19th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Helsinki
16–19 May 2009

Educational Workshop

EW11: Definitions and treatment outcome criteria in invasive fungal infections: an interactive workshop to reach a broader consensus

arranged with EORTC/ICHS

(European Organization for Research and Treatment of Cancer / Immunocompromised Host Society)

Convenors: **Claudio Viscoli (Genoa, IT)**
Johan Maertens (Leuven, BE)

Faculty: **Peter Donnelly (Nijmegen, NL)**
Raoul Herbrecht (Strasbourg, FR)
Brahm Segal (Buffalo, US)

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

UMC St Radboud

Definitions of invasive fungal infections

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UMC St Radboud

EORTC-IFICG & NIAID-MSG

Defining Opportunistic Invasive Fungal Infections in Immunocompromised Patients with Cancer and Hematopoietic Stem Cell Transplants: An International Consensus

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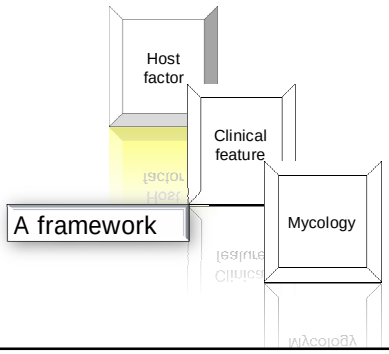
[1]European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group, Brussels; and [2]National Institute of Allergy and Infectious Diseases Mycoses Study Group, National Institutes of Health, Bethesda, Maryland

Clinical Infectious Diseases 2002; 34:7–14

2002

UMC St Radboud

Defining invasive fungal disease



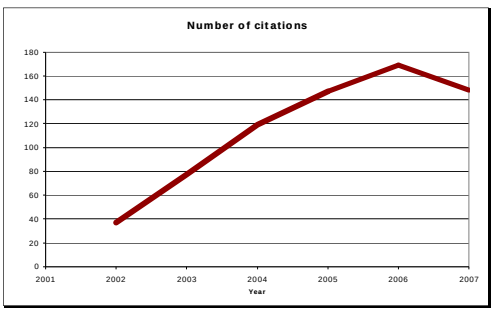
Strengths

Who uses the EORTC/MSG definitions?

