Novel Antifungals and Emerging Resistance Issues

Peter G Pappas, MD, FACP

Emeritus Professor of Medicine

PI, Mycoses Study Group

Division of Infectious Diseases

University of Alabama at Birmingham

Disclaimers

- Research support: Astellas, Merck, Amplyx, Cidara, Scynexis, Mayne, F2G
- Scientific advisor: Appili, Mayne, Cidara, Scynexis, F2G
- Equities: NA
- Speaker: NA

Why the need for new antifungals?

- Antifungal resistance (AFR) to existing agents
- Toxicity concerns
- Expense/access
- Bioavailability (eg, availability in both oral and parenteral formulations)
- Emerging pathogens (eg, *C glabrata*, *C auris, AFR Aspergillus* and other molds) are a global concern

Antifungal resistance major concerns

Molds:

- *Aspergillus* spp (25% of EU isolates R to itra and other azoles)
- *Mucorales* spp (same concerns as always, only isavu and posa reliably active azoles vs these molds)

Candida spp:

- MDR *C glabrata, C auris*
- Emerging issues with *C albicans*, *C paraspilosis* (AFR up to 10%)

Cryptococcus spp:

- AFR is a concern, but *azole tolerance* may be more common

Endemic fungi:

- No serious concerns

How to define AFR?

- *Intrinsic*: all or almost all isolates within a species demonstrate resistance to a compound without prior exposure. Examples include: *C krusei* (flu); *C lusitaniae* (AmB); *A lentulus* and *A terreus* (AmB), *A calidoustus*
- *Acquired:* refers to spontaneous mutations or recombination with subsequent selection following exposure to an antifungal compound
- Azole resistance can be broadly categorized into CPY51A (e.g.,alteration in binding affinity) and non-CYP51A mechanisms (e.g., efflux pumps) in molds, and ERG 11 in yeasts

Resistance Considerations for Candida

- Intrinsic resistance is the main driver of anti-fungal resistance
- Typically this happens by selection of resistant organisms as plasmid gene transfer doesn't occur in fungi
- Agricultural azole use could play a role
  - Comparison of fruit from organic vs. non-organic farms showed large difference in fluconazole MICs of *Candida*
  - Genetically related means of resistance found in clinical and soil sources of *Candida tropicalis*
  - Similar circumstances have led to MDR *Aspergillus* in the Netherlands
- High tolerance for large scale genetic alterations, in particular *C. glabrata*
  - Due to conditions in the host
  - Translocations, rearrangements, and new chromosomes

Arendrup, *Clinical Microbiology and Infection*, 2013; Yang, *PLoS One*, 2012; Verweij, *Lancet ID,* 2009; Perlin, *Curr Clin Micro Rpt*, 2015

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/I**
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**

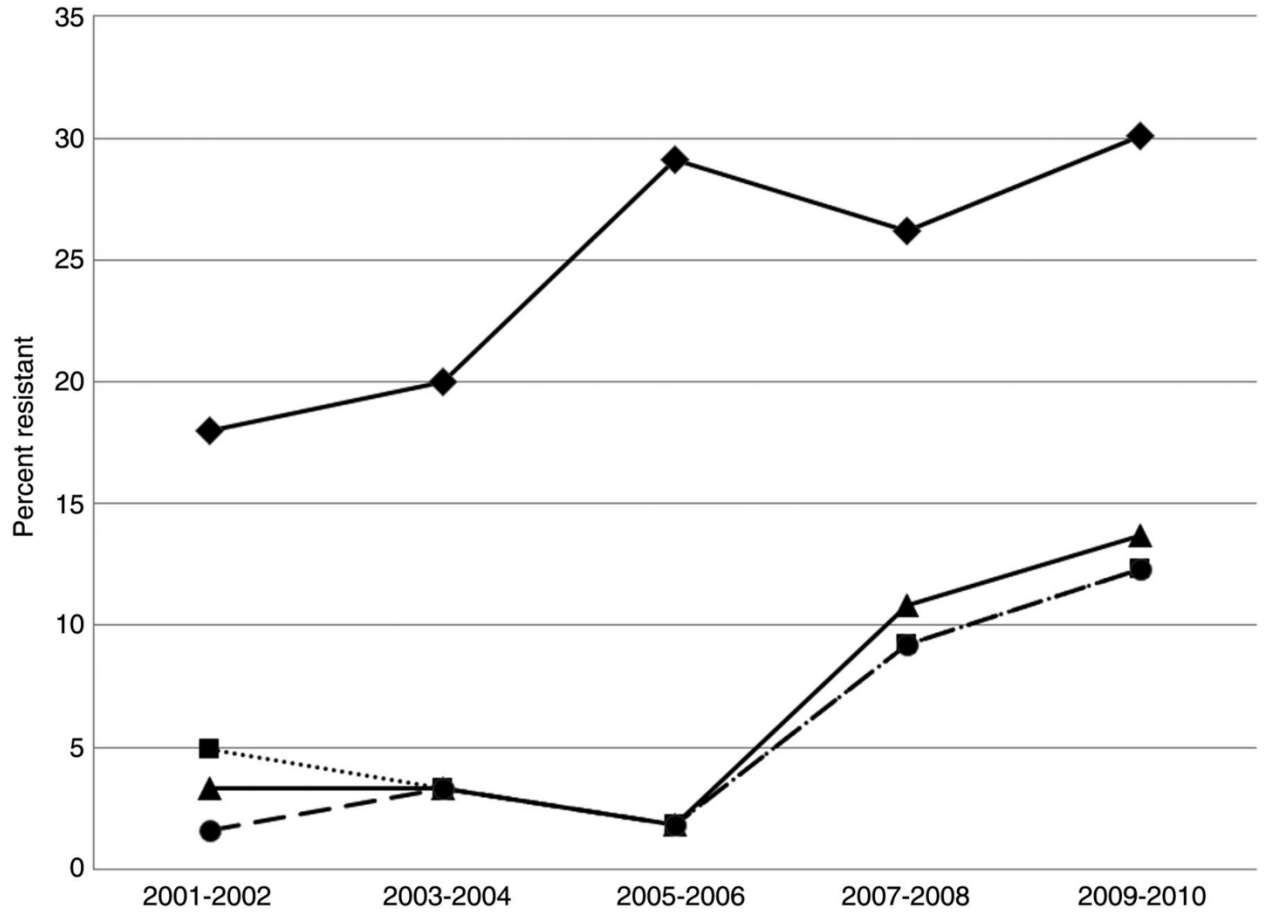
S = susceptible; S^{DD} = susceptible-dose dependent; R = resistant; I = intermediate; NS, non-susceptible

Fluconazole: Risk factors for resistance

- Prior exposure (Lortholary, 2011)
  - Decreased prevalence of *C. albicans*
  - Increased prevalence of *C. glabrata* and *C. krusei*
- Suboptimal dosing (Shah, 2012; Pai 2007)
  - IDSA guidelines recommend 6-12mg/kg/day for candidemia
  - Less has been associated with increased resistance and mortality
- Exposure to antibacterial agents (Ben-Ami 2012)
  - Association between exposure to bactrim, carbapenems, clindamycin, and colistin
  - Cephalosporins negatively associated
  - Metronidazole associated with *C. glabrata*
- Collateral Damage
  - Among *C. glabrata* isolates, fluconazole exposure was also associated (trend, not quite significant) with voriconazole resistance (Chen 2012)

Echinocandins

- Treatment of choice for initial therapy in candidemia (Pappas 2016, Cornely 2012)
- Fungicidal against *Candida* species, limited activity against filamentous fungi, no activity against *Cryptococcus*
- Minimal drug-drug interactions
- Minimal adverse reactions due to the lack of an analogous pathway in mammals
- Intravenous only

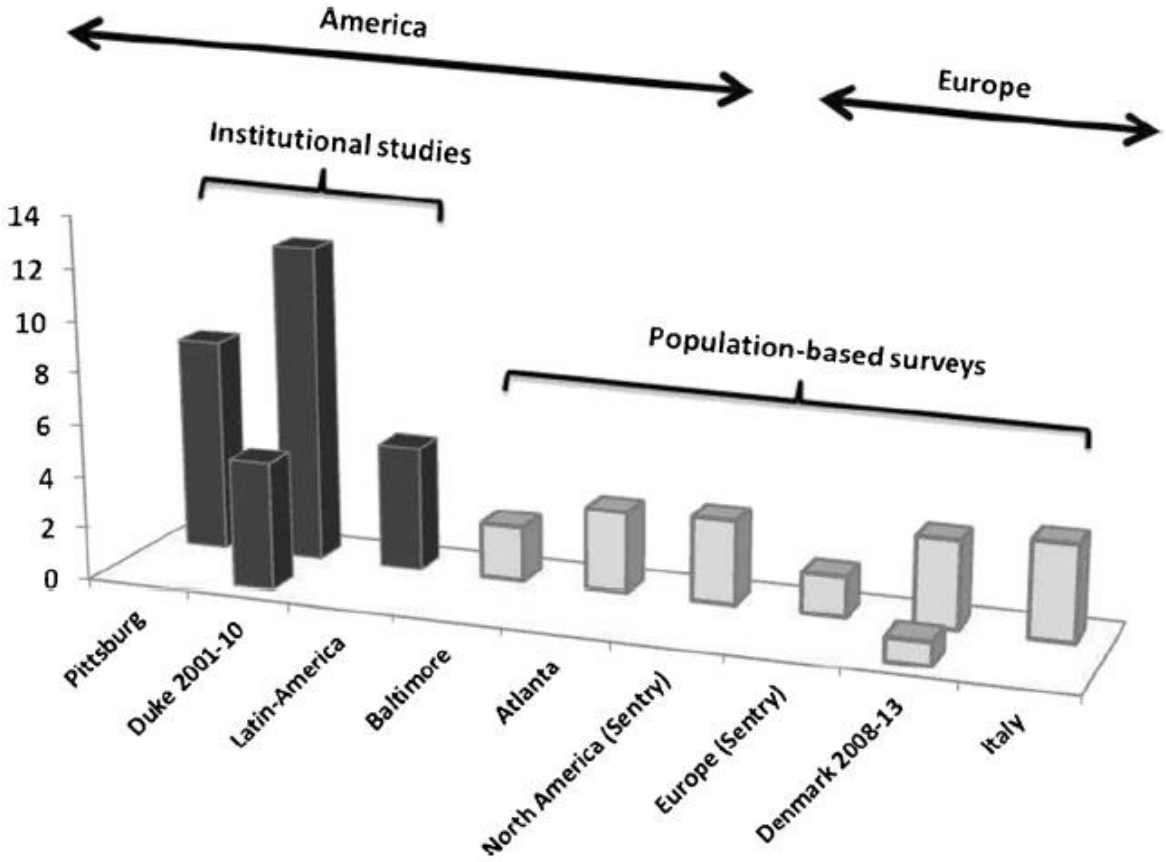


From: Increasing Echinocandin Resistance in Candida glabrata: Clinical Failure Correlates With Presence of FKS Mutations and Elevated Minimum Inhibitory Concentrations

