Control*. 2011;39:e15-e20.

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/wo ATG or TNF blockade (infliximab)
- CMV or RSV (active)
- Leukemia (active)
- Retransplantation
- Secondary graft failure
- Fungal (mould) 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

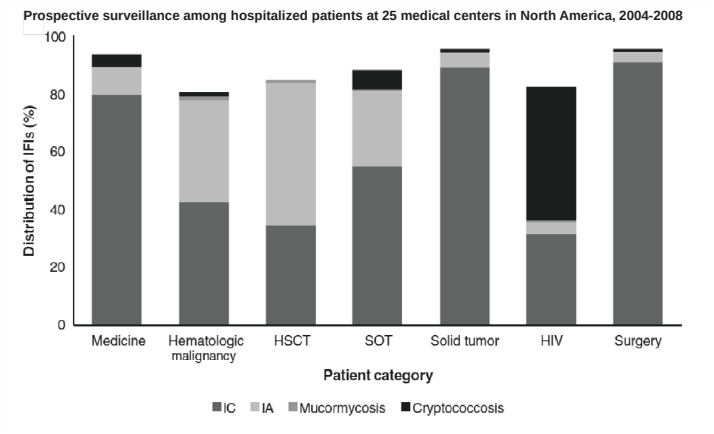
- Delayed chest closure
- Bronchiolitis obliterans

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.

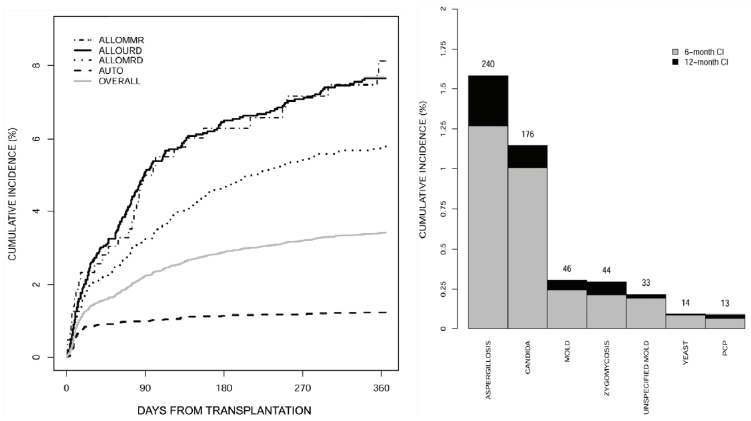
Invasive Fungal Infections: Population-Specific Etiologies



Azie N, et al. *Diagn Microbiol Infect Dis*. 2012;73:293–300.

IFI in HSCT Patients: Cumulative Incidence

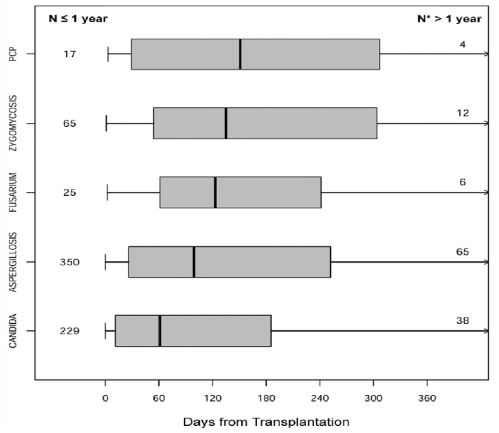
Patients from 23 US transplant centers 3/01-3/06 (TRANSNET)



ALLOMMR, allogeneic mismatched-related donor;
ALLOMRD, allogeneic matched-related donor; ALLOURD, allogeneic unrelated donor; AUTO, autologous.
Kontoyiannis DP, et al. *Clin Infect Dis*. 2010;50:1091-1100.

IFI in HSCT Patients: Time to Infection

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



Kontoyiannis DP, et al. *Clin Infect Dis*. 2010;50:1091-1100.

IFI in SOT Patients

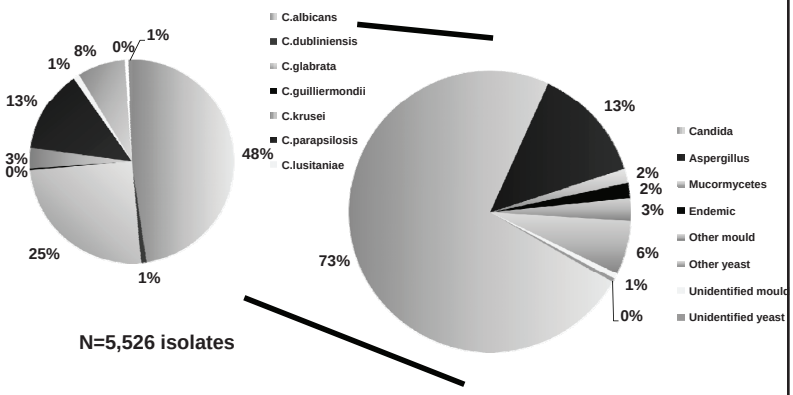
Patients from 23 US transplant centers 3/01-3/06 (TRANSNET)

