

**Bon Secours Richmond
Pharmacy and Therapeutics Committees
Anidulafungin (Eraxis®)
9/2006**

Recommendations:

- Anidulafungin is recommended for formulary addition and caspofungin (Cancidas) will be removed from formulary.
 - Anidulafungin is not a substrate, inhibitor or inducer of cytochrome P450 enzymes. It has only one known drug interaction (cyclosporine), but anidulafugin's does not require a dosage adjustment
 - Medications studied include rifampin, cyclosporine, tacrolimus, voriconazole, and amphotericin B
 - Anidulafungin has the longest half-life (26 hours) and the lowest protein binding (84%) of the echinocandins.
 - Anidulafungin is chemically degraded in the body and is not metabolized by the cytochrome P450 system
 - Anidulafungin does not require dosage adjustment for liver or renal dysfunction
 - Anidulafungin is less expensive than other echinocandins
 - Anidulafungin provides higher free levels than caspofungin and micafungin
 - Anidulafungin's adverse effect profile appears to be better than other echinocandins
 - Antifungal spectrums of echinocandins are equivalent.
 - Anidulafungin has a broad spectrum activity against Candida (including those strains that are resistant to polyenes and azoles), non-albicans strains and Aspergillus species. Potential synergy with azoles against Aspergillus has been demonstrated in vitro. It is inactive against Cryptococcus neoformans, Trichosporon spp., Zygomycetes and Fusarium. All echinocandins are less active against C. parapsilosis
 - Anidulafugin is the only echinocandin that has been studied in a randomized control trial versus fluconazole in candidemia and other invasive candida infections (phase three clinical trial, not published)

Efficacy Analysis: Global Success (MITT)* in Patients with Candidemia and other Candida Infections**, Package Insert			
Time Point	Eraxis 200 mg LD, 100 mg/day N=127	Fluconazole 800 mg LD, 400 mg/day N=118	Treatment Difference %, (95% C.I)
End of IV Therapy	75.6%	60.2%	15.4% (3.9, 27) (SS)
End of IV Therapy (candidemia)	75.9% (88/116)	61.2% (63/103)	14.7(2.5,26.9) (SS)
End of All Therapy	74%	56.8%	17.24% (2.9, 31.6) (SS)
2 Week Follow-up	64.6%	49.2%	15.4% (0.4, 30.4) (SS)
6 Week Follow-up	55.9%	44.1%	11.84% NS
Overall Study Mortality	22.8%	31.4%	NS
Mortality During Study Therapy	7.9%	14.4%	NS
Mortality Attributed to Candida	1.6%	4.2%	NS

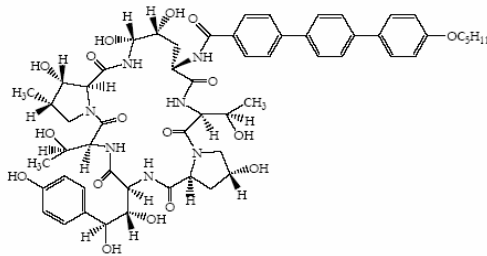
* Patients with at least 1 dose of study drug and a positive culture for Candida species for a normally sterile site, clinical cure or improvement and documented or presumed microbiological eradication

** Patients with C. krusei (fluconazole not active), candida endocarditis, osteomyelitis, and meningitis were excluded from the study

Note: there were only 6 neutropenic patients included in this study

- Anidulafugin has not been studied in sufficient numbers of patients with neutropenia to determine its efficacy in this patient population
- Anidulafungin and caspofungin are not FDA approved for pediatrics
- Fluconazole remains the drug of choice for initial treatment of Candida esophagitis.
 - Cancidas, Mycamine, and Eraxis are equally effective when compared to fluconazole for treatment of Candida esophagitis, but have higher relapse rates and are much more expensive (Caspofungin \$2772, Micafungin \$3338, anidulafungin \$1260 versus \$5.60-\$210 per treatment course for fluconazole). Eraxis may be used as an alternative for patients with fluconazole-resistant strains.
- Fluconazole remains the drug of choice for hematopoietic stem cell transplant (HSCT). Micafungin may be used as an alternative in the prophylactic treatment of patients undergoing hematopoietic stem cell transplant (HSCT), if the patient is intolerable to or is experiencing treatment failure with fluconazole.

Anidulafungin Structure



FDA Approved Indications and Dosage				
	Anidulafungin	Micafungin	Caspofungin	Fluconazole
Aspergillus			70 mg x1; 50 mg/day Cost/day = \$198.00	
Esophageal Candidiasis	100 mg x1; 50 mg/day Cost/day = \$90 Minimum of 14 days, 7 days past resolution of symptoms	150 mg/day Cost/day = \$238.44	50 mg/day Cost/day = \$198.00	200 mg x1; 100 mg/day Cost/day = \$0.4-\$15/day
Candidemia	200 mg x1; 100 mg/day Cost/day = \$180.00 Continue 14 days past last positive blood culture		70 mg x1; 50 mg/day Cost/day = \$198.00	400 mg/day Cost/day = \$0.8-\$30/day
Other Candida Infections (intra-abdominal abscess and peritonitis)	200 mg x1; 100 mg/day Cost/day = \$180.00		70 mg x1; 50 mg/day Cost/day = \$198.00	400 mg/day Cost/day = \$0.4-\$15/day
Candida prophylaxis in hematopoietic stem cell transplantation		50 mg/day Cost/day = \$79.48		400 mg/day Cost/day = \$0.4-\$15/day
Febrile Neutropenia; empiric therapy			70 mg x1; 50 mg/day Cost/day = \$198.00	400-800 mg/day Cost/day = \$0.4-\$15/day

Findings:

- Echinocandins (caspofungin, micafungin, and anidulafungin) inhibit cell wall formation; amphotericin binds to ergosterol and increases membrane permeability (fungicidal); fluconazole decreases ergosterol production.
- Anidulafungin is a noncompetitive inhibitor of (1,3)-beta-D-glucan synthase, and enzyme required for the synthesis of glucan (the polysaccharide that constitutes the major portion of the cell wall of many pathogenic fungi). Inhibition of glucan synthesis results in osmotic fragility and cell death in yeast, but is fungistatic in molds.
- The echinocandins have the same basic cyclic lipopeptide nucleus with their major structural difference in the N-terminus side chain.
- Polyenes (amphotericin b, echinocandins) display concentration dependent killing while azoles and flucytosine display time-dependent killing.
- Direct comparisons of echinocandins have not been performed
- The pharmacokinetic properties of anidulafungin determined from multiple-dose clinical studies indicate that it has a predictable and dose-proportional plasma concentration and exposure profile.
- When studied, the pharmacokinetics of anidulafungin in adolescent patients aged 2 to 17 years of age with fever and neutopenia did not differ significantly from those observed in adult patients. Patients receiving 0.75 mg/kg/day or 1.5 mg/kg/day had anidulafungin concentrations similar to those of adults receiving 50 or 100 mg/day.
- Anidulafungin elimination is independent of renal function, hepatic function, or possible age-dependent metabolic processes. This information cannot be extrapolated to other echinocandins; caspofungin is subject to biotransformation by metabolism and requires a dosage adjustment based on a calculation of body surface area rather than weight-adjusted scale in children.
- Anidulafungin is not dialyzable and may be administered without regard to the timing of hemodialysis.
- Anidulafungin is compatible with 0.9% NaCl and D5W after initial reconstitution with 20% (w/w) ethanol.

- Anidulafungin is insoluble in water and slightly soluble in ethanol. Caspofungin and micafungin are both freely soluble in water.
- Infusion rates of anidulafungin faster than 1.1 mg/minute cause histamine-mediated symptoms: rash, urticaria, flushing, pruritus, dyspnea, and hypotension.
- Anidulafungin has a broad spectrum activity against *Candida* (including those strains that are resistant to polyenes and azoles), non-albicans strains and *Aspergillus* species. Potential synergy with azoles against *Aspergillus* has been demonstrated in vitro. It is inactive against *Cryptococcus neoformans*, *Trichosporon* spp., *Zygomycetes* and *Fusarium*. All echinocandins are less active against *C. parapsilosis* and *C. guilliermondii*.
- No correlation between antifungal MICs and clinical outcome has been established.
- In vitro susceptibility testing for antifungal drugs has not undergone in vivo validation studies. Clinical outcomes are often more dependent on host factors.
- Esophageal Candidiasis: the echinocandins all have similar efficacy and response rates when treating esophageal candidiasis when compared to fluconazole; however, the echinocandins have a higher relapse rate.
- Anidulafungin has not been studied in endocarditis, osteomyelitis, or meningitis due to *Candida*. *It has also not been studied in sufficient numbers of neutropenic patients to determine efficacy in this group whereas caspofungin is FDA approved for empiric therapy of febrile neutropenic patients*
- Anidulafungin is the only echinocandin that has been studied in a head-to-head comparison against IV fluconazole in the treatment of candidemia
 - In a Phase III, multicenter, double-blind, randomized clinical trial, 200 mg loading dose then 100mg daily dose of anidulafungin was compared with 800 mg loading dose then 400mg daily dose of fluconazole in >250 patients with candidemia and/or Invasive Candidiasis. In that study, a global response was shown in 76% of patients receiving anidulafungin 100 mg/day and 60% of those receiving fluconazole 400 mg/day at the end of the treatment period (95% CI, 3.85-26.99); 65% and 49%, respectively, at 2-week follow-up (95% CI, 3.14-27.68); and 56% and 44%, respectively, at 6 week follow-up (95% CI, --0.6 to 24.28). Higher drop out rates due to ADRs or lack of efficacy were noted in the fluconazole arm (see table 4 below).
- Fluconazole has an FDA approved indication for the prophylactic treatment of candidiasis in HSCT patients
 - In adult patients undergoing HSCT, 41.7% treated prophylactically with only micafungin had a suspected fungal infection that required empiric antifungal therapy, compared to 22.6% of patients treated in combination with micafungin and fluconazole.
 - None of the patients who completed therapy with micafungin-fluconazole developed a fungal infection 4 weeks after treatment if they did not have a fungal infection during treatment
- Micafungin and caspofungin have been associated with similar adverse drug effects in humans. When comparing the side effect profiles listed in the package inserts anidulafungin is associated with less frequent side effects.
- Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with anidulafungin. Patients who develop abnormal liver function tests during therapy should be monitored for evidence of worsening hepatic function and evaluated for risk vs. benefit of continuing therapy.
- Unlike other echinocandins, studies have shown that it is safe to administer anidulafungin with cyclosporine.
- Anidulafungin is a Pregnancy Category C drug and should only be used during pregnancy if the potential benefit justifies the risk to the fetus. It is not known whether anidulafungin is excreted in human milk.
- Risk factors for invasive fungal infections: recent transplant, recent immunosuppressive medications or broad-spectrum antibiotics, IV catheter in place, neutropenia, hematological cancers, HIV

Sanford Guide To Antimicrobial Therapy 2006

	% of Isolates	Risk Factors	Fluconazole	Itraconazole	Voriconazole	Amphotericin B	Caspofungin	Micafungin Anidulafungin
C. albicans	45-63	HIV/AIDS, surgery	97% S	93% S	99% S	> 95% S	S	S
C. glabrata	12-24	Heme malignancies, azole prophylaxis	85-90% (S-DD)	50% R	92% S-I	> 95% S-I	S	S
C. parapsilosis	11-29	Azole prophylaxis, neonates, foreign bodies	99% S	4% S-DD	99% S	> 95% S	S-I	S-I
C. tropicalis	6-19	Neutropenia	98 S	58% S	99% S	>95% S	S	S
C. krusei	1-5	Heme malignancies, azole prophylaxis	5% R	69% S	99% S-I	> 95% S-I	S	S
C. guilliermondii	1	Azole prophylaxis, previous amphotericin	> 95% S	? S	> 95% S	? R	S	S
C. lusitanae	1	Previous amphotericin	> 95% S	? S	> 95% S	? R	S	S

	Dose	Cost per Dose
Anidulafungin Inj.	50 mg	\$90.00
Micafungin Inj.	150 mg	\$238.44
Micafungin Inj.	50 mg	\$79.48
Caspofungin Inj.	50 mg	\$198.00
Caspofungin Inj.	70 mg	\$198.00
Fluconazole Inj.	200 mg	\$15.06
Fluconazole PO	200 mg	\$0.36

	Micafungin (Mycamine®)	Caspofungin (Cancidas®)	Anidulafungin (Eraxis®)
Drug Class	Echinocandin – antifungal	Echinocandin – antifungal	Echinocandin – antifungal
Derived from	Coleoptioma empedri	Glarea lozoyensis	Aspergillus nidulans
Mechanism of Action	Inhibits β (1,3) D-glucan formation in the fungal <u>cell wall</u>	Inhibits β (1,3) D-glucan formation in the fungal <u>cell wall</u>	Inhibits β (1,3) D-glucan formation in the fungal <u>cell wall</u>
Metabolism	Liver (non CYP450)	Liver (hydrolysis and N-acetylation)	Anidulafungin undergoes slow chemical degradation at physiologic temperature and pH to a ring-opened peptide that lacks antifungal activity. Hepatic metabolism has not been observed.
Route of Elimination	Fecal	Fecal and Urinary	Fecal (unchanged 10%) and Urinary (1% - negligible renal clearance)
Cmax mg/l		7.5 (50 mg qd)	4.2 (50 mg qd), 7.2 (100mg qd)
Clearance (l/hr)	?	?	1
Elimination half-life	11-17 hours	9-11 hours	26 hours (adults) 20 to 23 hours (pediatrics)
Volume of Distribution (liters)	27	?	30-50
Protein Binding	99%	97%	84%
Molecular Weight	1292	1213	1140
In vitro activity	Candida spp (C. albicans, C. glabrata, C. krusei, C. parapsilosis, C. tropicalis, and azole-resistant Candida spp), Aspergillus spp	Candida spp (C. albicans, C. glabrata, C. guilliermondii, C. krusei, C. parapsilosis, C. tropicalis), Aspergillus spp (A. fumigatus, A. flavus, A. terreus)	Candida spp (albicans, C. glabrata, C. krusei, C. parapsilosis, and C. tropicalis, azole resistant candida spp), Aspergillus spp.
FDA approved indication(s)	Prophylaxis of Candida infection in HSCT patients Treatment of Esophageal Candidiasis	Empiric therapy for presumptive fungal infections in <i>febrile, neutropenic patients</i> Treatment of Candidemia Treatment of Candida associated infections involving intra-abdominal abscess, peritonitis, and pleural space infection Treatment of Esophageal Candidiasis Treatment of Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies	Treatment of Candidemia and other forms of Candida infections (intra-abdominal abscess, and peritonitis). Treatment of esophageal candidiasis.
Route of administration	IV over 1 hour	IV over 1 hour	IV; 50 mg over 1 hour; Infusion rate should not exceed 1.1mg/min.
Approved Doses	<u>Esophageal Candidiasis:</u> 150mg day <u>Candida infection prophylaxis in</u>	<u>Esophageal Candidiasis:</u> 50mg QDay <u>Invasive Aspergillosis:</u> 70mg loading dose,	<u>Esophageal Candidiasis:</u> 100 mg loading dose on Day 1, followed by 50 mg daily dose thereafter <u>Candidemia and other Candida Infections (intra-abdominal abscess and peritonitis):</u>

