

Treatment of rare and emerging fungal infections

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Emerging and rare medically important fungi

- **Dematiaceous moulds** (*Alternaria* sp, *Bipolaris* sp, *Exophiala* sp, *Wangiella* *Phialophora*, *S. prolificans*, *Cladophialophora bantiana*)
- **Hyaline septate moulds** (*Fusarium* sp, *S. apiospermum*, *Paecilomyces* sp, *Acremonium* sp)
- **Non septate Zygomycetes**
- **Endemic mycoses** (*Penicillium marneffe*, *Coccidioides immitis*, *Histoplasma capsulatum*)
- *Trichosporon* sp
- Non-albicans yeasts

Emerging fungal pathogens

- Changing epidemiology
- Frequent revisions in taxonomy
- Misidentification
- Tendency to be disseminated
- Dismal prognosis
- Refractory to conventional antifungal therapies, limited therapeutic options
- Encouraging results with new antifungals but the available data still scant
- Different amount of information for new compounds
- Given the infrequency, optimal treatment has not been established

Epidemiological considerations- emerging fungi

- Institutional and/or geographical differences^{1,2}
- Antifungal selective pressure
- Clinical outcomes may not correlate with virulence or resistance to drug
- Intensive epidemiologic surveillance is required

1 *Colombo et al Eur J Clin Microbiol Infect Dis 2003;22:470*

2 *Hachem et al Cancer 2004;101:1594*

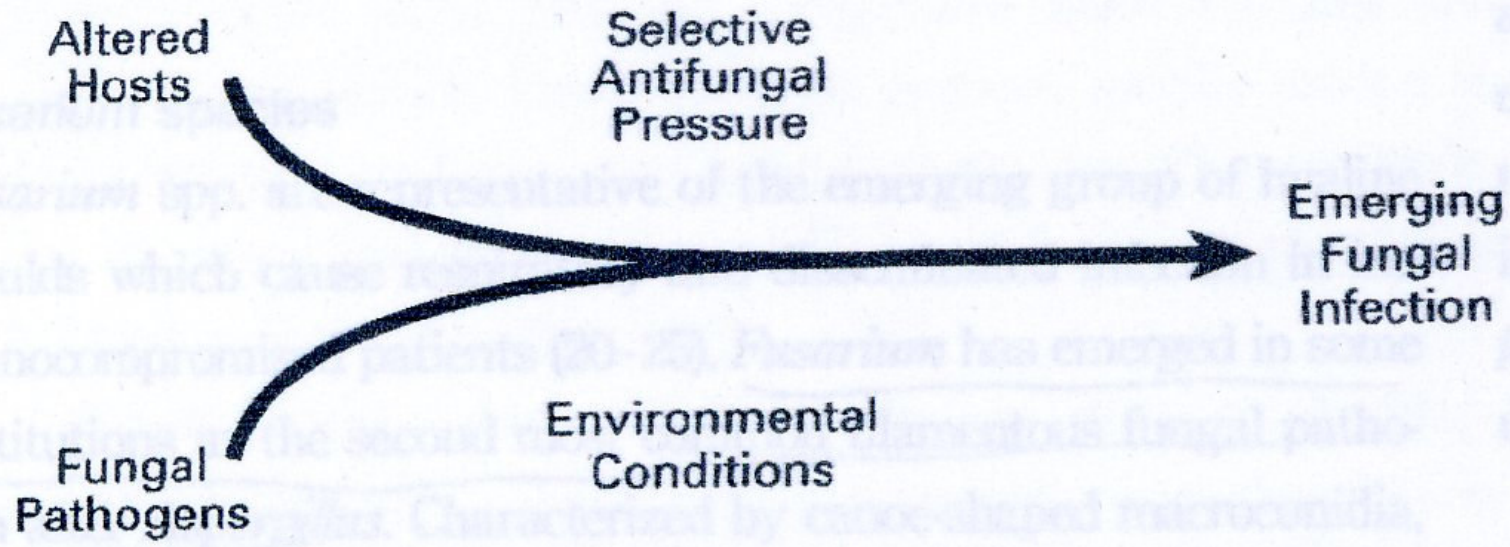
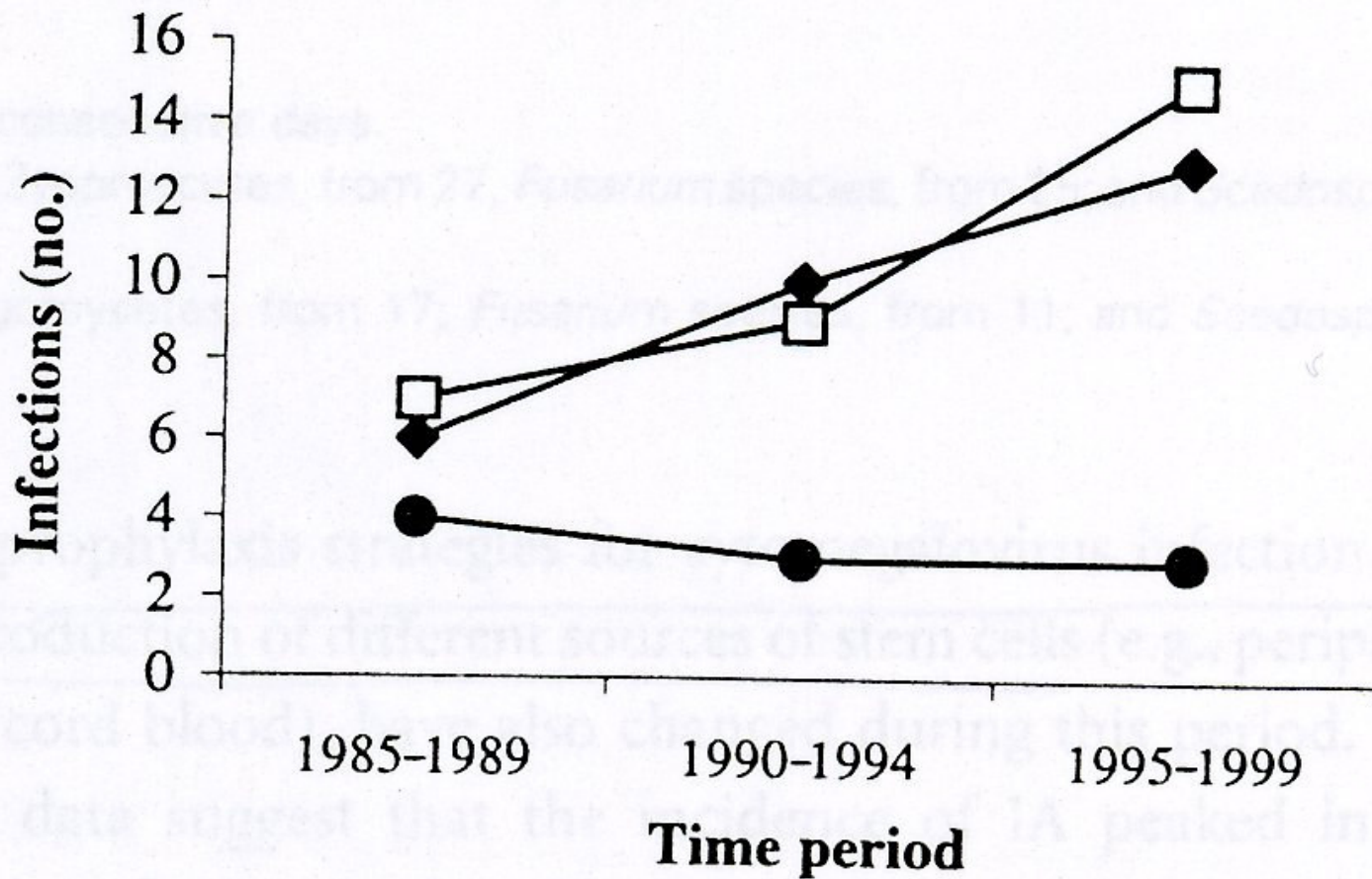


