Treatment of Fungal infections in Hematologic Malignancies

George Samonis M.D. PhD
Professor of Medicine
The University of Crete

www.cyhaema.com
Challenges of Diagnosing Opportunistic Infections at the Bedside

Bacterial?

Bedside Diagnosis

Viral?

Fungal?
Challenges of Diagnosing Opportunistic Infections at the Bedside
Usual fungal infections in immunocompromised patients

- Candidiasis
- Aspergillosis
- Mucormycosis
- Fusariosis
- Cryptococcosis
Risk factors for development of IFIs

- Neutropenia
- Lymphopenia
- Corticosteroids
- Immunosuppressives
- Chemotherapy
- Bone Marrow Transplantation
- Broad-spectrum antibiotics
- Mucositis
- Parenteral alimentation
- Central venous catheters (CVCs)
- Hospital construction
Hepatosplenic candidiasis  CT scan shows typical lucencies in the liver of a patient with acute myeloid leukemia who developed chronic disseminated candidiasis following recovery from prolonged neutropenia. Courtesy of Carol A Kauffman, MD.
Invasive Aspergillosis, IV Site

Bennett. In: Mandell, Bennett, Dolin, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 4th ed. 1995-2305-2311

www.cyhaema.com
Invasive Aspergillosis, Lung


www.cyhaema.com
“Halo” Sign on CT of Neutropenic Patient With Aspergillosis
Cerebral Aspergillosis
Mucormycosis 3 Days Later

 Courtesy of John E. Bennett, MD
Mucormycosis

Courtesy of John E. Bennett, MD
Mucormycosis

Courtesy of Carmen Turesky, FACHE, 813-872-322.
Incidence of Nosocomial Candidemia in Intensive Care Units (NNIS)

BSI per 1000 Central Line Days

- Non-albicans Candida spp
- C albicans
Increased Incidence of Mould Infection

Aspergillus spp

<table>
<thead>
<tr>
<th>Year Range</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976-1985</td>
<td>4.0%</td>
</tr>
<tr>
<td>1983-1989</td>
<td>6.0%</td>
</tr>
<tr>
<td>1974-1989</td>
<td>11.4%</td>
</tr>
<tr>
<td>1997-1998</td>
<td>13.0%</td>
</tr>
<tr>
<td>1996-2000</td>
<td>11.0%</td>
</tr>
</tbody>
</table>

Distribution of IA in the Post-Engraftment Phase of HSCT


Incidence of IA in HSCT

Number of Days Post HSCT

- <40 (n=57): 30%
- 40-180 (n=99): 53%
- >180 (n=31): 17%
Incidence of Aspergillosis in HSCT Recipients Is Growing

1-Year Cumulative Incidence of Aspergillosis at FHCRC* (%)

Data from 1990 through 1992 were obtained from another study.

*FHCRC, Fred Hutchinson Cancer Research Center

www.cyhaema.com
Invasive Aspergillosis Risk Increases During the Post-Engraftment Period


Pre-engraftment

Neutropenia

Post-engraftment

IA Risk

IA Risk

Immunosuppression:
GVHD
Corticosteroids
Diminished T-cell function
Aspergillus-Related Mortality in Allogeneic HSCT Remains Relatively High

Studies used crude mortality rate or attributable mortality rates. *Crude mortality rate at 4 months post IA diagnosis.

The Majority of IFIs Are Identified Post-mortem

Pre-mortem

Post-mortem

<table>
<thead>
<tr>
<th>Pre-mortem</th>
<th>Post-mortem</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.3%*</td>
<td>33%†</td>
</tr>
</tbody>
</table>

*Incidence of moulds and yeasts in AML patients (7.9% due to moulds).
†Prevalence of invasive moulds and Candida (22% due to moulds).