Clin Infect Dis. 2013;56(12):1724-1732. doi:10.1093/cid/cit136

Echinocandins

Fig. 1 Echinocandin resistance in *C. glabrata* in Europe and America. Resistance rate varies among different studies. The rate reported from institutional studies is higher than that from population-based surveys, where only the initial blood isolate is included to avoid biasing the data set. Adapted from Arendrup et al. [14]



Arendrup, *Curr Opin Infect Dis*, 2014

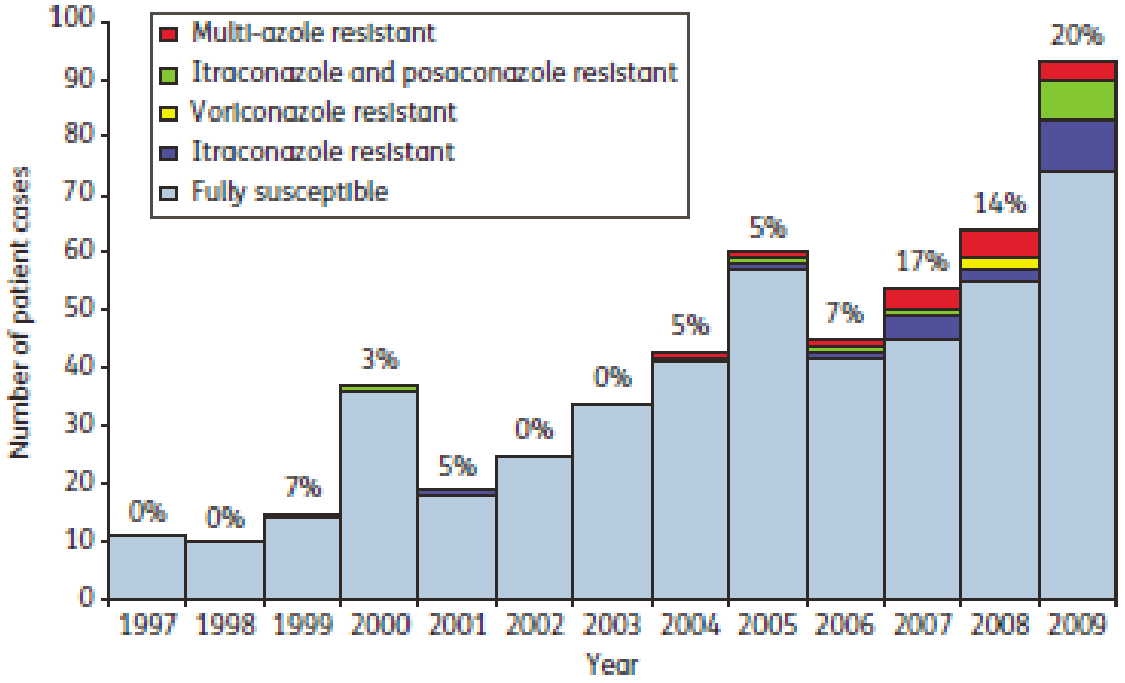
Candida Resistance Summary

- 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.
- Newer antifungal agents (ibrexafungerp, rezafungin, fosmanogepix) may play an important role in the treatment of infections due to MDR *Candida spp*

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, recent data support a significant impact on outcomes/mortality

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

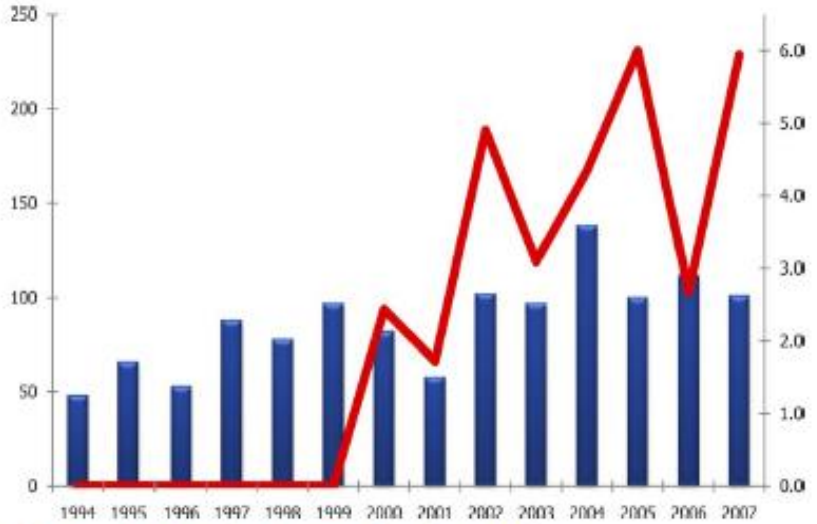
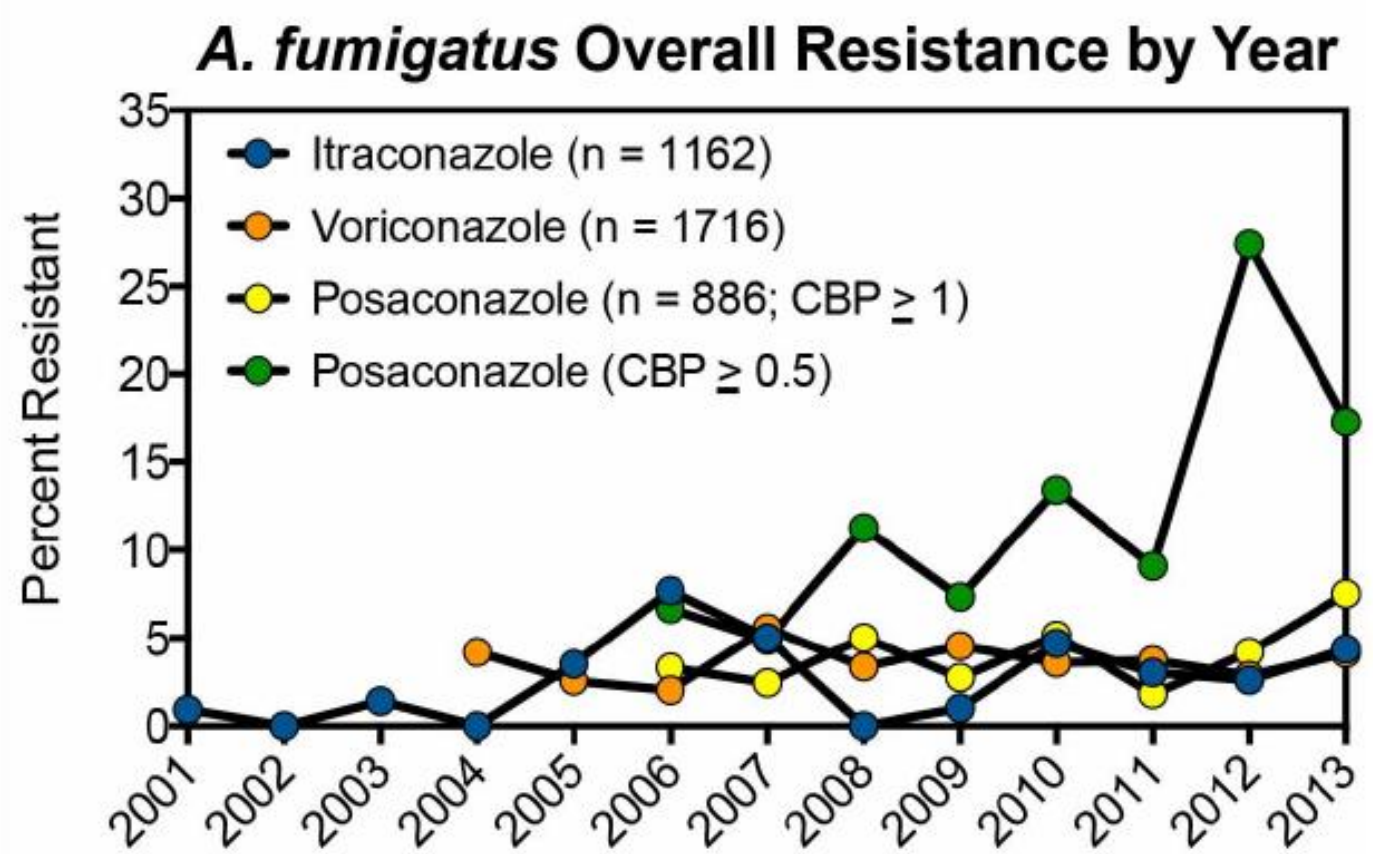


Figure 1. Epidemiology of ITZ Resistance in the *A. fumigatus* Isolates

Blue bars represent the number of patients with a positive *A. fumigatus* culture (left *y*-axis) and the red line represents the percentage of those patients with an ITZ+ isolate (right *y*-axis). The *x*-axis is the year.

doi:10.1371/journal.pmed.0050219.g001

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



N: 1819

Wiederhold et al. AAA 2014 (abstract)