Fig. 2. Concepts in emerging fungal infections.

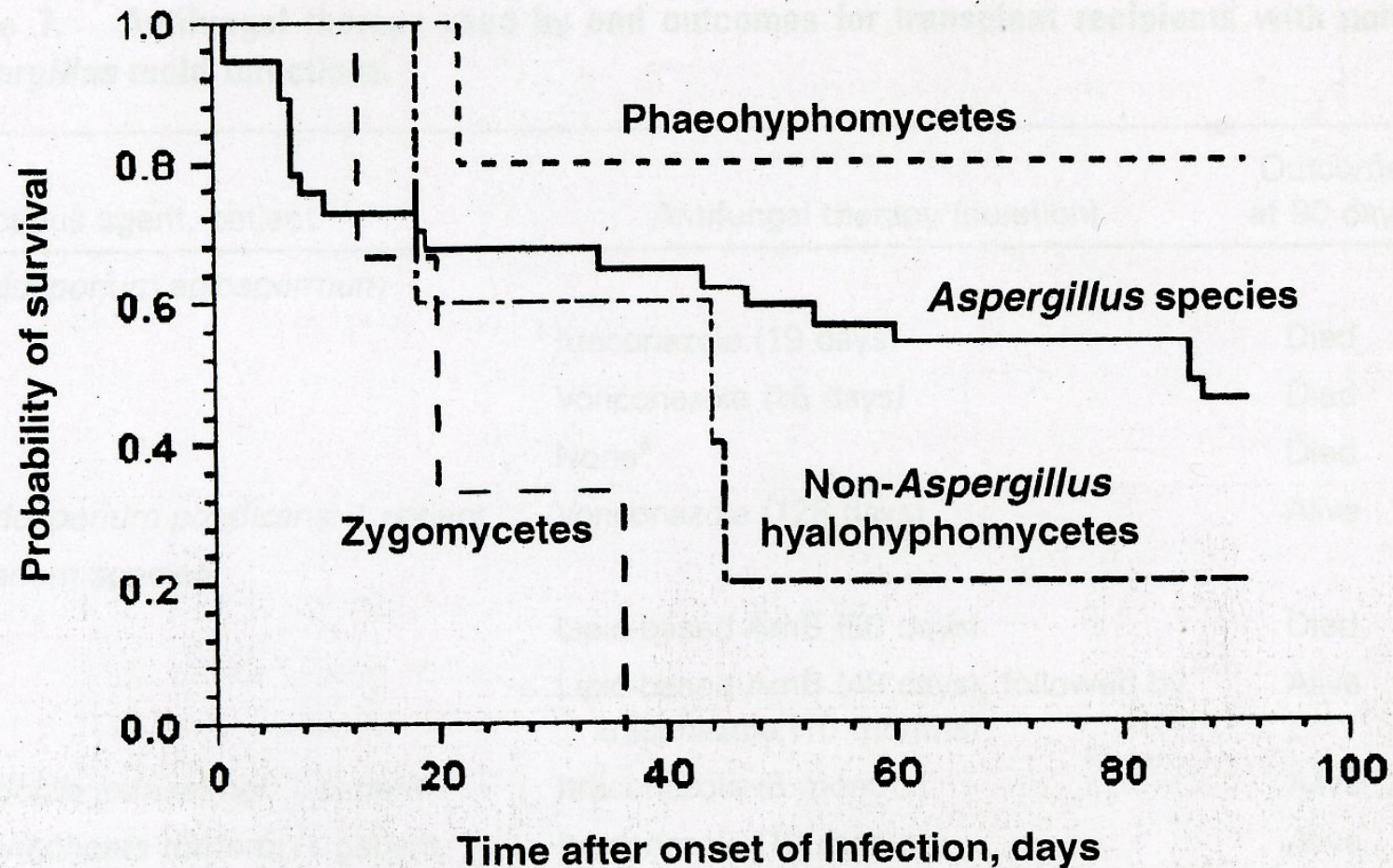
Single center experience

Marr et al, Clin Infect Dis 34:909,2002



Multicenter study

Husain et al, Clin Infect Dis 2003;37:221



Emerging mycoses (yeasts) characteristics

- *C. glabrata*,
C. krusei fluco-R
- *C. parapsilosis* foreign body and
biofilm formation
- *Rhodotorula* catheter related,
in *vitro* R to flu- and candins,
best azole in *vitro* posa
- *Trichosporon beigelli* Cross-reaction with crypto-
breakthrough infections with
empiric AmB in neutropenia