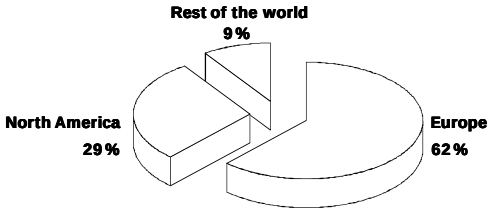
Clinical trials

Diagnostic tests

Citations of the original definitions

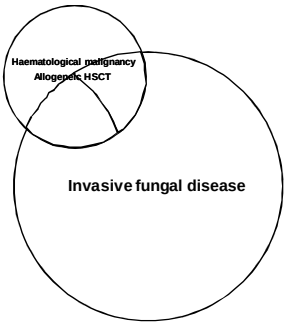


Citations of the original definitions



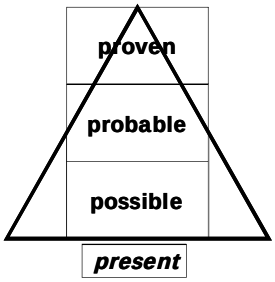
Limitations

Patients at risk of developing IFD

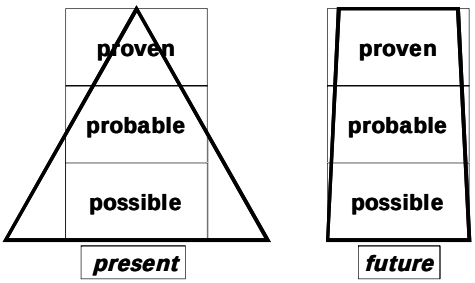


Donnelly – Definitions of invasive fungal infections

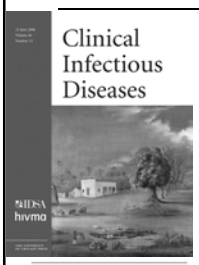
Goal of adapting definitions



Goal of adapting definitions



… finally…



MAJOR ARTICLE

Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group

Dee De Pauw,[1] Thomas J. Walsh,[2] J. Peter Donnelly,[3] David A. Stevens, John E. Edwards, Thierry Calandra, Peter G. Pappas, Johan Maertens, Olivier Lortholary, Carol A. Kauffman, David W. Denning, Thomas F. Patterson, Georg Maschmeyer, Jacques Bille, William E. Dismukes, Raoul Herbrecht, William W. Hope, Christopher C. Kibbler, Bart Jan Kullberg, Kieren A. Marr, Patricia Muñoz, Frank C. Odds, John R. Perfect, Angela Restrepo, Morton Ruhnke, Brahm H. Segal, Jack D. Sobel, Tania C. Sorrell, Claudio Viscoli, John R. Wingard, Theoklis Zaoutis, and John E. Bennett[4]

Background. Invasive fungal diseases are important causes of morbidity and mortality. Clarity and uniformity in defining these infections are important factors in improving the quality of clinical studies. A standard set of definitions strengthens the consistency and reproducibility of such studies.

Methods. After the introduction of the original European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group definitions, advances in diagnostic technology and the recognition of areas in need of improvement led to a revision of this document. The revision process started with a meeting of participants in 2003, to decide on the process and to draft the proposal. This was followed by several rounds of consultation until a final draft was approved in 2005. This was made available for 6 months to allow public comment, and then the manuscript was prepared and approved.

Results. The revised definitions retain the original classifications of "proven," "probable," and "possible" invasive fungal disease, but the definition of "probable" has been expanded, whereas the scope of the category "possible" has been diminished. The category of proven invasive fungal disease can apply to any patient, regardless of whether the patient is immunocompromised, whereas the probable and possible categories are proposed for immunocompromised patients only.

Conclusions. These revised definitions of invasive fungal disease are intended to advance clinical and epidemiological research and may serve as a useful model for defining other infections in high-risk patients.

Received 11 September 2007; accepted 26 February 2008; electronically published 5 May 2008.

[1] D.d.P. and T.J.W. served as cochairs and J.P.D. served as secretary for the EORTC/MSG Consensus Group.

Author affiliations are listed at the end of the text.

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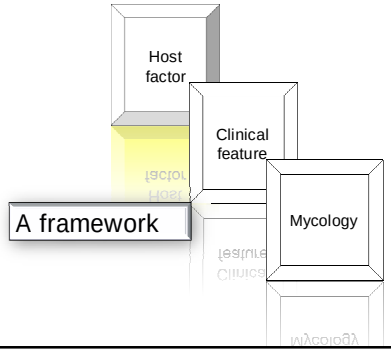
Clinical Infectious Diseases 2008; 46:1813–21

1058-4838/2008/4612-0002$15.00
DOI: 10.1086/588660

No change

Defining invasive fungal disease



EORTC / MSG

Definitions for invasive fungal disease

Changes

What $ in a name?

Invasive **F**ungal **I**nfection

⇩

Invasive **F**ungal **D**isease

2008

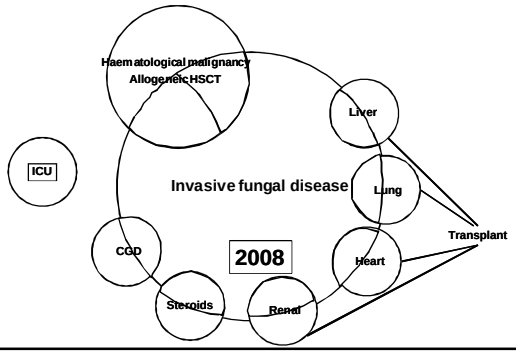
Definitions - Host factors

Host factor

- neutropenia
- 3 weeks corticosteroids
- Allogeneic HSCT recipient
- Treatment with other recognized T-cell immune suppressants
- Inherited severe immunodeficiency