IFI type	Kidney (*n* = 332)	Liver (*n* = 378)	Pancreas (*n* = 128)	Lung (*n* = 248)	Heart (*n* = 99)	Small bowel (*n* = 22)
Candidiasis	164 (49)	255 (68)	97 (76)	56 (23)	48 (49)	19 (85)
Aspergillosis	47 (14)	42 (11)	6 (5)	109 (44)	23 (23)	0 (0)
Zygomycosis	8 (2)	9 (2)	0 (0)	8 (3)	3 (3)	0 (0)
Other mold	10 (3.0)	9 (2.4)	4 (3.1)	49 (19.8)	7 (7.1)	0 (0.0)
Unspecified mold	7 (2.1)	8 (2.1)	0 (0.0)	7 (2.8)	2 (2.0)	0 (0.0)
Cryptococcosis	49 (15)	24 (6)	6 (5)	6 (2)	10 (10)	1 (5)
Endemic mycoses	33 (10)	17 (5)	8 (6)	3 (1)	3 (3)	0 (0)
Pneumocystosis	5 (1)	0 (0)	1 (1)	4 (2)	3 (3)	0 (0)
Other yeast	6 (1.8)	9 (2.4)	5 (3.9)	0 (0.0)	0 (0.0)	1 (5)
Unspecified yeast	3 (0.9)	5 (1.3)	1 (0.8)	6 (2.4)	0 (0.0)	1 (5)

Pappas P et al. *Clin Infect Dis*. 2010;50:1101–1111.

IFI: Fungal Pathogens

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



Azie N, et al. *Diagn Microbiol Infect Dis*. 2012;73:293–300.

New and Emerging Risk Factors

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

ECMO, extracorporeal membrane oxygenation

1. Compared to basiliximab (n=215) or ATG (n=85). Safdar N, et al. *Diagn Microbiol Infect Dis*. 2010;66:7-15.
2. Spellberg B, et al. *J Antimicrob Chemother*. 2012;67(3):715-722.
3. Garcia X. *J Intensive Care Med*. 2012: doi/ 0885066611432542.

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)

RISK FACTOR	ODDS RATIO (95% CI)
Fluconazole exposure	11.6 (2.28–58.8)
CV catheter	1.95 (1.10–3.47)
No. of antibiotics (mean)	2.31 (0.71–7.54)
TPN	0.16 (0.05–0.47)

Chow J, et al. *Clin Infect Dis*. 2008;46:1206-1213.

Prior Antifungal Exposure and Risk of Resistance

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

	OR	95%CI	P value
Reduced FLU susceptibility			
Age ≥15 yrs	2.45	1.39–4.31	0.002
Recent FLU exposure	2.17	1.51–3.13	<0.001
Reduced CASPO susceptibility			
Age <15 yrs	2.53	1.43–4.48	0.001
Recent CASPO exposure	4.79	2.47–9.28	<0.001

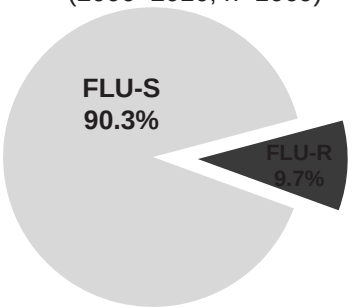
FLU, fluconazole; CASPO, caspofungin
Lortholary O, et al. Antimicrob Agents Chemother. 2011;55:532-538.

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:

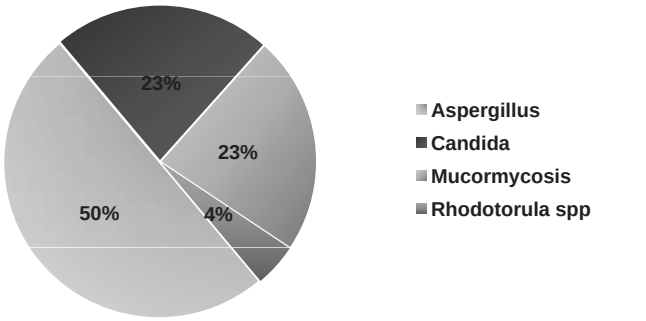
voriconazole-NS: 98.8% (MIC >0.5 µg/mL)

echinocandin-R: 8.0%–9.3% (all R isolates with acquired *fks1* or *fks2* mutation)

Pfaller MA, et al. *J Clin Microbiol* 2012;50:1199-1203.