Emerging mycoses (moulds) characteristics

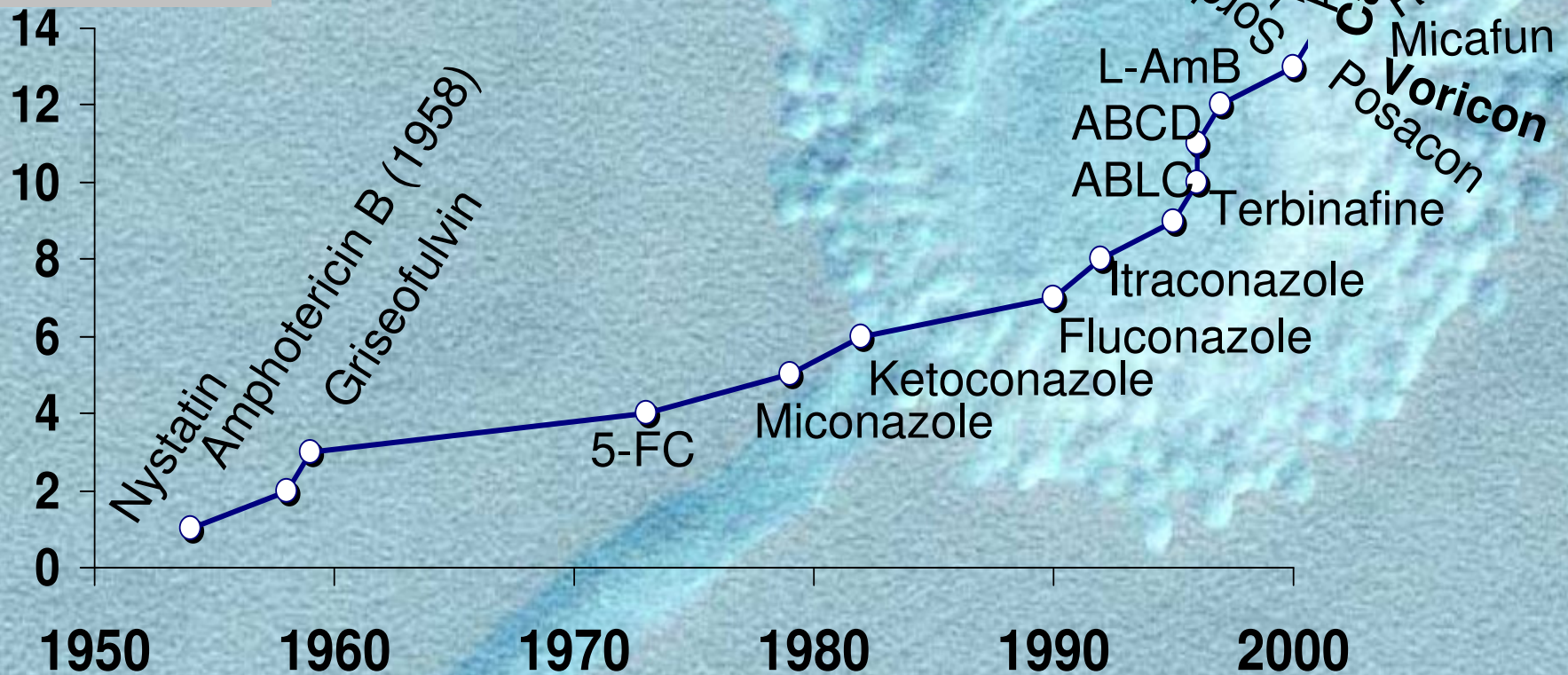
- *Aspergillus terreus* R to polyenes
- *Scedosporium apiospermum* (*Ps. boydii*)
- *Scedosporium prolificans* (*inflatum*) Multiresistant

- *Phaeohyphomycosis* recurrences, surgery

- *Zygomycosis* Posa-S, Vori-R
Caspofungin-R

Mycology: The Last 50 Years

of drugs



New triazoles

- Voriconazole (Pfizer)
- Posaconazole (Schering – Plough)
- Ravuconazole (Eisai/Bristol Myers Squibb)
- Vori and Ravu are i.v. or p.o., Posa only p.o.



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Voriconazole *in vitro* activity

- Active against yeasts and moulds
- Fungicidal for a range of filamentous fungi including:
 - Aspergillus sp*
 - Scedosporium sp*
 - Fusarium sp*
- Potent *in vitro* activity (fungistatic) shown against *Candida sp*, including *C.krusei* and *C.glabrata*
- Poor activity against Zygomycetes

Voriconazole efficacy – animal studies

- Pulmonary and invasive aspergillosis
- *A. fumigatus* endocarditis
- Fusariosis
- Pulmonary cryptococcosis
- Invasive candidiasis

Voriconazole – human studies

- Large-scale clinical trials: Efficacy in acute IA (primary therapy), candidal esophagitis, febrile neutropenia, refractory invasive candidiasis
- Smaller studies, case reports: Salvage therapy of IA, cerebral aspergillosis, Scedosporiosis, Fusariosis, Coccidioides meningitis....

VORICONAZOLE

clinical efficacy

<i>S.apiospermum</i>	2/6
<i>S.prolificans</i>	1/4
histoplasmosis,blastomycosis, coccidioidomycosis	3/5
phaeohyphomycoses (<i>Alternaria, Bipolaris, Exophiala</i>)	5/5
<i>paecilomyces</i>	1/3
total	12/23

**Fusariosis 45%, Scedosporiosis 30%,
penicilliosis 90%**

Perfect et al Clin Infect Dis 2003;36:1122

Denning DW Lancet 2003;362:1142

Highly active	Very active	Some activity	Inactive
<i>Candida albicans</i>	<i>Candida parapsilosis</i>	<i>Coccidioides immitis</i>	Zygomycetes
<i>Candida glabrata</i>	<i>Candida guilliermondii</i>	<i>Blastomyces dermatididis</i>	<i>Cryptococcus neoformans</i>
<i>Candida tropicalis</i>	<i>Aspergillus fumigatus</i>	<i>Scedosporium</i> spp	<i>Fusarium</i> spp
<i>Candida krusei</i>	<i>Aspergillus flavus</i>	<i>Paecilomyces variotii</i>	<i>Trichosporon</i> spp
<i>Candida kefyr</i>	<i>Aspergillus terreus</i>	<i>Histoplasma capsulatum</i>	
<i>Pneumocystis carinii</i> *	<i>Candida lusitanae</i>		

