Candida auris: Antifungal Clinical Trial Design Considerations

Luis Ostrosky-Zeichner, MD, FACP, FIDSA, FECMM

Professor and Vice Chair of Medicine

McGovern Medical School

President-elect

Mycoses Study Group

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- Pfizer
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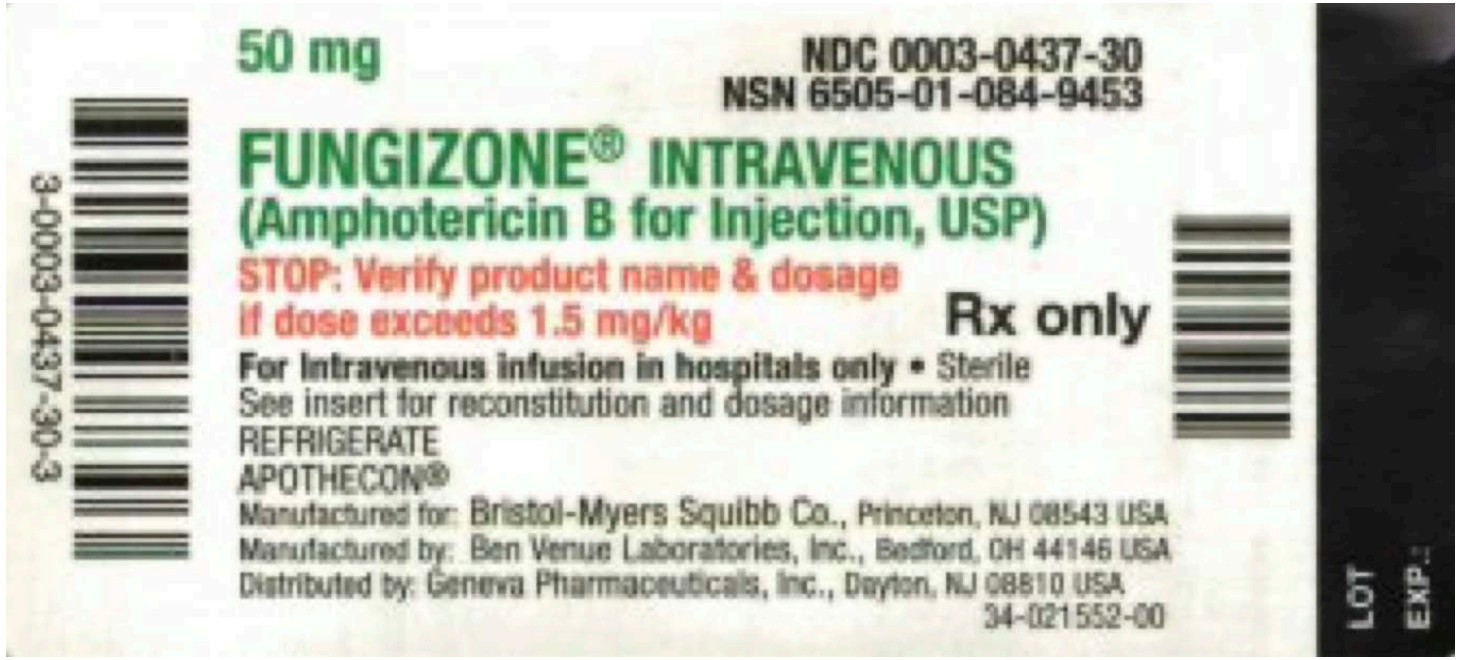
- Octapharma
- Biotoscana
- Stendhal
- Mayne
- Takeda
- RealTime labs

In the beginning there was Amphotericin B (*6-page PI*)