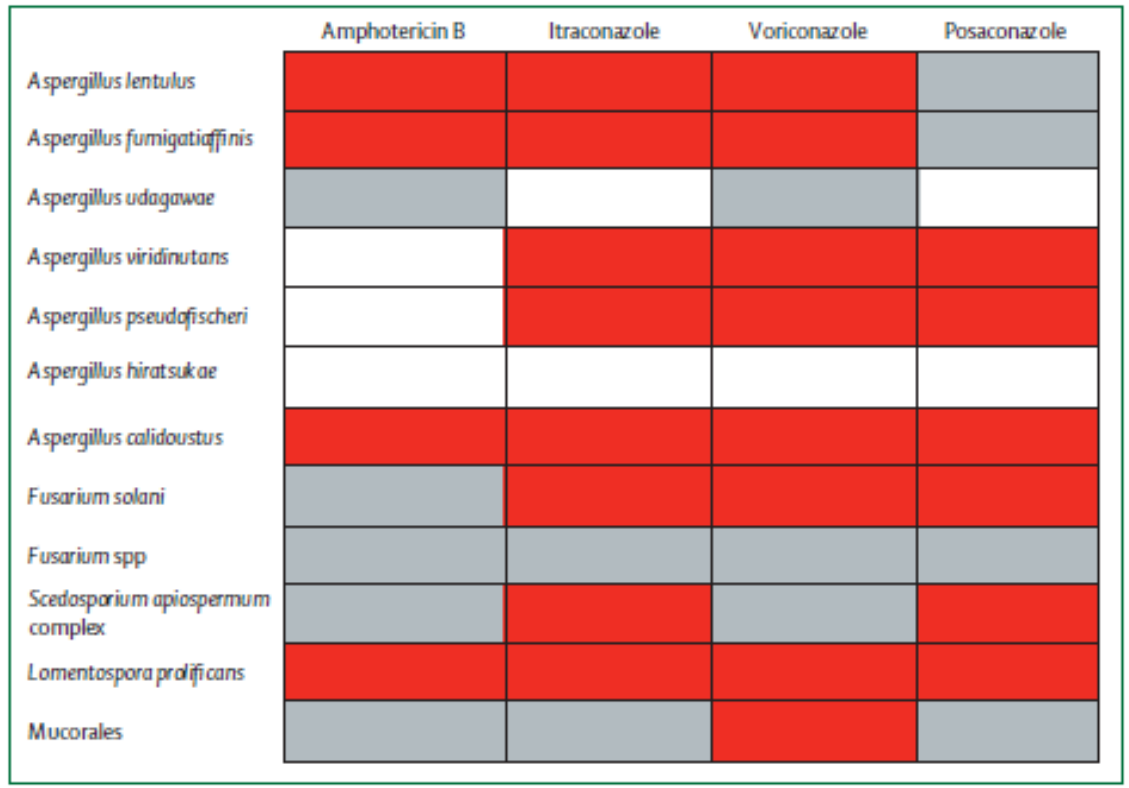


Figure 2: **Antifungal resistance in less common fungal species**
Red=species resistant to drug. White=species susceptible to drug. Grey=species has intermediate or low minimum inhibitory concentration to drug.

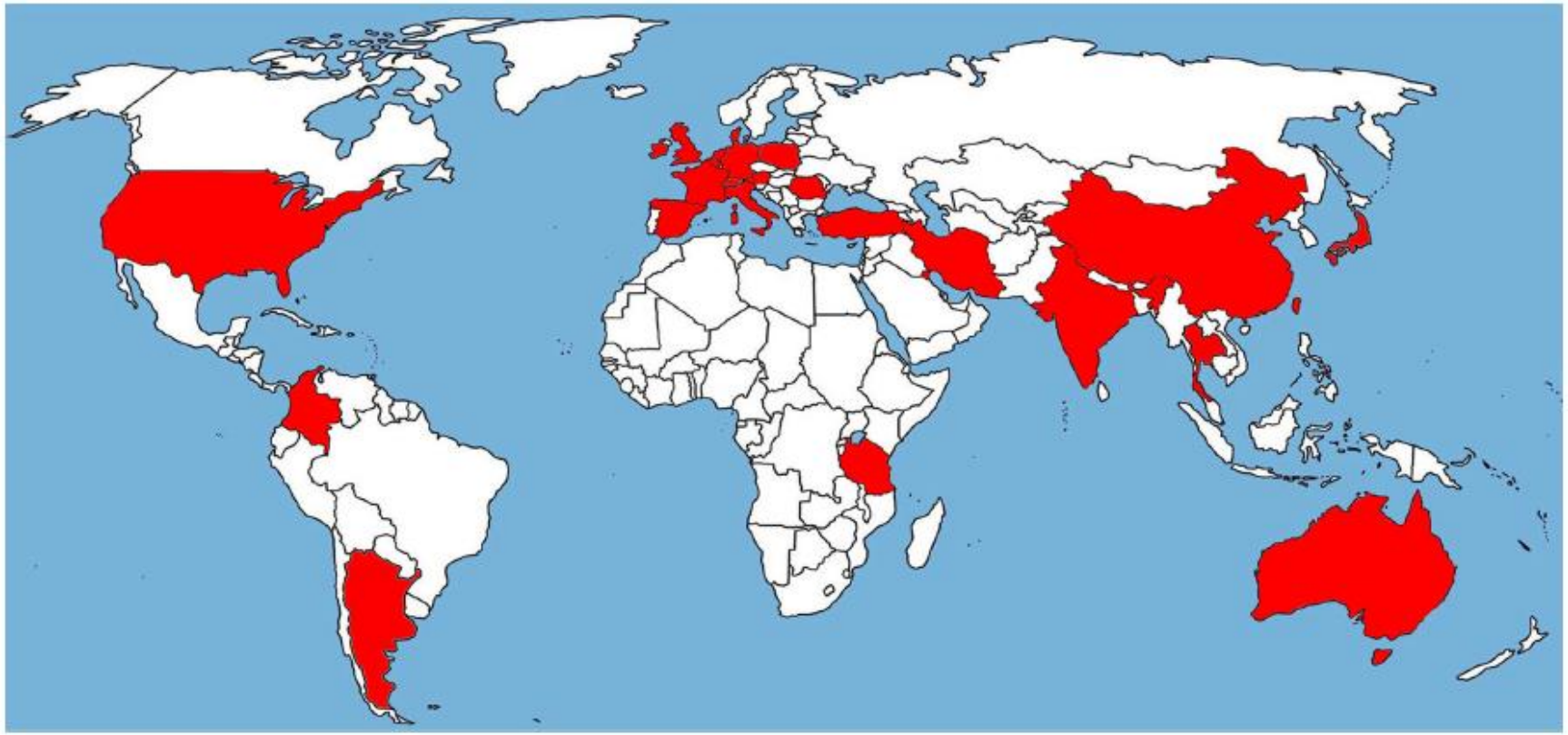


Figure 1. Countries that have reported triazole resistance in *A. fumigatus*. Countries with triazole resistance are depicted in red, while those with unknown resistance epidemiology are indicated in white.

Conclusions

- Emergence of azole resistance in *Aspergillus* spp is now a global problem
- Some regions in Northern Europe report azole resistant rates of 25%.
- Outcomes among infected patients are often poor
- Traditional antifungal susceptibility testing for azole resistance should become more routinely available, especially in regions of the world where AF prophylaxis is commonly practiced.
- Primary therapy with a polyene +/- echinocandin should be considered for IA, especially in regions where azole resistance is common
- Primary prophylaxis approaches in high use centers must be readdressed

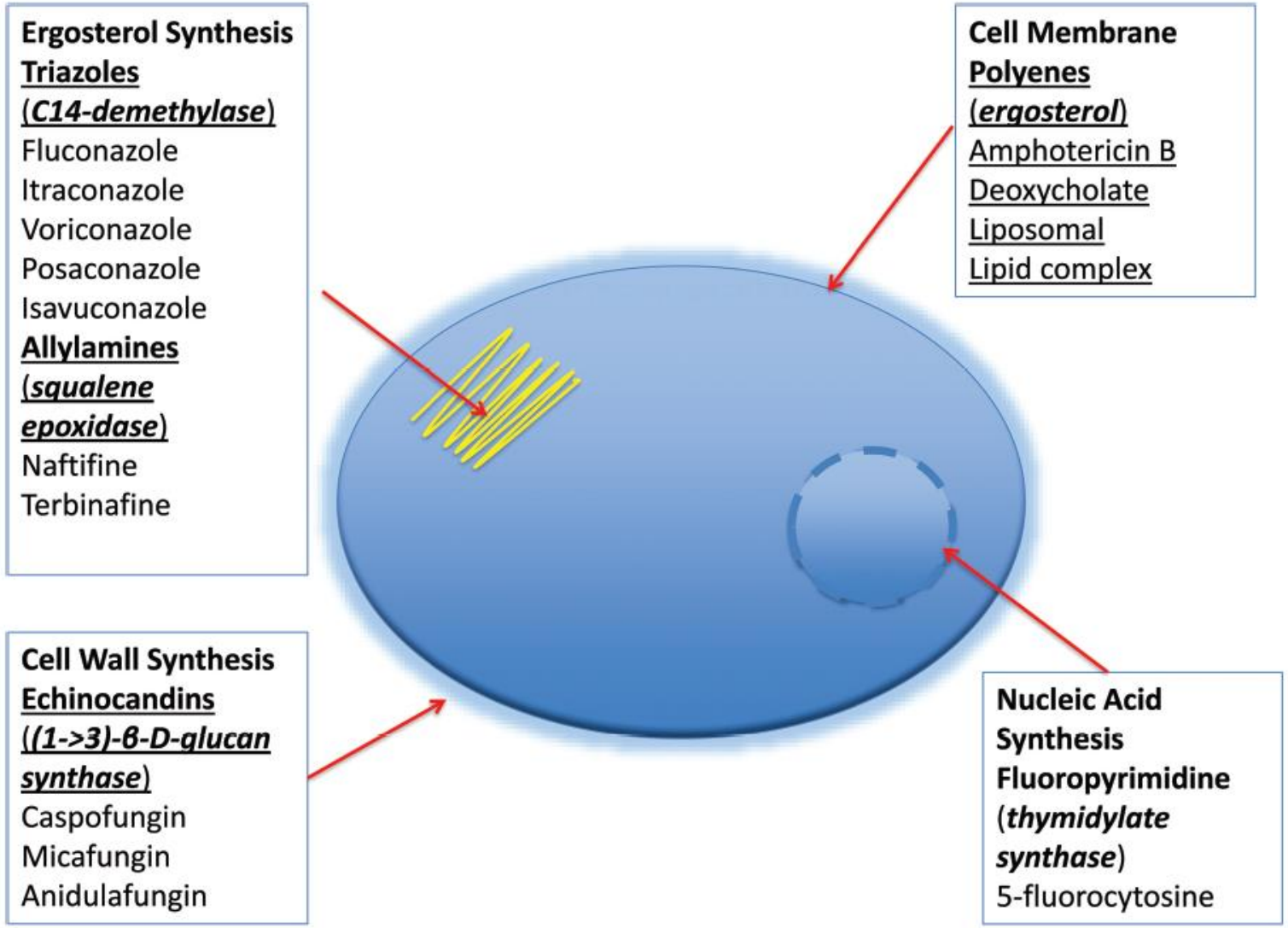


Figure 1. Cellular and biochemical targets of major classes of currently available antifungal agents.