2008

Patients at risk of developing IFD



Definitions - Clinical features

Lower respiratory tract IFD

Chronic disseminated candidiasis

Sinonasal IFD

Clinical feature

CNS IFD

No more major and no more minor

2008

Definitions - Clinical features

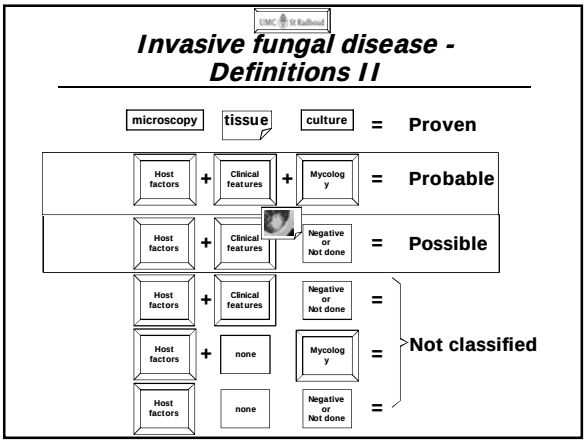
Lower respiratory tract IFD

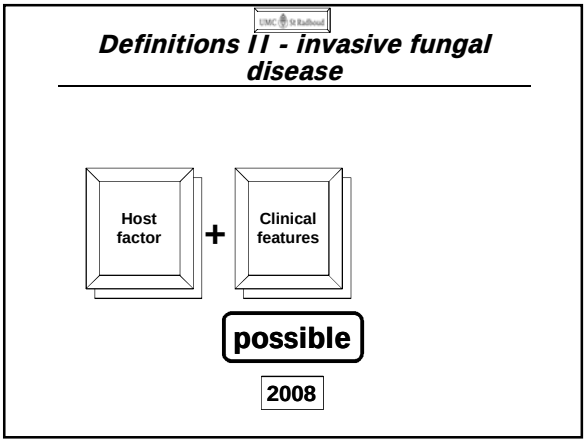
A) the presence of one of the following "specific" imaging signs on CT:-

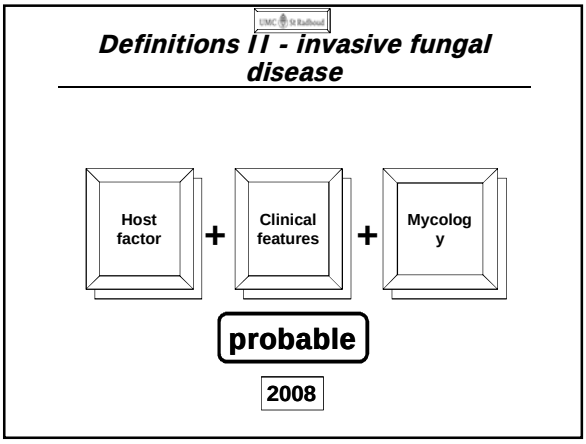
- **Dense well circumscribed lesions(s) with or without a halo sign**
- **Air crescent sign**
- **Cavity**

2008

Donnelly – Definitions of invasive fungal infections

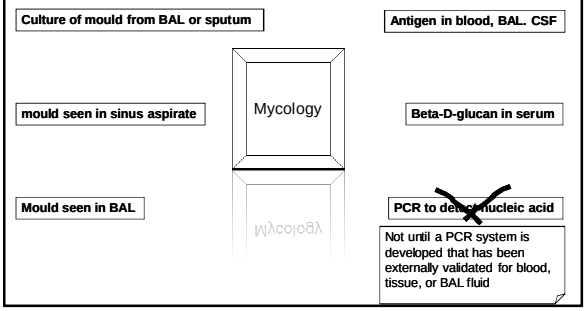






Donnelly – Definitions of invasive fungal infections

Definitions II - Mycology



The continuum of antifungal strategies

Radiological signs & clinical symptoms	None	None	Persistent febrile neutropenia	Clinical or Radiological signs	Clinical or radiological signs
Mycology Results	Negative	Positive Biomarker	Negative	Negative	Positive biomarker or microscopy or culture
Type of strategy	Prophylaxis	Pre-emptive	Empirical	"Pre-emptive "	Directed
Proof of IFD	No	No	No	Yes	Yes
IFI	No	Yes	No	No	yes

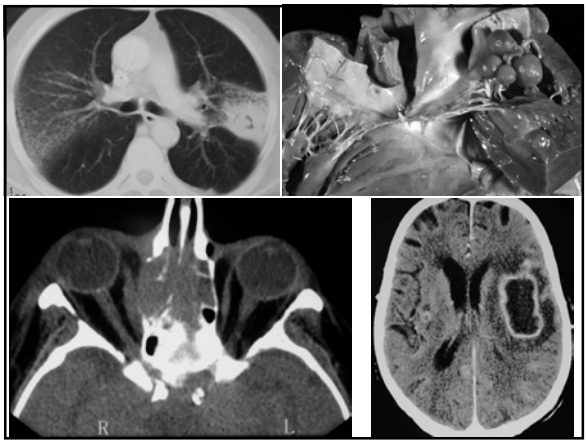
Herbrecht and Berceanu, Clin Infect Dis 2008; 46: 886-8.