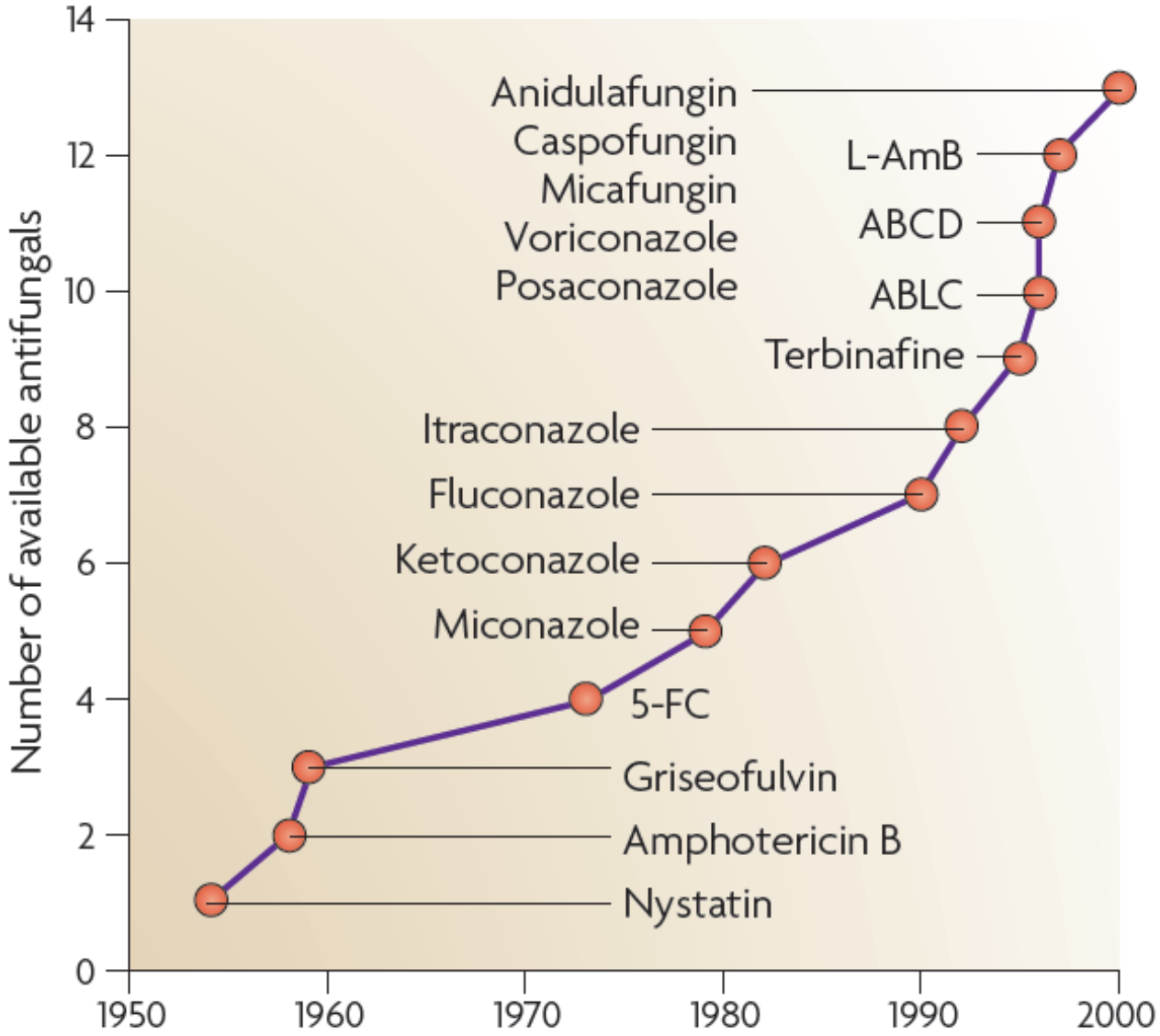
INDICATIONS AND USAGE

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.

