New therapeutical options: Inhalation, new compounds and combination.

Jens Schierbeck, MD, Chief physician in Intensive Care Unit, Odense University Hospital, Denmark. Clinical Associate Professor, University of Southern Denmark

Treatment of fungal infections in critically ill patients

Candidemia - Is it important?

- Increased morbidity and prolonged LOS
- Attributable mortality of 30-40%
- 10% of nosocomial infections in the ICU worldwide
- 3-fold increase in the incidense of fungal sepsis from 1979 to 2000
- Candida species rank fourth as a cause of nosocomial BSI
- Ranks very high on the scale of clinical frustrations!
- Timing of treatment is crucial

Inhalation

Aerosolized antifungals

Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America.

Walsh TJ, Anaissie EJ, Denning DW et al. Clin Infect Dis 2008;46(3):327-60.

Tracheobronchial aspergillosis

- Inhalational AmB in lipid formulations has been used for the prevention of invasive aspergillosis in lung transplant recipients, in whom tracheobronchial aspergillosis is especially important. However, this **modality remains investigational**

Prophylaxis against invasive aspergillosis

- Studies of aerosolized AmB have revealed **conflicting results**, in part because of **limitations of study design** and selection of patients at risk

Potential advantages and disadvantages of inhalation therapy with AmB

Advantages	Disadvantages
Achieves high local drug concentration in the lung	Insufficient penetration in cases of mucus plugging, excess secretion, and consolidation
Avoid undesirable systemic effects with reduced systemic toxicity	
Avoid drug interactions	Airborne evironmental contamination

Invasive fungal infections in lung transplantation: role of aerosolised amphotericin B.

Solé A. International Journal of Antimicrobial Agents 32 Suppl. 2 (2008) S161–S165

Who may benefit from aerosolised AmB?

Lung transplant recipients

- Lung transplant surgery - filamentous fungal infections ~ 6% (3−20%) - different prophylactic regimens with AmB
- Other solid organ transplant recipients (re-transplantation of the liver)

Patients with allogeneic haematopoietic progenitor transplant

- Prolonged neutropenia
- Acute / chronic graft-versus-host disease
- Prolonged corticosteroid treatment

Other haematology patients

- Acute myeloblastic leukaemia – polychemotherapy+neutropenia - IA risk of 18−20%

ICU patients

- Chronic obstructive pulmonary disease
- Broad-spectrum antibiotics
- Prolonged ICU stay
- Asymptomatic fungal colonisation

Conclusions
Aerosolized antifungals

- Several studies have been published using aerosolised Amphotericin B and failure of previous trials is related to
  - the design of the studies
  - lack of standardisation of dosing
  - lack of standardisation of nebulizer delivery methods and systems
  - lack of statistical power secondary to small numbers of patients
- Furthermore the method of drug delivery has not been explored in treatment of established fungal lung disease
- Large prospective trials need to be completed before routine treatment of pulmonary infections or the prophylaxis can take place

New compounds

Targets of the systemic antifungals

Rationale for combination antifungal therapy. Lewis RE, Kontoyiannis DP. Pharmacotherapy 2001;21:149S-164S. Review.
A clinical cohort trial of antifungal combination therapy: efficacy and toxicity in haematological cancer patients. Rieger CT, Ostermann H, Kolb HJ et al. J. Ann Hematol 2008; 87:915–922.

- Cell membrane of the fungus
  - Polyenes bind to ergosterol, thereby destabilizing the membrane
  - Triazoles inhibits ergosterol synthesis
- Cell wall of the fungus
  - Echinocandins (1→3-)beta-D-glucan synthesis
- DNA replication
  - Pyrimidine analogs (5-FC)

