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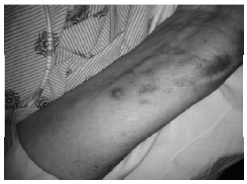
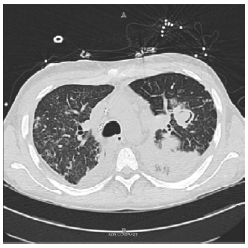
Major IFI in Heme Malignancy Patients

- Invasive candidiasis
  - Bloodstream
  - Tissue
- Invasive pulmonary mould infections
  - Aspergillosis, mucormycosis, fusariosis, and others





GAFFI Estimates

Burden of common life-threatening fungal infections

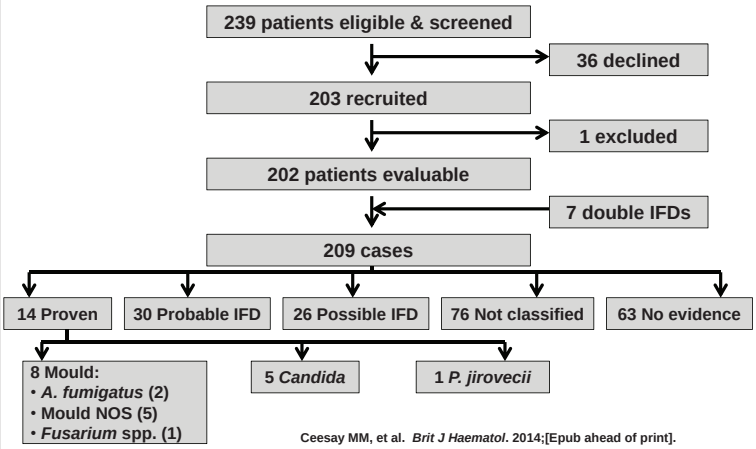
Fungal Infection	Case fatality rate	Estimated deaths	Comments
Cryptococcal meningitis	15-20% USA >50% developing world	600,000	CDC estimate
Pneumocystis pneumonia	~15% in AIDS ~50% non-AIDS	>80,000	Most cases in Africa not diagnosed and 100% mortality
Invasive aspergilosis	~50% mortality in developed world if treated	>100,000	Many missed diagnoses globally
Candida bloodstream infection	~40% mortality treated	>120,000	
Chronic pulmonary aspergilosis	~15% mortality in developed world	>450,000	Under-diagnosed and mistaken for tuberculosis
Severe asthma with fungal sensitisation (SAFS)	<1% but no good figures	~100,000 asthma deaths - ~50% related to SAFS	Uncertain
Total		>1,350,000	Probably a significant underestimate

Underestimates of Disease

- Diagnostic deficiencies
- Differences in diagnostic utilization
- Recent UK study: 203 heme patients followed with strict diagnostic algorithm
  - CT pre-treatment
  - 2/week serum galactomannan
  - Beta-D-glucan with suspicion
  - Tissue diagnoses

Ceesay MM, et al. *Brit J Haematol*. 2014;[Epub ahead of print].

Burden



Ceesay MM, et al. *Brit J Haematol*. 2014;[Epub ahead of print].

Diagnostic Test Impact

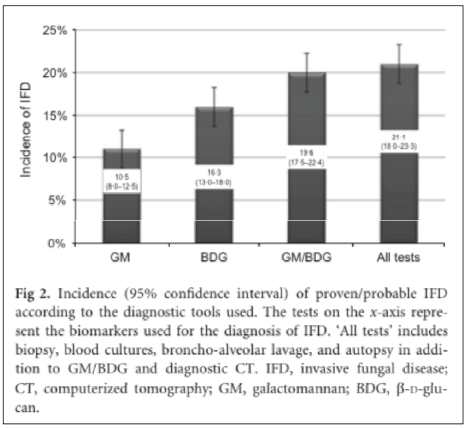
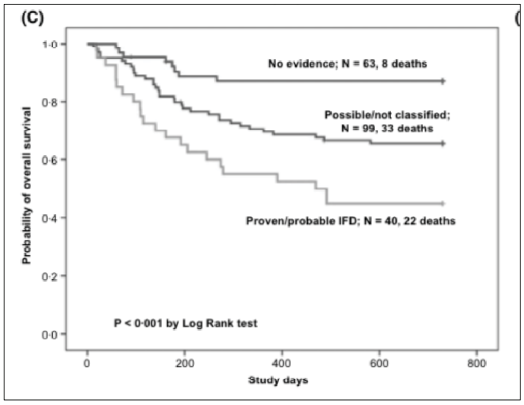


Fig 2. Incidence (95% confidence interval) of proven/probable IFD according to the diagnostic tools used. The tests on the *x*-axis represent the biomarkers used for the diagnosis of IFD. 'All tests' includes biopsy, blood cultures, broncho-alveolar lavage, and autopsy in addition to GM/BDG and diagnostic CT. IFD, invasive fungal disease; CT, computerized tomography; GM, galactomannan; BDG, β-D-glucan.

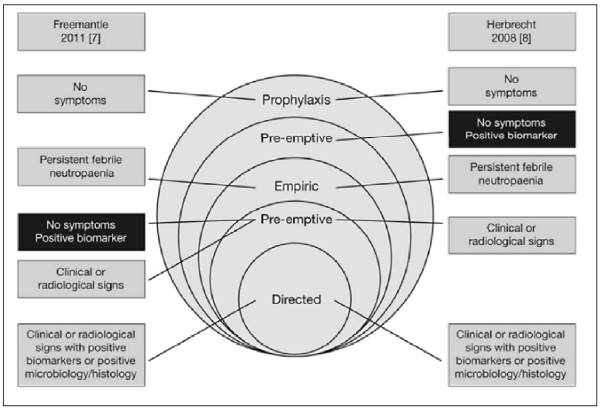
Ceesay MM, et al. *Brit J Haematol*. 2014;[Epub ahead of print].

Outcome



Ceesay MM, et al. *Brit J Haematol*. 2014;[Epub ahead of print].

What's the Cost of Disease vs. Fear?



Drgona L, et al. *Eur J Clin Microbiol Infect Dis*. 2014;33:7–21.

Significance of IFI

- High prevalence (host dependent)
- High morbidity
- High mortality
- Lack of diagnostics drive "fear"-based preventative therapies
  - Antifungal complications and costs

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Case #1

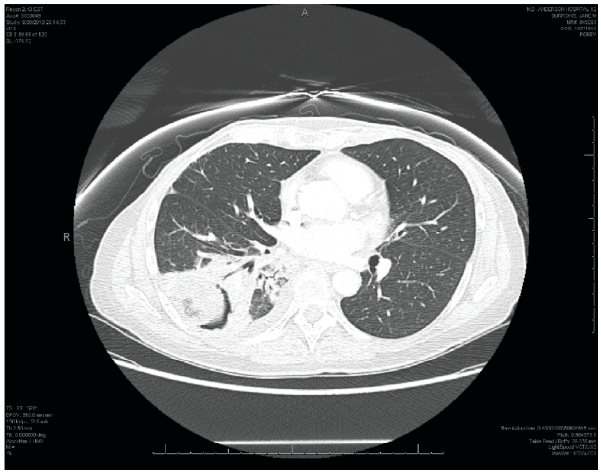
- 55-yo female with history of breast cancer s/p radiation and chemotherapy, now with treatment-related AML.
- She has recently undergone myeloablative chemotherapy, and has now completed her second round of consolidation therapy.
- She reports fatigue, malaise, fever and right-sided pleuritic chest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

Case #1

- Vital Signs: T 38^{o}C; HR 85; BP 123/64; RR 16; Sats 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

Case #1

- 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
- CT chest reveals the following…



Case #1

- Serum *Aspergillus* galactomanan **2.51**
- Bronchoscopy – bloody secretions in right mainstem bronchus. BAL GM **1.01**
- Pathology:
  - Fungal hyphae consistent with *Aspergillus* species are present in GMS stain of BAL fluid

Question #1

How would you respond to this information?

1. Increase voriconazole to 4 mg/kg q12 hours, add an echinocandin (ECH)
2. Stop voriconazole, begin AmB and ECH
3. Stop voriconazole, begin posaconazole IV
4. Continue voriconazole, add AmB and ECH
5. Continue current therapy unchanged

Case #1

The patient was started on LFAmB 5 mg/kg plus micafungin 100 mg daily. She worsened clinically over the next 3 days, requiring increasing O_2. She remained neutropenic and there was concern regarding antifungal resistance.

Micro Data

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

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

Case #1 Follow-up

Based on the culture and susceptibility data, LFAmB was stopped, and patient was placed on voriconazole 4 mg/kg q12h plus micafungin 100 mg daily. She experienced a complete clinical response.

Resistance Among *Aspergillus* spp.

