Treatment of rare and emerging fungal infections

EFISG Educational Workshop
15th ECCMID
April 2, 2005, Copenhagen

Helen Sambatakou
Lecturer in Medicine and Infectious Diseases,
University of Athens,
Greece
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 marneffei, 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\textsuperscript{1,2}
- Antifungal selective pressure
- Clinical outcomes may not correlate with virulence or resistance to drug
- Intensive epidemiologic surveillance is required

\textsuperscript{1} Colombo et al Eur J Clin Microbiol Infect Dis 2003;22:470
\textsuperscript{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

The graph shows the number of infections (no.) over different time periods:

- 1985-1989
- 1990-1994
- 1995-1999

The number of infections increases over time, particularly noticeable in the 1990-1994 and 1995-1999 periods.
Multicenter study
Husain et al, Clin Infect Dis 2003;37:221
Emerging mycoses (yeasts) characteristics

- **C. glabrata**, fluco-R
- **C. krusei**
- **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

- Nystatin
- Amphotericin B (1958)
- Griseofulvin
- 5-FC
- Miconazole
- Ketoconazole
- Fluconazole
- Itraconazole
- L-AmB
- ABCD
- ABLC
- Terbinafine
- Voricon
- Posacon
- Micafungin
- Caspofungin
- Sordarins
- Anidulafungin
- Ravucon
- XMP

Years

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.
The
New England
Journal of Medicine
Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY
VOLUME 347 AUGUST 8, 2002 NUMBER 8

THIS WEEK IN THE JOURNAL
Article Summaries ........................................... 381
Perspective: Stroke, Spasticity, and Botulinum Toxin ........................................... 382
L.F. Rowland

ORIGINAL ARTICLES
Antiretroviral-Drug Resistance among Patients Recently Infected with HIV ......................... 385
S.J. Little and Others
Intramuscular Injection of Botulinum Toxin for the Treatment of Wrist and Finger Spasticity after a Stroke ........................................... 395
A. Brashear and Others
Variant Cystic Fibrosis Phenotypes in the Absence of CFTR Mutations ......................... 401
Voriconazole versus Amphotericin B for Primary Therapy of Invasive Aspergillosis ......................... 408
R. Herbrecht and Others

IMAGES IN CLINICAL MEDICINE
Fistulizing Crohn's Disease ........................................... 416
V. Sanchez and E.V. Loftus

REVIEW ARTICLE
Medical Progress: Inflammatory Bowel Disease ........................................... 417
D.E. Podolsky

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL
A 48-Year-Old Man with Persistent Erosive Oral Lesions ........................................... 430
G.T. Gallagher and S. Litt

EDITORIALS
HIV Drug Resistance — A Chink in the Armor ........................................... 438
M.S. Hirsch
What Is Cystic Fibrosis? ........................................... 439
M.R. Knowles and P.R. Durie

CORRESPONDENCE
Psychological Sequela of September 11 ........................................... 443
Atrial Failing in Sleep Apnea Syndrome ........................................... 445
Imatinib Mesylate and Grey Hair ........................................... 446
Celiac Sprue ........................................... 446
Salt-Sensitive Hypertension ........................................... 448
Immune Thrombocytopenic Purpura ........................................... 449
Should Family Members Be Present during Cardiopulmonary Resuscitation? ........................................... 450
Campath 1H—Induced Complete Remission of Chronic Lymphocytic Leukemia despite p53 Gene Mutation and Resistance to Chemotherapy ........................................... 452

BOOK REVIEWS ........................................... 454
NOTICES ........................................... 456
CORRECTION ........................................... 458
CONTINUING MEDICAL EDUCATION ........................................... 459

Owned, published, and © copyrighted, 2002, by THE MASSACHUSETTS MEDICAL SOCIETY. All rights reserved.

Reprinted from THE NEW ENGLAND JOURNAL OF MEDICINE (ISSN 0028-4793). Published weekly from Editorial Offices at 10 Shattuck Street, Boston, Massachusetts 02115-6994 USA — Fax: (617) 734-4457

Business, Subscription Offices
860 Winter Street, Waltham, Massachusetts 02451-1412 USA — Fax: (781) 893-8103
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

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

Fusariosis 45%, Scedosporiosis 30%, penicilliosis 90%

*Perfect et al Clin Infect Dis 2003;36:1122*
<table>
<thead>
<tr>
<th>Highly active</th>
<th>Very active</th>
<th>Some activity</th>
<th>Inactive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida albicans</td>
<td>Candida parapsilosis</td>
<td>Coccidioides immitis</td>
<td>Zygomycetes</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>Candida gulliermondii</td>
<td>Blastomyces dermatitidis</td>
<td>Cryptococcus neoformans</td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>Aspergillus fumigatus</td>
<td>Scedosporium spp</td>
<td>Fusarium spp</td>
</tr>
<tr>
<td>Candida krusei</td>
<td>Aspergillus flavus</td>
<td>Paecilomyces variotii</td>
<td>Trichosporon spp</td>
</tr>
<tr>
<td>Candida kefyr</td>
<td>Aspergillus terreus</td>
<td>Histoplasma capsulatum</td>
<td></td>
</tr>
<tr>
<td>Pneumocystis carinii*</td>
<td>Candida lusitaniae</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 posaconazole 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 marneffei** – endemic dimorphic fungi

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

<table>
<thead>
<tr>
<th>Agent</th>
<th>yeast</th>
<th>Filamentous fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyenes</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Echinocandins</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Triazoles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
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


www.aspergillus. man.ac.uk
Breakthrough infections and drug resistance with emerging fungi. Warnings or an overestimation?

- Breakthrough Zygomycosis in HSCT patients receiving vori – 4 cases
  
- Breakthrough Zygomycosis (Vori vs AmBisome) 2/0, Aspergillosis 4/13, Candida 2/6

- Breakthrough yeast infections with C. glabrata, C. neoformans, and C. Krusei with vori

- S. prolificans resistance

3 Perfect et al., CID 2003;36:1122-31
<table>
<thead>
<tr>
<th>SUMMARY Reference</th>
<th>Breakthrough Incidence</th>
<th>Vori use / form/ duration th</th>
<th>Type of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marty NEJM</td>
<td>Zygom 4/119</td>
<td>Px - ET / Oral 21-99d</td>
<td>HSCT + GVHD</td>
</tr>
<tr>
<td>Clement EBMT abst</td>
<td>Zygom 4</td>
<td>Px / ET Oral /iv</td>
<td>HSCT + GVHD</td>
</tr>
<tr>
<td>Marr CID</td>
<td>Zygo + C. glabrata 13/139</td>
<td>Px/ Combo th Oral /iv 4 – 110 d</td>
<td>HSCT</td>
</tr>
<tr>
<td>Siwek CID</td>
<td>Zygom 4/45</td>
<td>Px Oral</td>
<td>HSCT + GVHD</td>
</tr>
<tr>
<td>Mattner JID</td>
<td>Zygom 1</td>
<td>Px Oral</td>
<td>Lung T</td>
</tr>
<tr>
<td>Vigouroux CID</td>
<td>Zygom 4/93</td>
<td>Px Oral 7-30 w</td>
<td>HSCT</td>
</tr>
</tbody>
</table>

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 hawaiitensis & 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 posa> itra 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

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
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)
Scedosporium prolificans