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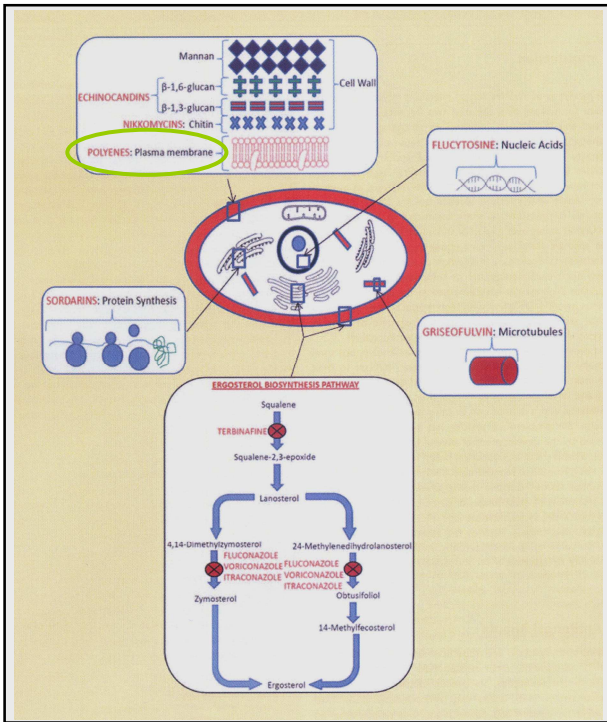
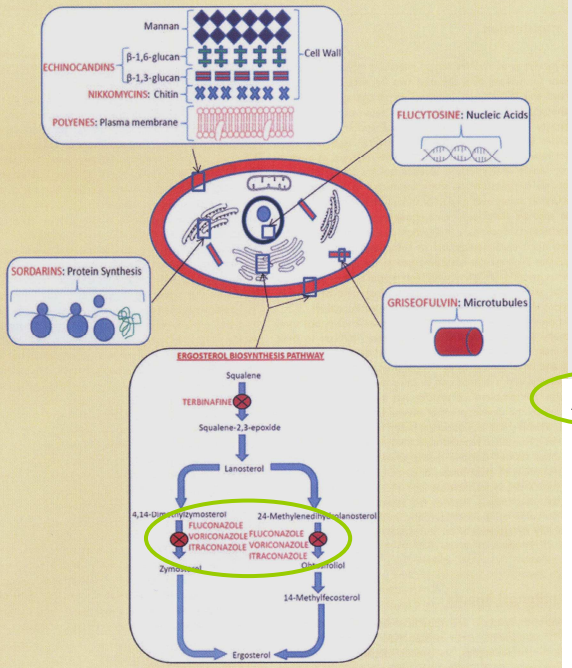


Recent Approaches to Antifungal Therapy for Invasive Mycoses.
Mathew BP, Nath M. ChemMedChem. 2009 Jan 23. [Epub ahead of print]

Polyenes

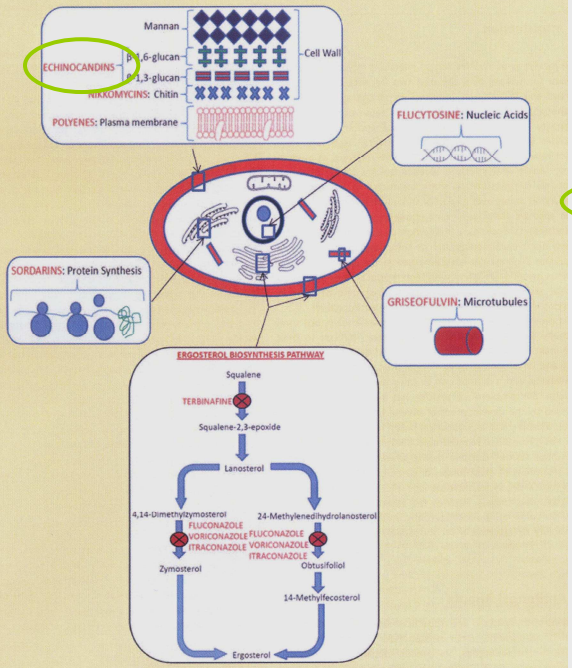
New formulations of AmB are developed through the use of lipid nanosferes -> water-soluble formulations with reduced nephrotoxicity



Recent Approaches to Antifungal Therapy for Invasive Mycoses.
Mathew BP, Nath M. ChemMedChem. 2009 Jan 23. [Epub ahead of print]