Conclusion

- **The revised definitions are for DISEASE not INFECTION**
- **They should make trials simpler and more representative**
- **The definitions are still not all inclusive eg ICU**
- **PCR needs to advance to the next level**
- **Failure to meet the definitions does NOT mean there is no IFD ….**
- **…… only that the criteria for defining IFD have not been met**

Treatment outcome definitions in invasive aspergillosis

Raoul Herbrecht
Strasbourg
France



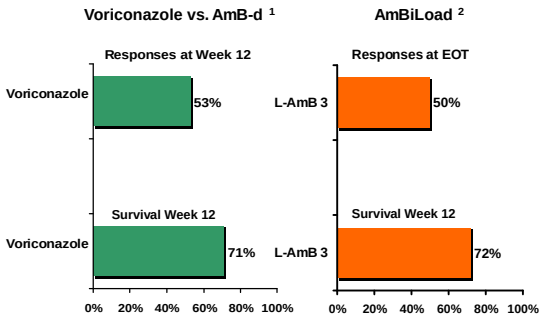
IDSA Guidelines 2008
Primary Therapy of Invasive Aspergillosis

Products		Rating
Voriconazole	Preferred therapy Voriconazole is recommended for the primary treatment of invasive aspergillosis in most patients	A-I
Liposomal amphotericin B	Alternative A randomized trial comparing two dosages of liposomal amphotericin B showed similar efficacy in both arms, suggesting that liposomal therapy could be considered as alternative primary therapy in some patients	A-I

Walsh et al., Clin Infect Dis, 2008

Herbrecht – Treatment outcome definitions in aspergillosis

Basis of the recommendations: results of the best arm in two randomized studies



[1]Herbrecht et al. N Engl J Med. 2002; 347:408-15
[2]Cornely et al. Clin Infect Dis 2007; 44:1289–97

Differences in response criteria

- **Complete response: similar criteria**
- **Partial response: differences**
  - **Voriconazole trial: improvement in clinical symptoms and decrease by** at least 50% **of the size of the radiological lesions**
  - **Ambiload trial: improvement in clinical signs and improvement in radiographic abnormalities. Factors considered for** major radiographic improvement **included:**
    - disappearance of the halo sign **and/or**
    - appearance of an air crescent sign **and/or**
    - decreased estimated size of the lesion

Herbrecht et al. N Engl J Med. 2002; 347:408-15
Cornely et al., Reply to Denning, Clin Infect Dis 2007; 45:1108-1110

Impact of these differences in criteria of partial response

	Voriconazole	L-AmB 3 mg/kg
Favorable response	**53%**	**50%**
- Complete response	**21%**	**1%**
- Partial response	**32%**	**49%**

Herbrecht et al. N Engl J Med. 2002; 347:408-15
Cornely et al. Clin Infect Dis 2007; 44:1289–97

Herbrecht – Treatment outcome definitions in aspergillosis

Consensus response criteria: summary

- **Success**
  - **Complete response**
  - **Partial response**
- **Failure**
  - **Stable disease**
  - **Progression**
  - **Death**

Segal et al, Clin Infect Dis 2008

Response criteria: Complete response

- **Survival and resolution of all attributable symptoms and signs of disease; plus Resolution of radiological lesions;**
- Persistence of only a scar or postoperative changes can be equated with a complete radiological response; plus
- Documented clearance of infected sites that are accessible to repeated sampling

Segal et al, Clin Infect Dis 2008

Response criteria: Partial response

- Survival and improvement of attributable symptoms and signs of disease; **plus**
- At least 25% reduction in diameter of radiological lesions; **plus**
- Documented clearance of infected sites that are accessible to repeated sampling

