Echinocandins for the Treatment of Invasive Candidiasis

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Disclosures/Conflict of Interest:

- Research grants: Astellas, Merck, Gilead, Cidara, IMMY, Vical, Amplyx
- Scientific advisory panel: Amplyx, Cidara, IMMY, Vical
- Speakers' bureau: none
- Equities, stock, employment: none

Background

- Over time, the echinocandins have received very favorable recommendations from groups developing treatment guidelines for IC
- Anidulafungin, micafungin and caspofungin are generally favored over fluconazole for treatment of proven and suspected IC
- Evolving data suggest that step down therapy to an azole is reasonable in certain clinical situations
- Echinocandin resistance is a growing concern, esp for *C glabrata.*
- Safety profile for echinocandins including, lack of DDI enhances their value

Pappas et al IDSA Clinical Practice Guidelines for the Management of Candidiasis. CID 2016; 62: 409-17
Ullman A et al. ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: developing European guidelines in clinical microbiology and infectious diseases. CMI 2012.

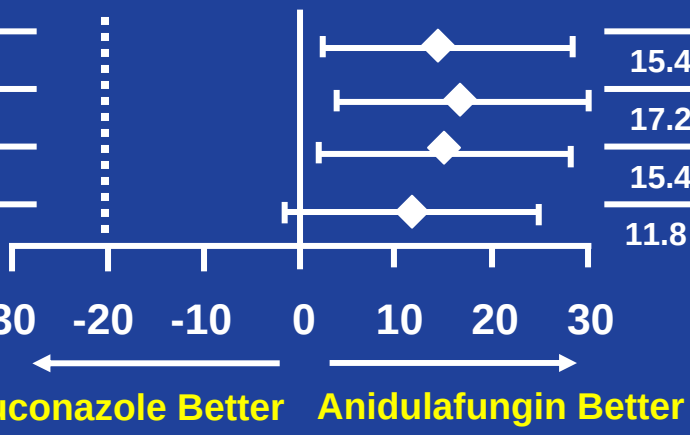
Anidulafungin vs Fluconazole

- Randomized, double-blind trial
- After 10 days of IV therapy, could switch to oral fluconazole
- ~250 patients with IC: 95% with candidemia, 10% with neutropenia
- Success rate: 75% with anidulafungin, 61% with fluconazole

Reboli et al. *N Engl J Med*. 2007;356:2472-2482.

Global Response to Treatment: MITT Population

End Point	Global Success: Fluconazole Group (N=118) Patients, n (%)	Global Success: Anidulafungin Group (N=127) Patients, n (%)	Absolute Percent Difference Between Treatments (95% CI)
End of IV therapy	71 (60.2)	96 (75.6)	15.4 (3.9 – 27.0)
End of all therapy	67 (56.8)	94 (74.0)	17.2 (5.5 – 29.0)
2-week follow-up	58 (49.2)	82 (64.6)	15.4 (3.1 – 27.7)
6-week follow-up	52 (44.1)	71 (55.9)	11.8 (-0.6 – 24.3)



Reboli et al. *N Engl J Med*. 2007;356:2472-2482.

Anidulafungin vs Fluconazole

	Anidulafungin	Fluconazole	*P* Value
Patients, n	127	118	–
Dose, mg/d	100	400	–
Candidemia, %	91	87	–
MITT success, %			
End of all therapy	74	57	.02
2-week follow-up	65	49	.02
6-week follow-up	56	44	NS
Mortality, %	23	31	NS

Reboli et al. *N Engl J Med*. 2007;356:2472-2482.

Micafungin vs Liposomal AMB

- A randomized, double-blind trial of approx 500 patients
- Enrollment criteria, end points similar to previous studies
- In the MITT analysis, 74.1% (247 patients) in the micafungin arm are were treated successfully vs 69.6% (247 patients) in the L-AMB arm (NS)

Kuse et al. *Lancet.* 2007;369:1519-1527.

Micafungin vs L-AMB

	Micafungin	L-AMB
Patients, n	264	267
Dose	100 mg/d	3 mg/kg/d
APACHE II score	15.8	15.6
Candidemia, %	84	86
MITT success, %	74	70
PP success, %	90	90
Deaths at 12 weeks, %	40	40

Kuse et al. *Lancet*. 2007;369:1519-1527.

Micafungin vs Caspofungin

- Completed randomized, double-blind study
  - Total enrollment, 595 patients
- Micafungin 100 mg or micafungin 150 mg vs CAS 50 mg/d
- More than 120 US and international sites, very rapid accrual (less than 2 years)
- Candidemia approval study for micafungin did not demonstrate important differences in outcome between any of the 3 arms

Pappas et al. *Clin Infect Dis*. 2007;45:883-893.