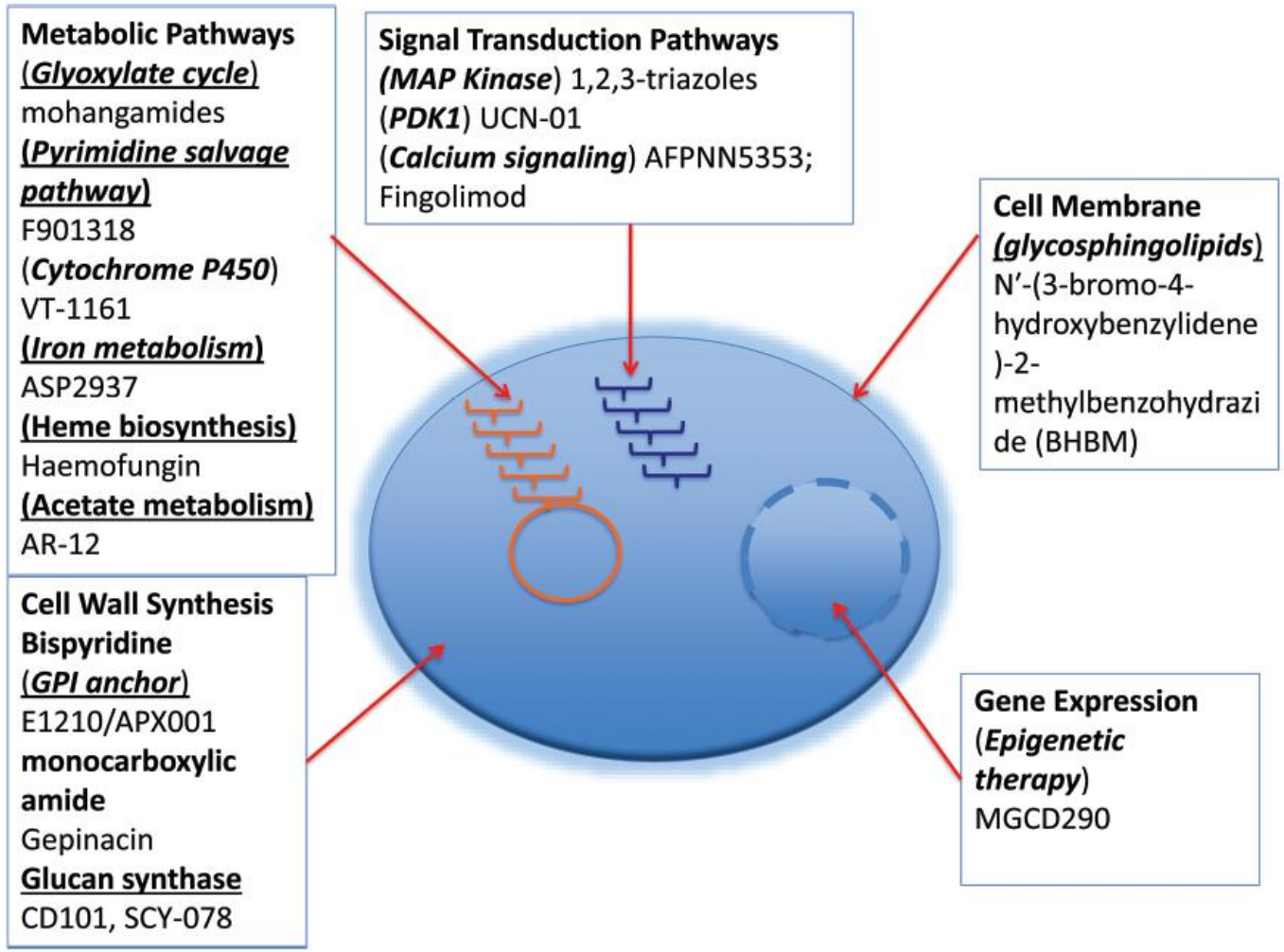
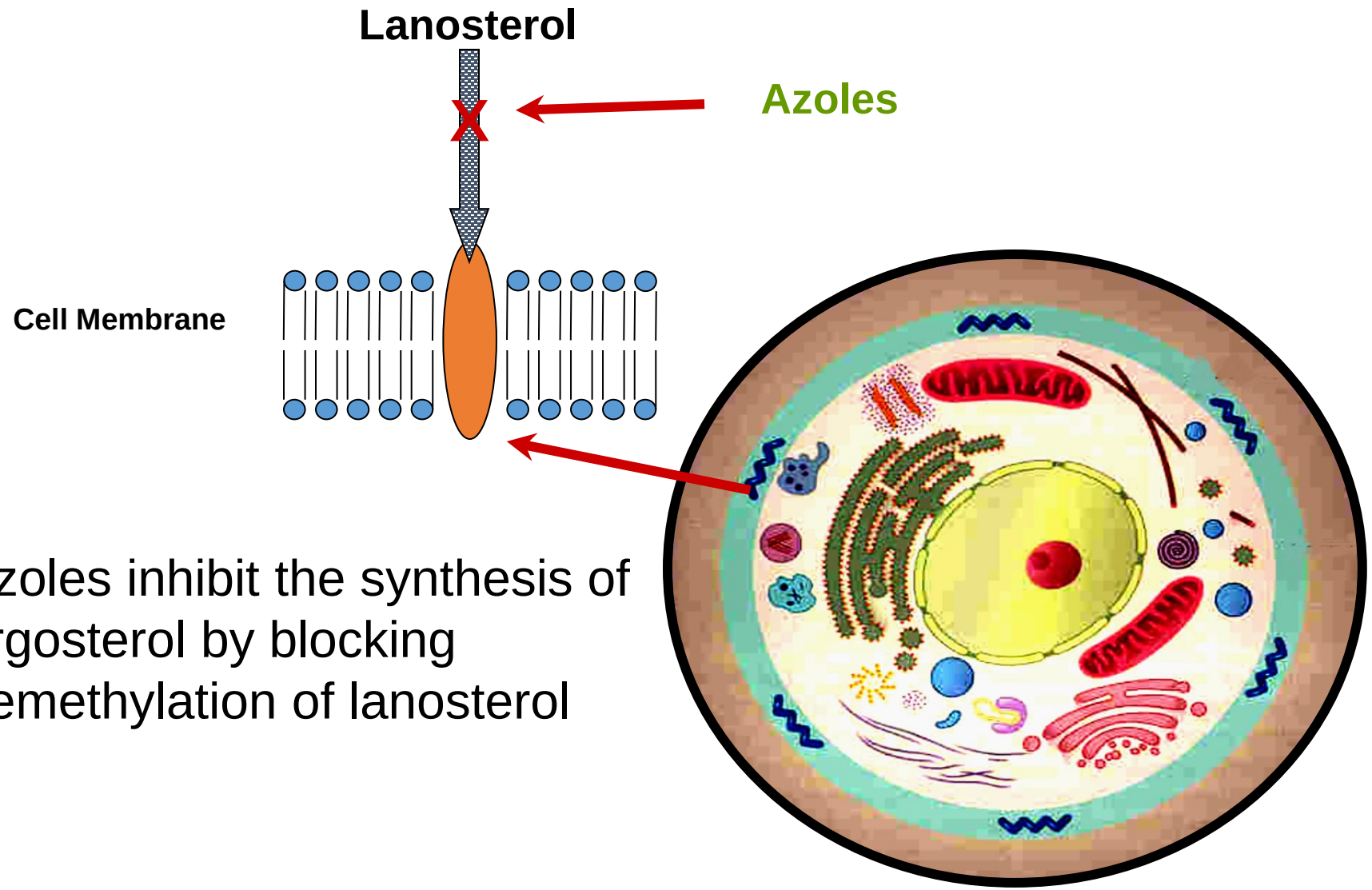


Figure 3. Cellular and biochemical targets of investigational agents against drug resistant fungal pathogens.

