IFI Practice Case

Changing Epidemiology of IFIs: Is Antifungal Resistance Really an Issue?

Back to IFI Practice Case

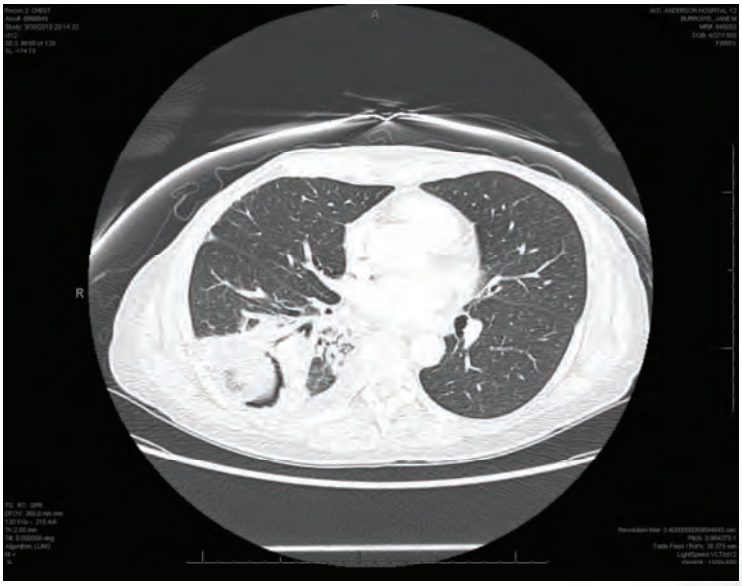
PETER G. PAPPAS, MD, FACP
William E. Dismukes Professor of Medicine
Principal Investigator, Mycoses Study Group
Division of Infectious Diseases
University of Alabama at Birmingham
Birmingham, AL

- 55-year-old female with history of breast cancer s/p radiation and chemotherapy, now with treatment-related AML
- She has recently undergone myeloablative chemotherapy, and has now completed her second round of consolidation therapy
- She reports fatigue, malaise, fever and right-sided pleuritic chest pain
- She reports dry cough, nausea and vomiting of 2 weeks duration. She has no other symptoms.
- She has received voriconazole antifungal prophylaxis during this and two previous episodes of neutropenia
- Current meds include vancomycin, cefepime, acyclovir and voriconazole 200 mg daily

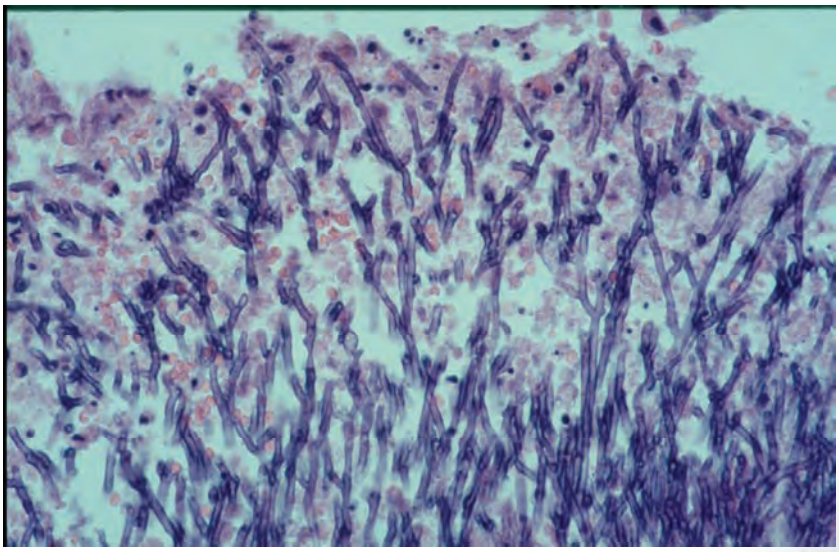
AML, acute myelogenous leukemia

- Vital Signs: Temp **38°C**; HR 85/min; BP 123/64 mmHg; RR 16/min; **94% on 4L NC**
- General: non-toxic, pale, alert and oriented x3
- HEENT: PERRL, extraocular movements are intact, nl conjuctivae
- Respiratory: **Right lower lobe rales**
- Cardiovascular: Normal rate, regular rhythm; no murmurs
- Chest: well-healed mastectomy scars
- Gastrointestinal: Soft, non-tender, non-distended, normal bowel sounds
- Skin: Warm, dry, no rash
- Extremity: no edema
- Neurologic: Alert, oriented, normal motor, sensory and cranial nerve function

- Laboratory: WBC 0.01; Hct 23%, platelets 27K
- LFTs, fluid balance profile, UA are normal
- PA and lateral CXR reveal RLL mass/infiltrate
  - No pleural effusion is noted



- Serum *Aspergillus* Galactomanan = 3.51
- Bronchoscopy – bloody secretions in right mainstem bronchus
- Pathology:
  – Fungal hyphae consistent with *Aspergillus* species are present in GMS stain of BAL fluid



Which antifungal regimen would you choose for this patient?

Follow-up

- Cultures of BAL grew *Aspergillus fumigatus*
- MICs were as follows:

Itraconazole	4.0 µg/mL
Voriconazole	4.0 µg/mL
Posaconazole	0.5 µg/mL
Micafungin	0.1 µg/mL
Amphotericin B	0.25 µg/mL

Brief History of Azole Resistance in *Aspergillus* spp.

- First recognized in 1990's in Europe
- Linked to the prolonged use of azoles in patients (e.g., UK), extensive agricultural use (e.g., The Netherlands, Denmark), and extensive use of azoles in non-agricultural industry (e.g., paints, building material, etc.)
- Originally there was no clear impact on treatment outcomes

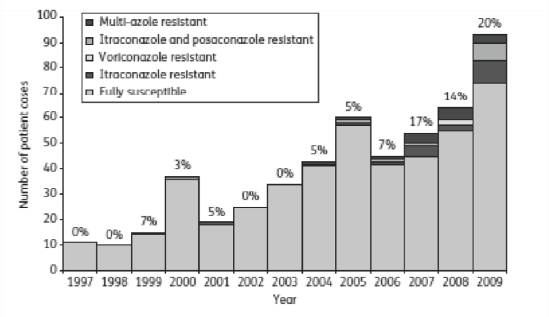
Resistance Among *Aspergillus* spp.

- Intrinsic resistance….well described in non-fumigatus *Aspergillus (*e.g.*, A. lentulus, A. terreus)*
- Acquired resistance to azoles, usually through ongoing or prior exposure

Mechanisms of 'Epidemic' Resistance

- Mutations of CYP51A gene (e.g., TR/L98H) are common to most azole-resistant isolates
- Resistance to itraconazole is most common; multiple azoles (e.g., itraconazole, voriconazole, posaconazole) is less common
- Mechanism is less well understood, some component of increased efflux pump activity
- Echinocandin/polyene resistance less common and less well understood

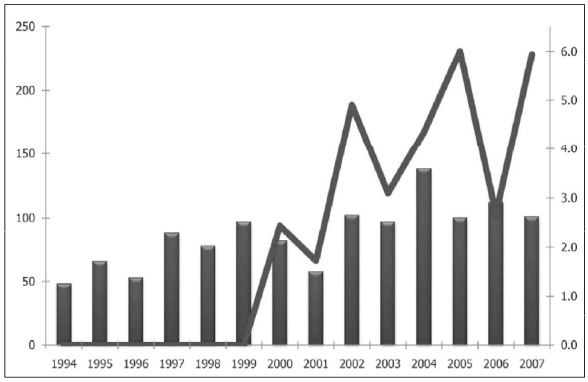
The Rise of Azole Resistance in Northern England



*** Percentages above each column indicate overall azole resistance for that year**

Bueid A, et al. *J Antimicrob Chemother.* 2010;65:2116-8.

The Emergence of Azole Resistance in The Netherlands



Blue bars: number of patients with a positive *A. fumigatus* culture (left *y*-axis)
red line represents the percentage of those patients with an ITZ isolate (right *y*-axis)

Snelders E, et al. *PloS Medicine.* 2008;5:1629-37.

Emergence of Azole Resistance While Receiving Therapy

- Several well-documented reports from Europe, Asia
- Most note a progressive, inexorable climb in MICs
- Poor outcomes correlated to high azole MICs
- Response to alternative compounds (either AmB or an echinocandin)
- Possibly decreased virulence associated with acquisition of azole resistance

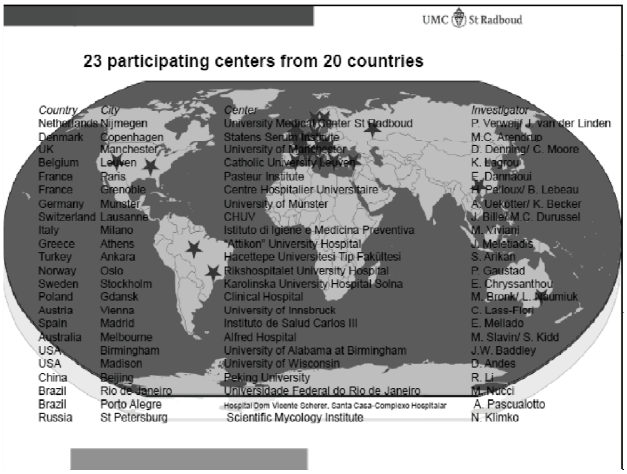
Emergence of Azole Resistance in *A. fumigatus*

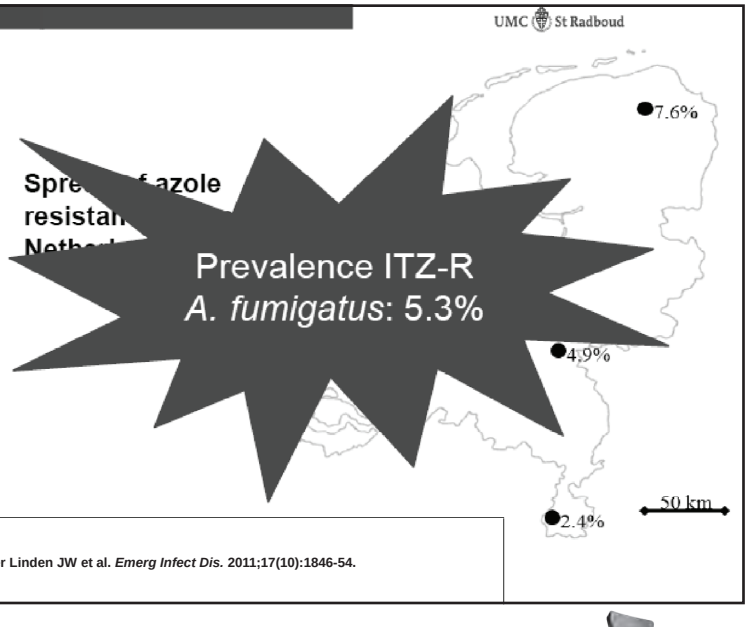
Susceptibility results obtained by CLSI/EUCAST microdilution (azoles) or by Etest (echinocandins) for four sequential isolates obtained from a CGD patient over a 127-week period.

Isolate no.	Week of collection	MIC (µg/mL)				
		Itraconazole	Voriconazole	Posaconazole	Anidulafungin	Caspofungin*
1	0	0.125/0.5	0.5/1	0.016/0.125	0.004	0.064
2	108	0.25/0.5	0.5/1	0.031/0.125	0.004	0.064
3	125	>16/>4	4/>4	0.25/0.5	0.004	0.064
4	127	>16/>4	4/>4	0.25/1	0.004	0.125
Controls						
NCPF2109	NA	0.063/0.5	0.125/1	<0.016/0.125	0.004	0.064
TR/L98H	NA	>16/>4	8/>4	0.5/0.5	ND	0.25

*MICs are rounded to nearest upper two-fold dilution value for the Etest endpoints.
Arendrup MC, et al. *PLoS One.* 2010;5(4):e10080.

Surveillance Collaboration for *Aspergillus* Resistance in Europe (SCARE)





van der Linden JW et al. *Emerg Infect Dis.* 2011;17(10):1846-54.