Micafungin vs Caspofungin

	Mica		Caspo
Dose, mg/d	100	150	50
Patients, n	191	199	188
Candidemia, %	85	84	86
MITT success, %	75	68	70
Mortality, %	29	33	26

Pappas et al. *Clin Infect Dis*. 2007;45:883-893.

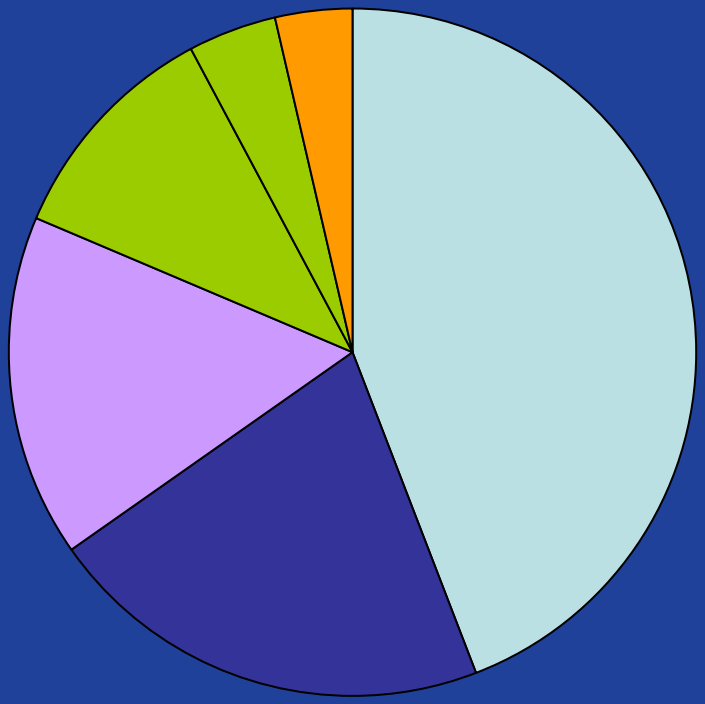
A Phase IV, Open-label Study Evaluating Efficacy and Safety of Intravenous Anidulafungin Followed by Oral Azole for the Treatment of Candidemia / Invasive Candidiasis

J. Vazquez, A. Reboli,[2]P. Pappas, T.F.Patterson, J. Reinhardt, P. Chin-Hong, E. Tobin, D. Kett, P. Biswas, R. Swanson

BMC Infect Dis 2014;14:97.

Epidemiology

Number of isolates of species at baseline (%)



C. albicans	112	(42)
C. glabrata	54	(24)
C. parapsilosis	41	(16)
C. tropicalis	27	(10)
C. krusei	11	(4)
Other	9	(4)

BMC Infect Dis 2014;14:97.

Duration of therapy

	N (%)	Median (days)	Range (days)
Total (MITT)	250		
IV ANID overall	250	6.0	1–31
IV ANID only	100 (40.0)	12.0	1–29
Study Day of switch to oral therapy	150 (60.0)	6	1–28
1–5	7 (4.7)		
6–14	133 (88.7)		
15–21	6 (4.0)		
22–28	4 (2.7)		

BMC Infect Dis 2014;14:97.

Criteria for oral switch

- Received at least 5 days of IV ANID therapy
- Afebrile for > 24 hours
- Able to tolerate oral therapy
- Last blood culture negative for *Candida* species
- Significant improvement in signs and symptoms of candidemia / invasive candidiasis
- Hemodynamically stable
- Absence of neutropenia

Response rates at EOT

Response at EOT	n/N	(%)	[95% CI]
Global response			
Success*	170/203	(83.7)	[78.7, 88.8]
Failure	33		
Missing/unknown	47		
Sensitivity analysis**	170/250	(68.0)	[62.2, 73.8]
Clinical response			
Success*	174/187	(93.0)	[89.4, 96.7]
Failure	13		
Missing/unknown	63		
Sensitivity analysis**	174/250	(69.6)	[63.9, 75.3]
Microbiological response			
Success*	183 /192	(95.3)	[92.3, 98.3]
Failure	9		
Missing/unknown	58		
Sensitivity analysis**	183/250	(73.2)	[67.7, 78.7]

CI, confidence interval; MITT population;
*Success based on the primary analysis with missing/unknown excluded;
**Sensitivity analysis with missing/unknown values set to failure

