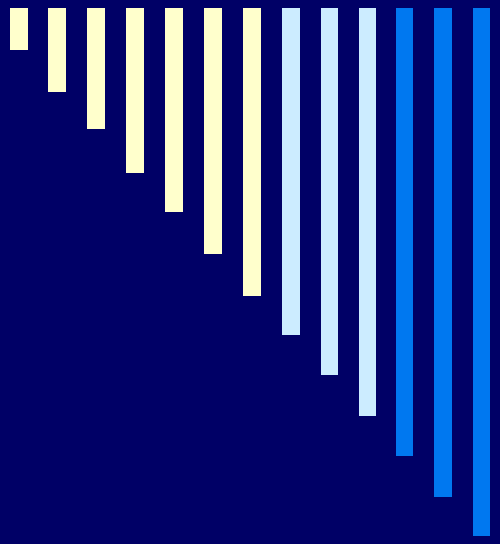

CURRENT AND NEWER ANTI-FUNGAL THERAPIES- MECHANISMS, INDICATIONS, LIMITATIONS AND PROBLEMS

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DM SEMINAR

Introduction

- The incidence of invasive fungal infections in critically ill intensive care unit (ICU) and surgical patients has been increasingly recognized.
- Invasive fungal infections are associated with crude mortality rates of 30–40%.
- Often recognized and treated late.
- Ampho B was initially considered gold standard.
- With the introduction of newer antifungals, the horizon has widened.

Antifungal drugs and mechanism of action

	Class of drug	Examples	Mechanism Of action
1.	Polyenes	Amphotericin B	Inserts into the fungal membrane in close association with ergosterol. The subsequent formation of porin channels leads to loss of transmembrane potential and impaired cellular function
2.	Azoles	Fluconazole, itraconazole, voriconazole etc.	Inhibition of the C14 alpha demethylation of lanosterol in fungi, which interfere with the synthesis of ergosterol in the fungal cell membrane
3.	Echinocandins	Caspofungin, mivafungin	Inhibit the synthesis of beta1,3-D glucan, which is integral to the structure and function of the fungal cell wall
4	Flucytosine		Inhibits cellular DNA and RNA synthesis

Conventional antifungal drugs

- Fluconazole
- Itraconazole
- Amphotericin B

Empirical antifungal therapy for febrile neutropenia

YEAR	ANTIFUNGAL COMPARATOR	SAMPLE SIZE	ENDPOINT	OUTCOME
1982	AmB vs Placebo	52	Infection	Favors AmB
1989	AmB vs Placebo	132	Defervescence	Favors AmB
1996	AmB vs FLU	112	Defervescence	Equivalence; Safety favors FLU

N Engl J Med 2002;346:278-280

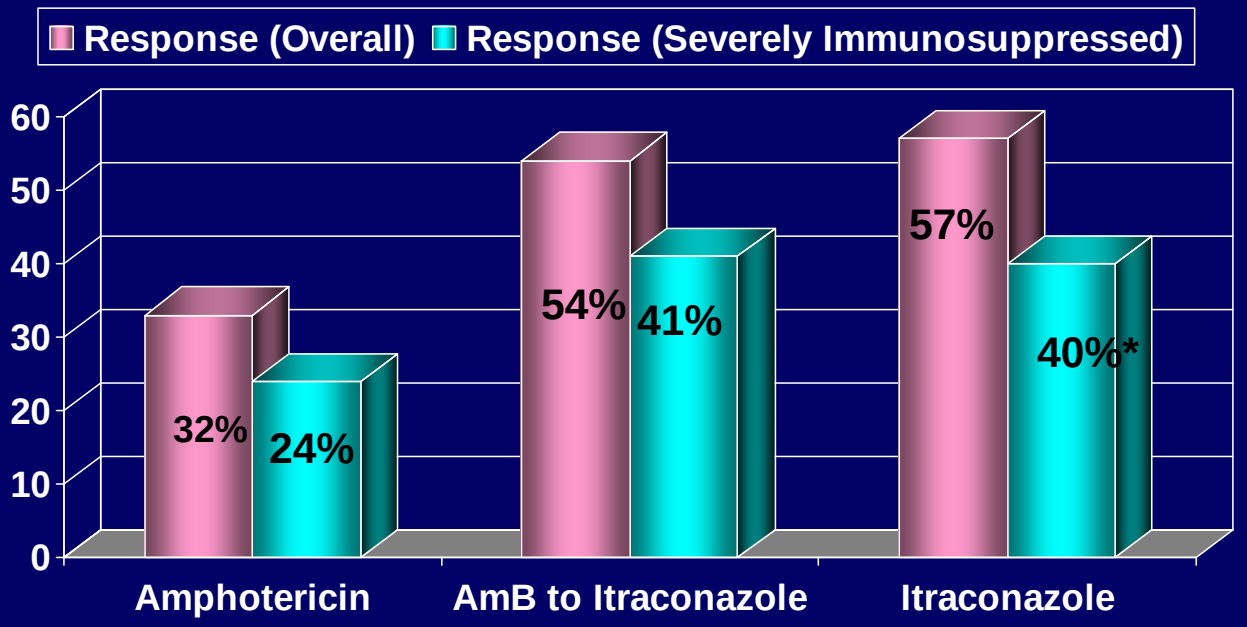
Empirical antifungal therapy for febrile neutropenia

Year	Antifungal comparator	Sample size	Endpoint	Outcome
1998	AmB Vs FLU	106	Composite	Equivalence;Safety favours FLU
1999	AmB Vs L-AmB	702	Composite	Equivalence;Secondary analysis favours AmB
2000	AmB Vs FLU	317	Composite	Equivalence; Safety favours FLU
2000	L-AmB Vs ABLC	204	Absence of toxic effects	Favours L-AmB
2001	AmB Vs ITRA	384	Composite	Equivalence; Secondary analysis favours ITRA

N Engl J Med 2002;346:278-280

Comparison of conventional antifungal drugs in invasive aspergillosis

Retrospective analysis of 595 patients with definite or probable invasive aspergillosis