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

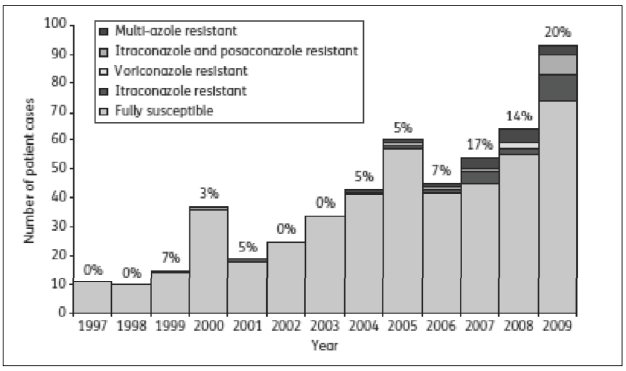
Brief History of Azole Resistance in *Aspergillus* spp.

- 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

Mechanisms of 'Epidemic' Resistance

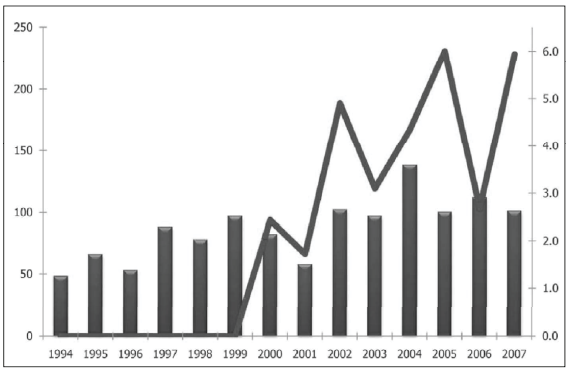
- Mutations of CYP51A gene (e.g., TR/L98H) are common to most azole-resistant isolates
- Resistance to itraconazole is most common, multiple azoles (e.g., itraconazole, voriconazole, posaconazole) less common
- Mechanism is less well understood, some component of increased efflux pump activity
- Echinocandin/polyene resistance less common and not well understood

The Rise of Azole Resistance in Northern England



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 by *A. fumigatus* During Azole Therapy

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.
***MICs are rounded to nearest upper two-fold dilution value for the Etest endpoints.**

		MIC (µg/ml)				
Isolate no.	**Week of collection**	**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

Arendrup MC, et al. *PLoS One*. 2010;5(4):e10080.

Azole Resistance by *A. fumigatus* in The Netherlands: Patient Characteristics

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.

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

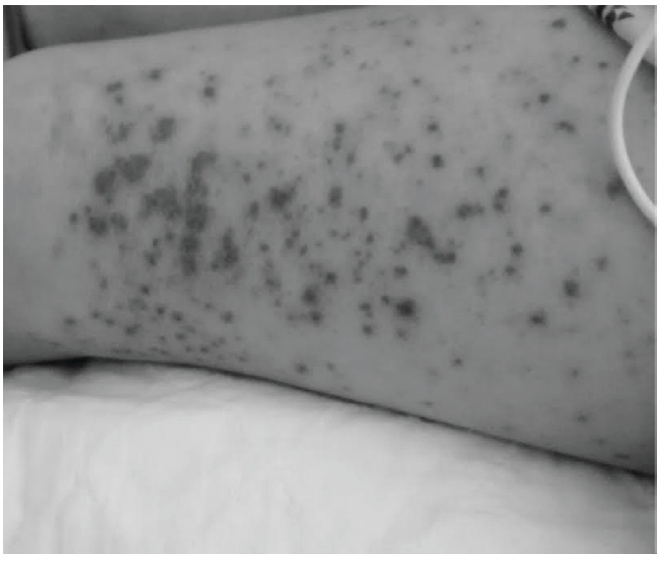
Case #2

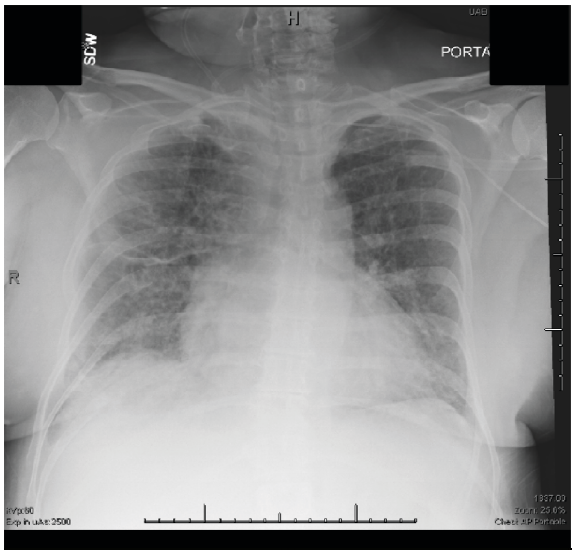
- 58-yo white female with history of MDS that subsequently transformed to AML, was admitted for induction chemotherapy with cytarabine and daunorubicin.
- Approximately 2 weeks post induction, she developed persistent fever and erythema around the Hickman catheter.
- Initial blood cultures were negative, and the catheter was removed.
- Two days later, she developed cough, hypoxia and rash on her legs.
- She was receiving vancomycin, cefepime, and fluconazole at this time.
- Laboratory results:
  - WBC: <500 cells/mm^3 ; Hemoglobin: 10 g/dL
  - Platelet count: 32,000/mm^3
  - Initial blood cultures are negative

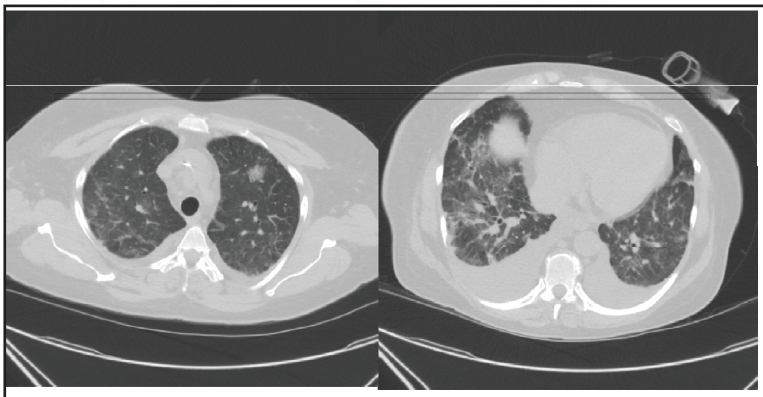
Physical Exam

Vitals: Temp 102.1°F; BP 81/60; HR 99; RR 18; Sats 96% on 4L

- **General**: Alert and oriented
- **HENT**: moist mucosa, clear oral cavity
- **Neck**: Supple, No JVD, No lymphadenopathy
- **Respiratory**: tachypneic, decreased breath sounds on right with fine crackles
- **Cardiovascular**: tachycardic, no murmurs
- **Gastrointestinal**: Soft, NT/ND, Normal bowel sounds
- **Skin**: Prior Hickman site with erythema, induration and fluctuance; reddish/violet non-blanching papules bilaterally on both thighs
- **Neurologic**: Alert, oriented, no focal defects







CT interpretation: There are diffuse nodular and ill-defined ground glass opacities throughout both lungs, most prominent in the bilateral lung bases. Multiple prominent bilateral hilar and mediastinal lymph nodes are present which are likely reactive. There are small right greater than left pleural effusions.

Question #2

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

1. Continue fluconazole, but increase to 800 mg/d
2. Begin voriconazole
3. Begin an echinocandin (anidulafungin, micafungin, or caspofungin)
4. Begin lipid formulation of AmB (L-AmB)
5. Begin combination L-AmB and fluconazole

Case #2

- Blood cultures return positive for *Candida glabrata* (fluconazole MIC >64 mcg/mL).
- Skin biopsy obtained previously reveals inflammatory cells but no yeast forms.
- Micafungin is begun, neutropenia resolved, and patient recovered from this episode.

Candida species Susceptibility Profile

Candida spp.	AMB*	FLUC	ITRA	VOR	Echino-candins
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

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.

Voriconazole Susceptibility of Fluconazole-Resistant *Candida* Isolates

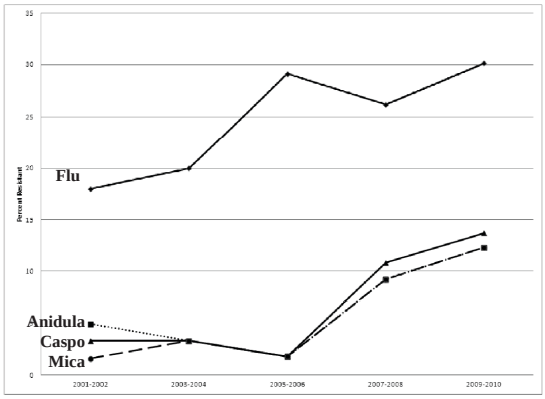
TABLE 4. *In vitro* susceptibilities of fluconazole-resistant isolates of *Candida* spp. to voriconazole as determined by CLSI disk diffusion testing[a]

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.