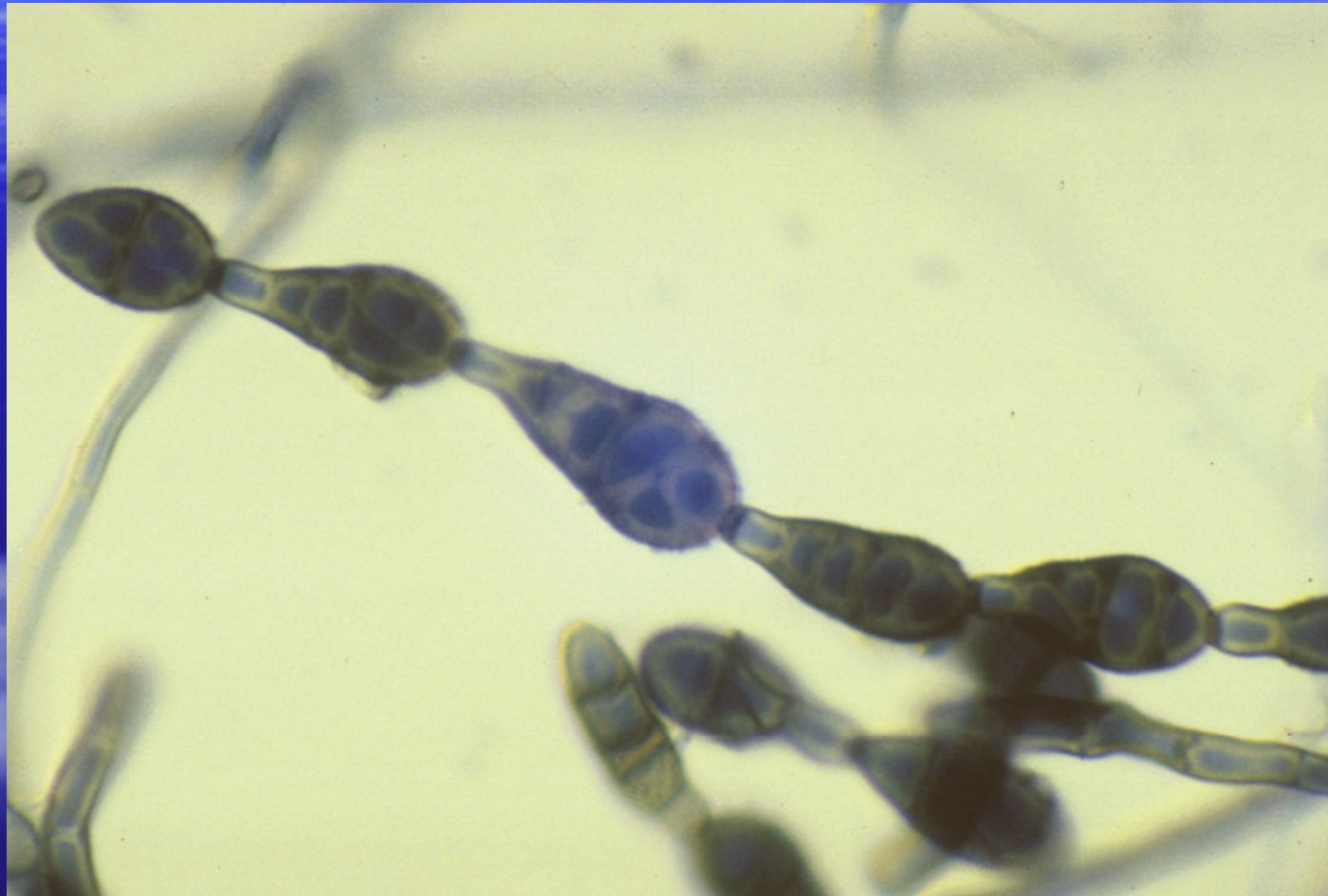
Highly active implies very low minimum inhibitory concentrations with fungicidal activity and good in-vivo activity, Very active implies low minimum inhibitory concentrations, but without fungicidal activity in most instances. Some activity implies detectable activity, which might have therapeutic potential for man (in some cases in combination with other drugs). Inactive implies no intrinsic activity. There are usually some differences between individual isolates within a species and there might be significant differences between echinocandins. *Only active against cyst form, and probably only useful for prophylaxis.