Medicine 2000;79:250-260

Lipid-Associated Amphotericin B alone versus in Combination with myograb in Patients with Invasive Candidiasis

Variable	No. (%) of patients who received lipid-associated amphotericin B: Plus placebo (n = 61)	Plus Mycograb (n = 56)	OR ± SE	95% CI	P
Primary efficacy variable					
Complete overall response by day 10	29 (48)	47 (84)	5.762 ± 1.561	2.408–13.787	<.001
Supportive analyses[a]	29 (48)	47 (84)	6.960 ± 1.273	2.698–17.954	<.001
Receipt of Abelcet or Ambisome	29 (48)	47 (84)	5.846 ± 1.251	2.428–14.077	<.001
Secondary efficacy variable					
Complete clinical response by day 10	32 (52)	48 (86)	5.437 ± 1.584	2.207–13.393	<.001
Mycological response by day 10	33 (54)	50 (89)	7.071 ± 1.653	2.640–18.938	<.001
Candida-attributable mortality by day 33	11 (18)	2 (4)	0.168 ± 2.211	0.036–0.797	.025

- Myograb is an antibody-Based inhibitor of Heat Shock Protein 90
- Hsp90 is a molecular chaperone present in the fungal cell wall and extracellular material
- Addition of myograb to conventional ampho B improves survival as well as culture conversion rate
- Mycograb was well tolerated
- Hsp90 inhibitors not only have direct antifungal activity, but they may also prevent fungi from developing resistance to fluconazole or caspofungin

Clinical Infectious Diseases 2006; 42:1404–13

Role of itraconazole in post TB aspergilloma and CNPA

- Patients suffering from aspergillosis treated with 6 months itraconazole therapy
- About half of the patients of aspergilloma and 85% of the patients of chronic necrotizing pulmonary aspergillosis improved by 3 months of therapy
- Relapses were seen in 8 out of the 37 patients

S. No.	Outcome	Aspergilloma (N=43)	Chronic necrotizing pulmonary aspergillosis (N=45)
1	Clinical improvement	22	39
2.	Radiological improvement	20	38
3.	Default	10	4
4.	No improvement	11	2

Lung India 2005; 22: 81-85

Comparison of effects of amphotericin B infused over 4 or 24 hours

	Infusion rate			
	Rapid (n=40)	Continuous (n=40)	P value	Relative risk (95% CI)
Reactions on day 1:				
Fever*	21 (53)	10 (25)	0.021	2.1 (1.1 to 3.9)
Chills or rigors	21 (53)	5 (13)	0.0003	4.2 (1.8 to 10)
Vomiting	14 (35)	4 (10)	0.009	3.5 (1.3 to 9.7)
Headache	4 (10)	0		
Others	1 (3)	0		
Overall reactions:				
Chills or rigors	25 (63)	8 (20)	0.0001	3.1 (1.6 to 6.1)
Vomiting	24 (60)	11 (28)	0.004	2.2 (1.2 to 3.8)
Headache	11 (28)	4 (10)		
Others	8 (20)	2 (5)		
Drugs after day 1:				
Meperidine	20 (50)	6 (15)	0.002	3.3 (1.5 to 7.4)
Steroids	18 (45)	3 (8)	0.0001	6 (1.9 to 19)
Acetaminophen	30 (75)	19 (48)	0.021	1.6 (1.1 to 2.3)
Dose reductions or infusion interruption	11 (28)	3 (8)	0.022	3.7 (1.1 to 12)

BMJ 2001;322:579–82

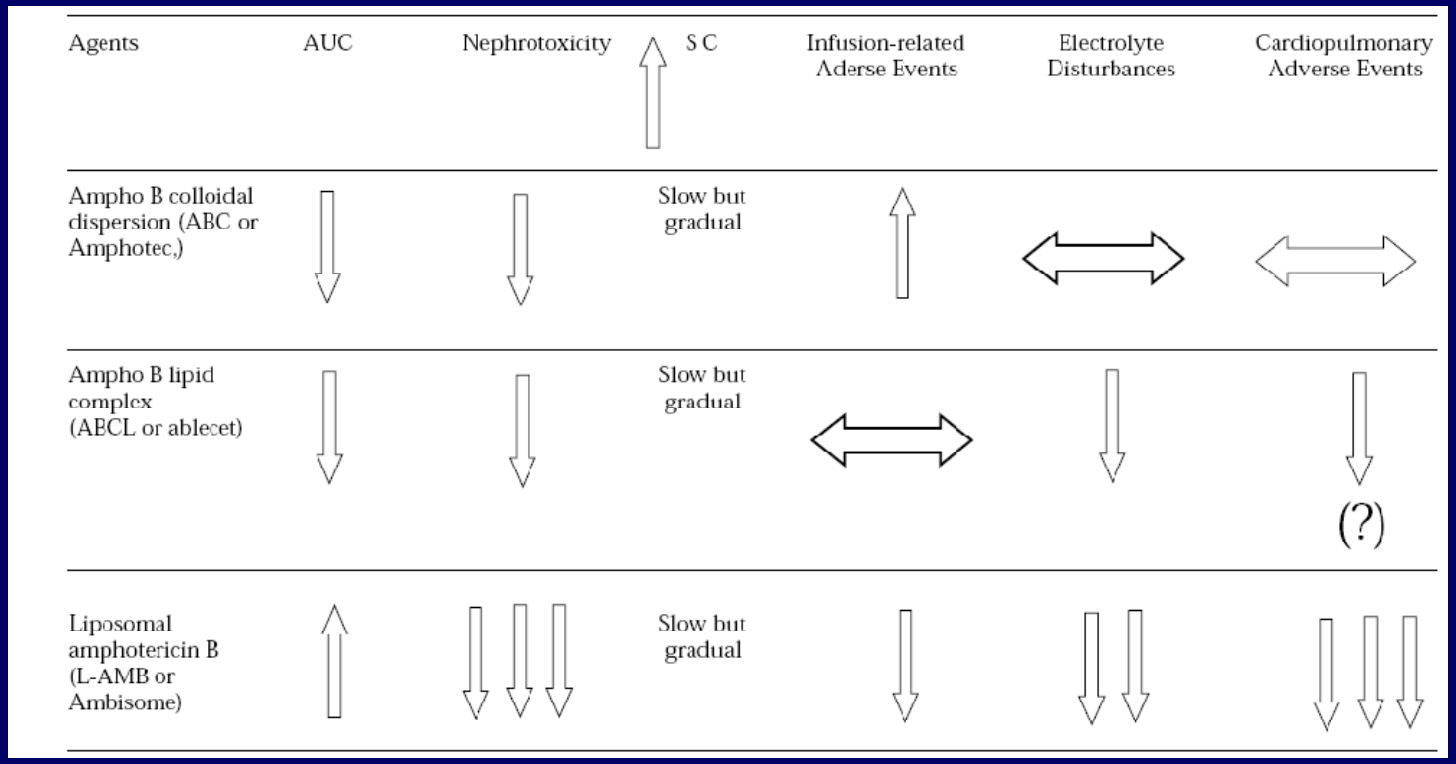
Comparison of effects of amphotericin B infused over 4 or 24 hours

