MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

The good news: Making best use of current and new antifungal therapy

Dr Tan Ban Hock
Senior Consultant
Department of Infectious Diseases
Singapore General Hospital
Singapore

ASIA FUNGAL WORKING GROUP
an ISHAM working group

Good news – best use of new and old antifungal agents

BH Tan
Department of Infectious Diseases
Singapore General Hospital

Aspergillosis Case-Fatality Rate: Systematic Review of the Literature

Swu-Jane Lin,[1] Jennifer Schranz,[2] and Steven M. Teutsch[3]

Clinical Infectious Diseases 2001; 32:358–66

Literature rv 1941 cases, 1995 – 1999

CFR (overall) 55%
CFR (HSCT) 86%
CFR (cns or dissem) 88%

Epidemiology and clinical characteristics of invasive mould infections: A multicenter, retrospective analysis in five Asian countries

P. Rotjanapan[1], Y. C. Chen[2], A. Chakrabarti[3], B. Y. Li[4], S. M. Rudramurthy[3], J. Yu[4], H. C. Kung[2], S. Watcharananan[1], A. L. Tan[5], S. E. Saffari[6] and B. H. Tan[7,*]

Medical Mycology, 2018, 56, 186–196

90-day mortality 32%

Invasive Aspergillosis in Patients with Acute Leukemia: Update on Morbidity and Mortality—SEIFEM-C Report

Clinical Infectious Diseases 2007; 44:1524–5

1987 – 1998: AMR 48%
1999 – 2003: AMR 39%
2002 – 2003: AMR 32%
2006: AMR 13%

AMR – attributable mortality rate; CFR – case fatality rate
Asiamold – all proven/probable invasive mould disease, 2012

Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial

	ISV	VRC	95% CI
All-cause mortality			
ITT 42d ACM	19%	20%	-1 (-7.8 to 5.7)
ITT 84d ACM	29%	31%	-1.4 (-9.2 to 6.3)
mITT 42d ACM	20%	23%	-2.6 (-12.2 to 6.9)
mITT 84d ACM	30%	37%	-5.5 (-16.1 to 5.1)
myITT 42d ACM	19%	22%	-2.7 (-12.9 to 7.5)
myITT 84d ACM	28%	36%	-5.7 (-17.1 to 5.6)

ITT: all who were enrolled, randomly assigned & received at least 1 dose of study drug
mITT: all ITT patients with proven or probable IMD
myITT: subset of mITT patients with proven or probable IA
ACM: all-cause mortality

Lancet 2016; 387: 760–69

Lancet 2016;387:760

ISV *vs* VRC – safety data

	ISV	VRC	p
Skin	**33%**	**42%**	**0.037**
Rash	7%	11%	
Erythema	4%	6%	
Eye	**15%**	**27%**	**0.002**
Impairment	2%	7%	
Photophobia	1%	2%	
Psy	**27%**	**33%**	**0.1515**
Hallucinations	2%	4%	
Hepatobiliary	**9%**	**16%**	**0.016**
↑ bilirubin	2%	4%	

Lancet 2016; 387: 760–69

From the 2018 ESCMID-ECMM-ERS aspergillosis guidelines

Host	Drug	SoR		
Neutropenic Allo-SCT (neutropenic) Allo-SCT (non-neutropenic)	ISV	AI	DIII, if mold-active prophylaxis	CIII for oral start
	VRC	AI		
	L-AmB	B1		
	Caspofungin	CII		
	Conv-AmB	DI		

HIV	VRC	AIII	Beware drug interactions!
SOT, any	VRC	AIII	Beware drug interactions!
SOT, any	LAmB	AII	
SOT, VRC contraindicated	Caspofungin	BIII	

Ullmann AJ et al. Clin Micro Infect 2018;24:e1

VITAL – ISV for mucormycosis

- Single-arm, open label – eligible if mucor by EORTC/MSG criteria
- Comparator – matched patients from FungiScope
- Each patient on ISV matched with up to 3 from FungiScope who received amB for proven/probable mucor
- Matching based on
  - Severe or not (ie CNS or disseminated = severe)
  - Surgery or not within 7 days of starting antifungal
  - Haematological malignancy or not

- 37 with mucormycosis (32 of which were "proven")
- Of 37, 21 for 1^0 treatment, 11 refractory to other treatment, 5 intolerant of other treatment
- **1^0 end point – response on D42 (data review committee-determined)**

Marty FM et al. Lancet Infect Dis 2016;16:828

	Isavuconazole	Amphotericin B
Number of patients	21	33
Year of diagnosis	2008–13	2005–13
Median age, years (IQR)	51 (46–57)	57 (49–65)
Sex		
Men	17 (81%)	22 (67%)
Women	4 (19%)	11 (33%)
Race		
White	12 (57%)	31 (94%)
Asian	8 (38%)	2 (6%)
Black	1 (5%)	0
Median weight, kg (IQR)	81 (53–91)	70 (58–80)
Underlying disorder		
Immunosuppressant use	9 (43%)	9 (27%)
Baseline neutropenia	4 (19%)	8 (24%)
Diabetes	4 (19%)	6 (18%)
HSCT	4 (19%)	5 (15%)
GVHD treatment	4 (19%)	3 (9%)
Solid organ transplant	1 (5%)	3 (9%)
Diagnostic certainty		
Proven	18 (86%)	20 (61%)
Probable	3 (14%)	13 (39%)
Pathogen		
Actinomucor spp	1 (5%)	0
Lichtheimia spp	2 (10%)	6 (18%)
Mucor spp	6 (29%)	5 (15%)
Mucorales moulds	6 (29%)	7 (21%)
Rhizomucor spp	2 (10%)	2 (6%)
Rhizopus spp	4 (19%)	13 (39%)
Disease location		
Pulmonary only	1 (5%)	10 (30%)
Pulmonary and other organ	8 (38%)	7 (21%)
Non-pulmonary only	12 (57%)	16 (48%)

	Isavuconazole	Amphotericin B
(Continued from previous column)		
Disseminated disease	8 (38%)	8 (24%)
Matching covariate†		
Haematological malignancy	11 (52%)	18 (55%)
Severe disease‡	12 (57%)	13 (39%)
Surgical treatment§	9 (43%)	13 (39%)
Primary treatment¶		
Isavuconazole	21 (100%)	0
Deoxycholate amphotericin B	0	7 (21%)
Liposomal amphotericin B	0	22 (67%)
Amphotericin B lipid complex	0	4 (12%)
Median daily dose, mg (range)		
Isavuconazole	200‖	..
Deoxycholate amphotericin B	..	70 (50–80)
Liposomal amphotericin B	..	350 (20–1000)
Amphotericin B lipid complex	..	325 (250–350)
Median treatment duration, days (IQR)		
Isavuconazole	102 (27–180)**	..
Amphotericin B	..	18 (13–34)
Amphotericin B followed by posaconazole‡	..	34 (14–111)

ISV for mucormycosis, primary end-point

	Isavuconazole	Amphotericin B	p value
Crude all-cause mortality, n/N (%; 95% CI)*	7/21 (33%; 14·6–57·0)	13/33 (39%; 22·9–57·9)	p=0·775†
Weighted all-cause mortality (%;‡ 95% CI)*	33%; 13·2–53·5	41%; 20·2–62·3	p=0·595§
Crude mortality by matching covariates, n/N (%)			
Haematological malignancy	5/11 (45%)	7/18 (39%)	NA
Severe disease¶	6/12 (50%)	8/13 (62%)	NA
Surgical treatment‖	4/9 (44%)	3/13 (23%)	NA

*weighted to the no. of controls (because not every case had the same no. of controls)