Temporal Trend in *C. glabrata* Resistance



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

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*

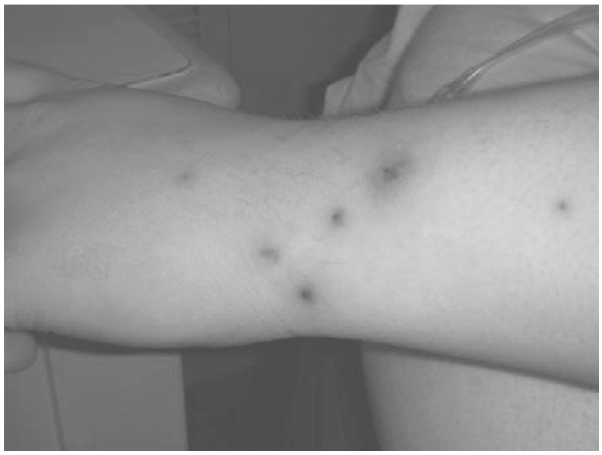
Pfaller MA, et al. *J Clin Microbiol*. 2007;45:1735-45.

Candida Resistance Summary

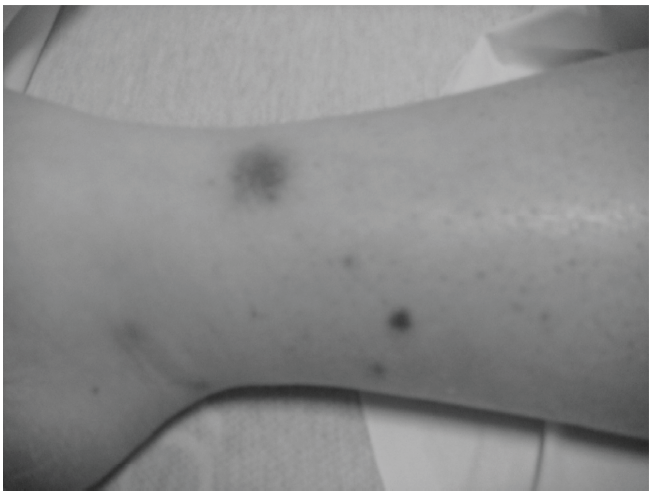
- Greatest concern is still azole-resistant *C. glabrata*
- Potential emergence of less common species with inherent or acquired azole resistance
- Most *Candida* remain highly susceptible to echinocandins, but emergence of acquired (*C. glabrata*) and intrinsic (*C. parapsilosis*) resistance is a concern.

Case #3

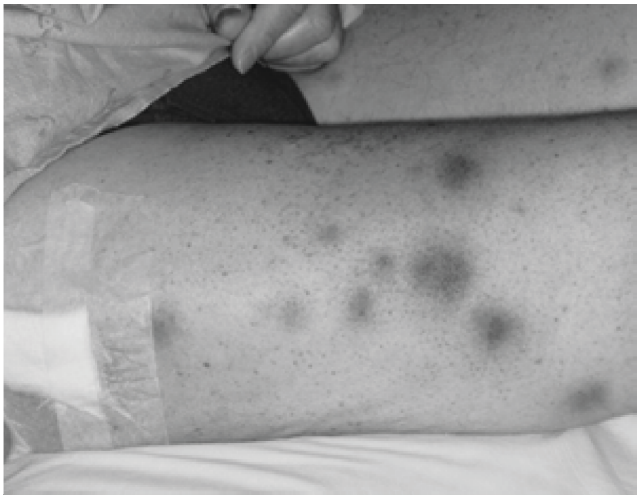
- 27-yo female with ALL with fever and neutropenia following induction chemotherapy.
- She is now day 32 with profound neutropenia and persistent fever.
- She has developed a slowly-evolving diffuse rash over the extremities and trunk.
- All cultures to date are negative.
- Current empiric antimicrobials are vancomycin, meropenem, flagyl and micafungin.



Left hand



Left leg just above the ankle



Question #3

What is the most likely cause of this rash and fever?

1. Candidiasis
2. Aspergillosis
3. Fusariosis
4. Mucormycosis
5. Meropenem

Case #3

- A skin biopsy is performed revealing fungal hyphae invading vasculature.
- Blood cultures are positive for a mold. Organism is identified as *Fusarium solani.*
- Voriconazole and LFAmB are initiated.
- Skin lesions continue to evolve, blood cultures become negative, but the patient continues the deteriorate clinically and dies without neutrophil recovery.

Fusariosis

- Disseminated fusariosis typically a late-occurring infection among patients with prolonged and profound neutropenia
- *Fusarium solani* and *F. oxysporum* most common, *F. verticulloides* and *F. proliferatum* rare
- Survival is uncommon with disseminated disease without neutrophil recovery
- Although voriconazole is approved for treatment of fusariosis, antifungal susceptibility testing among current drugs does not suggest a highly effective agent.

Other Fungi of Which You Should be Aware

- ***Mucorales* spp.** (often referred to as Zygomycetes): Most effective agent is AmB, not all species are susceptible to posaconazole
- ***Trichosporon* spp.** (esp. *T. asahii*): a yeast-like organism, causes disseminated disease with skin lesions. Usually AmB resistant, fluconazole and voriconazole (posaconazole?) are effective.

Other Fungi of Which You Should be Aware

- *Scedosporium apiospermum*
- *Scedosporium prolificans*
- *Paecilomyces* species
- Dematiaceous (pigmented) fungi: over 100 species cause human disease

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Prevention: A Key to Outcomes

- 1418 patients who received 1st allogeneic HCT FHCRC 1993–1997 vs. 2003–2007
  - Goal: evaluate significance of improvement in supportive care strategies
  - During later period, survival improved; lower hazard of death not preceded by relapse
    - Critical: prevention of CMV disease, GNR, fungal infections

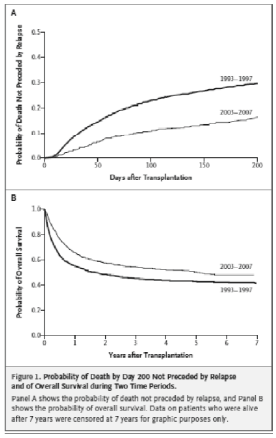
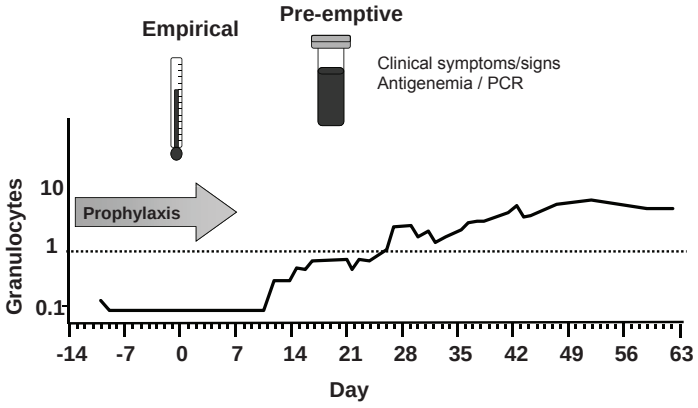


Figure 1. Probability of Death by Day 200 Not Preceded by Relapse and of Overall Survival during Two Time Periods.
Panel A shows the probability of death not preceded by relapse, and Panel B shows the probability of overall survival. Data on patients who were alive after 7 years were censored at 7 years for graphic purposes only.

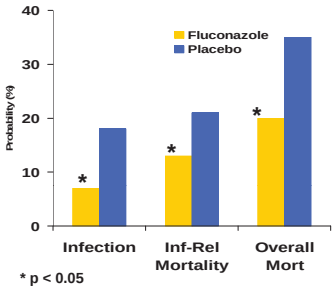
Gooley TA, et al. *N Engl J Med*. 2010;363:2091-101.

Prevention



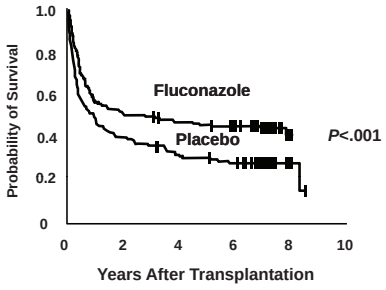
Fluconazole Prophylaxis

300 BMT patients randomized: 88% allografts
Fluconazole vs. Placebo→ conditioning - day 75



* p < 0.05

Slavin MA, et al. *J Infect Dis*. 1995;171:1545-52.



Marr KA, et al. *Blood*. 2000;96:2055-61.

Aspergillosis

- Aspergillosis 'emergence' in 1990's
  - Tripled incidence of documented disease
  - Previously considered to be a complication of neutropenia
  - Increase in late disease
    - Risks different during early and late periods
      - Early: Host, engraftment
      - Late: GVHD, PBSC, cellular engraftment

Marr KA, et al. *Blood*. 2002;100:4358-66.