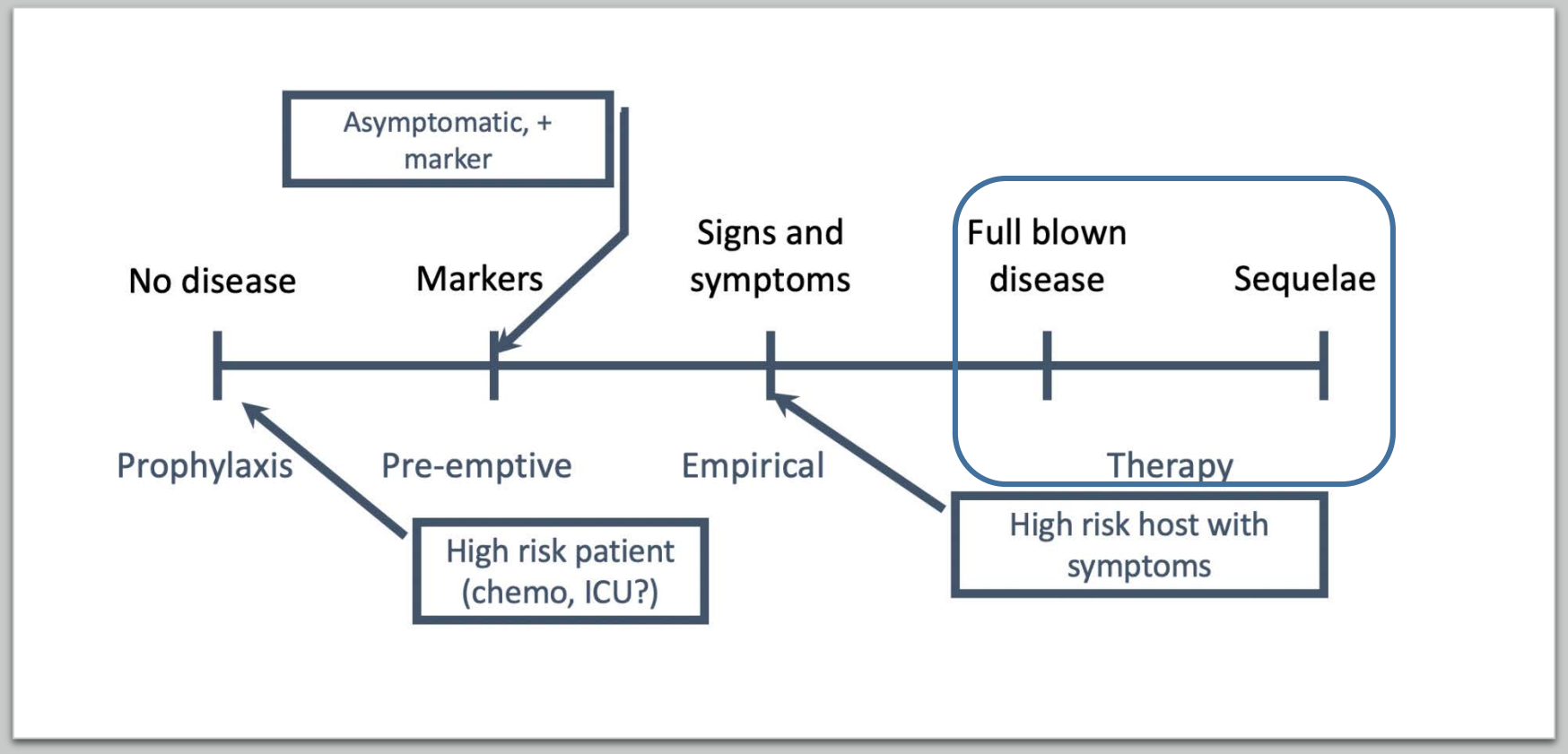
FUNGIZONE Intravenous is specifically intended to treat potentially life-threatening fungal infections: aspergillosis, cryptococcosis (torulosis), North American blastomycosis, systemic candidiasis, coccidioido-mycosis, histoplasmosis, zygomycosis including mucormycosis due to susceptible species of 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



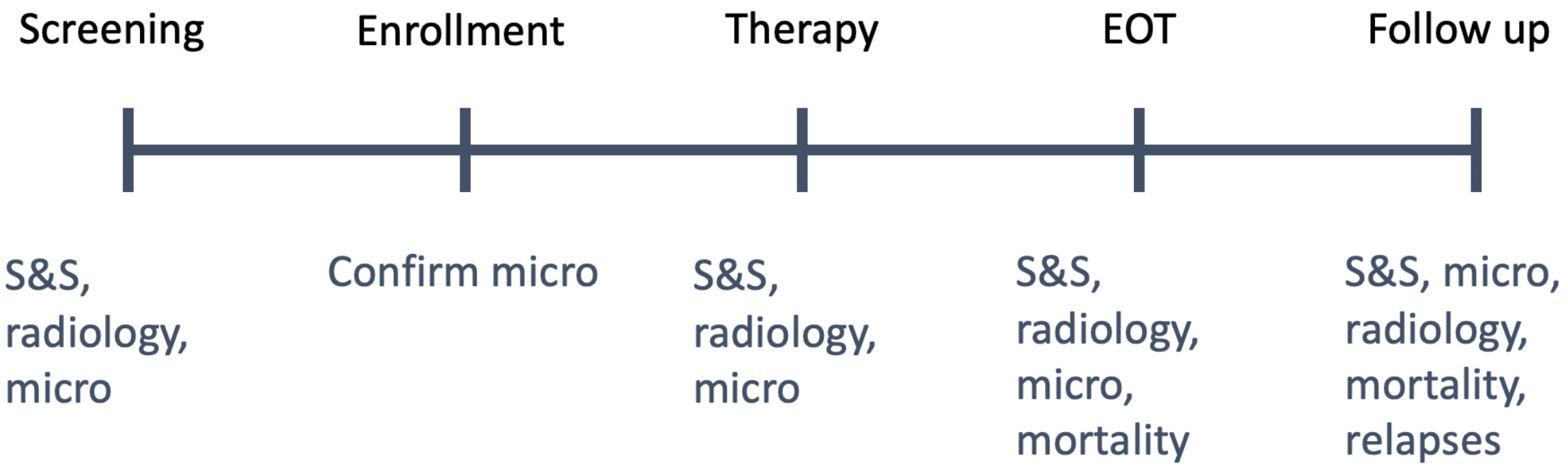
Ostrosky-Zeichner, et al. Nature Reviews Drug Discovery 2010.