Marty FM et al. Lancet Infect Dis 2016;16:828

ISV for mucormycosis, primary end-point

	Primary treatment group (N=21)	Refractory group (N=11)	Intolerant to other antifungals group (N=5)	Total (N=37)
DRC-assessed overall response at day 42				
Complete response	0	0	0	0
Partial response	3 (14%)	1 (9%)	0	4 (11%)
Stable disease	9 (43%)	4 (36%)	3 (60%)	16 (43%)
Progression of disease	1 (5%)	0	0	1 (3%)
Death	7 (33%)	4 (36%)	2 (40%)	13 (35%)
Missing data	1 (5%)	2 (18%)	0	3 (8%)
DRC-assessed overall response at day 84				
Complete response	1 (5%)	1 (9%)	0	2 (5%)
Partial response	1 (5%)	3 (27%)	1 (20%)	5 (14%)
Stable disease	9 (43%)	0	2 (40%)	11 (30%)
Progression of disease	0	1 (9%)	0	1 (3%)
Death	9 (43%)	4 (36%)	2 (40%)	15 (41%)
Missing	1 (5%)	2 (18%)	0	3 (8%)

65% survival (d42)

59% survival (d84)

Marty FM et al. Lancet Infect Dis 2016;16:828

Comparisons

- Fungiscope data (41 cases)[1] – overall survival 51.2%
- DEFEAT study[2]
  - LamB only – 30-day survival 89% (8/9), 90-day survival 78% (7/9)
  - LamB + deferasirox – 30-day survival 55% (6/11), 90-day survival 18% (2/11)
- Hi-dose (10mg/kg/d) LamB[3] – wk4 survival 79% (27/34), w12 survival 62% (21/34) [serum Cr doubled in 40%]

[1]Ruping MJGT et al. J Antimicrob Agents Chemother 2010;65:296

[2]Spellberg B et al. J Antimicrob Agents Chemother 2012;67:715

[3]Lanternier F et al. J Antimicrob Agents Chemother 2015;70:3116

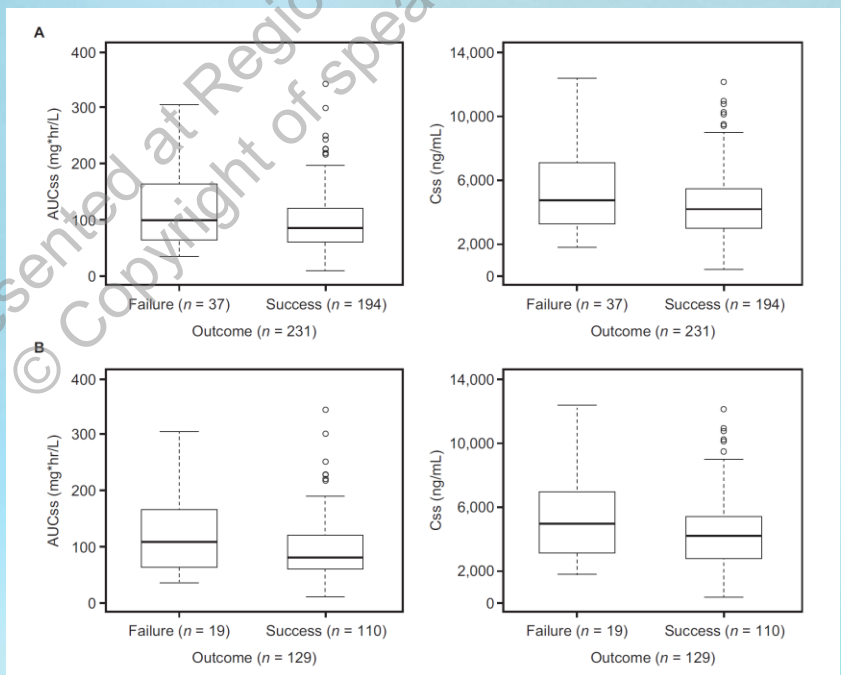
Isavuconazole – some PKPD information

- Oral has excellent bioavailability
- No need for dose adjustments btw po, IV
- Absorption not affected by food or drugs that raise pH
- C_{max} achieved at the end of 1-hr infusion or 90-180 min after oral dose
- High Vd
- Renal impairment doesn't affect C_{max} or AUC
- Hepatic impairment likely reduces clearance
- Does not appear in urine
- IV formulation has no cyclodextrin

McCarthy MW et al. Clin Pharmacokinet 2018

Exposure-response relationships

(data from SECURE study)



A: ITT population, B: mITT population

Desai AV et al. AAC 2017

Why no exposure-response relationship?

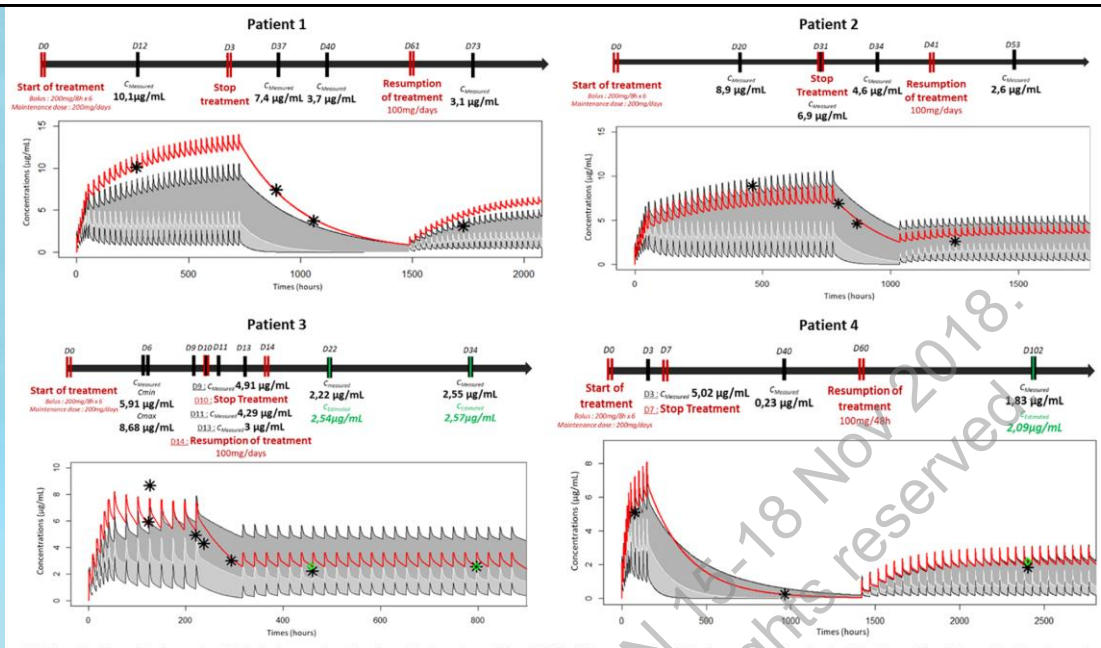
- A lot of non-compliance? (but no evidence for this)
- Perhaps there is a sigmoidal exposure-response relationship? Then all exposures were on plateau (ie, all exposures supra-threshold)
- Probably not necessary to do ISV TDM routinely
- TDM might be necessary if absorption is suspect (eg GVH), infection is in CNS, and if used in children (insufficient data)

Desai AV et al. AAC 2017

Encountered 4 patients whose levels were high and which exceeded the PK profiles of the SECURE study