	Micafungin (Mycamine®)	Caspofungin (Cancidas®)	Anidulafungin (Eraxis®)
	HSCT: 50mg QDay (1mg/kg if patient less than 50kg)	followed by 50mg QDay	single 200 mg loading dose on Day 1, followed by 100 mg daily dose thereafter.
Pediatric Dosing	Not FDA approved	Not FDA approved Age 2-17 years 50 mg/M ² /day	Not FDA approved Age 2-17 years old 0.75 mg/kg/day (equivalent serum levels to 50 mg per day in adult) 1.5 mg/kg/day (equivalent serum levels to 100 mg per day in adult)
Renal Insufficiency Dose Adjustment	None	None	None
Dialysis Adjustment	not dialyzable	not dialyzable	Not dialyzable, no adjustment needed
Hepatic Insufficiency Dose Adjustment	None, Child-Pugh score > 9 no clinical experience	Yes; Child-Pugh score 7-9 use 35mg QDay; Child-Pugh score > 9 no clinical experience	None ; Not hepatically metabolized; Slight decrease in AUC observed in patients with Child-Pugh C hepatic insufficiency, but still within range estimates for healthy subjects.
Adverse Effects	headache, fever, liver toxicity (↑transaminases, ↑alkaline phosphate, hyperbilirubinemia), phlebitis, histamine release, hemolysis, rash, anaphylaxis, nausea, vomiting, diarrhea pruritus, urticaria, leukopenia, pyrexia	headache, fever, liver toxicity, phlebitis, histamine release, hemolysis, rash, anaphylaxis, nausea, vomiting, diarrhea local irritation at infusion site, fever, chills, hypokalemia, proteinuria, nephrotoxicity	<u>Hypersensitivity</u> : Possible histamine-mediated symptoms have been reported with anidulafungin, including dyspnea, flushing, hypotension, pruritus, rash, and urticaria. These reactions are infrequent when the rate of anidulafungin infusion does not exceed 1.1 mg/minute. Diarrhea, ↑ ALT/AST/Alkaline Phosphatase, ↑ hepatic enzymes, hypokalemia, DVT, headache, nausea
Drug Interactions	Sirolimus (AUC increased 21%) Nifedipine (AUC & Cmax increased 18% and 42%, respectively)	Cyclosporine (increased Caspofungin's AUC 35%) Tacrolimus AUC decreased 20 % by Caspofungin Carbamazepine Caspofungin's dose may need to be increased Dexamethasone Caspofungin's dose may need to be increased Efavirenz Caspofungin's dose may need to be increased Nelfinavir Caspofungin's dose may need to be increased Nevirapine Caspofungin's dose may need to be increased Phenytoin Caspofungin's dose may need to be increased Rifampin (decrease Caspofungin's trough 30%)	Anidulafungin is not metabolized by human cytochrome P450 or by isolated human hepatocytes and does not inhibit clinically important human CYP isoforms. <i>No clinically relevant drug-drug interactions were observed with drugs likely to be co-administered with anidulafungin.</i> The steady state AUC of anidulafungin was increased 22% by cyclosporine, but no dose adjustment is warranted.
Cost	<u>Esophageal Candidiasis</u> ^{1,2} 150	<u>Esophageal Candidiasis</u> ^{3,4} Duration range = 7-21	<u>Esophageal Candidiasis</u> Duration range = 14-21

	Micafungin (Mycamine®)	Caspofungin (Cancidas®)	Anidulafungin (Eraxis®)
	<u>mg qd</u> Duration range = 10-30 days Mean = 15 days Cost = \$4066.20 <u>Prophylaxis of Candida in HSCT</u> <u>50 mg qd</u> Duration range = 6-51 days Mean = 19 days Cost = \$1716.84	days Mean = 9 days Cost = \$2794.59	Mean = 14 days Cost (14 days) = \$1350.00 <u>Candidemia/Candidiasis</u> Duration range = 14-42 Mean = 14 days Cost (21 days) = \$3,960.00

Eraxis 200 mg LD then 100 mg qd versus fluconazole 800 mg LD then 400 mg qd

Table 3. Global Success Rates of Anidulafungin Compared with Fluconazole in the Treatment of Candidemia and Invasive Candidiasis¹

<i>Timepoint</i>	<i>Anidulafungin (n = 127)</i>	<i>Fluconazole (n = 118)</i>	<i>Treatment Difference</i>
End of IV therapy	75.6%	60.2%	15.42% (95% CI, 3.9% to 27%)
End of all therapy	74%	56.8%	17.24% (95% CI, 2.9% to 31.6%)
2-week follow-up	64.6%	49.2%	15.41% (95% CI, 0.4% to 30.4%)
6-week follow-up	55.9%	44.1%	11.84% (95% CI, -3.4% to 27%)

Table 6 presents outcome and mortality data for the MITT population.

Table 6. Outcomes & Mortality in Candidemia and other <i>Candida</i> Infections			
	ERAXIS	Fluconazole	Between group difference^a (95% CI)
No. of MITT patients	127	118	
Favorable Outcomes (MITT) At End Of IV Therapy			
All MITT patients			
Candidemia	88/116 (75.9%)	63/103 (61.2%)	14.7 (2.5, 26.9)
Neutropenic	1/2	2/4	-
Non neutropenic	87/114 (76.3%)	61/99 (61.6%)	-
Multiple sites			
Peritoneal fluid/ intra-abdominal abscess	4/6	5/6	-
Blood/ peritoneum (intra-abdominal abscess)	2/2	0/2	-
Blood /bile	-	1/1	-
Blood/renal	-	1/1	-
Pancreas	-	0/3	-
Pelvic abscess	-	1/2	-
Pleural fluid	1/1	-	-
Blood/ pleural fluid	0/1	-	-
Blood/left thigh lesion biopsy	1/1	-	-
Total	8/11 (72.7%)	8/15 (53.3%)	-
Mortality			
Overall study mortality	29/127 (22.8 %)	37/118 (31.4%)	-
Mortality during study therapy	10/127 (7.9%)	17/118 (14.4%)	-
Mortality attributed to <i>Candida</i>	2/127 (1.6%)	5/118 (4.2%)	-

^a Calculated as ERAXIS minus fluconazole

Patient disposition is presented in Table 4.

Table 4. Patient Disposition and Reasons for Discontinuation in Candidemia and other <i>Candida</i> infection study		
	ERAXIS	Fluconazole
	n (%)	n (%)
Treated patients	131	125
Patients completing study through 6 week follow-up	94 (71.8)	80 (64.0)
Discontinuations from Study Medication		
Total discontinued from study medication	34 (26.0)	48 (38.4)
Discontinued due to adverse events	12 (9.2)	21 (16.8)
Discontinued due to lack of efficacy	11 (8.4)	16 (12.8)

Table 7. Endoscopy Results in Patients with Esophageal Candidiasis (Clinically Evaluable Population)

Endoscopic Response at End of Therapy				
Response	ERAXIS N= 231	Fluconazole N= 236	Treatment Difference ^a	95% CI
Endoscopic Success n, (%)	225 (97.4)	233 (98.7)	-1.3%	-3.8%, 1.2%
Cure	204 (88.3)	221 (93.6)		
	Improvement	21 (9.1)		
Failure n, (%)	6 (2.6)	3 (1.3)		
Endoscopic Relapse Rates at Follow-up, 2 Weeks Post-Treatment				
	ERAXIS	Fluconazole	Treatment Difference ^a	95% CI
Endoscopic Relapse, n/N (%)	120/225 (53.3%)	45/233 (19.3%)	34.0%	25.8%, 42.3%

^a Calculated as ERAXIS minus fluconazole

Table 8. Treatment-related ^a adverse events reported in ≥2.0% of subjects receiving ERAXIS or fluconazole therapy for candidemia/other *Candida* infections

	ERAXIS 100 mg ^b N = 131 N (%)	Fluconazole 400 mg ^b N = 125 N (%)
Subjects with at least 1 treatment-related AE	32 (24.4)	33 (26.4)
Gastrointestinal System		
Diarrhea	4 (3.1)	2 (1.6)
Investigations		
ALT ↑	3 (2.3)	4 (3.2)
AST ↑	1 (0.8)	3 (2.4)
Alkaline phosphatase ↑	2 (1.5)	5 (4.0)
Hepatic enzyme ↑	2 (1.5)	9 (7.2)
Metabolic and Nutritional Systems		
Hypokalemia	4 (3.1)	3 (2.4)
Vascular System		
Deep vein thrombosis	1 (0.8)	3 (2.4)

^a Treatment-related AEs are defined as those that are possibly or probably related to study treatment, as determined by the investigator.

^b Maintenance dose

(1) Endoscopic, Clinical, Mycological, and Cost Outcomes for Esophageal Candidiasis at End-of-Treatment

Treatment Outcome (median duration = 14 days)	Micafungin 150 mg/day	Fluconazole 200 mg/day	%Difference (95% CI)
	N = 260	N = 258	
Endoscopic Cure	228 (87.7%)	227 (88.0%)	-0.3% (-5.9, +5.3)
Clinical Cure	239 (91.9%)	237 (91.9%)	0.06% (-4.6, +4.8)
Overall Therapeutic Cure	223 (85.8%)	220 (85.3%)	0.5% (-5.6, +6.6)
Mycological Eradication	141/189 (74.6%)	149/192 (77.6%)	-3.0% (-11.6, +5.6)
Cost for median duration of 14 days	\$3795.12	\$210.84 (iv); \$5.45 (po)	\$3585

(2) Relapse of Esophageal Candidiasis at Week 2 and through Week 4 Post-Treatment in Patients with Overall Therapeutic Cure at the End of Treatment

Relapse	Micafungin 150 mg/day N = 223	Fluconazole 200 mg/day N = 220	% Difference (95% CI)
Relapse* at Week 2	40 (17.9%)	30 (13.6%)	4.3% (-2.5, 11.1)
Relapse* through Week 4 (cumulative)	73 (32.7%)	62 (28.2%)	4.6% (-4.0, 13.1)

(*) includes patients who died or were lost to follow-up, and those who received systemic anti-fungal therapy in the post-treatment period

(3) Favorable Response Rates and Cost Outcomes for Patients with Esophageal Candidiasis

	Caspofungin 50 mg/day	Fluconazole 200 mg/day	% Difference (95% CI)
Day 5-7 Post-treatment	66/81 (81.5%)	80/94 (85.1%)	-3.6 (-14.7, 7.5)
Cost Outcome for mean 9 days of treatment	\$2794.59	\$135.54	

(4) Relapse Rates at 2 Weeks and 4 Weeks Post-Therapy in Patients with Esophageal Candidiasis at Baseline

	Caspofungin	Fluconazole	% Difference (95% CI)
Week 2 post-treatment	7/66 (10.6%)	6/76 (7.9%)	2.7 (-6.9, 12.3)
Week 4 post-treatment	18/64 (28.1%)	12/72 (16.7%)	11.5 (-2.5, 25.4)

(5) Results from Clinical Study of Prophylaxis of Candida Infections in HSCT patients

Outcome of Prophylaxis	Micafungin 50mg/day (n=425)	Fluconazole 400mg/day (n=457)
Success*	343 (80.7%)	337 (73.7%)
Failure	82 (19.3%)	120 (26.3%)
All deaths ¹	18 (4.2%)	26 (5.7%)
Proven/probable fungal infection prior to death	1 (0.2%)	3 (0.7%)
Proven/probable fungal infection (not resulting in death) ¹	6 (1.4%)	8 (1.8%)
Suspected fungal infection ²	53 (12.5%)	83 (18.2%)
Lost to follow up	5 (1.2%)	3 (0.7%)

(*) difference (micafungin-fluconazole): +7.0% (95% CI = 1.5, 12.5)

(1) through end-of-study (4 weeks post-therapy)

(2) through end-of-therapy

Abstracts:

Safety and pharmacokinetics of intravenous anidulafungin in children with neutropenia at high risk for invasive fungal infections.

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Anidulafungin is an echinocandin with activity against *Candida* species and *Aspergillus* species. Adult dosages under study are 50 mg/day for esophageal candidiasis and 100 mg/day for invasive candidiasis and aspergillosis. Little is known, however, about the safety and pharmacokinetics of anidulafungin in children. A multicenter, ascending-dosage study of neutropenic pediatric patients was therefore conducted. Patients were divided into two age cohorts (2 to 11 years and 12 to 17 years) and were enrolled into sequential groups to receive 0.75 or 1.5 mg/kg of body weight/day. Blood samples were obtained following the first and fifth doses. Anidulafungin was assayed in plasma, and pharmacokinetic parameters were determined. Safety was assessed using National Cancer Institute (NCI) common toxicity criteria. Pharmacokinetic parameters were determined for 12 patients at each dosage (0.75 mg/kg/day or 1.5 mg/kg/day). Concentrations and drug exposures were similar for patients between age cohorts, and weight-adjusted clearance was consistent across age. No drug-related serious adverse events were observed. One patient had fever (NCI toxicity grade of 3), and one patient had facial erythema, which resolved with slowing the infusion rate. Anidulafungin in pediatric patients was well tolerated and can be dosed based on body weight. Pediatric patients receiving 0.75 mg/kg/day or 1.5 mg/kg/day have anidulafungin concentration profiles similar to those of adult patients receiving 50 or 100 mg/day, respectively.

TABLE 1. Demography and baseline characteristics

Characteristic	Value for:				All patients (n = 25)
	Low-dosage group (n = 13)		High-dosage group (n = 12)		
	Ages 2–11 yr (n = 6)	Ages 12–17 yr (n = 7)	Ages 2–11 yr (n = 6)	Ages 12–17 yr (n = 6)	
Median age in yr (range)	9 (3–11)	14 (13–16)	8 (2–11)	14 (13–16)	13 (2–16)
Gender (M:F) ^a	3:3	3:4	3:3	4:2	13:12
Race (n)					
Asian	0	0	1	0	1
Black/African-American	0	2	1	2	5
White	3	4	4	2	13
Hispanic/Latino	2	1	0	2	5
Other	1	0	0	0	1
Median wt in kg (range)	26.6 (15.2–56.2)	58.7 (48.1–99.2)	34.8 (15.8–41.2)	56.4 (22.0–86.0)	42.8 (15.2–99.2)
Comorbid diseases (n)					
Acute lymphocytic leukemia	1	2	1	0	4
Acute myelogenous leukemia	1	3	2	0	6
Chronic myelogenous leukemia	1	0	0	0	1
Lymphoma	0	0	1	0	1
Sarcoma	0	1	0	0	1
Neuroblastoma	1	0	0	0	1
Aplastic anemia	0	1	1	4	6
Inherited immunodeficiency	1	0	0	1	2

^a M, male; F, female.

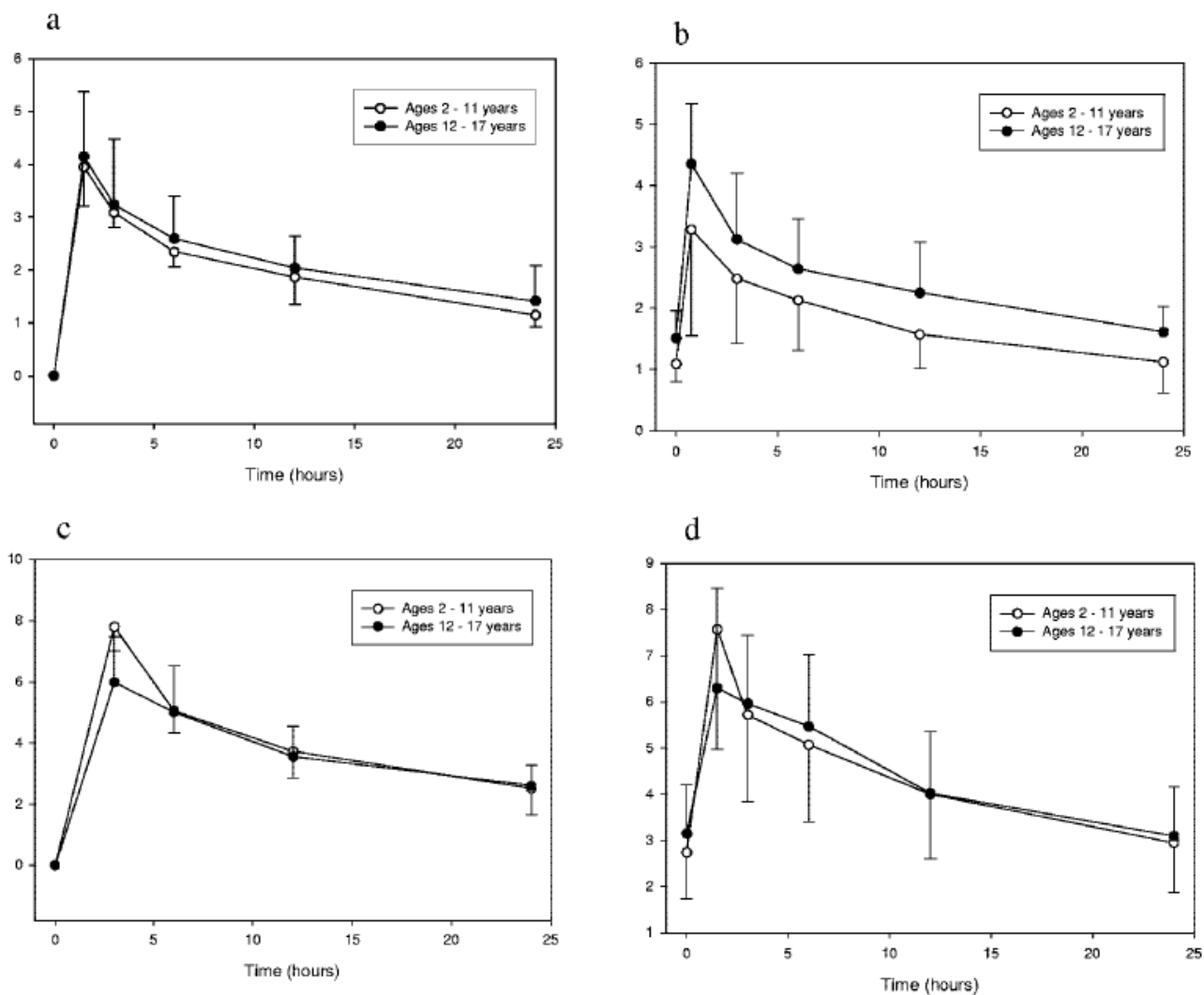


FIG. 1. (a) Anidulafungin plasma concentration-time profiles in children with compromised immunity and neutropenia after receiving a 1.5-mg/kg anidulafungin loading dose. (b) Steady-state anidulafungin plasma concentration-time profiles in these patients after receiving maintenance dosages of 0.75 mg/kg/day of anidulafungin (day 5). (c) Anidulafungin plasma concentration-time profiles in children with compromised immunity and neutropenia after receiving a 3.0-mg/kg anidulafungin loading dose. (d) Steady-state anidulafungin plasma concentration-time profiles for these patients after receiving maintenance dosages of 1.5 mg/kg/day of anidulafungin (day 5).