	Infusion rate			
	Rapid (n=40)	Continuous (n=40)	P value	Median difference (95% CI)
Calculated creatinine clearance*:				
Minimal clearance:baseline	0.62 (0.29-1.05)	0.80 (0.39-1.10)	0.013	0.12 (0.03 to 0.22)
Clearance at end of study:baseline	0.65 (0.29-1.26)	0.86 (0.44-1.91)	0.001	0.19 (0.09 to 0.29)
Electrolyte abnormalities:				
No (%) with hypokalaemia (<2.5 mmol/l)	10 (25)	4 (10)	0.139	
No (%) with hypernatraemia (>155 mmol/l)	3 (8)	2 (5)	1.0	
No (%) with hypomagnesaemia (<0.5 mmol/l)	19 (48)	17 (43)	0.822	

- Both infusion related adverse reactions and nephrotoxicity were less in 24 hr infusion group
- All 7 deaths in 80 patients studied occurred in rapid infusion group

BMJ 2001;322:579–82

Comparison of different forms of amphotericin B



Agents	AUC	Nephrotoxicity	S C	Infusion-related Aderse Events	Electrolyte Disturbances	Cardiopulmonary Adverse Events
Ampho B colloidal dispersion (ABC or Amphotec,)	↓	↓	Slow but gradual	↑	↔	↔
Ampho B lipid complex (AECL or ablecet)	↓	↓	Slow but gradual	↔	↓	↓ (?)
Liposomal amphotericin B (L-AMB or Ambisome)	↑	↓↓↓	Slow but gradual	↓	↓↓	↓↓↓

Indian J Pediatr 2004; 71 (3) : 253-259

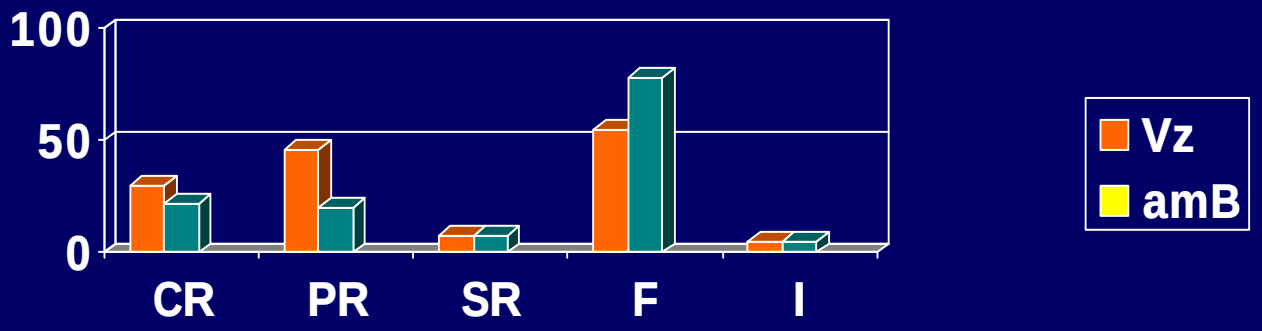
Problems with itraconazole therapy

- Inhibition of the cytochrome P-450 system
- Important complications
  - Life-threatening cardiac dysrhythmias
  - Ergotism, with risk of vasospasm leading to cerebral or extremity ischemia
  - Inhibition of dexamethasone and methylprednisolone
  - Contraindicated with lovastatin and simvastatin

New antifungal drugs

- Voriconazole
- Caspofungin

Voriconazole versus amphotericin B in invasive aspergillosis



- Mostly immunocompromised patients ampho B (n=133), voriconazole (n=144)
- In ITT population, a successful outcome at week 12 was observed in 49.7% of voriconazole group and 27.8% of ampho B group
- At week 12,survival rate was 70.8 percent in the patients in the MITT population who were treated with voriconazole, as compared with 57.9 percent in the amphotericin B group(hazard ratio, 0.59)
- Significantly fewer adverse events in voriconazole group

N Engl J Med 2002;347:408-15.

Role of voriconazole in invasive aspergillosis in immunocompromised patients

- A total of 116 patients were assessed. IA was proven in 48 (41%) and probable in 68 (59%).
- Significantly improved response rate in cerebral (16%) and disseminated aspergillosis (50%) as compared to historical controls of amphotericin B.
- Adverse events were trivial.