Patient	Clinical information						Pharmacogenetics	Pharmacokinetic parameters			Individualized dose adjustment	
	Sex	Age, years	Ethnic group	BMI (kg/m²)	Co-prescription	Adverse effects	CYP3A4*1 CYP3A5*3	Clearance (L/h)	Distribution volume (L)	Half-life (h)	New dose (mg/24 h)	TDM
1	Male	70	Caucasian	20.8	Methotrexate Prednisone Esomeprazole	Patellar tendinopathy	CYP3A4: 1*/1* CYP3A5: 3*/3*	0.62	120.23	190.01	100	
2	Female	52	Caucasian	20.2	Prednisone	Discomfort	CYP3A4: 1*/22* CYP3A5: 3*/3*	1.09	196.77	161.28	100	
3	Male	38	Caucasian		Prednisone		CYP3A4: 1*/1* CYP3A5: 3*/3*	1.41	88.14	69.00	100	2.22 µg/mL measured for 2.54 µg/mL estimated 2.55 µg/mL measured for 2.57 µg/mL estimated
4	Female	50	Caucasian		Levothyrox Oxazepam Zopiclone Clonazepam		CYP3A4: 1*/22* CYP3A5: 3*/3*	1.03	141.23	134.40	100	1.83 µg/mL measured for 2.09 µg/mL estimated

Darnaud L et al. Drugs R&D October 2018



Median kinetic profile (curve in white), "extremes" profiles found in less than 5% and 95% of the population (black curves) and estimated kinetic profile of the patient (red curve); the black stars represent the measured concentrations while the green ones represent the estimated trough concentrations in case of individualized dosage adjustment and the therapeutic drug monitoring confirmed the estimated values.

"... we suggest collecting one blood sample just before the first maintenance dose to provide an estimation of the patient's most likely pharmacokinetic profile using Desai's POP-PK model. If the profile fits .... there is no need for TDM ..."

Darnaud L et al. Drugs R&D October 2018

Compound (mg)	Enzymatic target	Effect on isavuconazole	Isavuconazole effect on compound
Warfarin (20)	CYP2C9	No effect	11–20% increase in mean AUC
Atorvastatin (20)	OATP1B1 and P-gp substrate	No effect	137% increase in mean AUC
Methotrexate (7.5)	BCRP, OAT1, and OAT3 substrate	No effect	No effect
Digoxin (0.5)	P-gp substrate	No effect	125% increase in mean AUC
Metformin (850)	OCT1, OCT2, and MATE1 substrate	No effect	152% increase in mean AUC
Cyclosporine (300)	CYP3A4	No effect	29% increase in AUC
Mycophenolic acid (1000)	CYP3A4	No effect	35% increase in AUC
Prednisone (20)	CYP3A4	No effect	8% increase in AUC
Tacrolimus (5)	CYP3A4	No effect	125% increase in AUC
Sirolimus (2)	CYP3A4	No effect	84% increase in AUC
Rifampin (600)	CYP3A4	90% decrease in AUC	
Ketoconazole (200 twice daily)	CYP3A4	422% increase in AUC	127% increase in AUC
Midazolam (3)	CYP3A4	No effect	103% increase in AUC
Ethinyl estradiol	CYP3A4	No effect	8% increase in AUC
Lopinavir/ritonavir (400/100)	CYP3A4	113% increase in AUC	27% decrease in lopinavir AUC 31% decrease in ritonavir AUC

McCarthy MW et al. Clin Pharmacokinet 2018

Isavuconazole Treatment of a Patient with Disseminated Mucormycosis

Peixoto D et al. J Clin Microbiol 2014;52:1016

MDS-AML, relapsed after HSCT, developed brain and skin lesions while on salvage therapy. Skin biopsy *Rhizopus pusillus*. Improved with LamB x 4 wk but worsened on po posaconazole. Re-institution of LamB →
K, Mg wasting, so ISV with good effect

Widespread *Lichtheimia* Infection in a Patient with Extensive Burns: Opportunities for Novel Antifungal Agents

Thielen BK et al. Mycopathologia 2018

47% burns developing white patches on Integra, skin, biopsy with non-septate hyphae (eventually Lichtheimia). Posaconazole started but more whitepatches. LamB started but Cr rose, urine output fell. ISV → good response, total 6 wk

To prefer ISV or VRC?

Listed advantages of ISV

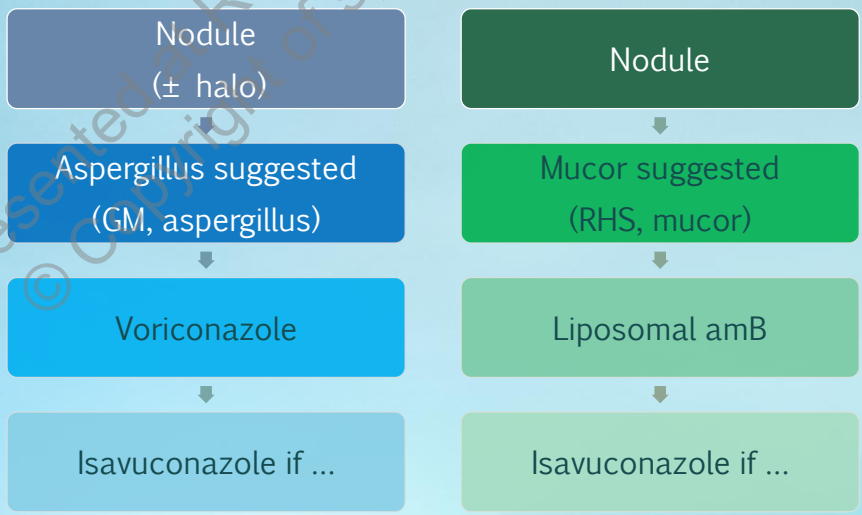
- Water-soluble, no cyclodextrin vehicle – no worries about accumulation in ESRD
- Favourable side effect profile in SECURE study (wrt LFT)
- No QT prolongation (it shortens QT)

But

- Small clinical experience thus far
- Role of TDM uncertain

Rybak JM et al. Pharmacother 2015;35:1037

Lung nodules in compromised hosts – a personal approach



If ... QTc prolonged, Cr precarious, concomitant nephrotoxic agent, pt on HD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Anidulafungin versus Fluconazole for Invasive Candidiasis

Annette C. Reboli, M.D., Coleman Rotstein, M.D., Peter G. Pappas, M.D., Stanley W. Chapman, M.D., Daniel H. Kett, M.D., Deepali Kumar, M.D., Robert Betts, M.D., Michele Wible, M.S., Beth P. Goldstein, Ph.D., Jennifer Schranz, M.D., David S. Krause, M.D., and Thomas J. Walsh, M.D., for the Anidulafungin Study Group

The New England Journal of Medicine

COMPARISON OF CASPOFUNGIN AND AMPHOTERICIN B FOR INVASIVE CANDIDIASIS

JORGE MORA-DUARTE, M.D., ROBERT BETTS, M.D., COLEMAN ROTSTEIN, M.D., ARNALDO LOPES COLOMBO, M.D., LUIS THOMPSON-MOYA, M.D., JUANITA SMIETANA, B.S., ROBERT LUPINACCI, M.S., CAROLE SABLE, M.D., NICHOLAS KARTSONIS, M.D., AND JOHN PERFECT, M.D., FOR THE CASPOFUNGIN INVASIVE CANDIDIASIS STUDY GROUP*

Results

NEJM 2002;347:2020-9 **TABLE 4.** FAVORABLE RESPONSES TO TREATMENT.