Summary and conclusions

- De-escalation to oral therapy was shown to be effective in the treatment of candidemia / invasive candidiasis
- De-escalation was effective and tolerable in a wide range of patients, including those with baseline infections due to less common *Candida* species
- Efficacy and safety was comparable to prior studies using longer term IV regimens
- De-escalation should ease the burden of long-term parenteral therapy to manage these infections without compromising efficacy

MSG-02: A combined analysis of treatment outcomes among patients with invasive candidiasis

- Study represents patient-level data for 7 large treatment trials for candidiasis performed and published since 1994
- Almost 2000 pts included in the analysis
- Greater mortality associated with higher APACHE II score, immunosuppression, and *C tropicalis* infection
- Lower mortality associated with primary echinocandin therapy and CVC removal

Andes DR et al CID 2012; 54:1110-22

Aggregate Data from 8 Candidemia Studies (MSG 02)

Table 2. Frequency of Host, Disease, and Organism Factors in Patients With Invasive Candidiasis

Factors	Variable	Patients, No.[a]	Patients, %[b]
Demographics	Age, mean ± SD, y	55.1 ± 17.64	...
	Male sex	1102	57.5
	Female sex	813	42.5
Risks and comorbid conditions	Central venous catheters[c]	1492	78.0
	Surgery[d]	659	34.4
	Neutropenia[d]	139	9.0
	Malignancy	410	28.2
	Transplantation	69	4.8
	Immunosuppressive therapy[c]	440	28.6
	ICU[c]	531	54.1
	TPN[c]	410	31.9
	Mechanical ventilation[c]	410	31.9
	Renal dysfunction[c] (creatinine >3.0 mg/L or hemodialysis)	223	12.4

Andes DR et al CID 2012; 54:1110-22

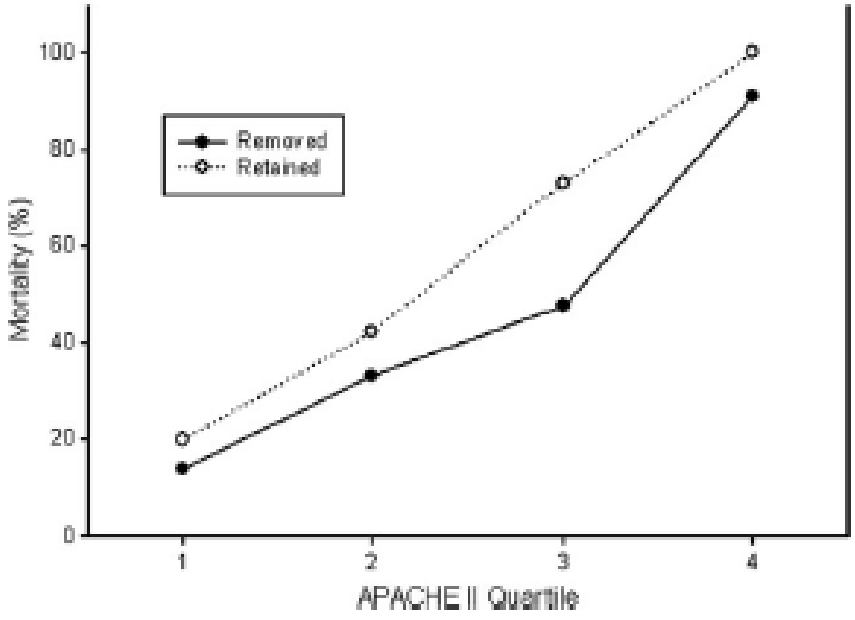


Figure 1. Impact of severity of illness and central venous catheter (CVC) management on patient mortality. Each symbol represents the mortality rate as a percentage for patients in 1 of 4 Acute Physiology and Chronic Health Evaluation (APACHE) II score quartiles: quartile 1, 0–11; 2, 12–23; 3, 24–35; and 4, 36–47. Closed symbols represent patients with CVC removal; open symbols, patients with CVC retention. Differences in mortality were statistically significant for quartiles 1, 2, and 3 (quartile 1, $P = .05$; 2, $P = .01$; 3, $P = .002$; and 4, $P = .41$).