TABLE 2. Single-dose pharmacokinetic profile of anidulafungin in children with compromised immunity and neutropenia

Parameter	Value for group with dose				Value for all patients (n = 24)	
	1.5 mg/kg (n = 12)		3.0 mg/kg (n = 12)		1.5 mg/kg (n = 12)	3.0 mg/kg (n = 12)
	Ages 2–11 yr (n = 6)	Ages 12–17 yr (n = 6)	Ages 2–11 yr (n = 6)	Ages 12–17 yr (n = 6)		
C_{max} (mg/ml)						
Mean (SD)	3.95 (0.74)	4.10 (1.11)	7.80 (0.76)	5.99 (1.50)	4.02 (0.9)	6.90 (1.13)
Range	3.04–4.91	2.98–6.08	6.93–8.97	4.06–7.88	2.98–6.08	4.06–8.97
AUC _{0–24} (mg·h/ml)						
Mean (SD)	46.3 (8.70)	49.6 (14.6)	92.3 (11.9)	87.2 (23.6)	48.0 (11.6)	89.7 (18.0)
Range	34.7–54.1	40.0–78.7	77.4–107.5	56.1–119.2	34.7–78.7	56.1–119.2
$t_{1/2}$ (h)						
Mean (SD)	17.3 (3.7)	24.3 (8.7)	18.3 (6.7)	20.8 (4.8)	20.8 (6.2)	19.5 (5.8)
Range	14.7–24.7	13.3–36.0	14.2–31.8	17.4–29.3	13.3–36	14.2–31.8
CL/kg (liters/h/kg)						
Mean (SD)	0.0208 (0.0052)	0.0143 (0.0062)	0.0200 (0.0058)	0.0181 (0.0078)	0.0175 (0.0057)	0.0191 (0.0068)
Range	0.0145–0.0275	0.0054–0.0199	0.0102–0.0266	0.0116–0.0316	0.0054–0.0275	0.0102–0.0316
V_{ss} (liters/kg)						
Mean (SD)	0.488 (0.086)	0.430 (0.133)	0.474 (0.036)	0.523 (0.193)	0.459 (0.110)	0.499 (0.115)
Range	0.399–0.602	0.267–0.610	0.421–0.529	0.375–0.857	0.267–0.610	0.375–0.857

TABLE 3. Multiple-dose pharmacokinetic profile of anidulafungin in children with compromised immunity and neutropenia

Parameter	Value for group with dose				Value for all patients (n = 24)	
	0.75 mg/kg/day (n = 12)		1.50 mg/kg/day (n = 12)		0.75 mg/kg/day (n = 12)	1.5 mg/kg/day (n = 12)
	Ages 2–11 yr (n = 6)	Ages 12–17 yr (n = 6)	Ages 2–11 yr (n = 6)	Ages 12–17 yr (n = 6)		
C_{max} (mg/ml)						
Mean (SD)	3.32 (1.66)	4.35 (0.98)	7.57 (2.59)	6.88 (1.67)	3.83 (1.32)	7.23 (2.13)
Range	0.91–5.98	3.1–5.57	5.22–12.3	3.71–8.66	0.91–5.98	3.71–12.3
AUC _{ss} (mg·h/ml)						
Mean (SD)	41.1 (15.8)	56.2 (15.6)	96.1 (38.0)	102.9 (29.0)	48.6 (15.7)	99.5 (33.5)
Range	16.5–57.8	31.8–79.8	43.2–155.7	50.3–134.1	16.5–79.8	43.2–155.7
$t_{1/2}$ (h)						
Mean (SD)	20.3 (7.9)	26.0 (10.2)	18.9 (3.5)	21.1 (5.2)	23.1 (9.0)	19.9 (4.3)
Range	13.9–35.1	12.0–38.9	13.6–24.1	15.0–27.8	12.0–38.9	13.6–27.8
CL/kg (liters/h/kg)						
Mean (SD)	0.0217 (0.0123)	0.0133 (0.0031)	0.0163 (0.0048)	0.0156 (0.0079)	0.0175 (0.0077)	0.0159 (0.0063)
Range	0.0113–0.0446	0.0095–0.018	0.0094–0.0231	0.0096–0.0311	0.0095–0.0446	0.0094–0.0311
V_{ss} (liters/kg)						
Mean (SD)	0.575 (0.243)	0.499 (0.231)	0.419 (0.066)	0.449 (0.166)	0.537 (0.237)	0.434 (0.116)
Range	0.337–0.962	0.163–0.803	0.319–0.5	0.314–0.73	0.163–0.962	0.314–0.730

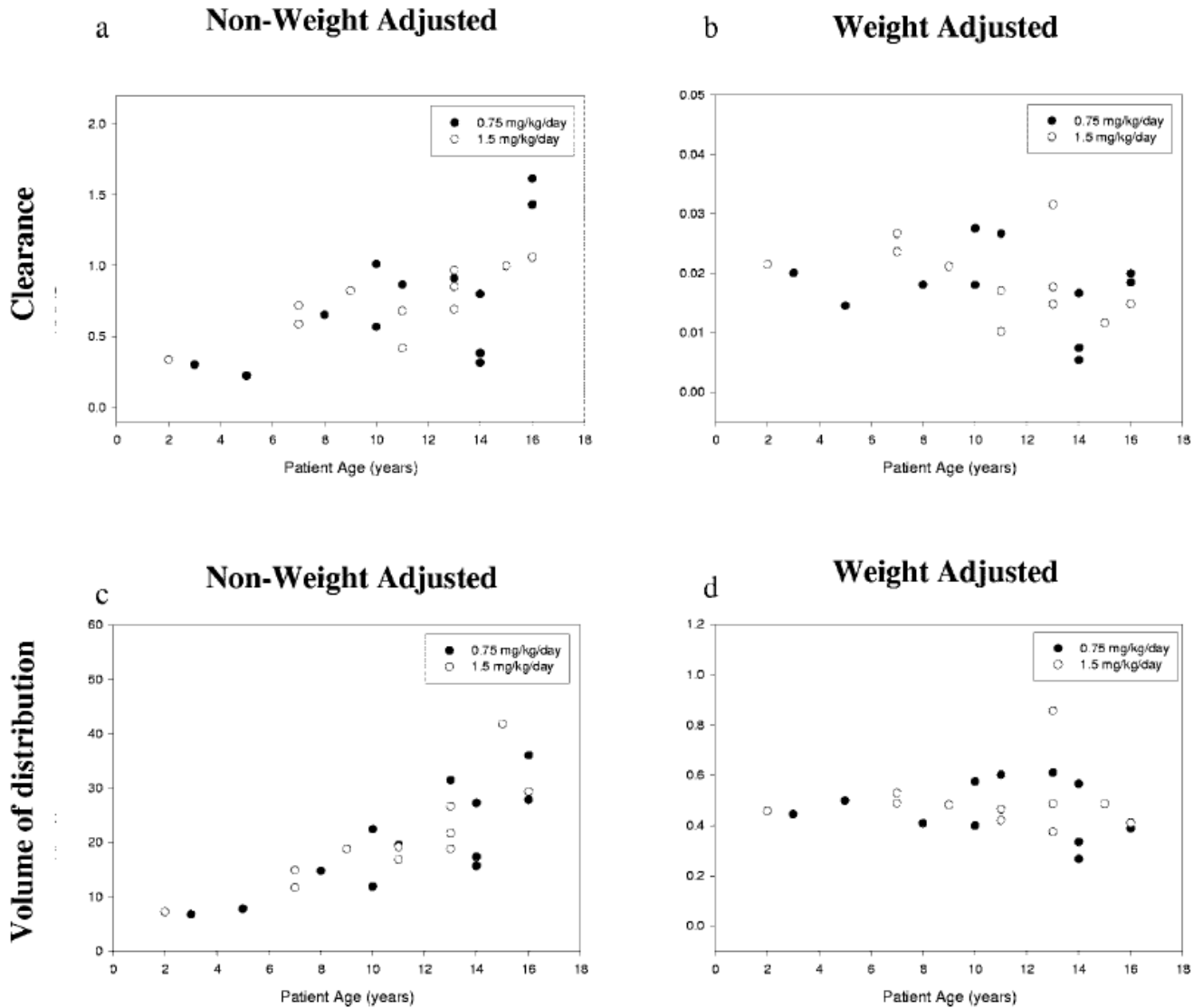


FIG. 2. Non-weight-adjusted (a) and weight-normalized (b) anidulafungin clearance versus patient age on day 1 of infusion, and non-weight-adjusted (c) and weight-normalized (d) anidulafungin volume of distribution versus patient age.

Safety and pharmacokinetics of coadministered voriconazole and anidulafungin.

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There is considerable interest in combining echinocandin and triazole antifungal agents for treatment of invasive fungal infections; however, information is needed regarding the tolerability and potential for pharmacokinetic interactions. Anidulafungin is a semisynthetic echinocandin, and voriconazole is an extended-spectrum triazole. In a random sequence, 17 subjects received anidulafungin with placebo, voriconazole with placebo, and anidulafungin with voriconazole. Anidulafungin was administered intravenously: 200 mg on day 1, then 100 mg/d on days 2 through 4. Voriconazole was administered orally: 400 mg every 12 hours on day 1, then 200 mg every 12 hours on days 2 to 4. No dose-limiting toxicities or serious adverse events occurred, and all adverse events were mild and consistent with the known safety profiles of both drugs. Pharmacokinetic parameters were not affected by coadministration. The geometric mean ratio (90% confidence interval) of the combination/drug alone for AUC(SS) was 97.4% (94.9-99.9), 97.4% (92.1-103.0), and 94.4% (87.0-102.5) for anidulafungin, voriconazole, and the voriconazole metabolite, respectively.

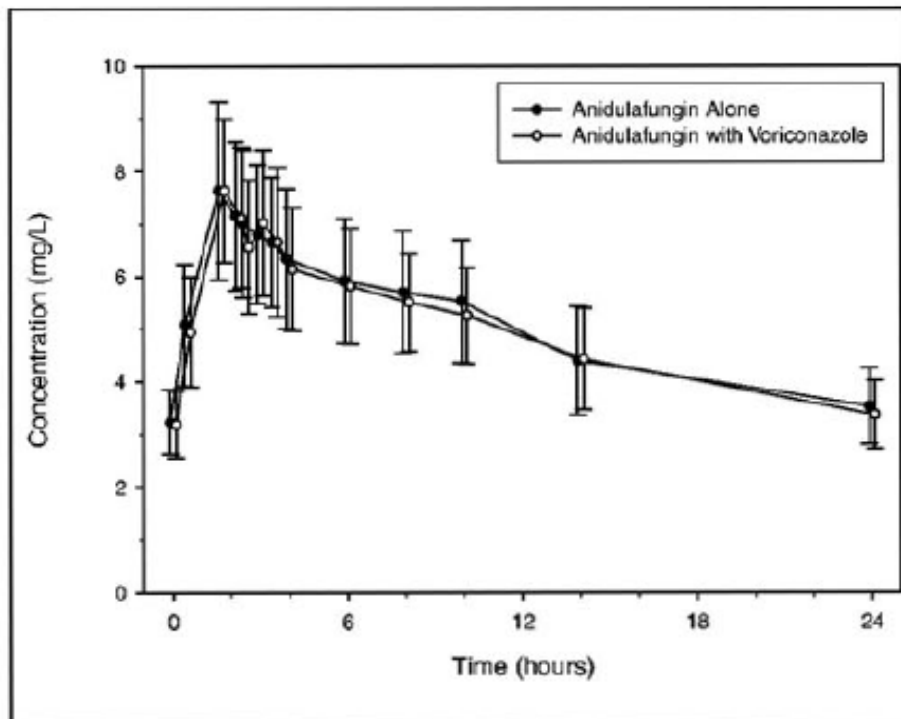


Figure 1. Steady-state plasma concentration-time profile of anidulafungin (mean \pm standard deviation) following administration of anidulafungin alone or in combination with voriconazole. Data time points are slightly offset for ease of reading.

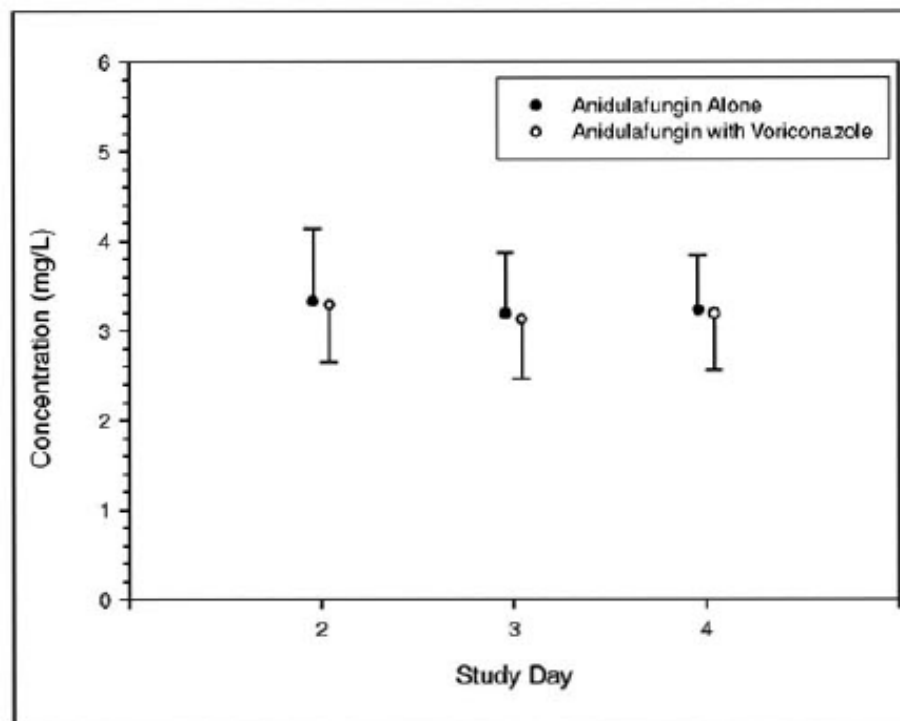


Figure 2. Anidulafungin trough concentrations in plasma (mean \pm standard deviation) following administration of anidulafungin alone or in combination with voriconazole.