How Can We Better Identify Patients With IFI During Life?

www.cyhaema.com
Invasive Aspergillosis
Role of Early Diagnosis & Therapy

Have We Made Progress??
Non-Culture Based Diagnosis of Invasive Aspergillosis

- Galactomannan
  - Sandwich ELISA (Platelia)

- PCR
  - 18s ribosomal DNA
  - Multi-copy or single target genes

- β-D-glucan
  - Amebocyte *Limulus* lysate
  - Chromogenic (Glucatell, FungiTec G)
  - Kinetic (Wako)
Early diagnosis and treatment of invasive aspergillosis

- Impact of early diagnosis of IA in patients with acute leukemia:
  - 90% mortality when treatment instigated ≥ 10 days after first clinical or radiological sign of disease
  - 40% mortality when treatment is instigated early

- Serial HR CT scanning:
  - early and systematic high resolution CT scan in high-risk patients improves outcome

Relationship between hospital mortality and the timing of antifungal treatment

Patients with Satisfactory Treatment Response categorized by Baseline CT Findings

Satisfactory Response (CR/PR) vs. Nodular lesion with Halo
- ALL Treated: 52%
- Vori Arm: 62%
- Ampho Arm: 41%

Satisfactory Response (CR/PR) vs. Nodular lesion without Halo*
- ALL Treated: 29%
- Vori Arm: 42%
- Ampho Arm: 16%

*Note: Required positive mycology

Greene R et al. ECCMID 2003

www.cyhaema.com
Utility of Galactomannan Detection in BAL Samples

<table>
<thead>
<tr>
<th># pt</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>160</td>
<td>47</td>
<td>93</td>
<td>73</td>
<td>82</td>
</tr>
<tr>
<td>Serum</td>
<td>85</td>
<td>100</td>
<td>100</td>
<td>88</td>
</tr>
<tr>
<td>BAL</td>
<td>93</td>
<td>100</td>
<td>100</td>
<td>88</td>
</tr>
</tbody>
</table>

GM detection in CT-based BAL fluid has a high PPV for diagnosing IPA early in untreated patients

Treatment definitions

- **Prophylactic therapy**: Use of antifungals from chemotherapy until prolonged febrile neutropenia
  
  Chance of infection: **remote**

- **Empirical therapy**: Use of antifungals from febrile neutropenia to culture and/or tissue evidence of fungal infection
  
  Chance of infection: **possible**

- **Preemptive therapy**: Use of antifungals based on early clinical and/or laboratory markers of invasive disease
  
  Chance of infection: **probable**
Lack of Consensus on the Use of Empirical Antifungal Therapy

Pros
- Reduces mortality
- Addresses diagnostic concerns

Cons
- Development of resistance
- Toxicity
- Cost

Persistent or recurring fever of unknown origin
>38°C

Persistent neutropenia
Absolute neutrophil count <500 cells/mm³

Broad-Spectrum antibiotics
>96 h

Antifungal treatment evolution

- **AMB deoxycholate**
- **5-fluocytosine**
- **1\textsuperscript{st} generation azoles (ketoconazole, miconazole)**
- **2\textsuperscript{nd} generation triazoles (fluconazole, itraconazole)**
- **Lipid and liposomal formulations of AMB**
- **Extended spectrum triazoles (voriconazole, posaconazole)**
- **Echinocandins (caspofungin, micafungin, anidulafungin)**
Cellular Targets of Antifungal Therapy

- **Polyenes:** Target membrane function
- **Azoles:** Target ergosterol synthesis
- **Echinocandins:** Target cell wall synthesis

www.cyhaema.com
Fluconazole: Not a good choice for empirical therapy in certain patients

- Pts on azole prophylaxis
- Pts with sinusitis or pneumonia
- Pts with prolonged neutropenia (e.g. leukemia)
- Pts with history of invasive aspergillosis (IA) or positive surveillance cultures for Aspergillus spp.
- Pts at institutions undergoing construction
### L-AMB vs. AMB for empirical therapy of febrile neutropenia

<table>
<thead>
<tr>
<th></th>
<th>Ambisome®</th>
<th>AMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>343</td>
<td>344</td>
</tr>
<tr>
<td>Acute Leukemia</td>
<td>168</td>
<td>165</td>
</tr>
<tr>
<td>Success</td>
<td>50</td>
<td>49</td>
</tr>
<tr>
<td>BFI (%) *</td>
<td>3.2</td>
<td>7.8</td>
</tr>
<tr>
<td>Infusion Fever (%) †</td>
<td>17</td>
<td>44</td>
</tr>
<tr>
<td>Nephrotoxicity (%)</td>
<td>19</td>
<td>34</td>
</tr>
</tbody>
</table>

