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

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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.

In 2002, a consensus group of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) published standard definitions for invasive fungal infections for clinical and epidemiological research [1]. These definitions were developed to facilitate the identification of reasonably homogeneous groups of patients for clinical and epidemiologic research, to help design clinical trials to evaluate new drugs and management strategies, and, last but not least, to foster communication between

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international researchers. The definitions assigned 3 levels of probability to the diagnosis of invasive fungal infection that develops in immunocompromised patients with cancer and in hematopoietic stem cell transplant recipients—namely, "proven," "probable," and "possible" invasive fungal infection. The definitions established a formal framework for defining invasive fungal infection with a variable certainty of diagnosis. Proven invasive fungal infection required only that a fungus be detected by histological analysis or culture of a specimen of tissue taken from a site of disease; in the case of *Cryptococcus neoformans,* detection of capsular antigen in CSF or a positive result of an India ink preparation of CSF was considered sufficient to establish a diagnosis of proven cryptococcosis. By contrast, probable and possible invasive fungal infections hinged on 3 elements—namely, a host factor that identified the patients at risk, clinical signs and symptoms consistent with the disease entity, and mycological evidence that encompassed culture and microscopic analysis but also indirect tests, such as antigen detection. These EORTC/MSG Consensus Group definitions have been used in major trials of antifungal drug efficacy, in strategy trials [2–6], for the formulation of clinical practice guidelines [7], for validation of diagnostic tests [8–13], and for performance of epidemiologic studies [14].

The previously published definitions were not without their shortcomings. For instance, the original category of possible invasive fungal infection allowed too many dubious cases to be included, particularly those involving neutropenia, nonspecific pulmonary infiltrates, and persistent fever refractory to broad-spectrum antibiotics but with no evidence of invasive fungal infection [15]. These cases may represent patients at higher risk of invasive fungal infection but are quite different from the cases, also defined as possible cases, for which more specific pulmonary abnormalities, such as a halo or air-crescent sign characteristic of invasive aspergillosis, were present. Indeed, the definitions were modified to allow enrollment of similar cases into clinical trials, because they are considered to represent likely invasive fungal disease even without supporting mycological evidence [2, 16]. This pragmatic approach solved the problem of recruitment of representative cases, but it clearly highlighted the need to refine further the definitions, to distinguish dubious cases from the more likely cases when mycological evidence was not forthcoming. The growing body of evidence regarding the value of high-resolution CT of chest and abdomen [17] and of indirect diagnostic tests—such as the detection of galactomannan in body fluids other than serum and plasma, of β-D-glucan in serum, and of fungal DNA in body fluids by PCR—provided additional incentive to review the definitions [18, 19]. The original definitions were also restricted to patients with cancer and to recipients of hematopoietic stem cell transplants; however, invasive fungal infections are known to affect other populations, including recipients of solid-organ transplants and patients with primary immunodeficiencies (e.g., chronic granulomatous disorder) [20, 21]. Finally, it was considered appropriate to explore the possibility of formulating specific criteria for diseases caused by less common fungal pathogens.

REVISION PROCESS

The EORTC/MSG Consensus Group met in Chicago, Illinois, on 14 September 2003 during the 43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and included 13 members from the EORTC and 17 from the MSG. J. Powers also participated for the US Food and Drug Administration (FDA), and there were 5 observers from 4 pharmaceutical companies (J. Rex [Astra Zeneca], C. Sable [Merck], M. Bresnik [Gilead], and G. Triggs and A. Baruch [Pfizer]). B.d.P. and T.J.W. were confirmed as joint chairs, and J.P.D. was designated as secretary for the group. Three subcommittees were appointed to prepare proposals for mold infection, candidiasis, and endemic mycoses. The proposals were collated by the secretary, who integrated them into a general framework. They were then circulated by electronic mail to all group members. The ensuing comments again were centrally combined for a subsequent round of electronic consultation. The remaining issues that appeared difficult to solve by the electronic route were addressed in open meetings during the 15th European Congress of Clinical Microbiology and Infectious Disease in Copenhagen, Denmark, and the 45th Annual ICAAC in Washington, DC. A majority vote was decisive when a consensus among the members could not be achieved. The final draft was made available to the wider community for comment at the Doctor Fungus Web site [22] and The Aspergillus Web site [23]. Thereafter, the manuscript was prepared and was circulated among all group members for their final approval.