Table I Steady-State Pharmacokinetic Parameters of Anidulafungin (Mean \pm Standard Deviation) Following Administration of Anidulafungin Alone or in Combination With Voriconazole

Pharmacokinetic Parameter	Anidulafungin Alone	Anidulafungin + Voriconazole	Statistical Comparison	
			Geometric Mean Ratio, %	90% Confidence Interval, %
C_{max} , mg/L	7.87 \pm 1.64	7.91 \pm 1.32	100.6	96.9-104.4
AUC_{SS} , mg•h/L	120.3 \pm 24.1	117.9 \pm 21.4	97.4	94.9-99.9
CL, L/h	0.868 \pm 0.198	0.880 \pm 0.187	102.7	100.1-105.4
V_{SS} , L	40.1 \pm 9.6	41.5 \pm 8.8	104.5	99.5-109.8
$t_{1/2}$, h	40.2 \pm 5.7	38.9 \pm 2.7	97.8	92.8-103.1

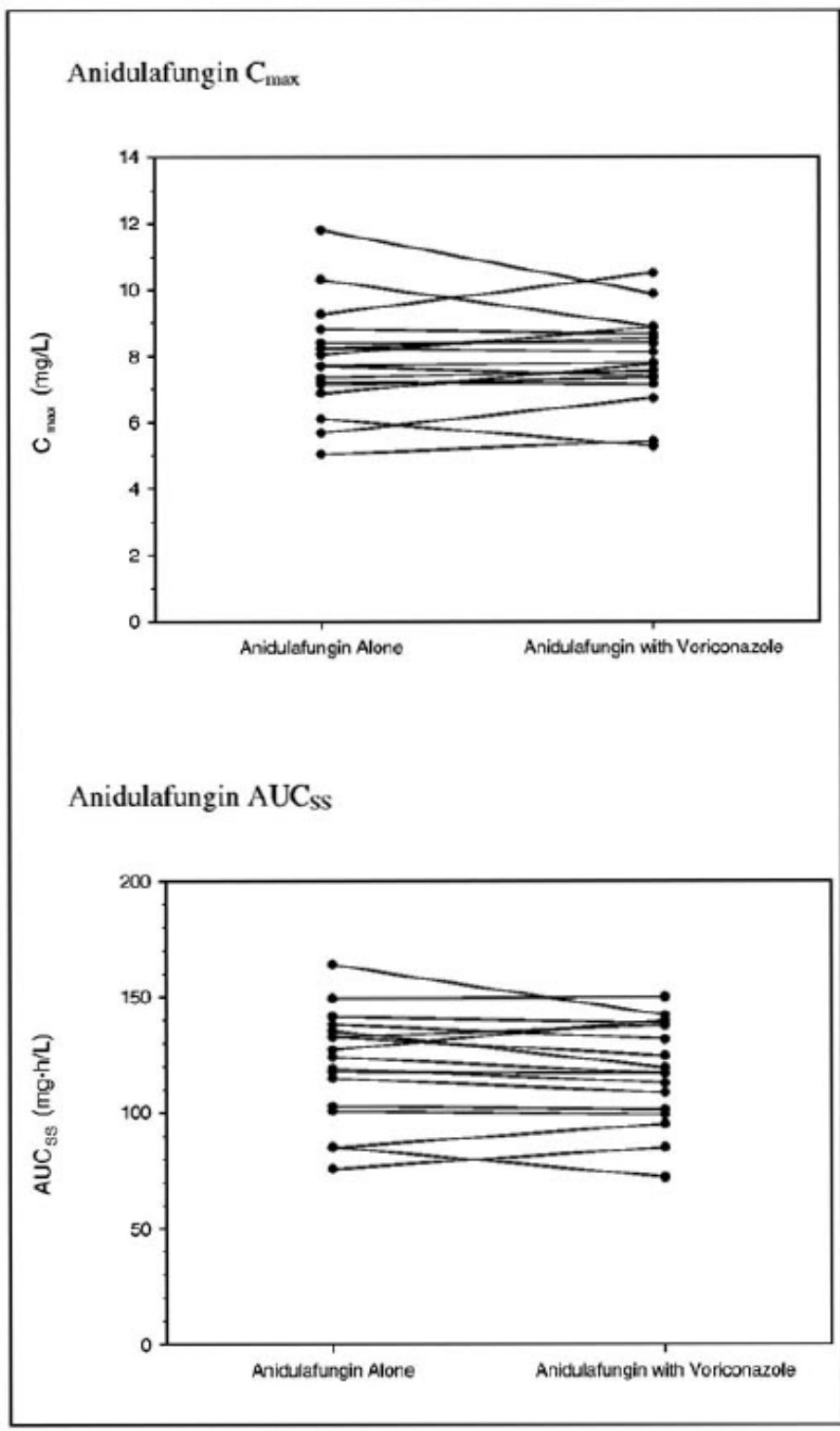


Figure 3. Individual anidulafungin C_{max} and AUC_{ss} parameters following administration of anidulafungin alone or in combination with voriconazole.

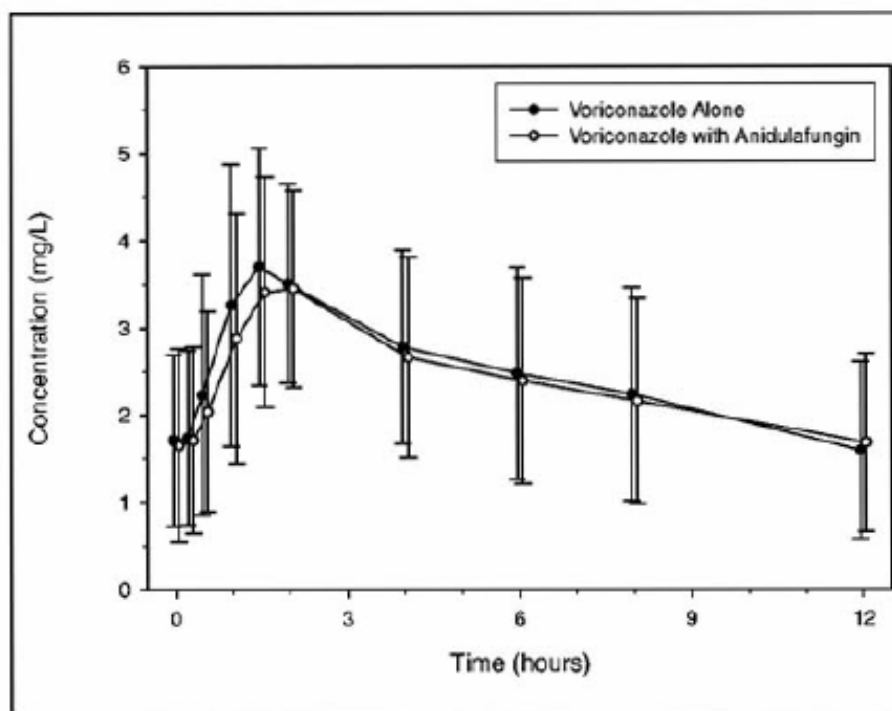


Figure 4. Steady-state plasma concentration-time profile of voriconazole (mean \pm standard deviation) following administration of voriconazole alone or in combination with anidulafungin. Data time points are slightly offset for ease of reading.

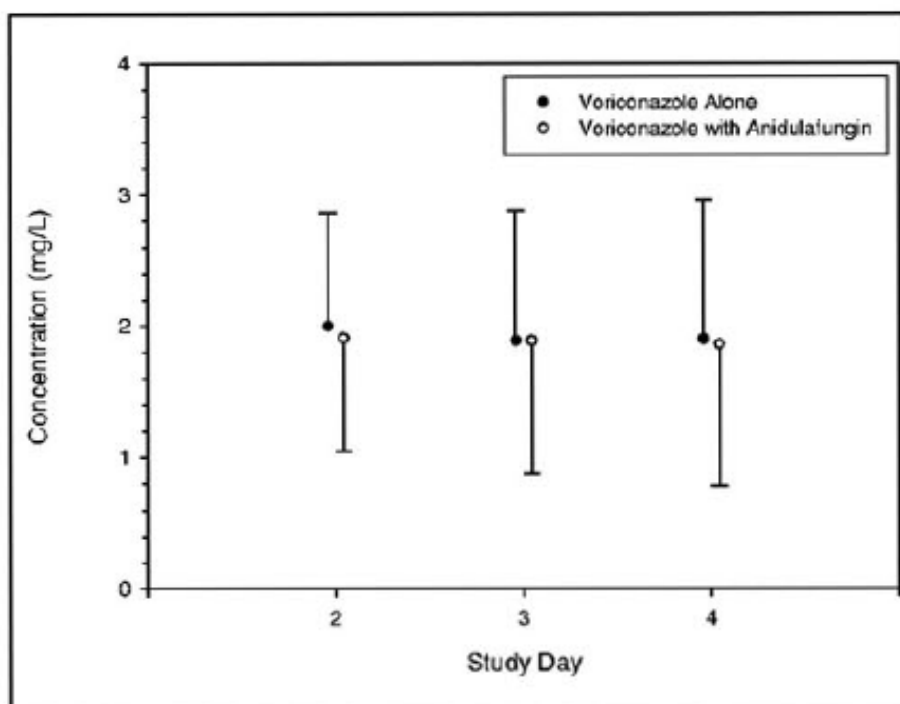


Figure 5. Voriconazole trough concentrations in plasma (mean \pm standard deviation) following administration of voriconazole alone or in combination with anidulafungin.

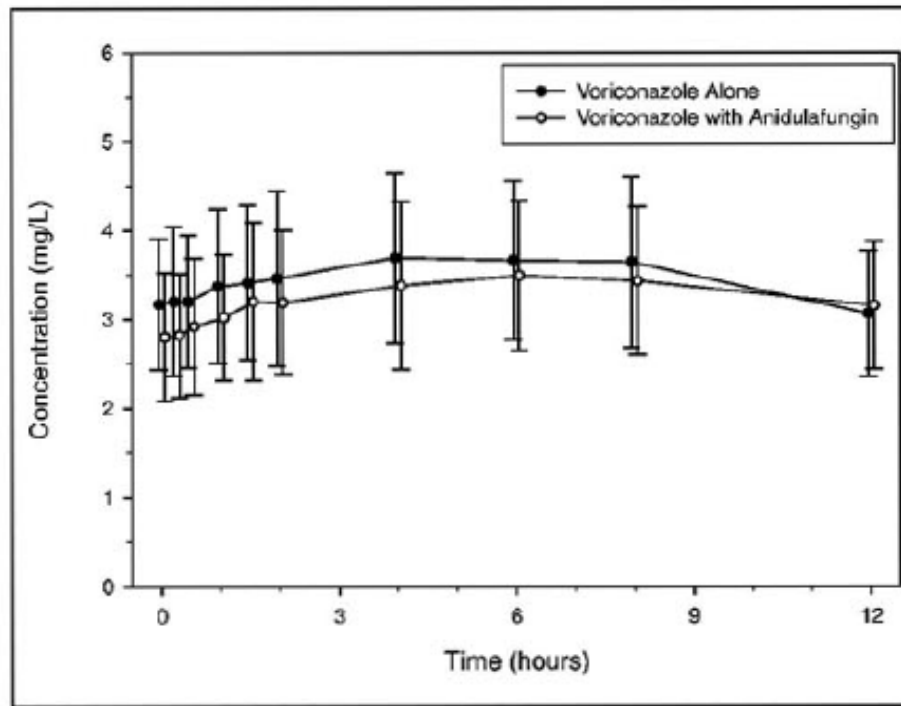


Figure 6. Steady-state plasma concentration-time profile of voriconazole N-oxide metabolite (mean \pm standard deviation) following administration of voriconazole alone or in combination with anidulafungin. Data time points are slightly offset for ease of reading.

Table II Steady-State Pharmacokinetic Parameters of Voriconazole (Mean \pm Standard Deviation) Following Administration of Voriconazole Alone or in Combination With Anidulafungin

Pharmacokinetic Parameter	Voriconazole Alone	Anidulafungin + Voriconazole	Statistical Comparison	
			Geometric Mean Ratio, %	90% Confidence Interval, %
C_{max} , mg/L	3.96 \pm 1.19	3.71 \pm 1.19	93.7	89.4-98.2
AUC_{SS} , mg•h/L	29.9 \pm 13.7	28.8 \pm 13.4	97.4	92.1-103.0

Table III Steady-State Pharmacokinetic Parameters of Voriconazole N-oxide Metabolite (Mean \pm Standard Deviation) Following Administration of Voriconazole Alone or in Combination With Anidulafungin

Pharmacokinetic Parameter	Voriconazole Alone	Anidulafungin + Voriconazole	Statistical Comparison	
			Geometric Mean Ratio, %	90% Confidence Interval, %
C_{max} , mg/L	3.86 \pm 0.97	3.70 \pm 0.91	95.7	87.3-104.9
AUC_{SS} , mg•h/L	41.9 \pm 10.3	39.6 \pm 9.3	94.4	87.0-102.5

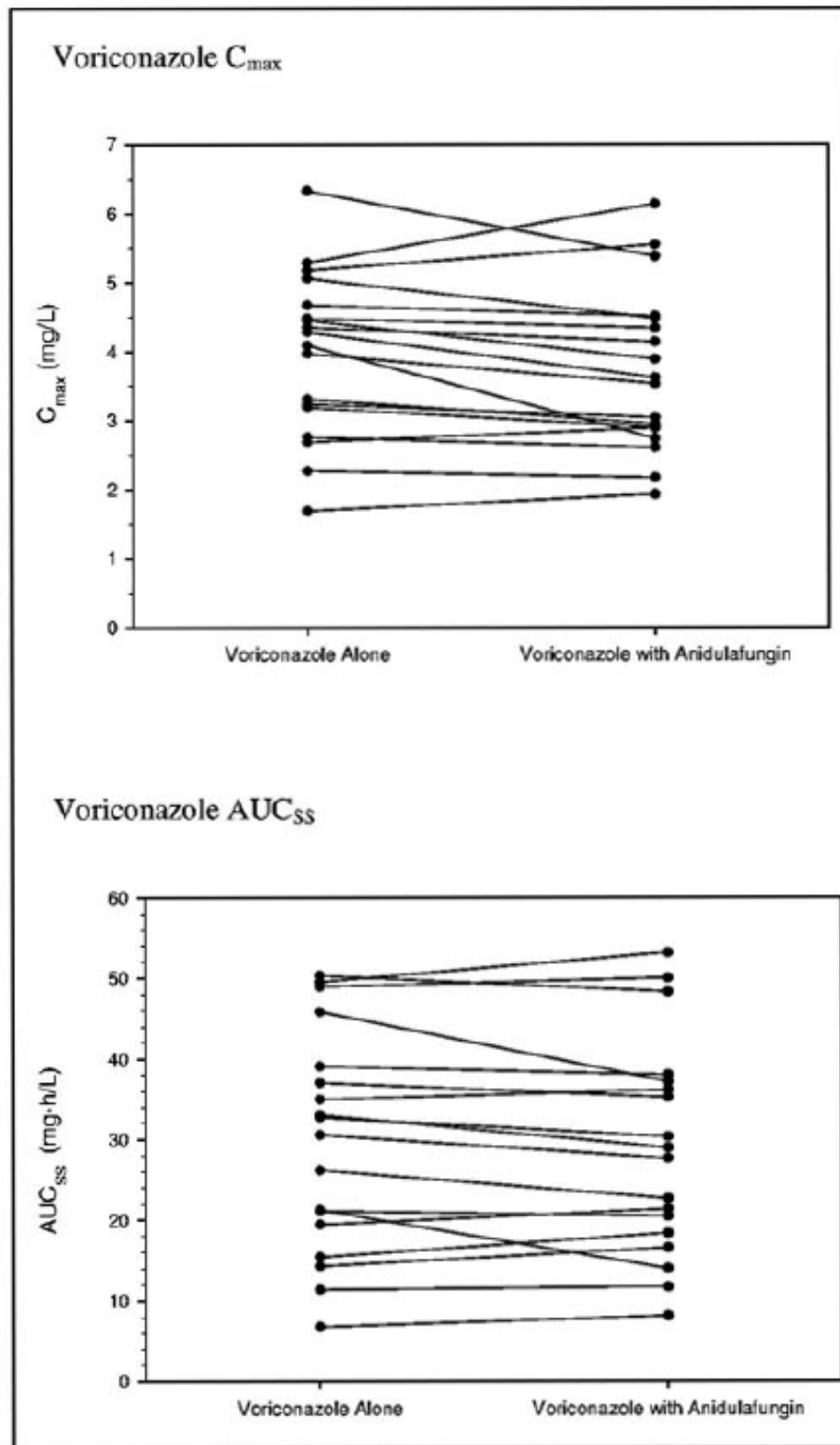


Figure 7. Individual voriconazole C_{max} and AUC_{SS} parameters following administration of voriconazole alone or in combination with anidulafungin.