Azoles

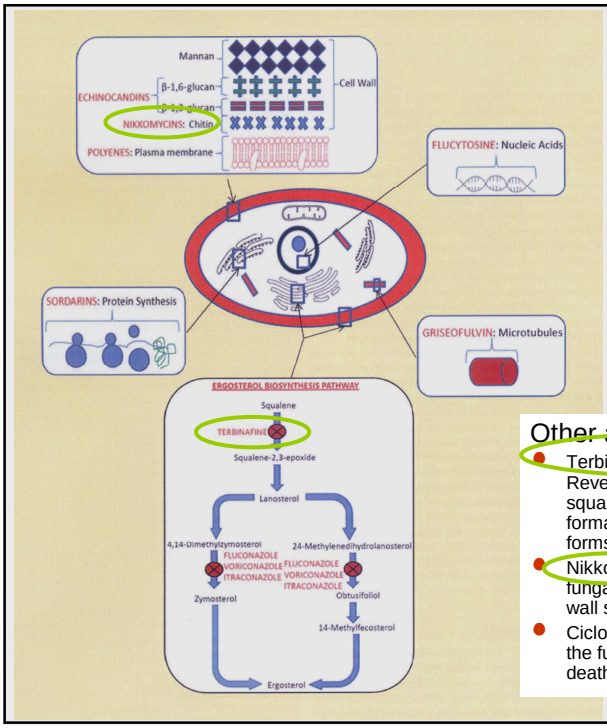
- Ravuconazole
  Eisai terminated the collaboration with Bristol-Myers Squibb. Further clinical studies are discontinued
- recently synthesized are a series of 1-([1H]-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-[(4-substituted-phenyl)-piperazin-1-yl]-propan-2-ol derivates as inhibitors cytochrome P450 14α-demethylase (CYP51)



Recent Approaches to Antifungal Therapy for Invasive Mycoses.
Mathew BP, Nath M. ChemMedChem. 2009 Jan 23. [Epub ahead of print]

Echinicandins

- Echinochandin-like lipopeptides are recently evaluated



Recent Approaches to Antifungal Therapy for Invasive Mycoses.
Mathew BP, Nath M. ChemMedChem. 2009 Jan 23. [Epub ahead of print]

Other agents

- Terbibafine, butenafine and naftinafine. Reversible noncompetitive inhibitors of squalene epoxidase responsible for the formation of lanosterol which ultimately forms ergosterol
- Nikkomycins are competitive inhibitors of fungal chitin synthases, necessary for fungal wall synthesis
- Ciclopiroxolamine. Essential constituents of the fungal cell –> growth inhibition –> fungal death

Recent Approaches to Antifungal Therapy for Invasive Mycoses.

Mathew BP, Nath M. ChemMedChem. 2009 Jan 23. [Epub ahead of print]

- Other agents
  - 1,3-dithian-2-yldine derivates
  - Arylamidine
  - Sordarins. Inteaction with the protein synthesis
  - Azasordarins
- Recently emerging treatments
  - Calcineurins as possible targets for antifungal drugs
  - Vaccination. Genetically altered pathogenic species for the development of live attenuated vaccines

Conclusions
New compounds

- several new antifungal drugs have been licensed and available on the market during the last 10-15 years
- there is still an urgent need for safer and more economical alternatives for antifungal therapy
- there is still ”difficult to treat patients” and combination therapy is one way to combat invasive infections due to multi-resistant species and for those patients who fail to respond to standard treatment

Combination therapy

Potential advantages and disadvantages of combination antifungal therapy

Advantages	Disadvantages
Enhanced rate and extent of killing (additivity, synergy)	Decreased rate and extent of killing (antagonism)
Increased anti-fungal spectrum	Increased risk of drug interactions
Minimal toxicity	Increased toxicity
Decreased likelihood of resistance	Increased costs
Enhanced tissue distribution (CNS)	

Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America.

Walsh TJ, Anaissie EJ, Denning DW, et al. Clin Infect Dis 2008;46(3):327-60.

- Invasive pulmonary aspergillosis**:**
  - In the absence of a well-controlled, prospective clinical trial, routine administration of combination therapy for primary therapy **is not routinely recommended** (B-II)
  - The committee recognizes, however, that in the context of **salvage therapy**, an additional antifungal agent might be added to current therapy, or combination antifungal drugs from different classes other than those in the initial regimen may be used (B-II)

Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America.

Walsh TJ, Anaissie EJ, Denning DW, et al. Clin Infect Dis 2008;46(3):327-60.