How Do We Analyze Infection Epidemiology and Prevention?

- Epidemiology: Incidence, probability
- Prevention: Think about the mission…
  - Current methods: time to 1st clinical event or time to 1st composite event as primary study endpoints
  - Problem: Current analytic methods are not adequate to analyze the impact of recurrent events

    They do not characterize the effects of a treatment or intervention, or adequately evaluate quality of life after the 1st clinical event

Infections = Recurrent Events

- Misleading possibilities
  - Treatment reduces the risk of initial infection but is not effective in lowering risk for subsequent infections
    - Example: many antibacterial drugs
  - Treatment reduces the risk of one infection but increases the risk for others
    - Example: ganciclovir prophylaxis
  - Treatment reduces the risk of one infection but increases the risk for death
    - Example: itraconazole

Mould-Active Azoles

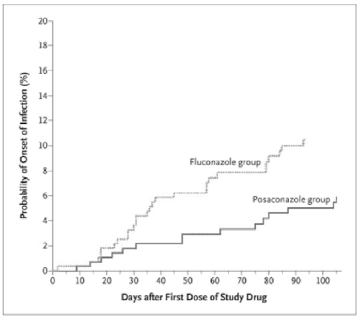
- Two randomized trials evaluating itraconazole solution in BMT patients
  - Both
    - Decreased invasive aspergillosis in itraconazole arm
    - Trend to worse survival in itraconazole arm
    - Toxicities of drug
      - GI tract toxicities
      - Drug interactions

Is decreased IA "caused" by informative censoring?

Winston DJ, et al. *Ann Intern Med*. 2003;138:705-713.
Marr KA, et al. *Blood*. 2004;103:1527-33.

Posaconazole

- FDA-approved for prophylaxis in allogeneic HSCT recipients with GVHD and AML
- Posaconazole vs. fluconazole (n=600 patients)
  - Drug with diagnosis of GVHD
  - Incident primary endpoint
- Solid oral tablet with better absorption, levels

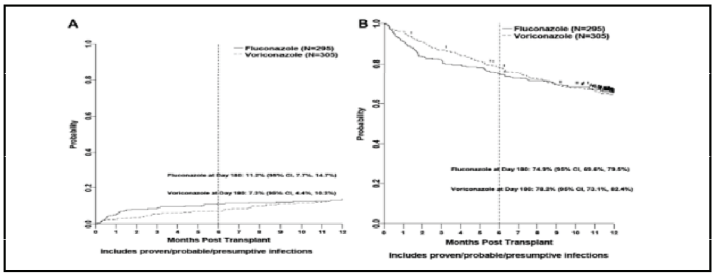


Ullmann AJ, et al. *N Engl J Med*. 2007;356:335-47.

Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation

John R. Wingard,[1] Shelly L. Carter,[2] Thomas J. Walsh,[3] Joanne Kurtzberg,[4] Trudy N. Small,[5] Lindsey R. Baden,[6] Iris D. Gerston,[2] Adam M. Mendizabal,[2] Helen L. Leather,[1] Dennis L. Confer,[7] Richard T. Maziarz,[8] Edward A. Stadtmauer,[9] Javier Bolaños-Meade,[10] Janice Brown,[11] John F. DiPersio,[12] Michael Boeckh,[13] and Kieren A. Marr,[10,13] for The Blood and Marrow Transplant Clinical Trials Network

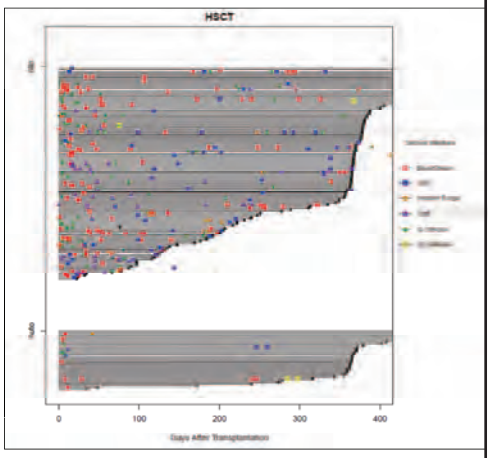
- Voriconazole vs. fluconazole at day 0
- Selected "moderate risk" allo BMT
- Primary endpoint- FFS at 6 mo.



Wingard JR, et al. *Blood*. 2010;116:5111-8.

Recurrent Events?

- 2012: Active consent with event capture, every 3 mo.
- Standardized definitions
- Different analytic methods

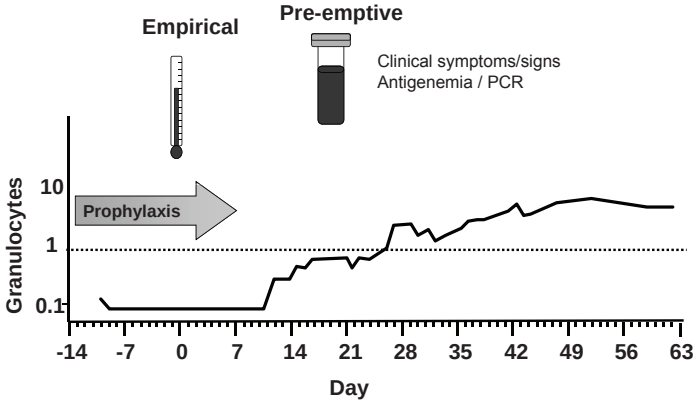


unpublished

My Take on IFI Prevention

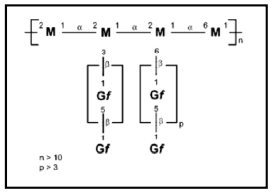
- Prophylaxis works
  - Candidiasis and aspergillosis
- Azoles are staple
- 2 mould-active drugs have unique advantages and limitations
  - Posaconazole
  - Voriconazole
- Variability in study design preclude valid comparisons
- Design does not adequately capture understanding of risks for *recurrent events*
- Risk – benefits are individual assessments
  - Need to better understand the "HIGH" risk group

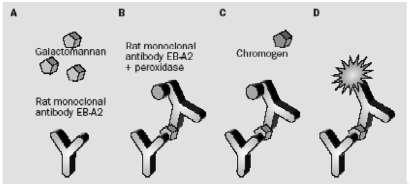
Prevention



Early Diagnostics: Galactomannan EIA

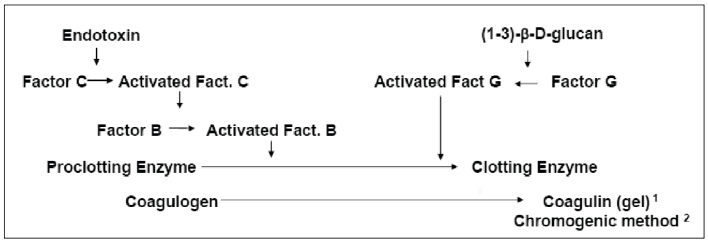
- Linear core of mannan with α1,2 and α1,6 linkages
- EbA2 detects antigenic side chain of β1,5 galactofuronosyl (multiple epitopes)
  - Double sandwich ELISA; monoclonal IgM
- Serum
- BAL





Fungitell (1-3)-β-D-Glucan

- Activates *Limulus* amebocyte lysate
- Factor G initiates cascade. Output measured by
  - Turbidity after gel clot: WB003 (Wako Pure Chem. Indust.)[1]
  - Chromogenic substrate: Fungitec G test (Seikagaku) and Fungitell, (Assoc. Cape Cod)[2]

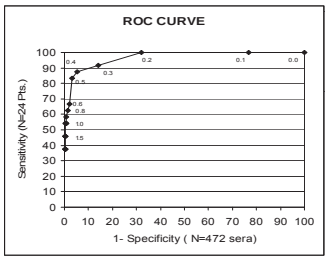


Developments

- A lot of controversy, still
- Slow development of other technologies for IA
  - Difficulties in understanding disease
  - Analytic complications
- What are the lessons learned with the *Platelia* GM EIA?

Lesson #1. Do It Right from the Beginning

- Early failure to define appropriate endpoints of this test hampered progress
- Sensitivity / Specificity using this cut-off: 80% / 80%

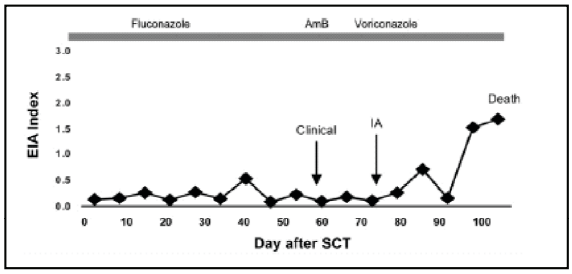


Timing (proven / probable)

	Cut-off 1.5	Cut-off 1.0	Cut-off 0.5
IA diagnosis	-1 days	-1 days	-10 days
Clinical onset	0 days	0 days	-6 days

Marr KA, et al. *J Infect Dis*. 2004;190:641-9.
Leeflang MM, et al. *Cochrane Database Syst Rev*. 2008:CD007394.