	Response to treatment, no. (%)				
Site or type	Complete	Partial	Stable	Failure	Total
Pulmonary and TBR	15 (18)	35 (42)	16 (19)	18 (21)	84
Cerebral	0	3 (16)	5 (26)	11 (58)	19
Disseminated	1 (17)	2 (33)	0	3 (50)	6
Sinus	0	0	2 (40)	3 (60)	5
Other[a]	0	0	1 (50)	1 (50)	2
Previous therapy					
Primary	10 (17)	25 (42)	11 (18)	14 (23)	60 (52)
Salvage	6 (11)	15 (27)	13 (23)	22 (39)	56 (48)
Total	16 (14)	40 (34)	24 (21)	36 (31)	116 (100)

Clinical Infectious Diseases 2002; 34:563–71

Voriconazole versus liposomal amphotericin B in febrile neutropenia

Response Indicator	Voriconazole (N=415)	Liposomal Amphotericin B (N=422)
Overall response — no. (%)	108 (26.0)	129 (30.6)
No breakthrough fungal infections within 7 days of end of therapy — no. (%)	407 (98.1)	401 (95.0)
Survival 7 days after end of therapy — no. (%)*	382 (92.0)	397 (94.1)
No discontinuation due to toxicity or lack of efficacy before recovery from neutropenia — no. (%)	374 (90.1)	394 (93.4)
Resolution of fever during neutropenia — no. (%)	135 (32.5)	154 (36.5)
Complete or partial response of patients with base-line fungal infections by end of treatment — no./total no. (%)	6/13 (46.2)	4/6 (66.7)

- No significant difference in efficacy.
- Voriconazole was superior in

- reducing documented breakthrough fungal infections (8% vs.21%).
- infusion-related toxicity.
- nephrotoxicity.

The low molecular weight of voriconazole may permit penetration into the endobronchial-lining fluid and other mucosal surfaces.

N Engl J Med 2002;346:225-34

Voriconazole versus amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients

	Voriconazole (n=248)	Amphotericin B/ fluconazole (n=122)	p
Primary success rate*	101 (41%)	50 (41%)	0·96
Success by pathogen			
C albicans	46/107 (43%)	30/63 (48%)	
C glabrata	12/36 (33%)	7/21 (33%)	
C parapsilosis	24/45 (53%)	10/19 (53%)	
C tropicalis	17/53 (32%)	1/16 (6%)	0·032
C krusei	1/4 (25%)	0/1	
Secondary success rate†	162 (65%)	87 (71%)	0·25
Success rate at end of treatment‡	173 (70%)	90 (74%)	0·42
Success rate 2 weeks after end of treatment‡	130 (52%)	64 (53%)	0·99
Success rate 6 weeks after end of treatment‡	110 (44%)	56 (46%)	0·78
All-cause 14-week mortality	88 (36%)	51 (42%)	0·23

- Blood culture negativity was also similar
- Significantly less adverse events in voriconazole group
- Drawbacks

1) small number of patients in ampho B + Fluconazole group

2) blinding was not possible due to different routes of administration

Lancet 2005;366:1435-42

Voriconazole treatment for less-common, emerging, or refractory fungal infections

- In the largest trial (n = 301 evaluable) immunocompromised patients (aged 11–87 yrs), recommended dosages of intravenous voriconazole given for median 18 days followed by oral therapy for median 69 days.
- In the total modified ITT cohort, 50% of patients achieved a satisfactory global response.
- 47% of 223 who failed to respond to previous therapy showed a satisfactory response.

Clin Infect Dis 2003; 36: 1122-31

Current indications of voriconazole therapy

- Treatment of invasive aspergillosis.
- Candidaemia in non-neutropenic patients.
- Disseminated infections caused by *Candida* species .
- Oesophageal candidiasis .
- Scedosporiosis and fusariosis who are refractory to or intolerant of other antifungal therapy.

Dosage and administration of voriconazole

Patient population	IV loading dose	IV maintainance	Oral loading	Oral maintainance
children		7 mg/kg q12h		200mg q12h
adults	6 mg/kg q12h day 1	4 mg/kg q12h	200–400mg q12h	100–200mg q12h

Drugs 2007; 67 (2): 269-298

Important pharmacokinetic considerations with voriconazole

- 96% oral bioavailability.
- Absorption decreases with food.
- Absorption not affected by increased gastric pH caused by H2 blockers and PPIs.
- Although uncertain drug bioavailability in critically ill patients, nasogastric tube administration of voriconazole has been documented to produce adequate serum levels.

  Eur J Clin Microbiol Infect Dis 2005;24:358–360
- Dose modification required in moderate hepatic dysfunction (Child-Pugh class B).
- IV voriconazole should not be used in moderate to severe renal impairment (creatinine clearance <50).
- Drug levels not affected by hemodialysis or peritoneal dialysis.

  J Antimicrob Chemother 2004;54 (1): 269-70

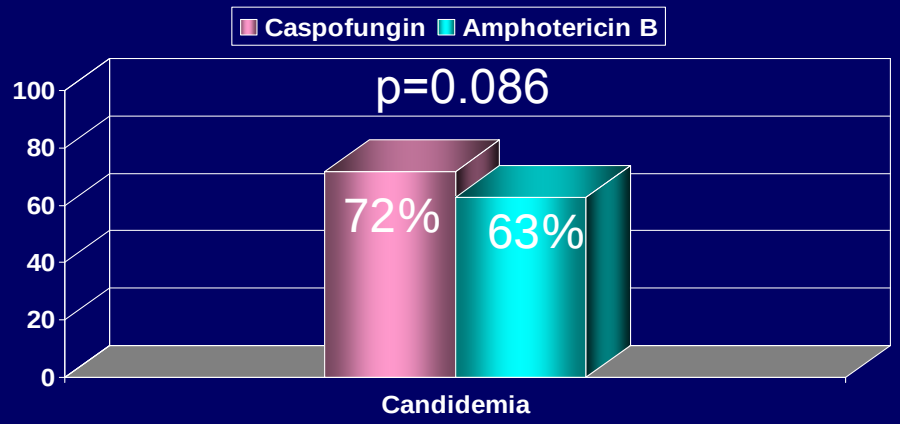
  Am J Kidney Dis 2005; 45 (1): 162-6

Clinically significant drug interactions with voriconazole

	Drug	Voriconazole level	Coadministered drug level	Comment
1.	Rifampicin	Significant ↓	Significant ↑	contraindicated
2.	Cyclosporin		Significant ↑	↓ cyclosporin dosage to half
3.	Tacrolimus		Significant ↑	↓ tacrolimus dose to 1/3
4.	Phenytoin	Significant ↓	Significant ↑	Monitor phenytoin levels
5.	Carbamazepine	significant ↓		contraindicated
6.	warfarin		Significant ↑	Monitor PT

Drugs 2007; 67 (2): 269-298

Caspofungin versus amphotericin B in invasive candidiasis



- Large double blind trial (n=224) of invasive candidiasis
- In patients who received atleast 5 days antifungal therapy , response rate was superior in caspofungin group (81% vs. 65%, p=0.035)
- The tolerability of caspofungin was significantly better
- Success rates in patients treated with caspofungin were independent from the candida species

N Engl J Med 2002;347:2020-29.