TIME POINT	MODIFIED INTENTION-TO-TREAT ANALYSIS		PATIENTS WHO MET CRITERIA FOR EVALUATION	
	CASPOFUNGIN (N=109)	AMPHOTERICIN B (N=115)	CASPOFUNGIN (N=88)	AMPHOTERICIN B (N=97)
	no. with a favorable response/total no. (%)			
End of intravenous therapy	80/109 (73.4)	71/115 (61.7)	71/88 (80.7)	63/97 (64.9)*
Absolute neutrophil count at enrollment				
<500/mm³	7/14 (50.0)	4/10 (40.0)	6/8 (75.0)	3/8 (37.5)
≥500/mm³	73/95 (76.8)	67/105 (63.8)	65/80 (81.2)	60/89 (67.4)
APACHE II score				
≤20	68/88 (77.3)	61/92 (66.3)	61/76 (80.3)	53/78 (67.9)
>20	12/21 (57.1)	10/23 (43.5)	10/12 (83.3)	10/19 (52.6)
Day 10 of intravenous therapy†	66/75 (88.0)	64/75 (85.3)	59/67 (88.1)	55/64 (85.9)
At end of all antifungal therapy	79/109 (72.5)	71/115 (61.7)	70/88 (79.5)	63/97 (64.9)‡
2 Weeks after treatment§	56/88 (63.6)	56/104 (53.8)	52/72 (72.2)	49/86 (57.0)
6–8 Weeks after treatment§	47/83 (56.6)	47/99 (47.5)	44/67 (65.7)	41/82 (50.0)

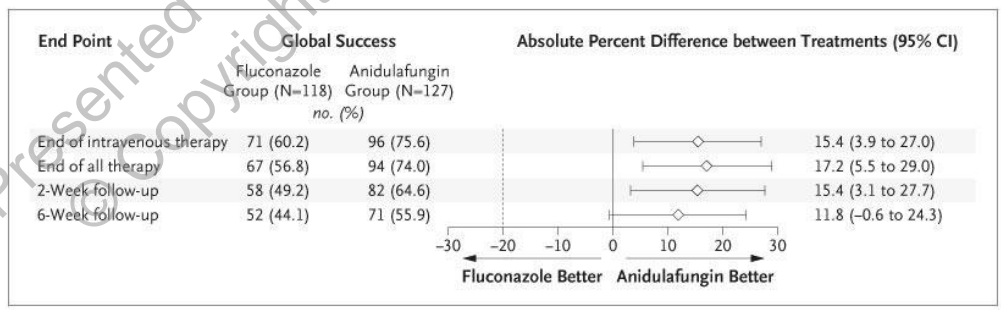
*P=0.03 for the difference between the two treatment groups.

†Only patients who received 10 days of intravenous therapy were included in the analysis.

‡P=0.05 for the difference between the two treatment groups.

§Treatment failures at the end of intravenous therapy were counted as treatment failures at all subsequent time points. Unfavorable responses after the end of intravenous therapy included all treatment failures at the primary time point and any relapses up until that point. Patients who had favorable responses at the end of intravenous therapy but subsequently withdrew from the study or were lost to follow-up were excluded from subsequent analyses unless a relapse was documented before withdrawal or loss to follow-up.

Global Response to Treatment for Prespecified Time Points (MITT Population)



Reboli AC et al. N Engl J Med 2007;356:2472

Candidemia Study: Baseline Patient Characteristics (MITT Population)

	Anidulafungin n=127	Fluconazole n=118
Mean APACHE* II score (range)	15.0 (2-42)	14.4 (3-36)
Predisposing factors: n (%)		
Central venous catheter	99 (78)	92 (78)
Broad-spectrum antibiotics	88 (69)	82 (70)
Recent surgery	53 (42)	51 (43)
Recent TPN†	31 (24)	31 (26)
Neoplastic disease	28 (22)	27 (23)
Immunosuppressive therapy	18 (14)	27 (23)
Disorder requiring transplantation	7 (6)	5 (4)
Renal insufficiency	47 (37)	41 (35)
Dialysis (all types)	21 (17)	18 (15)
Mechanical ventilation	32 (17)	13 (11)

*APACHE=Acute Physiology and Chronic Health Evaluation; †TPN=total parenteral nutrition.
Reboli AC et al. *N Engl J Med.* 2007;356:2472-2482.
Data on file. Pfizer Inc, New York, NY.

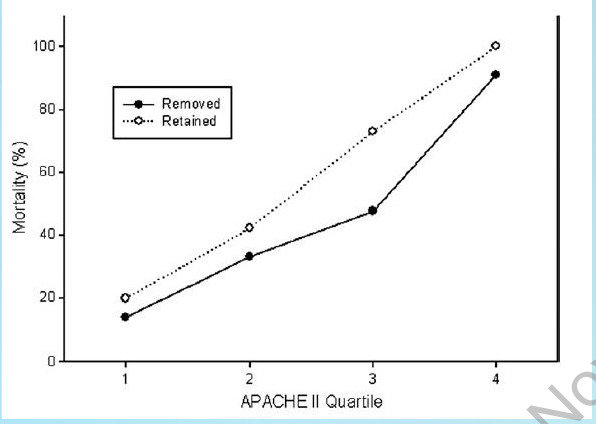
Impact of Treatment Strategy on Outcomes in Patients with Candidemia and Other Forms of Invasive Candidiasis: A Patient-Level Quantitative Review of Randomized Trials

7 RCTs, 1915 patients

Factors determining mortality (aggregate data set)
- Increasing age
- Higher APACHE II score
- Immunosuppressive therapy
- *Candida tropicalis*

Factors assoc with decreased mortality
- ✓ Removal of CVC (removal mort 28%, retention mort 41%, p<0.0001)
- ✓ Treatment with echinocandin

Andes DR et al. Clin Infect Dis 2012;52:1110



Removal of CVC had favorable impact on mortality in the lower 3 quartiles of APACHE scores (above)

Receipt of echinocandin had favorable impact on mortality in first 2 APACHE quartiles (no data shown)

Andes D et al. Clin Infect Dis 2012;54:1110

IDSA guide on candidemia (2009)

• Fluconazole (800mg loading, then 400mg om)	A1
• An echinocandin	A1
• Amphotericin B (0.5 – 1mg/kg/d)	A1*
• Lipid formulation of amphotericin B	A1*
• Voriconazole	A1

- *if other antifungals not available

Pappas PG et al. Clin Infect Dis 2009;48:503

Candida 2012 – ESCMID guide

Treatment of candidemia

- Anidulafungin A1
- Caspofungin A1
- Micafungin A1
- Ambisome B1
- Voriconazole B1
- Fluconazole C1

Cornely OA et al. Clin Micro Infect 2012;18(Supp 7):19

Inferiority of Fluconazole

- One study (Reboli)
- Outdone by anidulafungin at various time points in the end-point analysis (Reboli)
- Across range of APACHE scores (Reboli)
- Lack of activity against *C. krusei*, doubtful against *C. glabrata* (2nd most commonly-isolated species in the US, and several other developed countries)

Hence downgraded by ESCMID

Cornely OA et al. Clin Micro Infect 2012;18(Supp 7):19

IDSA guide on candidemia, 2016

- Echinocandin is recommended as initial therapy
- Fluconazole is an acceptable alternative in selected patients (eg not critically ill, unlikely to have fluconazole-resistant Candida)
- Lipid formulation of amB an alternative if intolerance, limited availability, or resistance to other agents
- Voriconazole offers little advantage over fluconazole for initial therapy

Pappas PG et al. Clin Infect Dis 2016;62:409

Breakthrough *C. parapsilosis* and *C. guilliermondii* blood stream infections in allogeneic hematopoietic stem cell transplant recipients receiving long-term caspofungin therapy

18yo male, failing HSCT, with IPA, now 2nd HSCT with VRC as 2⁰ proph
Switched to CSP on D7 (LFT abnormalities); no WBC recovery
D48, fever → bld c/s done → *C. parapsilosis*

46yo male undergoing HSCT with FLUC prophylaxis
CSP started on D6 empirical treatment for FN
Severe GVHD → multiple immunosuppressives → CMV infection
On d58 - 60, fever → daily bld c/s →all *C. parapsilosis*

32yo male, HSCT while on FLUC prophylaxis; with WBC engraftment D21
GVHD → multiple immunosuppressives →CMV infection, bacteremia
D95: switched from FLUC to CSP (LFT abnormalities)
D118: fever → bld c/s → *C. guilliermondii*