Table 3: **Range of activity of the echinocandins**

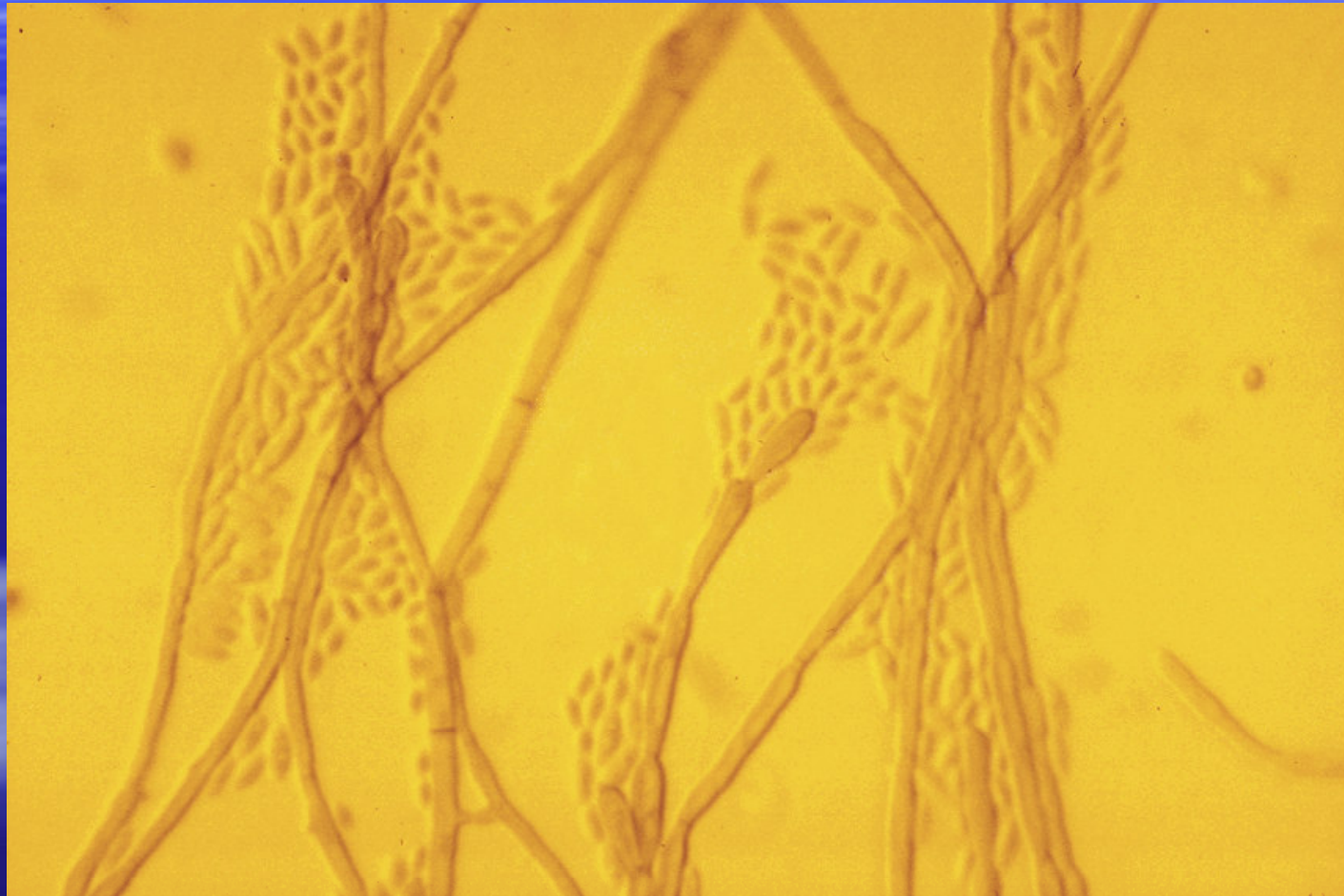
Paecilomyces sp

- Two medically important species: *P. varioti* and *P. lilacinus*
- Several outbreaks in the last two decades
- Because of their unpredictable antifungal activity, *Paecilomyces* should be identified to the species level.
- Consider high-dose L-AmB or voriconazole + surgery

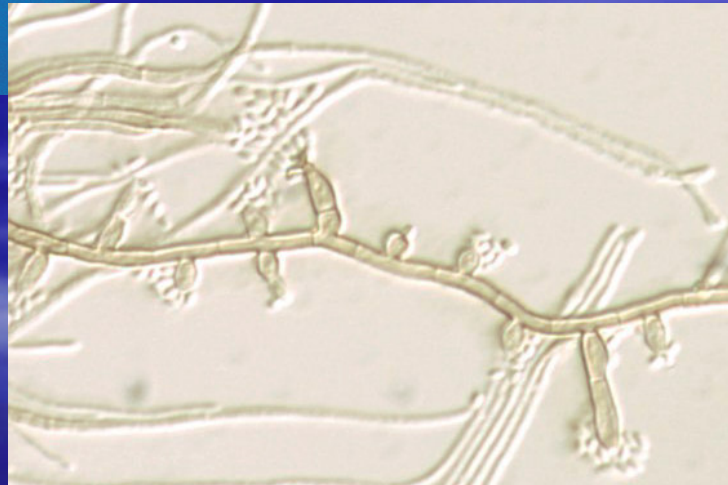
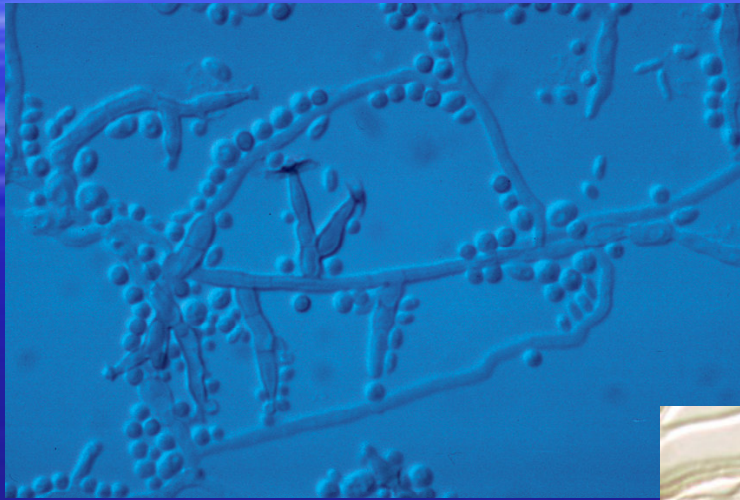
Alternaria alternata