Lesson #2. Difficult Analyses



- Difficulty in assessing disease
  - Natural history of infection not well understood
- Time-dependent variables not accounted for in per-patient performance testing – antifungals decrease performance
- Imperfect gold standards

Marr KA, Leisenring W. *Clin Infect Dis.* 2005:41(Suppl 6):S381-6.

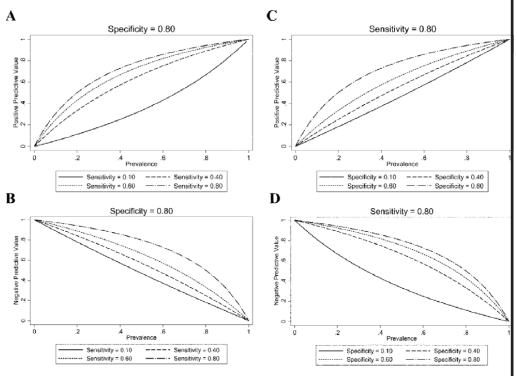
GM EIA Performance

- Continued understandings and uses of the galactomannan EIA
  - GM (polysaccharides that cross-react with the EbA2 Ab) is present in many sources - biological false-positives are real
  - BAL GM EIA useful
- Importance of testing groups with high probability of disease
- Adjunct to diagnosis vs. screening

Nucci M, et al. *PLoS One.* 2014;9:e87784.
Guigue N, et al. *N Engl J Med.* 2013;369:97-8.
Martin-Rabadan P, et al. *Clin Infect Dis*. 2012;55:e22-7.

Predictive Values

- Sensitivity – Specificity = test performance.
- Predictive values are a function of prevalence.
- Performance depends on patient population and intended use
- Increase prevalence:
  Increase PPV
  Decrease NPV



Marr KA, Leisenring W. *Clin Infect Dis.* 2005:41(Suppl 6):S381-6.

How Do You Resolve?

- Target the population better for pre-emptive treatment
  - Not just clinical risks
    - Genetics. Presentation.
  - Need to identify who has the >25% prevalence
- Utilize the negative-predictive value of the assay
  - Understanding the value of “negative” in de-escalating therapy

The Math of (Negative) Tests

- Negative predictive value
  - NPV is the probability a negative test is correct – either stop a drug (or don't start it)
- A good test might have sensitivity & specificity = 85%
  - If likelihood is ~ 10% (low risk), NPV is ≥ 98% *(wrong 1 in 50)*
  - If likelihood is ~ 33% (medium risk), NPV is ≥ 92% *(wrong 1 in 11)*
- To get to an NPV of ≥ 98% at likelihood of 33%...
  - You need sensitivity and specificity of 96%.
    →We don't have this in any of our fungal diagnostics.

As Prevalence Rises, NPV Falls

- This critical idea merits its own slide!
- If something is reasonably likely, a negative result has to be *very powerful* to be convincing
- Graphs: NPV is color-coded green where ≥95%

10% prevalence

Sensitivity ↓	Specificity 20%	30%	40%	50%	60%	70%	80%	90%	95%	96%	97%	98%	99%	100%
20%	69.2%	72.0%	75.0%	78.3%	81.8%	85.7%	90.0%	92.3%	94.7%	95.5%	96.4%	97.3%	98.2%	100%
30%	77.1%	79.4%	81.8%	84.4%	87.1%	90.0%	92.3%	94.7%	96.4%	97.1%	97.8%	98.4%	99.1%	100%
40%	81.8%	83.7%	85.7%	87.8%	90.0%	92.3%	94.7%	96.4%	97.3%	97.8%	98.4%	98.9%	99.4%	100%
50%	84.9%	86.5%	88.2%	90.0%	91.8%	93.8%	95.7%	96.9%	97.8%	98.2%	98.6%	99.1%	99.6%	100%
60%	87.1%	88.5%	90.0%	91.5%	93.1%	94.7%	96.4%	97.3%	98.2%	98.6%	98.9%	99.3%	99.8%	100%
70%	88.7%	90.0%	91.3%	92.6%	94.0%	95.5%	96.9%	97.8%	98.4%	98.6%	99.1%	99.3%	99.8%	100%
80%	90.0%	91.1%	92.3%	93.5%	94.7%	96.0%	97.3%	98.2%	98.6%	98.9%	99.3%	99.6%	99.8%	100%
90%	90.5%	91.6%	92.7%	93.9%	95.0%	96.2%	97.5%	98.1%	98.7%	98.9%	99.4%	99.6%	99.8%	100%
95%	91.0%	92.0%	93.1%	94.2%	95.3%	96.4%	97.6%	98.2%	98.8%	99.0%	99.4%	99.6%	99.8%	100%
96%	91.4%	92.4%	93.4%	94.5%	95.5%	96.6%	97.7%	98.3%	98.8%	99.0%	99.4%	99.6%	99.8%	100%
97%	91.8%	92.8%	93.8%	94.7%	95.7%	96.8%	97.8%	98.4%	98.9%	99.1%	99.4%	99.6%	99.8%	100%
98%	92.2%	93.2%	94.1%	95.1%	96.1%	97.1%	98.0%	98.6%	99.0%	99.2%	99.5%	99.7%	99.9%	100%
99%	92.6%	93.5%	94.5%	95.4%	96.4%	97.3%	98.2%	98.8%	99.1%	99.3%	99.6%	99.8%	99.9%	100%
100%	93.0%	93.9%	94.8%	95.7%	96.8%	97.6%	98.4%	99.0%	99.3%	99.4%	99.6%	99.8%	99.9%	100%

33% prevalence

Sensitivity ↓	Specificity 20%	30%	40%	50%	60%	70%	80%	90%	95%	96%	97%	98%	99%	100%
20%	33.4%	36.4%	40.0%	44.5%	50.0%	57.2%	66.7%	72.8%	78.3%	79.2%	80.0%	81.0%	81.8%	82.6%	83.4%
30%	42.9%	46.2%	50.0%	54.6%	60.0%	66.7%	75.0%	80.0%	84.2%	85.0%	85.7%	86.4%	87.0%	87.6%	88.2%
40%	50.0%	53.4%	57.2%	61.6%	66.7%	72.8%	80.0%	84.2%	87.5%	88.2%	88.9%	89.5%	90.0%	90.5%	90.9%
50%	55.6%	58.9%	62.5%	66.7%	70.6%	76.9%	83.4%	87.5%	90.3%	90.9%	91.4%	91.9%	92.3%	92.7%	93.0%
60%	60.0%	63.2%	66.7%	70.6%	73.7%	80.0%	85.7%	90.3%	92.3%	93.0%	93.3%	93.8%	94.1%	94.5%	94.7%
70%	63.7%	66.7%	70.0%	73.7%	77.8%	82.4%	87.5%	91.4%	93.3%	94.1%	94.4%	94.7%	95.0%	95.2%	95.5%
80%	66.7%	69.6%	72.8%	76.2%	80.0%	84.2%	88.9%	92.3%	94.1%	94.7%	95.0%	95.2%	95.5%	95.7%	96.0%
90%	68.0%	70.9%	73.9%	77.3%	81.0%	85.0%	89.5%	93.0%	94.5%	95.0%	95.2%	95.5%	95.7%	96.0%	96.2%
95%	69.8%	72.0%	75.0%	78.3%	81.8%	85.7%	90.0%	93.1%	94.7%	95.2%	95.5%	95.7%	96.0%	96.2%	96.4%
96%	70.4%	73.1%	76.0%	79.2%	82.6%	86.4%	90.5%	93.4%	95.0%	95.5%	95.7%	96.0%	96.2%	96.4%	96.6%
97%	71.5%	74.1%	76.9%	80.0%	83.4%	87.0%	90.9%	93.8%	95.2%	95.7%	96.0%	96.2%	96.4%	96.6%	96.8%
98%	72.6%	75.2%	78.0%	81.1%	84.6%	88.2%	91.9%	94.4%	95.7%	96.2%	96.4%	96.6%	96.8%	97.0%	97.2%
99%	73.6%	76.3%	79.1%	82.2%	85.7%	89.4%	93.0%	94.9%	96.2%	96.6%	96.8%	97.0%	97.2%	97.4%	97.6%
100%	74.7%	77.4%	80.2%	83.3%	86.9%	90.6%	94.1%	95.5%	96.7%	97.1%	97.3%	97.4%	97.6%	97.8%	98.0%

Clinical Trials

- Allo BMT / leukemia randomized (n=240) to standard treatment vs. biomarker-based approach. Primary endpoint: empirical antifungal therapy
- 32% in standard vs. 15% in biomarker group received AFT (p=0.002)