Emerging Pathogens: Mucormycosis

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



KNOW YOUR LOCAL EPIDEMIOLOGY !!!

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

New Treatment Strategies / Adjuncts?

- **New diagnostics / biomarkers**
  - PNA FISH™, galactomannan, PCR, β-D-Glucan
- **New drugs (investigational)[4]**
  - triazoles (isavuconazole, ravuconazole), echinocandins (aminocandin)
- **New formulations of existing agents**
  - posaconazole (IV[6], new oral formulation[5])
- **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[3]
  - immunostimulants / adjuvants – growth factors, interferon, Mycograb[2]
  - iron chelators (mucormycosis) – deferasirox[1]

LFAmB, lipid-based formulations of amphotericin B ; POS, posaconazole; ITRA, itraconazole; VORI, voriconazole

1.Spellberg B, et al. *J Antimicrob Chemother.* 2012;67(3):715-722.
2.Pachl J, et al. Clin Infect Dis. 2006;42:1404-1413.
3.Steinbach W, et al. *Med Mycol.* 2011';49(Suppl. 1):S77–S81.
4.Pitman S et al. Expert Opin. Emerg Drugs. 2011:16(3):559-586.
5.Krishna G, et al. *J Antimicrob Chemother.* 2012; doi: 10.1093/jac/dks268.
6.NCT01075984 http://clinicaltrials.gov/ct2/show/NCT01075984 (accessed 9/18/12)

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

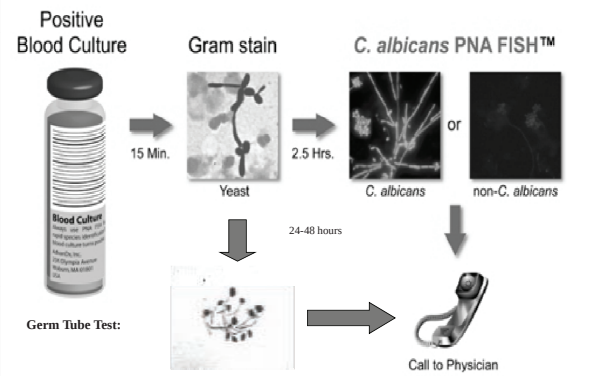
Diagnostic Methods

- **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

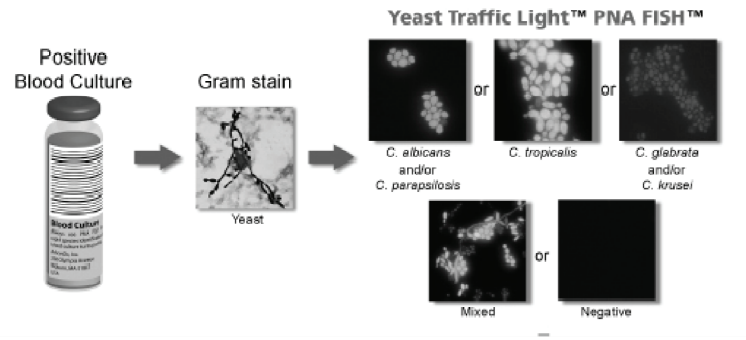
- Rapid identification: PNA-FISH
- Serum Beta-D-Glucan (BDG)
- Polymerase chain reaction (PCR)

Rapid Identification of *C. albicans* PNA FISH™



PNA FISH™. Available at http://www.advandx.com/Technology/PNA-FISH-Technology.aspx. Accessed September 27, 2012.

PNA FISH™: Identifying Multiple *Candida* spp.



PNA FISH™. Available at http://www.advandx.com/Technology/PNA-FISH-Technology.aspx. Accessed September 27, 2012.

(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.
Fungitell® Assay. Available at www.acciusa.com/clinical/assay.htm. Accessed September 27, 2012.

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%)

Outcome	Initial BDG (pg/mL)	Final BDG (pg/mL)	P value
Success	**573 ± 681**	**499 ± 635**	**0.03**
Failure	**1224 ± 1583**	**1293 ± 1283**	**0.29**

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

Jaijakul S, et al. *Clin Infect Dis*. 2012;55:521-526.

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%

Nguyen MH, et al. *Clin Infect Dis*. 2012;54:1240-1248.

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)

Cryptococcal Meningitis (n=62)	Serum	Plasma	Urine
CRAG LFA +	61	61	61
LFA +/-	1	1	0
LFA -	0	0	1

CRAG, cryptococcal antigen.
Lindsley MD, et al. *Clin Infect Dis*. 2011:53:321-325.
Jarvis JN, et al. *Clin Infect Dis*. 2011:53:1019-1023.