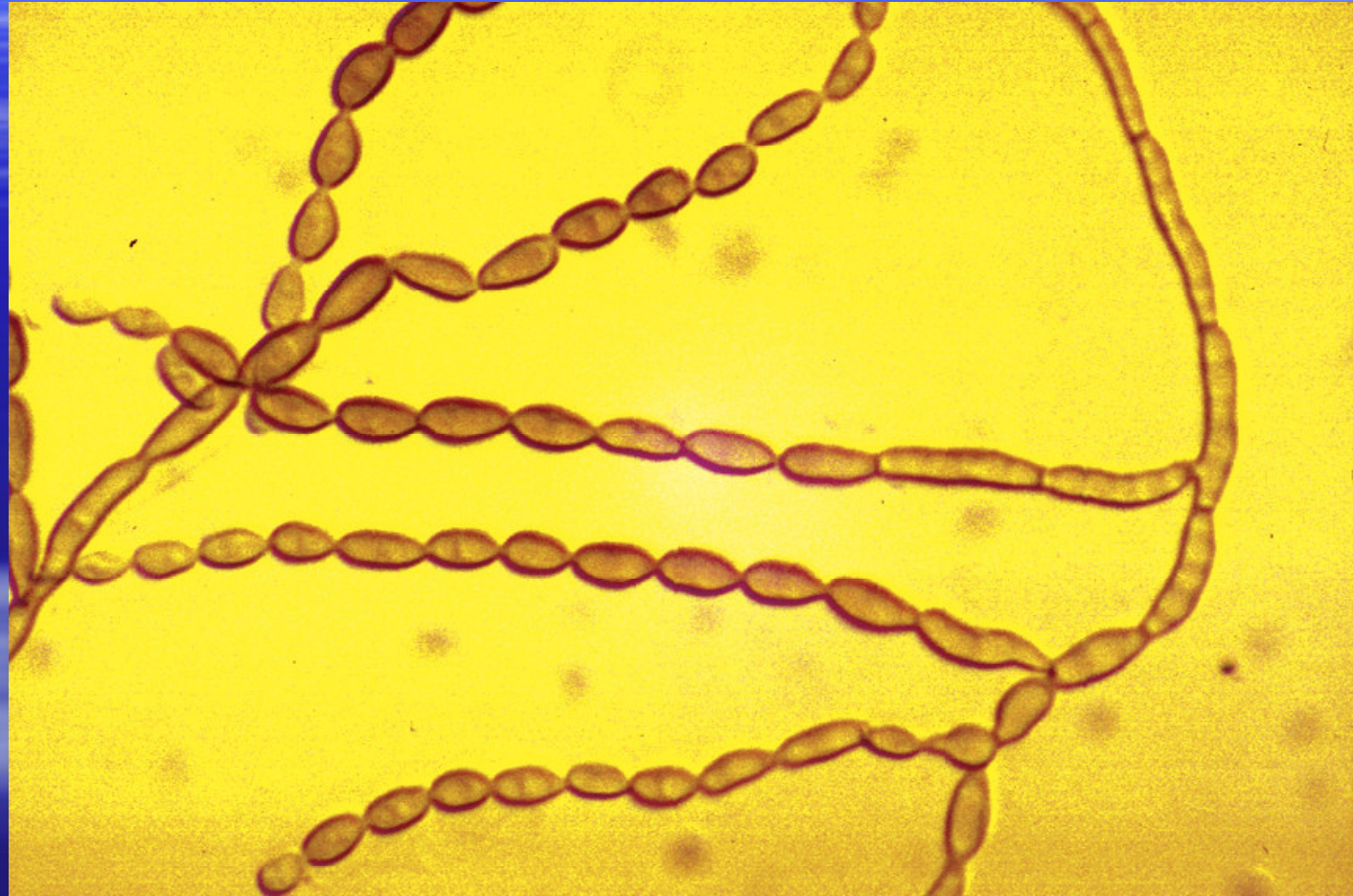
Wangiella dermatitidis



Phialophora richardsiae & Phialophora verrucosa



Cladophialophora bantiana



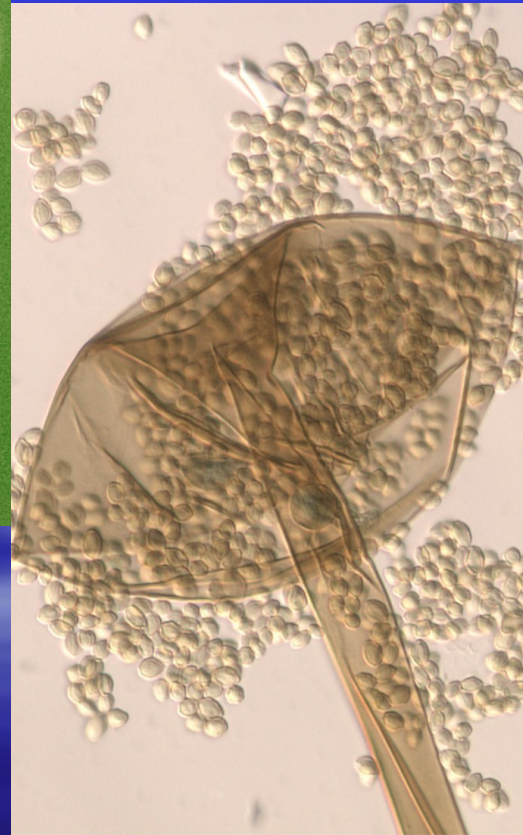
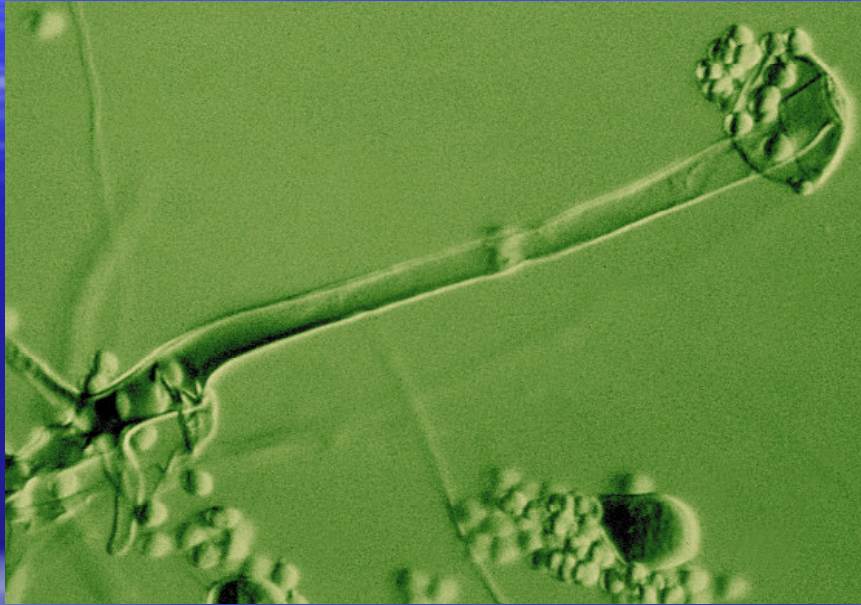
Zygomycetes

three sections strategy

- **High doses of D-AmB or L-AmB**
- Posaconazole: activity in vitro, in animal models. A response to salvage posa- therapy 70% in 23 BMT patients with proven or probable zygomycosis*
- Voriconazole, echinocandins inactive
- **Surgical debridement**
- **Control of underlying disease** (diabetic ketoacidosis, neutropenia)

* *Greenberg et al. abstract M 1757, 43th ICAAC, 2003*

Mucorales
Rhizopus arrhizus (oryzae)