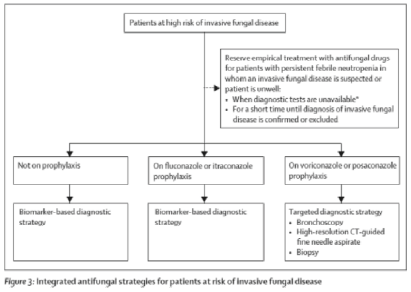


Figure 3: Integrated antifungal strategies for patients at risk of invasive fungal disease

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

We are all Bayesians

- If we were suspicious before
  - A negative test just doesn't satisfy
- A positive test is much more helpful
  - Having a diagnosis allows you to construct a coherent explanation
  - It can be a positive test for something else … that works just fine!
- Is pre-emptive therapy really a viable option?
  - Will need to identify the population with high likelihood… and believe in a negative finding

Conclusion

- Prophylaxis works with the right drugs, right patients
- Problems with analysis of recurrent events and endpoints in clinical trials
- Diagnostics based on culture and histopathology are *poor*
  - Better technology is not the only answer
- Analytic methods suffer from poor gold standards, poor analyses to account for time-dependency
- Availability will allow for development of different prevention and treatment algorithms
  - Inherent challenges to existing paradigms and the way we think…
- Being able to identify real risks and understand probabilities is the key variable

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

Case Presentation: Breakthrough Infection on Antifungal Prophylaxis

- 23-year-old female
- AML, monocytic variant
  - Successful induction and consolidation chemotherapy (7+3)
  - Achieved complete response
- Offered Matched Unrelated Donor (MUD) allogeneic stem cell transplant (SCT)
  - Declined: Patient wished to defer transplant

Thanks! to Dr. Monica Slavin for case details

Relapsed AML 6 Months Later

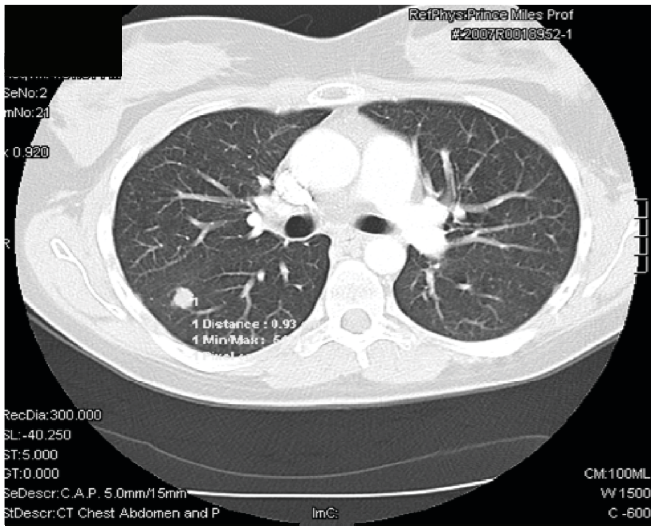
- Re-induction 7+3 HiDAC
- Posaconazole oral 200 mg tid with fatty meal
- Refractory disease following HiDAC

Progress

- Further chemotherapy: clofarabine
  - Gram-negative sepsis *Serratia marcescens*
  - Refractory disease
- Further chemotherapy: Etoposide / cyclophosphamide
  - Refractory disease
- Further chemotherapy:
  - FLAG + gemtuzumab (Mylotarg – anti CD33)
- Bone marrow: hypocellular, hypoplastic, no blasts
  - Absolute neutropenia (<0.1) x 5 months

Progress

- VRE right-sided endocarditis
- CT Chest –normal 2 weeks earlier but ongoing fever during VRE bacteremia and endocarditis prompted repeat CT chest scan



What to do Next?

6 months posaconazole prophylaxis and neutropenia:

- What is the likely etiology?
- How to evaluate?
- What therapy to use?

Question

What is the Likely Etiology?

1. VRE
2. Azole-susceptible *Aspergillus* spp.
3. Azole-resistant *Aspergillus* spp.
4. Mucormycosis
5. Other resistant mould
6. *Candida* spp.

Question

How Should the Diagnosis be Established?

1. Blood culture
2. Serum galactomannan testing
3. Bronchoalveolar lavage
4. Lung biopsy
5. No further diagnostic tests needed due to characteristic findings on CT

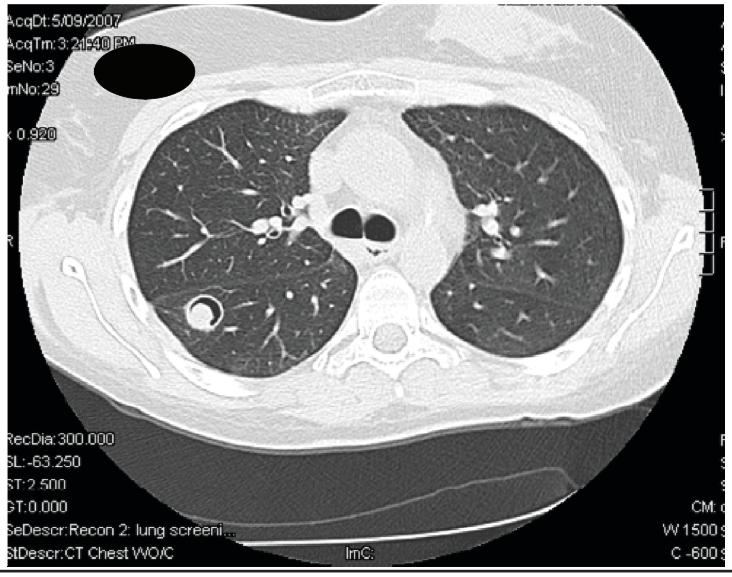
Question

What Antifungal Therapy would you Initiate?

1. Liposomal amphotericin B
2. Voriconazole
3. Echinocandin
4. Voriconazole + echinocandin
5. Liposomal amphotericin B + echinocandin
6. None, pending additional evaluation

Progress

- Liposomal amphotericin B 3 mg/kg/day
- Bronchoscopy performed
  - Results were negative for all tests done including BAL GM



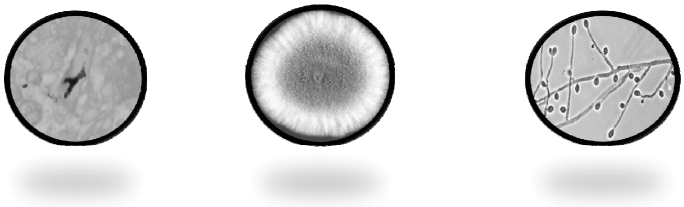
Question

Should Additional Procedures be Performed?

1. Fine needle aspirate of lung lesion
2. Repeat bronchoscopy
3. BAL PCR testing
4. Open lung biopsy
5. No, continue empirical treatment

Clinical Course

- Wedge resection apical segment of right lower lobe:
  - Histology: septate hyphae,
  - Culture *Scedosporium apiospermum*
  - Therapy: voriconazole + terbinafine 250 mg bid



Outcome

- Transplant indicated for relapsed high cytogenetic risk AML, initially refractory to re-induction therapy
- MUD allogeneic BMT 6 weeks after IFI documented
- Died of non-infective etiology 2 weeks post allogeneic BMT

Aspergillus and Mould Infections

- 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?
- Management of mould infections prior to stem cell transplant?
- What therapy should be initiated?

Summary: Posaconazole Prophylaxis and Breakthrough IFI

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

Ullmann AJ, et al. *N Engl J Med.* 2007:356:335-47.
Cornely OA, et al. *N Engl J Med.* 2007:356:348-59.

Breakthroughs with Posaconazole Prophylaxis in SCT

- Posaconazole prophylaxis D1–100, longer if steroids
- Jan 2007–Dec 2008. Followed 6 months post SCT
- 106 patients:
  - unrelated donor 42%, cord blood 26%, myeloablative 89%, mean duration neutropenia 19.6 (2–107) days
- Breakthrough infection in 8 (7.5%)
  - Breakthroughs on posaconazole: *C. glabrata* (3), *C. albicans* (2), *Aspergillus* (2), Cocci (1)
- Mean peak & trough posaconazole levels <400 ng/mL

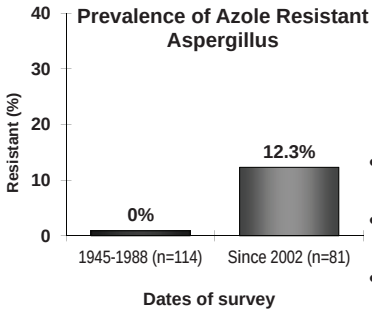
Winston DJ, et al. *Biol Blood Marrow Transplant.* 2011;17:507-15.