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
} ? Limited utility

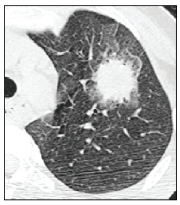
Wheat LJ, et al. *Clin Infect Dis*. 2007;45:807-825.
Thompson GR, et al. *Chest*. 2012;[ePub ahead of print].
Durkin M, et al. Clin Vaccine Immunol. 2009;16:1453-1456.
Galgiani JN, et al. *Clin Infect Dis*. 2005;41:1217-1223.
Durkin M, et al. Clin Infect Dis. 2008;47:e69-73.

Invasive Molds

Aspergillosis

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

Radiologic Diagnosis of IA
CXR: Unreliable; HRCT: Excellent

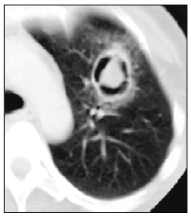


Halo Sign

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.
Caillot D, et al. *J Clin Oncol.* 2001;19:253-259.

High-Resolution CT: ? Specificity for IFI

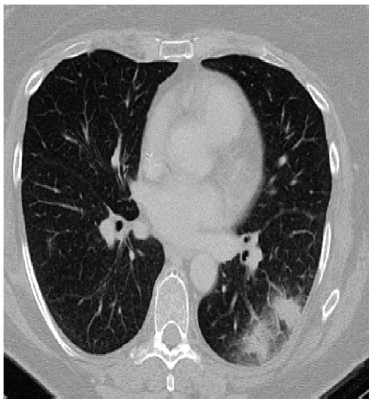
111 consecutive HSCT patients with proven pneumonia

CT within 24 h of symptoms

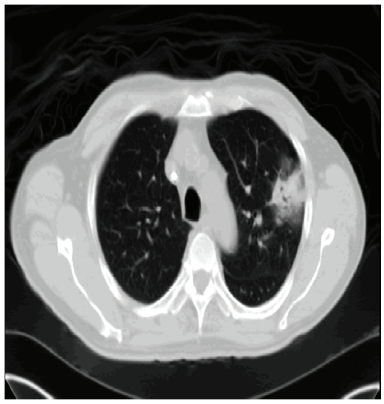
Viruses: 57; Bacteria: 26; Fungi: 21; Protozoa: 1

	Fungus	Bacteria	Respiratory Syncytial Virus	Cyto-megalovirus
Nodules (≥1 cm)	62%	19%	10%	14%
Halo	48%	8%	10%	5%
Smaller Nodules Ground Glass Opacities Consolidation	No significant difference			

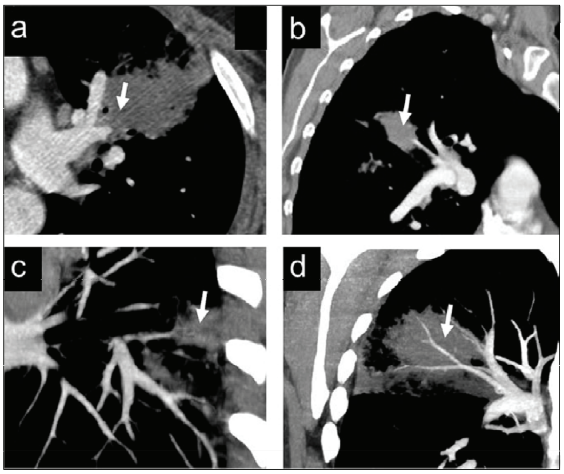
Escuissato D, et al. *AJR Am J Roentgenol*. 2005;185:608-615.



Pulmonary Aspergillosis



Pulmonary TB



High Resolution CT Angiography: Invasive Fungal Infection (IFI)

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

CT Angiography	Final Diagnosis (IFI)	
	(+)	(-)
Positive	**4**	**0**
Negative	**1 ***	**9**

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

Sonnet S, et al. *AJR Am J Roentgenol*. 2005;185:746-751.

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

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

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

Stanzani M, et al. *Clin Infect Dis*. 2012;54:610-616.

Clues Favoring Mucormycosis Over Aspergillosis

Epidemiology/Host

- Institutions with ↑ rates of Mucor
- Iron overload
- Hyperglycemia ± diabetes mellitus
- Prior voriconazole/ echinocandin use

Clinical/Lab/Radiology

- Community-acquired sinusitis (pansinusitis/ethmoid inv.)
- Necrotic lesions – hard palate
- Chest wall cellulitis adjacent to pulmonary infarct
- Acute vascular event (e.g., GI bleed)
- CT: Multiple nodules (>10); pl. eff
- Reversed halo sign
- CT: 'Fungal pneumonia' despite good voriconazole levels
- CT: 'Fungal pneumonia' – multiple (-) GM/Glucan levels

Kontoyiannis DP, et al. *Blood*. 2011;118:1216-1224.