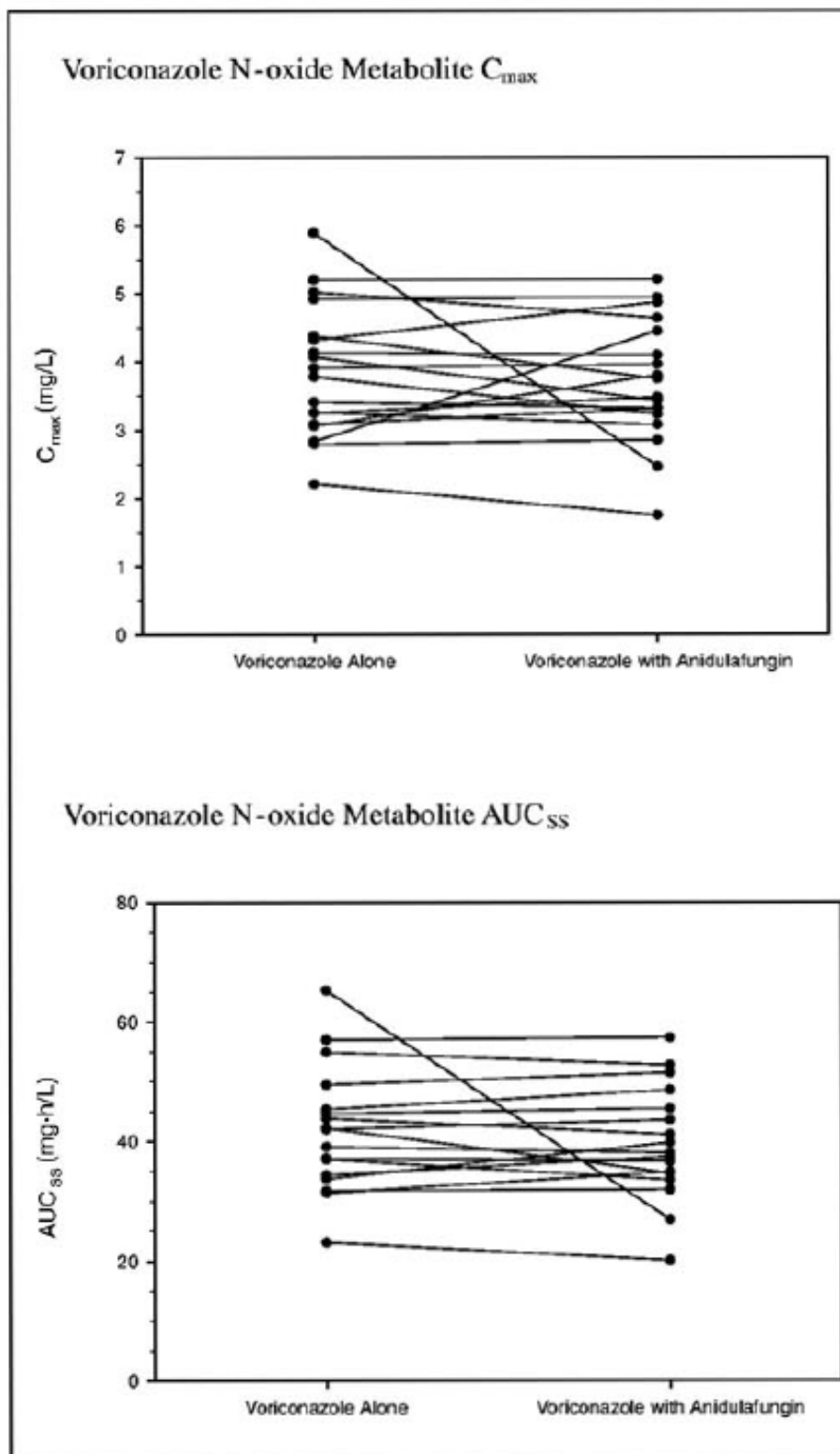


Figure 8. Individual voriconazole N-oxide metabolite C_{max} and AUC_{ss} parameters following administration of voriconazole alone or in combination with anidulafungin.

Table IV Number of Subjects Reporting Drug-Related Adverse Events

Adverse Event	Anidulafungin + Oral Placebo (n = 17)	Voriconazole + IV Placebo (n = 18)	Anidulafungin + Voriconazole (n = 18)
Total	5	9	12
Dizziness	0	3	0
Headache	1	2	2
Injection site reaction	4	3	5
Nausea	0	1	0
Photophobia	0	0	4
Vision blurred	0	0	1
Visual disturbance	0	2	5

Effectiveness of anidulafungin in eradicating *Candida* species in invasive candidiasis.

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In a phase 2 open-label, dose-ranging study in patients with candidemia, anidulafungin was effective in eradicating *Candida albicans* and other species of *Candida*. The anidulafungin MIC distribution showed that *Candida albicans* and *C. glabrata* were the most susceptible species and *C. parapsilosis* was the least susceptible species.

TABLE 1. Distribution of baseline *Candida* species and anidulafungin MICs

Species [no. of isolates (%)] ^a	n ^b	MIC ^c range	MIC ₅₀	MIC ₉₀	MIC ₉₀ (n) in survey ^d
All species [127 (100)]	114	0.03–8	0.25	2	
<i>C. albicans</i> [62 (49)]	59	0.03–4	0.12	0.25	0.06 (500)
<i>C. glabrata</i> [36 (28)]	31	0.06–0.5	0.25	0.25	0.12 (105)
<i>C. parapsilosis</i> [11 (9.5)]	11	4–8	4	8	4 (106)
<i>C. tropicalis</i> [10 (8.6)]	7	0.12–2	0.5		0.06 (106)
<i>C. krusei</i> [5 (4.3)]	4	0.12–0.25			0.06 (23)
Other ^e [3 (2.4)]	2	0.12–0.5			

^a All isolates from the three treatment groups combined; microbiological intent-to-treat population (all patients who received anidulafungin and had *Candida* isolated at baseline).

^b Baseline isolates for which MICs were available; microbiological intent-to-treat population.

^c MICs in µg/ml; 100% inhibition for study isolates.

^d Data from survey of >800 *Candida* bloodstream isolates (10); MICs in µg/ml, prominent inhibition endpoint.

^e One each of *C. dubliniensis*, *C. famata*, and *Candida* sp.

TABLE 2. Eradication rates of the more frequently isolated *Candida* species

Species [no. of isolates (%) ^a]	No. eradicated/no. total (%)			
	Daily dose (mg)			All doses
	50	75	100	
All species [73 (100)]	14/19 (74)	23/27 (85)	24/27 (89)	61/73 (84)
<i>C. albicans</i> [34 (47)]	5/6 (83)	12/14 (86)	11/14 (79)	28/34 (82)
<i>C. glabrata</i> [21 (29)]	6/7 (86)	4/4 (100)	10/10 (100)	20/21 (95)
<i>C. parapsilosis</i> [7 (9.6)]	2/3 (67)	3/3 (100)	1/1 (100)	6/7 (86)
<i>C. tropicalis</i> [6 (8.2)]	0/1 (0)	3/3 (100)	2/2 (100)	5/6 (83)

^a Evaluable population at follow-up.

TABLE 3. Response to therapy by MIC and daily dose of anidulafungin for baseline isolates of *Candida* spp.

MIC (μ g/ml)	No. of isolates tested (<i>n</i>) and % success (%S) by anidulafungin dose (mg/day)							
	50		75		100		All	
	<i>n</i>	%S	<i>n</i>	%S	<i>n</i>	%S	<i>n</i>	%S
0.03			1	0			1	0
0.06			2	100	2	100	4	100
0.12	3	66	7	71	7	100	17	82
0.25	10	70	8	88	13	77	31	77
0.5	1	100	1	100	1	0	3	66
1								
2			1	100	1	100	2	100
4	2	50	2	100	2	100	6	83
8	1	100					1	100
Unknown ^a	2	100	5	100	2	100	9	100

^a Unknown, MIC not determined.

Assessment of the safety and pharmacokinetics of anidulafungin when administered with cyclosporine.

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Anidulafungin is a novel antifungal agent of the echinocandin class that is intended for the treatment of invasive fungal disease. It is likely that anidulafungin will be coadministered with cyclosporine. In vitro studies and clinical studies were performed to evaluate the effect of anidulafungin on cyclosporine metabolism and to investigate the safety and pharmacokinetics of anidulafungin when concomitantly administered with cyclosporine. The potential for anidulafungin to inhibit the metabolism of cyclosporine was evaluated by pooled human hepatic microsomal protein fractions in vitro, incubating 3H-cyclosporine with different concentrations of anidulafungin. The safety of coadministration and the effects of cyclosporine on the pharmacokinetics of anidulafungin were assessed in a multiple-dose, open-label clinical study of 12 healthy volunteers. Subjects received a 200-mg intravenous loading dose of anidulafungin, followed by a daily 100-mg intravenous maintenance dose on days 2 through 8. An oral solution of cyclosporine (Neoral oral solution; 100 mg/mL) 1.25 mg/kg was also administered to subjects twice daily on days 5 through 8. In the in vitro study, the addition of anidulafungin had no effect on cyclosporine metabolism by human hepatic microsomal protein fractions. In the clinical study, no dose-limiting toxicities or serious adverse events occurred. A small increase in anidulafungin concentrations and drug exposure (22%) was observed after 4 days of dosing with cyclosporine and was not considered to be clinically relevant. The results

support the concomitant use of anidulafungin and cyclosporine without the need for dosage adjustments of either drug.

Table I Pharmacokinetic Parameters of Anidulafungin in the Absence (Day 4) and Presence (Day 8) of Cyclosporine

Parameter	Day 4 ^a (n = 11)	Day 8 ^a (n = 11)	Day 8/Day 4 (n = 11)	% Change
C _{max} , mg/L	7.5 (32.5)	8.1 (32.8)	1.08	8
C _{trough} , mg/L	2.8 (32.8)	4.0 (31.7)	1.43	43*
AUC ₀₋₂₄ , mg•h/L	104.5 (28.7)	127.6 (30.5)	1.22	22*
CL, L/h	1.04 (33.1)	0.87 (35.3)	0.837	-16*

Values presented as mean with coefficient of variation (%CV).

a. Data for 1 of 12 subjects are not included in these analyses because this subject did not complete the study.

*Statistically significant ($P < .05$).

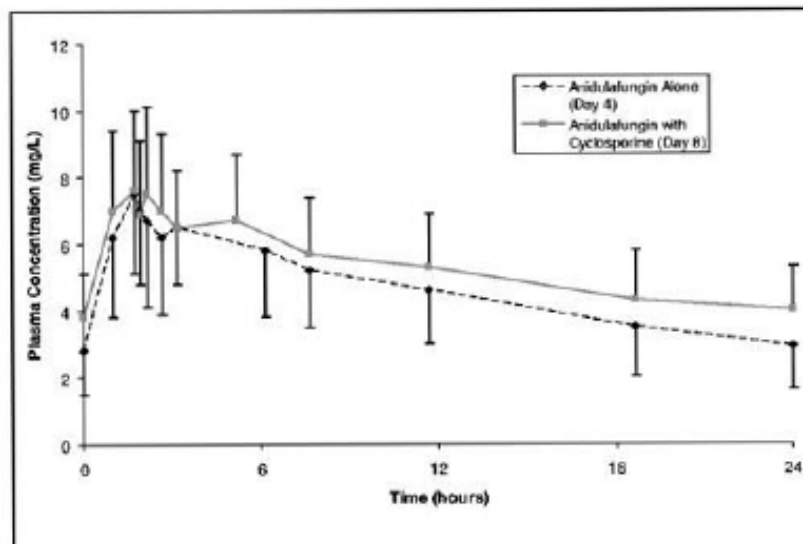


Figure 1. Mean (SD) plasma anidulafungin concentrations without (day 4) and with (day 8) concomitant administration of cyclosporine.

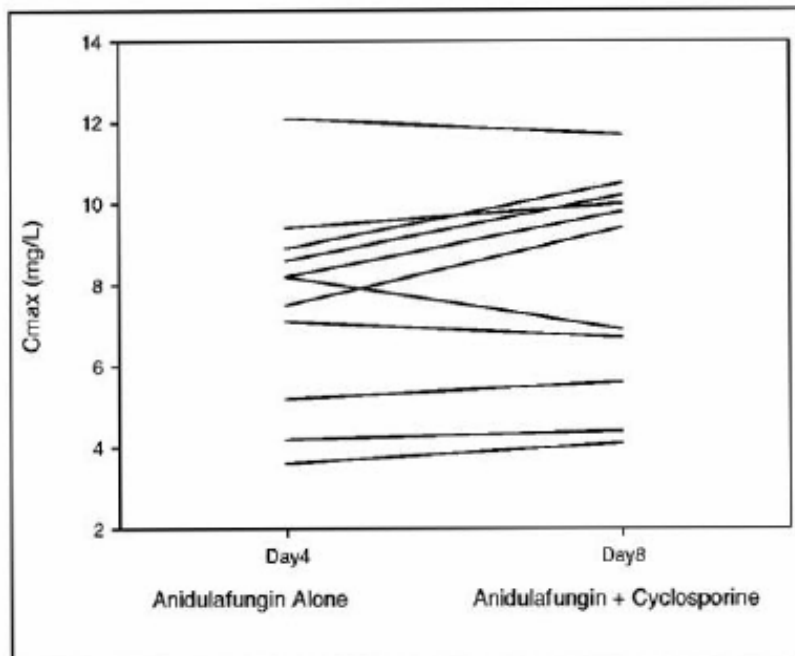


Figure 2. Individual observations of anidulafungin maximum concentration (C_{max}) without (day 4) and with (day 8) concomitant administration of cyclosporine.

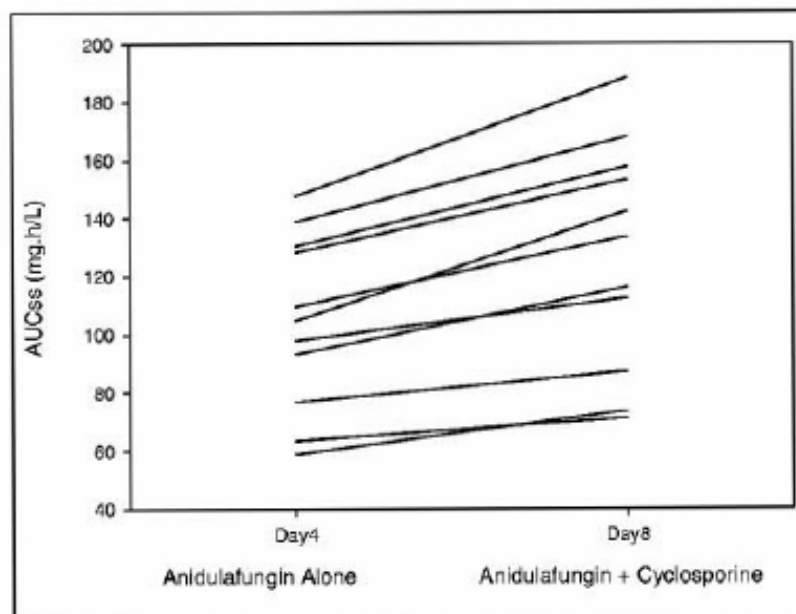


Figure 3. Individual estimates of anidulafungin area under the plasma concentration-time curve at steady-state (AUC_{ss}) without (day 4) and with (day 8) concomitant administration of cyclosporine.

Table II Statistical Comparison of Anidulafungin Systemic Exposure Parameters Measured in the Absence (Day 4) and Presence (Day 8) of Cyclosporine^a

Parameter	Geometric Least Square Means		Ratio	90% Confidence Interval
	Day 4	Day 8	Day 8/Day 4	
C _{max} , mg/L	7.4	7.9	1.07	100-115
AUC _{ss} , mg•h/L	104	126	1.21	118-125 ^b

a. Parameters estimated using linear mixed-effects modeling.

b. The 90% confidence interval does not fall completely within the 80% to 125% bioequivalence interval.

A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis.

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Anidulafungin is a novel antifungal agent of the echinocandin class. This randomized, double-blind, double-dummy study compared the efficacy and safety of intravenous anidulafungin to that of oral fluconazole in 601 patients with endoscopically and microbiologically documented esophageal candidiasis. Patients received intravenous anidulafungin (100 mg on day 1, followed by 50 mg per day) or oral fluconazole (200 mg on day 1, followed by 100 mg per day) for 7 days beyond resolution of symptoms (range, 14-21 days). At the end of therapy, the rate of endoscopic success for anidulafungin (242 [97.2%] of 249 treated patients) was found to be statistically noninferior to that for fluconazole (252 [98.8%] of 255 treated patients; treatment difference, -1.6%; 95% confidence interval, -4.1 to 0.8). The safety profile of anidulafungin was similar to that of fluconazole; treatment-related adverse events occurred in 9.3% and 12.0% of patients, respectively. Laboratory parameters were similar between treatment arms. Anidulafungin is as safe and effective as oral fluconazole for the treatment of esophageal candidiasis, when assessed at the completion of therapy.

Table 1. Selected demographic and baseline characteristics of study participants.

Characteristic	Intravenous anidulafungin group (<i>n</i> = 300)	Oral fluconazole group (<i>n</i> = 301)
Age, years		
Mean ± SD	37.5 ± 10.4	37.0 ± 9.6
Range	18–69	18–65
Sex		
Male	127 (42.3)	145 (48.2)
Female	173 (57.7)	156 (51.8)
Ethnicity ^a		
White	44 (14.7)	41 (13.6)
Black	146 (48.7)	144 (47.8)
Hispanic	1 (0.3)	2 (0.7)
Asian	46 (15.3)	46 (15.3)
Other	62 (20.7)	68 (15.3)
AIDS	223 (74.3)	233 (77.4)
Endoscopy grade		
1	61 (20.3)	53 (17.6)
2	112 (37.3)	101 (33.6)
3	127 (42.3)	147 (48.8)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

^a Ethnic information for 1 patient in the anidulafungin group is missing.