How do we use antifungals in *Candida* (mostly)?

Reference (Patient No.; Enrollment Dates)	Drugs and Maintenance Regimens	Design	Inclusion	Host or Disease Factor Exclusion	Treatment Duration	Modified Intent-to-Treat Population	Primary Outcome	Secondary Outcome
Rex et al, 1994 [46] (237; 1989–1993)	Fluconazole 400 mg/d vs amphotericin B 0.5–0.6 mg/kg/d	Randomized, double blinded	Candidemia and fever or hypotension	Neutropenia, hematologic malignancy, HIV, transplant, pregnancy	≥14 d after last positive blood culture	Receipt of ≥1 d of antifungal drug	Clinical and microbiologic success at EOT	All-cause death at EOT
Mora-Duarte et al, 2002 [48] (239; 1997–2001)	Caspofungin 50 mg/d vs amphotericin B 0.6–0.7 mg/kg/d (0.7–1.0 for neutropenic patients)	Randomized, double blinded	Candidemia or invasive candidiasis	Endocarditis, osteomyelitis, meningitis	10 d intravenous and all therapy >14 d after last positive culture	Receipt of ≥1 d of antifungal drug	Clinical and microbiologic success and absence of toxicity-required change in therapy at EOT	All-cause death at EOT
Rex et al 2003 [45] (236; 1995–1999)	Fluconazole 800 mg/d vs amphotericin B 0.6–0.7 mg/kg/d and fluconazole 800 mg/d	Randomized, double blinded	Candidemia and fever or hypotension	Neutropenia, pregnancy, *Candida krusei*	≥14 d after last positive blood culture, amphotericin B component 5–8 d	Receipt of ≥1 d of antifungal drug	Clinical and microbiologic success at EOT	All-cause death at EOT
Kullberg et al 2005 [47] (422; 1998–2003)	Voriconazole 3 mg/kg every 12 h for 3 d, then possible switch to 200 mg oral twice daily vs amphotericin B 0.7–1.0 mg/kg/d followed by fluconazole 400 mg/d	Randomized, double blinded	Candidemia and fever or hypotension	Neutropenia, AIDS, chronic granulomatous disease, aplastic anemia, hepatic and renal dysfunction, pregnancy	≥14 d after last positive blood culture	Receipt of ≥1 d of antifungal drug	Clinical and microbiologic success at 12 wk and EOT	All-cause death at 30 d
Reboli et al 2007 [43] (245; 2003–2004)	Anidulafungin 100 mg/d vs fluconazole 400 mg/d	Randomized, double blinded	Candidemia or invasive candidiasis	Pregnancy	≥14 d after last positive blood culture	Receipt of ≥1 d of antifungal drug and document fungal infection	Clinical and microbiologic success at EOT	All-cause death within 30 d
Kuse et al 2007 [41] (264; 2003–2004)	Micafungin 100 mg/d vs liposomal amphotericin B 3 mg/kg/d	Randomized, double blinded	Candidemia or invasive candidiasis	Hepatic dysfunction	>14 d	Receipt of ≥1 d of antifungal drug	Clinical and microbiologic success at EOT	All-cause death within 30 d
Pappas et al 2007 [49] (595; 2004–2006)	Micafungin 100 or 150 mg/d for ≥10 d then possible switch to fluconazole 400 mg/d vs caspofungin 50 mg/d for ≥10 d then possible switch to fluconazole 400 mg/d	Randomized, double blinded	Candidemia or invasive candidiasis	Hepatic dysfunction, pregnancy, cyclosporin use, endocarditis, osteomyelitis, meningitis	≥14 d after last positive blood culture	Receipt of ≥1 d of antifungal drug and documentation of fungal infection	Clinical and microbiologic success at EOT	All-cause death within 30 d