Serum Galactomannan Assay: IA

False-positives

Other fungi (*Histoplasma*, *Cryptococcus*, *Fusarium*, *Paecilomyces*)

Piperacillin/tazobactam

Amoxicillin/clavulanate

Solid organ transplantation

GI flora (*Bifidobacterium*)

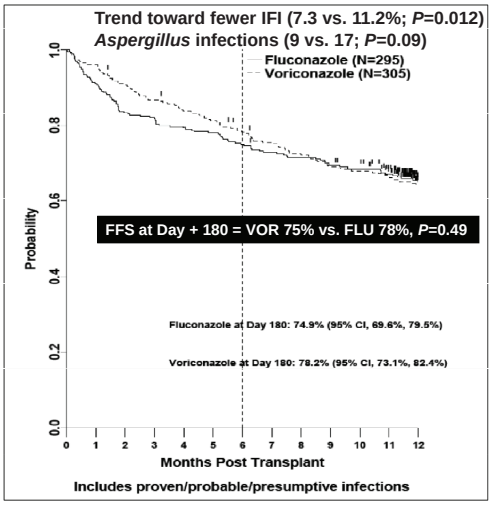
False-negatives

Antifungal use

Focal infection

Aquino VR, et al. *Mycopathologia.* 2007;163:191-202.
Hope WW, et al. *Lancet Infect Dis*. 2005;5:609-622.

Voriconazole vs. Pre-emptive



FFS, fungal-free survival
Wingard JR, et al. *Blood.* 2010;116:5111-5118.

Galactomannan (GM) in Bronchoalveolar Lavage (BAL)

Prospective, single center, ICU study (2005–2006), N=1109	
High-risk patients with suspected IA	110
Hematologic malignancy	33%
Neutropenia	22%
Deaths	73/110
Autopsy	69/73 (95%)
Proven IA	26
Probable IA	8
GM in BAL: Sensitivity	88%
GM in BAL: Specificity	87%
GM in Serum: Sensitivity	42%
(+) GM-BAL with (-) GM-serum and (-) BAL culture	11/26 (40%)

Meersseman W, et al. *Am J Respir Crit Care Med*. 2008;177:27-34.

Utility of BAL: PCR/GM (Invasive Aspergillosis)

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

	PPV (%)	NPV (%)	OR
PCR	74	77	9.7
GM (≥0.5)	92	88	86.3
Either +	75	89	23.4
Both +	100	79	

- GM + PCR : Positivity → Diagnosis highly likely

PPV, positive predictive value; NPV, negative predictive value; OR, odds ratio.
Reinwald M, et al. *Eur J Hematol*. 2012;89:120-127.

Lateral Flow Device (LFD) Immunoassay Invasive Aspergillosis

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

Time	LFD	BDG	GM
1 hr	**0/5**	**0/5**	**1/5**
D + 3	**12/25**	**0/25**	**1/25**
D + 5	**14/17**	**4/17**	**10/17**
D + 7	**6/6**	**6/6**	**6/6**
Uninfected	**0/10**	**2/10**	**0/10**

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

LFD, lateral-flow device; BDG, beta-D-glucan; GM, galactomannan.
Thornton C, et al. *Clin Vacc Immunol*. 2008;15:1095-1105.
Wiederhold NP et al. *Clin Vacc Immunol* 2009;16:1844-1846.
Dufresne ST, et al. *PLOS One*. 2012;7:1.

PCR: IFI

Fungal DNA Extraction

Varied sensitivity/specificity

False +/-

No standardization

No external validation

Home-brewed

Not Ready for Primetime

Donnelly JP. *Clin Infect Dis*. 2006;42:487-489.
White PL, et al. *J Clin Microbiol*. 2010;48:1231-2140.

Diagnosis of Invasive Fungal Infection: Summary

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

Infection	Biomarker
Candidiasis	β-D-Glucan; PCR
Aspergillosis	Galactomannan; β-D-Glucan; PCR
Cryptococcosis	Antigen (LA; EIA; Lat Flow) (Serum, CSF)
Histoplasmosis	Antigen (Urine, Serum)
Blastomycosis	Antigen
Coccidioidomycosis	Antibody (? Antigen)
Paracocci	Antibody (? Antigen)
Mucormycosis	? Investigational
Pneumocystosis	β-D-Glucan; PCR

Ideal Test: **Rapid, non-invasive; high sensitivity/specificity; help early targeted treatment; help predict/monitor response; inexpensive**

NOTES

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"

Bardes CL. *N Engl J Med*. 2012;366:782-783.