- The role of combination therapy in the treatment of invasive aspergillosis as primary or salvage therapy **is uncertain** and warrants a prospective, controlled clinical trial
- Primary combination therapy is not routinely recommended based on **lack of clinical data**; addition of another agent or switch to another drug class for salvage therapy may be considered in individual patients
- Combination therapy with voriconazole and caspofungin is used for CNS aspergillosis but **with minimal data** to date
- Systemic antifungal therapy with AMB and 5-flourocytosine has also been reported in several cases. Although 5-flourocytosine penetrates well into the vitreous humor, its role in enhancing the antifungal combination therapy against aspergillosis **is not established**, and it has been noted to be antagonistic in vitro against some *Aspergillus* strains
- However, **critical gaps in knowledge remain** regarding management of these infections, including the use of combination therapy ……

Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America.

Pappas PG, Kauffman CA, Andes D, et al. Clin Infect Dis. 2009;48(5):503-35.

Flucytosine

- Flucytosine is rarely administered as a single agent but is usually given in combination with AmB for patients with invasive diseases, such as *Candida* endocarditis or meningitis.
- The combination of AmB and flucytosine is appealing because of the in vitro synergism noted with the combination and the excellent CSF concentrations achieved by flucytosine. The length of therapy with AmB alone or in combination with flucytosine has not been defined, but the Expert Panel favors several weeks of therapy before transition to treatment with an azole (after the patient has shown clinical and CSF improvement).

What is the treatment for candida endophthalmitis?

- AmB-d at a dosage of 0.7–1 mg/kg daily, combined with flucytosine at a dosage of 25 mg/kg administered 4 times daily, ***is recommended for advancing lesions or lesions threatening the macula*** (A-III).
- Fluconazole at a dosage of 400–800 mg daily (loading dose of 12 mg/kg then 6–12 mg/kg daily) is an acceptable alternative for less severe endophthalmitis (BIII).
- LFAmB at a dosage of 3–5 mg/kg daily, voriconazole at a dosage of 6 mg/kg twice daily for 2 doses and 3–4 mg/kg twice daily thereafter, or an echinocandin can be used to treat patients who are intolerant of or experiencing treatment failure with AmB-d in combination with flucytosine or fluconazole (B-III).

A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis.

Bennett JE, Dismukes WE, Duma RJ, et al. N Engl J Med 1979;301:126–31.

Effect variable	AmB	AmB+flucytosine
Improved or cured	11 patients	16 patients
Failures or relapses	11 patients	3 patients
Dead	5 patients	5 patients
More rapid sterilization of CBF	$p < 0.001$	
Less nephrotoxicity	$p < 0.05$	

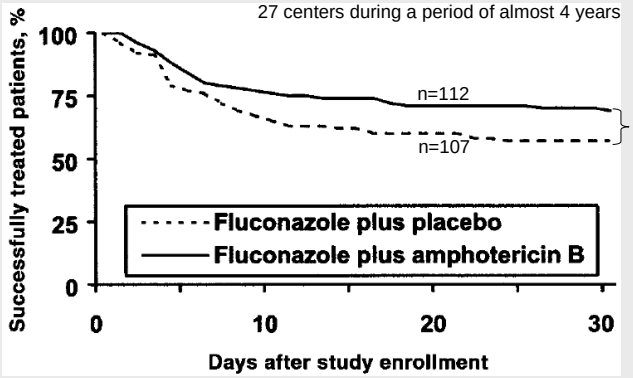
- Amphotericin B vs. amphotericin B and flucytosine therapy for cryptococcal meningitis
- In 50 patients with 51 courses of therapy adherent to the protocol
  - 27 courses were with amphotericin B
  - 24 with the combination.
- The combination regimen was given for six weeks and amphotericin B for 10 weeks
- Adverse reactions to flucytosine occurred in 11 of 34 patients but were not life threatening
- We conclude that combined flucytosine-amphoericin B therapy is the regimen of choice in cryptococcal meningitis

Reference Candida	n	Setup	Combination	Results
Guidelines for treatment of candidiasis. Pappas PG, Rex JH, Sobel JD, et al. Clin Infect Dis 2004; 38:161–189.	-	empirically justified (IDSA guidelines 2004)	AmB+5-FC	Primary treatment of complicated invasive candidiasis (meningitis, endocarditis, peritonitis, endophthalmitis)
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 patients. Rex JH, Pappas PG, Karchmer AW, et al. Clin Infect Dis 2003; 36:1221–1228.	219	randomized, blinded, multicenter	Flu+placebo vs Flu+AmB	Overall success rates ● 56%, Flu+placebo ● 69% Flu+AmB, p=0.043 BSI failed to clear in ● 17%, Flu+placebo ● 6% Flu+AmB, (p=0.02)
Multiple-species candidemia in patients with cancer. Boktour MR, Kontoyiannis DP, Hanna HA, et al. Cancer 2004;101:1860–1865.	33	retrospective	AmB+flu	MSC, response rate ● 35%, single agent ● 75%, combination

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 patients.