Salvage therapy for IA with caspofungin

- First study to document the efficacy and safety of an echinocandin for the treatment of IA.
- Approximately two-thirds of the patients had received 14 days of standard therapy
- One-third of these patients were refractory to more than one antifungal drugs
- More favorable responses were observed among patients enrolled because of intolerance to therapy, compared with those enrolled because of infection refractory to therapy (p=0.03).

Analysis, type of response to caspofungin therapy	No. (%) of patients	95% CI
Primary[a]		
Complete	4 (5)	…
Partial	33 (40)	…
Total	37 (44.6)	33.7–55.9
Secondary[b]		
Complete	4 (6)	…
Partial	33 (50)	…
Total	37 (56.1)	43.3–68.3

a- MITT population, received atleast 1 dose of caspofungin

b- evaluable patients received atleast 7 days of caspofungin

Clinical Infectious Diseases 2004; 39:1563–71

Salvage therapy for IA with caspofungin

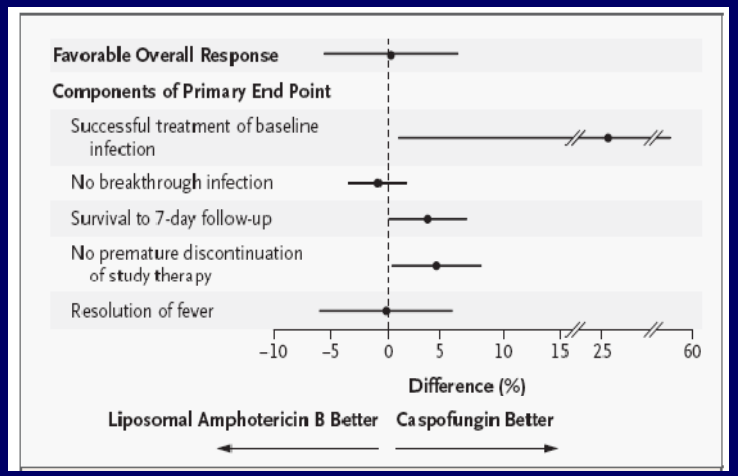
	Pulmonary	Disseminated	Single organ	overall
Number of Patients	64	13	6	83
Favorable (CR/PR)	32 (50%)	3 (23%)	2 (33%)	37 (44.6%)

- Trend toward a higher proportion of favorable response with pulmonary disease, compared with those with extrapulmonary disease (p=0.11),
- Also among patients with neutropenia, compared with those without neutropenia, at baseline (p=0.11)

Clinical Infectious Diseases 2004; 39:1563–71

Caspofungin versus liposomal amphotericin B as empirical therapy in febrile neutropenic patients

- Efficacy was evaluated in 1095 patients (556 receiving caspofungin and 539 receiving liposomal amphotericin B
- Significantly better success in the treatment of patients with a baseline invasive infection (p=0.04; aspergillus :42% vs 8%, candida : 67% vs 42%)
- Nephrotoxicity, infusion-related toxicity and other adverse events were lower in the caspofungin arm



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

Adverse effects of caspofungin

Variable	Invasive candidiasis (%)		Empirical antifungal therapy (%)	
	Caspofungin	Conventional AmB	Caspofungin	Liposomal AmB
Nephrotoxicity	8	25	3	12
Infusion-events	20	49	35	52
Fever	7	23	17	19
Chills	5	26	14	25
Rash	1	3	6	5
↑ ALT	4	8	9	9
↑ AST	2	9	7	8
↑ bilirubin	3	9	3	5

- Very low rate of adverse events compared with other antifungal drugs
- Renal tolerability is excellent, even on prolonged treatment

JAPI 2006;54:943-948

Important pharmacokinetic and pharmacodyanamic considerations of caspofungin

- Poor oral bioavailability
- Cytochrome P450 enzyme system is not involved
- No dose reduction is required with renal insufficiency
- With moderate hepatic insufficiency (Child-Pugh score 7-9) need a reduction of the maintenance dose to 35 mg/day
- No published data on use in severe hepatic insufficiency
- The coadministration of caspofungin with potent enzyme inducers such as efavirenz, rifampicin, dexamethasone, phenytoin or carbamazepine requires a maintenance dose of 70 mg/day.

Newer antifungals

- Micafungin
- Anidulafungin
- Posaconazole

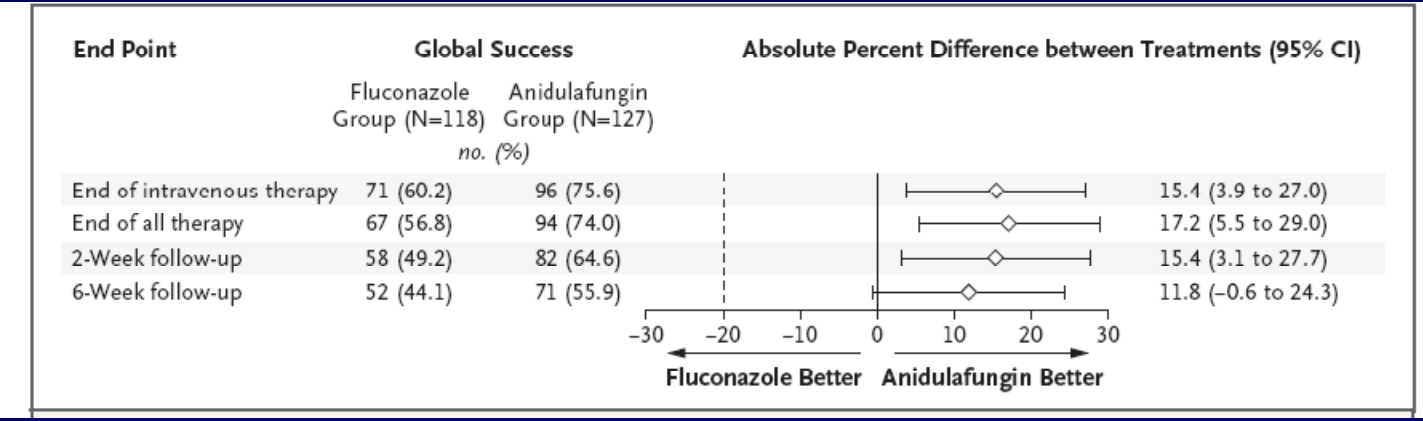
Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis

	Micafungin		Liposomal amphotericin B		Difference in proportion (95% CI)
	Number of patients	Number treated successfully (%)	Number of patients	Number treated successfully (%)	
Overall	247	183 (74·1%)	247	172 (69·6%)	4·5% (−3·5 to 12·4)
Complete response*		159 (64·4%)		150 (60·7%)	
Partial response*		24 (9·7%)		22 (8·9%)	
Neutropenic status at baseline					4·9% (−3·0 to 12·8)†
<500 cells per µL	32	19 (59·4%)	25	14 (56·0%)	
≥500 cells per µL	215	164 (76·3%)	222	158 (71·2%)	

- Micafungin was as effective as liposomal amphoB
- Efficacy was independent of the *Candida* spp and primary site of infection, as well as neutropenic status, APACHE II score
- Fewer adverse events with micafungin

Lancet 2007; 369: 1519–27

Anidulafungin versus Fluconazole for Invasive Candidiasis



End Point	Global Success		Absolute Percent Difference between Treatments (95% CI)
	Fluconazole Group (N=118)	Anidulafungin Group (N=127)	
	no. (%)		
End of intravenous therapy	71 (60.2)	96 (75.6)	15.4 (3.9 to 27.0)
End of all therapy	67 (56.8)	94 (74.0)	17.2 (5.5 to 29.0)
2-Week follow-up	58 (49.2)	82 (64.6)	15.4 (3.1 to 27.7)
6-Week follow-up	52 (44.1)	71 (55.9)	11.8 (−0.6 to 24.3)

- Patients were randomly assigned to receive either intravenous anidulafungin (200 mg on day 1 and then 100 mg daily) or intravenous fluconazole (800 mg on day 1 and then 400 mg daily).
- Anidulafungin was found to be non-inferior to fluconazole
- Adverse events were significantly less in anidulafungin group as compared to fluconazole group (1.5% vs 7.5%,p=0.02)

N Engl J Med 2007;356:2472-82

Clinical Roles of newer echinocandins- F.D.A.approved indications -

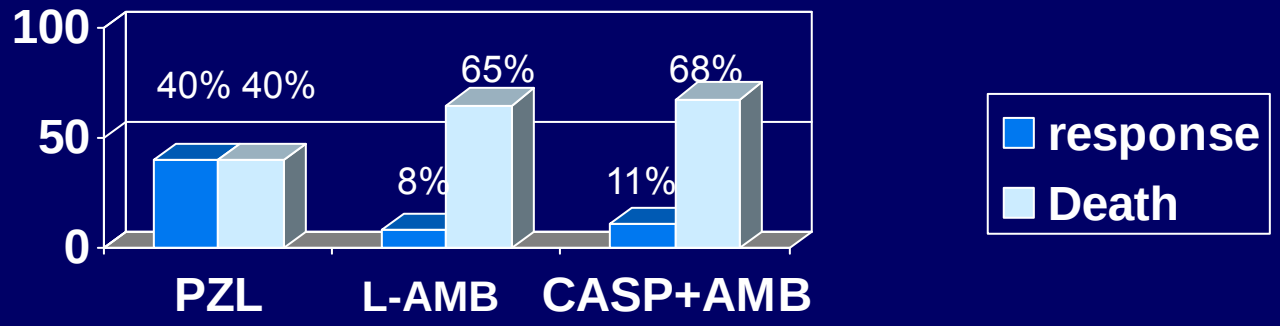
- Micafungin
  - Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation
  - Treatment of esophageal candidiasis
- Anidulafungin
  - Candidemia
  - Intra-abdominal abscess and peritonitis due to *Candida* infection
  - Esophageal candidiasis

Eur J Clin Micro Infect Dis 2004;23:805-812

Potential situations where echinocandin therapy may be preferable to ampho B in presumed or fungal infections

- In settings in which there is a high rate of non-*albicans* species of *Candida*
- In septic patients who clinically are suspected of having a fungal infection
- In patients with preexisting renal disease in whom antifungal therapy is needed
- In patients on other nephrotoxic drugs
- In the acute setting in patients for whom there may be an option to de-escalate to voriconazole orally

Posaconazole for salvage therapy in aspergillosis



- RCT with 38 patients in divided in 3 groups
- By multivariate analysis, posaconazole therapy independently improved response (9.5; 95% confidence interval, 2.8–32.5; $p<0.001$).
- HD-LPD/AMB alone or in combination was associated with a significantly higher rate of nephrotoxicity ($p<0.02$) and hepatotoxicity ($p<0.03$).

Leukemia 2007;20:887-894

Posaconazole in treatment of invasive fungal infections caused by zygomyces

- A total of 79% (n=24) of patients had a complete or partial response to posaconazole therapy
- Almost 90% of these patients received posaconazole as monotherapy

Species	success rate
Rhizopus	83%
Mucor	83%
Rhizomucor	50%
Cullinghamella	33%

Posaconazole can be considered as a treatment option in zygomycosis when other therapies fail

***Antimicrob Agents Chemotherapy* 2006;50(1):126–133.**

Current role of Posaconazole

- Treatment of fungal infections caused by zygomycetes.
- Second-line agent for refractory fungal infections caused by *Aspergillus* species and other filamentous fungi.
- Prophylaxis against IFIs in patients with hematologic malignancies at a high risk of infection.
- Posaconazole should not be routinely used for oropharyngeal candidiasis.

