Medical Mycology September 2006, **44**, S285–S288

Taylor & Francis
Taylor & Francis Group

Consensus definitions for invasive fungal disease: Strengths, limitations, and revisions

J. PETER DONNELLY

Department of Hematology and Nijmegen University Centre for Infectious Diseases, University Medical Centre St Radboud, Radboud University Nijmegen, Nijmegen, The Netherlands

The European Organization for Research and Treatment of Cancer (EORTC)/ Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) consensus definitions for opportunistic invasive fungal infections have achieved their objective in fostering better communication between researchers but their limitations necessitated revision. In the last two years a group of experts drawn from both sides of the Atlantic have agreed a proposal for a new set of definitions that attempt to rectify omissions and problems arising from the original set whilst preserving their basic principles.

Keywords definitions, invasive fungal diseases, aspergillosis, consensus

Introduction

It is five years since the consensus group of 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) published standard definitions for invasive fungal infections for clinical and epidemiological research [1]. The original EORTC/MSG definitions were restricted to immunocompromised patients with cancer and haematopoietic stem cell transplants and assigned three levels of probability to the diagnosis, namely, "proven", "probable" and "possible" invasive fungal infection. Importantly, these definitions contained three elements for diagnosis comprising host factors, clinical features and mycological evidence and created a framework for making use of imaging to detect disease activity as well as indirect tests such as antigen detection to supply evidence of fungal disease. The original EORTC/MSG definitions clearly met a need as they have been adopted in virtually every scientific endeavour from validating diagnostic tests [2–7] to evaluating antifungal agents for treating invasive fungal disease [8–10]. These definitions represented an attempt to establish specific, reproducible guidelines for allowing entry of patients into clinical studies on the basis of standardized criteria. Notably, these were explicitly not recommended for managing patients in daily clinical practice.

Strengths

That the definitions achieved their primary goal of fostering communication to allow the results of studies of invasive fungal diseases to be interpreted and compared more uniformly is attested by the fact that almost every institution involved from licensing authorities such as the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) (Points to consider on the clinical evaluation of new agents for invasive fungal infections evaluating new agents http://www.emea.eu.int/pdfs/ human/ewp/134301en.pdf), to the pharmaceutical and diagnostic industry have adopted them. Moreover medical specialists dealing with invasive fungal diseases have also embraced the definitions routinely referring to infections as proven, probable or possible invasive fungal diseases. Readier use is also being made of computed tomography (CT) scans and tests such as galactomannan (GM) antigen detection on the other hand. Indeed, the British Society of Medical Mycology

Correspondence: J. Peter Donnelly, Department of Hematology and Nijmegen University Centre for Infectious Diseases, University Medical Centre St Radboud, Radboud University Nijmegen, Geert Grooteplein Zuid 8, 6525 GA Nijmegen, The Netherlands. Tel: +31-(0)24-361-9987; E-mail: p.donnelly@usa.net

DOI: 10.1080/13693780600826707

based its proposal for microbiology, histopathology, radiology, and clinical auditing standards, on the assumption that such tests were routinely being used to diagnose invasive fungal disease [11]. The definitions have also taken hold in daily practice on haematology wards and in microbiology laboratories. Indeed a recent study showed that the number of neutropenic patients receiving antifungal therapy could be reduced by half from 35% to 14% without any increase in mortality using the definitions to decide when therapy should be given pre-emptively [12].

Limitations

However, attempts to go beyond research purposes and use the definitions for clinical decision making for individual patients carries the risk of under-treatment if therapy is postponed until an invasive fungal disease had developed sufficiently to meet the criteria for a proven or probable disease. Subira *et al.* [13] also caused some alarm having found that 64% of their patients with proven invasive aspergillosis at autopsy did not meet any of the criteria for diagnosis before death. Admittedly these authors applied the definitions retrospectively to a population for which there was no uniform standard of care in place but the point was well taken. Whereas inappropriate use, as such, should not be regarded as a shortcoming of the definitions, there was concern that the definitions did not cast the net wide enough to be able to include every proven and probable case in clinical studies [14]. Indeed, significant numbers of patients with invasive disease eventually classified as proven or probable invasive fungal disease might be excluded from entry into a trial on the efficacy of an antifungal regimen if the criteria for the proven and probable categories are applied strictly at entry. A typical representative of this ineligible group would be a neutropenic patient with a pulmonary infiltrate characteristic of invasive aspergillosis such as a halo or air-crescent sign for whom no mycological evidence of disease is available. This was obviated in two recent therapeutic trials by applying modified EORTC/MSG definitions to allow such cases to be included for the simple reason that the experts felt such cases represent likely invasive fungal diseases even though the mycological evidence is lacking [8,15]. Although elegant, such modifications are not ideal if the definitions are to attain universal acceptance. It was also apparent that the possible category was of limited value for determining the performance of mycological tests such as the polymerase chain reaction (PCR) since performance was highest when the cases of possible invasive fungal disease were assumed to represent no disease or excluded altogether from the analysis (Table 1) [16,17]. Last but not least the original definitions were restricted to patients with cancer and haematological malignancies whilst these infections affect other populations including recipients of organ transplants and those with chronic granulomatous disorder [18,19].