Kabbara N et al. Haematologica 2008;93:639

Fatal *Trichosporon* fungemia in patients with hematologic malignancies

European Journal of Haematology 84 (441–447)

Of 33 cases of trichosporonemia, 30 (91%) were breakthrough infections
18/30 of these cases had been on micafungin

Selection of Resistant Fungi in Liver Transplant Recipients During Use of Newer Antifungal Agents — A Report of Two Cases

Ann Acad Med Singapore 2011;40:287-90

Breakthrough mycoses on echinocandins

Primary prophylaxis

- CSP, MCF
- Median incidence 1.4% (0-6.6%)
- Duration of echinocandin exposure before b'thru: 63.5d (37-75)
- Candidiasis, aspergillosis, trichosporonosis, fusariosis, cryptococcemia

Therapeutic use

- CSP, MCF, ANF
- Median incidence 0% (0-13.6%)
- 13.6% - single study with 22 evaluable cases EOT
- Duration of use: 12-26d (CSP); 9 & 15d (MCF); 8 & 13d (ANF)
- Aspergillosis, candidiasis, zygomycosis, fusariosis

Sun HY et al. IJAA 2010;35:211

2 broad groups of Candida

Where caspofungin and anidulafungin are concerned

- *C. albicans, C. glabrata, C. tropicalis, C. krusei, C. kefyr* – all with very low MICs
- *C. parapsilosis, C. guillermondii, C. lusitaniae* – with somewhat higher MICs
- ***What is the clinical significance of these "somewhat higher" MICs?***

Why higher echinocandin MICs in *C. parapsilosis*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2008, p. 2305–2312 Vol. 52, No. 7
0066-4804/08/$08.00+0 doi:10.1128/AAC.00262-08

A Naturally Occurring Proline-to-Alanine Amino Acid Change in Fks1p in *Candida parapsilosis*, *Candida orthopsilosis*, and *Candida metapsilosis* Accounts for Reduced Echinocandin Susceptibility▽

Guillermo Garcia-Effron,[1] Santosh K. Katiyar,[2] Steven Park,[1] Thomas D. Edlind,[2] and David S. Perlin[1]*

These investigators

Purified GS from *C. parapsilosis* and from *C. albicans*

Inserted P660A mutation into *C. albicans* and extracted the GS from such mutant strains and measured MIC of such strains, as well as the amount of echinocandin needed to inhibit GS from mutant strains

TABLE 1. Profiles of in vitro whole-cell susceptibility (MIC) and GS inhibition (IC_{50}) in the strains included in the study

Organism	Strain	FKS1-HS1 sequence or genotype[a]	Origin	MIC (μg/ml)[b]			IC_{50} (ng/ml)[c]		
				ANF	CSF	MCF	ANF	CSF	MCF
C. parapsilosis	22019	FLTLSLRDA	ATCC	1.10	1.40	1.60	442.03 ± 38.41	21.21 ± 2.27	245.27 ± 37.17
C. parapsilosis	H4	FLTLSLRDA	Clinical	2.24	2.24	1.12	110.12 ± 16.44	79.19 ± 7.69	340.83 ± 41.98
C. parapsilosis	H5	FLTLSLRDA	Clinical	1.59	2.24	1.26	237.07 ± 19.86	12.53 ± 2.30	493.63 ± 134.27
C. orthopsilosis	H10	FLTLSLRDA	Clinical	0.79	1.00	0.63	163.17 ± 67.33	58.16 ± 3.66	152.70 ± 17.71
C. orthopsilosis	981224	FLTLSLRDA	Clinical	1.26	0.79	1.26	141.90 ± 13.77	75.26 ± 19.53	77.52 ± 45.08
C. metapsilosis	am-2006-0113	FLTLSLRDA	Clinical	0.63	0.79	1.59	126.40 ± 2.26	40.28 ± 5.94	70.32 ± 1.10
C. metapsilosis	960161	FLTLSLRDA	Clinical	0.79	1.00	1.59	133.30 ± 7.36	25.15 ± 0.43	113.73 ± 16.16
S. cerevisiae	BY4742	FLVLSLRDP	Parental	0.03	0.03	0.03	107.37 ± 14.90	65.54 ± 15.26	159.45 ± 7.00
S. cerevisiae	BY4742-P649A	FLVLSLRDA	Laboratory mutant	0.5	0.5	0.5	1,663.00 ± 18.00	1,328.67 ± 10.02	5,199.00 ± 132.94
S. cerevisiae	BY4742-FKS1Δ	*fks1D453-649::URA3*	Laboratory mutant	0.015	0.02	0.015	ND	ND	ND
C. albicans	Sc5314	FLTLSLRDP	Control strain	0.08	0.40	0.05	0.89 ± 0.06	3.88 ± 0.08	58.25 ± 0.32
C. albicans	90028	FLTLSLRDP	ATCC	0.02	0.20	0.03	1.63 ± 0.16	0.52 ± 0.04	10.20 ± 5.20
C. albicans	36082	FLTLSLRDP	ATCC	0.02	0.20	0.02	1.83 ± 0.10	0.60 ± 0.10	18.88 ± 2.00
C. albicans	M122	FLTLSLRDH	Clinical	0.15	4.00	0.25	530.13 ± 156.38	79.48 ± 5.92	943.10 ± 82.65
C. glabrata	90030	FLILSLRDP	ATCC	0.05	0.10	0.06	3.77 ± 1.44	3.12 ± 0.56	0.68 ± 0.27
C. glabrata	T51916	FLILSLRDT	Clinical	1.59	2.00	0.40	206.86 ± 15.03	157.50 ± 12.32	112.35 ± 2.05

Note;

- ✓ MIC of *C. parapsilosis* (and sibling strains) for all echinocandins higher than MIC of *C. albicans*
- ✓ IC30 of echinocandins for GS enzyme also higher for GS extracted from *C. parapsilosis* than for GS from wild-type *C. albicans*
- ✓ Inserting mutation into *S. cerevisiae* raises the MIC and the IC30 of its GS

Initial Use of Echinocandins Does Not Negatively Influence Outcome in *Candida parapsilosis* Bloodstream Infection: A Propensity Score Analysis

Subset of CANDIPOP study

Prospective multi-center survey (over 12 months) of candidemia in 29 hospitals in Spain

Looked for factors predicting "clinical failure" in 194 participants with *C. parapsilosis* in bloodstream

"Clinical failure" – any death between days 3 and 30 of + blood c/s or persistence of candidemia after 72 hrs of therapy

Fernandez-Ruiz M et al. Clin Infect Dis 2014;58:1413

	Univariate Analysis			Multivariate Analysis		
Variable	OR	95% CI	*P* Value	Adjusted OR	95% CI	*P* Value[b]
Orotracheal intubation at diagnosis	4.67	2.32–9.38	.000	2.81	1.19–6.65	.018
Septic shock	7.17	2.63–19.56	.000	2.91	.88–9.64	.081
Hematogenous dissemination	6.75	1.32–34.56	.016	7.42	.67–82.44	.103
Early CVC removal (≤48 h)	0.41	.20–.86	.016	0.43	.19–.96	.040
Initial antifungal therapy						
Azole-based regimen	1	. . .	. . .	1	. . .	. . .
Echinocandin-based regimen	1.34	.60–2.97	.479	1.73	.66–4.54	.265
Amphotericin B–based regimen	0.99	.40–2.45	.989	0.99	.34–2.89	.996
Combination regimen	0.86	.31–2.36	.769	1.06	.33–3.43	.922

In candidemia with *C. parapsilosis*, orotracheal intubation was only stat sig risk factor for mortality, and CVC removal was only stat sig protective factor

Initial therapy with an echinocandin was not a factor that predicted "clinical failure"