Andes DR et al CID 2012; 54:1110-22

MSG 02: Multivariable Analysis

Variable	P value	OR	CI
Age	0.02	1.01	1.0-1.02
APACHE II	0.0001	1.11	1.08-1.14
Immunotherapy	0.001	1.69	1.18-2.44
C tropicalis	0.01	1.64	1.11-2.39
1° echinocandin	0.02	0.65	0.45-0.94
CVC removal	0.0001	0.50	0.35-0.72

Andes DR et al CID 2012; 54:1110-22

C parapsilosis

In addition to evidence from prospective studies, several retrospective studies confirm that ECH primary therapy for C parapsilosis is an acceptable practice:

- Chiotis K et al. Comparative effectiveness of echinocandins versus fluconazole therapy for the treatment of adult candidaemia due to Candida parapsilosis: a retrospective observational cohort study of the Mycoses Study Group (MSG-12). JAC 2016; 71: 3536-9.

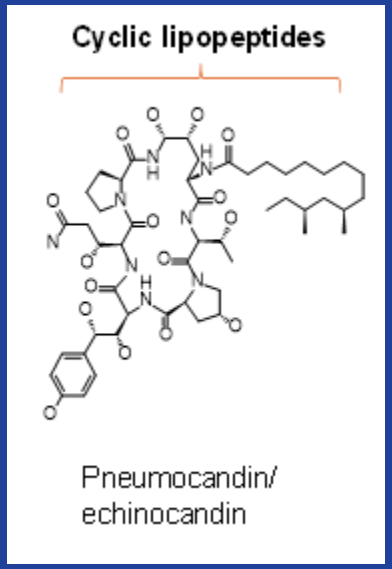
Echinocandins

- In most cases the agents of choice as initial therapy for moderately severe-severe IC. *De-escalation to flu*
- Are echinocandins first line therapy for treatment of presumed IC? *Yes*
- Are echinocandins are the best choice for *C parapsilosis? They are a good choice in most instances*
- Role in CNS candidiasis? *Not in adults, due to very poor penetration and reports of CNS relapse/persistence*
- An adequate replacement for AMB +/- 5-flucytosine for *Candida* endocarditis? *Yes*
- Is it reasonable to assume that caspofungin, micafungin, and anidulafungin are interchangeable treatments for IC? *Yes*

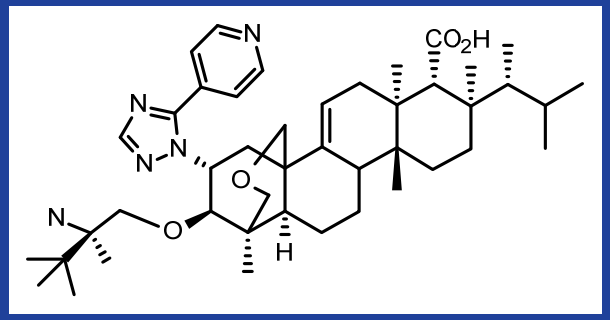
Newer Agents

SCY-078 (Scynexis): Novel Structural Class Differentiating *In Vitro* Activity and Pharmacokinetics

- SCY-078 is a first in class, structurally novel triterpene enfumafungin-derivative, orally bioavailable ß-1,3-glucan synthesis inhibitor (GSI), with *in vitro* activity against *Aspergillus spp*. and *Candida spp.*, including multi-drug resistant strains
- Phase 2 study of oral formulation complete for candidemia
- Phase 3 study for refractory invasive candidiasis in progress
- Intravenous formulation in development



SCY-078



SCY-078 in vitro activity

TABLE 4 Cutoff values and clinical breakpoints employed for comparison of SCY-078 to anidulafungin, caspofungin, and micafungin against *Candida* spp.[c]

Species and antifungal agent	Cutoff value (mg/liter)		CBP[a] (mg/liter)		
	WT-UL	ECV[b]	S	I	R
C. albicans					
SCY-078	0.5				
Anidulafungin		0.12	≤0.25	0.5	≥1
Caspofungin		0.12	≤0.25	0.5	≥1
Micafungin		0.03	≤0.25	0.5	≥1
C. glabrata					
SCY-078	2				
Anidulafungin		0.25	≤0.12	0.25	≥0.5
Caspofungin		0.12	≤0.12	0.25	≥0.5
Micafungin		0.03	≤0.06	0.12	≥0.25
C. tropicalis					
SCY-078	1				
Anidulafungin		0.12	≤0.25	0.5	≥1
Caspofungin		0.12	≤0.25	0.5	≥1
Micafungin		0.12	≤0.25	0.5	≥1
C. parapsilosis					
SCY-078	1				
Anidulafungin		4	≤2	4	≥8
Caspofungin		1	≤2	4	≥8
Micafungin		4	≤2	4	≥8
C. krusei					
SCY-078	4				
Anidulafungin		0.12	≤0.25	0.5	≥1
Caspofungin		0.25	≤0.25	0.5	≥1
Micafungin		0.12	≤0.25	0.5	≥1