Azole Resistance by *Aspergillus* in The Netherlands

Table 1. Characteristics of screened susceptible and resistant isolates of *Aspergillus* spp., the Netherlands, 2007–2009*

Source and species	No. (%) susceptible, n = 1,978	No. (%) resistant, n = 84
Specimen source		
Sputum	1,397 (70.6)	64 (76.2)
Ear swab	176 (8.9)	3 (3.6)
BAL fluid	97 (4.9)	6 (7.1)
Bronchus secretion	66 (3.3)	2 (2.4)
Throat/nasal swab	66 (3.3)	1 (1.2)
Tissue	55 (2.8)	5 (6.0)
Skin swab/nail	38 (1.9)	1 (1.2)
Mouth wash	26 (1.3)	1 (1.2)
Pus/wound swab	16 (0.8)	1 (1.2)
Bronchial wash	11 (0.6)	0
Feces	8 (0.4)	0
Unknown	22 (1.1)	0
Species		
A. fumigatus	1,710 (86.5)	82 (97.6)
A. flavus	98 (5.0)	0
A. niger	52 (2.6)	2 (2.4)
A. terreus	35 (1.8)	0
A. nidulans	14 (0.7)	0
A. versicolor	13 (0.7)	0
A. glaucus	6 (0.3)	0
Unknown	50 (2.5)	0

*BAL, bronchoalveolar lavage.

van der Linden JW, et al. *Emerg Infect Dis.* 2011;17:1846-54.

Azole Resistance by *Aspergillus* in The Netherlands

Table 4. Characteristics of patients with azole-resistant invasive aspergillosis, the Netherlands, 2007–2009*

Patient age, y/ sex	Underlying disease	Disease	No. positive cultures†	Resistance mechanism	VCZ MIC, mg/L	Prior azole treatment (duration)‡	Treatment§	Outcome at 12 wk
66/M	Lung carcinoma	Proven pulmonary aspergillosis	1	TR/L98H	4	None	VCZ	Died
59/M	Hematologic malignancy, allo-SCT, GvHD	Proven pulmonary aspergillosis	4	TR/L98H	8	VCZ (>1 mo)	VCZ	Died
54/M	Acute myeloid leukemia, relapse, allo-HSCT	Proven pulmonary aspergillosis	1	TR/L98H	8	ITZ (2–4 wk)	VCZ	Died
50/M	Non-Hodgkin lymphoma, allo-SCT, GvHD, lung cavities	Probable pulmonary aspergillosis	2	TR/L98H	16	VCZ (>1 mo)	VCZ	Died
36/F	Breast carcinoma with metastasis	Probable pulmonary aspergillosis	1	TR/L98H	1	None	VCZ	Died
13/F	Non-Hodgkin lymphoma	Proven pulmonary and CNS aspergillosis	1	TR/L98H	16	None	VCZ, CAS, AMB	Died
58/M	Liver transplantation for hepatic failure after methotrexate treatment for arteritis	Proven pulmonary and CNS aspergillosis	5	TR/L98H	2	None	AMB, VCZ	Died
60/M	Acute myeloid leukemia, allo-SCT, GvHD	Proven pulmonary and CNS aspergillosis	3	TR/L98H	4	FCZ (1–2 wk)	VCZ, CAS, AMB, POS	Survived

*VCZ, voriconazole; allo-SCT, allogeneic hematopoietic stem cell transplantation; GvHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; ITZ, itraconazole; CNS, central nervous system; CAS, caspofungin; AMB, amphotericin B; FCZ, fluconazole; POS, posaconazole.
† All cultures were *Aspergillus fumigatus*.
‡Azole treatment <12 wk before the first culturing of an azole-resistant isolate.
§Azole treatment after first culturing of resistant isolate.

van der Linden JW, et al. *Emerg Infect Dis.* 2011;17:1846-54.

Aspergillosis due to Voriconazole Highly Resistant *Aspergillus fumigatus* and Recovery of Genetically Related Resistant Isolates From Domiciles

Jan W. M. van der Linden,[1,2,a] Simone M. T. Camps,[1,2,a] Greetje A. Kampinga,[3] Jan P. A. Arends,[3] Yvette J. Debets-Ossenkopp,[4] Pieter J. A. Haas,[5] Bart J. A. Rijnders,[6] Ed J. Kuijper,[7] Frank H. van Tiel,[8] János Varga,[9] Anna Karawajczyk,[10] J. Zoll,[1,2] Willem J. G. Melchers,[1,2] and Paul E. Verweij[1,2]

[1]Department of Medical Microbiology, and [2]Nijmegen Institute for Infection, Inflammation and Immunity (N4i), Radboud University Nijmegen Medical Centre, [3]Department of Medical Microbiology, University of Groningen, University Medical Center Groningen, [4]Department of Medical Microbiology, VU–University Medical Centre, Amsterdam, [5]Department of Medical Microbiology, University Medical Centre Utrecht, [6]Department of Internal Medicine, Division of Infectious Diseases, Erasmus Medical Centre, Rotterdam, [7]Department of Medical Microbiology, Leiden University Medical Centre, and [8]Department of Medical Microbiology, University Medical Centre Maastricht, The Netherlands; [9]Department of Microbiology, University of Szeged, Hungary; and [10]LeadPharma Medicine B.V., Nijmegen, The Netherlands

van der Linden JWM, et al. *Clin Infect Dis.* 2013;57:513-20.

Aspergillosis Due to Voriconazole Highly Resistant *A. fumigatus*

Sex/ Age	Month of Isolation/ Site	City	MIC (mg/L) ITZ	VCZ	POS	Underlying Condition	*Aspergillus* Disease [30]	Previous Azole Exposure[a]	Treatment	Outcome at 12 wk
F/11	Dec 2009/sputum	Utrecht	4	>16	0.25	Relapse ALL, HSCT, GVHD	Probable IA	None	VCZ, CAS	Persistent infection
M/70	Jan 2010/ear	Amsterdam	>16	>16	2	Chronic otitis externa, sinusitis, and paralysis of abducens nerve	IA[b]	None	L-AMB, AND	Persistent infection
F/51	Jan 2010/ abdominal abscess	Nijmegen	2	>16	0.5	Kidney transplant	Proven IA	None	VCZ, POS	Died
F/9	Feb 2010/sputum	Amsterdam	4	>16	0.5	Cystic fibrosis	No IA	None	None	Alive
M/69	Feb 2010/sputum	Amsterdam	>16	>16	2	Lung carcinoma, radiation	No IA	None	None	Alive
M/54	Mar 2010/sputum	Groningen	1	>16	0.25	Multiple myeloma, autologous HSCT, relapse	Probable IA	None	VCZ, L-AMB	Died
F/54	Mar 2010/sputum	Groningen	16	>16	0.5	Cystic fibrosis, bilateral lung transplant	Proven IA	VCZ	L-AMB	Alive
F/65	May 2010/biopsy	Amsterdam	4	>16	1	Chronic otitis after cholesteatoma surgery	Proven IA	None	Surgery, L-AMB	Alive
M/76	May 2010/sputum	Amsterdam	>16	>16	1	Lung fibrosis	None	None	None	Alive
M/70	Jun 2010/sputum	Amsterdam	1	>16	0.25	High energetic trauma, ICU admission	None	None	None	Died
M/59	Jul 2010/brain biopsy	Amsterdam	4	>16	1	β-thalassemia and diabetes mellitus	Proven IA	None	VCZ, L-AMB, CAS	Died
F/21	Sep 2010/sputum	Nijmegen	2	>16	0.5	Cystic fibrosis	ABPA	VCZ	None	Alive
F/49	Oct 2010/sputum	Groningen	>16	>16	2	COPD, unilateral lung transplant	None	None	L-AMB, VCZ	Alive
F/64	Nov 2010/sputum	Leiden	>16	>16	2	COPD	No IA	None	None	Alive
F/50	Jan 2011/sputum	Utrecht	>16	>16	1	NHB-cell lymphoma, allo-SCT	Probable IA	VCZ	VCZ	Died

van der Linden JWM, et al. *Clin Infect Dis*. 2013;57:513-20.

Conclusions

- Emergence of azole resistance in *Aspergillus* spp. is real and expanding to regions outside of Europe, including Asia, India and the Middle East
- Some regions report azole-resistance rates of 10%–20%
- Outcomes are generally poor when confronted with one of these organisms in the clinical setting
- Traditional antifungal susceptibility testing for azole resistance should become more routinely available, especially in regions of the world where antifungal prophylaxis is commonly practiced. Rapid assays to determine resistance are in development.
- Primary therapy with a polyene +/- echinocandin should be considered for IA, especially in regions where azole resistance is common

Which antifungal regimen would you choose for this patient now?

- A 25-year-old man with Crohn's disease underwent laparotomy for repair of a small bowel fistula. A small segment of jejunum was resected during the procedure. He was febrile post-op, and received empiric treatment with piperacillin/tazobactam for 4 days.
- 4 days post-op, he is transferred to ICU after developing hypotension (90/50 mmHg)
- Laboratory results:
  - WBC count: 17,500/mm^3 (87% PMNs, 6% bands)
  - Hemoglobin: 10 g/dL
  - Platelet count: 152,000/mm^3

- Blood cultures are obtained. Vancomycin and fluconazole 400 mg/d are added empirically. BP becomes more stable, but otherwise he remains febrile and there is little clinical change.
- On post-op day 6, blood cultures return positive for yeast, which is subsequently identified as *Candida glabrata*.

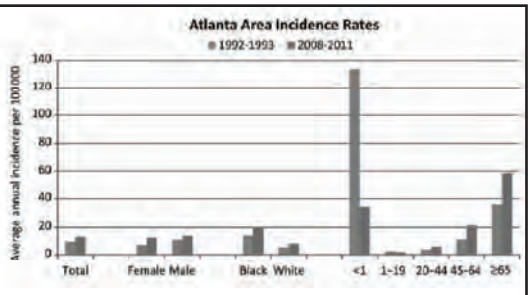
What is the best choice for antifungal therapy at this time?

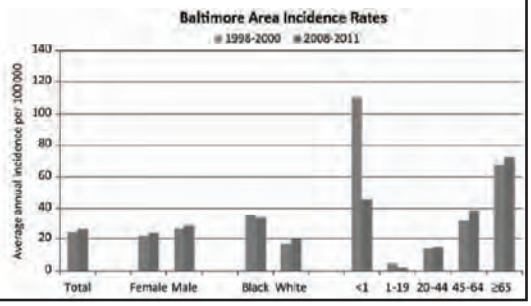
C. glabrata Emergence in U.S. Hospitals

	1992–2001 (N=3683)	2001–2011 (N=4638)	*P*
N (%) *C. glabrata*	559 (18%) →	1168 (25%)	<0.001
% Flu-R among *C. glabrata*	9% →	12%	0.006

Pfaller MA, et al. *J Clin Microbiol.* 2003;41:2176-9.
Pfaller MA, et al. *J Clin Microbiol.* 2009;47:3185-90.
Pfaller MA, et al. *J Clin Microbiol.* 2011;49:396-9.
Pfaller MA, et al. *J Clin Microbiol.* 2013; in press.

Changes in Incidence and Antifungal Drug Resistance in Candidemia

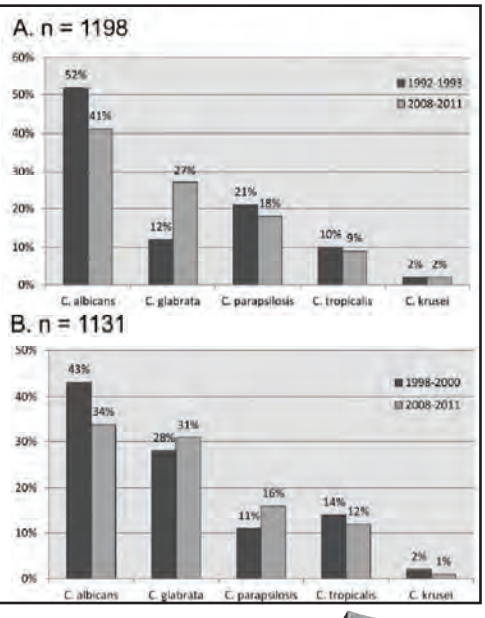




Results from population-based laboratory surveillance in Atlanta and Baltimore, 2008–2011

Cleveland AA, et al. *Clin Infect Dis*. 2012;55:1352-60.

Species Distribution for Candidemia in Atlanta and Baltimore, 2008–2011



Lockhart SR, et al. *J Clin Microbiol.* 2012;50:3435-42.

Antifungal Susceptibility for Candidemia Isolates in Atlanta and Baltimore, 2008–2011

Lockhart SR, et al. *J Clin Microbiol.* 2012;50:3435-42.