Revisions

Given these limitations the EORTC and MSG again convened in 2003 and drew a group of 30 experts equally from North America and Europe with Ben De Pauw of the EORTC's Invasive Fungal infections group and Tom Walsh of the Mycoses Study Group as joint chairs. The group set itself the task of revising the original definitions to accommodate these concerns whilst preserving the principles that underpinned them. The categories of proven and probable invasive fungal disease were acknowledged as being reliable and reproducible and the paradigm consisting of the three elements of host factors, clinical features and mycolo-

Table 1 Analysis of polymerase chain reaction (PCR) performance according to different definitions of disease status of invasive aspergillosis

Author	Performance indicator	True positive, proven & probable IA[†]; true negative = no IA[‡]	True positive, proven probable & possible IA; true negative, no IA	True positive, proven & probable IA; true negative, possible IA & no IA
Halliday *et al*. [1]	Sensitivity	100	70·6	100
	Specificity	75·4	75·4	74·7
	Positive predictive value	46·4	61·5	40·6
	Negative predictive value	100	82	100
White *et al*. [15]	Sensitivity	92·3	34	92·3
	Specificity	94·6	94·6	92·6
	Positive predictive value	60	69·2	46·2
	Negative predictive value	99·3	80·1	99·4

[†]IA = invasive aspergillosis.
[‡]Note: possible IA omitted altogether.

Table 2 Examples of possible invasive aspergillosis (IA)

Example	Host factor	Clinical features	Mycological evidence	Comment
1	Neutropenia following remission induction chemotherapy for acute myeloid leukaemia	None. HRCT negative	*Aspergillus* galactomannan detected in plasma	No evidence of invasive fungal disease
2	Neutropenia following allogeneic HSCT	Dry cough HRCT non specific infiltrates	Aspergillus fumigatus recovered from BAL	No evidence of invasive fungal disease
3	GVHD following allogeneic HSCT treated with corticosteroids	Cough, dyspnoea. HRCT bilateral opacities with a ground glass appearance	None	Unlikely to be a sign of invasive IA and more likely due to an alternative aetiology such as viral pneumonia
4	Neutropenia following allogeneic HSCT	Chest pain. HRCT halo signs	None	Likely to be a sign of invasive IA and unlikely explained by an alternative aetiology

BAL = Bronchoalveolar lavage, GVHD = graft versus host disease, HRCT = high resolution computer-assisted tomograpy, HSCT = haematopoietic stem cell transplant.

gical evidence was considered essential to the integrity of the definitions. However, the criteria required to classify possible invasive fungal disease were so permissive that many of the cases meeting them were actually unlikely to have a fungal infection at all. For instance in Table 2 only Example 4 would be considered by most to be likely to have invasive aspergillosis whereas persistent fever refractory to antibiotic therapy in a neutropenic patient with non-specific symptoms such as cough and dyspnoea is unlikely to represent invasive fungal disease. Inclusion of such patients in clinical trials would dilute a study population recruited to assess the efficacy of a given antifungal for therapy or prophylaxis. Hence, narrowing the definition of possible invasive fungal diseases was given a high priority. The group also recognized the accumulating evidence of the value of several diagnostic tests including the high resolution CT scan of chest and abdomen, the detection of GM in blood as well as in bronchoalveolar lavage fluid and of β–D-glucan in plasma, and fungal DNA by PCR in body fluid. These could function as valid surrogate markers provided they were not only precise but also accurate and capable of conveying useful information. Importantly such tests were required to have been validated with an accepted standard in place. Unfortunately this effectively ruled out PCR for the time being.

Throughout the process, two restrictions were applied: (i) the definition set should remain reproducible and (ii) it had to secure the possibility of comparing future data sets with those collected during clinical trials and observational studies that applied the original definitions of proven and probable invasive fungal infections. In this way the revised definitions aim to improve the strengths of the original set and reduce the limitations without losing site of the original purpose.