Table 2. Endoscopic responses at the completion of intravenous anidulafungin or oral fluconazole therapy.

Endoscopic response	No. (%) of patients		Treatment difference, % (95% CI)
	Intravenous anidulafungin group (<i>n</i> = 249)	Oral fluconazole group (<i>n</i> = 255)	
Success			
All	242 (97.2)	252 (98.8)	−1.6 (−4.1 to 0.8)
Cure	219 (88.0)	238 (93.3)	...
Improvement	23 (9.2)	14 (5.5)	...
Failure	7 (2.8)	3 (1.2)	...

Table 3. Clinical and mycological success at the completion of intravenous anidulafungin or oral fluconazole therapy.

Response	No. of patients with response/no. of patients with data (%)	
	Intravenous anidulafungin recipients	Oral fluconazole recipients
Clinical success	246/249 (98.8)	254/255 (99.6)
Mycological success	156/180 (86.7)	169/186 (90.9)

Table 4. Time to resolution of symptoms and duration of intravenous anidulafungin or oral fluconazole therapy.

Variable	Intravenous anidulafungin recipients (<i>n</i> = 249)	Oral fluconazole recipients (<i>n</i> = 255)
No. (%) of patients with resolution of symptoms ^a	248 (99.5)	251 (98.4)
Time to resolution of symptoms, ^a median days	5	5
Duration of therapy, median days	14	14

^a Odynophagia/dysphagia and retrosternal pain.

Table 5. Patients with treatment-related adverse events, by body system.

Body system, adverse event	Intravenous anidulafungin group (n = 300)	Oral fluconazole group (n = 301)
Blood and lymphatic disorders		
Neutropenia	1.0	...
Leukopenia	0.7	1.3
Digestive system		
Nausea	1.0	1.0
Vomiting	0.7	1.0
Dyspepsia aggravation	0.3	1.0
General disorders: pyrexia	0.7	1.0
CNS: headache	1.3	1.0
Vascular disorders: phlebitis/thrombophlebitis	1.3	1.3

NOTE. Adverse events occurred in $\geq 1.0\%$ of patients; relationship to use of study drug was determined by the investigator to be possibly or probably related or unknown.

Phase 2, randomized, dose-ranging study evaluating the safety and efficacy of anidulafungin in invasive candidiasis and candidemia.

Krause DS, Reinhardt J, Vazquez JA, Reboli A, Goldstein BP, Wible M, Henkel T; Anidulafungin Invasive Candidiasis Study Group.

Vicuron Pharmaceuticals Inc., 455 S. Gulph Rd., Suite 310, King of Prussia, PA 19406, USA. dkrause@vicuron.com

This study evaluated the safety and efficacy of anidulafungin, a novel echinocandin, in patients with invasive candidiasis, including candidemia. A total of 123 eligible patients were randomized to one of three intravenous regimens, 50, 75, or 100 mg once daily. Treatment continued for 2 weeks beyond resolution or improvement of signs and symptoms. The primary efficacy criterion was a successful global response rate (i.e., clinical and microbiological success) in the evaluable population at the follow-up (FU) visit, 2 weeks after end of therapy (EOT). One hundred twenty (120) patients received at least one dose of anidulafungin; 68 were evaluable. Review of adverse events and laboratory data indicated no dose response for safety parameters. Non-albicans *Candida* species accounted for approximately one-half of all isolates. Success rates at EOT were 84, 90, and 89% in the 50-, 75-, and 100-mg groups, respectively. At FU, the success rates were 72, 85, and 83%. Phase 3 studies of anidulafungin for the treatment of invasive candidiasis and candidemia are warranted.

TABLE 1. Patient populations

Characteristic	No. of patients			Total
	Anidulafungin dose group (mg)			
	50	75	100	
Randomized	42	40	41	123
Never received study drug	2	0	1	3
ITT	40	40	40	120
No baseline pathogen	3	0	1	4
MITT	37	40	39	116
<10 days of anidulafungin ^a	9	8	8	25
Concomitant antifungal therapy before EOT	3	1	1	5
Indeterminate clinical-microbiological response	0	1	2	3
Evaluable at EOT	25	30	28	83
Concomitant antifungal therapy before FU	1	3	1	5
Indeterminate clinical-microbiological response	6	1	3	10
Evaluable at FU	18	26	24	68

^a Patients who received at least 5 days of anidulafungin and had a clinical response of failure at EOT were not excluded from the evaluable populations.

TABLE 2. Baseline characteristics of ITT population

Characteristic	Value for anidulafungin dose group (mg) ^a		
	50	75	100
Age [median yr (range)]	52 (18–88)	54 (21–87)	59 (26–88)
Sex			
Male [<i>n</i> (%)]	13 (33)	21 (53)	18 (45)
Female [<i>n</i> (%)]	27 (68)	19 (48)	22 (55)
Wt (median [kg])	68.9	76.1	70.6
APACHE II score (mean ± SD)	13.4 ± 8.3	18.6 ± 9.7	15.0 ± 8.2
APACHE II score ≥20 [<i>n</i> (%)]	7 (18)	12 (30)	10 (25)
Absolute neutrophil count of <500 [<i>n</i> (%)]	7 (18)	5 (13)	4 (10)
Diabetes mellitus [<i>n</i> (%)]	13 (33)	12 (30)	11 (28)
Prior systemic antifungal treatment [<i>n</i> (%)]	23 (58)	28 (70)	31 (78)

^a Forty patients per group.

TABLE 3. Distribution of baseline *Candida* species by treatment group^a

Species or source	No. of patients (%)			Total
	Anidulafungin dose group (mg)			
	50	75	100	
<i>C. albicans</i>	20 (54)	20 (50)	22 (56)	62 (53)
<i>C. glabrata</i>	11 (30)	10 (25)	15 (38)	36 (31)
<i>C. parapsilosis</i>	6 (16)	4 (10)	1 (3)	11 (9)
<i>C. tropicalis</i>	1 (3)	6 (15)	3 (8)	10 (9)
<i>C. krusei</i>	2 (5)	3 (8)	0	5 (4)
Other species	2 (5)	0	1 (3)	3 (3)
Blood	36 (97)	37 (93)	36 (92)	109 (94)
Tissue	1 (3)	7 (18)	4 (10)	12 (10)
Both	0	4 (10)	1 (3)	5 (4)

^a 10 patients had multiple species isolated at baseline. There were 37, 40, and 39 members of the MITT population in the 50-, 75-, and 100-mg groups, respectively (total, 116).

TABLE 4. Successful responses by treatment group^a

Endpoint	No. of subjects with response/ No. of subjects in the population (%) for anidulafungin dose group (mg)		
	50	75	100
	Global response		
EOT	21/25 (84)	27/30 (90)	25/28 (89)
FU	13/18 (72)	22/26 (85)	20/24 (83)
Clinical response			
EOT	22/25 (88)	27/30 (90)	25/28 (89)
FU	13/18 (72)	22/26 (85)	20/24 (83)
Microbiological response ^b			
EOT	21/25 (84)	28/30 (93)	25/28 (89)
FU	14/18 (78)	22/26 (85)	21/24 (88)

^a Results are presented for evaluable patients.

^b Analyzed on a per-patient basis

TABLE 5. Safety summary

Adverse event	No. of patients (%) from anidulafungin dose group (mg)		
	50	75	100
Any event	38 (95)	38 (95)	38 (95)
Related event ^a	11 (28)	11 (28)	12 (30)
Hypokalemia	4 (10)	2 (5)	2 (5)
Increased GGT	1 (3)	0	2 (5)
Hypomagnesemia	1 (3)	1 (3)	1 (3)
Serious event ^b	20 (50)	17 (43)	18 (45)
Death	12 (30)	10 (25)	11 (28)
Sepsis ^c	4 (10)	2 (5)	0
Cardiac arrest ^c	1 (3)	3 (8)	1 (3)
Respiratory distress ^c	0	2 (5)	3 (8)
Multiorgan failure	3 (8)	1 (3)	0
Septic shock	1 (3)	2 (5)	0

^a Considered by the investigator to have a probable or possible relationship to treatment with anidulafungin. Related adverse events occurring in at least two patients overall are displayed. GGT, gamma glutamyl transferase.

^b Serious adverse events reported by ≥ 2 patients in any treatment group are presented.

^c Three cases of respiratory distress, two cases of sepsis, and one cardiac arrest were nonfatal.

[Antimicrob Agents Chemother.](#) 2006 Jan;50(1):143-7.

Open-label, randomized comparison of itraconazole versus caspofungin for prophylaxis in patients with hematologic malignancies.

[MattiuZZi GN](#), [Alvarado G](#), [Giles FJ](#), [Ostrosky-Zeichner L](#), [Cortes J](#), [O'brien S](#), [Verstovsek S](#), [Faderl S](#), [Zhou X](#), [Raad II](#), [Bekele BN](#), [Leitz GJ](#), [Lopez-Roman I](#), [Estev EH](#).

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Invasive fungal infection remains the most common cause of infectious death in acute leukemia. In this open-label, randomized study, we compared the efficacy and safety of caspofungin with that of intravenous itraconazole for antifungal prophylaxis in patients undergoing induction chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome. Of 200 patients, 192 were evaluable for efficacy (86 for itraconazole, 106 for caspofungin). Duration of prophylaxis (median, 21 days [range, 1 to 38 days]), demographics, and prognostic factors were similar in both groups. Ninety-nine patients completed antifungal prophylaxis without developing fungal infection (44 [51%] with itraconazole, 55 [52%] with caspofungin). Twelve patients developed documented invasive fungal infections, five in the itraconazole group (four with candidemia and one with *Aspergillus* pneumonia), and seven in the caspofungin group (two with candidemia, two with disseminated trichosporon species, two with *Aspergillus* pneumonia, and one with disseminated *Fusarium* spp). Two patients in the itraconazole group and four in the caspofungin group died of fungal infection ($P = 0.57$). Grade 3 to 4 adverse event rates were comparable between groups; the most common event in both was reversible hyperbilirubinemia. No evidence of cardiovascular toxicity from intravenous itraconazole was noted among patients older than 60. In conclusion, intravenous itraconazole and caspofungin provided similar protection against invasive fungal infection during induction chemotherapy, and both drugs were well tolerated.

[Pediatr Infect Dis J.](#) 2005 Oct;24(10):858-66.

Multicenter study to assess safety and efficacy of INH-A21, a donor-selected human staphylococcal immunoglobulin, for prevention of nosocomial infections in very low birth weight infants.

[Bloom B](#), [Schelonka R](#), [Kueser T](#), [Walker W](#), [Jung E](#), [Kaufman D](#), [Kesler K](#), [Roberson D](#), [Patti J](#), [Hetherington S](#); [INH-A21 Phase II Study Team](#).

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BACKGROUND: Prophylactic administration of intravenous immunoglobulin has been inconsistent in reducing the risk of sepsis in very low birth weight (VLBW) infants presumably because of varying titers of organism specific IgG antibodies. INH-A21 is an intravenous immunoglobulin from donors with high titers of antistaphylococcal antibodies. This dose-ranging study explored safety and preliminary activity of INH-A21 for prevention of staphylococcal sepsis in VLBW infants. **METHODS:** This was a multicenter, double blind, group-sequential study. Infants with birth weights 500-1250 g were randomized to receive up to 4 doses of placebo, 250 mg/kg, 500 mg/kg or 750 mg/kg INH-A21. Safety and frequencies of sepsis were compared across treatment groups. **RESULTS:** All treatment groups had similar mean gestational age, birth weight, Apgar score and maternal use of antibiotics. Randomizations to 250 mg/kg (N = 94) and 500 mg/kg (N = 96) doses were terminated after interim analyses demonstrated a low probability of finding a difference when compared with placebo. Infants randomized to the INH-A21 750 mg/kg group (N = 157) had fewer episodes of *Staphylococcus aureus* sepsis [relative risk (RR), 0.37; 95% confidence interval (CI), 0.12-1.12; P = 0.14], candidemia (RR 0.34; 95% CI 0.09-1.22; P = 0.09) and mortality (RR 0.64; 95% CI 0.25-1.61; P = 0.27) when compared with the placebo-treated cohort (N = 158). No dose-related trends were observed for adverse events or morbidities associated with prematurity. **CONCLUSIONS:** INH-A21 750 mg/kg demonstrated potential to reduce sepsis caused by *S. aureus*, candidemia and mortality in VLBW infants. Although statistical significance was not reached, based on the magnitude of the estimated differences, the efficacy and safety of INH-A21 750 mg/kg should be evaluated in an adequately powered, well-controlled study.

[J Infect](#). 2005 Jun;50(5):443-9.

Invasive candidiasis in cancer patients: observations from a randomized clinical trial.

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BACKGROUND: Invasive candidiasis is a common and serious complication of cancer and its therapy. **METHODS:** We retrospectively identified patients with malignancies enrolled in a double-blind randomized trial of caspofungin (50 mg/day after a 70 mg loading dose) vs. conventional amphotericin B (0.6-1.0 mg/kg/day) as treatment of documented invasive candidiasis. A favorable response required complete resolution of signs and symptoms plus eradication of the *Candida* pathogen(s). The primary efficacy analysis used a modified intention-to-treat (MITT) approach that included all patients with a confirmed diagnosis of invasive candidiasis who received > or =1 dose of study medication. **RESULTS:** 74/224 (33%) patients in the MITT population had active malignancies. 25/30 (83%) hematological malignancies were acute or chronic leukaemias. 22/44 (50%) solid tumors were related to the gastrointestinal tract. Patients with hematological malignancies tended to be younger (median [range] age: 49 [19-74] vs. 59 [19-81] years) and have higher baseline acute physiology and chronic health evaluation (APACHE) II scores (mean [range]: 17 [0-28] vs. 15 [5-35]) than patients with solid tumors. Neutropenia [$<$ or $=$ 500/microl] was present on entry in 23 (77%) patients with hematological malignancies and in one (3%) patient with a solid tumor. Candidemia was demonstrated in 56 (88%) cancer patients. *C. albicans* was the single most frequent isolate in cancer patients, although the majority of cases were caused by non-*albicans* species. Cancer patients in the caspofungin arm had more hematological malignancies (55 vs. 29%), higher baseline APACHE II scores ($>$ 20 in 36 vs. 15%), more frequent neutropenia (42 vs. 24%), and less *C. albicans* infections (27 vs. 49%) than the amphotericin B-treated cancer patients. Favorable response rates were 11/18 (61%) and 6/12 (50%) for patients with hematological malignancies treated with caspofungin or amphotericin B, respectively; the corresponding outcomes in patients with solid tumors were 12/15 (80%) and 17/29 (59%) for the 2 treatment arms. 7/14 (50%) caspofungin- and 4/10 (40%) amphotericin B-treated patients who were neutropenic on entry responded favorably. All-cause mortality rates during the study for caspofungin recipients were 11/18 (61%) with hematological malignancies and 6/15 (40%) with solid tumors, and for amphotericin recipients were 4/12 (33%) with hematological malignancies and 6/29 (21%) with solid tumors. **CONCLUSIONS:** Underlying cancers, most commonly leukaemias and gastrointestinal tumors, were present in one-third of patients enrolled in this study of invasive candidiasis. Overall, 70% of caspofungin-treated and 56% of amphotericin B-treated cancer patients responded favorably. Response rates were lower for neutropenic leukaemic patients than for non-neutropenic patients with solid tumors in both treatment groups.

[Pediatr Crit Care Med](#). 2004 Nov;5(6):561-5.

Randomized comparison between fluconazole and itraconazole for the treatment of candidemia in a pediatric intensive care unit: a preliminary study.

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OBJECTIVE: Candida bloodstream infections have shown an increase in hospitalized patients, especially those receiving intensive care. The effectiveness of various azoles, especially itraconazole, in treatment of candidemia has not been fully evaluated. Our objective was to compare the efficacy and safety of enterally administered itraconazole vs. fluconazole in treatment of candidemia. **DESIGN:** Randomized, double-blind, controlled trial. **SETTING:** Pediatric intensive care unit of a referral and teaching hospital. **SUBJECTS:** Forty-three pediatric patients with candidemia, **INTERVENTION:** Patients received either fluconazole (n = 22) or itraconazole (n = 21), about 10 mg/kg orally or through a gastric tube, and were monitored for clinical and mycological cure (sterile fungal blood culture), blood counts, and liver and renal functions. **MEASUREMENTS AND MAIN RESULTS:** The clinical characteristics of two groups were comparable. The cure rate was similar in both the groups: itraconazole 17 of 21 (81%) and fluconazole 18 of 22 (82%). Crude mortality rate (itraconazole 9.5% and fluconazole 13.6%) was also comparable in two groups of patients. The frequency of electrolyte disturbance was very low and similar in both the groups. Blood urea, creatinine, liver enzymes, and serum bilirubin were not adversely affected. **CONCLUSIONS:** Itraconazole was as effective as fluconazole in nosocomial candidiasis in children receiving intensive care and was devoid of serious side effects.