* p=0.009 † p<0.001

Walsh NEJM 1999; 340:764

www.cyhaema.com
Polyene Therapy for Invasive Aspergillosis

Note: ABLC=amphotericin B lipid complex; L-AmB=liposomal amphotericin B; ABCD=amphotericin B colloidal dispersion; D-AMB=amphotericin B deoxycholate

Comparative Aspergillosis Study: Better Outcomes & Survival of Voriconazole

- Outcomes at wk 12
<table>
<thead>
<tr>
<th>Vori</th>
<th>AmB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>70.8%</td>
</tr>
<tr>
<td>Response</td>
<td>56.8%</td>
</tr>
</tbody>
</table>

- Poor efficacy of AmB prior “gold standard”
- Voriconazole recommended for primary therapy

- Questions?
  - Role of Other Licensed Antifungal therapy
  - Lipid for primary therapy
  - Efficacy in high risk
  - Combinations

Herbrecht R et al  *NEJM* 2002;347:408-15

www.cyhaema.com
Voriconazole vs. Ambisome® in febrile neutropenia

<table>
<thead>
<tr>
<th></th>
<th>Vorico (N=415)</th>
<th>LAMB (N=422)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite success</td>
<td>26%</td>
<td>31%</td>
<td>NS</td>
</tr>
<tr>
<td>Breakthrough fungal infections</td>
<td>1.9%</td>
<td>5%</td>
<td>0.002</td>
</tr>
<tr>
<td>Survival rate</td>
<td>87%</td>
<td>90%</td>
<td>NS</td>
</tr>
<tr>
<td>Toxicity-related withdrawal</td>
<td>13%</td>
<td>10%</td>
<td>NS</td>
</tr>
<tr>
<td>Nephrotoxicity (SCr&gt;1.5)</td>
<td>11%</td>
<td>19%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Visual changes</td>
<td>4.3%</td>
<td>0.5%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Βορικοναζόλη
Πότε χρειάζεται «monitoring»;

- Υποψία δυσαπορρόφησης (βλεννογονίτιδα, GvHD)
- Επιδείνωση νόσου
- Συγχορήγηση φαρμάκων που επάγουν το P-450
- Παχυσαρκία
- Παιδιατρικό πληθυσμό
- Rx > 30 μέρες
- Μετάβαση σε μονοθεραπεία από τους θεραπείς
- Σε υποψία μη συμμόρφωσης στη θεραπεία
- Ανεξήγητη ηπατοτοξικότητα
Cyclodextrin Toxicity

- Unmodified cyclodextrins, namely α- and β-cyclodextrins, are typically reabsorbed and concentrated in the renal tubule, interacting with and extracting cholesterol and other lipid membrane components from cellular structures.
- >300 mg/kg/d in rats produced reversible renal tubular vacuolation
- Human dose = 48 mg/kg/d (toxicity?)
Subtherapeutic Voriconazole - Omeprazole

Omeprazole = competitive inhibitor of CYP2C19

40 mg omeprazole daily
\( \frac{2}{3} \) Voriconazole AUC 141%
Posaconazole: broad spectrum of activity

- only oral formulation
- variable absorption
- variable bioavailability

Established for prophylaxis in acute leukemia and HSCT
Posaconazole

- First randomized trial demonstrating efficacy of antifungal prophylaxis in HSCT recipients with severe GVHD

- Posaconazole is effective and safe in the prevention of IFIs in HSCT recipients during the high-risk period and reduces fungal-related mortality

Παράγοντες που επηρεάζουν την απορρόφηση της ποσακοναζόλης

- Η2 ή PPI θεραπεία
- Πτωχή απορρόφηση PO
- Σοβαρή διάρροια
- GvHD (γαστρεντερικό σύστημα)
- Καταστροφή φραγμού βλεννογόνων
- Συμμόρφωση!