At the first meeting, all group members agreed to the need to refine and revise the definitions. It was also agreed unanimously that the definition set should remain easily reproducible and should offer the opportunity for a reasonable comparison of future data sets with data sets that had been collected in clinical trials that involved patients with proven and probable invasive fungal infections according to the original definitions. Finally, the group set out to reexamine the feasibility of using the definitions for treatment purposes, to devise a means of extending their applicability to other patient groups, to review the relevance of the findings obtained from studies based on the definitions for clinical practice, and to attempt to incorporate all the available laboratory tests and imaging techniques into the definitions.

REVISED DEFINITIONS

The term "invasive fungal disease" (IFD) was adopted to reflect more accurately the notion that we are dealing with a disease process caused by fungal infection. An adequate diagnostic evaluation of the infectious disease process, to exclude an alternative etiology, was deemed to be a necessary prerequisite to classify it as an IFD. The group reaffirmed that the definitions should be used only to assist in research and that the integrity of the original definitions with the classifications of proven, probable, and possible IFD would be preserved (tables 1–3). Infections caused by *Pneumocystis jiroveci* are not included. The criteria for proven and probable IFD (tables 1 and 2) were modified to reflect advances in indirect tests, whereas the category of possible IFD (table 3) was revised to include only cases that are highly likely to be caused by a fungal etiology, although mycological evidence is lacking. Hence, the definitions of probable and possible IFD were based on the same 3 elements as were the original definitions: host factors, clinical manifestations, and mycological evidence.

Host factors are not synonymous with risk factors but are characteristics by which individuals predisposed to acquire IFD can be recognized. Consequently, the presence of fever was removed as a host factor because it represents a clinical feature, not a host factor, and is nonspecific for IFD. The host factors were extended to receipt of a solid-organ transplant, hereditary immunodeficiencies, connective tissue disorders, and receipt of immunosuppressive agents—for example, corticosteroids or T cell immunosuppressants, such as calcineurin inhibitors, anti–TNF-α drugs, anti-lymphocyte antibodies, or purine analogues. The distinction between "minor" and "major" clinical criteria was abandoned in favor of more-characteristic and objectively verifiable evidence, such as the findings on medical imaging that indicated a disease process consistent with IFD by use of a standardized glossary of definitions. For example, in the case of chest CT imaging to categorize pulmonary lesions, the vast majority of immunocompromised patients with invasive pulmonary aspergillosis have focal rather than diffuse pulmonary infiltrates and present with at least 1 macronodule, with or without a halo sign [24]. These infections can also manifest as wedge-shaped infiltrates and segmental or lobar consolidation. Although none of the imaging findings is pathognomonic for IFD, the observation that, in the appropriate patient population, the outcome of antifungal therapy did not differ between febrile patients with nodular lesions and patients with mycological evidence of an IFD supports the use of this clinical criterion [17]. A similar consideration applies to patients with lesions on CT or ultrasound that are regarded as typical for chronic disseminated candidiasis. In the original definitions, patients with such lesions were defined as having probable hepatosplenic candidiasis without any need for mycological support. In the revised definitions, such cases are classified as possible IFD, thereby retaining the consistency of the definitions and preserving the distinction between probable IFD and possible IFD. For a patient with appropriate host factors and clinical evidence of pulmonary disease, bronchoalveolar lavage fluid that yields *Aspergillus,* Zygomycetes, *Fusarium,* or *Scedosporium* species or other pathogenic molds would constitute mycological support and would allow the case to be classified as probable pulmonary IFD.

As with the original definitions, indirect tests were considered for inclusion only if they were validated and standardized. Furthermore, because commercial tests for diagnostic use had to provide criteria for interpretation to gain approval, it was decided to rely entirely on the thresholds recommended by the manufacturer. On the basis of recent studies, the Platelia *Aspergillus* galactomannan EIA could be applied to CSF and bronchoalveolar lavage fluid, as well as plasma and serum. The β-D-glucan assay also was included as a marker for probable IFD, because this test detects other species of fungi besides *Aspergillus,* and a commercial test for it (Fungitell assay; Associates of Cape Cod) has been approved by the FDA. By contrast, molecular methods of detecting fungi in clinical specimens, such as PCR, were not included in the definitions because there is as yet no standard, and none of the techniques has been clinically validated.

