Candida auris: Antifungal Clinical Trial Design Considerations

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Disclosures - Research funding and/or personal honoraria for consulting or speaking from:

- Pfizer
- Merck
- Astellas
- Cidara
- Scynexis
- F2G
- Amplyx
- Gilead
- Therapeutics, Inc
- Viracor
- Octapharma
- Biotoscana
- Stendhal
- Mayne
- Takeda
- RealTime labs
In the beginning there was Amphotericin B (6-page PI)

INDICATIONS AND USAGE
FUNGIZONE Intravenous (Amphotericin B for Injection, USP) should be administered primarily to patients with progressive, potentially life-threatening fungal infections. This potent drug should not be used to treat noninvasive fungal infections, such as oral thrush, vaginal candidiasis, and esophageal candidiasis in patients with normal neutrophil counts.
FUNGIZONE Intravenous is specifically intended to treat potentially life-threatening fungal infections: aspergillosis, cryptococcosis (torulosis), North American blastomycosis, systemic candidiasis, coccidioido-mycosis, histoplasmosis, zygomycosis including mucormycosis due to susceptible species of the genera Absidia, Mucor, and Rhizopus, and infections due to related susceptible species of Conidiobolus and Basidiobolus, and sporotrichosis.
Amphotericin B may be useful in the treatment of American mucocutaneous leishmaniasis, but it is not the drug of choice as primary therapy.
Brief history of antifungals

How do we use antifungals in *Candida* (mostly)?
We have a pretty good system.
Anatomy of a Candida trial
Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium


CID 2019
Common pitfalls- Disease definitions updated

### Table 1. Criteria for Proven Invasive Fungal Disease

<table>
<thead>
<tr>
<th>Fungus</th>
<th>Microscopic Analysis: Sterile Material</th>
<th>Culture: Sterile Material</th>
<th>Blood</th>
<th>Serology</th>
<th>Tissue Nucleic Acid Diagnosis</th>
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<tbody>
<tr>
<td><strong>Molds</strong></td>
<td>Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage</td>
<td>Recovery of a hyaline or pigmented mold by culture of a specimen obtained by a sterile procedure from a normally sterile site consistent with an infectious disease process, excluding BAL fluid, a parasternal or mastoid sinus cavity specimen, and urine</td>
<td>Blood culture that yields a mold (e.g., Fusarium species) in the context of a compatible infectious disease process</td>
<td>Not applicable</td>
<td>Amplification of fungal DNA by PCR combined with DNA sequencing when molds are seen in formalin-fixed paraffin-embedded tissue</td>
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<tr>
<td><strong>Yeast</strong></td>
<td>Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy in which yeast cells, for example, Cryptococcus species indicating encapsulated budding yeasts or Candida species showing pseudohyphae or true hyphae</td>
<td>Recovery of a yeast by culture of a sample obtained by a sterile procedure (including a fresh sample placed &lt;24 hours ago) from a normally sterile site showing a clinical or radiological abnormality consistent with an infectious disease process</td>
<td>Blood culture that yields yeast (e.g., Cryptococcus or Candida species) or yeast-like fungi (e.g., Trichosporon species)</td>
<td>Cryptococcal antigen in cerebrospinal fluid or blood confirms cryptococcosis</td>
<td>Amplification of fungal DNA by PCR combined with DNA sequencing when yeasts are seen in formalin-fixed paraffin-embedded tissue</td>
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<tr>
<td><strong>Pneumocystis</strong></td>
<td>Detection of the organism microscopically in tissue, BAL fluid, or exudates using direct or immunofluorescence staining</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>Endemic mycoses</strong></td>
<td>Histopathology or direct microscopy of specimens obtained from an affected site showing the distinctive form of the fungus</td>
<td>Recovery of the fungus from specimens from an affected site</td>
<td>Blood culture that yields the fungus</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
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</table>

### Table 3. Other Probable Invasive Diseases

<table>
<thead>
<tr>
<th>Candidiasis</th>
<th>Candida albicans</th>
<th>Candida tropicalis</th>
<th>Candida glabrata</th>
<th>Candida krusei</th>
</tr>
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<tbody>
<tr>
<td><strong>Clinical features</strong></td>
<td>At least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks:</td>
<td>Small, target-like abscesses in liver or spleen (bull’s-eye lesions) in the brain, or meningeval enhancement</td>
<td>Progressive retinal exudates or vitreal opacities on ophtalmologic examination</td>
<td>Positive Tzanck smear</td>
</tr>
<tr>
<td><strong>Mycological evidence</strong></td>
<td>D-glucose (Fungitell) ≤80 ng/mL (48 mg/L) detected in at least 2 consecutive serum samples provided that other etiologies have been excluded</td>
<td>Positive Tzanck smear</td>
<td></td>
<td></td>
</tr>
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</table>
Common pitfalls- Outcome adjudication guidelines are outdated

Defining Responses to Therapy and Study Outcomes in Clinical Trials of Invasive Fungal Diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer Consensus Criteria

Brahm H. Segal,1 Raoul Herbrecht,2 David A. Stevens,3,4 Luis Ostrosky-Zeichner,4 Jack Sobel,4 Claudio Viscoli,2,5 Thomas J. Walsh,2 Johan Maertens,6 Thomas F. Patterson,7 John R. Perfect,2 Bertrand Dupont,7 John R. Wingard,4 Thierry Calandra,2 Carol A. Kauffman,8 John R. Graybill,9 Lindsey R. Baden,9 Peter G. Pappas,10 John E. Bennett,11 Dimitrios P. Kontoyiannis,12 Catherine Cordonnier,9 Maria Anna Viviani,13 Jacques Bille,14 Nikolaos G. Almyroudis,15 L. Joseph Wheat,16 Wolfgang Greninger,16 Eric J. Bové,16 Steven M. Holland,11 Bart-Jan Kullberg,18 William E. Dismukes,11 and Ben E. De Pauw11

Table 1. General criteria for global responses to antifungal therapy.