	Susceptibility profile of Atlanta isolates				Susceptibility profile of Baltimore isolates			
Species and antifungal agent	No. of isolates	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	% Resistant isolates	No. of isolates	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	% Resistant isolates
All species	**1141**				**1068**			
Fluconazole		1	16	8.2		1	16	6.5
Voriconazole		0.06	0.5	1.1		0.06	0.5	0.9
Caspofungin		0.06	0.25	1.0		0.06	0.25	1.0
Anidulafungin		0.03	1	1.0		0.03	1	1.0
Micafungin		0.03	1	1.0		0.03	1	1.0
C. albicans	**489**				**388**			
Fluconazole		0.5	2	2.2		0.5	1	2.3
Voriconazole		0.03	0.125	0.6		0.03	0.125	1.3
Caspofungin		0.03	0.06	0.6		0.03	0.06	0.3
Anidulafungin		0.015	0.06	0.4		0.03	0.06	0.3
Micafungin		0.03	0.03	0.4		0.015	0.03	0.3
C. glabrata	**318**				**352**			
Fluconazole		8	64	13.2		8	64	10.8
Voriconazole		0.25	2			0.25	1	
Caspofungin		0.06	0.125	2.5		0.06	0.125	2.3
Anidulafungin		0.06	0.125	3.1		0.06	0.125	2.3
Micafungin		0.015	0.03	2.8		0.015	0.03	2.5

Candida Species Susceptibility Profile

Candida spp.	AMB*	FLUC	ITRA	VOR	Echinocandins
C. albicans	S	S	S	S	S
C. tropicals	S	S	S	S	S
C. parapsilosis	S	S	S	S	S/?
C. glabrata	S / NS	S^{DD} / R	S^{DD} / R	S / NS	S / R
C. krusei	S / NS	R	S^{DD} to R	S	S
C. lusitaniae	S / R	S	S	S	S

*No established breakpoints
S = susceptible; S^{DD} = susceptible-dose dependent; R = resistant; I = intermediate; NS, non-susceptible

Candida: Emerging Resistance Issues

- ***C. krusei***
  - Fluconazole resistant
- ***C. glabrata***
  - Azoles (10%–25% of all isolates)
  - Echinocandins (3%–10% of all isolates)
  - Azole and echinocandin co-resistance (10%–20% of azole-R isolates)
- ***C. parapsilosis***
  - Echinocandins (elevated MICs, intrinsic)
  - Azoles (~4% acquired)
- **Rare species**
  - Intrinsic resistance to azoles and echinocandins
  - *C. guilliermondii*, *C. rugosa*

Pfaller MA, et al. *J Clin Microbiol.* 2007;45:735-45.

Geographic Variability of *Candida* spp.

TABLE 2. Geographic variation in frequency of common and uncommon species of *Candida*: ARTEMIS, 2001 to 2007[a]

Species	Species distribution (%) by region (total no. of isolates)[b]:					
	APAC (44,674)	EU (109,643)	AF/ME (8,259)	LAM (27,395)	NAM (11,682)	Total (201,653)
C. albicans	64.4	67.9	67.1	51.8	48.9	63.8
C. glabrata	12.6	11.3	8.8	7.4	21.1	11.6
C. tropicalis	11.7	4.9	6.6	13.2	7.3	7.7
C. parapsilosis	7.4	4.2	6.0	10.3	13.6	6.3
C. krusei	1.2	3.4	1.6	1.4	3.1	2.5
C. guilliermondii	0.4	0.5	0.1	2.2	0.5	0.7
C. inconspicua	<0.1	0.5		<0.1	<0.1	0.3
C. rugosa	0.4	<0.1	<0.1	1.2	<0.1	0.3
C. norvegensis	<0.1	0.2	<0.1	<0.1	0.2	0.1

[a] Includes all specimen types and all locations in hospitals from 133 institutions.
[b] Abbreviations: APAC, Asia-Pacific; EU, Europe; AF/ME, Africa-Middle East; LAM, Latin America; NAM, North America.

Pfaller MA, et al. *J Clin Microbiol.* 2010;48:1366-77.

Trends in Fluconazole Resistance Among *Candida* Isolates as Determined by CLSI Disk Diffusion Testing, 1997–2007

Pfaller MA, et al. *J Clin Microbiol.* 2010;48:1366-77.

Species	1997–2000		2001–2004		2005–2007	
	No. of isolates tested	% R	No. of isolates tested	% R	No. of isolates tested	% R
C. albicans	39,152	0.9	71,027	1.4	57,598	1.4
C. glabrata	5,634	19.2	12,963	15.9	10,342	15.4
C. tropicalis	2,996	3.6	8,496	4.5	7,050	3.6
C. parapsilosis	2,633	2.5	7,783	3.5	5,005	3.6
C. krusei	1,207	65.8	2,840	77.5	2,239	70.3
C. guilliermondii	367	12.5	902	9.9	508	14.2
C. lusitaniae	276	2.9	674	4.3	559	6.6
C. kefyr	182	3.3	527	3.6	517	1.7
C. inconspicua	9	55.6	276	52.2	290	54.1
C. famata	123	17.1	375	12.5	247	6.9
C. rugosa	35	34.3	238	50.7	134	10.4
C. dubliniensis	1	0.0	113	2.7	197	2.0
C. norvegensis	11	54.5	135	36.3	113	46.0
C. lipolytica	7	0.0	80	37.5	50	14.0
C. sake			20	10.0	67	11.9
C. pelliculosa	1	0.0	47	0.0	40	15.0
C. apicola					57	1.8
C. zeylanoides	4	0.0	50	28.0	20	15.0
C. valida			9	66.7	12	58.3
C. intermedia			10	0.0	14	7.1
C. pulcherrima			9	0.0	8	0.0
C. haemulonii			6	0.0	3	33.3
C. sellanoidea					7	0.0
C. utilis					6	0.0
C. humicola			2	50.0	4	50.0
C. lambica					5	80.0
C. ciferrii					2	50.0
C. colliculosa					2	0.0
C. holmii					1	0.0
C. marina					1	0.0
C. sphaerica					1	0.0
Candida spp.[c]	2,591	10.5	6,186	8.2	3,558	10.1

Fluconazole and Voriconazole Susceptibility by Global Region

Species	Antifungal agent	APAC		EU		AF/ME		LAM		NAM	
		No. of isolates	% R	No. of isolates	% R	No. of isolates	% R	No. of isolates	% R	No. of isolates	% R
C. albicans	Fluconazole	28,781	0.9	74,408	1.3	5,530	0.6	14,178	2.1	5,718	5.1
	Voriconazole	27,827	0.8	72,873	1.1	5,502	0.3	13,711	1.7	5,681	3.6
C. glabrata	Fluconazole	5,629	13.0	12,439	16.3	728	16.2	2,039	15.1	2,470	19.5
	Voriconazole	5,515	8.2	12,288	9.8	705	8.1	2,000	11.3	2,460	14.6
C. tropicalis	Fluconazole	5,178	6.5	5,349	2.9	544	2.6	3,625	2.6	850	4.4
	Voriconazole	5,062	8.4	5,128	3.9	542	2.4	3,522	3.7	836	5.3
C. parapsilosis	Fluconazole	3,294	4.3	4,578	2.6	499	15.0	2,830	2.1	1,587	3.5
	Voriconazole	3,120	1.7	4,497	1.1	496	11.1	2,779	0.9	1,517	2.4
C. krusei	Fluconazole	532	73.5	3,678	80.8	134	72.4	370	66.8	361	74.0
	Voriconazole	516	5.0	3,637	7.7	134	4.5	351	14.0	363	5.5
C. guilliermondii	Fluconazole	178	13.5	567	13.8	12	8.3	590	9.0	63	7.9
	Voriconazole	175	10.9	558	6.1	12	0.0	567	3.7	63	4.8
C. inconspicua	Fluconazole	4	25.0	558	53.0			2	100.0	2	100.0
	Voriconazole	4	0.0	555	3.8			2	50.0	2	0.0
C. rugosa	Fluconazole	165	32.1	89	10.1	1	0.0	339	55.5	9	22.2
	Voriconazole	145	6.9	87	1.1	1	0.0	338	32.8	9	11.1
C. norvegensis	Fluconazole	7	14.3	204	49.0	1	0.0	13	0.0	21	0.0
	Voriconazole	7	0.0	203	4.9	1	0.0	13	0.0	21	0.0

Pfaller MA, et al. *J Clin Microbiol.* 2010;48:1366-77.

Voriconazole Susceptibility of Fluconazole-Resistant *Candida* Isolates

TABLE 4. *In vitro* susceptibilities of fluconazole-resistant isolates of *Candida* spp. to voriconazole as determined by CLSI disk diffusion testing[a]

Species	No. of isolates tested	% S	% SDD	% R
C. albicans	1,782	28.1	8.4	63.6
C. glabrata	3,550	19.1	21.7	59.2
C. tropicalis	629	17.0	15.3	67.7
C. parapsilosis	431	39.2	20.4	40.4
C. krusei	3,889	79.6	11.3	9.2
C. guilliermondii	157	43.9	16.6	39.5
C. lusitaniae	63	55.6	17.5	27.0
C. kefyr	27	66.7	7.4	25.9
C. inconspicua	297	83.8	10.1	6.1
C. famata	62	37.1	24.2	38.7
C. rugosa	242	28.1	21.5	50.4
C. dubliniensis	8	62.5	0.0	37.5
C. norvegensis	100	81.0	10.0	9.0
C. lipolytica	37	29.7	27.0	43.2
C. sake	9	44.4	11.1	44.4
C. pelliculosa	6	16.7	16.7	66.7
C. apicola	1	0.0	0.0	100.0
C. zeylanoides	15	46.7	26.7	26.7
C. valida	14	71.4	7.1	21.4
C. intermedia	1	100.0	0.0	0.0
C. haemulonii	1	0.0	0.0	100.0
C. humicola	3	0.0	33.3	66.7
C. lambica	4	25.0	50.0	25.0
C. ciferrii	1	0.0	100.0	0.0
Candida spp.[b]	850	47.6	14.6	37.8

[a] Isolates obtained from 133 institutions, 2001 to 2007. The zone diameters for voriconazole disk diffusion susceptibility categories were as follows: S, ≥17 mm; SDD, 14 to 16 mm; R, ≤13 mm.
[b] *Candida* species not otherwise identified.

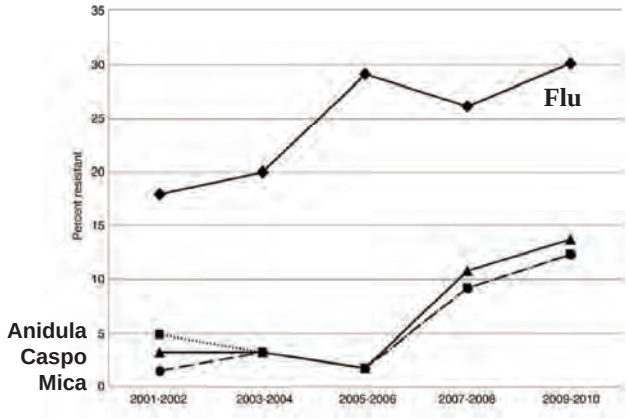
Pfaller MA, et al. *J Clin Microbiol.* 2010;48:1366-77.

Resistance of *C. glabrata* to Fluconazole and Echinocandins in Multicenter and Hospital-Based Surveillance Studies in the US

Study Type (ref)	Time period	No. of isolates	% FLU-R	% ECH-R
Sentinel[1]	2008–2011	526	9.1	2.3
Population based[2]	2008–2011	670	12.0	3.0
Hospital 1[3]	2004–2007	31	16.0	0.0
Hospital 2[4]	2001–2010	313	24.9	6.7

1. Pfaller MA, et al. *J Clin Microbiol*. 2012;50:1199-1203.
2. Cleveland AA, et al. *Clin Infect Dis*. 2012; 55:1352-61.
3. Diekema DJ, et al. Diag Microbiol Infect Dis. 2012;73:45-8.
4. Alexander BD, et al. *Clin Infect Dis*. 2013;56:1724-32.

Temporal Trends of Antifungal Resistance by *C. glabrata* Isolates



Alexander BD, et al. *Clin Infect Dis*. 2013;56:1724-32.

Variables Impacting Treatment Outcome or Mortality of *C. glabrata* Infection

	Treatment Success		Mortality	
	10-Day	30-Day	10-Day	30-Day
Variable	*P* Values (Univariable Analysis)			
Adult vs pediatric (age <18 y)	NS	NS	.02	NS
Underlying disease	NS	NS	NS	NS
Malignancy	NS	NS	.023[a]	.033[a]
End-stage liver disease	NS	NS	.0392	.0124[a]
Acute renal failure	NS	NS	NS	.0295
Breakthrough infection	NS	NS	NS	.0018
Directed therapy drug class				
Polyene vs other	NS	NS	NS	.0073[a]
Polyene vs azole	NS	NS	NS	.0223
Polyene vs echinocandin	NS	NS	NS	.0099
FKS mutation	.0391	NS	NS	.0374
Echinocandin-resistant MIC				
Caspofungin	NS	NS	NS	.0119
Micafungin	NS	NS	NS	.025
Prior antifungal Therapy	NS	NS	NS	.005
Azole	NS	NS	NS	.0017[a]
Under intensive care[b]	NS	NS	<.0001[a]	<.001[a]

Alexander BD, et al. *Clin Infect Dis*. 2013;56:1724-32.