THE CATEGORIES

Proven IFD. There was general agreement that the category of proven IFD should be retained, requiring proof of IFD by demonstration of fungal elements in diseased tissue for most conditions (table 1). Revisions were made to this category to reflect advances in indirect assays that are highly specific for the infection being detected. By its very nature, this category is likely to be valid irrespective of host factors or clinical features. Individual IFD entities—for example, proven aspergillosis—require culture and identification. Failing this, the disease is designated as proven mold IFD (table 1). The histological appearance of the endemic dimorphic fungi, *Histoplasma capsulatum,* as small intracellular budding yeasts; *Coccidioides* species as spherules; *Paracoccidioides brasiliensis* as large yeasts with multiple daughter yeasts in a "pilot-wheel configuration"; and *Blastomyces dermatitidis* as thick-walled, broad-based budding yeasts is sufficiently distinctive to permit a definitive diagnosis (table 3). *H. capsulatum* variety *capsulatum* resembles *Candida glabrata* or *Leishmania* species in tissue but can be distinguished from them by characteristic histological features of granulomatous inflammation in histoplasmosis in some patient groups and by staining with silver, which shows staining for the fungi but not for *Leishmania* species.

The category of proven IFD was modified to reflect advances

Table 1. Criteria for proven invasive fungal disease except for endemic mycoses.

Analysis and specimen	Molds[a]	Yeasts[a]
Microscopic analysis: sterile material	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	Histopathologic, cytopathologic, or direct microscopic examination[b] 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 indicated by encapsulated budding yeasts or *Candida* species showing pseudohyphae or true hyphae[c]
Culture		
Sterile material	Recovery of a mold or "black yeast" 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 bronchoalveolar lavage fluid, a cranial sinus cavity specimen, and urine	Recovery of a yeast by culture of a sample obtained by a sterile procedure (including a freshly placed [<24 h ago] drain) from a normally sterile site showing a clinical or radiological abnormality consistent with an infectious disease process
Blood	Blood culture that yields a mold[d] (e.g., *Fusarium* species) in the context of a compatible infectious disease process	Blood culture that yields yeast (e.g., *Cryptococcus* or *Candida* species) or yeast-like fungi (e.g., *Trichosporon* species)
Serological analysis: CSF	Not applicable	Cryptococcal antigen in CSF indicates disseminated cryptococcosis

[a] If culture is available, append the identification at the genus or species level from the culture results.

[b] Tissue and cells submitted for histopathologic or cytopathologic studies should be stained by Grocott-Gomorri methenamine silver stain or by periodic acid Schiff stain, to facilitate inspection of fungal structures. Whenever possible, wet mounts of specimens from foci related to invasive fungal disease should be stained with a fluorescent dye (e.g., calcofluor or blankophor).

[c] *Candida, Trichosporon,* and yeast-like *Geotrichum* species and *Blastoschizomyces capitatus* may also form pseudohyphae or true hyphae.

[d] Recovery of *Aspergillus* species from blood cultures invariably represents contamination.

Table 2. Criteria for probable invasive fungal disease except for endemic mycoses.

- Host factors[a]
  - Recent history of neutropenia ($<0.5 \times 10^9$ neutrophils/L [<500 neutrophils/mm^3] for >10 days) temporally related to the onset of fungal disease
  - Receipt of an allogeneic stem cell transplant
  - Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for >3 weeks
  - Treatment with other recognized T cell immunosuppressants, such as cyclosporine, TNF-α blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days
  - Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)
- Clinical criteria[b]
  - Lower respiratory tract fungal disease[c]
    - The presence of 1 of the following 3 signs on CT:
      - Dense, well-circumscribed lesions(s) with or without a halo sign
      - Air-crescent sign
      - Cavity
  - Tracheobronchitis
    - Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis
  - Sinonasal infection
    - Imaging showing sinusitis plus at least 1 of the following 3 signs:
      - Acute localized pain (including pain radiating to the eye)
      - Nasal ulcer with black eschar
      - Extension from the paranasal sinus across bony barriers, including into the orbit
  - CNS infection
    - 1 of the following 2 signs:
      - Focal lesions on imaging
      - Meningeal enhancement on MRI or CT
  - Disseminated candidiasis[d]
    - At least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks:
      - Small, target-like abscesses (bull's-eye lesions) in liver or spleen
      - Progressive retinal exudates on ophthalmologic examination
- Mycological criteria
  - Direct test (cytology, direct microscopy, or culture)
    - Mold in sputum, bronchoalveolar lavage fluid, bronchial brush, or sinus aspirate samples, indicated by 1 of the following:
      - Presence of fungal elements indicating a mold
      - Recovery by culture of a mold (e.g., *Aspergillus, Fusarium,* Zygomycetes, or *Scedosporium* species)
  - Indirect tests (detection of antigen or cell-wall constituents)[e]
    - Aspergillosis
      - Galactomannan antigen detected in plasma, serum, bronchoalveolar lavage fluid, or CSF
    - Invasive fungal disease other than cryptococcosis and zygomycoses
      - β-D-glucan detected in serum