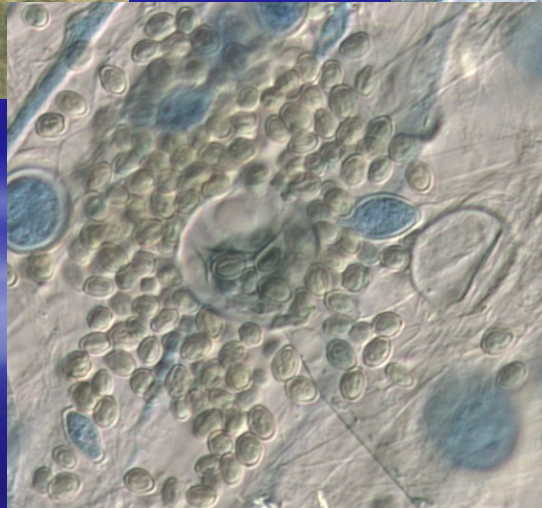
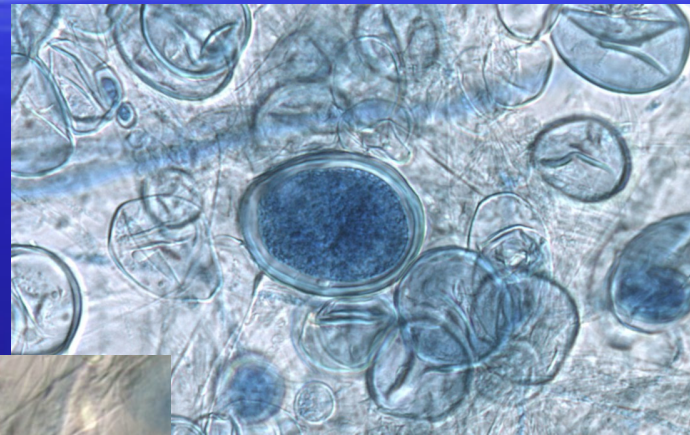
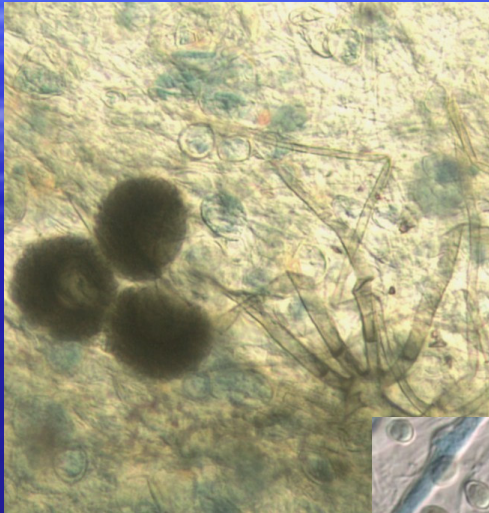
Mucorales

Absidia corymbifera



Mucorales

Rhizopus schipperae



Penicillium marneffe – endemic dimorphic fungi

- Important emerging pathogen in HIV infected patients in Southeast Asia or travellers to an endemic area
- Penicilloles has also been detected in immunocompetent children and adults
- *P. marneffe* is usually susceptible to both AmB and azoles
- Secondary lifelong prophylaxis in HIV individuals
- Impact of HAART?

Cidal activity - any clinical significance?

Agent	yeast	Filamentous fungi
Polyenes	+	+
Echinocandins	+	-
Triazoles		
Voriconazole	-	+
Itraconazole	-	+/-
Fluconazole	-	-

- *In vitro* experiments and animal models may **ONLY SUGGEST** what should be tested in humans

Pharmacological considerations and future perspectives in the era of new antifungal agents

Sambatakou H.: 'Posaconazole: pharmacology and drug interactions'. September 2002

www.aspergillus.man.ac.uk

Breakthrough infections and drug resistance with emerging fungi. Warnings or an overestimation?

- Breakthrough Zygomycosis in HSCT patients receiving voriconazole – 4 cases¹
- Breakthrough Zygomycosis (Voriconazole vs Amphotericin B) 2/0, Aspergillosis 4/13, *Candida* 2/6²
- Breakthrough yeast infections with *C. glabrata*, *C. neoformans*, and *C. Krusei* with voriconazole
- *S. prolificans* resistance³

1 Marty F., Cosimi L. N Engl J Med 2004;350;9:950-2

2 Walsh T et al., N Engl J Med 2002 ;346(4):225-234

3 Perfect et al., CID 2003;36:1122-31

Breakthrough fungal infections - VRC

	SUMMARY Reference	Breakthrough I Incidence	Vori use / form/ duration th	Type of patients
04 {	Marty NEJM	Zygom 4/119	Px - ET / Oral 21-99d	HSCT + GVHD
	Clement EBMT abst	Zygom 4	Px /ET Oral /iv	HSCT + GVHD
	Marr CID	Zygo + C.glabrata 13/139	Px/ Combo th Oral /iv 4 – 110 d	HSCT
	Siwek CID	Zygom 4/45	Px Oral	HSCT + GVHD
05 {	Mattner JID	Zygom 1	Px Oral	Lung T
	Vigouroux CID	Zygom 4/93	Px Oral 7-30 w	HSCT

NOTE Px: Prophylaxis / ET: empiric therapy / CI: Confirmed Infection
 HSCT: Heamatol. Stem Cell Transplant / GVHD: Graf vs Host Disease

conclusions

- Emerging mycoses are a threat!!
- The outcome is usually very poor
- Special attention should be paid to the epidemiology of *Asp. Terreus* because of its intrinsic resistance to AmphoB
- Extended-spectrum azoles and echinocandins hold promise to expand our limited therapeutic options, but their role remains to be determined
- Increasing resistance to these new and very useful antifungal agents might be induced by their widespread use

New considerations, challenges

- Combination antifungal therapy
- Immunomodulatory treatment
- New diagnostic modalities (non-culture based assays)
- In these infections, the host plays the major role in outcome!!!
- EARLY initiation of OPTIMAL treatment and CONTROL of the underlying disease: key components!!!

*“ In God we trust,
from others we require data”*

BEN DE PAUW

Bipolaris hawaiiensis & Bipolaris spicifera



Curvularia lunata



Exophiala jeanselmei



Paecilomyces lilacinus



Phaeohyphomycosis

(*Alternaria*, *Bipolaris*, *Cladophialophora*,
Wangiella, *Curvularia*, *Exophiala*...)