The Novel Antifungals

Azoles



Azoles inhibit the synthesis of ergosterol by blocking demethylation of lanosterol

Azole Agents: Spectrum of In Vitro Activity

	Flu	Itra	Vori	Posa	Isavu
Candida spp.	+	+	+	+	+
Aspergillus spp.	-	+	+	+	+
Cryptococcus	+	+	+	+	+
Histoplasma/ Coccidioides/ Blastomyces	+	+	+	+	+
Zygomycetes	-	+/-	-	+	+

SUBA Itraconazole

- The SUBA™ process produces microencapsulated nanoparticles of itraconazole dispersed in a polymer matrix, which are less soluble in stomach acid. This creates significantly improved solubility in the higher pH of the upper small intestine, resulting in improved absorption.
- More predictable serum levels, less patient to patient variability
- Roughly twice the serum level for about ½ the dose compared to conventional itraconazole 65mg SUBA vs 100mg conventional itra
- Same safety profile as for conventional itraconazole

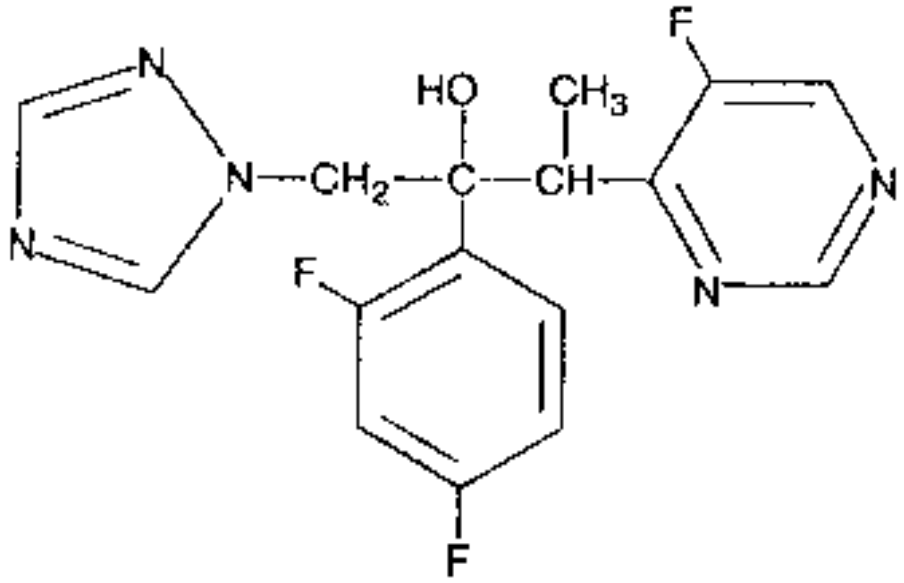
MSG-15 (SUBA itra vs conventional itra for endemic fungal infections

- Open label trial comparing SUBA itra to conventional itra for newly diagnosed histo, blasto, coccidioidomycosis, sporo
- Dosing 200 mg itra vs 130 mg SUBA itra, both given bid
- Duration 6 months, then transition to conventional therapy
- Primary endpoints are PK and safety related, secondary endpoints are clinical
- N=92 evaluable subjects from15 sites
- Safety and efficacy were similar,PK more predictable for SUBA-itra

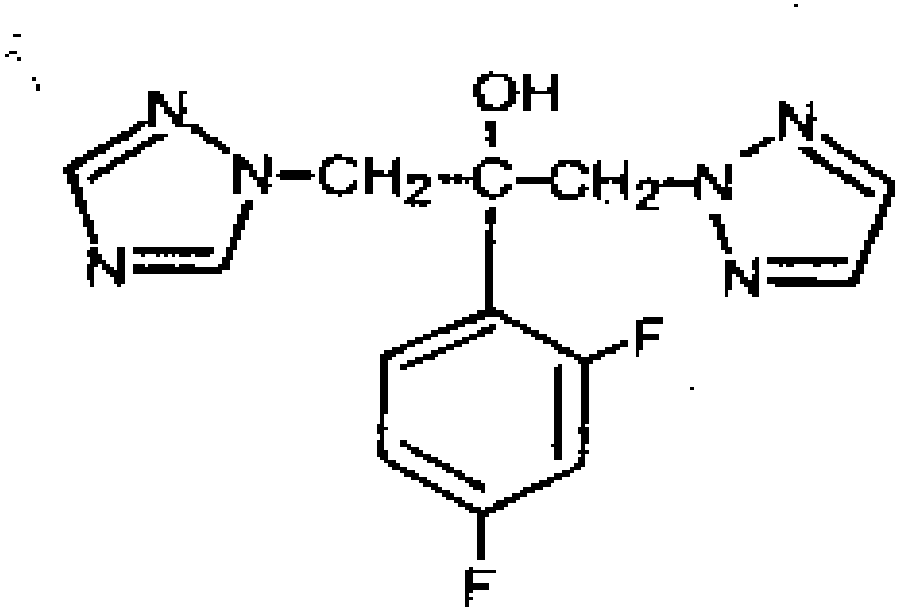
Where does SUBA-itraconazole fit?

- Does it replace po conventional itraconazole?
- Perhaps best suited for those with absorption issues?
- Useful for those in whom adequate itraconazole levels are not easily achievable?
- Perhaps for use among patients requiring mold prophylaxis, eg lung transplant recipients
- Costs need to be comparable with coventional itraconazole
- FDA approved in US, could replace conventional itra (similar to *posa* ER tabs vs *posa* suspension)

Voriconazole



Voriconazole



Fluconazole

Voriconazole

- First mold-active azole (2003), approved for treatment of invasive aspergillosis
- Visual disturbances (enhanced brightness or blurred vision) develop ~ 30 min after dose, transient (last ~ 30 min), reversible, and occur in ~ 30% of patients. No permanent sequelae.
- Mild hepatoxicity in 10-30% patients, generally related to higher plasma levels.
- Skin rash, including photosensitivity associated erythema and desquamation.
- VORI-drug interactions must always be considered.
- Systemic fluorosis with periostitis, neuropathy,etc

Voriconazole

- Broad spectrum activity against opportunistic fungi
  - *Aspergillus spp*
  - *Candida spp*
  - *Cryptococcus sp*
  - *Fusarium spp (variable)*
  - *Scedosporium apiospermum*
  - Dematiaceous moulds
- Activity against endemic fungi
  - *Blastomyces*
  - *Coccidioides*
  - *Histoplasma*
  - *Paracoccidiodes*
- Minimal activity against
  - Zygomycetes (*Mucor* and *Rhizopus spp*)

Voriconazole: Important Considerations

- Main toxicity is elevated LFTs, skin rash, and visual hallucinations/photopsia. Serial monitoring LFTs
- Increased risk of skin cancer with prolonged use
- Strongly advise use of sunscreen
- Therapeutic drug monitoring (TDM) is necessary for prolonged therapy, target levels are 1-5 µg/ml

Posaconazole

- Analogue of itraconazole
- Oral capsule extended release, oral suspension, and IV (not available everywhere)
- Half-life 25 hours
- Fungicidal against *Aspergillus*, *Scedosporium apiospermum,* certain dematiaceous molds
- Highly active against Zygomycetes; unreliable versus *Fusarium* species
- Broadest antifungal spectrum among azoles

Current Indications and Uses of Posaconazole

- Prophylaxis for IFI in pts with heme malignancies and SCT
- Primary therapy for invasive aspergillosis
- Step down therapy for mucormycosis
- Treatment for non-life-threatening, non-CNS endemic mycoses
- Treatment of dematiaceous fungal infections (black or pigmented molds)

Posaconazole: Important Considerations

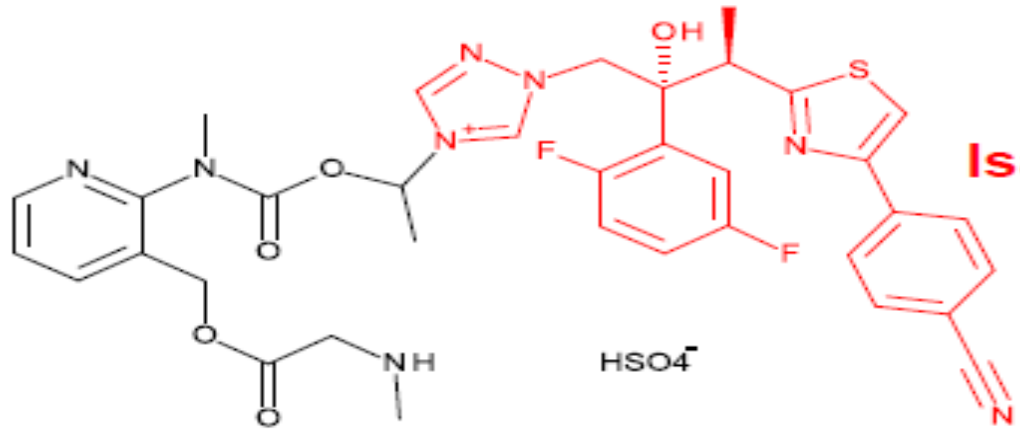
- Important DDI’s, but generally less than posaconazole, similar to itraconazole
- Main toxicity is elevated LFTs, fluid retention, and hypertension
- Probably should not be administered those with advanced CHF
- Therapeutic drug monitoring (TDM) is necessary for prolonged therapy, target levels are 1-5 µg/ml

Isavuconazole

- Isavuconazonium sulfate is the prodrug
- Parenteral and oral, bioequivalent
- Prolonged T1/2, allowing for once daily dosing
- Broad in vitro spectrum activity very similar to posaconazole vs. *Aspergillus*, *Mucorales*, other molds, *Candida* spp, *Cryptococcus* spp, endemic mycoses
- Approved for treatment of invasive aspergillosis and step down therapy for mucormycosis