We have a pretty good system



Anatomy of a *Candida* trial

Common pitfalls- Disease definitions updated

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

J. Peter Donnelly,[1] Sharon C. Chen,[2] Carol A. Kauffman,[3] William J. Steinbach,[4] John W. Baddley,[5] Paul E. Verweij,[6] Cornelius J. Clancy,[7] John R. Wingard,[8] Shawn R. Lockhart,[9] Andreas H. Groll,[10] Tania C. Sorrell,[11] Matteo Bassetti,[12] Hamdi Akan,[13] Barbara D. Alexander,[14] David Andes,[15] Elie Azoulay,[16] Ralf Bialek,[17] Robert W. Bradsher Jr,[18] Stephane Bretagne,[19] Thierry Calandra,[20] Angela M. Caliendo,[21] Elio Castagnola,[22] Mario Cruciani,[23] Manuel Cuenca-Estrella,[24] Catherine F. Decker,[25] Sujal R. Desai,[26] Brian Fisher,[27] Thomas Harrison,[28] Claus Peter Heussel,[29] Henrik E. Jensen,[30] Christopher C. Kibbler,[31] Dimitrios P. Kontoyiannis,[32] Bart-Jan Kullberg,[33] Katrien Lagrou,[34] Frédéric Lamoth,[35] Thomas Lehrnbecher,[36] Jurgen Loeffler,[37] Olivier Lortholary,[38] Johan Maertens,[39] Oscar Marchetti,[20] Kieren A. Marr,[40] Henry Masur,[41] Jacques F. Meis,[42] C. Orla Morrisey,[43] Marcio Nucci,[44] Luis Ostrosky-Zeichner,[45] Livio Pagano,[46] Thomas F. Patterson,[47] John R. Perfect,[14] Zdenek Racil,[48] Emmanuel Roilides,[49] Marcus Ruhnke,[50] Cornelia Schaefer Prokop,[51] Shmuel Shoham,[40] Monica A. Slavin,[52] David A. Stevens,[53] George R. Thompson III,[54] Jose A. Vazquez,[55] Claudio Viscoli,[56] Thomas J. Walsh,[57] Adilia Warris,[58] L. Joseph Wheat,[59] P. Lewis White,[60] Theoklis E. Zaoutis,[61] and Peter G. Pappas[5]

CID 2019

Common pitfalls- Disease definitions updated

Table 1. Criteria for Proven Invasive Fungal Disease

Fungus	Microscopic Analysis: Sterile Material	Culture: Sterile Material	Blood	Serology	Tissue Nucleic Acid Diagnosis
Molds[a]	Histopathologic, cytopathologic, or direct microscopic examination[b] 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	Recovery of a hyaline or pigmented mold by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding BAL fluid, a paranasal or mastoid sinus cavity specimen, and urine	Blood culture that yields a mold[c] (eg, *Fusarium* species) in the context of a compatible infectious disease process	Not applicable	Amplification of fungal DNA by PCR combined with DNA sequencing when molds are seen in formalin-fixed paraffin-embedded tissue
Yeasts[a]	Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes) showing yeast cells, for example, *Cryptococcus* species indicating encapsulated budding yeasts or *Candida* species showing pseudohyphae or true hyphae[d]	Recovery of a yeast by culture of a sample obtained by a sterile procedure (including a freshly placed [<24 hours ago] drain) from a normally sterile site showing a clinical or radiological abnormality consistent with an infectious disease process	Blood culture that yields yeast (eg, *Cryptococcus* or *Candida* species) or yeast-like fungi (eg, *Trichosporon* species)	Cryptococcal antigen in cerebrospinal fluid or blood confirms cryptococcosis	Amplification of fungal DNA by PCR combined with DNA sequencing when yeasts are seen in formalin-fixed paraffin-embedded tissue
Pneumocystis	Detection of the organism microscopically in tissue, BAL fluid, expectorated sputum using conventional or immunofluorescence staining	Not applicable	Not applicable	Not applicable	Not applicable
Endemic mycoses	Histopathology or direct microscopy of specimens obtained from an affected site showing the distinctive form of the fungus	Recovery by culture of the fungus from specimens from an affected site	Blood culture that yields the fungus	Not applicable	Not applicable