Υποθεραπευτικές ή μη ανιχνεύσιμες συγκέντρώσεις ποσακοναζόλης
Echinocandins

- Latest class of antifungal drugs

- First discovered in 1970s in screening programs for new antibiotics

- Cell-wall active agents:

  - Inhibition of (1, 3)-β-D glucan synthetase → cell wall glucan depletion → osmotic instability → cell lysis
Echinocandins

- Formerly known as Pneumocandins due to activity against *Pneumocystis carinii*

- Rapidly fungicidal against most *Candidae* including azole-resistant strains

- Fungistatic against most *Aspergillus* spp

- Limited or no activity against *Fusarium* spp and *Zygomycetes.*

- No activity against *Cryptococcus neoformans.*

www.cyhaema.com
Mechanism of action involves a target specific for fungus.

Inhibitor of 1,3-β-D-glucan synthase

Enzyme is present in fungal, but not mammalian, cells.

Glucan is essential to fungal cell wall integrity.

Without it, fungal cells are osmotically fragile and easily lysed.
Echinocandins

- IV administration
- Long half life
- CNS penetration: poor
- Dose: once daily
- Little infusion related toxicity
- Little or no renal and hepatic toxicity
- Drug-drug interaction limited (cyclosporin)
- Potential combination with other antifungals (AMB or azoles)
- Animal data suggest synergistic effect

Echinocandins: Caspofungin Anidulafungin Micafungin

www.cyhaema.com
Echinocandins: In vitro activity

Minimum inhibitory concentrations of the echinocandins against *Candida* species

<table>
<thead>
<tr>
<th><em>Candida</em> species</th>
<th>Anidulafungin</th>
<th>Micafungin*</th>
<th>Caspofungin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt; (µg/ml)</td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/ml)</td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt; (µg/ml)</td>
</tr>
<tr>
<td><em>albicans</em></td>
<td>0.03</td>
<td>0.03</td>
<td>0.015-0.03</td>
</tr>
<tr>
<td><em>glabrata</em></td>
<td>0.03</td>
<td>0.13</td>
<td>0.015-0.03</td>
</tr>
<tr>
<td><em>tropicalis</em></td>
<td>0.03</td>
<td>0.13</td>
<td>0.03</td>
</tr>
<tr>
<td><em>dubliniensis</em></td>
<td>0.03</td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td><em>krusei</em></td>
<td>0.06</td>
<td>0.13</td>
<td>0.06-0.13</td>
</tr>
<tr>
<td><em>lusitaniae</em></td>
<td>0.06</td>
<td>0.25</td>
<td>0.06</td>
</tr>
<tr>
<td><em>parapsilosis</em></td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><em>guilliermondii</em></td>
<td>ND</td>
<td>1</td>
<td>ND</td>
</tr>
</tbody>
</table>

MIC<sub>50</sub> or MIC<sub>90</sub> = minimum inhibitory concentration for 50% or 90%, respectively, of tested strains; ND = not done.

Caspofungin in Invasive Aspergillosis

- Well-documented disease
- Efficacy
  - High risk pts
  - Progressive infection
  - Multiple prior antifungals
- Excellent tolerability
- Clinical utility
  - No data for primary therapy
  - Combination therapy
  - Optimal dose not known


Proven/Probable IA

<table>
<thead>
<tr>
<th></th>
<th>Caspofungin (n=56)</th>
<th>Historical Controls (n=206)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/PR (%)</td>
<td>41%</td>
<td>17%</td>
</tr>
</tbody>
</table>

www.cyhaema.com
## Efficacy of Caspofungin vs Empirical L-AmB in Neutropenic Patients*

<table>
<thead>
<tr>
<th></th>
<th>Caspo (556)</th>
<th>L-AmB (539)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite Success</strong></td>
<td>33.9%</td>
<td>33.7%</td>
</tr>
<tr>
<td><strong>Success Baseline Infections</strong></td>
<td>14/27 (52%)</td>
<td>7/27 (26%)</td>
</tr>
<tr>
<td><strong>Breakthrough Infections</strong></td>
<td>29 (5.2%)</td>
<td>24 (4.5%)</td>
</tr>
<tr>
<td><strong>Etiological Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspergillus</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Candida</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Fusarium</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Zygomycetes</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Patients may have had more than one organism

Anidulafungin

Clinical data

Anidulafungin vs Fluconazole

Reboli A.C. et al.