[Antimicrob Agents Chemother](#). 2004 Jun;48(6):2021-4.

Phase 2, randomized, dose-ranging study evaluating the safety and efficacy of anidulafungin in invasive candidiasis and candidemia.

[Krause DS](#), [Reinhardt J](#), [Vazquez JA](#), [Reboli A](#), [Goldstein BP](#), [Wible M](#), [Henkel T](#); [Anidulafungin Invasive Candidiasis Study Group](#).

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This study evaluated the safety and efficacy of anidulafungin, a novel echinocandin, in patients with invasive candidiasis, including candidemia. A total of 123 eligible patients were randomized to one of three intravenous regimens, 50, 75, or 100 mg once daily. Treatment continued for 2 weeks beyond resolution or improvement of signs and symptoms. The primary efficacy criterion was a successful global response rate (i.e., clinical and microbiological success) in the evaluable population at the follow-up (FU) visit, 2 weeks after end of therapy (EOT). One hundred twenty (120) patients received at least one dose of anidulafungin; 68 were evaluable. Review of adverse events and laboratory data indicated no dose response for safety parameters. Non-albicans Candida species accounted for approximately one-half of all isolates. Success rates at EOT were 84, 90, and 89% in the 50-, 75-, and 100-mg groups, respectively. At FU, the success rates were 72, 85, and 83%. Phase 3 studies of anidulafungin for the treatment of invasive candidiasis and candidemia are warranted.

[Clin Infect Dis](#). 2003 Sep 1;37(5):634-43. Epub 2003 Aug 14.

A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients.

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We conducted a prospective, multicenter observational study of adults (n=1447) and children (n=144) with candidemia at tertiary care centers in the United States in parallel with a candidemia treatment trial that included nonneutropenic adults. Candida albicans was the most common bloodstream isolate recovered from adults and children (45% vs. 49%) and was associated with high mortality (47% among adults vs. 29% among children). Three-month survival was better among children than among adults (76% vs. 54%; P<.001). Most children received amphotericin B as initial therapy, whereas most adults received fluconazole. In adults, Candida parapsilosis fungemia was associated with lower mortality than was non-parapsilosis candidemia (24% vs. 46%; P<.001). Mortality was similar among subjects with Candida glabrata or non-glabrata candidemia; mortality was also similar among subjects with C. glabrata candidemia who received fluconazole rather than other antifungal therapy. Subjects in the observational cohort had higher Acute Physiology and Chronic Health Evaluation II scores than did participants in the clinical trial (18.6 vs. 16.1), which suggests that the former subjects are more often excluded from therapeutic trials.

- [Crit Care Med](#). 2003 Jul;31(7):1938-46.
Fluconazole improves survival in septic shock: a randomized double-blind prospective study.

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OBJECTIVE: To demonstrate whether fluconazole reduces multiple organ failure and mortality in early septic shock (<24 hrs). **DESIGN:** A prospective randomized double-blind study. **SETTING:** A medical and surgical adult intensive care unit in a tertiary referral center. **PATIENTS:** Values were obtained from 71 general adult intensive care unit patients. **INTERVENTIONS:** During a 2.5-yr period, December 1998-June 2001, 71 patients with septic shock attributed to either nosocomial pneumonia (n = 37) or intra-abdominal sepsis (n = 34) were admitted to our intensive care unit and met the criteria of early septic shock and were entered into this study. All patients were randomized by our clinical pharmacist to receive daily either 200 mg of fluconazole in isotonic saline (fluconazole group = 32) or isotonic saline alone (placebo group = 39) intravenously during the course of their septic shock. **MEASUREMENTS AND MAIN RESULTS:** All patients were closely monitored with pulmonary artery catheters and parameters to calculate daily organ dysfunction and Acute Physiology and Chronic Health Evaluation II scores. There was a highly significant increase in 30-day survival in the fluconazole-treated patients compared with the placebo patients (78% vs. 46%). However, fluconazole was found to be more effective in patients with septic shock attributed to intra-abdominal sepsis than to nosocomial pneumonia. Increased survival in the intra-abdominal sepsis clinical category was mirrored by a significantly lower number of organ failures in the treated group compared with the placebo group whereas the number of organ failures in the fluconazole group attributed to nosocomial pneumonia were not significantly increased compared with the control group. The septic shock state was considered in all cases to be attributed to bacterial and not to disseminated yeast infection with the exception of one patient in the control group who was admitted with candidemia. The mechanisms by which fluconazole exerts its protective effect against septic shock in patients is far from clear. However, fluconazole has been shown to enhance bactericidal activity of neutrophils and also to inhibit transmigration and adhesion of neutrophils in capillaries of distant organs. **CONCLUSIONS:** The development of organ failure and mortality in septic shock was significantly reduced by fluconazole given intravenously. The mechanism of action of fluconazole in reducing multiple organ dysfunction in this group of patients may be attributed to the ability of fluconazole to increase recruitment, improve bactericidal activity of neutrophils, and to contain microorganisms locally.

[Clin Infect Dis](#). 2003 May 15;36(10):1221-8. Epub 2003 May 8.

A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in nonneutropenic subjects.

[Rex JH](#), [Pappas PG](#), [Karchmer AW](#), [Sobel J](#), [Edwards JE](#), [Hadley S](#), [Brass C](#), [Vazquez JA](#), [Chapman SW](#), [Horowitz HW](#), [Zervos M](#), [McKinsey D](#), [Lee J](#), [Babinchak T](#), [Bradsher RW](#), [Cleary JD](#), [Cohen DM](#), [Danziger L](#), [Goldman M](#), [Goodman J](#), [Hilton E](#), [Hvslop NE](#), [Kett DH](#), [Lutz J](#), [Rubin RH](#), [Scheld WM](#), [Schuster M](#), [Simmons B](#), [Stein DK](#), [Washburn RG](#), [Mautner L](#), [Chu TC](#), [Panzer H](#), [Rosenstein RB](#), [Booth J](#); [National Institute of Allergy and Infectious Diseases Mycoses Study Group](#).

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A randomized, blinded, multicenter trial was conducted to compare fluconazole (800 mg per day) plus placebo with fluconazole plus amphotericin B (AmB) deoxycholate (0.7 mg/kg per day, with the placebo/AmB component given only for the first 5-6 days) as therapy for candidemia due to species other than *Candida krusei* in adults without neutropenia. A total of 219 patients met criteria for a modified intent-to-treat analysis. The groups were similar except that those who were treated with fluconazole plus placebo had a higher mean (+/- standard error) Acute Physiology and Chronic Health Evaluation II score (16.8+/-0.6 vs. 15.0+/-0.7; P=.039). Success rates on study day 30 by Kaplan-Meier time-to-failure analysis were 57% for fluconazole plus placebo and 69% for fluconazole plus AmB (P=.08). Overall success rates were 56% (60 of 107 patients) and 69% (77 of 112 patients; P=.043), respectively; the bloodstream infection failed to clear in 17% and 6% of subjects, respectively (P=.02). In nonneutropenic subjects, the combination of fluconazole plus AmB was not antagonistic compared with fluconazole alone, and the combination trended toward improved success and more-rapid clearance from the bloodstream.

[N Engl J Med.](#) 2002 Dec 19;347(25):2020-9.

Comparison of caspofungin and amphotericin B for invasive candidiasis.

[Mora-Duarte J](#), [Betts R](#), [Rotstein C](#), [Colombo AL](#), [Thompson-Moya L](#), [Smietana J](#), [Lupinacci R](#), [Sable C](#), [Kartsonis N](#), [Perfect J](#); [Caspofungin Invasive Candidiasis Study Group](#).

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BACKGROUND: Caspofungin is an echinocandin agent with fungicidal activity against candida species. We performed a double-blind trial to compare caspofungin with amphotericin B deoxycholate for the primary treatment of invasive candidiasis. **METHODS:** We enrolled patients who had clinical evidence of infection and a positive culture for candida species from blood or another site. Patients were stratified according to the severity of disease, as indicated by the Acute Physiology and Chronic Health Evaluation (APACHE II) score, and the presence or absence of neutropenia and were randomly assigned to receive either caspofungin or amphotericin B. The study was designed to compare the efficacy of caspofungin with that of amphotericin B in patients with invasive candidiasis and in a subgroup with candidemia. **RESULTS:** Of the 239 patients enrolled, 224 were included in the modified intention-to-treat analysis. Base-line characteristics, including the percentage of patients with neutropenia and the mean APACHE II score, were similar in the two treatment groups. A modified intention-to-treat analysis showed that the efficacy of caspofungin was similar to that of amphotericin B, with successful outcomes in 73.4 percent of the patients treated with caspofungin and in 61.7 percent of those treated with amphotericin B (difference after adjustment for APACHE II score and neutropenic status, 12.7 percentage points; 95.6 percent confidence interval, -0.7 to 26.0). An analysis of patients who met prespecified criteria for evaluation showed that caspofungin was superior, with a favorable response in 80.7 percent of patients, as compared with 64.9 percent of those who received amphotericin B (difference, 15.4 percentage points; 95.6 percent confidence interval, 1.1 to 29.7). Caspofungin was as effective as amphotericin B in patients who had candidemia, with a favorable response in 71.7 percent and 62.8 percent of patients, respectively (difference, 10.0 percentage points; 95.0 percent confidence interval, -4.5 to 24.5). There were significantly fewer drug-related adverse events in the caspofungin group than in the amphotericin B group. **CONCLUSIONS:** Caspofungin is at least as effective as amphotericin B for the treatment of invasive candidiasis and, more specifically, candidemia. Copyright 2002 Massachusetts Medical Society

[Eur J Clin Microbiol Infect Dis.](#) 1997 May;16(5):337-45.

Multicenter randomized trial of fluconazole versus amphotericin B for treatment of candidemia in non-neutropenic patients. Canadian Candidemia Study Group.

[Phillips P](#), [Shafran S](#), [Garber G](#), [Rotstein C](#), [Smaill E](#), [Fong I](#), [Salit I](#), [Miller M](#), [Williams K](#), [Conly JM](#), [Singer J](#), [Ioannou S](#).

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A randomized trial was conducted to compare the efficacy and safety of fluconazole versus that of amphotericin B in the treatment of candidemia in non-neutropenic adults. Enrollment was stratified by disease severity (APACHE II score). Patients were randomized (1:1) to receive amphotericin B 0.6 mg/kg/day (cumulative dose 8 mg/kg) or fluconazole 800 mg intravenous loading dose, then 400 mg daily for four weeks (intravenous for at least 10 days). Patients were monitored for six months. A total of 106 patients were enrolled. A protocol amendment implemented midway through the trial required patients to be removed from the study and treated with amphotericin B if species identification indicated candidemia due to *Candida glabrata* or *Candida krusei*. Baseline characteristics were similar for the two groups; 103 patients (fluconazole, 50; amphotericin B, 53) met the major enrollment criteria. The intention-to-treat analysis indicated successful therapy in 50% of fluconazole recipients compared to 58% of the amphotericin B group ($p = 0.39$; one-sided 95% CI, -8 to 24%). The efficacy analysis included 84 patients (fluconazole, 42; amphotericin B, 42); successful outcomes were observed in 57% and 62% of cases in the fluconazole and amphotericin B groups, respectively ($p = 0.66$; one-sided 95% CI, -12 to 22%). The mortality at day 14 for the fluconazole group was 26% and for the amphotericin B group 21% ($p = 0.52$; chi-square test) and remained similar throughout the course of follow-up. Drug-related adverse events were more frequent with amphotericin B than with fluconazole and prompted switching of therapy for two (4%) and zero cases, respectively. Fluconazole and amphotericin B were associated with similar clinical response rates and survival in the treatment of candidemia among non-neutropenic patients; however, drug-related adverse events were more frequent with amphotericin B.

- [Antimicrob Agents Chemother.](#) 1995 Jan;39(1):40-4.

Antifungal susceptibility testing of isolates from a randomized, multicenter trial of fluconazole versus amphotericin B as treatment of nonneutropenic patients with candidemia. NIAID Mycoses Study Group and the Candidemia Study Group.

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The antifungal susceptibilities of 232 pathogenic blood stream *Candida* isolates collected during a recently completed trial comparing fluconazole (400 mg/day) with amphotericin B (0.5 mg/kg of body weight per day) as treatment for candidemia in the nonneutropenic patient were determined both by the National committee for Clinical Laboratory Standards M27-P macrobroth methodology and by a less cumbersome broth microdilution methodology. For amphotericin B, M27-P yielded a very narrow range of MICs (0.125 to 1 microgram/ml) and there were no susceptibility differences among species. For fluconazole, a broad range of MICs were seen (0.125 to > 64 micrograms/ml), with characteristic MICs seen for each species in the rank order *Candida albicans* < *C. parapsilosis* approximately equal to *C. lusitanae* < *C. glabrata* approximately equal to *C. krusei* approximately equal to *C. lipolytica*. The MIC distribution for *C. tropicalis* was bimodal and could not be ranked. Both microdilution MICs were within one tube dilution of the M27-P MIC for > 90% of isolates with amphotericin B and for > or = 77% of isolates with fluconazole. For both methods, elevated MICs did not predict treatment failure. In the case of amphotericin B, the MIC range was too narrow to permit identification of resistant isolates. In the case of fluconazole, MICs for isolates associated with failure to clear the bloodstream consistently were equivalent to the median MIC for the given species. Successful courses of therapy were seen with four isolates from four patients despite MICs of > or = 32 micrograms/ml. As MICs obtained by M27-P and similar methods correlate with responsiveness to fluconazole therapy in animal models and in AIDS patients with oropharyngeal candidiasis, the lack of correlation in this setting suggests that the MICs for these isolates are at or below the relevant fluconazole breakpoint for this dose of fluconazole and patient setting and that host factors such as failure to exchange intravenous catheters were more important than MIC in predicting outcome.

[N Engl J Med](#). 1994 Nov 17;331(20):1325-30.

A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. Candidemia Study Group and the National Institute.

[Rex JH](#), [Bennett JE](#), [Sugar AM](#), [Pappas PG](#), [van der Horst CM](#), [Edwards JE](#), [Washburn RG](#), [Scheld WM](#), [Karchmer AW](#), [Dine AP](#), et al.

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BACKGROUND. Amphotericin B has long been the standard treatment for candidemia, but its use is complicated by its toxicity. More recently, fluconazole, a water-soluble triazole with activity against candida species and little toxicity, has become available. We conducted a multicenter randomized trial that compared amphotericin B with fluconazole as treatment for candidemia. **METHODS.** To be eligible, patients had to have a positive blood culture for candida species, a neutrophil count > or = 500 per cubic millimeter, and no major immunodeficiency. Patients were randomly assigned to receive either amphotericin B (0.5 to 0.6 mg per kilogram of body weight per day) or fluconazole (400 mg per day), each continued for at least 14 days after the last positive blood culture. Outcomes were assessed by a group of investigators blinded to treatment assignment. **RESULTS.** Of the 237 patients enrolled, 206 met all entry criteria. The most common diagnoses were renal failure, nonhematologic cancer, and gastrointestinal disease. There was no statistically significant difference in outcome: of the 103 patients treated with amphotericin B, 81 (79 percent) were judged to have been treated successfully, as were 72 of the 103 patients treated with fluconazole (70 percent $P = 0.22$; 95 percent confidence interval for the difference, -5 to 23 percent). The bloodstream infection failed to clear in 12 patients in the amphotericin group and 15 in the fluconazole group; the species most commonly associated with failure was *Candida albicans*. There were 41 deaths in the amphotericin group and 34 deaths in the fluconazole group ($P = 0.20$). Intravascular catheters appeared to be the most frequent source of candidemia. There was less toxicity with fluconazole than with amphotericin B. **CONCLUSIONS.** In patients without neutropenia and without major immunodeficiency, fluconazole and amphotericin B are not significantly different in their effectiveness in treating candidemia.

[Intensive Care Med](#). 2002 Dec;28(12):1708-17. Epub 2002 Nov 1.

Prevention of severe Candida infections in nonneutropenic, high-risk, critically ill patients: a randomized, double-blind, placebo-controlled trial in patients treated by selective digestive decontamination.