A Medical Paradigm-Shift

- **History of "Patient-centered"**
  - Enid Balint (1969): psychotherapy technique for illnesses that are psychosomatic
  - Taken on new 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 – <u>not</u> "Doctor centered"

Bardes CL. *N Engl J Med*. 2012;366:782-783.

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?

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

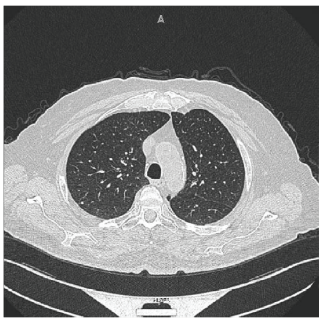
Patient #1

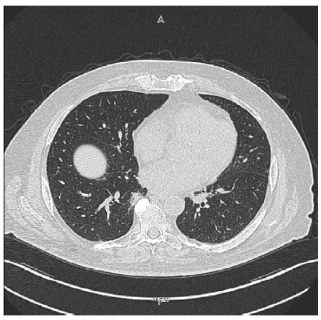
70-year-old M with follicular lymphoma diagnosed in 2004.
s/p fludarabine, rituximab, with minimal response.
Progressive adenopathy in 2008, s/p cytoxan + rituximab.
2012 – being evaluated for a MUD transplant

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

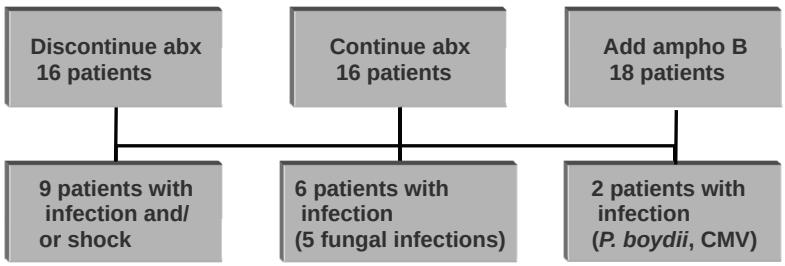
- Clinical trials: what works with consideration of risk-benefits?
- In this patient
  - What are you trying to prevent?
  - Who is the patient?
    - Renal disease
    - Liver disease
    - Mucositis (IV / oral)

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:



Pizzo PA, et al. *Am J Med.* 1982;72:101-111.

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

APACHE = Acute Physiology and Chronic Health Evaluation

Smith D, Kauffman CA. *Crit Care Med.* 2010;38:S380-387.

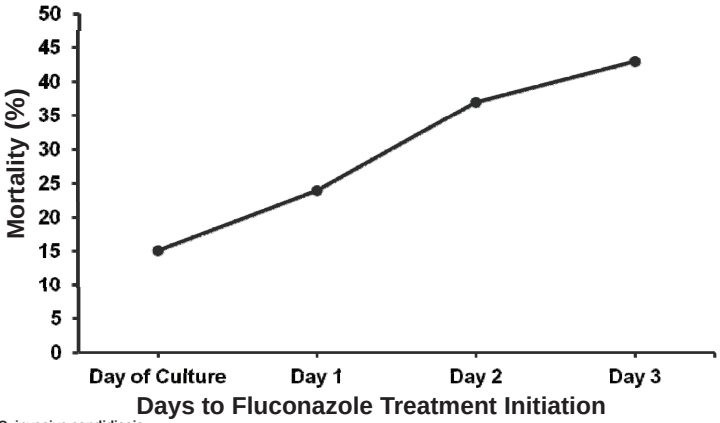
Risk Factors for IFD (cont'd)

Medical Interventions

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

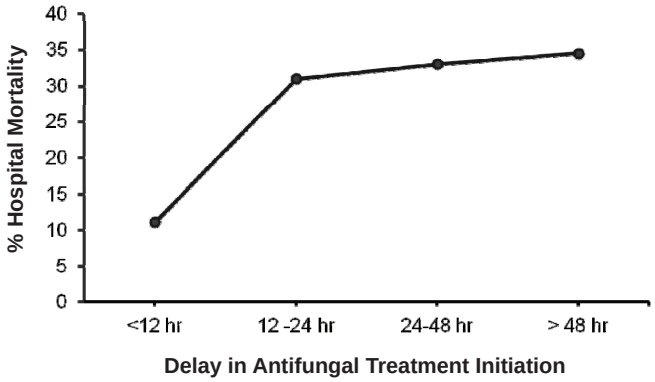
Smith D, Kauffman CA. *Crit Care Med.* 2010;38:S380-387.

Relationship Between Time to IC Treatment and Hospital Mortality



IC, invasive candidiasis
Adapted from Garey KW, et al. *Clin Infect Dis.* 2006; 43:25–31.

