Antifungal therapy: lessons learned over the past 30 years.

J. E. Edwards, Jr., M.D.
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“A scientist over the age of 60 does more harm than good.”

Thomas Huxley
1825-1895

Nick Name: “Darwin’s Bulldog”
Acknowledgement:
This discussion is formatted after the address to the IDSA of W.E. Dismukes, 2006. However, it contains personal perspectives of lessons learned.

Basic Axiom
Nearly All of Our Therapeutic Strategies Are Based Insufficient Therapeutic Trials

Optimal therapy for cryptococcal meningitis

Optimal therapy for candidemia according to severity of illness

Length of therapy for candidemia

Optimal therapy for cocci meningitis

Optimal therapy for mucormycosis
Lesson 1:
It is extremely challenging to study antifungal drugs for regulatory agency approval or in general

*Double blinded, comparative, superiority trials: most desirable

Fungal diseases: comparatively infrequent

Multicenter trials usually necessary

Patients have multiple co-morbidities

Fungal cells are eukaryotic: toxicity high drug therapy is expected

* Viewpoints
The Facts Behind the Randomized Controlled Trials for Antifungal Agents
Yee-Chun Chen1,2, Hsiang-Chi Kung1,3, Shan-Chwen Chang1,2
Lesson 1: Continued:
Challenge of antifungal studies

Armamentarium of diagnostic tool is highly limited

Few surrogate markers exist for fungal infections

Exclusions for enrollment are extensive

Exclusions for enrollment may lead to an unrepresentative population of patients being studied

Study results may not be applicable for clinical practice
Lesson 1: Continued
Challenge of antifungal studies,
Things Change

Clinical practice may change during the prolonged study period

Microbial flora may change

Regulatory approval criteria may change

Definitions may change

Diagnostic tests and their acceptance may change
Lesson 1: Continued Challenge of antifungal studies:
There is no standardization for the choice of endpoints

- All Cause Mortality
- Fungal Related Mortality
- Break Through Fungal Infection
- Composite Endpoint
- Microbiologic Cure
- Clinical Cure
- Time of the End Point Analysis
- Surrogate Marker End Point
- Cost of Care
- Use of Alternative Strategies
- Toxicity
- Retrospective Subgroup Analysis
Is there a need for combination therapy in the first place?

Definite:
- Aspergillosis
- Mucormycosis
- Fusarum, Scedoporium, and other moulds
- Coccidiomycosis

Probable
- Cryptococcosis
- Candidiasis: Especially specific forms such as endocarditis, osteomyelitis, and endophthalmitis
Lesson 1: Continued
Combination therapy studies are particularly challenging

Combination therapy studies are highly desirable

Usually multiple pharmaceutical companies are necessary

Study design is progressively more intricate

Toxicity issues may escalate

Considerations in Clinical Trials of Combination Antifungal Therapy: John H. Powers CID 39: S228: 2004
Successfully Treated *Candida krusei* Infection of the Lumbar Spine with Combined Caspofungin/posaconazole Therapy: Schilling et al. Medical Mycology Jan 2007

Fig. 1  Sagittal-oriented MRI imaging of lumbar spine, T1 spin echo contrast enhanced, July 2005, before surgery and antifungal therapy.

Fig. 2  Sagittal-oriented MRI imaging of lumbar spine, T1 spin echo contrast enhanced, September 2005, after surgery and during caspofungin therapy.
Lesson 1: Continued Challenge of antifungal studies:
Pharmaceutical Therapy Interest Declining

Interest in antimicrobials in general diminishing

Multiple antifungals have been introduced recently

Discovery and development time prior to approval is very long

Costs of development are very high

Need for newer antifungals remains very great:
Resistance arising, increased frequency of fungal

Bad Bugs, No Drugs: www.idsociety.org
Lesson 2: On the basis of lesson 1, it is best to have collaborative efforts involved in antifungal study design strategies

Mycosis Study Group: Combination of Federal Government, industry, and academia (has been discontinued)

Consensus development of definitions of clinical infections

Consensus guidelines for therapeutic study strategies

Networks of centers containing appropriate patient populations

End Result: Meaningful guidelines for therapy in practice
Lesson 3: A therapeutic clinical trial with limitations is better than no therapeutic trial at all. Example: candidemia trials
Table 1. Details of clinical trials of treatments for candidemia.