Table 3. Other Probable Invasive Diseases

Candidiasis
Host factors
Recent history of neutropenia <0.5 × 10^9 neutrophils/L (<500 neutrophils/mm^3 for >10 days) temporally related to the onset of invasive fungal disease
Hematologic malignancy
Receipt of an allogeneic stem cell transplant
Solid organ transplant recipient
Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a therapeutic dose of ≥0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 days
Treatment with other recognized T-cell immunosuppressants, such as calcineurin inhibitors, tumor necrosis factor-a blockers, lymphocyte-specific monoclonal antibodies, immunosuppressive nucleoside analogues during the past 90 days
Inherited severe immunodeficiency (such as chronic granulomatous disease, STAT 3 deficiency, CARD9 deficiency, STAT-1 gain of function, or severe combined immunodeficiency)
Acute graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids
Clinical features
At least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks:
Small, target-like abscesses in liver or spleen (bull's-eye lesions) or in the brain, or, meningeal enhancement
Progressive retinal exudates or vitreal opacities on ophthalmologic examination
Mycological evidence
ß-D-glucan (Fungitell) ≥80 ng/L (pg/mL) detected in at least 2 consecutive serum samples provided that other etiologies have been excluded
Positive T2Candida[a]

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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,[22] David A. Stevens,[9,10] Luis Ostrosky-Zeichner,[4] Jack Sobel,[7] Claudio Viscoli,[28,29] Thomas J. Walsh,[12] Johan Maertens,[30] Thomas F. Patterson,[5] John R. Perfect,[2] Bertrand Dupont,[23] John R. Wingard,[8] Thierry Calandra,[21] Carol A. Kauffman,[6] John R. Graybill,[5] Lindsey R. Baden,[15] Peter G. Pappas,[11] John E. Bennett,[13] Dimitrios P. Kontoyiannis,[3] Catherine Cordonnier,[24] Maria Anna Viviani,[27] Jacques Bille,[20] Nikolaos G. Almyroudis,[1] L. Joseph Wheat,[14] Wolfgang Graninger,[25,26] Eric J. Bow,[16] Steven M. Holland,[13] Bart-Jan Kullberg,[18,19] William E. Dismukes,[11] and Ben E. De Pauw[17]

CID 2008:47

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

Outcome, response	Criteria
Success	
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
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
Failure	
Stable response[a]	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
Progression of fungal disease	Evidence of progressive fungal disease based on a composite of clinical, radiological, and mycological criteria
Death	Death during the prespecified period of evaluation, regardless of attribution

Common pitfalls- Signs and symptoms

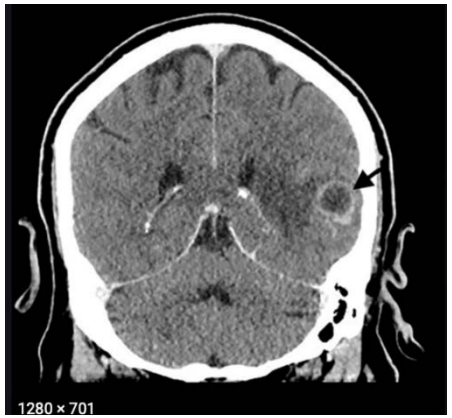
- Not always present, even in the setting of of proven disease
- When present can be multifactorial given the complexity of patients
  - Underlying disease
  - Other interventions
  - Other infections
- May or may not correlate with clinical improvement

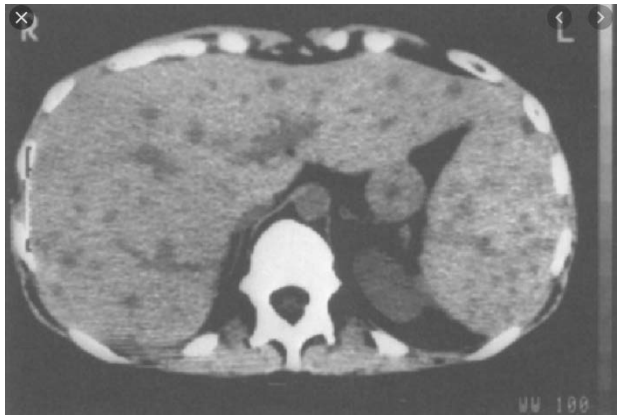
Common pitfalls- Microbiology and pathology