Isavuconazonium: Novel Prodrug

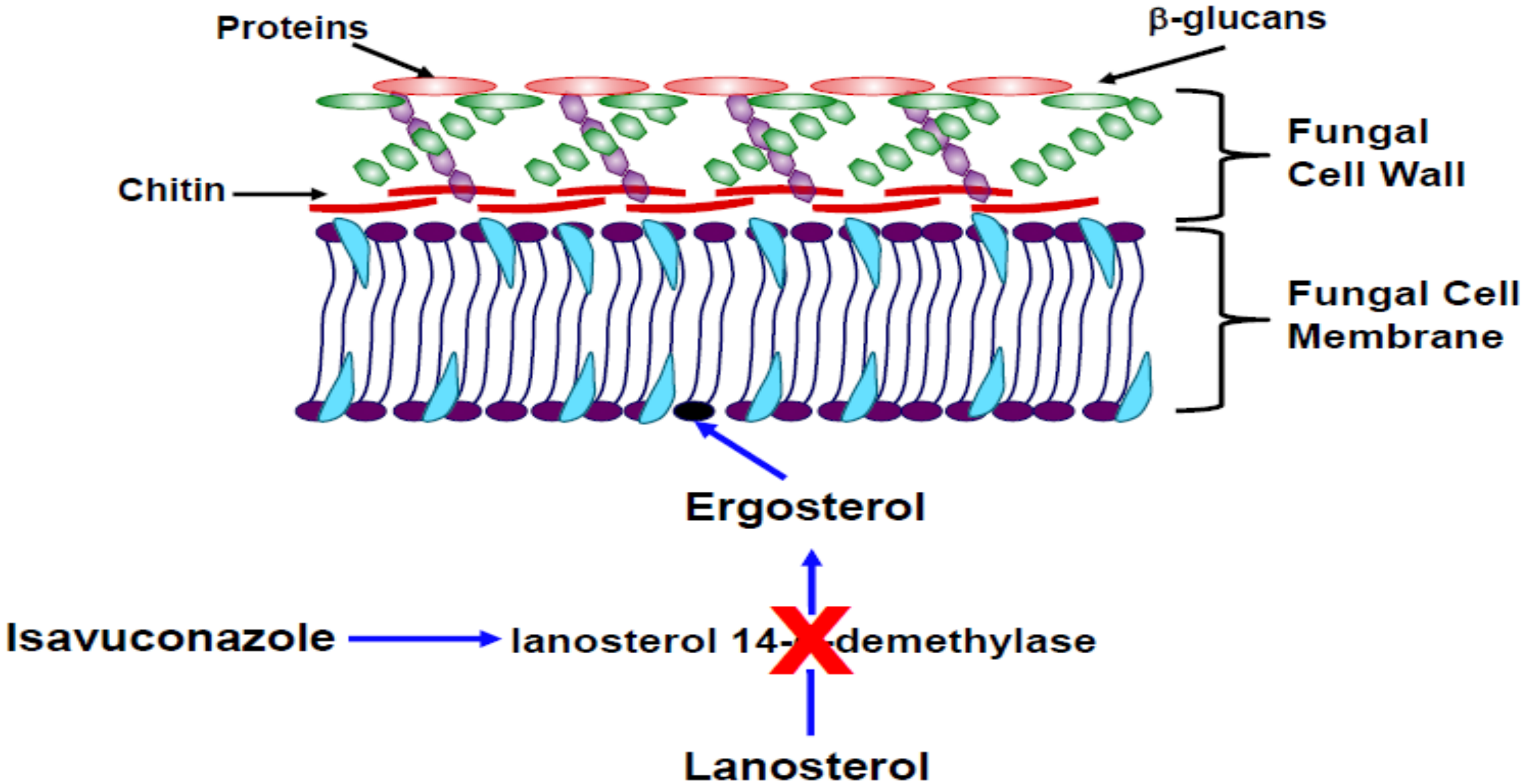
Cleavage Product



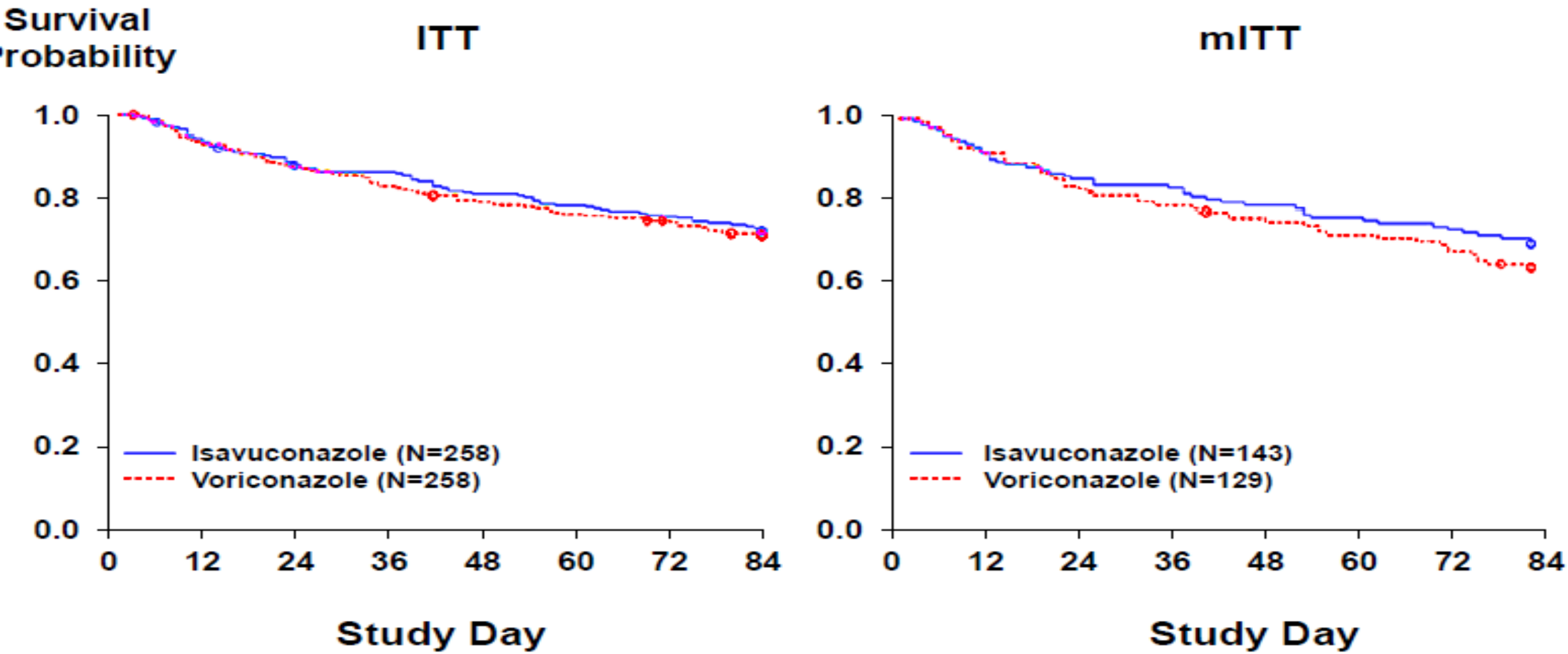
Isavuconazole (ISA)

- IV and oral formulations
- Rapidly hydrolyzed by esterases
- Active moiety isavuconazole
- Highly water soluble prodrug
  - IV formulation: no cyclodextrin

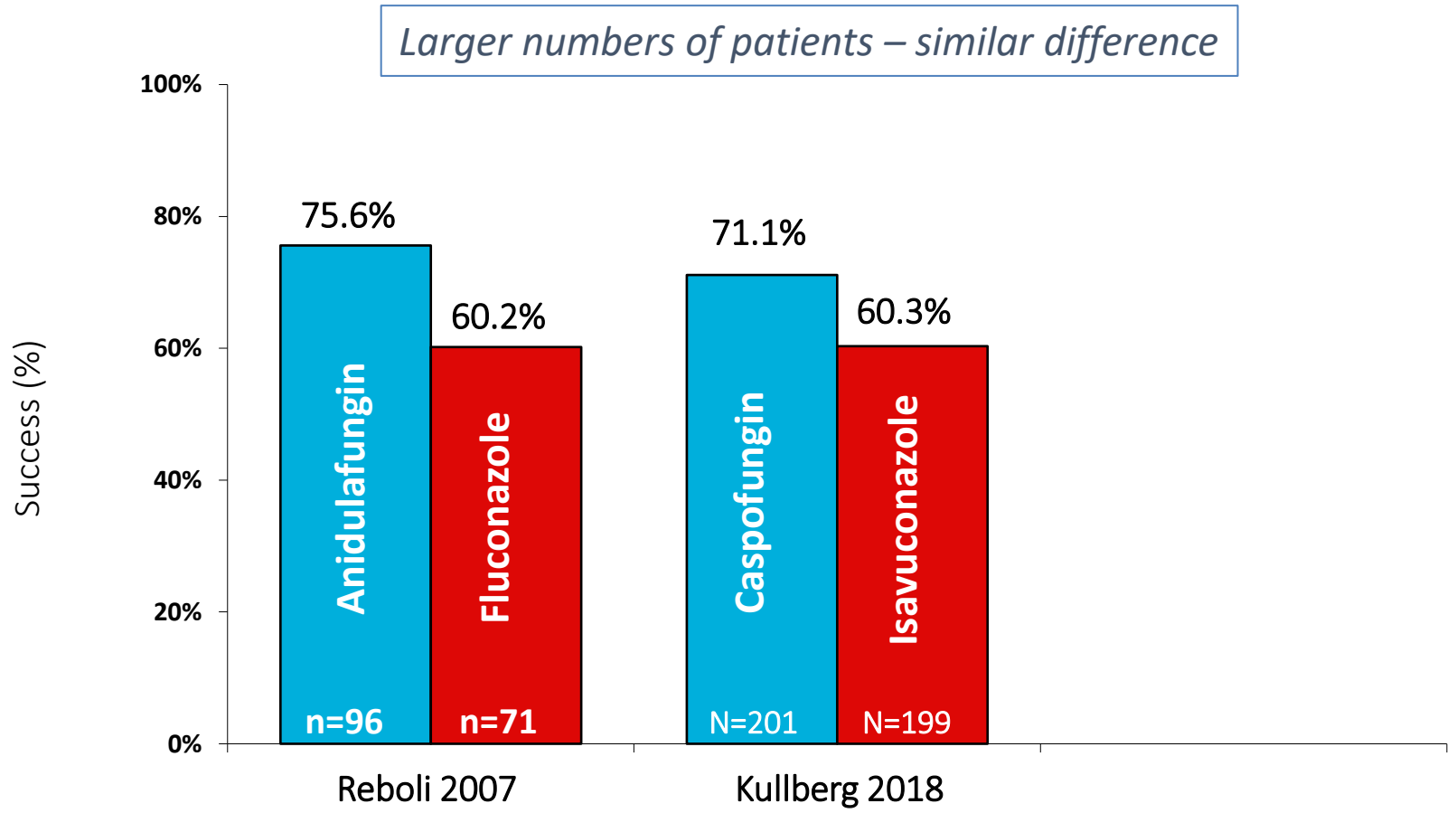
Isavuconazole Mechanism of Action



Study 0104: Survival Probabilities Over Time (ITT and mITT)



Isavuconazole vs. caspofungin invasive candidiasis: *the second azole vs. echinocandin trial*