References

1 Ascioglu S, Rex JH, de Pauw B, *et al*. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: An international consensus. *Clin Infect Dis* 2002; **34**: 7–14.

2 Marr KA, Balajee SA, McLaughlin L, *et al*. Detection of galactomannan antigenemia by enzyme immunoassay for the diagnosis of invasive aspergillosis: variables that affect performance. *J Infect Dis* 2004; **190**: 641–649.

3 Maertens J, Glasmacher A, Selleslag D, *et al*. Evaluation of serum sandwich enzyme-linked immunosorbent assay for circulating galactomannan during caspofungin therapy: Results from the caspofungin invasive aspergillosis study. *Clin Infect Dis* 2005; **41**: e9–14.

4 Millon L, Piarroux R, Deconinck E, *et al*. Use of real-time PCR to process the first galactomannan-positive serum sample in diagnosing invasive aspergillosis. *J Clin Microbiol* 2005; **43**(10): 5097–5101.

5 Pazos C, Ponton J, Del Palacio A. Contribution of (1 →3)-beta-D-glucan chromogenic assay to diagnosis and therapeutic monitoring of invasive aspergillosis in neutropenic adult patients: a comparison with serial screening for circulating galactomannan. *J Clin Microbiol* 2005; **43**: 299–305.

6 Kawazu M, Kanda Y, Nannya Y, *et al*. Prospective comparison of the diagnostic potential of real-time PCR, double-sandwich enzyme-linked immunosorbent assay for galactomannan, and a (1 →3)-beta-D-glucan test in weekly screening for invasive aspergillosis in patients with hematological disorders. *J Clin Microbiol* 2004; **42**: 2733–2741.

7 Donnelly JP. Polymerase chain reaction for diagnosing invasive aspergillosis: getting closer but still a ways to go. *Clin Infect Dis* 2006; **42**: 487–489.

8 Herbrecht R, Denning DW, Patterson TF, *et al*. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; **347**: 408–415.

9 Walsh TJ, Pappas P, Winston DJ, *et al*. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002; **346**: 225–234.
10 Walsh TJ, Teppler H, Donowitz GR, *et al*. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med* 2004; **351**: 1391–1402.
11 Denning DW, Kibbler CC, Barnes RA. British Society for Medical Mycology proposed standards of care for patients with invasive fungal infections. *Lancet Infect Dis* 2003; **3**: 230–240.
12 Maertens J, Theunissen K, Verhoef G, *et al*. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. *Clin Infect Dis* 2005; **41**: 1242–1250.
13 Subira M, Martino R, Franquet T, *et al*. Invasive pulmonary aspergillosis in patients with hematologic malignancies: survival and prognostic factors. *Haematologica* 2002; **87**: 528–534.
14 de Pauw BE, Patterson TF. Should the consensus guidelines' specific criteria for the diagnosis of invasive fungal infection be changed? *Clin Infect Dis* 2005; **41** Suppl 6: S377–S380.
15 Cornely OA, Maertens J, Bresnik M, *et al*. Liposomal amphotericin B (L-AmB) as initial therapy for invasive filamentous fungal infections (IFFI): a randomized, prospective trial of a high loading regimen vs. standard dosing (AmBiLoad Trial). American Society of Hematology 47th Annual Meeting, Atlanta, GA, 2005. Abstracts *Blood* 2005, **106**: 3222.
16 Halliday C, Hoile R, Sorrell T, *et al*. Role of prospective screening of blood for invasive aspergillosis by polymerase chain reaction in febrile neutropenic recipients of haematopoietic stem cell transplants and patients with acute leukaemia. *Br J Haematol* 2006; **132**: 478–486.
17 White PL, Linton CJ, Perry MD, *et al*. The evolution and evaluation of a whole blood polymerase chain reaction assay for the detection of invasive aspergillosis in hematology patients in a routine clinical setting. *Clin Infect Dis* 2006; **42**: 479–486.
18 Patterson TF, Kirkpatrick WR, White M, *et al*. Invasive aspergillosis. Disease spectrum, treatment practices, and outcomes. I3 Aspergillus Study Group. *Medicine (Baltimore)* 2000; **7**: 250–260.
19 Hope WW, Walsh TJ, Denning DW. The invasive and saprophytic syndromes due to *Aspergillus* spp. *Med Mycol* 2005; **43** Suppl 1: S207–S238.