NOTE. Probable IFD requires the presence of a host factor, a clinical criterion, and a mycological criterion. Cases that meet the criteria for a host factor and a clinical criterion but for which mycological criteria are absent are considered possible IFD.

[a] Host factors are not synonymous with risk factors and are characteristics by which individuals predisposed to invasive fungal diseases can be recognized. They are intended primarily to apply to patients given treatment for malignant disease and to recipients of allogeneic hematopoietic stem cell and solid-organ transplants. These host factors are also applicable to patients who receive corticosteroids and other T cell suppressants as well as to patients with primary immunodeficiencies.

[b] Must be consistent with the mycological findings, if any, and must be temporally related to current episode.

[c] Every reasonable attempt should be made to exclude an alternative etiology.

[d] The presence of signs and symptoms consistent with sepsis syndrome indicates acute disseminated disease, whereas their absence denotes chronic disseminated disease.

[e] These tests are primarily applicable to aspergillosis and candidiasis and are not useful in diagnosing infections due to *Cryptococcus* species or Zygomycetes (e.g., *Rhizopus, Mucor,* or *Absidia* species). Detection of nucleic acid is not included, because there are as yet no validated or standardized methods.

Table 3. Criteria for the diagnosis of endemic mycoses.

Diagnosis and criteria
Proven endemic mycosis
In a host with an illness consistent with an endemic mycosis, 1 of the following:
Recovery in culture from a specimen obtained from the affected site or from blood
Histopathologic or direct microscopic demonstration of appropriate morphologic forms with a truly distinctive appearance characteristic of dimorphic fungi, such as *Coccidioides* species spherules, *Blastomyces dermatitidis* thick-walled broad-based budding yeasts, *Paracoccidioides brasiliensis* multiple budding yeast cells, and, in the case of histoplasmosis, the presence of characteristic intracellular yeast forms in a phagocyte in a peripheral blood smear or in tissue macrophages
For coccidioidomycosis, demonstration of coccidioidal antibody in CSF, or a 2-dilution rise measured in 2 consecutive blood samples tested concurrently in the setting of an ongoing infectious disease process
For paracoccidioidomycosis, demonstration in 2 consecutive serum samples of a precipitin band to paracoccidioidin concurrently in the setting of an ongoing infectious disease process
Probable endemic mycosis
Presence of a host factor, including but not limited to those specified in table 2, plus a clinical picture consistent with endemic mycosis and mycological evidence, such as a positive *Histoplasma* antigen test result from urine, blood, or CSF

NOTE. Endemic mycoses includes histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, sporotrichosis, and infection due to *Penicillium marneffei*. Onset within 3 months after presentation defines a primary pulmonary infection. There is no category of possible endemic mycosis, as such, because neither host factors nor clinical features are sufficiently specific; such cases are considered to be of value too limited to include in clinical trials, epidemiological studies, or evaluations of diagnostic tests.

in our understanding of *Coccidioides* serological characteristics. Consequently, the presence of coccidioidal antibody in CSF was considered to be sufficient to fulfill the criteria for proven coccidioidomycosis. Similarly, the presence of capsular antigen in CSF was considered to be sufficiently distinctive to establish a diagnosis of disseminated cryptococcosis [25]. Urinary *Histoplasma* antigen supports a diagnosis of probable endemic mycosis, in conjunction with appropriate host and clinical criteria (table 3), but cannot be considered sufficient evidence of proven histoplasmosis, because *Histoplasma* antigen is also found in urine and serum of patients with coccidioidomycosis and blastomycosis [26].