- 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





Common pitfalls- Mortality as an endpoint

Hospital-Acquired Candidemia

The Attributable Mortality and Excess Length of Stay

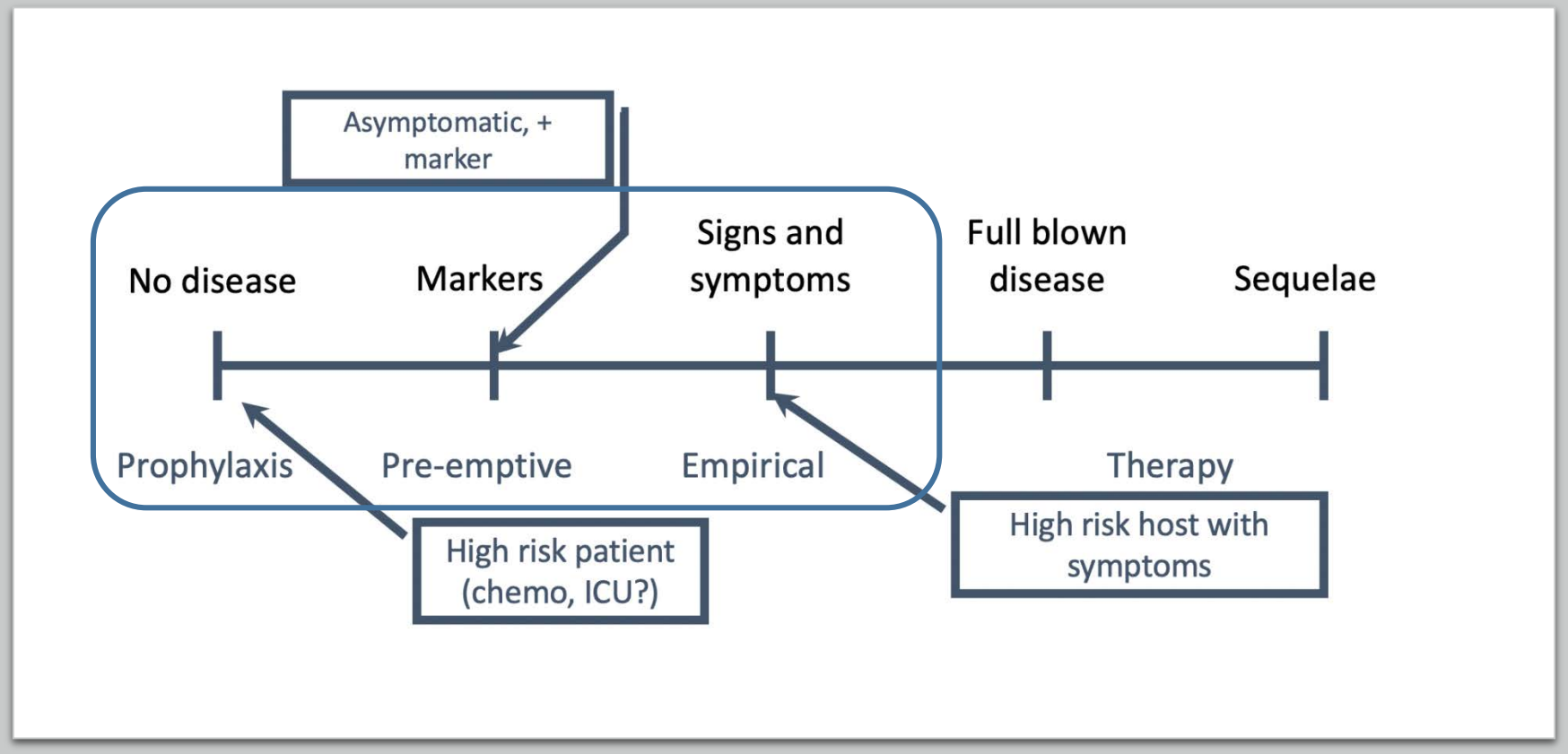
Sergio B. Wey, MD; Motomi Mori, MS; Michael A. Pfaller, MD;
Robert F. Woolson, PhD; Richard P. Wenzel, MD, MSc

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 ($P < .0001$).