Fernandez-Ruiz M et al. Clin Infect Dis 2014;58:1413

Species (no. tested)	Antifungal agent[a]	No. at an MIC/MEC (μg/ml) of: 0.007	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128
Non-*Candida* yeasts																
Cryptococcus neoformans (84)	ANF												84			
	CSF											11	73			
	MCF												84			
	FLC							3	14	24	26	15	2			
	ITR			8	18	24	22	11	1							
	PSC		1	4	19	30	16	12	2							
	VRC	4	17	29	29	5										
Rhodotorula mucilaginosa (5)	ANF												5			
	CSF											2	3			
	MCF												5			
	FLC															5
	ITR								2	2		1				
	PSC								2	2	1					
	VRC							2			3					
Saccharomyces cerevisiae (6)	ANF				1	1	2	2								
	CSF					2	3	1								
	MCF					5	1									
	FLC								3	2	1					
	ITR						2	2	2							
	PSC						2	2	2							
	VRC			3	2	1										
Trichosporon asahii (9)	ANF												9			
	CSF										1	3	5			
	MCF												9			
	FLC							2		5	1					1
	ITR					1	1	5	2							
	PSC					2	3	3	1							
	VRC		1	2	3	1	1	1								

Pfaller MA et al. J Clin Microbiol 2013;51:2571

TABLE 1 Distribution of non-duplicate yeast isolates in blood or bone marrow specimens

Fungus	Number of isolates	(%)
Total yeast isolates	2155	100
Candida species	1980	91.9
Non-*Candida* spp.	175	8.1
Cryptococcus species[a,b]	109	5.1
Trichosporon species[a,c]	23	1.1
Rhodotorula species[a]	10	0.5
Kodamaea (Pichia) ohmeri[d]	7	0.3
Malassezia species[a,d]	4	0.2
Hansenula anomala (Pichia anomala)[d]	4	0.2
Hansenula polymorpha[d]	2	0.1
Yarrowia lipolytica[d]	2	0.1
Other non-*Candida* yeast[e]	14	0.6

[a]these yeasts have reduced susceptibility to echinocandins; ECMM recommends against echinocandins

Lin S-Y et al. Mycoses 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia

Oliver A. Cornely, M.D., Johan Maertens, M.D., Drew J. Winston, M.D., John Perfect, M.D., Andrew J. Ullmann, M.D., Thomas J. Walsh, M.D., David Helfgott, M.D., Jerzy Holowiecki, M.D., Dick Stockelberg, M.D., Yeow-Tee Goh, M.D., Mario Petrini, M.D., Cathy Hardalo, M.D., Ramachandran Suresh, Ph.D., and David Angulo-Gonzalez, M.D.*

N ENGL J MED 356;4 WWW.NEJM.ORG JANUARY 25, 2007

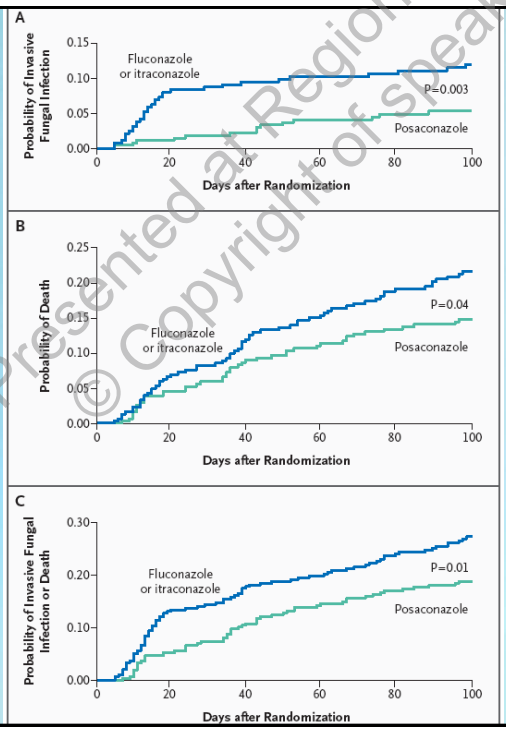


Figure 1. Kaplan–Meier Curves for Time to Invasive Fungal Infection (Panel A), Death from Any Cause (Panel B), and Invasive Fungal Infection or Death (Panel C) over the 100-Day Period after Randomization.

P values were estimated with the log-rank test. Data were censored on the last date of contact or on day 100 after randomization, whichever was sooner.

When using posaconazole, note

- Diarrhoea ↓ bioavailability by 59% (AAC 2010;54:207)
- Bioavailability poor in fasting state, enhanced with food or hi-calorie nutritious meals or acid-carbonated beverages (AAC 2009;53:4749)
- Plasma levels low (<500ng/ml) when diarrhoea or mucositis, and low plasma level was a/w breakthrough IFI (AAC 2009;53:5224)
- Some suggestion that avoiding PPIs helps elevate posa lvls (AAC 2009;53:4749, AAC 2009;53:3608)

Network meta-analysis, Singapore

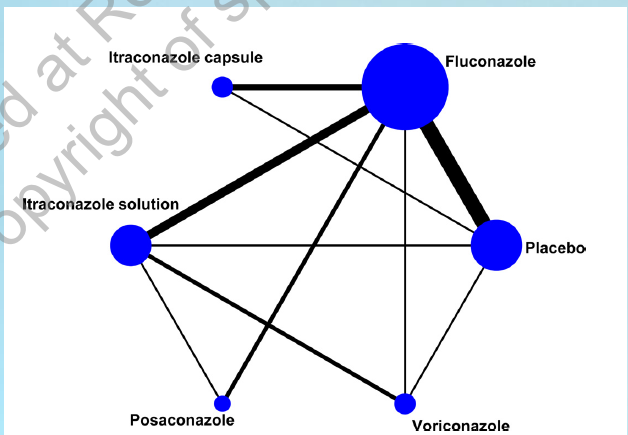


FIG 3 Network of all direct comparisons between triazole antifungal agents. The sizes of the nodes indicate the numbers of participants, and the widths of the lines indicate the numbers of included trials.

Zhao YJ et al. Antimicrob Agents Chemother 2016;60:376

Network meta-analysis, Singapore

Placebo	1.77 (0.85,3.71)	0.51 (0.02,15.28)	1.11 (0.47,2.62)	**0.12 (0.02,0.61)**	0.75 (0.26,2.14)
0.14 (0.08,0.25)	Fluconazole	0.29 (0.01,9.34)	0.62 (0.37,1.04)	**0.07 (0.01,0.29)**	**0.42 (0.20,0.90)**
0.33 (0.06,1.66)	2.35 (0.42,13.17)	Itraconazole capsule	2.18 (0.06,73.14)	0.23 (0.01,10.05)	1.47 (0.04,51.97)
0.08 (0.03,0.20)	0.58 (0.26,1.28)	0.25 (0.04,1.60)	Itraconazole solution	**0.10 (0.02,0.47)**	0.67 (0.28,1.61)
0.20 (0.05,0.78)	1.47 (0.43,4.98)	0.62 (0.08,5.15)	2.54 (0.64,10.16)	Posaconazole	**6.46 (1.22,34.04)**
0.09 (0.02,0.34)	0.64 (0.18,2.20)	0.27 (0.03,2.25)	1.10 (0.29,4.23)	0.43 (0.08,2.43)	Voriconazole