Anidulafungin versus Fluconazole for Invasive Candidiasis.

Global success at the end of IV therapy

ECALTA® demonstrated superiority vs fluconazole:

- Significantly greater response rate in the anidulafungin group
- Difference: 15.4% (95% CI: 3.9% to 27.0%)

Mean (median) duration of IV therapy:

- fluconazole: 12.1 (11) days
- anidulafungin: 13.5 (14) days

Micafungin 100 mg/day

L-AmB 3 mg/kg/day

Randomisation (1:1)

Treatment period†

2–4 weeks‡

Post-treatment period

12 weeks

*2.0 mg/kg/day in patients weighing ≤ 40 kg
†Treatment continued until at least one week after resolution of clinical signs and symptoms and obtaining of two sequential negative blood cultures
‡Maximum 8 weeks in chronic disseminated candidiasis, Candida osteomyelitis or Candida endocarditis
Phase III study micafungin vs. L-AmB
Overall treatment success


mITT = modified intent-to-treat; PP = per-protocol set
Patients were stratified by region and APACHE II score (≤ 20 or > 20)

Treatment period†

Max 4 weeks†

Post-treatment period

6 weeks‡

*70 mg loading dose on Day 1
†8 weeks in chronic disseminated candidiasis or Candida endophthalmitis; switch to oral fluconazole permitted after 10 days in patients meeting protocol-specified criteria
‡Time from last dose day of protocol-defined antifungal therapy to final evaluation

CAS = caspofungin

**Phase III study micafungin vs. caspofungin**

**Treatment success**

- **Micafungin 100 mg/day**: 76.4%
- **Micafungin 150 mg/day**: 71.4%
- **Caspofungin 50 mg/day**: 72.3%

*Loading dose 70 mg; mITT population*
Evaluation of Caspofungin or Micafungin as Empiric Antifungal Therapy in Adult Patients With Persistent Febrile Neutropenia: A Retrospective, Observational, Sequential Cohort Analysis

David W. Kubiak, PharmD¹; Julie M. Bryar, BA¹,²; Anne M. McDonnell, PharmD¹; Jorge O. Delgado-Flores, PharmD¹; Emily Mui, PharmD¹; Lindsey R. Baden, MD¹,³,⁴; and Francisco M. Marty, MD¹,³,⁴
Conclusions

Micafungin as effective and safe as caspofungin in empirical treatment of fungal infections in patients with febrile neutropenia
Empirical micafungin treatment of IFIs in hematologic malignancies

Leukemia & Lymphoma, January 2009; 50(1): 92–100

ORIGINAL ARTICLE: CLINICAL

Efficacy and safety of micafungin, an echinocandin antifungal agent, on invasive fungal infections in patients with hematological disorders

KAZUO TAMURA¹, AKIO URABE², MINORU YOSHIDA³, AKIHISA KANAMARU⁴, YOSHIHISA KODERA⁵, SHINICHIRO OKAMOTO⁶, SHIGEFUMI MAESAKI⁷, & TOHRU MASAOKA⁸
Empirical micafungin treatment of IFIs in hematologic malignancies

Efficacy

Micafungin monotherapy: 66.1% (109/165)

Mica + Ampho B and/or azoles: 78.1% (25/32)

‘For the patients who were in grave conditions and suffered from probable to proven IFIs, combination of micafungin and azoles or amphotericin B could be considered.’
Micafungin vs fluconazole for prophylaxis of invasive fungal infections during neutropenia in hematopoietic stem cell transplantation patients

Study endpoints

- **Primary endpoint: treatment success** (absence of proven, probable, or suspected systemic fungal infection until the end of prophylaxis therapy and the absence of a proven or probable systemic fungal infection until the end of the 42-day post-treatment period)

- **Secondary endpoints included**: use of systemic antifungal agents for treatment of suspected fungal infections; frequency of proven or probable fungal infections throughout the post-treatment period; pathogen-based frequency of proven infections

Phase III study micafungin vs. fluconazole
Overall treatment success


$p = 0.03$

Micafungin vs. Fluconazole

<table>
<thead>
<tr>
<th>Treatment success (%)</th>
<th>n</th>
<th>Micafungin</th>
<th>Fluconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>80.0</td>
<td>73.5</td>
</tr>
</tbody>
</table>

n = 425 457

www.cyhaema.com
Is combination of antifungals indicated?
Randomized blinded trial of high-dose fluconazole plus placebo vs fluconazole plus AMB as therapy for candidemia in non-neutropenic patients.