Rex JH, Pappas PG, Karchmer AW, et al. Clin Infect Dis 2003; 36:1221–1228.

27 centers during a period of almost 4 years



The proportion of subjects still successfully treated for the first 30 days of the study, by Kaplan-Meier analysis of time to failure. By the log-rank test, the 2 curves do not differ (p=0.08).

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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 patients.

Rex JH, Pappas PG, Karchmer AW, et al. Clin Infect Dis 2003; 36:1221–1228.

Study arms	% failed clearance from BS	p
Flu+placebo	17	0.02
Flu+AmB	6	

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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 patients.

Rex JH, Pappas PG, Karchmer AW, et al. Clin Infect Dis 2003; 36:1221–1228.

Conclusion

- 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.

Multiple-species candidemia in patients with cancer.

Boktour MR, Kontoyiannis DP, Hanna HA, et al. Cancer 2004;101:1860–1865.

Therapy and Outcome Data for Patients with MSC and Patients with *Candida albicans* Candidemia

Variable	No. of patients (%)		
	MSC (n = 33)	*C. albicans* candidemia (n = 66)	P value[a]
Antifungal therapy use	30 (91)	54 (82)	NS
Fluconazole	12	37	0.02
AMB deoxycholate	4	7	NS
Lipid formulation of AMB	10	7	0.05
Combination (polyene plus fluconazole)	4 (12)	3 (5)	NS
Had response to antifungal therapy	14 (47)	40 (74)	0.01
Had response to primary single-agent therapy	9 (35)	35 (69)	0.004
Had response to combination therapy (polyene plus fluconazole)	3 (75)	2 (67)	NS
30-day mortality	15 (45)	22 (33)	NS

AMB: amphotericin B; NS: not statistically significant; MSC: multiple-species candidemia.

[a] Univariate analysis.

33 patients with cancer who had candidemia (diagnosed between 1993 and 2000) caused by more than 1 *Candida* species. This group of 33 patients was compared with a control group of 66 patients with cancer who had *C. albicans* candidemia that arose soon before or soon after each case of MSC that was investigated in the current study.

Reference Aspergillus	n		Combination	Results
Efficacy and toxicity of caspofungin in combination with liposomal AmB as primary or salvage treatment of IA in patients with hematologic malignancies. Kontoyiannis DP, Hachem R, Lewis RE et al. Cancer 2003;98: 292–299.	48	retrospective	Caspo/L-AmB	Favorable response ● 42%. Response rate in patients with progres-sive documented IA was low (18%)
Refractory Aspergillus pneumonia in patients with acute leukemia: successful therapy with combination caspofungin and liposomal amphotericin. Aliff TB, Maslak PG, Jurcic JG, et al. Cancer 2003;97(4):1025-32.	30	retrospective	Caspo/AmB/L-AmB	Favorable response ● 75%
Combination antifungal therapy for invasive aspergillosis. Marr KA, Boeckh M, Carter RA et al. Clin Infect Dis 2004 ;39: 797–802	47	retrospective	Vori vs Vori/caspo	● Improved 3-month survival in the combination group; p=0.048. ● The probability of death due to asperg. was lowest in the combination group
Multicenter, noncomparative study of caspofungin in combination with other antifungals as salvage therapy in adults with invasive aspergillosis. Maertens J, Glasmacher A, Herbrecht R et al. Cancer 2006;107:2888–97.	53	open-label noncompara multicenter	Caspo/triazole Caspo/polyene	Favorable response ● 57% of patients with neutropenia ● 54% who received an AHST ●Survival at day 84 was 55%.
A clinical cohort trial of antifungal combination therapy: efficacy and toxicity in haematological cancer patients. Rieger CT, Ostermann H, Kolb HJ et al. Ann Hematol 2008; 87:915–922.	56	retrospective	Vori/caspo vs L-AMB/triazole vs L-AMB/caspo	● Favourable response was 65%, ● Mortality at the end of treatment was 11% and 34% 3 months after initiation of combination therapy

Refractory Aspergillus pneumonia in patients with acute leukemia: successful therapy with combination caspofungin and liposomal amphotericin.