Probable IFD. Cases of probable IFD require that a host factor, clinical features, and mycological evidence be present, as outlined in tables 2 and 3.

Possible IFD. The category of possible IFD was retained but was defined more strictly to include only those cases with the appropriate host factors and with sufficient clinical evidence consistent with IFD but for which there was no mycological support (table 2). However, this category was not considered appropriate for endemic mycosis, because host factors and clinical features are not sufficiently specific and because such cases would be of value too limited to include in clinical trials, epidemiological studies, or evaluations of diagnostic tests.

COMMENTS

Implications of the revised category of possible IFD. After enrollment into an interventional or diagnostic study, every effort should be made to upgrade the certainty of diagnosis for patients with possible IFD to the category of proven or probable IFD. These definitions may be applied at different times during the period of risk. For example, although a case might not meet the definition of possible, probable, or proven IFD at the beginning of a period of high risk, during which prophylaxis is given, the case may continue to evolve, such that the criteria may be met later.

The overrepresentation of dubious cases that resulted from the application of the original definitions made it imperative to redress the balance and to capture more patients with a higher probability of IFD while excluding patients who are unlikely to have invasive mycosis. Some members even argued that the category of possible IFD, as defined in the original set of definitions, should be abolished altogether. However, such a decision would reduce dramatically the number of candidates eligible for clinical studies of fungal pneumonia, making randomized trials nearly impossible to conduct. The corollary of retaining a better-defined category of possible IFD, to reduce the number of doubtful cases, was that greater emphasis was placed on mycological evidence for the categories of proven and probable IFD. This allows the category of possible IFD to be reserved for clinical manifestations fully consistent with fungal etiology but for which there is no mycological evidence available, although a reasonable attempt has been made to exclude an alternative etiology.

Non–culture-based diagnostic tests. There was much discussion about indirect mycological tests, especially assays for detection of antigen and β-D-glucan. Since the first definitions were published [1], the FDA has approved the *Aspergillus* galactomannan EIA and, more recently, the assay for β-D-glucan, on the grounds that they were standardized, were validated, are available, and are fit to convey useful information [8, 19, 27]. However, controversy arose about the interpretation of the index for the galactomannan assay, which was originally set at 1.5 and was applied in Europe but which was lowered to 0.5

after review by the FDA. This cutoff value has been shown recently to improve the overall performance of the test for adult hematology patients [28]. Because the issue remains contentious, the decision was made to place the onus on the manufacturers of commercial tests and to adopt whatever threshold values they recommend.

We had hoped that nucleic acid–detection tests, such as PCR, would have improved enough to incorporate the results of these tests into the definitions. However, standardization and validation have not yet been attained for these platforms.

Limitations of the revised definitions. The revised definitions apply to immunocompromised patients but not necessarily to critically ill patients in the intensive care unit who, nonetheless, may develop possible or probable IFD [29]. The group recognized this as an omission but was unable to find a sufficient basis for identifying the appropriate host factors, even though there may be mycological evidence, such as recovery of *Aspergillus* species from bronchial secretions or a positive β-D-glucan test result. The group, therefore, concluded that the body of evidence supporting a diagnosis other than proven IFD is not sufficiently mature at present.

The definitions are not a substitute for complete clinicopathologic descriptions and classifications of IFD, as have been published recently for aspergillosis [21]. The failure to meet the criteria for IFD does not mean that there is no IFD, only that there is insufficient evidence to support the diagnosis. This is the most compelling reason for not employing these definitions in daily clinical practice.

We anticipate that the field of diagnosis will continue to evolve, so that there will come a time when the definitions may be formally evaluated for their sensitivity and specificity. Until then, additional revisions of the present set of definitions are likely, but they should be contemplated carefully. The words and phrases chosen here were selected on the basis of extensive debate and discussion. Seemingly, slight changes may have unexpectedly profound consequences in the design, implementation, and interpretation of clinical trials.

These revised definitions of IFD categories are intended to advance clinical and epidemiological research and, as such, may serve as a useful model for defining other infections in high-risk patients. The definitions are not meant to be used to guide clinical practice but must be applied consistently if they are to continue to achieve their primary goal of fostering communication, furthering our understanding of the epidemiology and evolution of IFD, and facilitating our ability to test the efficacy of therapeutic regimens and strategies.