Relationship Between Time to Treatment for IC and Hospital Mortality



Adapted from Morrell M, et al. *Antimicrob Agents Chemother.* 2005;49:3640–3645.

Empiric Antifungal Treatment in Non-Neutropenic Patients with Suspected IC

2009 IDSA Recommendations

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

Pappas PG, et al. *Clin Infect Dis*. 2009;48:503-535.

Empiric Antifungal Treatment in Non-Neutropenic Patients with Suspected IC

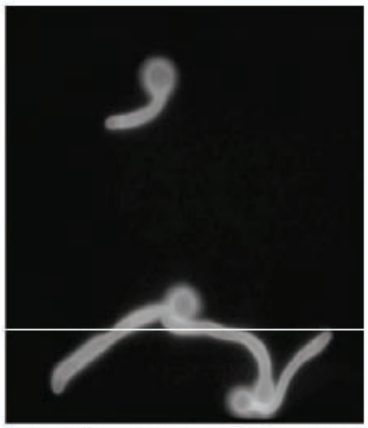
2009 IDSA Recommendations (cont'd)

- 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

Pappas PG, et al. *Clin Infect Dis*. 2009;48:503-535.

Patient #2 (cont'd)

- Blood: *Candida* species
- Are there diagnostic tests that can be used to identify species earlier?
  - Germ tube testing standard: hyphae produced after 2-3 h of incubation
  - PNA-FISH: 90-minute test
    - *C. albicans*
    - *C. glabrata*



Candida albicans displaying germ tube morphology. Public Health Image Library ID#295.

For confirmed candidiasis, do you routinely test for susceptibility?

General Pattern of Susceptibility of *Candida* Species

Species	Fluconazole	Itraconazole	Posaconazole	Voriconazole	AmB	Echinocandin
C. albicans	S	S	S	S	S	S
C. glabrata	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S to I	S
C. tropicalis	S	S	S	S	S	S
C. parapsilosis	S	S	S	S	S	S to R*
C. krusei	R	S-DD to R	S	S	S to I	S

S = susceptible; S-DD = susceptibility dose-dependent; R = resistant; I = intermediately susceptible
*Echinocandin resistance to *C. parapsilosis* isolates is uncommon
Adapted from Pappas PG, et al. *Clin Infect Dis.* 2009;48:512.

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…

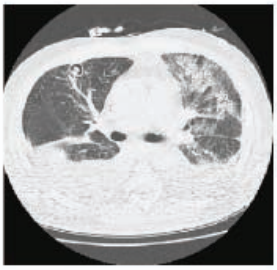
- Controversy in management of complicated abdominal infections with consideration of population-based data
- Patient specific management
  - Should he have been treated with fluconazole earlier?

Take-home Practice Points

PATIENT #3

Patient #3

- 22-year-old Japanese male currently day 82 s/p PBSCT from an unrelated donor.
- Currently receiving 2 mg/kg/day prednisone for skin and (mild) gut GVHD. Develops fever, dyspnea on exertion and CXR shows bilateral LL infiltrates, effusions.
- Currently receiving prophylactic trm/slf, acyclovir, fluconazole; last CMV PCR 1 week ago
- not-detectable.
- BAL performed immediately.

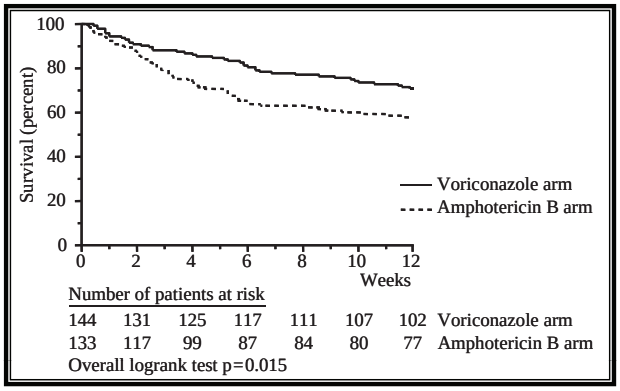


PBSCT, peripheral blood stem cell transplant; BAL, bronchoalveolar lavage

What tests would you perform on the BAL?

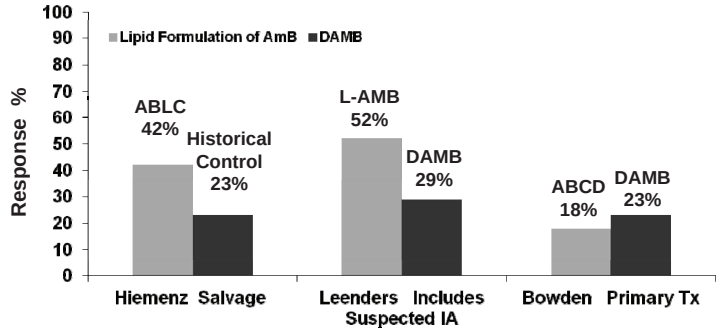
Antimicrobial therapy would include broad spectrum coverage for bacteria and which other antifungal agents?