The combination of fluconazole and AMB was evaluated versus monotherapy with high-dose fluconazole in 219 non-neutropenic patients. No difference in survival between the two groups; however, candidemia cleared more rapidly with combination therapy, suggesting potential use in persistent Candida infections.

48 patients with documented or possible IA

- The majority (65%) received CAS/L-AMB as salvage therapy for progressive IA despite ≥7 days of previous L-AMB monotherapy

- Overall response rate 42%

- No significant toxicity

- Factors associated with failure: documented IA, significant steroid use, duration of combination therapy < 14 days

- Response rate in patients with progressive documented IA 18%

**Conclusions:** The CAS/L-AMB combination is a promising preemptive therapy.
Salvage therapy with the combination of voriconazole and caspofungin was associated with reduced mortality, compared with voriconazole monotherapy.
Micafungin (FK463), alone or in combination with other systemic antifungal agents, for the treatment of acute invasive aspergillosis

David W. Denning a,⁎, Kieren A. Marr b, Wendi M. Lau c, David P. Facklam c, Voravit Ratanatharathorn d, Cornelia Becker e, Andrew J. Ullmann f, Nita L. Seibel g, Patricia M. Flynn h, Jo-Anne H. van Burik i, Donald N. Buell c, Thomas F. Patterson j

a Education and Research Centre, Wythenshawe Hospital and University of Manchester, Academic Department of Medicine and Surgery, Southmoor Road, Manchester M23 9LT, UK
b Fred Hutchinson Cancer Research Center, and University of Washington, Seattle, WA, USA
c Astellas Pharma US, Inc., Deerfield, IL, USA
d Karmanos Cancer Center, Wayne State University, Detroit, MI, USA
e Medizinische Klinik and Poliklinik II, Leipzig, Germany
f Johannes Gutenberg-Universitaet III, Medizinische Klinik und Poliklinik, Mainz, Germany
g Children's National Medical Center, Washington, DC, USA
h St. Jude Children's Research Hospital, Memphis, TN, USA
i University of Minnesota, Minneapolis, MN, USA
j The University of Texas Health Science Center, San Antonio, TX, USA

Accepted 7 March 2006
Available online 6 May 2006
Randomized comparison of safety and pharmacokinetics of caspofungin, liposomal amphotericin B, and the combination of both in allogeneic hematopoietic stem cell recipients.


CASLAMB combination therapy in immunocompromised aHSCT patients was as safe as monotherapy with CAS or LAMB and had similar plasma pharmacokinetics, lending support to further investigations of the combination in the management of patients with invasive opportunistic mycoses.

Toward more effective antifungal therapy: the prospects of combination therapy

Dimitrios P. Kontoyiannis and Russell E. Lewis

Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas M. D. Anderson Cancer Center, and College of Pharmacy, University of Houston, Houston, TX, USA

A

Primary Therapy Trial

Randomize

Proven or probable invasive aspergillosis

Voriconazole

Voriconazole Plus Echinocandin

B

Salvage Therapy Trial

Evidence of progression by galactomannan, PCR, or worsening CT scan?

Randomize

Voriconazole Plus Echinocandin

Lipid Amphotericin B Formulation Plus Echinocandin

No

Continue Voriconazole
Conclusions

- Patients at high risk may benefit from empirical therapy
- Patients under close surveillance may receive preemptive treatment after early prodromal clues of infection
- No clear drug of choice, decisions should be individualized
- Lipid AMB, voriconazole and echinocandins: high risk pts
- Fluconazole, itraconazole: lower risk pts
- Limited data point out to combination treatments for selected high risk pts
Future issues

- Should we move from empirical to preemptive therapy based on surrogate markers of early diagnosis of IFIs?

- Is sequence of antifungals important?

- Which combinations are more effective?