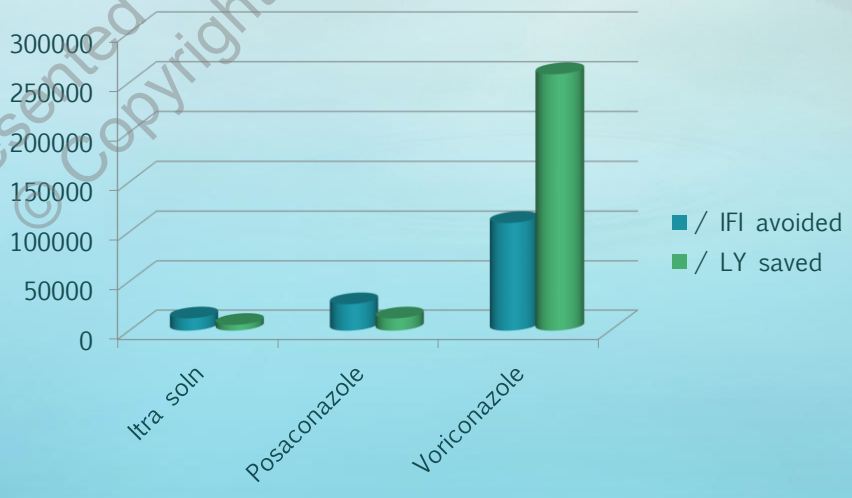
Invasive *Candida* infection Invasive *Aspergillus* infection

Posa > effective at preventing Aspergillus than
- Placebo (OR, 0.12 [95%CI 0.02-0.61])
- Fluconazole (OR, 0.07 [95%CI 0.01-0.29])
- Itra solution (OR, 0.1 [95%CI 0.01-0.47])
- Vori (OR, 6.46, [95%CI 1.22 – 34.04])

At preventing mortality
- Posa > effective than fluc, itra soln
- Fluc > effective than placebo
- Vori ≈ more effective than others (trend, p>0.05)
- Posa ≈ Vori

Zhao YJ et al. Antimicrob Agents Chemother 2016;60:376

ICERs of azoles in HSCT (incl vori)



Y axis units SGD; ICER – incremental cost effectiveness ratio

Zhao YJ et al. Antimicrob Agents Chemother 2016;60:376

Breakthrough *Rhizopus* infection on posaconazole prophylaxis following allogeneic stem cell transplantation

Bone Marrow Transplantation (2008) 42, 551–552

Breakthrough Disseminated *Scedosporium prolificans* Infection in a Patient with Relapsed Leukaemia on Prolonged Voriconazole Followed by Posaconazole Prophylaxis

M. R. Ananda-Rajah · A. Grigg · M. A. Slavin

Mycopathologia (2008) 166:83–86

Posa breakthrough - French data (Jan'07 – Dec'10)

- Considered only pts receiving POS for prophylaxis in haematological malignancy AND had had it for at least 7 days = 270 pts
- Excluded if IFI was diagnosed >15days after stopping POS
- Hence breakthrough rate = 9/270 = 3.2%

- Candidemia (*C. glabrata*) = 2
- Inv pulm aspergillosis (IPA) = 3
- Disseminated fusariosis = 2
- Pulmonary mucormycosis = 2

5 of these isolates were tested for (S) to POS – 4 had high MICs.

Both *C. glabrata* isolates had high MIC to POS.

Lerolle N et al. Clin Micro Infect 2014;20:0952

Posa breakthrough - French data (Jan 2007 – Dec 2010)#

- Considered only pts receiving POS for prophylaxis in haematological malignancy AND had had it for at least 7 days = 270 pts
- Excluded if IFI was diagnosed >15days after stopping POS
- Hence breakthrough rate = 9/270 = 3.2%

- Candidemia (*C. glabrata*) = 2
- Inv pulm aspergillosis (IPA) = 3
- Disseminated fusariosis = 2
- Pulmonary mucormycosis = 2

POS level <0.3 was independent risk factor for IFI (RR 7.9)

Lerolle N et al. Clin Micro Infect 2014;20:0952

all suspension

Low POS levels

- 36 pts receiving POS-susp (200mg TID) for prophylaxis
- Blood samples taken "at steady state" (min 5 days)

- Prevalence of low POS level (<500ng/ml) = 44%

- Main factors a/w low POS levels = diarrhea, mucositis

Lebeaux D et al. Antimicrob Agents Chemother 2009;53:5224

How to maximise POS levels (susp)

- Administer 200mg QID (if unable to tolerate food)
- Take with (or within 20 minutes of) a high-fat meal
- Take with any meal
- Take with a nutritional beverage
- Take with acidic carbonated beverage
- Avoid proton pump inhibitors

Pea F et al. Antimicrob Agents Chemother 2009;53:3608

Krishna G et al. Antimicrob Agents Chemother 2009;53:3609

POS tab PK – not affected by acid suppression?

- 20 healthy volunteers
- Single dose (400mg POS) taken with nothing, antacid, ranitidine, esomeprazole or metoclopramide
- 10-day washout periods between doses
- No diff in C_{max}, $AUC_{0\text{-}inf}$, $t_{½}$

But note – single dose only, all healthy

Kraft WK et al. Antimicrob Agents Chemother 2014

Tablet POS achieves better levels than suspension

- POS for prophylaxis, myeloid malignancies
- [POS] measured after at least 7 days, always 4hr after morning dose

	POS-susp	POS-tab
Median C_{ss} (ng/ml)	390	1740*
% ≥ 700ng/ml	17%	97%*

P = stat sig

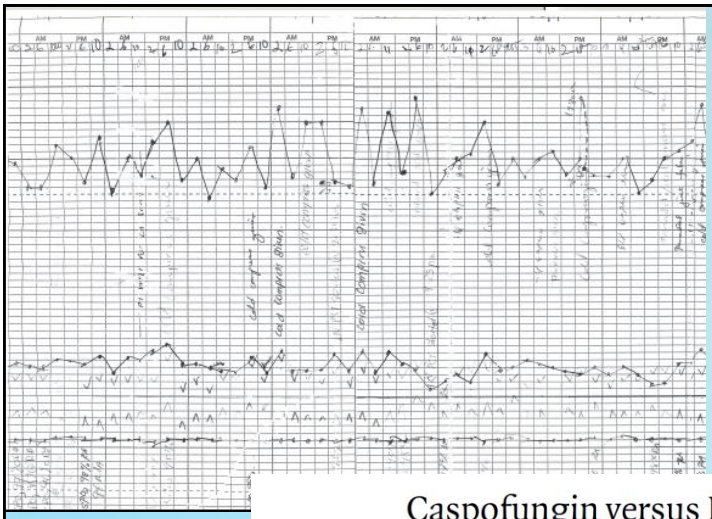
Cumpston A et al. AAC 2015;59:4424

- ➢ All patients on POS (prophylaxis/therapeutic)
- ➢ [POS] measured after at least 5 days
- ➢ Timing of monitoring at physician's discretion

	POS-susp	POS-tab
Median (ng/ml)	798	1655*
% > 700ng/ml	58	90*

* Stat sig, favouring tab, despite 100% of tab pts being on acid-suppression (vs 79% in susp)

Durani U et al. AAC 2015;58:4914



Caspofungin versus Liposomal Amphotericin B for Empirical Antifungal Therapy in Patients with Persistent Fever and Neutropenia

Thomas J. Walsh, M.D., Hedy Teppler, M.D., Gerald R. Donowitz, M.D., Johan A. Maertens, M.D., Lindsey R. Baden, M.D., Anna Dmoszynska, M.D., Ph.D., Oliver A. Cornely, M.D., Michael R. Bourque, M.S., Robert J. Lupinacci, M.S., Carole A. Sable, M.D., and Ben E. dePauw, M.D., Ph.D.