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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. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med **2002**; 347:408–15.
3. 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**; 346:225–34.
4. 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**; 351:1391–402.
5. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med **2007**; 356:335–47.
6. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med **2007**; 356:348–59.
7. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis **2008**; 46:327–60.
8. Marr KA, Balajee SA, McLaughlin L, Tabouret M, Bentsen C, Walsh

TJ. Detection of galactomannan antigenemia by enzyme immunoassay for the diagnosis of invasive aspergillosis: variables that affect performance. J Infect Dis **2004**; 190:641–9.

9. 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.
10. Ostrosky-Zeichner L, Alexander BD, Kett DH, et al. Multicenter clinical evaluation of the (1→3) β-D-glucan assay as an aid to diagnosis of fungal infections in humans. Clin Infect Dis **2005**; 41:654–9.
11. Pazos C, Ponton J, Del Palacio A. Contribution of (1→3)-β-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.
12. 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)-β-D-glucan test in weekly screening for invasive aspergillosis in patients with hematological disorders. J Clin Microbiol **2004**; 42:2733–41.
13. Donnelly JP. Polymerase chain reaction for diagnosing invasive aspergillosis: getting closer but still a ways to go. Clin Infect Dis **2006**; 42: 487–9.
14. Cornillet A, Camus C, Nimubona S, et al. Comparison of epidemiological, clinical, and biological features of invasive aspergillosis in neutropenic and nonneutropenic patients: a 6-year survey. Clin Infect Dis **2006**; 43:577–84.
15. Borlenghi E, Cattaneo C, Capucci MA, et al. Usefulness of the MSG/IFICG/EORTC diagnostic criteria of invasive pulmonary aspergillosis in the clinical management of patients with acute leukaemia developing pulmonary infiltrates. Ann Hematol **2007**; 86:205–10.
16. Cornely OA, Maertens J, Bresnik M, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). Clin Infect Dis **2007**; 44:1289–97.
17. Greene RE, Schlamm HT, Oestmann JW, et al. Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. Clin Infect Dis **2007**; 44:373–9.
18. Hope WW, Walsh TJ, Denning DW. Laboratory diagnosis of invasive aspergillosis. Lancet Infect Dis **2005**; 5:609–22.
19. Odabasi Z, Mattiuzzi G, Estey E, et al. β-D-Glucan as a diagnostic adjunct for invasive fungal infections: validation, cutoff development, and performance in patients with acute myelogenous leukemia and myelodysplastic syndrome. Clin Infect Dis **2004**; 39:199–205.
20. Patterson TF, Kirkpatrick WR, White M, et al. Invasive aspergillosis: disease spectrum, treatment practices, and outcomes. I3 Aspergillus Study Group. Medicine (Baltimore) **2000**; 79:250–60.
21. Hope WW, Walsh TJ, Denning DW. The invasive and saprophytic syndromes due to *Aspergillus* spp. Med Mycol **2005**; 43(Suppl 1): S207–38.
22. Doctor Fungus. Available at: http://www.doctorfungus.org. Accessed 28 April 2008.
23. The Aspergillus Web site. Available at: http://www.aspergillus.org.uk. Accessed 28 April 2008.
24. Austin JH, Muller NL, Friedman PJ, et al. Glossary of terms for CT of the lungs: recommendations of the Nomenclature Committee of the Fleischner Society. Radiology **1996**; 200:327–31.
25. Goodman JS, Kaufman L, Koenig MG. Diagnosis of cryptococcal meningitis: value of immunologic detection of cryptococcal antigen. N Engl J Med **1971**; 285:434–6.
26. Pappagianis D. Serologic studies in coccidioidomycosis. Semin Respir Infect **2001**; 16:242–50.
27. Obayashi T, Yoshida M, Mori T, et al. Plasma (1→3)-β-D-glucan measurement in diagnosis of invasive deep mycosis and fungal febrile episodes. Lancet **1995**; 345:17–20.
28. Maertens JA, Klont R, Masson C, et al. Optimization of the cutoff value for the *Aspergillus* double-sandwich enzyme immunoassay. Clin Infect Dis **2007**; 44:1329–36.
29. Meersseman W, Lagrou K, Maertens J, Van Wijngaerden E. Invasive aspergillosis in the intensive care unit. Clin Infect Dis **2007**; 45:205–16.