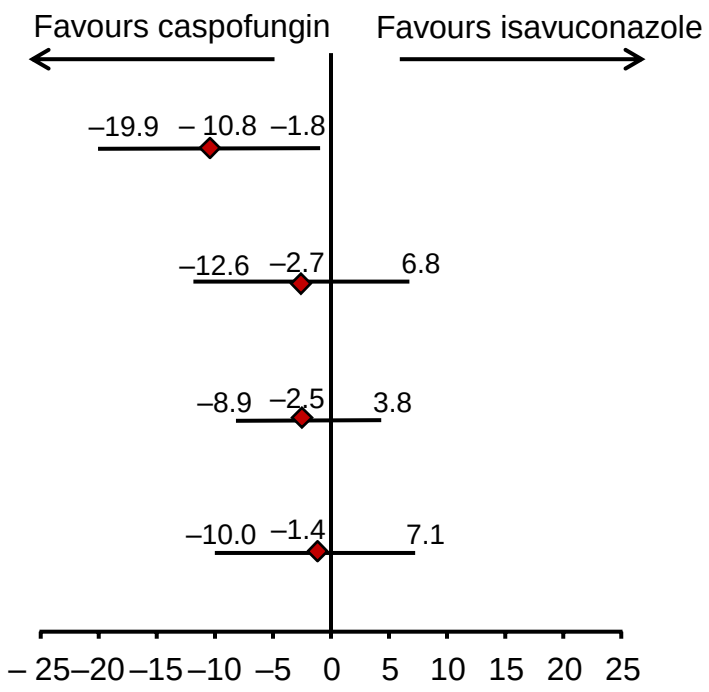


1. Reboli AC, et al. *N Engl J Med* 2007; 356(24):2472–82
2. Kullberg BJ, et al. Clin Infect Dis 2018 in press; presented at ECCMID 2016, Abstr #O423

Efficacy outcomes

Category, n (%)	Isavuconazole (n = 199)	Caspofungin (n = 201)
Successful overall response at EOIV*	**120 (60.3)**	**143 (71.1)**
Successful overall response at EOT + 2 weeks	109 (54.8)	115 (57.2)
All-cause mortality Day 14	29 (14.6)	25 (12.4)
All-cause mortality Day 56	61 (30.7)	60 (29.9)

*Stratified by geographical region and baseline neutropenia status



Adjusted difference (%; 95% CI) between isavuconazole versus caspofungin

Safety and tolerability

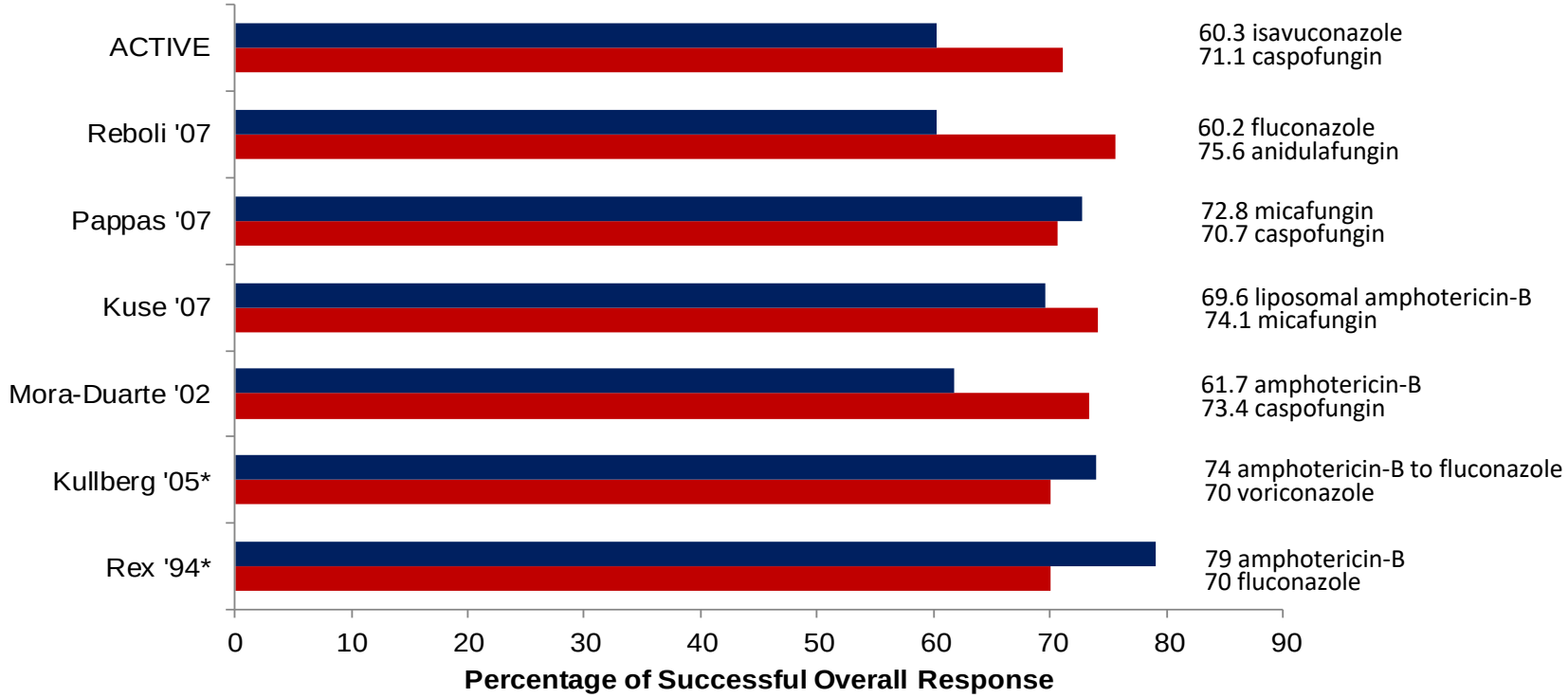
Overview of treatment emergent adverse events (TEAEs) and death

Safety population, n (%)	Isavuconazole (n = 220)	Caspofungin (n = 220)
Number of subjects ≥1 TEAE	209 (95.0)	208 (94.5)
Study drug-related TEAE	78 (35.5)	71 (32.3)
Serious TEAE	112 (50.9)	106 (48.2)
Study drug-related serious TEAE	19 (8.6)	12 (5.5)
TEAE leading to discontinuation of study drug	22 (10.0)	23 (10.5)
Study drug-related TEAE leading to discontinuation	11 (5.0)	11 (5.0)
Death	66 (30.0)	68 (30.9)

Most frequent TEAEs (≥10% of patients in either treatment groups)

TEAE, n (%)	Isavuconazole (n = 220)	Caspofungin (n = 220)
Hypokalaemia	43 (19.5)	45 (20.5)
Pyrexia	40 (18.2)	41 (18.6)
Diarrhoea	34 (15.5)	41 (18.6)
Vomiting	34 (15.5)	39 (17.7)
Constipation	32 (14.5)	24 (10.9)
Hypotension	25 (11.4)	28 (12.7)
Nausea	22 (10.0)	31 (14.1)
Hypomagnesaemia	19 (8.6)	29 (13.2)

Comparison of outcomes at EOIV treatment for various invasive candidiasis trials



*Rex et. al. and Kullberg et. al. - Overall response assessment not at EOIV treatment

Oral azoles in the treatment of IFIs

Fungal Disease	First Choice Azole	Alternative Azole
Candidiasis		
Candidemia	Flu	Vori
Invasive Disease	Flu	Vori
Coccidioidomycosis		
Nonmeningeal	Itra or Flu	Posa
Meningeal	Flu	—
Cryptococcosis		
Primary Rx	Flu	Vori
Maintenance Rx	Flu	Vori

Oral azoles in the treatment of IFIs

Fungal Disease	First Choice	Alternate
Aspergillosis	Vori, Posa,Isavu	NA
Blastomycosis	Itra	Posa, Vori, Flu
Histoplasmosis	Itra	Posa/Vori
Paracoccidioidomycosis	Itra	Posa, Vori
Sporotrichosis	Itra	Posa
Mucormycosis	Posa	Isavu