Variables Impacting Treatment Outcome of *C. glabrata* Invasive Candidiasis

TABLE 5 Association of *FKS* mutations, prior echinocandin exposure, and echinocandin MICs with clinical failure

Predictor variable	No. of successes (n = 44)	No. of failures (n = 22)	*P* value	Odds ratio	95% CI	% PPV[a]	% NPV[b]
Presence of *FKS* mutation	1	9	0.0001	29.7	3.44–257.5	90 (9/10)	77 (43/56)
Prior echinocandin exposure	8	13	0.002	6.50	2.07–20.4	62 (13/21)	80 (36/45)
Caspofungin MIC of >0.5 μg/ml (BMD-RPMI)	6	7	0.10	2.96	0.85–10.3	54 (7/13)	72 (38/52)
Caspofungin MIC of >0.06 μg/ml (BMD-AM3)	2	8	0.002	12.0	2.27–63.4	80 (8/10)	75 (42/56)
Caspofungin MIC of >0.25 μg/ml (YeastOne)	6	9	0.03	4.39	1.31–14.7	60 (9/15)	75 (38/51)
Caspofungin MIC of >0.25 μg/ml (Etest)	3	11	0.0001	13.7	3.24–57.7	79 (11/14)	79 (41/52)

[a] Positive predictive value (PPV) is the percentage of positive tests associated with failure.
[b] Negative predictive value (NPV) is the percentage of negative tests associated with success.

Shields RK, et al. *Antimicrob Agent Chemother.* 2013; 57: 3528-35.

C. parapsilosis and Echinocandins

- *C. parapsilosis* isolated in 53% of cancer pts who developed candidemia while receiving caspofungin therapy[1]
- Strong correlation between caspofungin usage and a 400% increase in *C. parapsilosis* BSI[2]
- Species-specific incidence of *C. parapsilosis* BSI has doubled in US between 1993 and 2011[3]
- Pre exposure to caspofungin associated with a decreased prevalence of *C. albicans* in favor of *C. parapsilosis*[4]
- Improved response in treating pts with *C. parapsilosis* BSI with high-dose caspofungin (150 mg/d) vs standard dose (70 mg load/50 mg daily): 81% vs 61%; not statistically significant[5]

1. Sipsas NV, et al. *Cancer*. 2009;115:4745-52.
2. Forrest GN, et al. *J Infect*. 2008;56:126-9.
3. Cleveland AA, et al. *Clin Infect Dis*. 2012;55:1352-61.
4. Lortholary O, et al. *Antimicrob Agents Chemother*. 2011;55:532-8.
5. Betts RF, et al. *Clin Infect Dis*. 2009;48:1676-84.

Candida Resistance Summary

- Greatest concern is still azole-resistant *C. glabrata*
- Potential emergence of less common species with inherent or acquired azole resistance
- Most *Candida* remain highly susceptible to echinocandins, but emergence of acquired (*C. glabrata*) and intrinsic (*C. parapsilosis*) resistance is a concern

What is the best choice for antifungal therapy at this time?

IFI Practice Case

Assessing the Value of New Diagnostic Approaches in Clinical Mycology: A Potential Win-Win Situation

Back to IFI Practice Case

THOMAS F. PATTERSON, MD, FACP, FIDSA

Chief, Division of Infectious Diseases
Professor of Medicine
Director, San Antonio Center for Medical Mycology
The University of Texas Health Science Center at San Antonio
San Antonio, TX

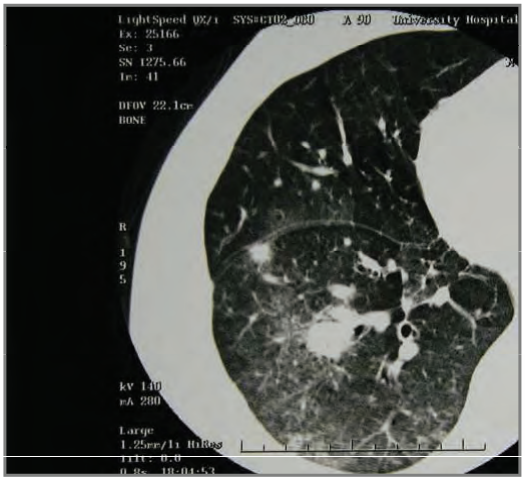
A Diagnostic Dilemma

You are called to see a 45-year-old patient post allogeneic SCT on long-term secondary oral voriconazole prophylaxis following presumed IPA; now on empiric piperacillin/tazobactam for fever

- Progressive pulmonary infiltrates
- Persistent fever
- Galactomannan positive OD=0.5

SCT, stem cell transplantation; IPA, invasive pulmonary aspergillosis

Chest CT



What is the most likely diagnosis?

What do you do next?

What are likely diagnostic considerations?

What would you do to establish a diagnosis?

What is the most appropriate antifungal management?

Diagnosis of Invasive Fungal Infection

- What is the likely pathogen in breakthrough?
- Should we monitor triazole levels?
- Is bronchoscopy a useful investigation?
- Is triazole resistance an issue?
- Is there a role for surgery?

Summary: Posaconazole & Voriconazole Prophylaxis and Breakthrough IFI

	Posaconazole	Fluconazole
N	**605**	**539**
Breakthrough IFI	**20 (3%)**	**45 (8%)**
***Aspergillus* (Culture/GM)**	**45%**	**80%**
Mould	**20%**	**9%**
Candida	**35%**	**10%**

- **Voriconazole:* 45 pts with secondary prophylaxis; relapses: candidemia (1), scedosporiosis (1); 1 new mucormycosis**

Ullmann AJ, et al. *N Engl J Med*. 2007:356:335-47.
Cornely OA, et al. *N Engl J Med*. 2007:356:348-59.
***Cordonnier C, et al. *Haematologica*. 2010;95:1762-8.**

How Can We Make a Diagnosis of Invasive Aspergillosis?

- Importance of culture confirmation when possible
- Utility of "halo" sign in neutropenic patients
  - Not specific for *Aspergillus*
- Non-culture-based methods to facilitate diagnosis
  - Galactomannan, (1→3)-β-D-glucan
  - PCR not yet established—but much closer!
- Possible impact of antifungal resistance

Importance of assessing patient's risk for invasive fungal infection

Is Bronchoscopy Useful?

- Yield culture and cytology on bronchoalveolar lavage (BAL) 30% in neutropenic patients with abnormal CT and proven invasive aspergillosis
- More likely in those with extensive changes and less antifungal exposure

Reichenberger F, et al. *Bone Marrow Transplant*. 1999: 24:1195-9.

Utility of Galactomannan (GM) Detection in Bronchoalveolar Lavage (BAL) Samples

Number of patients: 160	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Serum	47	93	73	82
BAL	85	100	100	88

GM detection in CT-based BAL fluid has a high positive predictive value (PPV) for diagnosing invasive pulmonary aspergillosis (IPA) early in untreated patients

GM index <0.5 in BAL virtually excludes diagnosis

Becker MJ, et al. *Br J Haematol*. 2003;121:448-57.
D'Haese J, et al. *J Clin Microbiol*. 2012;50:1258-63.

Platelia *Aspergillus* EIA for Detection of Galactomannan in BAL Fluid in Solid Organ Transplant Recipients

Group	GM			
	0.5 cutoff		1.0 cutoff	
	No. positive/ total no.	% (95% CI)[c]	No. positive/ total no.	% (95% CI)
Invasive pulmonary aspergillosis	9/11	81.8 (52.3–94.9)	9/11	81.8 (52.3–94.8)
Surveillance controls[a]	5/119	4.2 (1.8–9.4)	4/119	3.4 (1.3–8.4)
Diagnostic controls[b]	18/66	27.3 (18.0–39.1)	8/66	12.1 (6.2–22.1)
Surveillance and diagnostic	23/185	12.4 (8.4–17.9)	12/185	6.5 (3.7–11.0)
Noncolonized controls	11/150	7.3 (4.1–12.6)	2/150	1.3 (0.4–4.7)
Colonized controls (*Aspergillus* or mold)	12/56	21.4 (12.7–33.8)	8/56	14.3 (7.4–25.8)
Healthy controls with HIV infection	0/56	0 (0.0–6.4)	0/56	0 (0.0–6.4)

- Sensitivity 81.8% and specificity 95.8% in lung transplant patients evaluated for infection or rejection
- Serum positive in 19.3% of pts with positive BAL sample
- False positive: lung transplant, colonization, radiographic abnormalities

EIA, enzyme immunoassay
Husain S, et al. *Clin Vacc Immunol*. 2008;15:1760-3

PCR for Invasive Aspergillosis

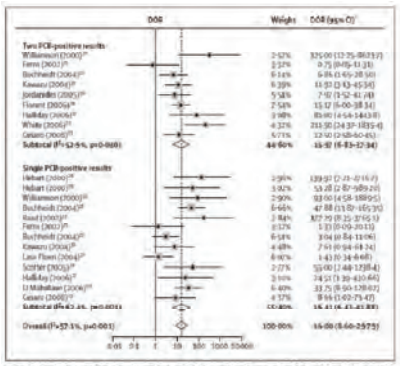


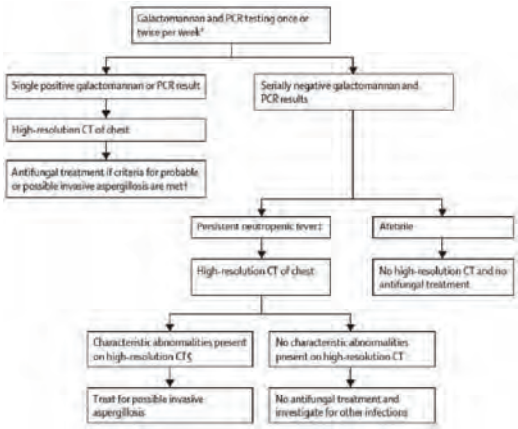
Figure 2: Forest plots of the diagnostic odds ratios (DORs) resulting from studies that used two PCR-positive results and those that used a single PCR-positive result
Random-effects models were used for meta-analysis. Weighting was by inverse-variance method.

- Variable sensitivity / specificity
- Limited per test positivity
- Technical false positives/negatives
- Lack of standardized targets/reagents
- Not externally validated
- Not yet accepted as diagnostic criteria, but closer!

Donnelly JP. *Clin Infect Dis.* 2006;42:487-9.
Mengoli C, et al. *Lancet Infect Dis.* 2009;9:89-86.
White PL, et al. *J Clin Microbiol.* 2010;48:1231-40.

GM & PCR vs. Culture & Histology for Antifungal Therapy in High-risk Hematology Patients

Open-label, parallel-group, randomized trial



Morrissey CO, et al. *Lancet Infect Dis.* 2013;13:519-28.

Results

	Standard diagnosis group (n=122)	Biomarker diagnosis group (n=118)
Median age, years (IQR)	49 (36–57)	48 (35–54)
Number of men	82 (67%)	67 (57%)
Positive galactomannan result*	1 (1%)	0
Positive PCR result†	11 (9%)	5 (4%)

	Standard diagnosis group (n=122)	Biomarker diagnosis group (n=118)	% difference between groups (95% CI)	p value
Received empirical treatment with antifungal drugs	39 (32%)	18 (15%)	17% (4 to 26)	0·002
Mortality				
All-cause	18 (15%)	12 (10%)	5% (−4 to 14)	0·31
Invasive aspergillosis-related	6 (5%)	3 (3%)	2% (−2·5 to 7·3)	0·5
Other invasive fungal disease-related*	0	2 (2%)	—	0·24
Incidence of invasive aspergillosis				
Proven	1 (1%)	1 (1%)	—	1·0
Probable	0	16 (14%)	−14% (−20 to −7)	<0·0001
Possible	0	6 (5%)	−5% (−9 to −1)	0·013
Incidence of other invasive fungal disease†				
Proven	4 (3%)	5 (4%)	—	0·75
Probable	0	1 (1%)	—	0·49

Morrissey CO, et al. *Lancet Infect Dis.* 2013;13:519-28.

GM & PCR vs. Culture & Histology for Antifungal Therapy in High-risk Hematology Patients

	Standard diagnosis group	Biomarker diagnosis group	p value
Fluconazole or itraconazole prophylaxis	1/94 (1%)	16/95 (17%)	<0·0001
Voriconazole or posaconazole prophylaxis	0/22	1/19 (5%)	0·67
Fluconazole prophylaxis	0/45	5/40 (13%)	0·02
Itraconazole, voriconazole, or posaconazole prophylaxis	1/71 (1%)	12/74 (16%)	0·002
Allogeneic stem-cell transplantation	0/92	16/99 (16%)	<0·0001
Acute leukaemia	1/30 (3%)	1/19 (5%)	1·0

Data are n/N (%).