- The number of these moulds continues to increase
- Relapses early and late
- ***Exophiala*** infection from contaminated steroids*
- Many of them are neurotropic
- The optimal medical and surgical treatment has not yet been established
- Extended spectrum triazoles: excellent activity
- Vori- less toxic alternative than AmB for CNS infection

* ***MMWR 2002:51(49);1109***

Phaeohyphomycosis

- High dose D-AmB or L-AmB or itraconazole or voriconazole
- In an animal model of *Ramichloridium* brain infection posaconazole and D-AmB*
- Echinocandins: variable in vitro activity; less potent than new azoles
- **Surgery** is essential
- Treatment experience from case reports and small retrospective series

* *Al-Abdely et al Antimicrob Agents Chemother* 2000; 44(5):1159

A. Terreus infections

- *In vitro* and animal models suggest resistance to polyenes
- Retrospective review of 83 proven and probable cases of *A. terreus* infection
- Lung infection (90%); HSCT (45%)
- Overall mortality (66%), vori: 56% and polyene 73%
- Multivariable analysis: vori associated with improved survival (p=0.03)

Steinbach et al, ICAAC, 2003

Fusarium infections

- Commonly R to AmB and fluconazole-breakthrough infections on empiric AmB therapy
- *F.solani* the most common pathogen, occasionally pathogenic: *F.moniliforme*, *F.oxysporum*, *F.proliferatum*
- In some centers, the third leading cause of fungal infections

- **Treatment of choice:** voriconazole or high doses of D-AmB or L-AmB,
- Posaconazole: promising activity (in vitro and animal data)
- **Immune reconstitution and control of the underlying disease a major factor for a favorable outcome in disseminated infection**

Fusarium solani



scedosporiosis

- Some strains of *S.apiospermum* and all strains of *S.prolificans* are intrinsically resistant *in vitro* to AmB.
- Variable *in vitro* resistance to itraconazole
- Caspofungin has demonstrated *in vitro* activity against *S.apiospermum* but no activity against *S.prolificans*
- **Voriconazole** FDA approval for *S.apiospermum* refractory to other therapies (60% efficacy series of case reports). *S. prolificans* less susceptible, but occasionally clinical response
- Posaconazole (*in vitro*, case reports), ravuconazole effective
- *In vitro* report of synergism AmB+pentamidine

scedosporiosis

Treatment of choice has not been established

- *S. Apiospermum*:

voriconazole or itraconazole+ surgery

- *S. prolificans*:

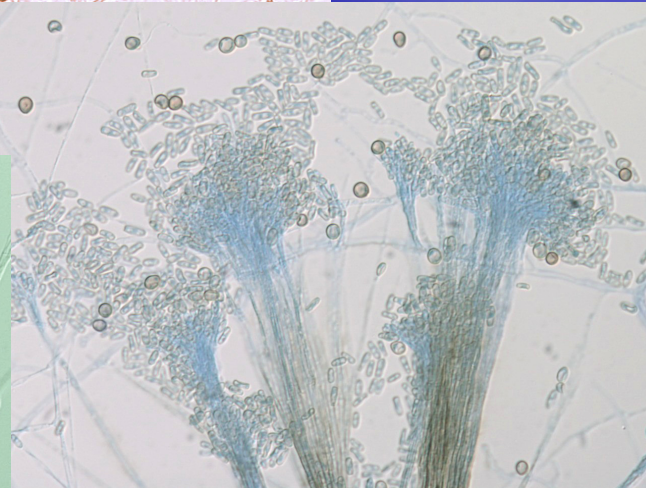
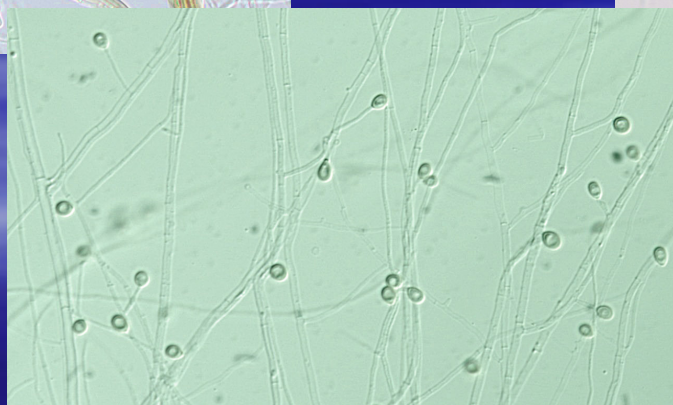
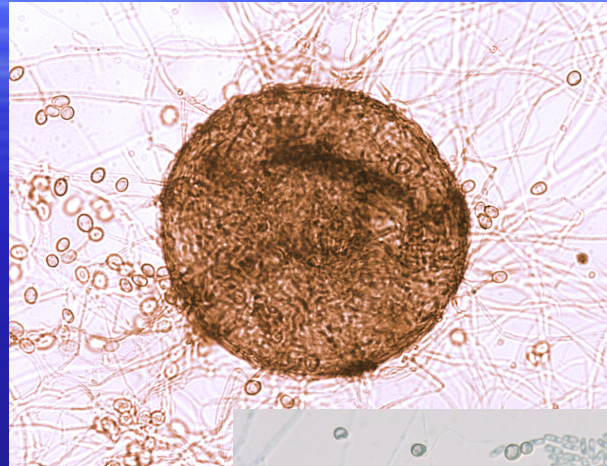
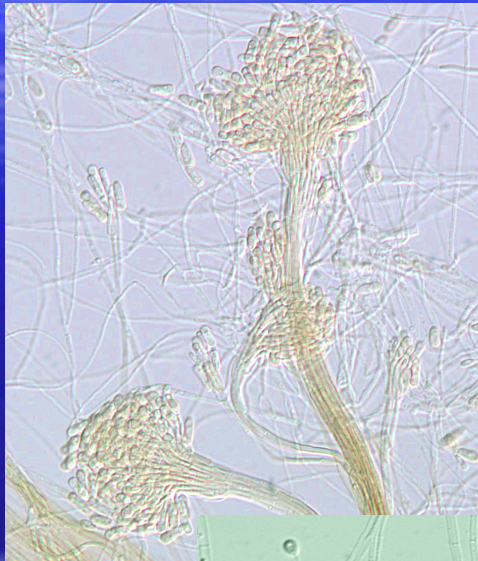
unknown – consider high dose L-AmB? or voriconazole?
or itraconazole+ **surgery**

Itraconazole+ terbinafine synergistic against *Sc prolificans*

restoration of immune competence

surgical resection the only definitive therapy for *S. prolificans*

Pseudallescheria boydii (*Scedosporium apiospermum*)



Scenedosporium prolificans