Segal et al, Clin Infect Dis 2008

Herbrecht – Treatment outcome definitions in aspergillosis

Role of antigenemia

- **Persistence of positive antigenemia is associated with failure to respond and with death (Boutboul et al., CID 2002; Maertens et al., Blood, 2002; Salonen et al., Scand J Infect Dis, 2000; Woods et al, ASH, 2006)**
- **But only 60 to 70% baseline positive galactomannan**
- **Need for an assessment in a prospective trial**
- **Cannot fully replace clinical and radiological signs and symptoms**
- **Is not validated for decision to stop therapy**

Response criteria: Stable disease

- Survival and minor or no improvement in attributable symptoms and signs of disease; **plus**
- Radiological stabilization (defined as a 0%–25% reduction in the diameter of the lesion); **or**
- Persistent isolation of mould or histological presence of invasive hyphae in infected sites
- In cases of radiological stabilization (defined as a 0 - 25% reduction in the diameter of the lesion), resolution of all attributable symptoms and signs of fungal disease can be equated with a partial response
- In cases of radiological stabilization, biopsy of an infected site (e.g., lung biopsy) showing no evidence of hyphae and negative culture results can be equated with a partial response

Segal et al, Clin Infect Dis 2008

Response assessment

- **Time point: End of randomized therapy**
  - **Logical time point to assess the study drug efficacy**
  - **Major difference for drug available as IV form only or as IV + oral form**
    - Voriconazole trial
      - Voriconazole: median EOT = 77 days (IV = 10 days)
      - Amphotericin B : median EOT = 10 days
    - Ambiload trial
      - Liposomal AmB 3 mg: median EOT = 15 days
      - Liposomal AmB 10 mg: median EOT = 14 days

Herbrecht – Treatment outcome definitions in aspergillosis

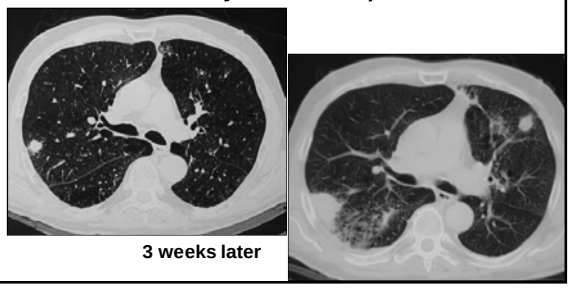
Stable response (classified as a failure) and duration of randomized therapy

	Time point	Stable
ABCD [2]	**13 j**	**34%**
AmB deoxycholate[2]	**15 j**	**28%**
Liposomal AmB (1 mg/kg) [3]	**18 j**	**<15%**
Liposomal AmB (4 mg/kg) [3]	**19 j**	**< 2%**
Voriconazole [1]	**77 j**	**8%**
Amphotéricine B + OLAT [1]	**84 j**	**6%**

[1] *Herbrecht et al. NEJM 2002*
[2] *Bowden et al., CID 2002*
[3] *Ellis et al., CID 1998*

Progression: Are "unfavorable" responses always unfavorable for the patient?

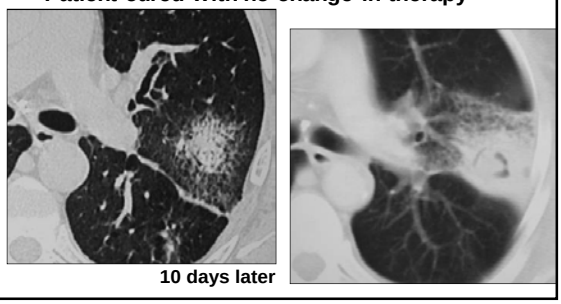
True progression with a worsening of previous lesion and appearance of a new lesion in the absence of recovery from neutropenia



3 weeks later

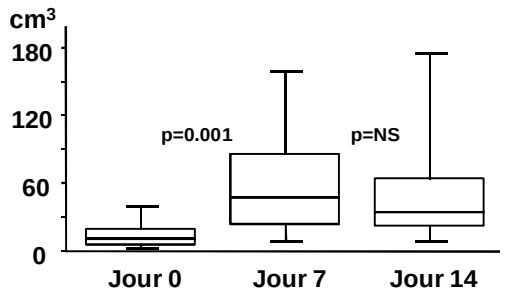
Are "unfavorable" responses always unfavorable for the patient?