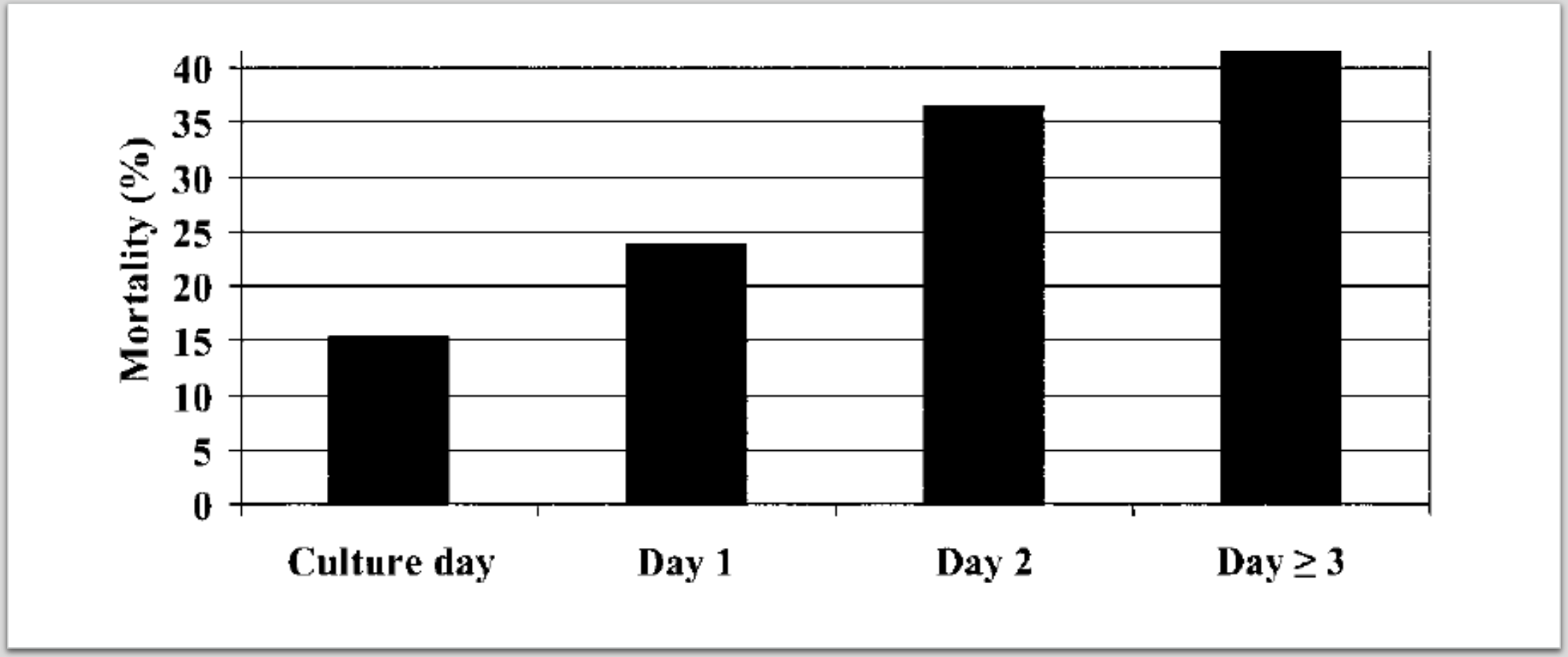
Don’t bring up problems without bringing solutions

- 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*)



Garey, et al. CID 2006.

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

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

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Advance Access Publication Date: 14 May 2020
Review Article

Review Article

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

[1]University of Alabama at Birmingham Medical Center, Department of Medicine, Division of Infectious, Diseases, Birmingham, Alabama, USA, [2]University of Minnesota, Department of Medicine, Division of Infectious Diseases & International Medicine, Minneapolis, Minnesota, USA, [3]University of Texas at Houston, MD Anderson Cancer Center, Houston, Texas, USA, [4]University of Michigan, Department of Medicine, Division of Infectious Diseases, Ann Arbor, Michigan, USA, [5]The University of Texas McGovern Medical School. Division of Infectious Diseases, Houston, Texas, USA, [6]Washington University, Department of Medicine, Division of Infectious Diseases, St Louis, Missouri, USA, [7]University of California at Davis, Department of Internal Medicine, Division of Infectious Diseases and Department of Medical Microbiology & Immunology, Davis, California, USA, [8]University of Sydney, Westmead Hospital, Sydney, Australia and [9]Duke University Medical Center, Department of Medicine, Division of Infectious Diseases, Durham, North Carolina, USA

Homework

THANK YOU

Luis.Ostrosky-Zeichner@uth.tmc.edu

@DrLuisO