Polyene Therapy vs. Voriconazole for Invasive Aspergillosis (IA)



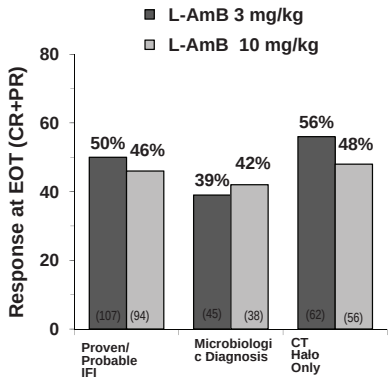
Herbrecht R, et al. *N Eng J Med*. 2002;347:408-415.

Polyene Therapy for Invasive Aspergillosis (IA)



Hiemenz JW, et al. *Blood*. 1995;86(suppl 1):849a.
Leenders AC, et al. *Br J Haematol*. 1998;103:205-212.
Bowden RA, et al. *Clin Infect Dis*. 2002;35:359-66.

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



14-day loading dose of L-AmB 3 or 10 mg/kg/d followed by L-AmB 3 mg/kg/d

	L-AmB	
	3 mg/kg/d	10 mg/kg/d
IPA	96%	97%
CT Halo	58	60
Allo-SCT	16	19
Neutropenia	71	76
Survival	72	59
Toxicity	20	32

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
Cornely O, et al. *Clin Infect Dis*. 2007;44:1289-97.

Combination Therapy: Randomized Trial

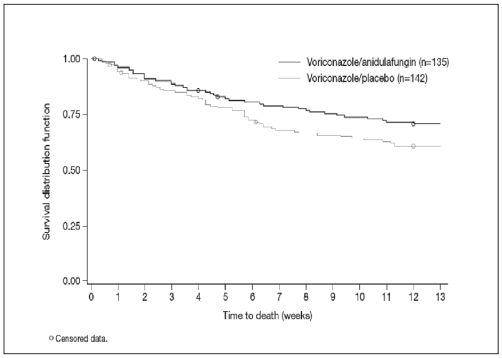
- Different design of study
  - Primary endpoint, patients
- 459 patients randomized in 93 centers, 24 countries (2008–2011)
  - Data review committee adjudicated cases
  - Presented at ECCMID, London
- 228 combination voriconazole + anidulafungin vs. 226 monotherapy
  - Matched well

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).

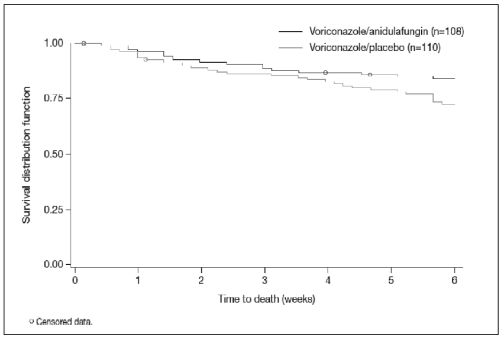


Probable IA with GM

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

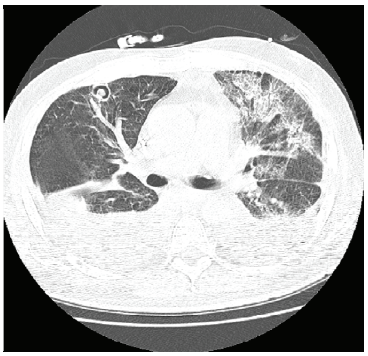
Culture/cytology/histopath – 54 pts (20%); GM (BAL or serum) – 218 pts (80%)

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

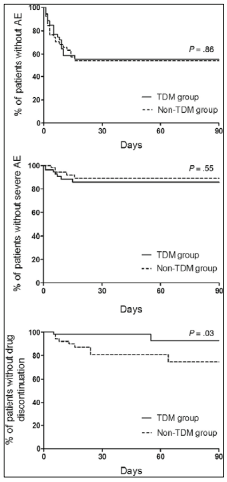
- Diagnostic certainty
  - Is this failure?
  - Are there other tests that can be helpful?
- If this is failure, what options do we have?
  - Increase voriconazole dose?
  - Add another drug?
  - Change drug?
- How do you interpret the liver enzyme abnormalities?
  - Drug?
  - GVHD?

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



Park WB, et al. *Clin Infect Dis*. 2012;55:1080-1087.

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