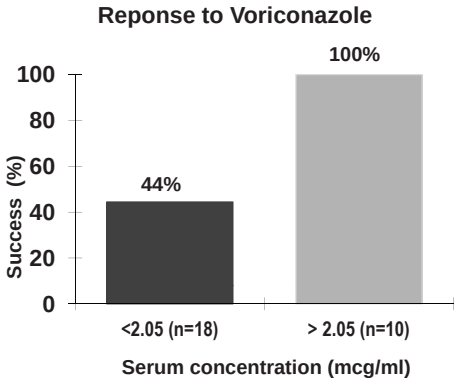
Table 4: Incidence of proven and probable invasive aspergillosis by subgroup in the intention-to-treat population

Morrissey CO, et al. *Lancet Infect Dis.* 2013;13:519-28.

Benefits of Screening with Serum PCR with High Negative Predictive Value

- Fewer missed diagnoses
- Faster diagnosis with better outcomes
- Reduced cost of prophylactic antifungal therapy or reduced cost of empiric therapy
- Of little value in patients on voriconazole or posaconazole prophylaxis

Therapeutic Drug Monitoring: Voriconazole Serum Concentration and Response



- Random voriconazole levels in patients with progression (n=17) or toxicity (n=11)
- Better responses in patients with higher levels
- Improved outcomes with dose escalation in patients with levels <2 mcg/mL

Smith J, et al. *Antimicrob Agents Chemother.* 2006;50:1570-2.

Measurement of Voriconazole Serum Concentrations

- **Potential reasons to monitor include:**
  - **Nonlinear kinetic profile**
  - **Dependence on CYP2C19**
  - **Extensive metabolizers with 2- to 4-fold lower exposure than heterozygous & poor metabolizers**
  - **High inter-patient variability**
- **Prior studies failed to detect relationship between outcome and concentrations**
  - **Trend for lower responses with random levels <0.5 µg/mL**
- **Levels in hematopoietic stem cell transplantation (HSCT) undetectable in 15%**

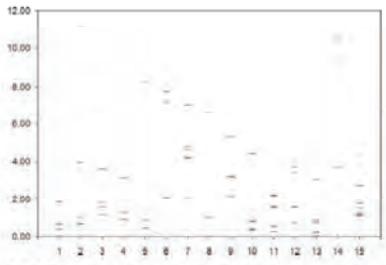


FIGURE 2. Voriconazole levels in 15 patients in whom ≥4 values were available illustrating variability.

Lutsar I, et al. *Clin Infect Dis.* 2003;36:1087-93.
Trifilio S, et al. *Cancer.* 2007;109:1532-5.

Posaconazole Plasma Concentrations and Global Response: IA

Quartile	No. of subjects*	Plasma C_{max}		Plasma C_{avg}		No. (%) of responders
		Mean ng/mL	CV (%)	Mean ng/mL	CV (%)	
1	17	142	51	134	45	4 (24)
2	17	467	27	411	21	9 (53)
3	17	852	15	719	12	9 (53)
4	16	1480	16	1250	28	12 (75)

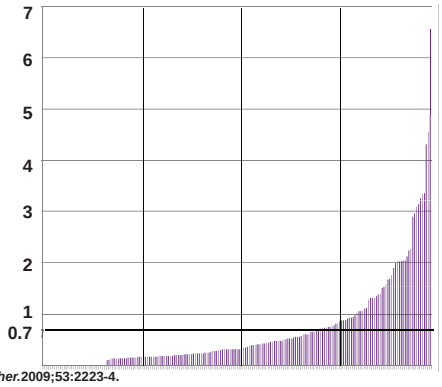
C_{avg} = average plasma concentration; C_{max} = maximum plasma concentration; CV = coefficient of variation.

*Data were available for 67 patients with available plasma concentrations of posaconazole.

MITT, modified intent to treat subset
Walsh TJ, et al. *Clin Infect Dis*. 2007;44:2-12.

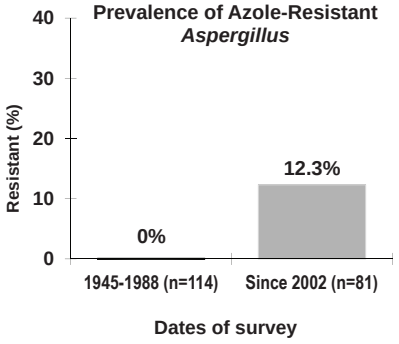
Posaconazole Therapeutic Drug Monitoring: A Reference Laboratory's Experience

- **Posaconazole serum drug levels have wide inter-patient variability**
- **Posaconazole FDA briefing document recommends a serum level of >0.7 µg/mL**
- **Reference laboratory reported undetectable levels in 16.3% of samples; and 70.3% less than 0.7 µg/mL**



Thompson GR, et al. *Antimicrob Agents Chemother.*2009;53:2223-4.
Gubbins PO, et al. *Antimicrob Agents Chemother.* 2006;50:1993-9.
Krishna GM, et al. *Pharmacotherapy.* 2007;27:1627-36.
Krishna G, et al. *Antimicrob Agents Chemother.* 2009;53:958-66.
Ullmann AJ, et al. *Antimicrob Agents Chemother.* 2006;50:658-66.

Azole Resistance in *Aspergillus*



- Detection of multi-azole-resistant *Aspergillus* in Dutch medical centers since 2002*:*
  - Cross resistance to voriconazole, itraconazole, posaconazole, ravuconazole
  - MICs 0.5–16 µg/mL
- A new *cyp51A* gene mutation in 12 of 13 isolates;TR_{34}/L98H
- Associated with itraconazole prophylaxis in 4 patients
- Responses in most patients with voriconazole or posaconazole

Verweij PE, et al. *N Engl J Med.* 2007;356:1481-3.

Azole Resistance in *A. fumigatus*

Sex/ Age	Month of Isolation/ Site	City	MIC (mg/L) ITZ	VCZ	POS
F/11	Dec 2009/sputum	Utrecht	4	>16	0.25
M/70	Jan 2010/ear	Amsterdam	>16	>16	2
F/51	Jan 2010/ abdominal abscess	Nijmegen	2	>16	0.5
F/9	Feb 2010/sputum	Amsterdam	4	>16	0.5
M/69	Feb 2010/sputum	Amsterdam	>16	>16	2
M/54	Mar 2010/sputum	Groningen	1	>16	0.25
F/54	Mar 2010/sputum	Groningen	16	>16	0.5
F/65	May 2010/biopsy	Amsterdam	4	>16	1
M/76	May 2010/sputum	Amsterdam	>16	>16	1
M/70	Jun 2010/sputum	Amsterdam	1	>16	0.25
M/59	Jul 2010/brain biopsy	Amsterdam	4	>16	1
F/21	Sep 2010/sputum	Nijmegen	2	>16	0.5
F/49	Oct 2010/sputum	Groningen	>16	>16	2
F/64	Nov 2010/sputum	Leiden	>16	>16	2
F/50	Jan 2011/sputum	Utrecht	>16	>16	1

TR_{46}/Y121F/T289A found in 15 patients

6 = no disease
1 = ABPA
8 = IA
5/8 died
2/8 had persistent infection

ABPA, allergic bronchopulmonary aspergillosis

van der Linden JWM, et al, *Clin Infect Dis.* 2013;57:513-20.

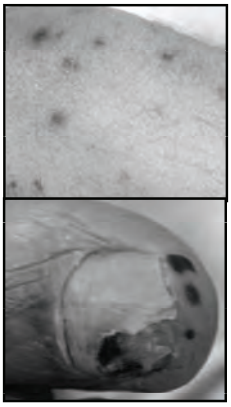
Azole Resistance in *A. fumigatus*

Site	City	Location	No. of Resistant Colonies	TR_{46}/ Y121F/ T289A	TR_{34}/ L98H
1	Nijmegen	Hospital restaurant	3	. . .	3
		Hospital pediatrics department	9	2	7
		Outside hospital	5	. . .	5
2	Schaijk	Living room	2	. . .	2
		Basement	3	. . .	3
		Back yard	7	. . .	7
3	Schaijk	Living room	1	. . .	1
		Conservatory	5	. .	5
		Back yard	3	. .	3
4	Overasselt	Kitchen	6	1	5
		Basement	7	. .	7
		Back yard	7	. .	7
5	Schaijk	Living room	6	. . .	6
		Basement	3	. .	3
		Back yard	3	. . .	3
6	Berghem	Living room	. . .	. . .	. . .
7	Schaijk	Hall	13	3	10
		Balcony	6	. . .	6
8	Groningen	Hospital entrance[a]	. . .	. .	.
		Outside hospital	29	2	27
9	Scharmer	Living room	4	1	3
		Back yard	6	3	3
10	Garmerwolde	Living room[a]	.	.	.
		Back yard	12	2	10

Ratio of TR_{34}/L98H versus TR_{46}/Y121F/T289A 9:1

van der Linden JWM, et al. *Clin Infect Dis.* 2013;57:513-20.

Emerging Fungal Infections: *Scedosporium* & *Fusarium*

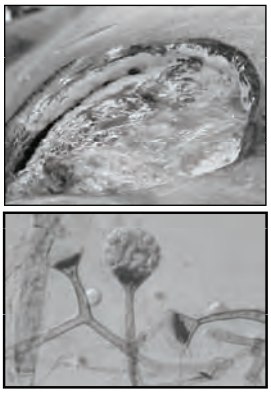


- Refractory to available agents: mortality 50% to >80%
- In vitro/in vivo: voriconazole, posaconazole, isavuconazole
- Potential activity of combination therapy: echinocandins
- Efficacy in patients refractory or intolerant to standard therapy:

Voriconazole	**# pts**	**Response**
Fusarium	11	45%
Scedosporium	10	30%
Posaconazole	**# pts**	**Response**
Fusarium	18	39%

Patterson TF, et al. *N Engl J Med.* 2009;361:287-96.
Perfect JR, et al. *Clin Infect Dis.* 2003;36;1122-31.
Raad I, et al. *Clin Infect Dis.* 2006;42:1398-403.

Emerging Resistant Mycoses: Mucormycosis



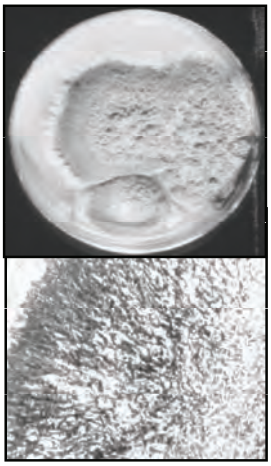
- Emergence on suppressive therapy (voriconazole, echinocandin):
  - Severely immunosuppressed (allo BMT)
- Other clinical presentations: trauma, burns
  - Trauma victims: polymicrobial wound infection including *Apophysomyces elegans*
  - May not grow in culture (homogenized tissue)
- In vivo activity: posaconazole
  - Clinical trials (Greenberg, *AAC* 2006;50:126-33)
    - 71% response in 55 patients
- Primary therapy with high-dose lipid formulation of amphotericin B
- Potential immunomodulatory activity of echinocandins in combination therapy

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

Anderson D. *Lancet.* 27 Jan 2005. http://image.thelancet.com/extra/05let1078web.pdf

Phaeohyphomycoses (Black Fungi)

- Mycotic infections caused by dematiaceous fungi (melanin in cell walls): Masson Fontana stain
- Tropical, subtropical and temperate zones
- 72 patients with disseminated infection
  - Central nervous system, cutaneous lesions, pulmonary disease
  - Overall mortality: 79%
- Etiologic agents
  - *Scedosporium prolificans* (most common—42%); *Bipolaris spicifera* (8%), *Wangiella dermatitidis* (7%), Others: *Phialemonium, Phialophora, Alternaria*, *Curvularia*, *Exserohilum*, *Exophiala…*
- Therapy: newer azoles, lipid AmB



Revankar SG, et al. *Clin Infect Dis.* 2002;34:467-76.