DRUG RESISTANCE

- Microbiological resistance- Nonsusceptibility of a fungus to an antifungal agent by in vitro susceptibility testing, in which the MIC of the drug exceeds the susceptibility breakpoint for that organism
- Primary(intrinsic) or secondary (acquired)
- Primary resistance- e.g.*Candida krusei* to fluconazole and of *Cryptococcus neoformans* to echinocandins
- Secondary resistance-e.g. fluconazole resistance among *Candida albicans* and *C. neoformans* strains
- Clinical resistance- Failure to eradicate a fungal infection despite the administration of an antifungal agent with in vitro activity against the organism

Principal factors determining antifungal clinical resistance

Factor	Implication
Wrong diagnosis	Weak diagnostics and/or IRIS
Net state of immunosuppression	Improvement in immunity of host is essential
High burden of fungus at initiation of treatment	Earlier treatment intervention improves outcome
Strain acquisition of increased virulence	Probably less of a problem than host factors but can be measured
Pharmacokinetics and/or pharmacodynamics	Drug toxicity, drug–drug interaction, drug levels
Site of infection	Drug penetration, tissue necrosis, foreign body- role of surgery
Length of treatment and/or compliance	patient and clinician may lose focus on long-term drug administration
Underlying disease	Final arbitrator in most invasive mycoses

Limitations of drug susceptibility testing

- MIC values not always directly associated with response .
- Although in vitro resistance predicts treatment failure in patients with HIV infection with oropharyngeal or esophageal candidiasis , no such correlation has been replicated in other settings .
- 90–60 rule- 90% of susceptible strains will respond and 60% of resistant strain will still respond.
- MIC levels not always the most optimal measure of resistance- minimal effective concentration better alternative.
- Mold infections- exposure detects activity against conidia rather than against the hyphal structures.

Drug susceptibility pattern in different species of candida

Candida spp.	Fluconazole S≤8, DD >8-≤32, R>64	Itraconazole S<0.125, DD 0.25–05, R>1	Voriconazole S≤1, DD=2 R>4	Posaconazole[a] S≤1, R>4	Echinocandins[b] S≤1, I>1, R>2	Amphotericin B S≤1, R≥2
C. albicans	S	S	S	S	S	S
C. glabrata	S-DD to R	S-DD to R	S-DD	S	S	S to I
C. parapsilosis	S	S	S	S	S to I[c]	S
C. tropicalis	S	S	S	S	S	S
C. krusei	R	S-DD to R	S	S	S	S to I
C. lusitaniae	S	S	S	S	S to I[c]	S to R
C. guilliermondii	S	S	S	S	S	S to R
C. dubliniensis	S-DD	S	S	S	S	S

- Cross resistance amongst azoles and between azoles and amphoterecin is major concern
- Routine amphotericin B testing against Candida spp. is not warranted

Curr Opin Infect Dis 19:538–543.

Drug susceptibility pattern in different species of molds

Mold species	Itraconazole	Voriconazole	Posaconazole	Echinocandin	Amphotericin B
Aspergillus fumigatus	S	S	S	S	S
Aspergillus terreus	S	S	S	S	R
Scedosporium apiospermum	S	S	S	R	R
Scedosporium prolificans	R	R[a]	R[a]	R	R
Fusarium solanii	R	S to R	S	R	S
Zygomycetes	R	R	S	R	S

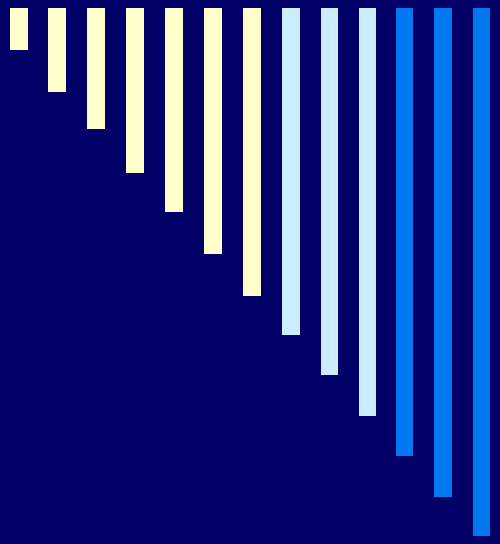
- Fluconazole is ineffective against all molds
- Itraconazole, voriconazole, and posaconazole offer better activity
- Posaconazole in-vitro activity is superior to voriconazole against Fusarium spp. and Zygomycetes

Curr Opin Infect Dis 19:538–543.

Drug resistance in candida species- Indian scenario

Species	Amphotericin B	Fluconazole	Itraconazole
C. tropicalis (49)	6.1% (3)	3.9% (2)	3.9% (2)
C. parapsilosis (28)	7.1% (2)	0	0
C. albicans (23)	4.3% (1)	8.7% (2)	4.3% (1)
C. krusei (1)	100% (1)	100% (1)	100% (1)
C. glabrata (1)	0%	0%	0%

Jpn J Infect Dis 2005;58:344-348



When to start antifungals?

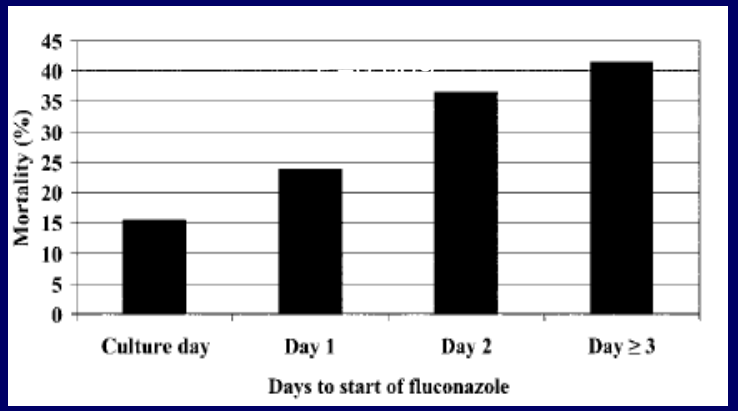
Impact of delay in starting antifungals on mortality