- **Increased size of the lesion after neutrophil recovery and air crescent sign**
- **Patient cured with no change in therapy**



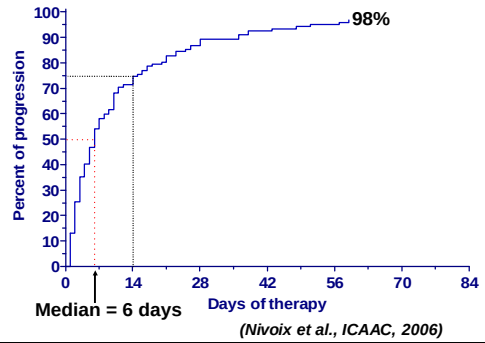
10 days later

Volume of lesions on CT scan in patients with favorable outcome



(Caillot et al., J Clin Oncol. 2001; 19: 253-259)

Time to progression in 122 patients who progressed under therapy



(Nivoix et al., ICAAC, 2006)

Consensus response criteria: summary

- **Success**
  - **Complete response**
  - **Partial response**
- **Failure**
  - **Stable disease**
  - **Progression**
  - **Death**

Segal et al, Clin Infect Dis 2008

Herbrecht – Treatment outcome definitions in aspergillosis

Survival

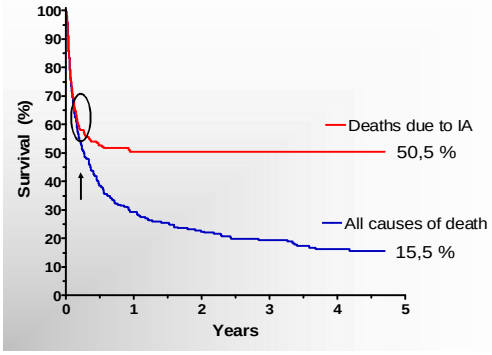
- **Assessment has been made at week 12 in both voriconazole trial and Ambiload trial**
- **However consensus recommendation is now 6 weeks (but suggestion to keep 12 week survival as a secondary end point)**

Consensus response criteria: summary

- **Success**
  - **Complete response**
  - **Partial response**
- **Failure**
  - **Stable disease**
  - **Progression**
  - **Death whatever the cause of death**

Segal et al, Clin Infect Dis 2008

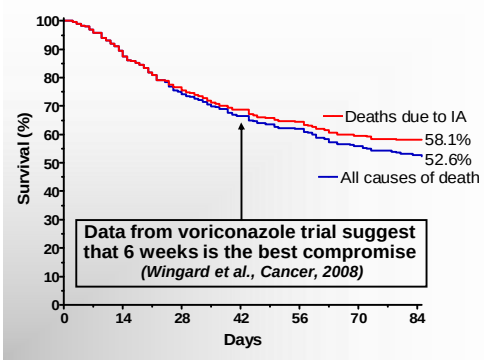
Overall and specific survival in invasive aspergillosis



(Nivoix et al., ICAAC, 2006)

Herbrecht – Treatment outcome definitions in aspergillosis

Overall and specific survival in invasive aspergillosis



(Nivoix et al., ICAAC, 2006)

Conclusion

- **Aspergillosis is difficult to diagnose and to treat**
- **Response is difficult to assess**
- **Need for consensus criteria**
- **Need for an expert panel for assessment in clinical trials**
- **Importance of clinical feeling in front of a patient**

Treatment outcome definitions in candidaemia and other froms of invasive candidiasis

Brahm Segal MD
Roswell Park Cancer Institute
Buffalo, NY

Defining treatment outcomes in antifungal trials

- EORTC/MSG consensus criteria to diagnose IFD have been valuable in establishing eligibility criteria for antifungal trials
- Until recently, there was a lack of consensus definitions of outcomes of IFD that will form a standard for evaluating treatment success and failure in clinical trials

Defining treatment outcomes in antifungal trials

- In some fields, definitions of therapeutic responses are widely accepted
  - Oncology: overall survival and progression-free survival are standard criteria
- Antifungal trials are more complicated
  - Different host factors predisposing to IFDs
  - Different manifestations of IFDs
  - Different therapeutic endpoints to demonstrate effect of antifungal drug

Segal – Treatment outcome definitions

Time-line

- Concept developed in 2005
- Published in 2008
- 30 authors from Europe, U.S., and Canada
- Major pathogens
  - Candidiasis
  - aspergillosis and other moulds
  - histoplasmosis, coccidioidomycosis
  - Cryptococcus