Quantitative PCR Detection of DNA in Serum for Early Diagnosis of Mucormycosis

	Quantification Cycle			
	Acory Assay	Muc1 Assay	Muc1 Assay	Rmuc Assay
Amount of Mucorales, DNA in Volume Tested (10 µL)	*Lichtheimia corymbifera/ L. ramosa/L. ornata*	*Rhizopus oryzae*	*Mucor racemosus/ M. ramosissimus*	*Rhizomucor pusillus*
300 fg	35/28/30	34	32/35	39
30 fg	37/32/33	36	35/37	41
15 fg	39/34/35	38	37/38	45
7.5 fg	42/39/41	43	>46/>46	>46
3.7 fg	>46/43/>46	>46	>46/>46	>46
1.9 fg	>46/>46/>46	>46	>46/>46	>46
0.9 fg	>46	>46	>46/>46	>46

DNA detected in 9/10 patients,
5/9 detected 1–8 days prior to first radiological or clinical features

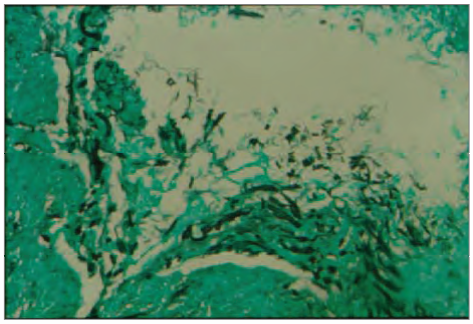
Millon L, et al. *Clin Infect Dis.* 2013;56:e95-101.
www.epa.gov/nerlcwww/moldtech.htm#primers

- Diagnostic evaluation/progress
- Day 2: BAL performed
  - BAL galactomannan index positive: OD=1.0
- Day 4
  - Sputum culture – positive for yeast
  - BAL fungal culture positive for *Aspergillus flavus*
  - MICs

	AmB	Itra	Vori	Posa
A. flavus	**1 µg/mL**	**0.5 µg/mL**	**0.25 µg/mL**	**0.25 µg/mL**

Clinical Course

- Persistent fever; progressive infiltrates
- Bronchoscopy with transbronchial biopsy



- Culture positive for *Rhizopus oryzae*

Lessons Learned: Patient Case 2 Diagnosis of Invasive Mould Infections

- *Aspergillus*: still the most important pathogen in breakthrough on prophylaxis
  - NB: other moulds are possible, especially in highly immunosuppressed patients
- Triazole levels: logistical problems and lack of target levels for prophylaxis—may be useful even with weight-based dosing
- Triazole resistance not widespread (?)
- Bronchoscopy with BAL GM: useful test

IFI Practice Case

Optimized Antifungal Prophylaxis for At-risk Patients: Impact of Host-related Factors

Back to IFI Practice Case

JOHN R. PERFECT, MD

James B. Duke Professor of Medicine
Chief, Division of Infectious Diseases and International Health
Duke University Medical Center
Durham, NC

IFI Practice Case 3

Infection Mimics Host Immunity - Can we prevent it ?

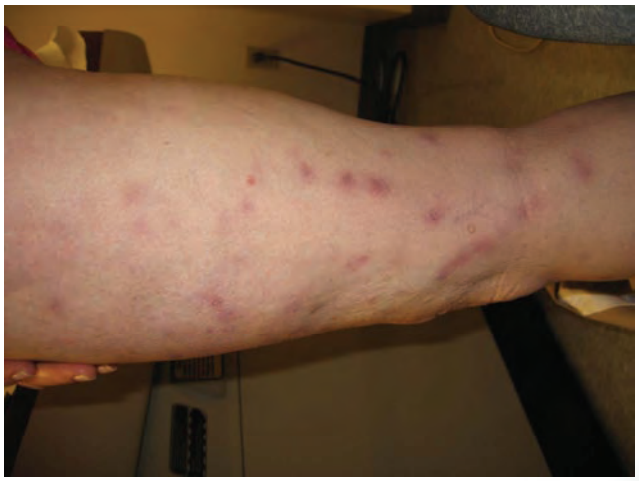
- 60-year-old female with advanced CLL begins injections of her thighs with alemtuzumab (Campath)
  - Neutrophil count rises
  - CD4 count drastically drops
- Prior to her injections, she had recurrent sinusitis and 1–2 cases of pneumonia per year over the last 5 years
- At the time of starting alemtuzumab, she was feeling relatively well with no fever, cough, or sinus complaints

CLL, chronic lymphocytic leukemia

If this patient was at your institution, would you include antifungal prophylaxis?

Clinical Case

Skin lesions develop (non painful, nodular, slightly pruritic)



Microsporidiosis

- 1000 species in 144 genera
- Multiple lines of evidence that Microsporidian are fungi.
  - Beta-tubulin analysis suggest sister group to the Zygomycota*
- Water contamination, zoonosis, auto infection
- Immunosuppression: AIDS and immunosuppressive drugs
- Treatment: albendazole

***** Keeling PJ, et al. *Fungal Genet Biol*. 2003;38:298-309.

Do you think antifungal prophylaxis could have prevented this infection?

Antifungal Prophylaxis: To Prevent or Not "The Principles"

- **Safety** **(Do no harm)**
- **Efficacy** **(Evidence-based data)**
- **Cost** **(Balance between IFD costs and drug acquisition costs)**
- **Consequence** **(It is life-threatening or disease management altering)**
- **Prevalence** **(10% rule)**
- **Resistance** **(Azole/echinocandin resistance always lurking)**

IFD, invasive fungal disease
Perfect JR. *Am J Med*. 1993;94:233-4.

Prophylaxis is Really to Prevent Invasive Fungal Infections and to Allow the Underlying Disease to be Adequately Managed

Three examples of evidence-based antifungal prophylaxis in high-risk patients:

(1) Patients with AML/MDS during neutropenia and bone marrow transplantation (Aspergillosis)

(2) Intensive Care Unit (Candidiasis)

(3) Advanced HIV infection and *Cryptococcus* infection (Cryptococcosis)

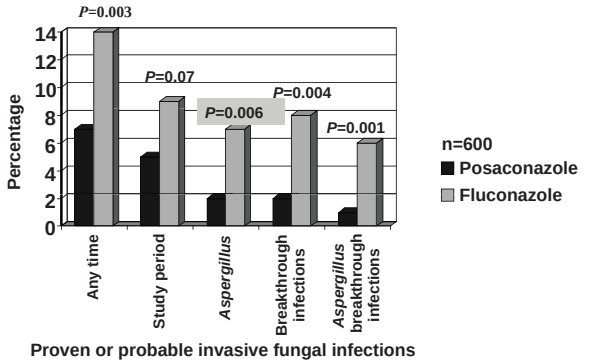
AML, acute myeloid leukemia; MDS, myelodysplastic syndrome

Bone Marrow Transplantation

- Landmark studies show fluconazole benefit of prophylaxis including long-term survival[1,2]
- In certain patients mould infections may matter (itraconazole vs. fluconazole)[3]
  - In graft-versus-host disease, aspergillosis does matter (Posaconazole Prevention)[4]
- If integrate biomarkers, there may be less distinction between fluconazole vs. voriconazole[5]
- Cost depends on incidence of disease[6]

1. Goodman JL, et al. *N Engl J Med*. 1992;326:845-51.
2. Slavin MA, et al. *J Infect Dis*. 1995;171:1545-52.
3. Marr KA, et al. *Blood*. 2004;1003:1527-1533.
4. Ullmann AJ, et al. *N Engl J Med*. 2007;356:335-347.
5. Wingard JR, et al. *Blood*. 2010;116: 5111-8.
6. Mauskopf J, et al. *Am J Health Syst Pharm*. 2013;70:1518-27.

Antifungal Prophylaxis in Allogeneic HSCT Recipients with GvHD



HSCT, hematopoietic stem cell transplantation; GvHD, graft-versus-host disease

Ullmann AJ, et al. *N Engl J Med*. 2007;356:335-47.

Micafungin vs. Fluconazole: Prophylaxis in HSCT

Randomized, double-blind, comparative study (N = 882)

Result, % (n)	Micafungin (n = 425)	Fluconazole (n = 457)	*P* Value
Overall success rate*	80.0% (340)	73.5% (336)	.03
Breakthrough infections	2% (7)	2% (11)	.481
Breakthrough aspergillosis	<1% (1)	2% (7)	.071
Use of empiric therapy	15.1% (64)	21.4% (98)	.024
Death	4.2% (18)	5.7% (26)	.322
Treatment-related adverse event	15.1%	16.9%	NS

*Defined as the absence of proven, probable, or suspected IFI during the study period.

van Burik JA, et al. *Clin Infect Dis*. 2004;39:1407-1416.

Duke Allogeneic HSCT – Current Fungal Prophylaxis Protocol

Risk Group	Fungal Prophylactic Regimen
Non-myeloablative MRD, MMRD, MUD and UCT	Voriconazole 200 mg BID through day +100
Myeloablative MRD, MMRD, URD and UCR	Voriconazole 200 mg BID through day +100
Graft-versus-host disease	Posaconazole 200 mg TID (alternative: voriconazole + inhaled ABLC)

MMRD , mismatched related donor; MRD, matched related donor; MUD, matched unrelated donor; UCT, umbilical cord transplant; ABLC, amphotericin B lipid complex.

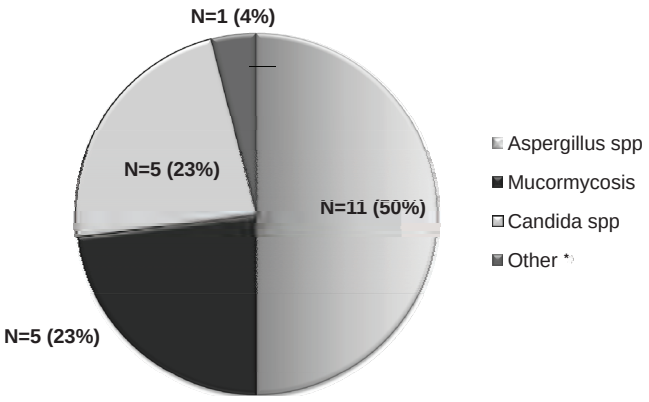
Duke Retrospective Evaluation: Results

- 280 allogeneic HSCT episodes occurred in 257 patients (2009–2011)
- Proven/probable IFI identified in 22 transplant episodes (7.9%)
  - 14/22 (64%) proven
  - 8/22 (36%) probable
- Median onset of IFI post-HSCT was 95 days (range 1–980 days)

Patient Characteristics at IFI Onset

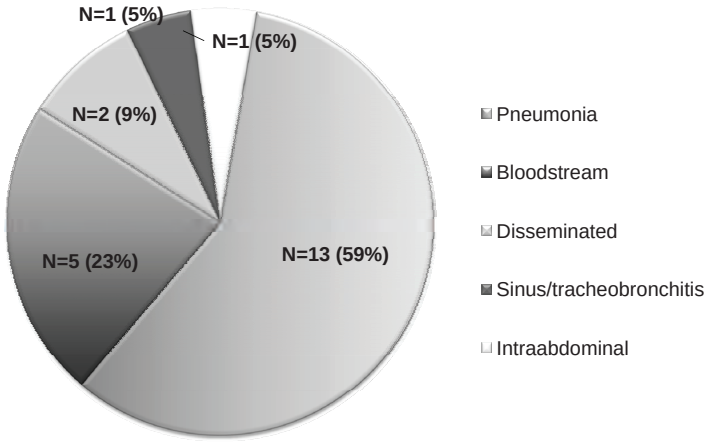
Characteristic	n=22
Median age, years (range)	54 (33–73)
Male gender, n (%)	9 (41)
Graft-versus-host disease, n (%)	14 (64)
Neutropenic, n (%)	6 (27)
Underlying diagnosis	
• Aplastic anemia	1 (5)
• Acute lymphoblastic leukemia	3 (14)
• Acute myelogenous leukemia	8 (36)
• Chronic myelogenous leukemia	1 (5)
• Hodgkin lymphoma	1 (5)
• Myelodysplastic syndrome	2 (9)
• Multiple myeloma	1 (5)
• Non-Hodgkin lymphoma	3 (14)
• T-cell leukemia/lymphoma	2 (9)

Fungal Pathogens Associated with IFIs

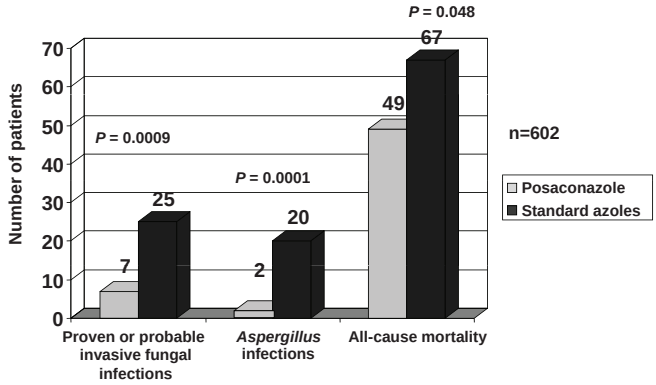


***Rhodotorula* spp.**

Types of IFIs



Antifungal Prophylaxis in Neutropenic Patients with AML or MDS



Cornely OA, et al. *N Engl J Med*. 2007;356:348-359.

Duke Data: High Risk AML/MDS

- Kung et al
  - Retrospective, single center, DUMC data
  - January 2003–December 2010
  - *N* = 130 (65 posaconazole [P] / 65 fluconazole [F])
  - Inclusion
    - AML/MDS receiving first induction or re-induction chemo
  - Exclusion
    - Receiving other antifungals or prior IFI one month prior to initiation of chemotherapy

Kung et al. Presented at the 52nd ICAAC, 2012.