- Timing of the administration of antifungal therapy
  - Within 12 hours in 9 (5.7%) of patients
  - Within 12 and 24 hours in 86 (54.8%) of patients
  - Within 24 and 48 hours in 52 (33.1%) of patients
- Patients receiving antifungal treatment within 12 h of having a positive blood sample for culture drawn had a lower (11.1%) risk of hospital mortality than patients begun on antifungal treatment after 12 h (33.1%) (p =0.167)
- Independent determinants (by multivariate analysis) of hospital mortality
  - APACHE II score (one-point increments) (p=0.001)
  - Prior antibiotic treatment (p=0.028)
  - Administration of antifungal treatment 12 hours after having the first positive blood sample for cultures (p=0.018)

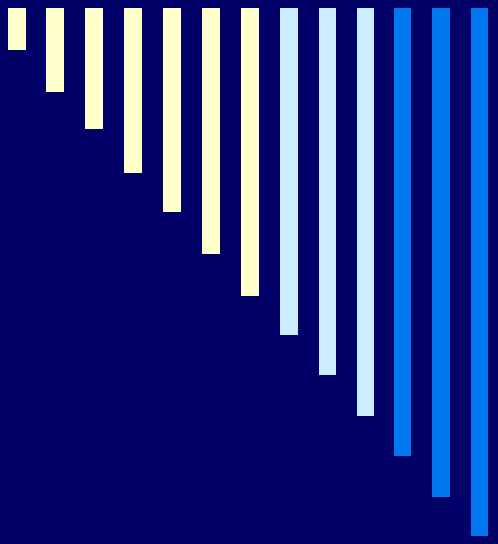
Antimicrobial agents chemother 2005;49:3640-3645

Impact of time of initiation of fluconazole therapy on mortality in patients with candidemia

- Retrospective cohort study of 230 patients from 4 medical centers
- 162 patients (70%) with nonsurgical hospital admission
- 192 patients with no previous fluconazole treatment
- Significant increase in mortality with delay in initiation of antifungal therapy (p=0.009)



Clinical Infectious Diseases 2006; 43:25–31



What is the role of empirical antifungals in critically ill non–neutropenic patients ?

Risk factors for candidemia

- Prolonged use of antibacterial antibiotics
- Presence of central venous catheters
- Hyperalimentation
- Surgery (especially that which transects the gut wall)
- Prolonged ICU stay
- Colonization by *Candida* of multiple nonsterile sites

Important to differentiate between candida colonization and infection

- Colonization index- the ratio of the number of culture-positive sites to the number of sites cultured
- A threshold of 0.5 is associated with high risk of tissue invasion
- Strong pathophysiological link between fungal colonization and subsequent infection established using pulsed-field gel electrophoresis

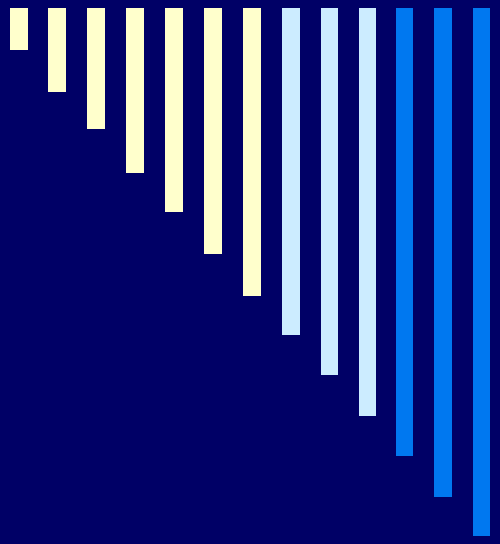
Ann Surg 1994;220:751-758

Candida score

Variable	Coefficient (β)	Standard Error	Wald χ^2	*p* Value
Multifocal *Candida* species colonization	1.112	.379	8.625	.003
Surgery on ICU admission	.997	.319	9.761	.002
Severe sepsis	2.038	.314	42.014	.000
Total parenteral nutrition	.908	.389	5.451	.020
Constant	−4.916	.485	102.732	.000

- A total of 1667 ICU patients from 70 teaching hospitals in spain
- Candida score = 1 (total parenteral nutrition) + 1(surgery) +1 (multifocal *Candida* species colonization) + 2 (severe sepsis)
- A cut off of 2.5 was proposed

Crit Care Med 2006; 34(3):730-737



What is the role of antifungal prophylaxis?

Role of antifungal drugs in prophylaxis in non- neutropenic critically ill patients

Estimated risk	Examples	Incidence without fluconazole prophylaxis (IFIs/100 patients)	Incidence with fluconazole prophylaxis (IFIs/100 patients)	Number avoided/ 100 patients	Number needed to treat to prevent one episode of IFI[a]
Low (≤1%)	absence of risk factors[b]	1	0.47	0.53	188 (147–345)
Average (2%)	unselected ICU population[b]	2	0.94	1.06	94 (74–172)
High (11%)	one of diabetes, new onset haemodialysis, TPN prior to ICU entry or broad-spectrum antibiotics[b]	11	5.2	5.8	17 (13–31)
High (17%)	one of diabetes, new onset haemodialysis or TPN prior to ICU entry[c]	17	8.0	9.0	11 (9–20)
Highest (20%)	one of diabetes, new onset haemodialysis or TPN prior to ICU entry, and broad-spectrum antibiotics[c]	20	9.4	10.6	9 (7–17)

- Antifungal prophylaxis reduces incidence of proven invasive fungal infection by 50% and improves mortality by 25%
- Individual trials did not show the same but pooled analysis does show benefit
- Major limitations- 1) small number of studies and small number of patients

  2) studies not sufficiently powered to determine adverse effects of fluconazole

Journal of Antimicrobial Chemotherapy 2006 ;57: 628–638

Take home message

- Conventional antifungal drugs are still the first line agents
- They are associated with significant side effects and drug interactions
- Increasing drug resistance and discontinuation of therapy due to adverse events has led to high failure rate with conventional antifungals
- Newer antifungals have shown equal or better efficacy with less toxicity leading to better clinical outcomes in invasive fungal infections
- Decision to start empirical antifungal therapy should be individualized taking into consideration the risk factors for invasive fungal infections
- Early institution of therapy improves outcome