WT-UL – Wild-type upper limit, defined as two 2-fold dilutions higher than the modal MIC

ECV – Epidemiologic cut-off value

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SCY-078 in vitro activity

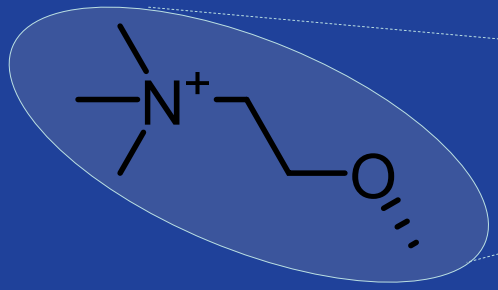
TABLE 1 MIC distributions of SCY-078 and 3 echinocandins against WT and ER *Candida* spp. isolates

Species	Phenotype (no. of isolates)	Modal MIC[a] (range [mg/liter])			
		SCY-078	Anidulafungin	Caspofungin	Micafungin
C. albicans	WT (61)	0.12 (0.03–0.25)	0.015 (≤0.008–0.06)	0.03 (0.015–0.06)	0.015 (≤0.008–0.06)
	ER (8)	NM (0.06–2)	0.12 (≤0.008–1)	2 (0.015–2)	0.06 (0.015–2)
C. glabrata	WT (39)	0.5 (0.25–1)	0.06 (0.015–0.25)	0.06 (0.03–0.25)	0.015 (≤0.008–0.03)
	ER (28)	1 (0.12–16)	1 (0.015–4)	0.5 (0.03–16)	0.06 (≤0.008–4)
C. tropicalis	WT (30)	0.25 (0.06–2)	0.015 (≤0.008–0.06)	0.03 (0.015–0.12)	0.03 (0.015–0.06)
	ER (1)	2	2	2	2
C. parapsilosis	WT (43)	0.25 (0.12–4)	2 (0.5–4)	0.5 (0.25–2)	2 (0.5–2)
C. krusei	WT (30)	0.5–1 (0.25–2)	0.03 (0.03–0.25)	0.12 (0.06–0.25)	0.12 (0.06–0.25)
	ER (4)	1 (1–4)	0.06 (0.03–0.5)	NM (0.06–1)	0.12 (0.06–0.25)

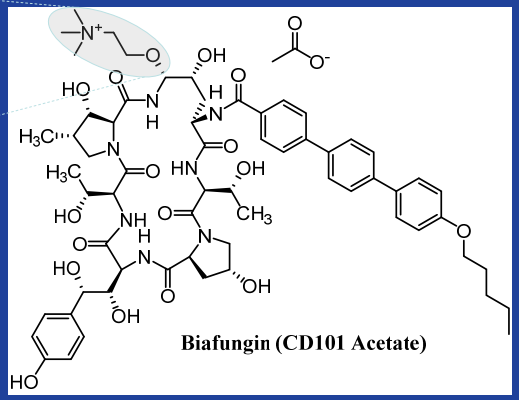
- Retains activity in echinocandin resistance
- Impacted less by FKS mutations than the echinocandins
- Partially overlapping but independent bindings site

Pfaller AAC 2017; Jiménez-Ortigosa AAC 2017

CD101 (Cidara): A novel echinocandin



Structural modification yields superior chemical & biological properties



Permanent charge and highly stable ring structure…

- Eliminates toxic degradation products: improved safety & dose range
- Prolongs PK: once weekly dosing
- Allows high exposures: treats less susceptible pathogens
- Enables multiple formulations: systemic and topical

Phase 2 study currently enrolling

CIDARA THERAPEUTICS

CD101 *in vitro* activity

Table 2
Antimicrobial activity of CD101, anidulafungin, caspofungin, and micafungin tested against isolates included in the study.

Organisms/Organism Groups	No. of isolates at MIC/MEC (μg/mL; cumulative %)								
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2
Candida glabrata (121)									
CD101		3 (2.5)	69 (59.5)	22 (77.7)	25 (98.3)	1 (99.2)	0 (99.2)	1 (100.0)	
Anidulafungin		1 (0.8)	38 (32.2)	43 (67.8)	37 (98.3)	1 (99.2)	0 (99.2)	1 (100.0)	
Caspofungin	4 (3.3)	44 (39.7)	59 (88.4)	12 (98.3)	1 (99.2)	0 (99.2)	0 (99.2)	1 (100.0)	
Micafungin	68 (56.2)	43 (91.7)	8 (98.3)	0 (98.3)	1 (99.2)	1 (100.0)			

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Ευχαριστώ πολύ!