Duke Data: Results

- Primary Endpoint
  - Proven/probable/possible IFIs: **P superior to F** (9.2% vs 27%, p=0.012)
  - Proven/probable IFIs: **P superior to F** (0% vs 10.8%, p=0.0013)
- Secondary Endpoint
  - 100-day mortality: P = F (21.5% vs 24.6%, p=0.68)
  - Overall mortality: P = F (50.8% vs 50.8%)
- Multiple logistic regression model found fluconazole prophylaxis and duration of neutropenia to be 2 significant predictors of breakthrough IFI

Kung et al. Presented at the 52nd ICAAC, 2012.

Duke Retrospective Evaluation, Non-HSCT Acute Leukemia/MDS

- Aim: characterize the primary pathogens and types of IFIs occurring in patients with AML/MDS
- Study population: patients with AML and MDS
- Methods
  - Retrospective review
  - Patients identified via inpatient encounters in DEDUCE utilizing specific ICD-9 codes for leukemia and MDS
  - January 1, 2009 through July 22, 2012
  - EORTC/MSG* definitions utilized for identification of IFI

*De Pauw B, et al. *Clin Infect Dis*. 2008;46(12):1813-21.

Retrospective Evaluation: Results

- Ultimately identified 325 patients
- 19 IFIs occurring in 18 patients with either AML or MDS (12 proven, 7 probable) (5.9%)
- Median onset of IFI was 22 days (range 4–207)

Retrospective Evaluation: Results

Characteristic	n=18
Median age, years (range)	64 (24–77)
Male gender, n (%)	11 (61)
AML, n (%)	13 (72)
MDS, n (%)	5 (28)
Induction chemotherapy, n (%)	3 (17)
Re-induction chemotherapy, n (%)	10 (56)
Other therapy, n (%)	5 (28)
Neutropenic, n (%)	14 (78)
Receiving prophylaxis, n (%)	8 (44)
-Fluconazole, n (%)	7 (39)
-Posaconazole, n (%)	1 (5)

Prophylaxis Needs Focus

- Genetic susceptibility[1]
- Integrative pre-emptive strategies with biomarkers[2,3,4]
- Maybe we could use these biomarkers to stop antifungals (negative predictive value) as well as start them early

1. Georgiadou SP, et al. *Bone Marrow Transplant*. 2013;48:141-3.
2. Cordonnier C, et al. *Haematalogica*. 2010;95:1762-8.
3. Maertens J, et al. *Clin Infect Dis*. 2005;41:1242-50.
4. Wingard JR, et al. *Blood*. 2010;116:5111-8.

Genetic Susceptibility for Aspergillosis and Candidiasis

- Prediction of risk for prophylaxis and pre-emptive strategies
- Progress is being made:
  - Aspergillosis
    - Plasminogen allele influences susceptibility to invasive aspergillosis in mice and humans[1]
    - Toll-like receptor 4 polymorphisms (TLRs)[2]
  - Candidiasis
    - Dectin1/CARD9,[3] CASPASE-12,[4] cytokine genes,[5] TLRs[6]

1. Zaas AK, et al. *PloS Genet*. 2008;4:e1000101.
2. Bochud PY, et al. *N Engl J Med*. 2008;359:1766-1777.
3. Rosentul DC, et al. *J Infect Dis*. 2011;204:1138-1145.
4. Rosentul DC, et al. *Eur J Clin Microbiol Infect Dis*. 2012;31:277-280.
5. Johnson MD, et al. *Clin Infect Dis*. 2012;54:502-510.
6. Plantiga TS, et al. *J Infect Dis*. 2012;205:934-943.

Zygomycosis Superinfections on Voriconazole

- More than 20 cases reported to date[1-9]
  - Majority of patients
    - HSCT recipients receiving corticosteroids for GvHD *and*
    - Voriconazole prophylaxis
- Is there a correlation?
  - Cancer patients[10]
    - 27 patients with zygomycosis and 54 patients with invasive aspergillosis
    - Of 27 patients, only 15 received voriconazole
    - Only 15 met criteria for definite infection
  - Transplant patients[11]
    - 393 transplant recipients
    - Voriconazole more frequently associated with breakthrough infections due to Zygomycetes of *Fusarium* rather than *Aspergillus* (OR=24.0)

It is the voriconazole effect on the mould[12]

1. Chayakulkeeree M, et al. *Eur J Clin Microbiol Infect Dis*. 2006;25:215-29.
2. Ritz N, et al. *Eur J Pediatr*. 2005;164:231-5.
3. Kobayashi K, et al. *Haematology*. 2004;89:ECR42.
4. Marty FM, et al. *N Engl J Med*. 2004; 350:950-2.
5. Oren I, et al. *Clin Infect Dis*. 2005;40:770-1.
6. Vigorouz S, et al. *Clin Infect Dis*. 2005;40:e35-e37.
7. Siwek GT, et al. *Clin Infect Dis*. 2004;39:584-7.
8. Mattner F, t al. Scand J Infect Dis. 2004;36:312-4.
9. Imhof A, et al. *Clin Infect Dis*. 2004;39:743-6.
10. Kontoyiannis DP, et al. *J Infect Dis*. 2005;191:1350-60.
11. Park BJ, et al. 44th ICAAC (Abstract M-666-2004).
12. Lewis RE, et al. *Virulence*. 2011;2:348-55.

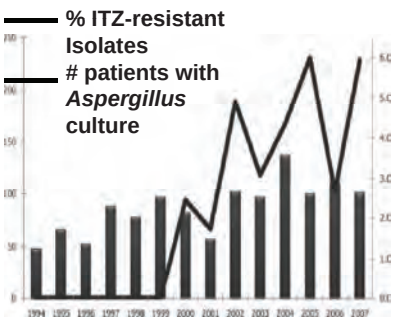
Fluconazole Resistance Among *Candida* Blood Isolates

Program	Years	# Tested	% Fluconazole Resistant			
			C. albicans	*C. glabrata*	*C. parapsilosis*	*C. tropicalis*
CDC	92-93	394	1	14	0	2
CDC	98-00	944	1	10	0	6
Quebec	94-98	442	1	9	0	0
SENTRY	97-00	2,047	1	7	0	1
EIEIO	98-01	254	0	10	0	0
ARTEMIS	01-02	3,724	1	9	1	1

At Duke, fluconazole-resistant strains: *C. glabrata* (50%); *C. tropicalis* (16%); *C. albicans* (12%); *C. parapsilosis* (6%).

Adapted from Pfaller MA, et al. *Clin Microbiol Rev*. 2006;19(2):435-447.

Itraconazole (ITZ) Resistance in *A. fumigatus* Isolates



- ITZ-resistant isolates were found in 32 of 1,219 patients with invasive aspergillosis over a 14-year period[1]
- ITZ-resistant isolates also showed elevated minimum inhibitory concentrations of voriconazole, ravuconazole, and posaconazole[1]
- Recent USA (TRANSNET Data): 96% azole susceptible with *A. calidoustus* most resistant[2]
- Prophylaxis (Fungicides) in the environment associated with voriconazole-resistant aspergillosis[3]

1. Snelders E, et al. *PLoS Med*. 2008;5(11):e219.
2. Baddley JW, et al. *J Clin Microbiol*. 2009;47:3271-75.
3. van der Linden JW, et al. *Clin Infect Dis*. 2013;57:513-20.

Echinocandin Resistance is Not a Novelty

- Review of 293 episodes of *C. glabrata* bloodstream infection from 2001–2010
- Resistance to echinocandins increased from 4.9% to 12.3%
- Among 78 fluconazole-resistant isolates, 14.1% were resistant to echinocandin
- 7.9% harbored a FKS mutation and were related to prior echinocandin therapy
- 80% (8/10) of patients infected with FKS mutants exhibiting intermediate/resistant MICs to echinocandins failed to respond to echinocandin treatment
- Price to pay for echinocandin resistance, but not much in immunocompromised hosts*

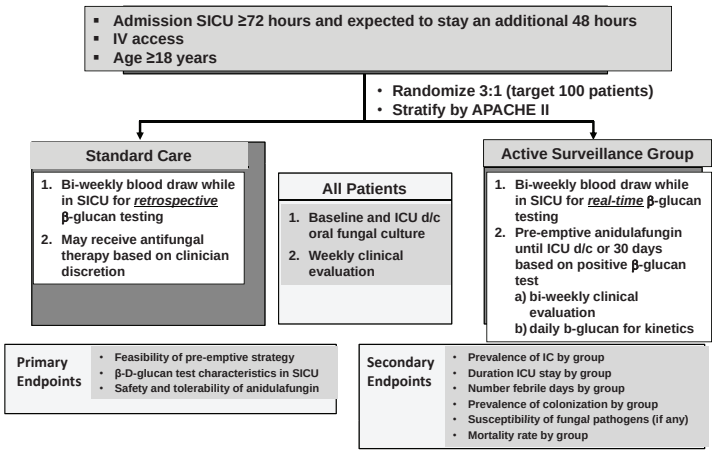
Alexander BD, et al. *Clin Infect Dis*. 2013;56:1724-32.
***Ben-Ami R, Kontoyiannis DP. *Virulence*. 2012;3:95-7.**

Prophylaxis in the Intensive Care Unit

- Double-blind, placebo-controlled study of caspofungin
- 222 adults included after screening 16,000 patients
- Incidence of proven/probable invasive candidiasis, placebo vs. caspofungin, was 16.7% vs. 9.8% (p=0.14)
- With a pre-emptive approach based on β-glucan, the number of proven/probable infections was significantly reduced
- No difference in secondary endpoints of mortality, initiation of antifungals, or length of stay
- Bottom line: We need to use our biomarkers!

Presented at the Society for Healthcare Epidemiology of America (SHEA) 2011 Annual Scientific Meeting, Dallas, TX. Abstract LB-15.

Strategy Concept: Study Design



SICU, surgical ICU; IC, invasive candidiasis

Results of Beta-D-Glucan-Driven ICU Strategy

- 64 study pts/>1000 pts screened
- 47 pts (pre-emptive); 17 pts (empiric)
- Sensitivity 100%; specificity 75%; PPV 30%; NPV 100% with 2 sequential positive tests
- Antifungal drugs had significant impact on lower BDG levels; rate of decline steeper with treatment
- Pre-emptive arm: 7.3% IFIs
- Empiric arm: 17.6% IFIs

***P*= 0.47**

- False positive rate 23% with 80 pg/mL x 2
- 4 pts (8.5%) receiving antifungal therapy despite negative BDG
- This is a pilot study; needs a large multicenter study

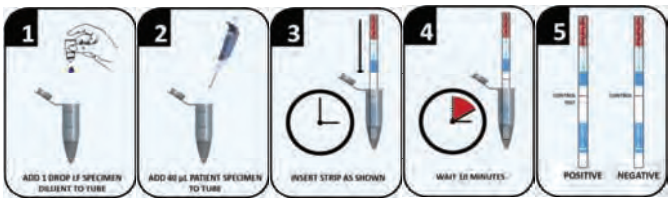
Hanson KE, et al. *PloS One.* 2012;7(8):e42282.

Prophylaxis for Cryptococcosis

- It works but has the landscape changed for another strategy??
- Fluconazole and itraconazole reduce frequency of primary cryptococcosis[1,2] but IDSA Guidelines[3] do not recommend it (relative infrequency, lack of survival benefit, possible drug- interactions, creation of drug-resistant strains, compliance, and costs)
- Prophylaxis for cryptococcal meningitis works in resource-limited settings[4,5,6] **BUT**
- Better Strategy: Pre-emptive strategy with cryptococcal antigen screening by Lateral Flow Assay[7,8]

1. Powderly WG, et al. *N Engl J Med*. 1995;332:700-5.
2. McKinsey DS, et al *Clin Infect Dis*. 1999;28:1049-56.
3. Perfect JR, et al. *Clin Infect Dis*. 2010;50:291-322.
4. Chetchotisakd P, et al. *HIV Med*. 2004;5:140-3.
5. Parkes-Ratanshi R, et al. *Lancet Infect Dis*. 2011;11:933-41.
6. Chang LW, et al *Cochrane Database Syst Rev*. 2005; CD004773.
7. Meya DB, et al. *Clin Infect Dis*. 2010;51:448-55.
8. Klausner JD, et al. *Lancet Infect Dis*. 2012;12:431-2.

CrAg Lateral Flow Assay: Method



A simple, cheap assay: could save lives and costs
(A great translational merger of basic science and the business world)

CrAG, cryptococcal antigen
Slide courtesy of Sean Bauman, PhD. Immuno-Mycologics, Inc. (IMMY)

The Rest of the Story!