Aliff TB, Maslak PG, Jurcic JG, et al. Cancer 2003;97(4):1025-32.

Acute Leukemia/Intensive Chemotherapy Subgroup (n = 20)

Aspect	No. of patients (%)
Diagnosis	
AML	15 (80)
ALL	5 (20)
Leukemia status	
Newly diagnosed	10 (50)
Recurrent/refractory	10 (50)
Chemotherapy regimens used	
Anthracycline/cytarabine combinations	16 (80)
High-dose cytarabine containing	9 (45)
Response to combination antifungal therapy	
Favorable	15 (75)
Unfavorable	5 (25)

AML: acute myeloid leukemia; ALL: acute lymphoid leukemia.

Refractory Aspergillus pneumonia in patients with acute leukemia: successful therapy with combination caspofungin and liposomal amphotericin.
Aliff TB, Maslak PG, Jurcic JG, et al. Cancer 2003;97(4):1025-32.

Conclusions

- The antifungal combination of caspofungin and amphotericin can be administered safely to high-risk patients with hematologic malignancies
- Although an absolute assessment of efficacy is limited by the design of this study, encouraging outcomes were noted for many patients

Combination antifungal therapy for invasive aspergillosis.
Marr KA, Boeckh M, Carter RA, Kim HW, Corey L. Clin Infect Dis. 2004;39(6):797-802.

Methods

- We evaluated the outcomes of patients with aspergillosis who experienced failure of initial therapy with amphotericin B formulations and received either
  - voriconazole (n=31) or
  - combination of voriconazole and caspofungin (n=16)

  for salvage therapy

Combination antifungal therapy for invasive aspergillosis.

Marr KA, Boeckh M, Carter RA, Kim HW, Corey L. Clin Infect Dis. 2004;39(6):797-802.

Results

- The combination of voriconazole and caspofungin was associated with **improved 3-month survival rate**, compared with voriconazole alone (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.17–1.1; p=0.048).
- In multivariable models, salvage therapy with the combination of voriconazole and caspofungin was associated with **reduced mortality**, compared with therapy with voriconazole (HR, 0.28; 95% CI, 0.28–0.92; Pp.011), independent of other prognostic variables (e.g., receipt of transplant and type of conditioning therapy).
- The probability of death due to aspergillosis was lowest in patients who received the combination regimen.

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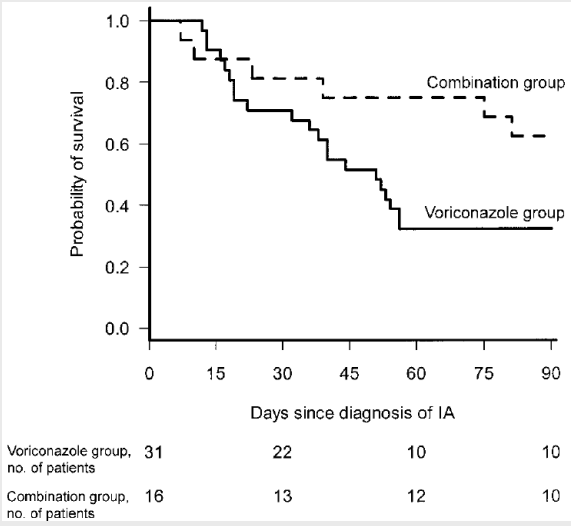
Combination antifungal therapy for invasive aspergillosis.

Marr KA, Boeckh M, Carter RA, Kim HW, Corey L. Clin Infect Dis. 2004;39(6):797-802.



Kaplan-Meier probability of survival after diagnosis of proven or probable invasive aspergillosis in patients treated with voriconazole alone or voriconazole with caspofungin.

P=0.048, calculated from the likelihood ratio test using Cox regression.

The number of patients evaluable during each time period is indicated.

Combination antifungal therapy for invasive aspergillosis.
Marr KA, Boeckh M, Carter RA, Kim HW, Corey L. Clin Infect Dis. 2004;39(6):797-802.

Conclusions

- Randomized trials are warranted to determine whether this combination should be used as primary therapy for aspergillosis.