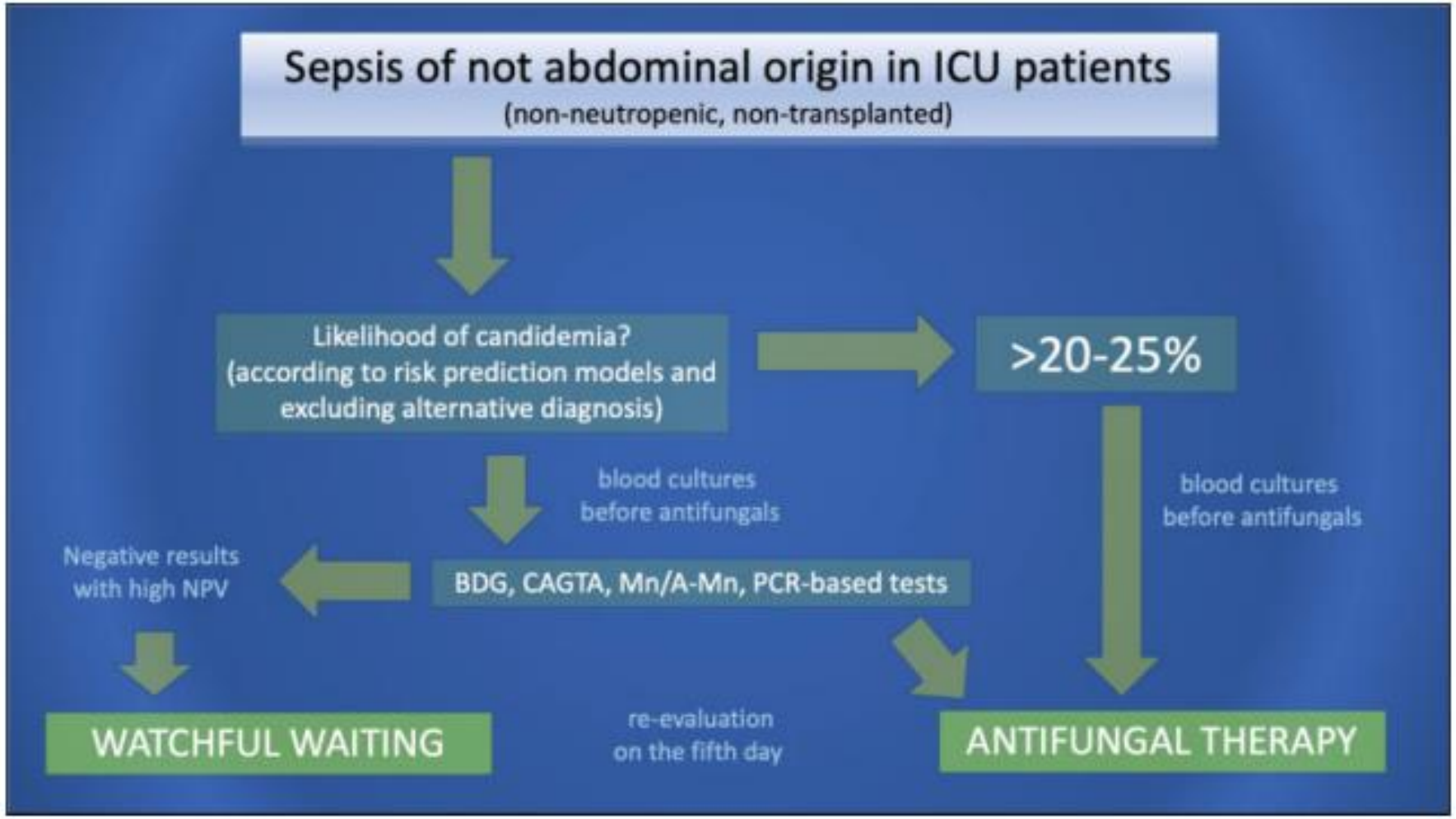


Fig. 1 Possible diagnostic algorithm in ICU patients with suspected candidemia according to the combined task force of the systemic inflammation and sepsis and infection sections of ESICM and the critically ill patients study group of ESCMID.[17] (Modified from Martin-Loeches et al 2019[17].) A-Mn, antimannan antibodies; BDG, (1,3)-β-D-glucan; CAGTA, *C. albicans* germ tube antigen; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; ESICM, European Society of Intensive Care Medicine; ICU, intensive care unit; Mn, mannan antigen; PCR, polymerase chain reaction.

Candidemia – Who is at risk?

Table 2. Risk for candidemia is a continuum.[a]

- General risk factors upon admission to hospital
  - Hematologic malignancy
  - Neutropenia
  - Abdominal surgery
  - Solid organ transplant
  - Premature infant
  - Older adult (>70 years of age)
- Specific exposures that further increase risk (OR odds ratio)
  - Intensive Care Unit stay >7 days (OR, 9.73)
  - Central venous catheter (OR, 7.23)
  - Dialysis (OR, 18.13)
  - Antibiotics (OR, 1.73 per antibiotic class)
  - Total parenteral nutrition (OR, 8.87)
  - Colonization (OR, 10.37)

[a]Compiled from refs 44 and 96.

Pfaller Medical Mycology 2016

Case #1

- 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 a 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

Case #1

- Blood cultures are obtained. Vancomycin and fluconazole 400 mg/d are added empirically to piperacillin/tazo. BP stablizes, 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 albicans*.

Question #1

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

1. Continue fluconazole, but increase to 800mg/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

Question #1

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

1. Continue fluconazole, but increase to 800mg/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

Hospital Course

- *Candida albicans* MICs: Flu 0.5, Mica 0.01, AmB 0.5
- Patient becomes afebrile and transferred to surgical floor
- Follow up blood cultures from day 8 post-op are negative.
- Taking oral meds on post-op day 12, ready for discharge home

Question #2

What should the patient receive as antifungal therapy at discharge?

1. Continue micafungin via PICC line through post-op day 22 (14 d from first negative BC
2. Transition to po fluconazole 400 mg d through po day 22
3. Obtain compassionate rezafungin and administer as a single dose at discharge
4. There is no need for continued antifungal therapy

Question #2

What should the patient receive as antifungal therapy at discharge?

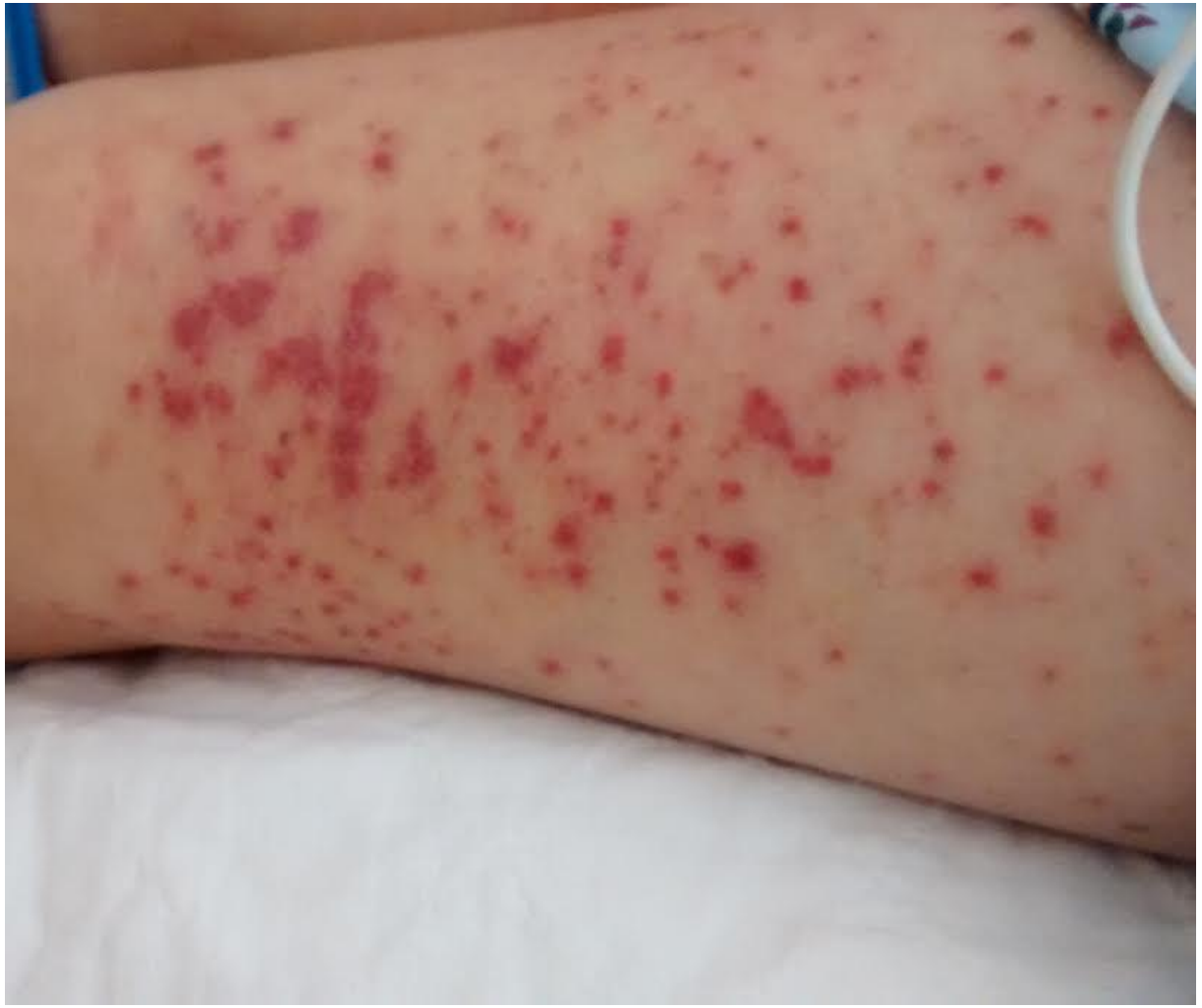
1. Continue micafungin via PICC line through post-op day 22 (14 d from first negative BC
2. Transition to po fluconazole 400 mg d through po day 22
3. Obtain compassionate rezafungin and administer as a single dose at discharge
4. There is no need for continued antifungal therapy

Case #2

58 YOWF with AML was admitted after a second round of consolidation chemotherapy. She has been receiving fluconazole continuously since induction chemo 12 weeks ago. On day 3 of this admission she developed persistent fever, and has developed and erythema around the Hickman catheter.

Initial blood cultures were negative, and the catheter was removed. Fluconazole was stopped; Micafungin was started in addition to empiric vancomycin and cefepime.

Now, on day 10 of neutropenia and fever, she has a developed widespread erythematous rash which is palpable, non-blanching and non-painful.



Other lab results:

- Serum galactomannin 0.085
- Bronchoscopy negative for growth
- Dermatology biopsy:
  - **prelim read shows a large collection of neutrophils concerning for infectious etiology. very concerning for disseminated candidiasis.**
- Blood cultures positive for *Candida glabrata*

Question #1

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

1. Continue fluconazole, but increase to 800mg/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

Question #1

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

1. Continue fluconazole, but increase to 800mg/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

Hospital Course

3 days after being drawn, 2/2 blood cultures return positive for *Candida glabrata* (fluconazole MIC >64 mcg/ml, micafungin MIC >0.5).

Lipid AmB 5mg/kg is initiated. 3 days later repeat BC are negative, neutropenia resolves within 7 d, and the pt is discharged home after completing a 14 day course of LAmB.

Help is on the way: Investigational antifungal compounds

- SCY078 (Scynexis): po available only for now. Glucan synthase inhibitor, similar MOA to the echinocandins. Phase II study favorable. Salvage study in progress (FURI)
- Rezafungin (Cidara): long acting ECH, similar to anidulafungin. Phase 3 IC study recently completed with favorable results. Additional plans for large (400-600 pts) study of allo SCT pts for primary AF/PJP prophylaxis. Only iv
- Fosmanogepix: excellent activity vs Candida spp (except *C krusei*), including *C auris.* Active vs *Cryptococcus* spp, *Aspergillus*. Available iv/po. IC study in progress.

Help is on the way: Continued

- Olorofim (F2G): active vs many molds, including *Scedosporium, Lomentosporum, Aspergillus*, *Fusarium, Scopulariopsis,* dematiaceous molds. Ongoing ‘salvage’ study among mold infected pts not responding to other AFT. IAstudy planned soon. Available po only
- Matinas (M2307): Orally/iv available cochleate formulation of AmB. New delivery method. Possibly less toxic than conventional AmB. Other compounds being considered (amikacin, atovaquone). Crypto meningitis, VVC and severe OPC/EC studies in progress.
- T2307(Toyama):iv only, mitochondrial inhibition, in vitro activity vs all Candida spp, Cryptococcus, Aspergillus. Ph II trial in development


Thank you!
Beartooth Plateau, Montana