- Treated with albendazole for 4 weeks with some improvement and eventually cleared
- 3 months later diagnosed with invasive sinusitis/osteomyelitis with *Fusarium*/*Aspergillus* treated with voriconazole
- 3 months later presents with chronic pneumonia

  (resected lesion in R lung and attempted to clean out pulmonary artery with *Rhizopus*)
- Died of uncontrolled CLL with mucormycosis and MDR *Stenotrophomonas*

Summary

"Invasive Fungal Disease (IFD) do not occur in a vacuum. They are associated with serious underlying diseases. We must spend our energies on controlling these underlying diseases and if that means preventing a complication like IFD than so be it but use the six general principles as your guide"

IFI Practice Case

Optimizing Outcomes with Appropriate Antifungal Use

Back to IFI Practice Case

ELIZABETH S. DODDS ASHLEY
PHARMD, MHS, FCCP, BCPS

Associate Director of Clinical Pharmacy Service
Department of Pharmacy at the University of Rochester Medical Center
Rochester, NY

- An 83-year-old man presents with primary complaint of cough for 3 months, CT scan notable for pneumothorax, new pleural effusion and pulmonary nodules
  - PMH:
    - Rheumatoid arthritis – treated with leflunamide and rituximab
    - 2009 – treated for actinomycosis
- Admitted for pigtail catheter placement and cultures of pleural fluid revealed *Aspergillus fumigatus*
- Therapy begun with voriconazole 400 mg po bid × 2 doses followed by 200 mg po bid

- At day 7 of therapy, the following laboratory values are available:
  - Serum creatinine: 0.62 mg/dL
  - AST/ALT: 26/20 IU/L
  - Total bilirubin: 0.2 mg/dL
  - Voriconazole: 9 mcg/mL
- Patient denies reports of any visual disturbances or hallucinations

What is the best course of action for this patient?

Getting Antifungal Therapy Right-Stewarding a Precious Resource

- New antifungal stewardship programs have begun to emerge
  - Review of all new antifungal prescriptions or those subject to review
  - Guideline development for treatment, diagnostics and monitoring
  - Implementation of an antifungal management team
  - Mandatory ID consults for all patients with IFI
  - Weekly rounds in high-risk areas for appropriate prophylaxis

Reduction in Overall Antifungal Use

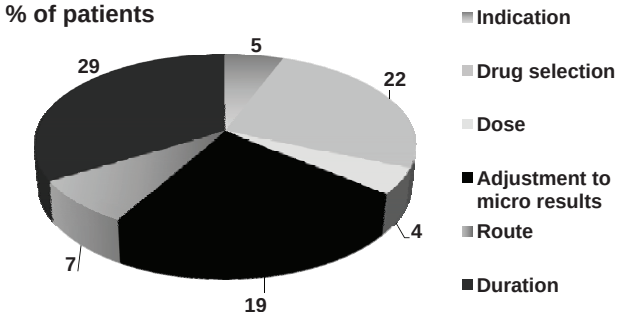
	Dispensed DDD/1,000 patient days			Cost of antifungal treatment		
	Pre-intervention	Intervention	Change (%)	Pre-intervention	Intervention	Change (%)
Voriconazole IV	246.14	168.77	-31.4	$331,210.11	$224,239.08	-32.2
Voriconazole PO	666.66	721.82	+8.2	$231,997.30	$256,460.88	+10.5
Caspofungin	822.70	656.82	-20.2	$1,863,765.88	$1,467,699.48	-21.2
Lipid amphotericin B	1238.72	1411.06	+13.9	$702,414.05	$810,306.12	+12.5
Global				$3,129,387.34	$2,758,705.56	-11.8

Overall savings: $370,681.78

Lopez-Medrano F, et al. *Clin Microbiol Infect.* 2013;19:56-61.

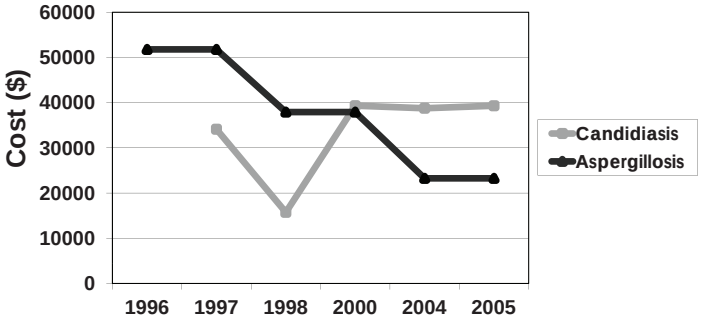
Stewardship – Targeted Interventions

A review of an antifungal stewardship program after 453 patient reviews



Valerio M, et al. Poster presentation at the 53rd Annual ICAAC Conference. Denver, CO, September 10-13, 2013.

Changing Costs with Time



Wilson LS, et al. *Value in Health.* 2002;5:26-34.
Zaoutis TE, et al. *Clin Infect Dis.* 2005;41:1232-9.
Rentz AM, et al. *Clin Infect Dis.* 1998;27:781-88.
Dodds Ashley E, et al. *Pharmacother.* 2012;32:890-901.

Contributors to Cost

Category	IFI group cost (n=200)	Control group cost (n=200)	Attributable IFI cost	% difference
Pharmacy	$22,030	$11,239	$10,791	37%
Antifungals	$4524	$528	$3996	14%
Other meds	$17,506	$10,711	$6,795	23%
Non-pharmacy	$49,801	$31,367	$18,434	63%
Ward	$12,952	$6,803	$6,149	21%
Laboratory	$11,872	$6,679	$5,193	18%
Professional fee	$2,755	$2,247	$509	2%
Radiology	$4,402	$2,386	$2,016	7%
Procedures	$5,522	$5,290	$232	1%
Other	$12,298	$7,964	$4,334	15%
Total	$71,831	$42,606	$29,225	

Dodds Ashley E, et al. *Pharmacother.* 2012;32:890-901.

Inappropriate Therapy Can Cost More

Outcome	Appropriate Therapy Group (n=22)	Inappropriate Therapy Group (n=145)	p Value
Mortality No. (%)	6 (27.3)	38 (26.2)	>0.999
LOS (d)	7.3	15.2	<0.001
Post-culture LOS (d)	7.0	10.4	0.037
Total cost ($)	15,832	33,021	<0.001

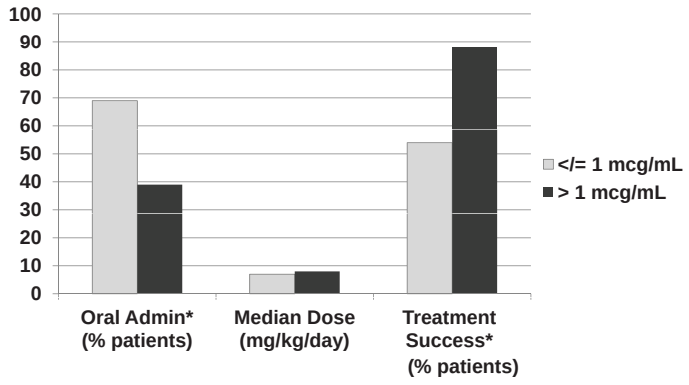
Arnold HM, et al. *Pharmacotherapy.* 2010;30:361-8.

Antifungal Stewardship Outcomes

- 6-year program with antifungal management team
  - Significant increase in chest CT for diagnosis
  - Trend toward less combination antifungal therapy
  - Significant increase in use of fluconazole as first-line for candidemia
  - Stable antifungal use over the study period
  - Drive toward more serum drug concentration monitoring

Mondain V, et al. *Infection.* 2013;41:621-8.

Voriconazole Concentrations – Outcomes



Pascual A, et al. *Clin Infect Dis.* 2008;46:201-11.

*= statistically significant (p≤0.05)

Posaconazole Concentrations Outcomes

	Study #1		Study #2	
Quartile	C_{avg} (ng/mL)	Clinical failure	C_{avg} (ng/mL)	Clinical failure
1st	21.5–557 (289)	44% (28/63)	89.7–322 (206)	55% (23/53)
2nd	557–915 (736)	21% (13/63)	322–490 (406)	37% (20/54)
3rd	915–1,563 (1,239)	18% (11/63)	490–733.5 (612)	46% (25/54)
4th	1,563–3,650 (2,607)	18% (11/63)	733.5–2,200 (1,467)	28% (15/54)

Jang SH, et al. *Clin Pharmacol Ther.* 2010;88:115-9.

Antifungal Drug Concentration Monitoring

Evidence For Monitoring	Evidence Against Monitoring
Large and unpredictable variability of blood concentrations	Real-time measurements not routinely available
Multiple factors influencing drug absorption, distribution and elimination, including age, genetic background, compliance and gastrointestinal function, co-medication, and liver and/or renal function	Target blood concentrations not established; lacking data from prospective controlled studies systematically exploring efficacy and toxicity associated with drug over- or under-dosing
Emergence of fungal pathogens with decreased susceptibility requiring optimal adjustment of drug exposure	Drug blood concentration might not reflect exposure and efficacy in infected tissues
Multiple clinical reports of failure associated with drug under-dosing and toxicity associated with drug over-dosing	

Andes D, et al. *Antimicrob Agents Chemother.* 2009;53:24-34.

Target Drug Concentrations

Drug	Indication	Time of first measurement (hr)	Target blood concentration (mcg/mL)	
			Efficacy	Safety
Flucytosine	Routine during first week of therapy, renal insufficiency, lacking response to therapy	3–5	Peak >20	Peak <50
Itraconazole	Routine during first week of therapy, lacking response, gastrointestinal dysfunction, co-medication	4–7	Prophy: trough of >0.5 Therapy: trough of >1 to 2	N/A
Voriconazole	Lacking response; gastrointestinal dysfunction, co-medication, IV to PO conversion, severe hepatopathy, unexplained neurological symptoms	4–7	Prophy: trough of >0.5 Therapy: trough of >1 to 2	Trough of <6
Posaconazole	Lacking response, gastrointestinal dysfunction, therapy with proton pump inhibitors, co-medication	4–7	Prophy: trough of >0.5 Therapy: trough of >0.5 to 1.5	N/A

Andes D, et al. *Antimicrob Agents Chemother.* 2009;53:24-34.

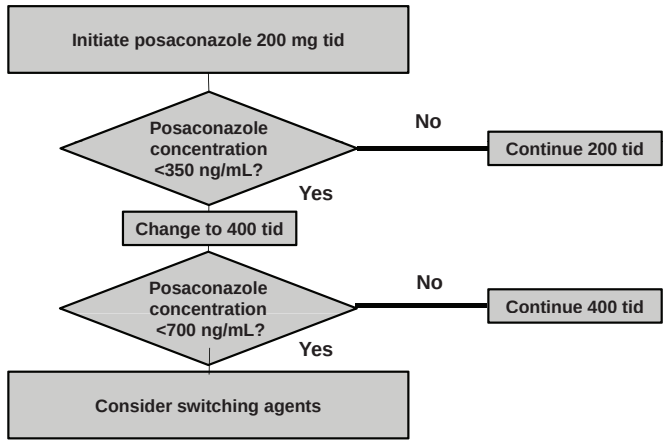
Responding to Concentrations – Voriconazole

Empiric dose adjustment algorithm

Voriconazole serum concentration	Dose Adjustment
≤1 mcg/mL AND lack of response	50% dose increase
1–5.5 mcg/mL	No change
>5.5 mcg/mL	d/c therapy if evidence of toxicity

Pascual A, et al. *Clin Infect Dis.* 2008;46:201-11.

Proposed Dose-Adjustment Algorithm



Jang SH, et al. *Clin Pharmacol and Ther.* 2010;88:115-9.

- **A review of concomitant medications revealed the following:**

•	psyllium	1 packet	Oral	Daily
•	finasteride	5 mg	Oral	Daily
•	docusate sodium	100 mg	Oral	Q12H SCH
•	guaiFENesin	1,200 mg	Oral	Q12H SCH
•	voriconazole	200 mg	Oral	Q12H SCH
•	heparin (porcine)	5,000	SC	Q8H
•	aspirin	81 mg	Oral	Daily
•	calcium-vitamin D	1 tablet	Oral	Q12H SCH
•	cholecalciferol	1,000 U	Oral	Daily
•	leflunomide	10 mg	Oral	Daily
•	pantoprazole	40 mg	Oral	QAM
•	multi-vitamin	1 tablet	Oral	Daily
•	metoprolol	50 mg	Oral	Daily
•	lovastatin	20 mg	Oral	Nightly

The voriconazole dose was decreased to 200 mg po q48 hours

A repeat voriconazole concentration was obtained 10 days after the dose adjustment

What do you think the concentration was?

Conclusions

- Optimizing antifungal therapy requires careful consideration of:
  - Appropriate agent selection
  - Drug- drug interactions that may decrease efficacy or increase toxicity
  - Appropriate application of therapeutic drug monitoring