Voriconazole Prophylaxis: Allogeneic SCT (2003–2006)

- Prospective, randomized, double-blind trial (600 patients)
- Duration day 0 → days +100/+180
- Serum GM twice weekly x 60 days, once- to twice-weekly until day +100
- Both arms similar in
  - Patient, disease type, transplant type, engraftment rate
  - Acute/chronic GVHD, non-fungal infection, study withdrawal
- IFI: 28 proven, 33 probable, 18 presumptive
  - Proven/probable/presumptive IFI similar in 2 arms
  - 6 months: voriconazole 7.3%, fluconazole 11.2% (p=0.12); 12 months: voriconazole 12.7%, fluconazole 13.7%
  - *Aspergillus:* voriconazole 9, fluconazole 17 (p=0.09); *Candida* 6 and 3, Mucorales, 5 and 4
- Less empiric antifungal therapy with voriconazole, 24.1% vs 30.2%
- Fungal-free survival at 6 months: voriconazole 78%, fluconazole 75%
- Conclusion: efficacies of voriconazole and fluconazole are similar with close monitoring and early therapy

Wingard JR, et al. *Blood*. 2010;116:5111-8.

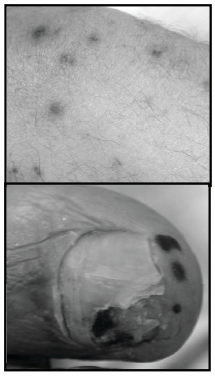
Azole Resistance in *Aspergillus*



- 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
- Variable responses to voriconazole or posaconazole
- Linked to fungicides

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

Emerging Fungal Infections: *Scedosporium* & *Fusarium*

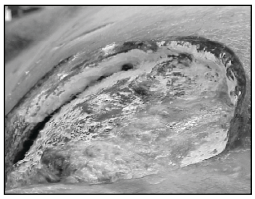


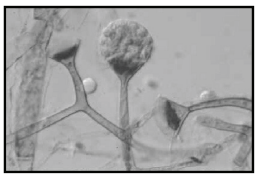
- Refractory to available agents: mortality 50% to >80%
- In vitro/in vivo: voriconazole, posaconazole, isavuconazole
- Potential activity of combination therapy: echinocandins
- Efficacy in patients refractory or intolerant to standard therapy:

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





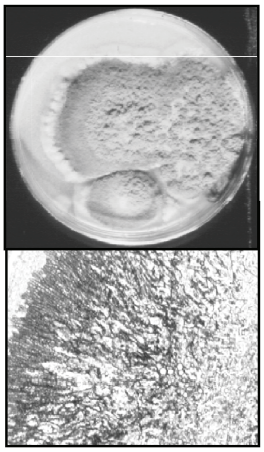
- Emergence on suppressive therapy (voriconazole, echinocandin):
  - Severely immunosuppressed (allo BMT)
- Other clinical presentations: trauma, burns
  - Trauma victims: polymicrobial wound infection including *Apophysomyces elegans*
  - May not grow in culture (homogenized tissue)
- In vivo activity: 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)**

Andresen D, et al. *Lancet.* 2005;365:5-11.

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.

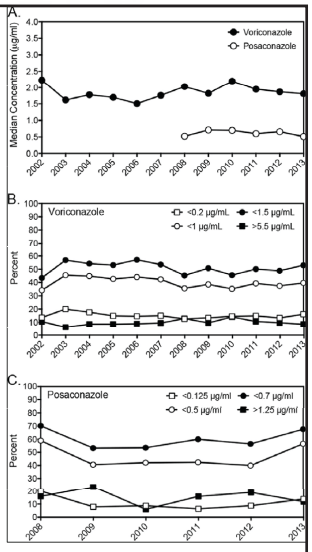
Therapeutic Drug Monitoring

Azoles:

- Itraconazole: absorption concerns
  38% <0.25 µg/mL
- Posaconazole: absorption concerns
  58% < 0.7 µg/mL
- Voriconazole: pharmacogenetic differences
  50% <1.5 µg/mL; 10.4% >5.5 µg/mL
- Isavuconazole: no data available

Echinocandins – not recommended

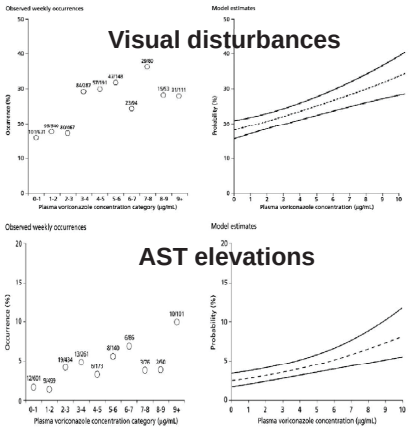
Polyenes - not recommended



Slide courtesy George R Thompson III. Thanks GR!
Wiederhold NP, et al. *Antimicrob. Agents Chemother.* 2014;58:424-31.

Voriconazole Serum Concentrations and Adverse Events

- **Correlation between adverse events and plasma concentrations**
- **Plasma voriconazole concentrations >6 µg/mL associated with increased toxicity**
- **Visual events: ~25%–35%**
- **Liver abnormalities: ~8%–15%**
- **No cut-off level predictive of adverse event**



Tan K, et al. *J Clin Pharmacol*. 2006;46:235-43.

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%

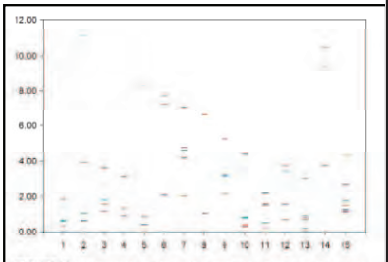
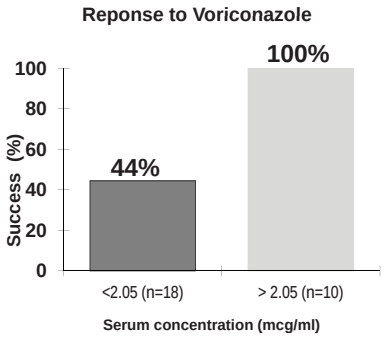


FIGURE 2. Voriconazole levels in 15 patients in whom ≥4 values were available illustrating variability.

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

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.

Challenging Recommended Oral and Intravenous Voriconazole Doses for Improved Efficacy and Safety: Population Pharmacokinetics–Based Analysis of Adult Patients With Invasive Fungal Infections

Andres Pascual,[1,a] Chantal Csajka,[2,4,a] Thierry Buclin,[2] Saskia Bolay,[1] Jacques Bille,[3] Thierry Calandra,[1] and Oscar Marchetti[1]

[1]Infectious Diseases Service, [2]Division of Clinical Pharmacology and Toxicology, Department of Medicine, and [3]Institute of Microbiology, Centre Hospitalier Universitaire Vaudois, University of Lausanne, and [4]Department of Pharmaceutical Sciences, University of Geneva, Switzerland

Population PK (NONMEM) analysis:
Suggest a minimum trough target of 1.5 mg/L (>85% chance of response) & maximum of 4.5 mg/L (<15% chance of neurotoxicity)
IV doses OK, with TDM
Oral doses should be higher: 300–400 mg twice daily, with TDM

NB: 400 mg twice daily troughs >5 mg/L in 26% (PO) & 44% (IV)

Pascual A, et al. *Clin Infect Dis.* 2012;55:381-90.

Voriconazole: Important Considerations

- Watch for drug interactions
- Adverse events: hepatic, visual, erythroderma
  - Others: skin malignancy, fluoride toxicity, myalgias, memory loss, alopecia, perioral excoriation
- IV formulation: accumulation of cyclodextrin in renal insufficiency
  - Not recommended for creatinine clearance <50 mL/min
- No activity versus Mucorales
- Consideration for weight-based oral therapy/measurement of serum levels

Pascual A, et al, *Clin Infect Dis*. 2012;55:381-90.
Wermers RA, et al. *Clin Infect Dis*. 2011;52:604-11.
Baxter CG, et al. *J Antimicrob Chemother.* 2011;66:2136-9.
Zwald FO, et al. *Dermatol Surg.* 2012;38:1369-74.

Posaconazole Plasma Concentrations and Global Response in Invasive Aspergillosis

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)

Issues for consideration:

- Doses higher than 800 mg/d do not increase plasma concentrations
- Lack of IV formulation prolongs time to steady-state levels (~7days)
- Measurement of levels not widely available; higher doses unlikely to increase levels

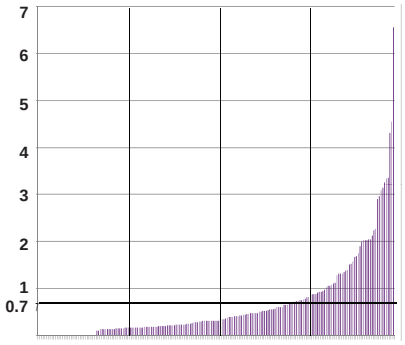
Walsh TJ, et al. *Clin Infect Dis.* 2007;44:2-12.