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

Brahm H. Segal MD, Raoul Herbrecht MD, David A. Stevens MD, Luis Ostrosky-Zeichner MD, Jack Sobel MD, Claudio Viscoli MD, Thomas J. Walsh MD, Johan Maertens MD, Thomas F. Patterson MD, John R. Perfect MD, Bertrand Dupont MD, John R. Wingard MD, Thierry Calandra MD, Carol A. Kauffman MD, John R. Graybill MD, Lindsey R. Baden MD, Peter G. Pappas MD, John E. Bennett MD, Dimitrios P. Kontoyiannis MD, Catherine Cordonnier MD, Maria Anna Viviani MD, Jacques Bille, MD, Nikolaos G. Almyroudis MD, L. Joseph Wheat MD, Wolfgang Graninger MD, PhD, Eric J. Bow MD, Steven M Holland MD, Bart-Jan Kullberg MD, William E. Dismukes, MD and Ben E. De Pauw MD.

Clin Infect Dis. 2008 September 1; 47(5): 674–683.

Consensus criteria

- Focus of these consensus criteria relate to clinical research rather than clinical practice.
- Define based on consensus what an international group of experts consider to be the most clinically meaningful therapeutic endpoints in antifungal clinical trials
  - But, consensus doesn't mean uniform agreement
  - More agreement than disagreement on what we thought would be controversial topics

Segal – Treatment outcome definitions

Approach

- Philosophy of what constitutes a successful outcome
  - How do we optimally measure how an antifungal drug performs?
- Lessons learned from prior antifungal trials
  - Can we make improvements?
- Evaluation of newer methods for assessing therapeutic endpoints (e.g., lab markers)
  - Are they ready for prime time or is more research needed?

"The Philosopher", by Rembrandt

General principles

- Global response requires survival and a positive effect on fungal disease
- With certain IFDs (e.g., candidaemia), cure is the goal of therapy.
- "Documented clearance" is more appropriate than "sterilization" since the yield of cultures can be variable, especially while patients are receiving antifungals
- Best proof of cure for these fungal diseases is absence of relapse after cessation of therapy
  - How much time is optimal?

Segal – Treatment outcome definitions

General principles

- primary analysis should include all patients in the intent-to-treat (ITT) or modified intent-to-treat (MITT) groups
- Completion of the assigned treatment regimen is generally a requirement for a successful outcome
  - "success with modification" is a potential option

General criteria for global responses to antifungal therapy

Success
Complete response: Survival within the pre-specified period of observation, and resolution of all attributable symptoms and signs of disease and radiological abnormalities, and mycological evidence of eradication of disease. **Partial response:** Survival within the pre-specified period of observation, and improvement in attributable symptoms and signs of disease and radiological abnormalities, and evidence of clearance of cultures or reduction of fungal burden assessed by a quantitative and validated laboratory marker

Failure

Stable response: Survival within the pre-specified period of observation and minor or no improvement in fungal disease, but no evidence of progression, based on a composite of clinical, radiological, and mycological criteria; or **Progression of Fungal Disease:** Evidence of progressive fungal disease based on a composite of clinical, radiological, and mycological criteria; or **Death:** Death during the pre-specified period of evaluation regardless of attribution

Segal – Treatment outcome definitions

Should survival be required for a positive therapeutic outcome?

- The majority of panel members considered survival through at least the time of assessment of the primary end point to be necessary, although not sufficient, for a successful outcome.

Case for requiring survival for a successful outcome

- Attribution of mortality is difficult in medically complex patients even in the minority who undergo autopsy.
- Drug toxicity may influence survival in ways not obvious to the investigator (e.g., drug-drug interactions) or at autopsy.
- interaction of antifungal drugs with host immunity is an area of growing interest
  - such interactions cannot be encapsulated solely by fungal markers, and may influence survival in ways we do not understand.
- Randomization is expected to balance the effect of variables unrelated to antifungal trial (e.g., death in a car accident) that affect survival in the ITT or MITT analysis.