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A clinical cohort trial of antifungal combination therapy: efficacy and toxicity in haematological cancer patients
Rieger CT, Ostermann H, Kolb HJ et al. Ann Hematol 2008; 87:915–922.

- All patients enrolled in this retrospective trial were treated in the Department of Haematology/Oncology at the University of Munich for haematological malignancies between 2001 and 2007.
- The data obtained for this study were collected by retrospective chart review. Data were obtained following a methodological protocol for the evaluation of antifungal therapy.

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A clinical cohort trial of antifungal combination therapy: efficacy and toxicity in haematological cancer patients

Rieger CT, Ostermann H, Kolb HJ et al. Ann Hematol 2008; 87:915–922.

Characteristic	Total number (%)
Underlying disease	56 (100%)
AML	35 (64%)
ALL	7 (13%)
SAA	4 (7%)
MM	3 (5%)
MDS	2 (4%)
CML	3 (5%)
CMML	1 (2%)
NHL	1 (2%)

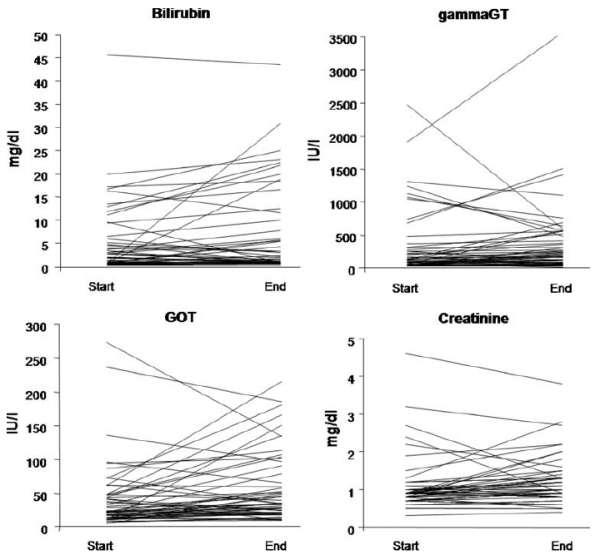
A clinical cohort trial of antifungal combination therapy: efficacy and toxicity in haematological cancer patients

Rieger CT, Ostermann H, Kolb HJ et al. Ann Hematol 2008; 87:915–922.

Characteristic	Total number (%)
Fungal pathogen	
Candida species	10 (18%)
Aspergillus species	35 (62%)
N/A (leads to "possible" IFI)	11 (20%)
IFI categories at study entry	
Possible	11 (20%)
Probable	15 (27%)
Proven	30 (53%)
Sites of fungal infection	
Pulmonary	43 (77%)
Disseminated/bloodcultures	10 (18%)
Paranasal sinus	3 (5%)
Source of microbiological proof	
Bloodculture	10 (18%)
Aspergillus antigen (ELISA)	15 (27%)
BAL (proof of *Aspergillus* spp.)	17 (30%)
Histology	3 (5%)

A clinical cohort trial of antifungal combination therapy: efficacy and toxicity in haematological cancer patients

Rieger CT, Ostermann H, Kolb HJ et al. Ann Hematol 2008; 87:915–922.



Toxicity data at baseline and end of treatment in the cohort.
There was no statistically significant increase in any of the examined parameters.

A clinical cohort trial of antifungal combination therapy: efficacy and toxicity in haematological cancer patients

Rieger CT, Ostermann H, Kolb HJ et al. Ann Hematol 2008; 87:915–922.

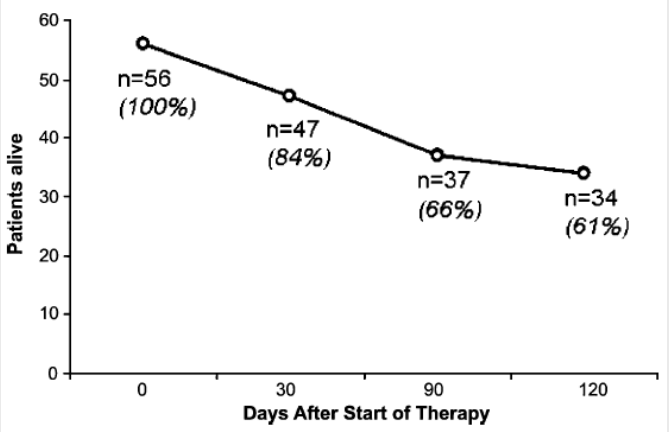


Fig. 2 Survival rates at the beginning and 30, 90 and 120 days after start of antifungal combination therapy

The survival rates at the beginning of antifungal combination therapy and on days 30, 90 and 120 after initiation of antifungal combination therapy.