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OBJECTIVE: Infections caused by *Candida* spp. are a major cause of morbidity and mortality in critically ill patients and usually develop from endogenous colonization. We assessed the effectiveness of adding fluconazole to a selective digestive decontamination regimen to prevent candidal infections. **DESIGN AND SETTING:** We performed a prospective, randomized, double-blind, placebo-controlled trial among medical and surgical intensive care unit patients at a large university hospital. **PATIENTS:** All adult patients mechanically ventilated for at least 48 h with an expectation to remain so for at least an additional 72 h, and receiving selective decontamination of the digestive tract. **INTERVENTIONS:** Patients were randomly assigned fluconazole 100 mg daily (n=103) or placebo (n=101). **MEASUREMENTS AND RESULTS:** *Candida* infections occurred less frequently in the fluconazole group (5.8%) than in the placebo group (16%; rate ratio 0.35; CI(95) 0.11-0.94). Some 90% of candidemia episodes occurred in the placebo group (rate ratio for fluconazole use 0.10; CI(95) 0.02-0.74). The rate of treatment failure, development of candidal infection, or increased colonization, was 32% in the fluconazole group and 67% in the placebo group (P<0.001). Crude in-hospital mortality was similar in the two groups (39% fluconazole vs. 41% placebo). **CONCLUSIONS:** Prophylactic use of fluconazole in a selected group of mechanically ventilated patients at high risk for infection reduces the incidence of *Candida* infections, in particular candidemia.

[Crit Care Med.](#) 2002 Aug;30(8):1808-14.

Candidemia as a cause of septic shock and multiple organ failure in nonimmunocompromised patients.

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OBJECTIVE: To describe outcomes of septic shock and multiple organ failure arising from candidemia. **DESIGN:** Secondary cohort analysis of data from the placebo arm of the North American Septic Shock Trial (NORASEPT II), the largest prospective, randomized, double-blind, controlled multiple center study of septic shock conducted to date, with predetermined end point analysis of outcomes. **SETTING:** Adult intensive care units in 105 hospitals in the United States and Canada. **SUBJECTS:** A cohort of ten purely candidemic patients in septic shock were compared with a cohort of 376 purely bacteremic patients in septic shock. Patients were not immunocompromised, because patients on corticosteroids, with neutropenia, or posttransplantation were excluded from enrollment in NORASEPT II. **MEASUREMENTS AND MAIN RESULTS:** Demographic variables, baseline characteristics, 28-day mortality rates, and multiple organ failure were compared for the two cohorts. Candidemic patients were more likely to have a history of underlying renal failure at baseline and to require dialysis at onset of septic shock. Both causes of septic shock are associated with an extremely high severity of illness (Acute Physiology and Chronic Health Evaluation II: candidemic septic shock, 32 +/- 10; bacteremic septic shock, 30 +/- 8; p=.44). More than 70% of patients with candidemia and septic shock were in multiple organ failure at days 3, 7, and 14; patients with candidemic septic shock sustained persistent multiple organ failure and showed delayed recovery from multiple organ failure compared with patients with bacteremic septic shock. Mortality rate at 28 days was 60% in candidemic septic shock and 46% in bacteremic septic shock (p=.38). **CONCLUSIONS:** Candidemia with septic shock is infrequent in nonimmunocompromised patients but has a very high mortality rate, a high likelihood of associated multiple organ failure, and possibly a delayed recovery from multiple organ failure. Patients with candidemic septic shock are more likely to have underlying renal failure at baseline.

[Diagn Microbiol Infect Dis.](#) 2000 Sep;38(1):1-5.

Evaluation of antiseptic-impregnated central venous catheters for prevention of catheter-related infection in intensive care unit patients.

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Central venous catheterization represents a significant medical advancement, particularly in the treatment of critical ill. However, there is a high risk of central venous catheters-related infection. A novel antiseptic central venous catheter, made of polyurethane and impregnated with chlorhexidine and silver sulfadiazine, was developed to reduce the risk of catheters-related infection. In this study, we did a randomized clinical study to determine the efficacy by using antiseptic catheters for the prevention of central venous catheters-related infection in the intensive care units. A total of 204 patients with 235 central venous catheters were studied at the surgical intensive care units at National Taiwan University Hospital between November 1998 and June 1999. Participants received either a standard triple-lumen polyurethane catheter or an antiseptic catheter (Arrow International, Reading, Pennsylvania, USA). Both were indistinguishable from each other. Compared to standard

polyurethane catheters, antiseptic catheters were less likely to be colonized by microorganisms when they were cultured at the removal (8.0 versus 20.0 colonized catheters per 100 catheters; relative risk 0.34 [95% CI, 0.15 to 0.74]; $p < 0.01$). There was no significant differences between both groups in catheter-related infections (0.9 versus 4.9 infections per 100 catheters; relative risk 0.17 [95% CI, 0.03 to 1.15]; $p = 0.07$). Gram-positive cocci and fungi were more likely to colonize in the standard polyurethane catheters ($p = 0.06$ and 0.04 , compared to antiseptic catheters respectively). Two of our cases in the control group died directly due to catheter-related candidemia. No adverse reactions such as hypersensitivity or leukopenia were found in the antiseptic catheter group. Our study showed that central venous catheters with antiseptic coating were safe and had less risk of colonization of bacteria and fungi than standard catheters in the critically ill patients.

[Clin Infect Dis](#). 2000 Jan;30(1):14-8.

Prospective multicenter surveillance study of funguria in hospitalized patients. The National Institute for Allergy and Infectious Diseases (NIAID) Mycoses Study Group.

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Although fungal urinary tract infections are an increasing nosocomial problem, the significance of funguria is still not clear. This multicenter prospective surveillance study of 861 patients was undertaken to define the epidemiology, management, and outcomes of funguria. Diabetes mellitus was present in 39% of patients, urinary tract abnormalities in 37.7%, and malignancy in 22.2%; only 10.9% had no underlying illnesses. Concomitant nonfungal infections were present in 85%, 90% had received antimicrobial agents, and 83.2% had urinary tract drainage devices. *Candida albicans* was found in 51.8% of patients and *Candida glabrata* in 15.6%. Microbiological and clinical outcomes were documented for 530 (61.6%) of the 861 patients. No specific therapy for funguria was given to 155 patients, and the yeast cleared from the urine of 117 (75.5%) of them. Of the 116 patients who had a catheter removed as the only treatment, the funguria cleared in 41 (35.3%). Antifungal therapy was given to 259 patients, eradicating funguria in 130 (50.2%). The rate of eradication with fluconazole was 45.5%, and with amphotericin B bladder irrigation it was 54.4%. Only 7 patients (1.3%) had documented candidemia. The mortality rate was 19.8%, reflecting the multiple serious underlying illnesses found in these patients with funguria.

[Clin Infect Dis](#). 1999 Feb;28(2):250-5.

Itraconazole oral solution as prophylaxis for fungal infections in neutropenic patients with hematologic malignancies: a randomized, placebo-controlled, double-blind, multicenter trial. GIMEMA Infection Program. Gruppo Italiano Malattie Ematologiche dell' Adulto.

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To evaluate the efficacy and safety of itraconazole oral solution for preventing fungal infections, a randomized, placebo-controlled, double-blind, multicenter trial was conducted: 405 neutropenic patients with hematologic malignancies were randomly assigned to receive either itraconazole, 2.5 mg/kg every 12 hours (201 patients), or placebo (204 patients). Proven and suspected deep fungal infection occurred in 24% of itraconazole recipients and in 33% of placebo recipients, a difference of 9 percentage points (95% confidence interval [CI], 0.6% to 22.5%; $P = .035$). Fungemia due to *Candida* species was documented in 0.5% of itraconazole recipients and in 4% of placebo recipients, a difference of 3.5 percentage points (95% CI, 0.5% to 6%; $P = .01$). Deaths due to candidemia occurred in none of the itraconazole recipients compared with 4 placebo recipients, a difference of 2 percentage points (95% CI, 0.05% to 4%; $P = .06$). Aspergillus infection was documented in four itraconazole recipients (one death) and one placebo recipient (one death). Side effects causing drug interruption occurred in 18% of itraconazole recipients and 13% of placebo recipients. Itraconazole oral solution was well-tolerated and effectively prevented proven and suspected deep fungal infection as well as systemic infection and death due to *Candida* species.

[Pharmacoeconomics](#). 1998 May;13(5):509-18.

Economic analysis of fluconazole versus amphotericin B for the treatment of candidemia in non-neutropenic patients.

[Dranitsaris G](#), [Phillips P](#), [Rotstein C](#), [Puodziunas A](#), [Shafran S](#), [Garber G](#), [Smaill F](#), [Salit I](#), [Miller M](#), [Williams K](#), [Conly J](#), [Singer J](#), [Ioannou S](#).

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Fluconazole (FLU) is an alternative to amphotericin B (AMB) for the treatment of candidemia in non-neutropenic patients. This agent has similar clinical efficacy but significantly reduced adverse effects compared with AMB. Using the database from a Canadian randomised multicentre comparative trial of FLU versus AMB in the treatment of non-neutropenic patients with candidemia, an economic analysis of antifungal therapy was conducted from a Canadian hospital perspective. Patient records were examined for information containing hospital resource consumption. This included the costs for primary intravenous therapy with either AMB or FLU, laboratory tests, patient clinical monitoring and adverse effects management. The robustness of the baseline results were then tested by a comprehensive sensitivity analysis. The mean duration of therapy in the AMB and FLU arms was 17.1 and 23.7 days, respectively ($p < 0.001$). Assuming that all of the FLU was administered intravenously, the outcomes of the baseline economic analysis revealed that the treatment cost for patients randomized to receive FLU was approximately 50% higher than that for patients treated with AMB [AMB: \$Can2370 vs FLU: \$Can3578; $p = 0.001$ (\$Can = Canadian dollars)]. In the sensitivity analysis, substitution to oral FLU after 7 days of intravenous therapy produced economic differences that were no longer statistically significant (AMB: \$Can2370 vs FLU: \$Can2705; $p = 0.10$). These results suggest that the FLU administration regimen used in the Canadian randomized trial for the treatment of candidemia in non-neutropenic patients may result in increased hospital costs compared with AMB. However, comparable expenditures could be realized if FLU is administered intravenously for the first 7 days and then orally in patients whose condition allows for reliable oral therapy.

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[J Clin Oncol](#). 1990 Jan;8(1):161-9.

A prospective randomized trial evaluating prophylactic antibiotics to prevent triple-lumen catheter-related sepsis in patients treated with immunotherapy.

[Bock SN](#), [Lee RE](#), [Fisher B](#), [Rubin JT](#), [Schwartzentruber DJ](#), [Wei JP](#), [Callender DP](#), [Yang JC](#), [Lotze MT](#), [Pizzo PA](#), et al.

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During a 15-month period, 92 patients undergoing 129 treatment episodes of immunotherapy with interleukin-2 (IL-2) alone or with immune cells underwent insertion of central venous catheters (CVCs) in the Surgery Branch, National Cancer Institute. Before each catheter insertion patients were prospectively randomized into one of three treatment groups; therapy with intravenous (IV) placebo using D5W, IV oxacillin, or change of the catheter to a new site every 72 hours. The mean duration of catheterization was 3.8 +/- 1.1 days. No patient in the oxacillin arm developed catheter-related sepsis, while eight patients in the control arms (five, line change, three, placebo) developed catheter-related sepsis ($P2 = .050$). Seven episodes of catheter-related sepsis were due to *Staphylococcus aureus* and one was due to *Staphylococcus epidermidis*. Catheter colonization was reduced significantly in the oxacillin arm versus control arms ($P = .0001$). *Staphylococcus aureus*, *Staphylococcus epidermidis*, and other coagulase-negative *Staphylococci* were sensitive to oxacillin in 89%, 60%, and 50% of cultures, respectively. No evidence of bacterial overgrowth, candida colonization, or candidemia was observed in these patients. Thus this trial demonstrates that treatment with prophylactic oxacillin can decrease the incidence of catheter-related sepsis in patients undergoing immunotherapy with interleukin-2 (IL-2). To our knowledge this is the first prospective randomized trial to evaluate the prophylactic use of systemic antibiotics in the prophylaxis of CVC sepsis.

[Bone Marrow Transplant](#). 1988 Sep;3(5):483-93.

Control of oral mucositis and candidiasis in marrow transplantation: a prospective, double-blind trial of chlorhexidine digluconate oral rinse.

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Conditioning chemoradiotherapy damages the mucosal barrier of the mouth and throat and often produces severe oral inflammation and infection. In a prospective, double-blind, randomized study, we examined the use of a chlorhexidine digluconate mouthrinse for prophylaxis against oral mucosal complications in 51 bone marrow transplant patients. Use of chlorhexidine mouthrinse produced significant reductions in the incidence and severity of oral mucositis. Mucositis also resolved more quickly in patients receiving chlorhexidine. Concomitant reductions in total oral streptococci (p less than 0.02- p less than 0.001) and oral candida (p less than 0.004) were seen in patients using chlorhexidine. Persistent clinical oral candidiasis (thrush) was observed in 15 to 27 control group patients (56%), but only transiently in two (8%) of 24 patients who used chlorhexidine rinse (p less than 0.001). Five of 27 control group patients (19%) had candidemia, while no candidemia was observed in the chlorhexidine group (p less than 0.03). Three deaths from disseminated candidiasis occurred in the placebo group; none occurred in patients who received chlorhexidine. Prophylactic use of chlorhexidine mouthrinse produces reductions in oral soft tissue disease and oral microbial burden in patients undergoing bone marrow transplantation. The reductions in mucositis and in oral candida infections observed with prophylactic chlorhexidine mouthrinse represent a significant advantage for patients undergoing marrow transplantation.

[Am J Surg](#). 1988 Feb;155(2):311-3.

Incidence and treatment of candida esophagitis in patients undergoing renal transplantation. Data from the Minnesota prospective randomized trial of cyclosporine versus antilymphocyte globulin-azathioprine.

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Of 224 consecutive renal transplant patients in a prospective, randomized immunosuppressive trial, candida esophagitis developed in 5 despite nystatin prophylaxis. No differences were noted between cyclosporine and antilymphocyte globulin-azathioprine immunosuppressive treatment. All patients were diabetic, and four were recipients of cadaver kidneys. Candida esophagitis occurred within 6 months after transplantation, and only one patient had recurrence. All patients responded to treatment consisting of 2 to 6 days of intravenous amphotericin B (0.2 to 2 mg/kg total dose). The prevalence of candida esophagitis was not related to rejection episodes. Three of five patients eventually died, one 2 weeks after resolution of candida esophagitis from a hypoglycemic episode, one from acute exacerbation of pulmonary failure and relapsing pancreatitis in association with candida esophagitis and therapy-resistant candidemia, and one 17 months after candida esophagitis from pulmonary edema. Our findings show that candida esophagitis by itself is an easily managed complication, but is also a sign of potentially increased morbidity in these patients.

[Am J Med](#). 1983 Jun;74(6):934-40.

Double-blind randomized study of prophylactic trimethoprim/sulfamethoxazole in granulocytopenic patients with hematologic malignancies.

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In a double blind study, oral prophylactic trimethoprim/sulfamethoxazole was evaluated for its utility in preventing serious infections in patients with hematologic malignancy. Of 58 evaluated granulocytopenic episodes in 47 patients, acute leukemia was the underlying malignancy in 46 episodes. Trimethoprim/sulfamethoxazole prophylaxis resulted in fewer microbiologically documented infections (seven versus 15; $p = 0.029$). This was primarily the result of a reduction in episodes of bacteremia in the trimethoprim/sulfamethoxazole-treated group as compared with the placebo-treated group (three versus nine episodes; $p = 0.05$). The combined frequency of disseminated candidiasis, candidemia, and esophagitis of presumed fungal etiology was greater in the trimethoprim/sulfamethoxazole-treated group (six) than in the placebo-treated group (two) but not significantly so ($p = 0.13$). Similarly, there were no significant differences between groups in the overall incidence of infectious complications, number of febrile days, use of parenteral antibiotics, or number of days following randomization to first infectious episode. Throat and rectal surveillance cultures more frequently revealed trimethoprim/sulfamethoxazole-resistant gram-negative bacilli and yeasts in the trimethoprim/sulfamethoxazole-treated group. More frequent emergence of yeast isolates from previously culture-negative patients was documented ($p = 0.033$). Thus, in this study, trimethoprim/sulfamethoxazole prophylaxis during granulocytopenia reduced the incidence of microbiologically documented infections. However, the emergence of resistant bacteria and of fungi may limit the potential usefulness of this approach.