<table>
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<tr>
<th>Outcome, response</th>
<th>Criteria</th>
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<td>Success</td>
<td>Complete response: Survival within the prespecified period of observation, resolution of all attributable symptoms and signs of disease and radiological abnormalities, and mycological evidence of eradication of disease</td>
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<tr>
<td></td>
<td>Partial response: Survival within the prespecified period of observation, improvement in attributable symptoms and signs of disease and radiological abnormalities, and evidence of clearance of cultures or reduction of fungal burden, as assessed by a quantitative and validated laboratory marker</td>
</tr>
<tr>
<td>Failure</td>
<td>Stable response: Survival within the prespecified period of observation and minor or no improvement in fungal disease, but no evidence of progression, as determined on the basis of a composite of clinical, radiological, and mycological criteria</td>
</tr>
<tr>
<td></td>
<td>Progression of fungal disease: Evidence of progressive fungal disease based on a composite of clinical, radiological, and mycological criteria</td>
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<tr>
<td></td>
<td>Death: Death during the prespecified period of evaluation, regardless of attribution</td>
</tr>
</tbody>
</table>
Common pitfalls- Signs and symptoms

• Not always present, even in the setting of proven disease
• When present can be multifactorial given the complexity of patients
  • Underlying disease
  • Other interventions
  • Other infections
• May or may not correlate with clinical improvement
Common pitfalls- Microbiology and pathology

- Slow growth, laborious ID and susceptibility
  - 3-5 days for *Candida*
  - 1 to 2 weeks for moulds
  - **Automatically narrows enrollment windows to critical times**
  - Blood cultures have poor sensitivity but very high specificity
  - Molecular ID not mainstream yet
  - Not always feasible to re-sample invasive sites

- Biomarkers and serologies
  - Hit or miss send outs, narrow enrollment windows
  - Generally accepted for enrollment
  - Despite ample data, not accepted as surrogates for outcomes
Common pitfalls - Radiology

• High sensitivity
• Low specificity
• Long term changes with very slow or no resolution
• Does not generally correlate with clinical improvement
• Radiation doses
Fifty of the 88 cases died, representing a crude mortality rate of 57%. Seventeen controls died for an overall mortality rate of 19%. The attributable mortality rate was 38% with a 95% confidence interval of 26% to 49%. Thirty-seven cases died whose matched controls lived (Table 2), and only four cases that lived had matched controls that died. The risk ratio was 2.94 with a 95% confidence interval of 1.95 to 4.43. Additionally, 23 (46%) of the deaths occurred in the first week after candidemia was detected. Nineteen (38%) of the 50 cases that died had an autopsy performed. In 14 (74%), *Candida* species infection was reported as the cause of death.

The median length of stay for the cases was 48 days, while the median for the controls was 40 days. This difference was statistically significant (*P* = .006). A further analysis of the length of stay for the 34 matched pairs that survived showed a median of 70 days for cases and 40 days as a median for length of stay in the control group (*P* < .0001).
Don’t bring up problems without bringing solutions

• Disease definitions need a nimble/dynamic process
• Need new panel for response/outcome definitions
  • De-emphasize signs and symptoms
  • Biomarkers as surrogate endpoints
  • De-emphasize radiology in outcomes
  • De-emphasize crude mortality and work toward attributable mortality
  • No composite endpoints
• Expand enrollment/prior antifungal windows until micro technology and biomarker availability catches up
• LPAD
• Small open label trials in high incidence areas (US and EX-US) with 20-30 well studied cases with contemporary controls along with strong preclinical and safety data.
The space we should be working on now
How should we be using antifungals? (*Candida*)

Next gen clinical trials

Molecular microbiology

POC Biomarkers

Strategy trials
Prophylaxis vs. pre-emptive vs. empirical vs. full blown

Personalized medicine
Uncommon pathogens
Resistant pathogens
Pharmacogenomics
Genetic risk
Clinical mycology today: A synopsis of the mycoses study group education and research consortium (MSGERC) second biennial meeting, September 27–30, 2018, Big Sky, Montana, a proposed global research agenda

Peter G. Pappas\textsuperscript{1,*}, David R. Boulware\textsuperscript{2}, Dimitrios P. Kontoyiannis\textsuperscript{3}, Marisa H. Miceli\textsuperscript{4}, Luis Ostrosky-Zeichner\textsuperscript{5}, Andrej Spec\textsuperscript{6}, George R. Thompson, III\textsuperscript{7}, Sharon Chen\textsuperscript{8}, John R. Perfect\textsuperscript{9} and MSGERC investigators

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THANK YOU

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