A clinical cohort trial of antifungal combination therapy: efficacy and toxicity in haematological cancer patients

Rieger CT, Ostermann H, Kolb HJ et al. Ann Hematol 2008; 87:915–922.

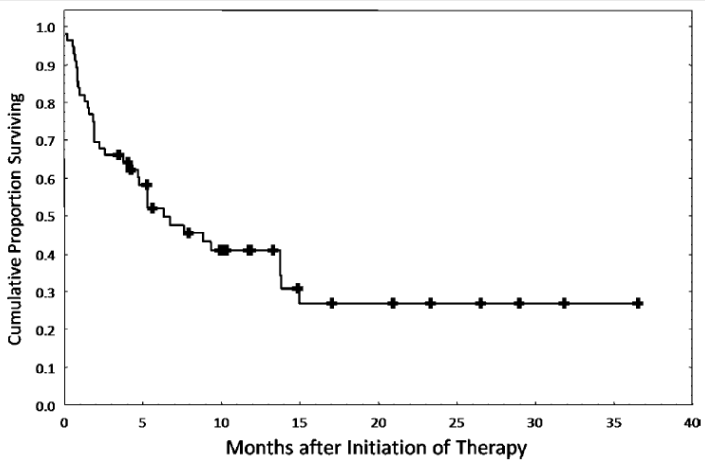


Fig. 3 Kaplan–Meier plot showing probability of survival after initiation of therapy. Median survival for all patients was 6.3 months

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A clinical cohort trial of antifungal combination therapy: efficacy and toxicity in haematological cancer patients

Rieger CT, Ostermann H, Kolb HJ et al. Ann Hematol 2008; 87:915–922.

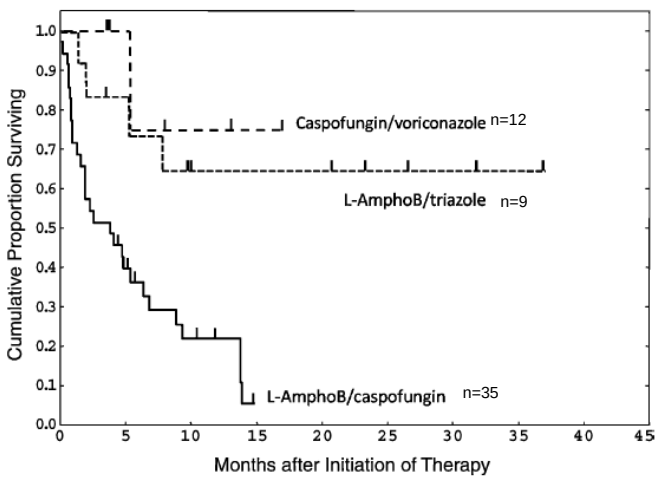

Fig. 4 Kaplan–Meier plot showing probability of survival for the different treatment groups within the cohort

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A clinical cohort trial of antifungal combination therapy: efficacy and toxicity in haematological cancer patients

Rieger CT, Ostermann H, Kolb HJ et al. Ann Hematol 2008; 87:915–922.

Conclusions

- Data show that concomitant use of all classes of antifungal drugs was feasible for first-line or salvage therapy in haematological high-risk patients
- The risk of treatment-related toxicity was moderate if antifungal drugs were applied in approved dosage
- Response rates and mortality in the cohort were better than those of antifungal monotherapy published in previous trials
- Prospective studies to evaluate the optimal combinations are needed

Conclusions

Combination therapy

- Antifungal combination therapy is increasingly applied in clinical practice although specific recommendations for such treatment are still lacking
- The role of combination therapy in the treatment of invasive aspergillosis as primary or salvage therapy is uncertain and the clinical evidence for combination therapy comes from relatively small retrospective case series or prospective open-label studies
- Randomized trials are warranted to determine whether combination therapy should be used in selected patients in the treatment of candidemia or aspergillosis


Thank you
Jens Schierbeck, MD, Chief physician in Intensive Care Unit, Odense University Hospital, Denmark. Clinical Associate Professor, University of Southern Denmark