Case against

- Because mortality may result from causes [seemingly] unrelated to the IFD, more direct markers of response to antifungal treatment (e.g., clearance of cultures in the case of candidaemia) should be used as primary end points instead of survival

Segal – Treatment outcome definitions

Conflicting data

- Recognizing when primary antifungal therapy fails is often not straightforward, particularly with inadequate or conflicting data
- Protocols should ideally pre-specify a rank order of the weight given to specific categories of data, with more weight generally given to objective than subjective data and to specific signs of fungal diseases than less specific signs (e.g., fever).

Therapeutic responses in candidaemia

- documented clearance of blood should be a requirement for a successful outcome.
- Even if symptoms and signs (e.g., fever) attributable to disease persist, they are non-specific and should not, by themselves, be equated with failure
- unless protocol pre-specifies that IV catheters be removed as a requirement for eligibility, catheter removal should not be considered in the outcome assessment

Need for documentation of clearance of infection

- Follow-up sampling of easily accessible sites, such as cerebrospinal fluid (CSF) in meningitis and persistent joint fluid in arthritis, should be required to evaluate therapeutic response
- If follow-up samples are not obtained, the response should either be scored as indeterminate or failure if other signs of progressive or poorly controlled disease (e.g., multiorgan failure) occur
- If additional cultures are not feasible (e.g., in cases of candidiasis involving visceral organs), survival and resolution or improvement of all attributable symptoms and signs of disease and radiological resolution was equated with a successful response

Segal – Treatment outcome definitions

Use of non-culture-based markers to assess therapeutic outcome

- There was inadequate evidence to rely on non-culture-based laboratory markers (e.g., clearance of serum beta-glucan or PCR detection) as surrogates of therapeutic outcome
- Development and validation of sensitive, non–culture-based laboratory assays (e.g., PCR) and, potentially, functional imaging modalities (e.g., PET scan imaging) are expected to facilitate both the early diagnosis of IFDs and the assessment of therapeutic response.

When to assess primary outcome?

- Time to assess primary outcomes in candidaemia should encompass not just clearance of blood, but also be adequate to detect early recrudescence of candidiasis and mortality directly or indirectly related to fungal disease
- Suggest a period of observation of at least 4 weeks from the time of enrollment
- End of therapy (EOT) response should be avoided as a primary endpoint in the view of most of the panel members since the time to stop therapy can be variable and EOT successes will not capture early relapses after discontinuation of therapy.

Successful response in candidaemia

Complete response:

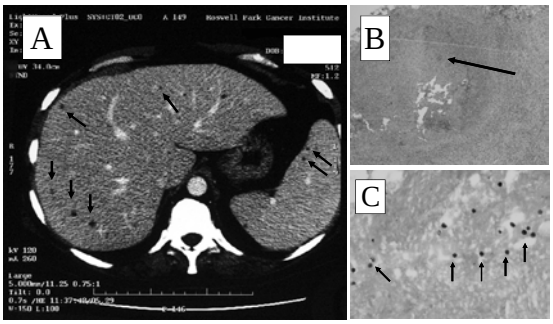
- Survival and resolution of all attributable symptoms and signs of disease; plus
- Documented clearance of blood in cases of candidaemia; plus
- Documented clearance of infected sites that are accessible to repeat sampling (e.g., CSF).
- If repeat cultures are not feasible (e.g., in cases of candidiasis involving visceral organs), survival and resolution of all attributable symptoms and signs of disease and radiological resolution can be equated with a complete response.

Segal – Treatment outcome definitions

Partial response

- Same as complete response, but doesn't require complete resolution of attributable symptoms and signs of infection
- scenario of persistent or recurrent fever despite clearance of blood should be globally assessed as at least a partial response, and therefore equated with a successful response

Hepatosplenic Candidiasis



Visceral candidiasis

- If repeat cultures are not feasible, survival and resolution of attributable symptoms and signs of disease and radiological improvement or stabilization can be equated with a partial response
- In visceral candidiasis (e.g., hepatosplenic candidiasis) with negative blood cultures at baseline, persistent fever may be the only attributable clinical sign of candidiasis and radiological abnormalities can persist for prolonged periods.
- In such situations, resolution of fever and stable radiological disease may be equated with a partial response.

Segal – Treatment outcome definitions

Conclusions

- 1st publication on consensus criteria for assessing therapeutic outcomes for major IFDs
- Criteria are both evidence-based and philosophically-based
- Gaps in knowledge, particularly related to non-culture-based tests as therapeutic markers
- criteria will need to be modified as new developments are made