Posaconazole Plasma Concentrations in Prophylaxis

Author	N and Population	Mean plasma level (ng/mL)
Cornely OA, et al. NEJM 2007	215 AML	583±381
Ullmann AJ, et al. NEJM 2007	82 chronic GVHD	1470
	158 acute GVHD	958
Winston DJ, et al. BBMT 2010	19 early post SCT	<400

Posaconazole Therapeutic Drug Monitoring: A Reference Laboratory's Experience

- **POS serum drug levels have wide interpatient 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 G, et al. *Pharmacother.* 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.

Posaconazole Tablet Formulation Therapeutic Drug Monitoring and Toxicity

- Posa tablets added to formulary (U of Chicago)
- Primary endpoint target serum concentrations (SC) (>0.5 prophy; >0.7 therapy)
- Secondary: toxicities
  - QTc prolongation, Inc. LFT
- 45 pts received posa
  - Median time to SC 7 days
  - Median SC 1400 ng/mL (range: 243–7060)
  - 33/41 pt (80.4) received loading doses
  - 37/45 (82.2%) therapeutic SC

Pettit N, et al. ICAAC 2014. Abstract #2720.

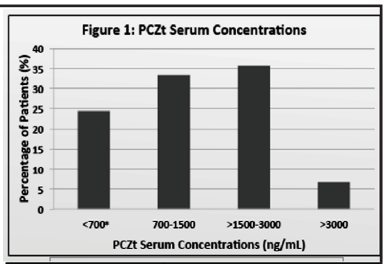
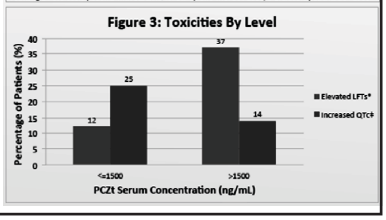
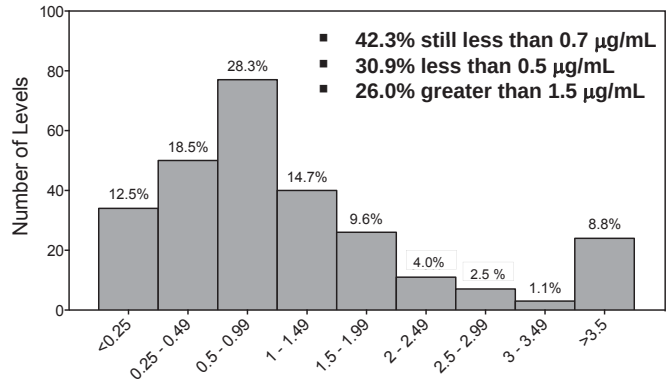


Table 2: Toxicities Based on Level	Number of Patients (%)	
	>1500 ng/mL (n=19)	>2000 ng/mL (n=12)
Elevated LFTs* (%)	7 (37)	4 (33)
QTc prolongation* (%)	2 (14)‡	1 (11)‡

*No statistically significant association with levels >1500 or >2000
‡ Among 14 evaluable patients with baseline/follow-up EKG with SC >1500, 9 evaluable patients SC >2000



Posaconazole Therapeutic Drug Monitoring After Tablet Approval: A Reference Laboratory's Experience



N. Wiederhold, UTHSCSA Fungus Testing Laboratory POS levels
January 1, 2014 – October 6, 2014

Is Bronchoscopy Useful?

- Yield of culture and cytology on bronchoalveolar lavage (BAL) 30% in neutropenic patients with abnormal CT and proven IA
- More likely in those with extensive changes and less antifungal exposure
- Endobronchial ultrasound: improved diagnostic yield for nodules
- Reduced need for surgical intervention
- Navigational systems improve access to peripheral pulmonary lesions
- Addition of molecular and biomarker tests to BAL

Reichenberger F, et al. *Bone Marrow Transplant.* 1999:24:1195-9.
Haas AR, et al. *Am J Respir Crit Care Med.* 2010:182:589-97.

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 useful to exclude diagnosis

Becker MJ, et al. *Br J Haematol.* 2003;121:448-57. D'Haese J, et al. *J Clin Microbiol.* 2012;50:1258-63. Guo YL, et al. *Chest.* 2010;138:817-24.

IDSA Guidelines for Treatment of Aspergillosis

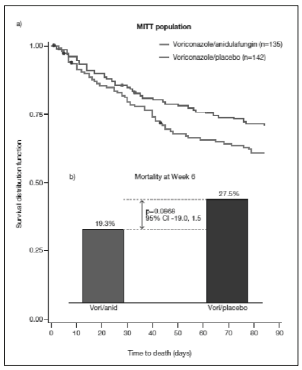
Condition	Primary therapy	Alternative
Invasive Pulmonary	Voriconazole	L-AMB, echinocandin, posaconazole, itraconazole
Invasive sinus	" "	" "
Tracheobronchial	" "	" "
Chronic necrotizing	" "	" "
CNS	" "	" "
Heart (endocarditis, etc)	"	" "
Bone/joint	" "	" "
Eye	Intraocular AMB	AND voriconazole
Empiric or Pre-emptive	L-AMB, itraconazole, voriconazole	
Prophylaxis	Posaconazole	Itraconazole, micafungin

Will this change?

Walsh TJ, IDSA 2008 Aspergillosis Guidelines. *Clin Infect Dis*. 2008; 46:327–60.
Maertens J, et al. Oral presentation. *ECCMID* 2014. Barcelona Spain.

Combination Therapy for Invasive Aspergillosis with Voriconazole and Anidulafungin

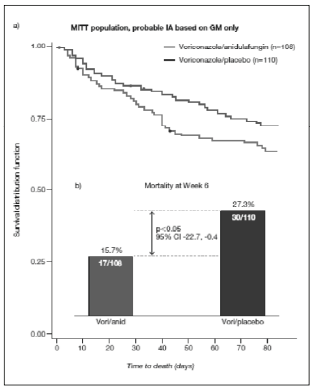
- 454 pts with invasive aspergillosis
  - 277 pts proven or probable IA
  - Primary endpoint overall survival at 6 weeks
- Overall mortality at 6 wks in MITT population:
  - Combo: 26/135 (19.3%)
  - Vori mono: 38/142 (27.5%)
  - p=0.0868
- No difference in adverse events



Marr KA, et al. Presented at *ECCMID* 2012. LB2812.

Combination Therapy for Invasive Aspergillosis with Voriconazole and Anidulafungin

- Of 277 pts in MITT population, 218 diagnosed by galactomannan (GM) detection in BAL or serum
- Overall mortality at 6 wks in GM-diagnosed population:
  - Combo: 17/108 (15.7%)
  - Vori mono: 30/110 (27.3%)
  - p<0.05
- Role of combination therapy in early disease?

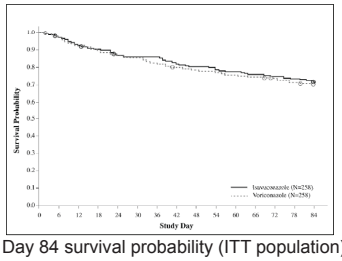


Marr KA, et al. Presented at *ECCMID* 2012. LB2812.

Isavuconazole vs. Voriconazole in Invasive Aspergillosis and Mould Infection

Isavuconazole

- New extended-spectrum triazole
- IV and PO formulations
  - No cyclodextrin in IV
  - No food effect for PO
- Results of voriconazole vs. isavuconazole phase 3 study have been presented.



Day 84 survival probability (ITT population)

Fewer (p<0.05) AEs were reported in the ISA treatment group

- Skin (33.5% vs. 43.5%)
- Eye (15.2% vs. 26.6%)
- Hepatobiliary disorders (8.9% vs. 16.2%)

Maertens J, et al. Presented at *ECCMID* 2014. Barcelona, Spain. Abstract #O230a.

Isavuconazole vs. Voriconazole in Invasive Aspergillosis and Mould Infection

Outcome ITT (n=516)	Isavuconazole	Voriconazole
Primary endpoint: **Overall mortality (6wk)**	**18.6%**	**20.2% (95% CI <10%)**
Success at EOT (proven/probable)	**35.0**	**36.4**
Drug-related AE	**42.4**	**59.8**

- Primary endpoint met for mortality at 6 wk (<10% inferiority)
- Similar composite outcomes at end of therapy (EOT) in patients with proven/probable disease
- Fewer drug-related adverse events with isavuconazole

Maertens J, et al. Presented at *ECCMID* 2014. Barcelona, Spain. Abstract #O230a.

Lessons Learned: Breakthrough Mould Infections

- *Aspergillus* still the most important pathogen in breakthrough on prophylaxis; NB: other moulds are possible, especially in highly immunosuppressed pts
- Triazole levels: logistical problems and lack of target levels for prophylaxis—but may be useful even with weight-based dosing
- Bronchoscopy with BAL GM: useful test
- *Aspergillus* triazole resistance (*probably*) not widespread
- Surgery and antifungal treatment (6 weeks) prior to stem cell transplant