<table>
<thead>
<tr>
<th>Agent class, study</th>
<th>Study design</th>
<th>Study population (percentage of subjects)</th>
<th>Treatment regimen (daily dose)</th>
<th>Efficacy rate ( \text{Success, } % )/ ( \text{F} )</th>
<th>Mortality rate, %</th>
<th>Persistent candidemia Rate, %/ ( \text{F} )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azoles</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Rex et al. [34]</td>
<td>Randomized, NB</td>
<td>Nonneutropenic patients</td>
<td>Flu (400 mg)</td>
<td>67/ .22</td>
<td>33</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AmB (0.5–0.6 mg/kg)</td>
<td>79</td>
<td>40</td>
<td>12</td>
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<tr>
<td>Phillips et al. [35]</td>
<td>Randomized, NB</td>
<td>Nonneutropenic patients</td>
<td>Flu (400 mg)</td>
<td>57/ .66</td>
<td>38</td>
<td>17/ .18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AmB (0.8 mg/kg)</td>
<td>62</td>
<td>34</td>
<td>7</td>
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<tr>
<td>Rex et al. [36]</td>
<td>Randomized, DB</td>
<td>Nonneutropenic patients</td>
<td>Flu (800 mg)</td>
<td>66/ .043</td>
<td>39</td>
<td>15/ .02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Flu (800 mg) plus AmB (0.7 mg/kg)</td>
<td>69</td>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td>Kullberg et al. [37]</td>
<td>Randomized, NB</td>
<td>Nonneutropenic patients</td>
<td>Vor (6 mg/kg)</td>
<td>65/ .25</td>
<td>36</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AmB (0.7–1.0 mg/kg) followed by Flu (400 mg)</td>
<td>71</td>
<td>42</td>
<td>NA</td>
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<tr>
<td><strong>Echinocandins</strong></td>
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<tr>
<td>Mora-Duarte et al. [38]</td>
<td>Randomized, DB</td>
<td>Nonneutropenic patients (89) and patients with candidemia (81)</td>
<td>Casp (50 mg)</td>
<td>73/ .06</td>
<td>34</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AmB (0.6–1.0 mg/kg)</td>
<td>62</td>
<td>30</td>
<td>9</td>
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<tr>
<td>Reboll et al. (unpublished data)</td>
<td>Randomized, DB</td>
<td>Nonneutropenic patients (97) and patients with candidemia (89)</td>
<td>Anid (100 mg)</td>
<td>76/ .01</td>
<td>23</td>
<td>6/.055</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Flu (400 mg)</td>
<td>60</td>
<td>31</td>
<td>14</td>
</tr>
</tbody>
</table>

**NOTE.** AmB, amphotericin B; Anid, anidulafungin; Casp, caspofungin; Flu, fluconazole; NA, not available; NB, nonblinded; Vor, voriconazole.
* Data are from the evaluable population for azole trials and from the modified intent-to-treat population for the echinocandins trials.
Lesson 4: It is extremely important to choose the right dose of antifungal for Phase II and Phase III trials.
Synergism vs Cryptococcal Meningitis

51 Courses, 10wks AMB Alone vs. 6 Weeks of Combo

Combo
5-FC: 150mg/kg/d +
Amb: 0.3 mg/kg/d

AMB: 0.4 mg/kg/d

Success %

Combo
Amb

67%
41%
Lesson 4: Continued, Complexities of selection of appropriate dose selection

200 mg fluconazole vs 0.4 mg/kg amphotericin B in cryptococcal meningitis in AIDS patients

Fluconazole: 34% Survival
Amphotericin B: 40% Survival

MSG Study, NEJM 326:83-9, 1992
Lesson 5: There is a need for more effective therapy for numerous fungal infections

Aspergillus mortality: Approximately 50%

Candidemia mortality: Approximately 40%

Mucormycosis mortality: Approximately 50%

Cocci Meningitis: Essentially non-curable, Indefinite suppression is standard
Lesson 6: Formulations of amphotericin continue to be highly useful

- Amphotericin deoxycholate
- Lipid formulation (Ambisome)
- Amphotericin Lipid Complex (ABLC)
Lesson 7: Azoles have been powerful additions to the antifungal armamentarium

- Fluconazole
- Itraconazole
- Voriconazole
- Posaconazole
Voriconazole Interactions

- Warfarin
- Cyclosporin
- Tacrolimus
- Sulfonurreas
- Statins
- Benzodiazepines
- Vinca Alkaloids
- Sirolimus
- Rifabutin
- Rifampicin
- Terfenadine
Lesson 9: Echinocandins have been powerful additions to the antifungal armamentarium and have little associated toxicity

Caspofungin

Micofungin

Anidulofungin
Lesson 10: Despite all the challenges, newer antifungals and newer treatment strategies can be developed
Deferasirox protects diabetic ketoacidotic mice infected intranasally with *R. oryzae*. Survival of mice infected with 10⁷ spores of *R. oryzae* 99-680 and 24 hours later treated with placebo (hydroxypropylcellulose carrier, n = 13), deferasirox (10 mg/kg, twice daily, n = 13), or deferoxamine (50 mg/kg, n = 6). *P < 0.009 compared with placebo- or deferoxamine-treated mice; **P = 0.047 compared with placebo-treated mice.