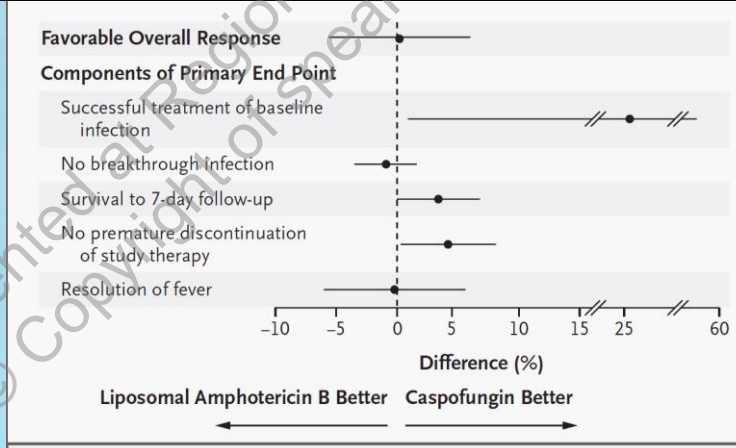


Figure 1. Differences between the Treatment Groups in the Rate of Overall Response and Components of the Primary End Point.

Differences between the treatment groups in the rate of overall response (adjusted) and individual components of the primary end point (observed) are shown, along with the 95.2 percent confidence intervals and 95 percent confidence intervals, respectively.

N Engl J Med 2004;351:1391-402.

Table 3. Results of the Safety Analyses.

Variable	Caspofungin (N=564)	Liposomal Amphotericin B (N=547)	Difference (95% CI)*	P Value
	percent of patients		*percentage points*	
Nephrotoxicity†	2.6	11.5	−8.9 (−12.0 to −5.9)	<0.001
Infusion-related event‡	35.1	51.6	−16.4 (−22.2 to −0.7)	<0.001
Discontinuation of study therapy because of a drug-related adverse event	5.0	8.0	−3.1 (−6.0 to −0.02)	0.04
Any drug-related adverse event§	54.4	69.3	−14.9 (−20.5 to −9.2)	<0.001

N Engl J Med 2004;351:1391-402.

Articles and Brief Reports — Infectious Complications in Hematology

Universal antifungal therapy is not needed in persistent febrile neutropenia: a tailored diagnostic and therapeutic approach

Aguilar-Guisado M et al. Haematologica 2012;97:464

Clinically Driven Diagnostic Antifungal Approach in Neutropenic Patients: A Prospective Feasibility Study

Girmenia C et al. J Clin Oncol 2010;28;667

Consensus guidelines for the use of empiric and diagnostic-driven antifungal treatment strategies in haematological malignancy, 2014

Morissey CO et al. Int Med J 2014;44:1298

Tailored approach - algorithm

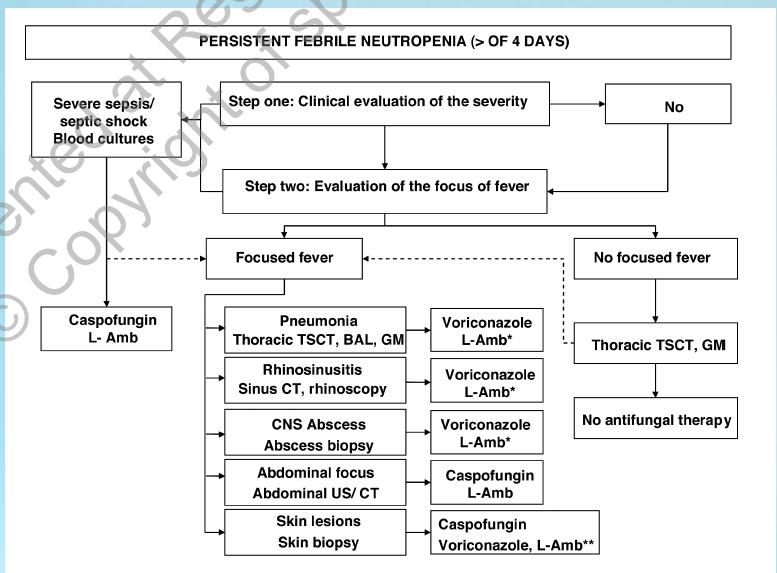
No shock, no sign of severity

- Blood cultures
- GM 2x/week
- CT thorax (btw 5th & 7th day of fever), & whenever resp sympt/sign, KIV BAL
- U/S Abdomen (CT if suspect neutr colitis)
- Other invx as dictated by symptoms/signs
- Watch

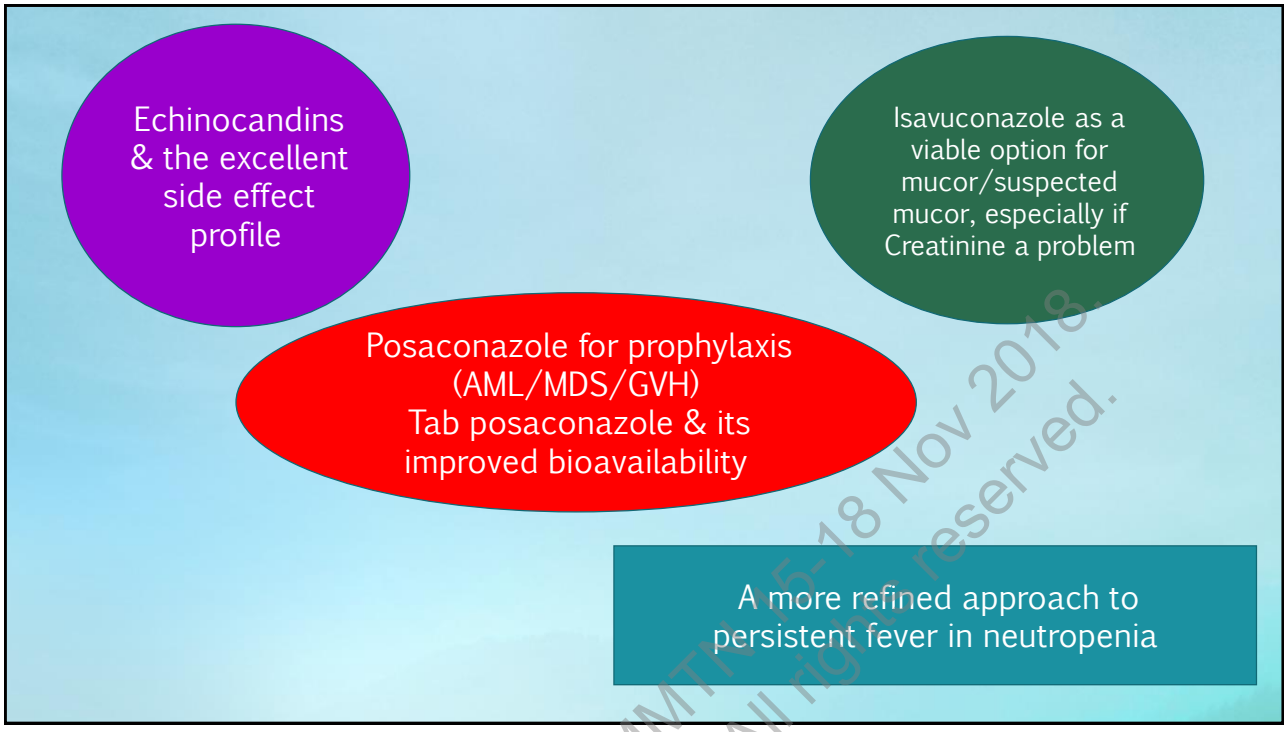
Shock or sign of severity

- Signs of severe sepsis or shock – caspo (alt: LamB)
- "Focus suspected of being fungus" (lung or CNS or sinus) – voriconazole (alt: LamB + caspo)
- Skin or abdomen focus – caspo (alt: fluc or LamB)

Aguilar-Guisado M et al. Haematologica 2012;97:464



Aguilar-Guisado M et al. Haematologica 2012;97:464



Q&A

Please use a microphone or submit a question card

Break

Refreshments are available outside

MMTN Session 2 will start in this room at **10:30am**

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